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CLINICAL STUDY PROTOCOL

CLINICAL STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF *WILATE* DURING PROPHYLAXIS IN PREVIOUSLY TREATED PATIENTS WITH VON WILLEBRAND DISEASE (VWD)

Investigational Product:	***Wilate***
Indication:	Routine prophylaxis in patients with VWD
Study Design:	Prospective, non-controlled, international, multi-centre phase 3 study
Sponsor:	**Octapharma AG** Seidenstrasse 2 CH-8853 Lachen Switzerland
Study Number:	WIL-31
EudraCT and/or IND Number:	**EudraCT** 2018-004675-13, **IND** 011303
Development Phase:	Phase 3
Planned Clinical Start:	Q2 2020
Planned Clinical End:	Q1 2022
Date of Protocol:	01-Mar-2021
Version:	07
Previous Protocol Versions:	06—26-Feb-2020 (for Ukraine only) 05—25-Feb-2020 04—23-Aug-2019 (for Ukraine only) 03—22-Aug-2019 02—13-Jun-2019 01—04-Feb-2019
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STUDY OUTLINE

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: *Wilate*	**Protocol Identification Code:** WIL-31
Name of Active Ingredient: Factor VIII/VWF concentrate human	**Date of Final Protocol:** 01-Mar-2021

Title of Study: Clinical Study to Investigate the Efficacy and Safety of *Wilate* during Prophylaxis in Previously Treated Patients with VWD

Number of Study Centre(s): Up to 14 sites worldwide

OBJECTIVES:

Primary Objective:

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

Secondary Objectives:

The secondary objectives of this study are to:

- Assess the incremental IVR of *Wilate* for VWF:Ac and FVIII:C over time
- Determine the pharmacokinetics (PK) of *Wilate* for VWF:Ac and FVIII:C in paediatric patients aged 6–16 years
- Assess the safety and tolerability of *Wilate*
- Determine *Wilate* consumption data

Additional Objectives:

Additional objectives of this study are to:

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

Study Design: Prospective, non-controlled, international, multi-centre phase 3 study

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Number of Patients: Around 40 patients, including at least 5 patients with VWD type 3, at least 6 patients aged 6–11 years, and at least 6 patients aged 12–16 years

Paediatric patients will undergo a 4-day PK assessment starting at the Baseline PK Visit, with the aim to obtain evaluable PK data from at least 6 patients aged 6–11 years (of which at least 4 evaluable) and at least 6 patients aged 12–16 years (of which at least 4 evaluable). Drop-outs will not be replaced.

PATIENT SELECTION CRITERIA:

Inclusion Criteria:

1. Patients aged ≥6 years at the time of screening
2. VWD type 1 (baseline von Willebrand factor activity [VWF:RCo], <30 IU/dL), 2A, 2B, 2M, or 3 according to medical history, requiring substitution therapy with a VWF-containing product to control bleeding
3. Currently receiving on-demand treatment with a VWF-containing product **AND** having experienced at least 6 BEs (excluding menstrual bleeds) over a period of 6 months, with at least 2 of these BEs treated with a VWF-containing product **AND** having records available to reliably evaluate the type, frequency, and treatment of BEs in this 6-month period

   OR

   Having switched to prophylactic treatment with a VWF-containing product within the past 2 years **AND** having records available to reliably evaluate the type, frequency, and treatment of BEs over a period of 6 months of on-demand treatment
4. Female patients of child-bearing potential must have a negative urine pregnancy test at screening and agree to use adequate birth control measures; in case hormonal contraception is used, the medication class should remain unchanged for the duration of the study
5. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted

Exclusion Criteria:

1. Having received on-demand or prophylactic treatment with a VWF-containing product, but having *no* records available to reliably evaluate the type, frequency, and treatment of BEs over a period of at least 6 months of on-demand treatment
2. History, or current suspicion, of VWF or FVIII inhibitors
3. Medical history of a thromboembolic event within 1 year before enrolment

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4. Severe liver or kidney diseases (alanine aminotransferase [ALAT] and aspartate transaminase [ASAT] levels >5 times of upper limit of normal, creatinine >120 µmol/L)
5. Platelet count <100,000/µL at screening (except for VWD type 2B)
6. Body weight <20 kg at screening
7. Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar drugs
8. Pregnant or breast-feeding at the time of enrolment
9. Cervical or uterine conditions causing abnormal uterine bleeding (including infection, dysplasia)
10. Treatment with any investigational medicinal product (IMP) in another interventional clinical study currently or within 4 weeks before enrolment
11. Other coagulation disorders or bleeding disorders due to anatomical reasons
12. Known hypersensitivity to any of the components of the study drug

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

The FVIII/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 VWF and human FVIII per vial.

***Wilate* Dosage for Baseline PK Assessment in Paediatric Patients (6–16 years):**

Single dose of 60 ± 10 IU/kg

***Wilate* Dosage for Prophylactic Treatment:**

For prophylactic treatment, *Wilate* should be administered 2–3 times per week at a dose of 20–40 IU/kg BW for 12 months.

The prophylactic dose for each patient will be determined by the Principal Investigator based on each patient's clinical condition and at the following time points:

- **At the Baseline IVR Visit in adult patients (≥17 years)**
  In adult patients, the first prophylactic dose will be administered at the time of the baseline IVR assessment.
- **At the Baseline PK Visit in paediatric patients (6–16 years)**
  In paediatric patients, the first prophylactic dose will be administered after completion of the PK phase.

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In case of unacceptably frequent spontaneous breakthrough BEs (i.e., more than 2 spontaneous BEs or 1 major spontaneous BE within a 30-day period), the dose of *Wilate* should be increased by approximately 5 IU/kg (depending on the entire content of the additional vial(s) that need(s) to be reconstituted). If, after a dose increase, patients still experience more than 2 spontaneous bleeding episodes, the dosing interval should be shortened from 2 times per week to 3 times per week.

Wilate *Dosage for the Treatment of Breakthrough BEs:*

The following should be used to guide dosing in the treatment of BEs:

Dose Type	Minor haemorrhage*	Major haemorrhage
Loading dose	20–40 IU/kg	40–60 IU/kg
Maintenance dose	20–30 IU/kg every 12–24 hours	20–40 IU/kg every 12–24 hours
Therapeutic goal	Maintain VWF:Ac (VWF:RCo) and FVIII:C trough levels >30%	Maintain VWF:Ac (VWF:RCo) and FVIII:C trough levels >50%

*Menstrual bleeds of regular intensity (i.e., minor menstrual haemorrhage) will be considered normal and are not expected to require therapy unless deemed necessary by the investigator and/or the patient.

Surgical Prophylaxis:

The following should be used to guide dosing in surgical prophylaxis:

Dose type	Minor surgeries (incl. tooth extractions)	Major surgeries
Loading dose	30–60 IU/kg	40–60 IU/kg
Maintenance dose	15–30 IU/kg, or half the loading dose, every 12–24 hours for up to 3 days	20–40 IU/kg, or half the loading dose, every 12–24 hours for up to 6 days or longer
Therapeutic goal	Achieve VWF:Ac (VWF:RCo) peak levels of 50% after loading dose and trough levels of >30% during maintenance doses	Achieve VWF:Ac (VWF:RCo) peak level of 100% after loading dose and trough levels of >50% during maintenance doses

DURATION OF TREATMENT:

The planned treatment duration per patient is 12 months

The study will be considered clinically completed when all enrolled patients have completed the planned observation period, including the Study Completion Visit.

The estimated start of the study (enrolment of first patient) is Q2 2020, and the estimated end

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of the study is Q1 2022.
Reference Therapy, Dose, Mode of Administration: None

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STUDY ENDPOINTS:

Primary Endpoint:

The primary endpoint of this study is to demonstrate that prophylactic treatment with WILATE lowers the patients' total annualized bleeding rate (TABR) observed during on-demand treatment by more than 50%.Secondary Endpoints:

- Spontaneous annualised bleeding rate (SABR), calculated in analogy with TABR
- Incremental IVR of *Wilate* for VWF:Ac (VWF:RCo and VWF:GPIbm) and FVIII:C (OS and CHR) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- For paediatric patients, baseline PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR) based on blood samples taken pre-dose and 1, 3, 9, 24, 48, and 72 hours after dosing
- Safety and tolerability of *Wilate* by monitoring adverse events (AEs) throughout the study
- *Wilate* consumption data (VWF/FVIII IU/kg per month per patient) for prophylaxis

Exploratory Endpoints:

- Efficacy of *Wilate* in the treatment of breakthrough BEs based on the proportion of BEs successfully treated with *Wilate*
- Efficacy of *Wilate* in surgical prophylaxis based on the proportion of surgeries successfully treated with *Wilate*
- QoL based on the scores of PROMIS-29 for all patients, SF-36v2 for patients aged ≥16 years, and SF-10 for patients aged 6–15 years
- Hemophilia Joint Health Score (HJHS)
- Pictorial Blood Loss Assessment Chart (PBAC) score for menstrual bleeds
- Annual rate of heavy (i.e., major) menstrual bleeds

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EFFICACY PARAMETERS:

For the evaluation of efficacy, the following parameters will be documented:

IMP Administration Data

The following parameters will be documented:

- Dates and times of IMP injections
- Doses of IMP in IU and IU/kg and IMP batch numbers
- Purpose of IMP injection (IVR, prophylaxis, prophylaxis of recurrent bleeding, treatment of BE, surgery, prophylaxis after surgery, or menstrual bleeds)

Bleeding Episode (BE) Data

Study participants will be instructed by the investigator on recording all BEs and in how to record them. For any BE occurring during the study, the following data will be recorded:

- BE type (spontaneous, traumatic, postoperative, other)
- BE site
- BE severity (minor or major, based on predefined criteria)
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended
- IMP administration data
- Assessment of the efficacy of treatment at the end of the BE

All of these parameters will be documented by the patient (together with the investigator in case of on-site treatments or together with the nurse in case a home-care service is used) in the patient diary. Patients who experience a major BE should be treated at the study site, if possible.

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

Assessment of Adherence with the Infusion Regimen

Throughout the study, adherence with the infusion regimen will be assessed. Any change of the prophylactic dose as determined by the Principal Investigator during the Baseline Visit will be documented in the patient records and eCRF, including start and end dates of each dose, reasons for dose change, or reasons for not implementing a required dose change.

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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 following predefined criteria:

Efficacy Assessment of the Treatment of Breakthrough BEs	
Excellent	Bleeding was completely stopped within 3 days in case of minor bleeds, within 7 days in case of major bleeds, and within 10 days in case of gastrointestinal bleeds
Good	Bleeding was completely stopped, but time and/or dose slightly exceeded expectations
Moderate	Bleeding could be stopped only by significantly exceeding time and/or dose expectations
None	Bleeding could be stopped only by using other VWF-containing products

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.'

Surgical Prophylaxis Data

The following surgery-related parameters will be documented:

- Type of surgery (planned or emergency)
- Location of surgery
- Severity of surgery (minor, major)
- Expected and actual duration of surgery
- Expected average/maximum and actual blood loss
- Pre-, intra-, and postoperative IMP administration data
- Pre-, intra-, and postoperative FVIII and VWF:Ac plasma levels
- Routine safety laboratory
- Presence of wound haematomas
- Vital signs
- Details on concomitantly administered medications
- Blood transfusion requirements
- Brief narrative describing the outcome of the intervention
- Efficacy assessment at the end of surgery by surgeon
- Efficacy assessment at the end of the postoperative period by haematologist
- Overall efficacy assessment at the end of the postoperative period by the investigator
- Monitoring of AEs

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

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

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

Efficacy in Surgical Prophylaxis

Efficacy will be assessed at the end of surgery by the surgeon and at end of the postoperative period by the haematologist. In both cases, predefined assessment criteria will be used. In addition, an overall assessment of efficacy will be made at the end of the postoperative period by the investigator.

At the End of Surgery (by Surgeon)

At the end of surgery, the haemostatic efficacy of *Wilate* will be assessed by the surgeon using the following predefined criteria:

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 haemostasis 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 maximum expected blood loss for the type of procedure in a patient with normal haemostasis.
Moderate	Intraoperative blood loss was higher than the maximum expected blood loss for the type of procedure performed in a patient with normal haemostasis, but haemostasis was controlled.
None	Haemostasis was uncontrolled, necessitating a change in the clotting factor replacement regimen.

At the End of the Postoperative Period (by Haematologist)

At the end of the postoperative period, the haemostatic efficacy of *Wilate* will be assessed by the haematologist using the following predefined criteria:

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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 VWF-containing product.

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 determined by the investigator based on the following algorithm:

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

QoL Questionnaires

For the assessment of quality of life, PROMIS-29 will be used for all patients. In addition, version 2 of the 36-Item Short Form Health Survey (SF-36v2) will be used for patients aged ≥16 years, and SF-10 will be used for patients aged 6–15 years. At each visit requiring QoL assessments, the questionnaires should be completed before starting any other visit assessment.

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PK PARAMETERS:

PK parameters will be assessed for VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR) assays based on actual IMP potencies.

The following PK parameters will be assessed:

- 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 (V_d)
- Clearance (CL)
- Incremental in vivo recovery (IVR)

SAFETY PARAMETERS:

The following drug safety information will be collected:

- Adverse events (AEs) and serious adverse events (SAEs)
- Pregnancy, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs

Laboratory Tests

The following laboratory parameters will be determined at the time points specified in the flow charts of assessments.

Central Laboratory

- VWF:Ac (VWF:RCo and VWF:GPIbm)
- FVIII:C (OS and CHR)
- Retention samples for possible virus marker and VWF/FVIII inhibitor testing
- VWF and FVIII inhibitor testing, in case inhibitor development is suspected
- Anti-parvovirus B19 antibody testing
- VWF multimers for patients with VWD type 2A and genotype for patients with VWD type 2B

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Local Laboratory

- **Haematology:** red blood cell count, white blood cell count, haemoglobin, haematocrit, and platelet count
- **Chemistry:** total bilirubin, alanine amino transferase, aspartate transaminase, blood urea nitrogen or Urea, serum creatinine
- **Urine pregnancy test** (in female patients of child-bearing potential)

AB0 blood-type testing as well as VWF:Ac and FVIII:C measurements in case of BEs or surgery will also be done by the local laboratories.

STUDY PROCEDURES:

Because all paediatric patients (6–16 years old) enrolled in the study will undergo PK assessment, whereas adult patients (≥17 years old) will not, the first two study visits differ between these two age cohorts.

Patients will participate in the following visits:

- Screening Visit
  - For adult patients
  - For paediatric patients
- Baseline Visit
  - Baseline IVR Visit for adult patients
  - Baseline PK Visit for paediatric patients
- 1-Month IVR Visit
- 2-Month IVR Visit
- 3-Month IVR Visit
- 6-Month IVR Visit
- 9-Month IVR Visit
- Study Completion (12-Month) Visit

Between the 3- and 6-Month Visits, the 6- and 9-Month Visits, and the 9- and 12-Month Visits, **monthly telephone contacts** will be performed.

Where needed, **external home-care companies** with experience in conducting clinical trials will be contracted, with trained nurses supporting patients by providing training, re-training, and oversight through home-care visit support throughout the study.

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SCREENING AND BASELINE VISITS FOR ADULT PATIENTS (≥17 YEARS OLD)

Screening Visit (Adult Patients)

The following assessments will be performed:

- **Obtaining voluntarily given, written (signed and dated) informed consent**
- **Inclusion and exclusion criteria**
- **Demographic and baseline characteristics**
- **Weight**
- **Height**
- **Medical history, including:**
  - VWD type
  - Prior medications
  - Birth control measures (for female patients of child-bearing potential)
  - History of heavy menstrual bleeding (for female patients)
- **Family history of VWD**
- **Vital signs**
- **Physical examination**
- **Blood samples for the following assessments:**
  - AB0 blood group, unless derivable from the baseline characteristics [local lab]
  - Routine safety laboratory [local lab]
- **Urine pregnancy test** (in female patients of child-bearing potential)
- **Concomitant medications**

During the Screening Visit, patients will also **receive a patient diary**. The investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting any BEs, treatment details, AEs, and concomitant medications. Menstrual bleeds will be documented in the **Pictorial Blood Loss Assessment Chart (PBAC)**. Therefore, female patients of child-bearing potential will also be instructed in completing the **PBAC**.

After the Screening Visit, eligible patients will participate in the Baseline IVR Visit, during which the IVR injection of *Wilate* will be administered.

For adult patients, the Screening Visit and the Baseline IVR Visit **may coincide**; however, note that administration of the first prophylactic dose of *Wilate* during the Baseline IVR Visit requires a **washout period of at least 72 hours** from the patient's previous administration of a VWF-containing product. If possible, the interval between the Screening Visit and the Baseline IVR Visit **should not exceed 2 weeks**.

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Between the Screening Visit and the Baseline IVR Visit, on-demand treatment of BEs or prophylactic treatment should be continued with the **patient's previously used VWF-containing product**.

Baseline IVR Visit (Adult Patients)

During the Baseline IVR Visit, the prophylactic dose and dosing interval of *Wilate* for each adult patient will be determined by the Principal Investigator based on the patient's clinical condition, and the first prophylactic dose will be administered after a washout period of **at least 72 hours** from the patient's latest administration of a VWF-containing product. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS
- **Confirm inclusion and exclusion criteria** (to be documented in patient records)
- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10 as applicable)

BEFORE INJECTION
- **Weight**
- **Blood samples**
  - VWF multimer pattern for VWD type 2A and genotype for VWD type 2B [central lab]
  - Anti-parvovirus B19 antibodies [central lab]
  - Retention samples for possible virus marker and VWF/FVIII inhibitor testing [central lab]

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION
- **Vital signs**
- **Blood samples**
  - VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR [central lab]
  - FVIII:C (OS and CHR) for IVR [central lab]

ANY TIME
- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Hemophilia Joint Health Score (HJHS)**
- **Target joint(s)**
- Re-confirm commitment to using **birth control measures** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

In adult patients, the first prophylactic injection of *Wilate* is administered during the Baseline IVR Visit.

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In case of **home treatment**, patients will be trained in how to correctly administer the IMP and provided with IMP. Patients will be re-supplied with IMP whenever necessary during the study.

SCREENING AND BASELINE VISITS FOR PAEDIATRIC PATIENTS

Screening Visit (Paediatric Patients)

The following assessments will be performed:

- **Obtaining voluntarily given, written (signed and dated) informed consent**
- **Inclusion and exclusion criteria**
- **Demographic and baseline characteristics**
- **Weight**
- **Height**
- **Medical history, including:**
  - VWD type
  - Prior medications
  - Birth control measures (for female patients of child-bearing potential)
  - History of heavy menstrual bleeding (for female patients)
- **Family history of VWD**
- **Vital signs**
- **Physical examination**
- **Blood samples for the following assessments:**
  - AB0 blood group, unless derivable from the baseline characteristics [local lab]
  - Routine safety laboratory [local lab]
  - VWF multimer pattern for VWD type 2A and genotype for VWD type 2B [central lab]
  - VWF:Ac (VWF:RCo and VWF:GPIbm) [central lab]
  - FVIII:C (OS and CHR) [central lab]
  - Anti-parvovirus B19 antibodies [central lab]
  - Retention samples for possible virus marker and VWF/FVIII inhibitor testing [central lab]
- **Urine pregnancy test** (in female patients of child-bearing potential)
- **Concomitant medications**

During the Screening Visit, patients will also **receive a patient diary**. The investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting any BEs, treatment details, AEs, and concomitant medications. Menstrual bleeds will be documented in the **Pictorial Blood Loss Assessment Chart (PBAC)**. Therefore, female patients of child-bearing potential will also be instructed in completing the **PBAC**.

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After the Screening Visit, eligible children will participate in the Baseline PK Visit.. The Screening Visit and the Baseline PK Visit **must not occur on the same day**. If possible, the interval between the Screening Visit and the Baseline PK Visit **should not exceed 2 weeks**.

Between the Screening Visit and the Baseline PK Visit, on-demand treatment of BEs or prophylactic treatment should be continued with the **patient's previously used VWF-containing product**..

Baseline PK Visit (Paediatric Patients)

During the Baseline PK Visit, paediatric patients will receive *Wilate* at a dose of 60 ± 10 IU/kg after a washout period of **at least 72 hours** from the patient's previous administration of a VWF-containing product. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS
- **Confirm inclusion and exclusion criteria** (to be documented in patient records)
- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10 as applicable)

BEFORE INJECTION
- **Weight**

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION
- **Vital signs**

WITHIN 60 MIN BEFORE AND 60±5 MIN, 3 H±30 MIN, 9±1 H, 24±2 H, 48±2 H, and 72±2 H AFTER INJECTION
- **Blood samples**
  - VWF:Ac (VWF:RCo) for PK [central lab]
  - FVIII:C (OS and CHR) for PK [central lab]

ANY TIME
- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Hemophilia Joint Health Score (HJHS)**
- **Target joint(s)**
- Re-confirm commitment to using **birth control measures** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

During this visit, the prophylactic dose and dosing interval of *Wilate* will be determined by the Principal Investigator based on the patient's clinical condition.

In paediatric patients, the first prophylactic injection of *Wilate* is administered after

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completion of the Baseline PK Visit.

In case of **home treatment**, patients will be trained in how to correctly administer the IMP and provided with IMP. Patients will be re-supplied with IMP whenever necessary during the study.

SUBSEQUENT VISITS FOR ALL PATIENTS

1-Month IVR Visit

The 1-Month IVR Visit will take place 1 month (±1 week) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE INJECTION
- **Weight**
- **Blood samples**
  - For VWF and FVIII inhibitor testing, *only if* inhibitor development is suspected

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION
- **Vital signs**
- **Blood samples**
  - VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR [central lab]
  - FVIII:C (OS and CHR) for IVR [central lab]

ANY TIME
- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Review of compliance** and adherence to the infusion regimen
- Re-confirm commitment to using **birth control measures** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

At the end of this and each of the following visits, IMP for home treatment will be given to patients as applicable.

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2-Month IVR Visit

The 2-Month IVR Visit will take place 2 months (±1 week) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Same assessments are for the 1-Month IVR Visit**

3-Month IVR Visit

The 3-Month IVR Visit will take place 3 months (±1 week) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Same assessments are for the 1-Month IVR Visit**
- **Urine pregnancy test** (in female patients of child-bearing potential)

6-Month IVR Visit

The 6-Month IVR Visit will take place 6 months (±2 weeks) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS

- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10 as applicable)
- **Same assessments as for 1-Month IVR Visit**
- **Urine pregnancy test** (in female patients of child-bearing potential)

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9-Month IVR Visit

The 9-Month IVR Visit will take place 9 months (±2 weeks) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Same assessments are for the 1-Month IVR Visit**

Study Completion (12-Month) Visit

The Study Completion Visit will take place 12 months (+2 weeks) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS

- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10 as applicable)

BEFORE INJECTION

- **Weight**
- **Blood samples**
  - Routine safety laboratory [local lab]
  - For VWF and FVIII inhibitor testing, *only if* inhibitor development is suspected [central lab]
  - Anti-parvovirus B19 antibodies [central lab], *only if* the sample at the Baseline Visit was negative, or if it was equivocal on both original and re-testing

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION

- **Vital signs**
- **Blood samples**
  - VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR [central lab]
  - FVIII:C (OS and CHR) for IVR [central lab]

ANY TIME

- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Review of compliance** and adherence to the infusion regimen
- **Hemophilia Joint Health Score (HJHS)**
- **Target joint(s)**

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- **Physical examination**
- **Urine pregnancy test** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

All used and unused IMP vials will be returned by the patients or their home-care providers.

Monthly Telephone Contacts

Monthly telephone contacts will be performed 4, 5, 7, 8, 10, and 11 months (±1 week) after the first prophylactic injection of *Wilate*. Should a patient visit the study centre at the time any of these telephone contacts are scheduled, the required assessments may also be performed during this visit.

The following assessments will be performed:

- Review of **compliance** with correctly **completing the patient diary,** including completing the PBAC (for female patients of child-bearing potential)
- Review of **adherence to the infusion regimen**
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

If any issues with completing the diaries or adhering to the infusion regimen are identified, the investigator or home-care provider will re-train the patient accordingly.

Unscheduled Visits and Additional Measures

If inhibitor development is suspected (e.g., based on an unexplained need to increase the dose, a lack of efficacy of IMP injections, or prolonged bleeding), VWF and FVIII inhibitor tests will be performed at the central laboratory 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. Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalisations for BEs or surgical interventions.

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Surgical Visits

Patients may undergo surgical interventions in the course of the study. Whether or not these patients will be hospitalised will depend on the type and severity of the surgery and be at the discretion of the investigator.

STATISTICAL ANALYSIS PLAN:

Determination of Sample Size

Assuming a mean TABR ratio ($TABR_{pr}$ / $TABR_{od}$) of 0.25 with a correlation of 0.5 between the two treatment regimens, a coefficient of variation of 10 in on-demand treatment, and a coefficient of variation of 10 in prophylactic treatment, 25 patients will be needed to reject the null hypothesis with a power of 80% using a paired t-test for log-transformed data

The primary approach to statistical analysis will be descriptive, complemented by exploratory confidence intervals (CIs) for means or proportions.

Efficacy of Prophylactic Treatment with *Wilate*

The primary endpoint of this study is to demonstrate that the TABR during prophylactic treatment with *Wilate* lowers the patients' TABR observed during on-demand treatment by more than 50%. To test whether the mean TABR during prophylactic treatment ($TABR_{pr}$) is less than half the mean TABR during on-demand treatment ($TABR_{od}$), the following pair of hypotheses will be tested using a paired t-test assuming log-normally distributed data:

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

at a one-sided alpha level of 2.5%. Corresponding two-sided 95% CIs for TABR will also be presented.

To assess the qualitative robustness of the inferential result the hypothesis will additionally be tested with the Wilcoxon (matched-pair signed rank) test on the log-transformed bleeding rate as a distribution-free alternative. Also, a 95% Hodges-Lehmann CI for the median difference will be reported.

In addition, intra-individual comparisons with each patient's documented historical TABR will be performed.

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Efficacy of *Wilate* in the Treatment of BEs

To assess the haemostatic efficacy of *Wilate* in the treatment of breakthrough BEs, a frequency distribution of all successfully treated BEs will be presented overall and by severity, along with an exploratory 95% CI. Statistical analyses of other secondary endpoints will be descriptive, including exploratory 95% CIs.

IVR Assessments

The results of IVR assessments over time will be presented per time point and as differences to baseline, along with 95% CIs for the mean differences.

PK Assessments in Paediatric Patients

The PK parameters will be summarized using descriptive statistics and the presentation of concentration vs time plots.

Safety Analysis

The analysis of safety will be based on the occurrence of AEs, results of safety laboratory testing, and the occurrence of parvovirus B19 seroconversions. Analysis of AEs will focus on treatment-emergent adverse events (TEAEs).

Time profiles of VWF and FVIII inhibitor testing results will be analysed 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 baseline and the end of study will be estimated, along with 95% Pearson-Clopper CIs.

FLOW CHART FOR IVR ASSESSMENT AND PROPHYLACTIC TREATMENT (ADULT PATIENTS, ≥17 YEARS)

Assessment	For details, see Section	Screening Visit	Baseline IVR Visit (may coincide with, and should if possible take place within 2 weeks after, Screening Visit)	1-Month IVR Visit (±1 week)	2-Month IVR Visit (±1 week)	3-Month IVR Visit (±1 week)	4-Month Call	5-Month-Call	6-Month IVR Visit (±2 weeks)	7-Month Call	8-Month Call	9-Month IVR Visit (±2 weeks)	10-Month Call	11-Month Call	Study Completion (12-Month) IVR Visit (+2 weeks)
Informed consent	10.3	x [4]					COMPLIANCE CALL*			COMPLIANCE CALL*			COMPLIANCE CALL*		
Inclusion and exclusion criteria	4.1	x	x												
Demographics	7.1.1	x													
Weight		x	x [1]	x [1]	x [1]	x [1]			x [1]			x [1]			x [1]
Height		x													
Medical history and prior medications	7.1.2	x													
Family history of VWD		x													
Vital signs	7.4.6	x	x [2]	x [2]	x [2]	x [2]			x [2]			x [2]			x [2]
Physical examination	7.4.6	x													x
Laboratory assessments															
LOCAL LAB															
Determination of AB0 blood group, unless derivable from medical history	7.1.1	x													
Routine safety laboratory	7.4.5	x													x [1]
CENTRAL LAB															
VWF multimer pattern for VWD type 2A and genotype for VWD type 2B	7.4.5		x												
VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR	7.4.5		x [2]	x [2]	x [2]	x [2]			x [2]			x [2]			x [2]
FVIII:C (OS and CHR) for IVR	7.4.5		x [2]	x [2]	x [2]	x [2]			x [2]			x [2]			x [2]
Anti-parvovirus B19 antibodies	7.4.5		x [1]												x [3]
VWF and FVIII inhibitors (•)	7.4.5			(•) [1]	(•) [1]	(•) [1]			(•) [1]			(•) [1]			(•) [1]
Retention samples for possible virus marker and VWF/FVIII inhibitor testing	7.4.5		x [1]												
Quality of life using PROMIS-29 and SF-36v2 or SF-10, as applicable	7.2.6		x [4]						x [4]						x [4]
Hemophilia Joint Health Score (HJHS)	7.2.7		x [1]												x [1]
Documentation of target joint(s) [5]	7.2.7		x [1]												x [1]
Urine pregnancy test [6]		x				x			x						x
Re-confirm commitment to using birth control measures [6]			x	x	x	x			x			x			
Patient diary review, including PBAC [6] completion	7.2.8		x	x	x	x			x			x			x
Assessment of compliance and adherence to infusion regimen	5.7.2			x	x	x			x			x			x
Adverse event monitoring	7.3		x	x	x	x			x			x			x
Concomitant medications	7.1.2	x	x	x	x	x			x			x			x

FLOW CHART FOR IVR ASSESSMENT AND PROPHYLACTIC TREATMENT (ADULT PATIENTS)—Continued

IVR = in vivo recovery, VWD = von Willebrand disease, VWF:Ac = VWF activity, GP1b = glycoprotein 1b, FVIII = factor VIII, FVIII:C = factor VIII procoagulant activity, OS = one-stage assay, CHR = chromogenic assay, PBAC = Pictorial Blood Loss Assessment Chart, PROMIS = Patient-Reported Outcomes Measurement Information System, SF-36v2 = 36-Item Short Form Health Survey (version 2), SF-10 = 10-Item Short Form Health Survey

LEGEND TO THE FLOW CHART FOR IVR ASSESSMENT AND PROPHYLACTIC TREATMENT (ADULT PATIENTS)

* **COMPLIANCE CALL:** monthly telephone calls to take place ±1 week to review compliance with completing diary, obtaining PBAC (for female patients of child-bearing potential), adherence with infusion regimen, AEs, and concomitant medications (see **Section 6.1.11**)

(•) If inhibitor development is suspected

[1] Before injection

[2] Within 60 min before and 60±5 min after injection

[3] Before injection, if sample at the Baseline IVR Visit was negative, or if it was equivocal on both original and re-testing

[4] Before starting any other visit assessment

[5] Target joint(s) are defined as having 3 or more spontaneous bleeding episodes into a single joint within 6 consecutive months preceding the Baseline Visit or the Study Completion Visit

[6] In female patients of child-bearing potential

FLOW CHART FOR PK ASSESSMENT AND PROPHYLACTIC TREATMENT (PAEDIATRIC PATIENTS, 6–16 YEARS)

Assessment	For details, see Section	Screening Visit	Baseline PK Visit (must not coincide with, and should if possible take place within 2 weeks after, Screening Visit)	1-Month IVR Visit (±1 week)	2-Month IVR Visit (±1 week)	3-Month IVR Visit (±1 week)	4-Month Call*	5-Month-Call*	6-Month IVR Visit (±2 weeks)	7-Month Call*	8-Month Call*	9-Month IVR Visit (±2 weeks)	10-Month Call*	11-Month Call*	Study Completion (12-Month) IVR Visit (+2 weeks)
Informed consent	10.3	x [5]					COMPLIANCE CALL*			COMPLIANCE CALL*			COMPLIANCE CALL*		
Inclusion and exclusion criteria	4.1	x	x												
Demographics	7.1.1	x													
Weight		x	x [1]	x [1]	x [1]	x [1]			x [1]			x [1]			x [1]
Height		x													
Medical history and prior medications	7.1.2	x													
Family history of VWD		x													
Vital signs	7.4.6	x	x [2]	x [2]	x [2]	x [2]			x [2]			x [2]			x [2]
Physical examination	7.4.6	x													x
Laboratory assessments															
LOCAL LAB															
Determination of AB0 blood group, unless derivable from medical history	7.1.1	x													
Routine safety laboratory	7.4.5	x													x [1]
CENTRAL LAB															
VWF multimer pattern for VWD type 2A and genotype for VWD type 2B	7.4.5	x													
VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR	7.4.5	x		x [2]	x [2]	x [2]			x [2]			x [2]			x [2]
FVIII:C (OS and CHR) for IVR	7.4.5	x		x [2]	x [2]	x [2]			x [2]			x [2]			x [2]
PK injection (60 ± 10 IU/kg)	5.4.1		x												
PK blood sampling for VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR)	7.3		x [3]												
Anti-parvovirus B19 antibodies	7.4.5	x													x [4]
VWF and FVIII inhibitors (•)	7.4.5			(•) [1]	(•) [1]	(•) [1]			(•) [1]			(•) [1]			(•) [1]
Retention samples for possible virus marker and VWF/FVIII inhibitor testing	7.4.5	x													
Quality of life using PROMIS-29 and SF-36v2 or SF-10, as applicable	7.2.6		x [5]						x [5]						x [5]
Hemophilia Joint Health Score (HJHS)	7.2.7		x [1]												x [1]
Documentation of target joint(s) [6]	7.2.7		x [1]												x [1]
Urine pregnancy test [7]		x				x			x						x
Re-confirm commitment to using birth control measures [7]			x	x	x	x			x			x			
Patient diary review, including PBAC [7] completion	7.2.8		x	x	x	x			x			x			x
Assessment of compliance and adherence to infusion regimen	5.7.2			x	x	x			x			x			x
Adverse event monitoring	7.3		x	x	x	x			x			x			x
Concomitant medications	7.1.2	x	x	x	x	x			x			x			x

FLOW CHART FOR PK ASSESSMENT AND PROPHYLACTIC TREATMENT (PAEDIATRIC PATIENTS)—Continued

IVR = in vivo recovery, VWD = von Willebrand disease, VWF:Ac = VWF activity, GP1b = glycoprotein 1b, FVIII = factor VIII, FVIII:C = factor VIII procoagulant activity, OS = one-stage assay, CHR = chromogenic assay, PBAC = Pictorial Blood Loss Assessment Chart, PROMIS = Patient-Reported Outcomes Measurement Information System, SF-36v2 = 36-Item Short Form Health Survey (version 2), SF-10 = 10-Item Short Form Health Survey

LEGEND TO THE FLOW CHART FOR PK ASSESSMENT AND PROPHYLACTIC TREATMENT (PAEDIATRIC PATIENTS)

* **COMPLIANCE CALL:** monthly telephone calls to take place ±1 week to review compliance with completing diary, obtaining PBAC (for female patients of child-bearing potential), adherence with infusion regimen, AEs, and concomitant medications (see **Section 6.1.11**)

(•) If inhibitor development is suspected

[1] Before injection

[2] Within 60 min before and 60±5 min after injection

[3] Blood samples for PK assessment to be taken within 60 min before injection and 60±5 min, 3 h (±30 min), 9±1 h, 24±2 h, 48±2 h, and 72±2 h after injection (central laboratory)

[4] Before injection, if sample at the Baseline PK Visit was negative, or if it was equivocal on both original and re-testing

[5] Before starting any other visit assessment

[6] Target joint(s) are defined as having 3 or more spontaneous bleeding episodes into a single joint within 6 consecutive months preceding the Baseline Visit or the Study Completion Visit.

[7] In female patients of child-bearing potential

FLOW CHART OF ASSESSMENTS FOR SURGICAL PROPHYLAXIS

Assessment	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
				Intra-operatively	End [1]			
Body weight		x						
Type of surgery	7.2.4	x						
Location of surgery	7.2.4	x						
Severity of surgery	7.2.4	x						
Expected duration of surgery	7.2.4	x						
Actual duration of surgery	7.2.4				x			
Expected average/maximum blood loss during surgery	7.2.4	x						
Actual blood loss and transfusions during surgery	7.2.4				x			
Administration of *Wilate*	7.2.1		x	(x)	(x)	(x)	(x)	(x)
FVIII:C plasma levels	7.2.4		# L	(#) L	(#) L	(#) [2] L	(#) L	(#) L
VWF:Ac plasma levels	7.4.5		# L	(#) L	(#) L	(#) [2] L	(#) L	(#) L
Routine safety laboratory	7.4.5	x				(x)	(x)	(x)
Presence of wound haematomas	7.2.4					x	x	x
Vital signs	7.2.4	x		x		x		
Efficacy assessments	7.2.5				S			H
Overall efficacy assessment	7.2.5							I
Brief narrative of outcome of the intervention	7.2.4							x
Concomitant medications	7.2.4	Throughout observation period						
Adverse event monitoring	7.3	Throughout observation period						

POP = postoperative, FVIII:C = factor VIII procoagulant activity, VWF:Ac = VWF activity, S = performed by surgeon, H = performed by haematologist, I = performed by investigator, L= can be performed in an optional manner by the local laboratory

( ) 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

PROTOCOL SIGNATURES

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

Signature of the Sponsor's Representative

[redacted]

Signature

02.03.2021

Date

[redacted]
Octapharma AG
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Signature of the Protocol Author

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Signature

01 Mar 2021

Date

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PROTOCOL SIGNATURES

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

[redacted]

March 3, 2021

Co-ordinating investigator Date

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[redacted]

Signature Date

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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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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Description
ABR	Annualised Bleeding Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Transaminase
BE	Bleeding Episode
BU	Bethesda Units
BW	Body Weight
CHR	Chromogenic (Assay)
CI	Confidence Interval
CRO	Contract Research Organisation
DDAVP	Desmopressin (1-deamino-8-D-arginine vasopressin)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVIII	Factor VIII
GP1b	Glycoprotein 1b
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
IU	International Units
IVR	In Vivo Recovery
MedDRA	Medical Dictionary for Regulatory Activities
OS	One-Stage (Assay)
PBAC	Pictorial Blood Loss Assessment Chart
PP	Per Protocol

Abbreviation	Description
PROMIS	The Patient-Reported Outcomes Measurement Information System®
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
QoL	Quality of Life
RCo	Ristocetin Co-factor
SABR	Spontaneous Annualised Bleeding Rate
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SF-36v2	36-Item Short Form Health Survey, version 2
SF-10	10-Item Short Form Health Survey
SURG	Surgery (Population)
TABR	Total Annualised Bleeding Rate
TEAE	Treatment-Emergent Adverse Event
USA	United States of America
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
VWF:Ac	Von Willebrand Factor Activity
VWF:GPIbm	Assay based on the spontaneous binding of VWF to a gain-of-function mutant GP1b fragment [1]
VWF:GP1bR	Assay based on the ristocetin-induced binding of VWF to a recombinant wild-type GP1b fragment [1]
VWF:RCo	VWF:RCo Ristocetin cofactor activity; assay that uses platelets and ristocetin

1 INTRODUCTION

1.1 Von Willebrand Disease

Inherited von Willebrand disease (VWD) is the most common inherited haemorrhagic disorder, with an estimated prevalence of 1 in every 100 individuals of either sex. There is wide geno- and phenotypic variability of the disease, and not all patients with VWD require treatment.

Three types of inherited VWD are known. Thus, whereas type 1 and type 3 disease are characterised by a quantitative deficiency of von Willebrand factor (VWF), VWD type 2 arises from a qualitative deficiency of VWF. There are various subtypes within the three inherited types of VWD. VWD may also be acquired.

Of the inherited forms, type 1 is the most common, accounting for 70–80% of cases, followed by type 2, which affects approximately 20% of patients. Type 3, the most severe form of VWD characterised by a complete absence of VWF, is rare and affects about 1–3% of all patients [2].

Treatment of VWD depends on the type and severity of the disease. Whereas mild to moderate forms of type 1 and type 2A disease often respond adequately to treatment with desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), DDAVP is contraindicated in type 2B and not effective in type 3 disease. Treatment with DDAVP may also be contraindicated for other clinical reasons or may be associated with significant side effects.

The appropriate treatment for the patients in whom DDAVP is ineffective or contraindicated are VWF/factor VIII (FVIII) concentrates, which have become the mainstay of VWD treatment. Cryoprecipitate, which is screened for viruses but not treated to inactivate them, is also rich in VWF, but is likely to be less safe than the viral-attenuated concentrates [3].

VWD affects all ethnic groups and both sexes. Women are more likely to experience symptoms of VWD and may pose a special treatment challenge because of the physiological events related to menstruation, pregnancy, and birth [4]. If untreated, pregnant women with VWD are at increased risk of postpartum bleeding. In women with VWD types 1 or 2, the levels of VWF and FVIII rise 2- to 3-fold during the second and third trimesters, but fall to baseline levels soon after delivery. By contrast, in VWD type 2B, the increase of the abnormal VWF can cause or worsen thrombocytopenia. In women with VWD type 3, VWF and FVIII do not increase during pregnancy, so that administration of VWF-containing products may be required during pregnancy and at birth [4].

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 cryo-precipitate and intended for the treatment of patients with VWD and/or haemophilia A. By introducing new biotechnological methods and optimised 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. Therefore, antigenicity and immunogenicity due to co-purified proteins are reduced to a minimum.

Overall, 15 prospective clinical studies with *Wilate* have been completed, 8 in patients with VWD and 7 in patients with haemophilia A. A summary of findings from nonclinical and clinical studies with *Wilate* is provided in the product's Investigator's Brochure (IB).

Wilate received its first market authorisation in Germany in February 2005. By November 2018, *Wilate* had been licensed in 68 countries worldwide.

1.3 Rationale for Conducting the Study

The purpose of this study is to obtain additional data on the safety and efficacy of *Wilate* in previously treated patients with VWD undergoing regular prophylaxis, thus supplementing the existing body of data to obtain approval of *Wilate* in the prophylactic treatment of patients with VWD in the USA.

1.4 Dose Rationale

The doses for prophylaxis (20–40 IU/kg *Wilate*/kg BW administered 2–3 times per week), the treatment of BEs, and perioperative prophylaxis (see **Section 5.4**) are as recommended in the product's European Summary of Product Characteristics.

1.5 Benefit-Risk Statement

The following adverse drug reactions (ADRs) 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, generalised 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. On rare occasions, fever has been observed.

- Patients with VWD, especially type 3 patients, may develop **neutralising antibodies (inhibitors) to VWF and/or FVIII**. If expected VWF:RCo and/or FVIII:C activity plasma levels are not attained or bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine whether a VWF inhibitor and/or factor VIII inhibitor is present. In patients with high titres of inhibitor, VWF therapy may not be effective, and other therapeutic options should be considered.
- 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.
- **Thrombotic events.** When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. Patients receiving FVIII-containing VWF products should be monitored for sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic events. The risk of occurrence of thrombotic events in patients using FVIII-containing VWF products is particularly increased in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted in accordance with current recommendations.

In view of its state-of-the-art manufacturing process and available clinical and post-marketing 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 efficacy of *Wilate* in the prophylactic treatment of previously treated patients (PTPs) with type 3, type 2 (except 2N), or severe type 1 VWD.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess the incremental IVR of *Wilate* for VWF:Ac and FVIII:C over time
- Determine the pharmacokinetics (PK) of *Wilate* for VWF:Ac and FVIII:C in paediatric patients aged 6–16 years
- Assess the safety and tolerability of *Wilate*
- Determine *Wilate* consumption data

2.3 Additional Objectives

Additional objectives of this study are to:

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

3 INVESTIGATIONAL PLAN

3.1 Study Endpoints

3.1.1 Primary Endpoint

The primary endpoint of this study is to demonstrate that prophylactic treatment with *Wilate* lowers the patients' total annualized bleeding rate (TABR) observed during on-demand treatment by more than 50%.The TABR will be calculated as the total number of spontaneous bleeds, traumatic bleeds, and other bleeds (except menstrual bleeds) occurring in the time period between first dose of the investigational medicinal product (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 surgery periods, will be excluded from the calculation of TABR.

Similar calculation rules will be applied for the computation of the TABR during the previously documented on-demand treatment regimen.

3.1.2 Secondary Endpoints

The secondary endpoints of this study are the:

- Spontaneous annualised bleeding rate (SABR), calculated in analogy with TABR
- Incremental IVR of *Wilate* for VWF:Ac (VWF:RCo and VWF:GPIbm) and FVIII:C (OS and CHR) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- For paediatric patients, baseline PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR) based on blood samples taken pre-dose and 1, 3, 9, 24, 48, and 72 hours after dosing
- Safety and tolerability of *Wilate* by monitoring adverse events (AEs) throughout the study
- *Wilate* consumption data (VWF/FVIII IU/kg per month per patient) for prophylaxis

3.1.3 Exploratory Endpoints

The exploratory endpoints of this study are:

- Efficacy of *Wilate* in the treatment of breakthrough BEs based on the proportion of BEs successfully treated with *Wilate*
- Efficacy of *Wilate* in surgical prophylaxis based on the proportion of surgeries successfully treated with *Wilate*
- QoL based on the score of PROMIS-29 for all patients, SF-36v2 for patients aged ≥16 years, and SF-10 for patients aged 6–15 years
- Hemophilia Joint Health Score (HJHS)
- Pictorial Blood Loss Assessment Chart (PBAC) score for menstrual bleeds
- Annual rate of heavy (i.e., major) menstrual bleeds

3.2 Overall Study Design and Plan

This is a prospective, non-controlled, international, multi-centre phase 3 study investigating the efficacy and safety of *Wilate* in previously treated patients with type 3, type 2 (except 2N), or severe type 1 VWD aged ≥6 years at the time of screening.

Overall, around 40 patients will be enrolled by approximately 14 study sites worldwide. Of the 40 patients, at least 5 patients should have type 3 VWD, at least 6 patients should be aged 6–11 years, and at least 6 patients should be aged 12–16 years.

Of the 40 patients, at least 25 patients should be evaluable for the primary endpoint.

Paediatric patients will undergo a 4-day PK assessment at the time of the Baseline PK Visit, with the aim to obtain evaluable PK data from at least 6 patients aged 6–11 years (of which at least 4 evaluable) and at least 6 patients aged 12–16 years (of which at least 4 evaluable).

The planned treatment duration per patient is 12 months.

The **primary objective** of this study is to determine the efficacy of *Wilate* in the prophylactic treatment of previously treated patients with type 3, type 2 (except 2N), or severe type 1 VWD. The efficacy of prophylactic treatment with *Wilate* will be assessed by comparing each patient's individual total annualized bleeding rate (TABR) under prophylactic treatment in this study with the TABR recorded for the same patient under at least 6 months of on-demand treatment.

The **secondary objectives** are to assess the incremental IVR of *Wilate* for VWF:Ac and FVIII:C over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment), the VWF:Ac and FVIII:C pharmacokinetics at baseline in paediatric patients aged 6–16 years, the product's safety and tolerability, and *Wilate* consumption data.

Additional objectives are to determine the efficacy of *Wilate* in the treatment of breakthrough bleeding episodes (BEs) and in surgical prophylaxis and to assess the patients' QoL during prophylaxis with *Wilate*, joint status, and menstrual bleeding intensity (in female patients of child-bearing potential).

Where needed, external home-care companies with experience in conducting clinical trials will be contracted, with trained nurses supporting patients by providing training, re-training, and oversight through home-care visit support throughout the study.

3.3 Discussion of Study Design

This prospective, non-controlled, international, multi-centre phase 3 study is designed to demonstrate that *Wilate* is efficacious in bleeding prophylaxis in patients with VWD.

Reduction of the annual bleeding rate (ABR) of patients with coagulation bleeding disorders such as haemophilia A has been used as an efficacy endpoint to reliably demonstrate the impact of prophylaxis on the bleeding rates of these patients.

In addition, it is expected that the quality of life of patients with VWD is considerably compromised. Therefore, it was considered valuable to investigate the QoL profile of enrolled patients, despite there not being any validated tools to determine QoL in patients with VWD.

4 STUDY POPULATION

4.1 Population Base

4.1.1 Number of Patients

Overall, around 40 PTPs aged ≥6 years at the time of screening will be enrolled into this study. Of the 40 patients, at least 5 patients should have type 3 VWD, at least 6 patients should be aged 6–11 years, and at least 6 patients should be aged 12–16 years.

4.1.2 Inclusion Criteria

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

1. Patients aged ≥6 years at the time of screening
2. VWD type 1 (baseline von Willebrand factor activity [VWF:RCo] <30 IU/dL), 2A, 2B, 2M, or 3 according to medical history requiring substitution therapy with a VWF-containing product to control bleeding
3. Currently receiving on-demand treatment with a VWF-containing product **AND** having experienced at least 6 BEs (excluding menstrual bleeds) over a period of 6 months, with at least 2 of these BEs treated with a VWF-containing product **AND** having records available to reliably evaluate the type, frequency, and treatment of BEs in this 6-month period

   OR

   Having switched to prophylactic treatment with a VWF-containing product within the past 2 years **AND** having records available to reliably evaluate the type, frequency, and treatment of BEs over a period of 6 months of on-demand treatment
4. Female patients of child-bearing potential must have a negative urine pregnancy test at screening and agree to use adequate birth control measures; in case hormonal contraception is used, the medication class should remain unchanged for the duration of the study
5. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted

4.1.3 Exclusion Criteria

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

1. Having received on-demand or prophylactic treatment with a VWF-containing product but having *no* records available to reliably evaluate the type, frequency, and treatment of BEs over a period of at least 6 months of on-demand treatment
2. History, or current suspicion, of VWF or FVIII inhibitors
3. Medical history of a thromboembolic event within 1 year before enrolment
4. Severe liver or kidney diseases (alanine aminotransferase [ALAT] and aspartate transaminase [ASAT] levels >5 times of upper limit of normal, creatinine >120 µmol/L)
5. Platelet count <100,000/µL at screening (except for VWD type 2B)
6. Body weight <20 kg at screening
7. Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar drugs
8. Pregnant or breast-feeding at the time of enrolment
9. Cervical or uterine conditions causing abnormal uterine bleeding (including infection, dysplasia)
10. Treatment with any IMP in another interventional clinical study currently or within 4 weeks before enrolment
11. Other coagulation disorders or bleeding disorders due to anatomical reasons
12. Known hypersensitivity to any of the components of the study drug

4.2 Prior and Concomitant Therapy

Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar drugs, and women having changed their hormonal contraception within 6 months before enrolment 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).

Forbidden Medication

No VWF/FVIII concentrates other than Wilate must be administered (except for emergency situations).

Patients permanently switching to another product within the study participation period will be assessed as treatment failures in the efficacy analyses. However, there are exceptions to this rule. Patients will hence not be considered treatment failures in the efficacy analyses, if:

- the use of another VWF/FVIII concentrate was due to an emergency case (example: accident requiring treatment with VWF without patient or treating facility having access to Investigational Medicinal Product [IMP])
- the IMP was not available for the patient in time (example: patient experiences a severe bleed but does not have enough product available).

The reason for a patient switching to another VWF product should be clearly documented in the CRF (and patient diary, if appropriate).

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

Drop-outs will not be replaced.

4.3.3 Assignment of Patients to Treatment

The investigator will enter a unique identifier for each patient (consisting of the study code, centre code, and patient number) in both the eCRF and the confidential patient identification list and inform the monitor of any new patient enrolled.

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

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 Characterisation of *Wilate*

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 VWF and human FVIII per vial. The ratio between VWF ristocetin co-factor activity (VWF:RCo) and FVIII:C is 1:1.

The product contains approximately 100 IU/ml human VWF when reconstituted with 5 ml/10 mL water for injections with 0.1% polysorbate 80. The specific activity of *Wilate* is ≥67 IU VWF:RCo/mg protein.

The injection or infusion rate should not exceed 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 at +2°C to +8°C (36°F to 46°F). 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. of +25°C or 77°F) 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 authorised 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 *Wilate* Dosage for PK Assessment in Paediatric Patients

For the PK assessment in paediatric patients (6–16 years), a single dose of 60 ± 10 IU/kg will be administered.

5.4.2 *Wilate* Dosage for Prophylactic Treatment

For prophylactic treatment, *Wilate* should be administered 2–3 times per week at a dose of 20–40 IU/kg BW for 12 months.

The prophylactic dose for each patient will be determined by the Principal Investigator based on each patient's clinical condition and at the following time points:

- At the Baseline IVR Visit (see **Section 6.1.2**) in adult patients (≥17 years)
  In adult patients, the first prophylactic dose will be administered at the time of the baseline IVR assessment.
- At the Baseline PK Visit (see **Section 6.1.4**) in paediatric patients (6–16 years)
  In paediatric patients, the first prophylactic dose will be administered after completion of the PK phase.

In case of unacceptably frequent spontaneous breakthrough BEs (i.e., more than 2 spontaneous BEs or 1 major spontaneous BE within a 30-day period), the dose of *Wilate* should be increased by approximately 5 IU/kg (depending on the entire content of the additional vials that need to be reconstituted). If, after a dose increase, patients still experience more than 2 spontaneous bleeding episodes, the dosing interval should be shortened from 2 times per week to 3 times per week.

5.4.3 *Wilate* Dose for the 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.

Generally, 1 IU/kg BW VWF:Ac (VWF:RCo) and FVIII:C raises the plasma level by 1.5–2% of normal activity for the respective protein. Usually, about 20–50 IU *Wilate*/kg BW are necessary to achieve adequate haemostasis. This will raise the VWF:Ac (VWF:RCo) and

FVIII:C in the patients by approx. 30–100%.

The following should be used to guide dosing in the treatment of BEs:

Dose type	Minor haemorrhage*	Major haemorrhage
Loading dose	20–40 IU/kg	40–60 IU/kg
Maintenance dose	20–30 IU/kg every 12–24 hours	20–40 IU/kg every 12–24 hours
Therapeutic goal	Maintain VWF:Ac (VWF:RCo) and FVIII:C trough levels >30%	Maintain VWF:Ac (VWF:RCo) and FVIII:C trough levels >50%

*Menstrual bleeds of regular intensity (i.e., minor menstrual haemorrhage) will be considered normal and are not expected to require therapy unless deemed necessary by the investigator and/or the patient.

5.4.4 Surgical Prophylaxis

For prevention of bleeding in case of surgery, levels of VWF:Ac (VWF:RCo) ≥60 IU/dL (≥60%) and FVIII:C levels ≥40 IU/dL (≥40%) should be achieved.

An appropriate dose should be re-administered every 12–24 hours of treatment. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of bleeding, and VWF:Ac (VWF:RCo) and FVIII:C levels.

In patients receiving FVIII-containing VWF products, plasma levels of FVIII:C should be monitored to reveal sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic events.

The following should be used to guide dosing in surgical prophylaxis:

Dose type	Minor surgeries (incl. tooth extractions)	Major surgeries
Loading dose	30–60 IU/kg	40–60 IU/kg
Maintenance dose	15–30 IU/kg, or half the loading dose, every 12–24 hours for up to 3 days	20–40 IU/kg, or half the loading dose, every 12–24 hours for up to 6 days or longer
Therapeutic goal	Achieve VWF:Ac (VWF:RCo) peak levels of 50% after loading dose and trough levels of >30% during maintenance doses	Achieve VWF:Ac (VWF:RCo) peak level of 100% after loading dose and trough levels of >50% during maintenance doses

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 or the US Prescribing Information.

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 used or unused IMP returned by patients.

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 and Adherence with Infusion Regimen

For all IVR assessments as well as for the PK assessment in paediatric patients, *Wilate* will be administered at the study site, with compliance under the control of the investigator.

Assessment of Adherence with the Infusion Regimen

Throughout the study, adherence with the infusion regimen will be assessed. Any change of the prophylactic dose as determined by the Principal Investigator during the Baseline Visit will be documented in the patient records and eCRF, including start and end dates of each dose, reasons for dose change, or reasons for not implementing a required dose change.

6 STUDY CONDUCT

The flow charts of assessments for prophylactic treatment by study visit are given on **pages 23** and **25**. The flow chart of assessments for surgical prophylaxis is given on **page 27**. Details on the individual assessments and methods are provided in **Section 7**.

6.1 Observations by Visit for Prophylactic Treatment

Because all paediatric patients enrolled in the study will undergo PK assessment, whereas adult patients will not, the first two study visits differ between these two age cohorts.

All enrolled patients will participate in the following study visits:

- Screening Visit
  - For adult patients
  - For paediatric patients
- Baseline Visit
  - Baseline IVR Visit for adult patients
  - Baseline PK Visit for paediatric patients
- 1-Month IVR Visit
- 2-Month IVR Visit
- 3-Month IVR Visit
- 6-Month IVR Visit
- 9-Month IVR Visit
- Study Completion (12-Month) Visit

Between the 3- and 6-Month Visits, the 6- and 9-Month Visits, and the 9- and 12-Month Visits, **monthly telephone contacts** will be performed.

Where needed, **external home-care companies** with experience in conducting clinical trials will be contracted, with trained nurses supporting patients by providing training, re-training, and oversight through home-care visit support throughout the study.

SCREENING AND BASELINE VISITS FOR ADULT PATIENTS (≥17 YEARS)

6.1.1 Screening Visit (Adult Patients)

The Screening Visit should take place **at least 72 hours** from the patient's latest administration of a VWF-containing product.

The following assessments will be performed:

- **Obtaining voluntarily given, written (signed and dated) informed consent**
- **Inclusion and exclusion criteria**
- **Demographic and baseline characteristics**
- **Weight**
- **Height**
- **Medical history, including:**
  - VWD type
  - Prior medications
  - Birth control measures (for female patients of child-bearing potential)
  - History of heavy menstrual bleeding (for female patients)
- **Family history of VWD**
- **Vital signs**
- **Physical examination**
- **Blood samples** for the following assessments:
  - AB0 blood group, unless derivable from the baseline characteristics [local lab]
  - Routine safety laboratory [local lab]
- **Urine pregnancy test** (in female patients of child-bearing potential)
- **Concomitant medications**

During the Screening Visit, patients will also **receive a patient diary**. The investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting any BEs, treatment details, AEs, and concomitant medications. Menstrual bleeds will be documented in the **Pictorial Blood Loss Assessment Chart (PBAC)**. Therefore, female patients of child-bearing potential will also be instructed in completing the **PBAC** (see **Section 7.2.8**).

After the Screening Visit, eligible patients will participate in the Baseline IVR Visit, during which the first prophylactic dose of *Wilate* will be administered.

For adult patients, the Screening Visit and the Baseline IVR Visit **may coincide**; however, note that administration of the first prophylactic dose of *Wilate* during the Baseline IVR Visit requires a **washout period of at least 72 hours** from the patient's previous administration of a VWF-containing product. If possible, the interval between the Screening Visit and the Baseline IVR Visit **should not exceed 2 weeks**.

Between the Screening Visit and the Baseline IVR Visit, on-demand treatment of BEs or prophylactic treatment should be continued with the **patient's previously used VWF-containing product**. Any BEs occurring between the Screening Visit and the Baseline IVR Visit will be **documented in the patient diary (menstrual bleeds in the PBAC)**. Also, any infusions with the patient's previous VWF-containing product during this time will be **documented in the patient diary as concomitant medication**.

6.1.2 Baseline IVR Visit (Adult Patients)

During the Baseline IVR Visit, the prophylactic dose and dosing interval of *Wilate* for each adult patient will be determined by the Principal Investigator based on the patient's clinical condition, and the first prophylactic dose will be administered after a washout period of **at least 72 hours** from the patient's latest administration of a VWF-containing product. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS

- **Confirm inclusion and exclusion criteria** (to be documented in patient records)
- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10 as applicable)

BEFORE INJECTION

- **Weight**
- **Blood samples**
  - VWF multimer pattern for VWD type 2A and genotype for VWD type 2B [central lab]
  - Anti-parvovirus B19 antibodies [central lab]
  - Retention samples for possible virus marker and VWF/FVIII inhibitor testing [central lab]

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION

- **Vital signs**
- **Blood samples**
  - VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR [central lab]
  - FVIII:C (OS and CHR) for IVR [central lab]

ANY TIME

- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Hemophilia Joint Health Score (HJHS)**
- **Target joint(s)**
- Re-confirm commitment to using **birth control measures** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

In adult patients, the first prophylactic injection of *Wilate* is administered during the Baseline IVR Visit.

In case of **home treatment**, patients will be trained in how to correctly administer the IMP and provided with IMP. Patients will be re-supplied with IMP whenever necessary during the study.

SCREENING AND BASELINE VISITS FOR PAEDIATRIC PATIENTS (6–16 YEARS)

6.1.3 Screening Visit (Paediatric Patients)

The following assessments will be performed:

- **Obtaining voluntarily given, written (signed and dated) informed consent**
- **Inclusion and exclusion criteria**
- **Demographic and baseline characteristics**
- **Weight**
- **Height**
- **Medical history, including:**
  - VWD type
  - Prior medications
  - Birth control measures (for female patients of child-bearing potential)
  - History of heavy menstrual bleeding (for female patients)
- **Family history of VWD**
- **Vital signs**
- **Physical examination**
- **Blood samples for the following assessments:**
  - AB0 blood group, unless derivable from the baseline characteristics [local lab]
  - Routine safety laboratory [local lab]
  - VWF multimer pattern for VWD type 2A and genotype for VWD type 2B [central lab]
  - VWF:Ac (VWF:RCo and VWF:GPIbm) [central lab]
  - FVIII:C (OS and CHR) [central lab]
  - Anti-parvovirus B19 antibodies [central lab]
  - Retention samples for possible virus marker and VWF/FVIII inhibitor testing [central lab]
- **Urine pregnancy test** (in female patients of child-bearing potential)
- **Concomitant medications**

During the Screening Visit, patients will also **receive a patient diary**. The investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting any BEs, treatment details, AEs, and concomitant medications. Menstrual bleeds will be documented in the **Pictorial Blood Loss Assessment Chart (PBAC)**. Therefore, female patients of child-bearing potential will also be instructed in completing the **PBAC** (see **Section 7.2.8**).

After the Screening Visit, eligible children will participate in the Baseline PK Visit. The Screening Visit and the Baseline PK Visit **must not occur on the same day**. If possible, the interval between the Screening Visit and the Baseline PK Visit **should not exceed 2 weeks**.

Between the Screening Visit and the Baseline PK Visit, on-demand treatment of BEs or prophylactic treatment should be continued with the **patient's previously used VWF-containing product**. Any BEs occurring between the Screening Visit and the Baseline PK Visit will be **documented in the patient diary (menstrual bleeds in the PBAC)**. Also, any infusions with

the patient's previous VWF-containing product during this time will be **documented in the patient diary as concomitant medication**.

6.1.4 Baseline PK Visit (Paediatric Patients)

During the Baseline PK Visit, paediatric patients will receive *Wilate* at a dose of 60 ± 10 IU/kg after a washout period of **at least 72 hours** from the patient's previous administration of a VWF-containing product. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS
- **Confirm inclusion and exclusion criteria (to be documented in patient records)**
- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10, as applicable)

BEFORE INJECTION
- **Weight**

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION
- **Vital signs**

WITHIN 60 MIN BEFORE AND 60±5 MIN, 3 H±30 MIN, 9±1 H, 24±2 H, 48±2 H, and 72±2 H AFTER INJECTION
- **Blood samples**
  - VWF:Ac (VWF:RCo) for PK [central lab]
  - FVIII:C (OS and CHR) for PK [central lab]

ANY TIME
- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Hemophilia Joint Health Score (HJHS)**
- **Target joint(s)**
- Re-confirm commitment to using **birth control measures** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

During this visit, the prophylactic dose and dosing interval of *Wilate* will be determined by the Principal Investigator based on the patient's clinical condition.

In paediatric patients, the first prophylactic injection of *Wilate* is administered after the Baseline PK Visit.

In case of **home treatment**, patients will be trained in how to correctly administer the IMP and provided with IMP. Patients will be re-supplied with IMP whenever necessary during the study.

After the Baseline IVR Visit in adults and the Baseline PK Visit in children, all subsequent visits will be the same for both age cohorts.

SUBSEQUENT VISITS FOR ALL PATIENTS

6.1.5 1-Month IVR Visit

The 1-Month IVR Visit will take place 1 month (±1 week) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE INJECTION
- **Weight**
- **Blood samples**
  - For VWF and FVIII inhibitor testing, *only if* inhibitor development is suspected

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION
- **Vital signs**
- **Blood samples**
  - VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR [central lab]
  - FVIII:C (OS and CHR) for IVR [central lab]

ANY TIME
- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Review of compliance** and adherence to the infusion regimen
- Re-confirm commitment to using **birth control measures** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

At the end of this and each of the following visits, IMP for home treatment will be given to patients as applicable.

6.1.6 2-Month IVR Visit

The 2-Month IVR visit will take place 2 months (±1 week) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Same assessments are for the 1-Month IVR Visit**

6.1.7 3-Month IVR Visit

The 3-Month IVR Visit will take place 3 months (±1 week) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Same assessments as for the 1-Month IVR Visit**
- **Urine pregnancy test** (in female patients of child-bearing potential)

6.1.8 6-Month IVR Visit

The 6-Month IVR Visit will take place 6 months (±2 weeks) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS
- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10 as applicable)

- **Same assessments as for 1-Month IVR Visit**
- **Urine pregnancy test** (in female patients of child-bearing potential)

6.1.9 9-Month IVR Visit

The 9-Month IVR Visit will take place 9 months (±2 weeks) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Same assessments are for the 1-Month IVR Visit**

6.1.10 Study Completion (12-Month) Visit

The Study Completion Visit will take place 12 months (+2 weeks) after the first prophylactic injection of *Wilate*.

During this visit, a prophylactic injection of *Wilate* will be administered. Patients should arrive at the centre within 3 hours before their next planned prophylactic dose. Patients must not be experiencing any bleeding.

The following assessments will be performed:

BEFORE ANY OTHER ASSESSMENTS

- **QoL questionnaires** (PROMIS-29 for all patients, SF-36v2 or SF-10 as applicable)

BEFORE INJECTION

- **Weight**
- **Blood samples**
  - Routine safety laboratory [local lab]
  - For VWF and FVIII inhibitor testing, *only if* inhibitor development is suspected [central lab]
  - Anti-parvovirus B19 antibodies [central lab], *only if* the sample at the Baseline Visit was negative, or if it was equivocal on both original and re-testing

WITHIN 60 MIN BEFORE AND 60±5 MIN AFTER INJECTION

- **Vital signs**
- **Blood samples**
  - VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR [central lab]
  - FVIII:C (OS and CHR) for IVR [central lab]

ANY TIME

- **Patient diary review, with documentation of PBAC** data and calculation of PBAC score by investigator (in female patients of child-bearing potential)
- **Review of compliance** and adherence to the infusion regimen
- **Hemophilia Joint Health Score (HJHS)**
- **Target joint(s)**
- **Physical examination**
- **Urine pregnancy test** (in female patients of child-bearing potential)
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

All used and unused IMP vials will be returned by the patients or their home-care providers.

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

6.1.11 Monthly Telephone Contacts

Monthly telephone contacts will be performed 4, 5, 7, 8, 10, and 11 months (± 1 week) after first prophylactic injection of *Wilate*. Should a patient visit the study centre at the time any of these telephone contacts are scheduled, the required assessments may also be performed during this visit.

The following assessments will be performed:

- Review of **compliance** with correctly **completing the patient diary and PBAC** (for female patients of child-bearing potential)
- Review of **adherence with the infusion regimen**
- Monitoring of **adverse events (AEs)**
- **Concomitant medications**

If any issues with completing the diaries or adhering to the infusion regimen are identified, the investigator or home-care provider will re-train the patient accordingly.

6.1.12 Unscheduled Visits and Additional Measures

If inhibitor development is suspected (e.g., based on an unexplained need to increase the dose, a lack of efficacy of IMP injections, or prolonged bleeding), VWF and FVIII inhibitor tests will be performed at the central laboratory and documented (see **Section 7.4.5.1**).

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.

Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalisations for BEs or surgical interventions.

6.1.13 Surgical Visits

Patients may undergo surgical interventions in the course of the study. Whether or not these patients will be hospitalised 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 mobilisation, should be used to prevent venous thromboembolism.

For the flow chart of assessments for surgical prophylaxis, see **page 27**.

For details on the surgery data to be documented and the surgical efficacy assessments to be performed, see **Section 7.2.4** and **Section 7.2.5**.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The planned treatment duration per patient is 12 months.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered clinically completed when all enrolled patients have completed the planned observation period, including the Study Completion Visit.

The estimated start of the study (enrolment of first patient) is Q2 2020, and the estimated end of the study is Q1 2022.

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 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 centre may apply for the reasons described below.

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 Centre

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

- The centre cannot comply with the requirements of the protocol.
- The centre 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, weight, height, and AB0 blood group.

7.1.2 Medical History and Prior Medications

The medical history will be obtained by patient interview and by collecting records of past diseases and treatments (e.g., hospital records), if available. Concomitant medications will also be obtained by interview.

For female patients of child-bearing potential, the birth control measures used within 6 months before enrolment will be documented. For all female patients, any history of heavy menstrual bleeding will be recorded. The Pictorial Blood Chart Assessment (PBAC) score calculated during the 6 months previous to Screening will be obtained in an observational study preceding this study, if applicable.

In addition, information about the patients' treatment with VWF-containing product will be collected. To be eligible for the study, complete records on the type, frequency, and treatment of BEs for at least 6 months of on-demand treatment must be available (see **Section 4.1.2**).

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

7.2 Efficacy Assessments

This section summarises the assessments to be performed for the calculation of the primary endpoint (see **Section 3.1.1**) as well as the secondary (see **Section 3.1.2)** and exploratory endpoints (see **Section 3.1.3**) of this study.

For details on laboratory analyses, see **Section 7.4.5**.

7.2.1 IMP Administration Data

The following parameters will be documented:

- Dates and times of IMP injections
- Doses of IMP in IU and IU/kg and IMP batch numbers
- Purpose of IMP injection (IVR, prophylaxis, prophylaxis of recurrent bleeding, treatment of BE, surgery, prophylaxis after surgery, or menstrual bleeds)

Injections administered for the purpose of prophylaxis of recurrent bleeding are those injections administered after bleeding cessation and in advance of the patient's next regular prophylactic dose.

7.2.2 Bleeding Episode (BE) Data

Study participants will be instructed by the investigator on recording all BEs and in how to record them. For any BE occurring during the study, the following data will be recorded:

- BE type (spontaneous, traumatic, postoperative, other)
- BE site
- BE severity (minor or major) (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 7.2.1**)
- Assessment of the efficacy of treatment at the end of the BE (see **Section 7.2.3**)

All of these parameters will be documented by the patient (together with the investigator in case of on-site treatments or together with the nurse in case a home-care service is used) in the patient diary. Patients who experience a major BE should be treated at the study site, if possible.

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

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.

Menstrual bleedings will not be counted towards the TABR.

BE severity and the severity of menstrual bleeds will be assessed using the criteria given in **Table 1**.

Table 1 Definition of the Severity of Bleeding

Bleeding severity	Description
Minor	**Mild haemarthrosis** (mild swelling, 'aura,' pain, warmth of the skin over the joint, change in range of motion, decrease in mobility and activity, slight difficulty in using the limb compared with baseline), **superficial muscle bleed** (pain and/or swelling and functional impairment compared with baseline), **soft-tissue bleeding** (scrapes, superficial cuts such as those cause by shaving razor, knife, or scissors, bleeding episodes that require frequent bandage changes, cutaneous bleeds with numerous bruises >1 cm), **oral bleeding** (superficial mouth bleeds, oozing or bleeding related to tooth eruption or extraction, spontaneous or after brushing/flossing, gum bleeding, bleeding after bites to lip or tongue), and **most nose bleeds** (i.e., those causing distress or interference with daily or social activities).
Major	**Generally requires hospitalization**; **causes incapacity**, significant pain, and substantial decrease in range of motion of affected joint (in case of joint bleeds); **includes** symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraabdominal, intraarticular, or pericardial bleeds), intramuscular bleeds with compartment syndrome, bleeds of the pelvic muscles, periorbital bleeds, gastrointestinal bleeds, central nervous system bleeds, heavy menstrual bleeding,* bleeding in the area of the neck or throat or pharynx, other major trauma, or bleeding causing a decrease in haemoglobin levels by 20 g/L (1.24 mmol/L) or more. *Heavy **menstrual bleeding is any menstrual bleeding** that impedes the ability to perform daily activities such as work, housework, exercise, or social activities during menstrual periods and should be considered 'major.' Criteria for heavy (i.e., major) menstrual bleeding may also include any of the following: changing pads/tampons more frequently than hourly; menstrual bleeding lasting 7 or more days; and the presence of clots >1 cm combined with a history of flooding or a PBAC score ≥185.

7.2.3 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	Bleeding was completely stopped within 3 days in case of minor bleeds, within 7 days in case of major bleeds, and within 10 days in case of gastrointestinal bleeds
Good	Bleeding was completely stopped, but time and/or dose slightly exceeded expectations
Moderate	Bleeding could be stopped only by significantly exceeding time and/or dose expectations
None	Bleeding could be stopped only by using other VWF-containing products

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.'

7.2.4 Surgical Prophylaxis Data

The following surgery-related parameters will be documented:

- Type of surgery (planned or emergency)
- Location of surgery
- Severity of surgery (minor, major) (see definitions under **(a)** below)
- Expected and actual duration of surgery
- Expected average/maximum and actual blood loss
- Pre-, intra-, and postoperative IMP administration data (see definitions under **(b)** below)
- Pre-, intra-, and postoperative FVIII and VWF:Ac plasma levels (see definitions under **(b)** below)
- Routine safety laboratory
- Presence of wound haematomas
- Vital signs
- Details on concomitantly administered products
- Blood transfusion requirements
- Brief narrative describing the outcome of the intervention
- Efficacy assessment at the end of surgery by surgeon (see **Section 7.2.5.1**)
- Efficacy assessment at the end of the postoperative period by haematologist (see **Section 7.2.5.2**)
- Overall efficacy assessment at the end of the postoperative period by the investigator (see **Section 7.2.5.3**)
- Monitoring of AEs

For details regarding the time points of data collection, refer to the flow chart of assessments for surgical prophylaxis on **page 27**.

(a) Severity of surgery

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

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

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 or her regular VWF treatment regimen.
- The **end of the postoperative period** is the time the patient returns to his or her regular VWF treatment regimen.

7.2.5 Efficacy in Surgical Prophylaxis

Efficacy will be assessed at the end of surgery by the surgeon (see **Section 7.2.5.1**) and at the end of the postoperative period by the haematologist (see **Section 7.2.5.2**). In both cases, predefined assessment criteria will be used. In addition, an overall assessment of efficacy will be made at the end of the postoperative period by the investigator (see **Section 7.2.5.3**).

7.2.5.1 At the End of Surgery (by Surgeon)

At the end of surgery, the haemostatic 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 haemostasis 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 maximum expected blood loss for the type of procedure in a patient with normal haemostasis
Moderate	Intraoperative blood loss was higher than the maximum expected blood loss for the type of procedure performed in a patient with normal haemostasis, but haemostasis was controlled
None	Haemostasis was uncontrolled, necessitating a change in the clotting factor replacement regimen

7.2.5.2 At the End of the Postoperative Period (by Haematologist)

At the end of the postoperative period, the haemostatic efficacy of *Wilate* will be assessed by the haematologist 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 VWF-containing product

7.2.5.3 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 based on the algorithm given in **Table 5.**

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

7.2.6 Quality of Life

For the assessment of QoL, the following instruments will be used:

- Patient-Reported Outcomes Measurement Information System (PROMIS)-29 [5–7] for patients of all ages. For patients 6–7 years of age, the questionnaire will be completed by the parent/legal guardian. Self-reported measures will be used for patients ≥8 years old.
- 36-Item Short Form Health Survey, version 2 (SF-36v2, [8]), for patients ≥16 years,
- 10-Item Short From Health Survey (SF-10, [9]) will be used for patients 6–15 years of age.

At each visit requiring QoL assessments, the questionnaires should be administered before starting any other visit assessment.

7.2.7 Joint Health Status

Joint health will be assessed using the Hemophilia Joint Health Score (HJHS) [10], which has been specifically validated for the assessment of clinical outcome in VWD [11].

Target joint(s) will also be documented. Target joint(s) are defined as having three or more spontaneous BEs into a single joint within 6 consecutive months preceding either the Baseline Visit or the Study Completion Visit.

7.2.8 Pictorial Blood Assessment Chart

Bleeding information from each menstrual period in this study will be collected in the Pictorial Blood Assessment Chart (PBAC) [12,13]. The PBAC will be provided to all female patients of child-bearing potential.

The investigator will train all relevant patients in how to complete the PBAC. At each study visit, the investigator will review the completed PBAC and calculate the PBAC score. In addition, the investigator will review, together with the patient, the severity assessment of the menstrual bleed using the criteria given in **Table 1**, **Section 7.2.2**. The data documented in the PBAC and the investigator-calculated final score will be recorded in the eCRF.

7.3 PK Assessments

PK parameters will be assessed for VWF:Ac (VWF:RCo) and FVIII:C using both the chromogenic (CHR) and one-stage (OS) assays based on actual IMP potencies.

The following PK parameters will be assessed:

- 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 (V_d)
- Clearance (CL)
- Incremental in vivo recovery (IVR)

7.4 Safety Assessments

7.4.1 Assessments for Safety Endpoints

The following drug safety information will be collected:

- Adverse events (AEs) and serious adverse events (SAEs) (for definitions and reporting requirements, see **Sections 7.4.2**, **7.4.3**, and **7.4.4**)
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs (see **Section 7.4.7**)

7.4.2 Adverse Events (AEs)

7.4.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable 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 led 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 patient is stable. All follow-up information collected will be made available to the Sponsor.

7.4.2.2 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 non-leading 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 eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. 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 7.4.2.3**, **7.4.3**, and **7.4.2.4**. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in **Section 7.4.2.5**.

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. Seroconversion for parvovirus B19 will be reported as an AE.

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.

7.4.2.3 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.

7.4.2.4 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 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 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 aetiology is unrelated to the IMP.
- **Unclassified:** reports which, for whatever reason, are not yet assessable, e.g., because of still outstanding information (can only be a temporary assessment).

7.4.2.5 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 IB.
- **Unexpected:** an ADR that is not listed in the current edition of the IB or that differs because of greater severity or greater specificity.

7.4.2.6 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.

7.4.2.7 Action(s) Taken

AEs requiring action or therapy must be treated with recognised 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 stabilised. Any relevant follow-up information will be reported to the Sponsor.

7.4.3 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 hospitalisation or prolongation of existing hospitalisation,
- 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 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 hospitalisation but may jeopardise the 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 VWF or FVIII inhibitors.

7.4.4 AE and SAE Reporting Timelines

All **SAEs**, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone or email to the clinical study team.

[redacted]

Phone:	[redacted]
Mobile:	[redacted]
Email:	[redacted]

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:

Octapharma's Corporate Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Straße 235, 1100 Vienna, Austria

Email:	[redacted]
24-hour emergency telephone number:	[redacted]

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 hospitalisations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalisations should not be considered SAEs.

7.4.5 Laboratory Tests

The following laboratory parameters will be determined at the time points specified in the flow charts of assessments on **pages 23**, **25** and **27**, in **Section 6**, and in **Table 6** and **Table 7**.

7.4.5.1 Central Laboratory

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

- **VWF:Ac** in vials used for baseline IVR injections as well as in plasma will be determined using VWF:RCo and VWF:GPIbm.
- **FVIII:C** will be measured in plasma at pre-specified time points using OS and CHR assays.

- For **VWF and FVIII inhibitor** testing, a retention sample will be collected and stored at the central laboratory. In addition, VWF and FVIII inhibitor testing will be performed at any time during the study in case inhibitor development is suspected. For the determination of VWF inhibitors, a mixing study based on VWF:RCo will be used. For the determination of FVIII inhibitors, the modified Bethesda assay (Nijmegen modification) using the OS assay will be used.
- **Virus safety** will be evaluated by taking a plasma sample for anti-parvovirus B19 antibody testing before the first injection of *Wilate*. All patients negative at baseline will be tested again at the Study Completion Visit. For patients with equivocal results at baseline, the same sample will be re-tested. If re-testing also yields an equivocal result, the patient will be tested again at the Study Completion Visit. In addition, a retention serum sample for possible virus marker testing will be taken and stored at the central laboratory.
- For patients with **VWD type 2A, VWF multimers** will be determined by a quantitative method.
- For patients with **VWD type 2B,** bidirectional sequencing of exon 28 and its intron-exon boundaries will be performed to confirm the VWD type. If no mutation is identified, an additional molecular testing will be performed to exclude pseudo-VWD

Central laboratory:

Covance Central Laboratory Services
Rue Moise-Marcinhes 7
1217 Geneva
Meyrin, Switzerland

SYNLAB Analytics & Services Germany GmbH
Responsible for testing of VWF:GPIbm only
Bayerstr. 53
80335 Munich, Germany

7.4.5.2 Local Laboratory

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

- **Haematology:** red blood cell count, white blood cell count, haemoglobin, haematocrit, and platelet count
- **Chemistry:** total bilirubin, alanine amino transferase, aspartate transaminase, blood urea nitrogen or urea, serum creatinine
- **Urine pregnancy test** (in female patients of child-bearing potential)

AB0 blood-type testing as well as VWF:Ac (VWF:RCo) and FVIII:C measurements in case of BEs or surgery will also be done by the local laboratories.

Table 6 Laboratory Assessments in Adult Patients (≥17 Years)

Laboratory Assessments	Screening Visit	Baseline IVR Visit	1-Month IVR Visit	2-Month IVR Visit	3-Month IVR Visit	6-Month IVR Visit	9-Month IVR Visit	Study Completion (12-Month) IVR Visit
LOCAL LAB								
Determination of AB0 blood group	x							
Routine safety laboratory	x							x [1]
Urine pregnancy test [4]	x				x	x		x
CENTRAL LAB								
VWF multimer pattern for VWD type 2A and genotype for VWD type 2B		x						
VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR		x [2]	x [2]	x [2]	x [2]	x [2]	x [2]	x [2]
FVIII:C (OS and CHR) for IVR		x [2]	x [2]	x [2]	x [2]	x [2]	x [2]	x [2]
Anti-parvovirus B19 antibodies		x [1]						x [3]
VWF and FVIII inhibitors (•)			(•) [1]	(•) [1]	(•) [1]	(•) [1]	(•) [1]	(•) [1]
Retention samples for possible virus marker and VWF/FVIII inhibitor testing		x [1]						

(•) If inhibitor development is suspected
[1] Before injection
[2] Within 60 min before and 60±5 min after injection
[3] Before injection, if sample at the Baseline IVR Visit was negative, or if it was equivocal on both original and re-testing
[4] In female patients of child-bearing potential

Table 7 Laboratory Assessments in Paediatric Patients (6–16 Years)

Laboratory Assessments	Screening Visit	Baseline PK Visit	1-Month IVR Visit	2-Month IVR Visit	3-Month IVR Visit	6-Month IVR Visit	9-Month IVR Visit	Study Completion (12-Month) IVR Visit
LOCAL LAB								
Determination of AB0 blood group, unless derivable from medical history	x							
Routine safety laboratory	x							x [1]
Urine pregnancy test [4]	x				x	x		x
CENTRAL LAB								
VWF multimer pattern for VWD type 2A and genotype for VWD type 2B	x							
VWF:Ac (VWF:RCo and VWF:GPIbm) for IVR	x		x [2]	x [2]	x [2]	x [2]	x [2]	x [2]
FVIII:C (OS and CHR) for IVR	x		x [2]	x [2]	x [2]	x [2]	x [2]	x [2]
PK blood sampling for VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR)		x [3]						
Anti-parvovirus B19 antibodies	x							x [4]
VWF and FVIII inhibitors (•)			(•) [1]	(•) [1]	(•) [1]	(•) [1]	(•) [1]	(•) [1]
Retention samples for possible virus marker and VWF/FVIII inhibitor testing	x							

(•) If inhibitor development is suspected
[1] Before injection
[2] Within 60 min before and 60±5 min after injection
[3] Blood samples for PK assessment to be taken within 60 min before injection and 60±5 min, 3 h (±30 min), 9±1 h, 24±2 h, 48±2 h, and 72±2 h after injection (central laboratory)
[4] Before injection, if sample at the Baseline PK Visit was negative, or if it was equivocal on both original and re-testing

7.4.6 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 during screening. In addition, weight will be measured at all visits prior to dosing.

7.4.7 Other Relevant Safety Information

(a) Post-study related safety reports

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 and to Octapharma's Corporate Drug Safety Unit (see **Section 7.4.4**).

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

(b) Pregnancies

Every effort will be made to avoid a pregnancy during the use of an IMP. Pregnancies occurring during the study (foetal exposure to the IMP) must be reported.

If a pregnancy occurs during the study, the investigator should complete the Pregnancy Notification Form and transmit it to the Clinical Trial Manager and to Octapharma's Corporate Drug Safety Unit (see **Section 7.4.4**).

Follow-up information on the outcome of both mother and foetus will be requested by a Sponsor representative.

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.

(c) 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.

(d) 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.

(e) 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.

(f) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected. One example of a lack of efficacy may be continued bleeding in a patient with VWD despite administration of coagulation factor. Lack of efficacy should be reported as an AE or, if the reaction fulfils one of the criteria for seriousness, as an SAE.

7.5 Appropriateness of Measurements

The criteria for assessing the safety and efficacy of *Wilate* in the treatment of BEs as well as in surgical prophylaxis are identical to those used in similar studies with *Wilate.*

Reduction of ABR of patients with coagulation bleeding disorders such as haemophilia A has been used as an efficacy endpoint to reliably demonstrate the impact of prophylaxis on the bleeding rates of these patients.

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 authorise 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.

Patients will usually treat themselves at home, and they will therefore be provided with a sufficient amount of IMP and a patient diary as well as the PBAC (women of child-bearing potential).

The patient diary/PBAC will be handed to the patient during the Screening Visit after inclusion into the study. The investigator will explain to the patient how to fill in the diary/PBAC and emphasize the importance of careful documentation.

At each follow-up visit at the study site, the patient will bring along the patient diary/PBAC for review and validation by site personnel.

During or after each follow-up visit, the information recorded in the patient diaries/PBACs will be transcribed to the eCRFs. The patient diaries/PBACs are classified as source data, and the originals will be included in the patient's medical record.

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 authorised 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 authorised 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 for 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 authorised 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

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

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

in favour of

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

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

9.2 Statistical Analysis

The primary approach to statistical analysis will be descriptive, presenting sampling statistics (n, mean, standard deviation, quartiles, and ranges) 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 set (SAF)** will include all patients who received at least one dose 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 dose of IMP after the Baseline IVR Visit in adults or the Baseline PK Visit in children.

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 primary study outcome parameter. 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.

The **pharmacokinetic (PK) set** will be a subset of the FAS, containing all patients for whom a valid PK profile was obtained at baseline.

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.
- The evaluation of the primary endpoint will be performed on the FAS (ITT analysis) and on the PP set (PP analysis).
- For secondary and exploratory endpoints, ITT and PP analyses will be carried out, unless these analysis sets differ by no more than 5% of patients.
- Analysis of the efficacy and safety of *Wilate* in surgeries will be based on the SURG set.
- Analysis of the PK properties of *Wilate* will be based on the PK set.

9.2.2 Efficacy Analysis Plan

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

Primarily, all obtained data on treatment characteristics (IMP dosages, frequencies, total consumption), VWF:Ac and FVIII:C incremental IVR of *Wilate* over time and BEs (duration, frequency, efficacy assessment) will be described using summary statistics.

Whenever sufficient reliable and comparable data on secondary endpoints (see **Section 3.1.2**) or exploratory endpoints (see **Section 3.1.3**) are available for similar historical on-demand treatment periods, exploratory statistical comparisons of these endpoints to on-demand treatment periods will be considered.

Efficacy of Prophylactic Treatment with Wilate

The efficacy of prophylactic treatment with *Wilate* will be assessed by comparing each patient's individual ABR under prophylactic treatment in this study with the ABR recorded for the same patient in a previous, non-interventional, study or with the ABR that can reliably be obtained from the patient's bleeding documentation.

Efficacy of prophylactic treatment with *Wilate* will be statistically evaluated by analysing the primary endpoint, i.e., demonstration that the TABR during prophylactic treatment lowers the patients' TABR during on-demand treatment by more than 50%.

To test whether the mean TABR during prophylactic treatment ($TABR_{pr}$) is less than half the historical mean TABR during on-demand treatment ($TABR_{od}$), the following pair of hypotheses will be tested using a paired t-test assuming log-normally distributed data:

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

at a one-sided alpha level of 2.5%. A corresponding two-sided 95% CI for the TABR will also be provided.

To assess the qualitative robustness of the inferential result, the hypothesis will additionally be tested with the Wilcoxon (matched-pair signed rank) test on the log-transformed bleeding rate as a distribution-free alternative. Also, a 95% Hodges-Lehmann CI for the median difference will be reported.

In addition to the comparison of the patients' TABR during on-demand and prophylactic treatment, intra-individual comparisons with each patient's documented historical TABR will be performed. For this, descriptive statistics for historical TABR and TABR during prophylactic treatment and their intra-individual differences will be tabulated. Descriptive statistics will also be presented for the SABR.

Efficacy of Wilate in the Treatment of Breakthrough Bleedings

To assess the haemostatic efficacy of *Wilate* in the treatment of breakthrough BEs during prophylaxis, a frequency distribution of all treated BEs that were successfully treated will be presented overall and by severity, along with an exploratory 95% CI for the proportion of successfully treated BEs.

Pharmacokinetic Analysis

All PK analyses will be based on the PK set. The following PK parameters for will be analysed:

- Area under the curve (AUC) and AUC_{norm} (normalized for the administered dose)
- In vivo half-life (T½)
- 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)

PK parameters will be computed for VWF:Ac (VWF:RCo) and FVIII:C. Both chromogenic (CHR) and one-stage (OS) assays, actual IMP potencies, and actual sampling times will be used in the calculations. PK parameters will be derived by non-compartmental methods.

The PK profiles of VWF:Ac and FVIII:C and the PK parameters derived from them will be summarized by descriptive statistics (including geometric means and standard deviations) as well as the presentation of concentration vs time plots (individual values and means).

Subgroup Analyses

Analyses of the primary endpoint assessing the efficacy of prophylactic treatment with *Wilate* and the secondary endpoint assessing the efficacy of *Wilate* in the treatment of breakthrough bleedings will be presented for the following subgroups:

- Age (6–11 years,' '12–16 years,' and '≥17 years')
- Race ('American Indian or Alaska Native,' 'Asian,' 'Black or African American,' 'Native Hawaiian or Other Pacific Islander,' 'White,' 'Other')
- Geographical region ('patients in the US,' 'patients outside the US')
- Sex ('female,' 'male')

Analysis of PK parameters will be presented by age ('6–11 years' and '12–16 years').

Efficacy of Wilate in Surgical Prophylaxis

To assess the efficacy of *Wilate* in surgical prophylaxis, a frequency distribution of the efficacy rating for all surgical procedures will be presented. All other surgery data (e.g., severity, type, IMP consumption) will be presented descriptively.

Efficacy of Wilate in Menstrual Bleeding

To assess the relative haemostatic efficacy of *Wilate* in the treatment of menstrual bleeding during prophylaxis compared to on-demand treatment, changes in the PBAC score will be analysed based on complete cycle data. Only women of childbearing potential will be included in the analysis, which will include estimates and 95% CIs for PBAC score changes.

Analysis of Other Endpoints

The statistical analysis of other endpoints will be descriptive, including exploratory 95% CIs.

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, 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 first IMP infusion. All TEAEs, related TEAEs (i.e., TEAEs probably or possibly related to the IMP), and serious TEAEs will be summarised 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 analysed 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 VWF and FVIII inhibitor testing results will be analysed 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 baseline 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 analysed 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 TABR 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 Randomisation, 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 Co-ordinating Investigator 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 patient 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, analyse, 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 Standard Operating Procedures) will be prepared by the Sponsor after completion of the study. The Coordinating 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-centre studies only in their entirety and not as individual centre 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.

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15 APPENDICES

Not applicable.