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CLINICAL STUDY PROTOCOL

CLINICAL STUDY TO INVESTIGATE THE EFFICACY, PHARMACOKINETICS, IMMUNOGENICITY AND SAFETY OF *WILATE* IN SEVERE VON WILLEBRAND DISEASE PATIENTS UNDER THE AGE OF 6 YEARS

Investigational Product:	VWF/FVIII concentrate from plasma of human donors (*wilate*)
Indication:	Routine prophylaxis in children under the age of 6 years with severe VWD
Study Design:	Open-label, prospective, non-controlled, international, multi-centre phase 3 study
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Strasse 235 A-1100 Vienna Austria
Study Number:	WIL-33
EudraCT and/or IND Number:	**EudraCT:** 2020-004344-28 **IND:** 011303
Development Phase:	Phase 3
Planned Clinical Start:	Quarter 3 2021
Planned Clinical End:	Quarter 2 2024
Initial Study Protocol V01: Protocol Amendment 1.0: **Amended Protocol V02:** Supplemental Amendment 2.0 Protocol Amendment 3.0: **Amended Protocol V03:**	**15-Jan-2021** 20-Aug-2021 (Moldova only, based on V01) **31-Aug-2021** 31-Aug-2021 (supplementing Protocol V02) 20-Nov-2022 (Germany only, based on V02) **05-Dec-2022**
Version:	Version 03
Co-ordinating Investigator:	[redacted] Paediatric Haematologist-Oncologist Loma Linda University Health 250 E Caroline St San Bernardino CA 92408, United States

STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: *wilate*	**Protocol Identification Code:** WIL-33
Name of Active Ingredient: VWF/FVIII concentrate human	**Date of Final Protocol:** 05-Dec-2022

Title of Study:

Clinical Study to Investigate the Efficacy, Pharmacokinetics, Immunogenicity and Safety of *wilate* in Severe von Willebrand Disease Patients under the Age of 6 Years

Indication:

Routine prophylaxis in children under 6 years of age with severe VWD

Number of Study Centre(s):

Up to 15 sites worldwide

Objectives:

Primary Objective:

The primary objective of this study is to determine the efficacy of *wilate* in the prophylactic treatment of up to 12 paediatric patients (eight evaluable) with severe VWD (defined as screening von Willebrand factor ristocetin cofactor activity [VWF:RCo] <20%) under the age of 6 years, for a period of 12 months.

Secondary Objectives:

The secondary objectives of this study are to:

- Determine the pharmacokinetics (PK) of *wilate* for VWF:Ac (VWF:RCo) and FVIII:C (one-stage [OS])
- Determine incremental in-vivo recovery (IVR) of *wilate* over time
- Evaluate the rate of traumatic and spontaneous breakthrough bleeds under prophylactic treatment, including the corresponding treatment efficacy
- Assess the treatment response in minor and major bleeds and surgeries
- Determine *wilate* consumption data for prophylactic treatment, on-demand treatment, and surgeries
- Investigate the immunogenic potential of *wilate* by screening for VWF and FVIII inhibitors
- Investigate the thrombogenic potential of *wilate*
- Assess the patients' joint status with the Haemophilia Joint Health Score (HJHS)
- Assess the safety and tolerability of *wilate*

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Exploratory Objectives:

The exploratory objective of this study is to investigate the VWF multimer composition in the hereditary type 3 VWD paediatric patients.

Study Design:

Open-label, prospective, non-controlled, international, multi-centre phase 3 study

Number of Subjects/Patients:

12 patients (eight evaluable) with VWD under the age of 6 years suffering from severe VWD defined as screening VWF:RCo <20%, regardless of prior treatment. At least four of these patients should be suffering from hereditary type 3 VWD. The remaining patients can be diagnosed with severe type 2 (except 2N) or severe type 1 VWD.

Subject/Patient Selection Criteria:

Inclusion Criteria:

1. Patients aged <6 years at the time of screening
2. Type 3 (at least four patients), severe type 2 (except 2N) or severe type 1 VWD (any of which with VWF:RCo <20%) according to medical history, requiring substitution therapy with a VWF-containing product
3. Minimum body weight 12.5 kg at the time of screening
4. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted (obtained from the patient's parent(s)/ legal guardian(s))

Exclusion Criteria:

1. History, or current suspicion of VWF or FVIII inhibitors
2. Injection of DDAVP or VWF-containing product within 72 hours prior to inclusion
3. Medical history of a thromboembolic event
4. Platelet count <100,000/µL at screening (except for VWD type 2B)
5. Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar drugs

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6. Treatment with any investigational medicinal product (IMP) in another interventional clinical study currently or within four weeks before enrolment
7. Other coagulation disorders or bleeding disorders
8. Known hypersensitivity to any of the components of the study drug

Test Product, Dose, and Mode of Administration:

The VWF/FVIII 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. At least three different *wilate* batches will be used.

wilate Dosage for PK Assessment:

Single dose of 80 IU/kg body-weight (BW). The exact dose calculated according to the nominal potency should be administered, with 70–85 IU/kg BW as the acceptable range.

wilate Dosage Recommendations for Prophylactic Treatment:

For prophylactic treatment, *wilate* should be administered 2–3 times per week at a recommended dose of 30–50 IU/kg BW over 12 months. The prophylactic dose and frequency for each patient will be determined by the responsible treating Investigator, based on the individual patient's clinical condition.

In case of unacceptably frequent breakthrough bleeding events (BEs) (i.e. two or more BEs within a 30-day period or one major BE), the dose of *wilate* should be increased by approximately 5 IU/kg BW (depending on the vial size of the additional vial(s) that need(s) to be injected) and/or the treatment frequency can be increased.

wilate Dosage Recommendations for the Treatment of BEs:

Dose Type	Minor haemorrhage	Major haemorrhage
Loading dose	30–50 IU/kg BW	50–80 IU/kg BW
Maintenance dose	30–40 IU/kg BW every 12–24 hours	30–50 IU/kg BW every 12–24 hours
Therapeutic goal	Maintain VWF:Ac and FVIII:C trough levels >30%	Maintain VWF:Ac and FVIII:C trough levels >50%

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wilate Dosage Recommendations for Surgical Prophylaxis:

Dose type	Minor surgeries (including tooth extractions)	Major surgeries
Loading dose	40–60 IU/kg BW	60–80 IU/kg BW
Maintenance dose	20–30 IU/kg BW, or half the loading dose, every 12–24 hours for up to 3 days	30–40 IU/kg BW, or half the loading dose, every 12–24 hours for up to 6 days or longer
Therapeutic goal	Achieve VWF:Ac peak levels of 50% after loading dose and trough levels of >30% during maintenance doses	Achieve VWF:Ac peak level of 100% after loading dose and trough levels of >50% during maintenance doses

Duration of Treatment:

The planned prophylactic treatment duration per patient is 12 months (+2 weeks time-window).

The study will be considered clinically completed when all enrolled patients have completed the planned observation period (i.e. last visit of last patient).

Reference Therapy, Dose, Mode of Administration:

None.

Study Outcome Parameters (Primary and Secondary Endpoints):

Efficacy Parameters:

Primary Endpoint:

The primary endpoint of this study is to determine the total annualised bleeding rate (tABR) during prophylactic treatment with *wilate*.

Secondary Endpoints:

The secondary endpoints of this study are to determine:

- PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS) based on blood samples taken pre-dose (baseline), 15 minutes, 3, 9, 24, 48 and 72 hours after dosing of 80 IU/kg BW *wilate.*
- Incremental in-vivo recovery (IVR) of *wilate* for VWF:Ac (VWF:RCo) and FVIII:C (OS) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)

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- Efficacy of *wilate* in the prevention and treatment of spontaneous and traumatic breakthrough BEs based on their rate and the proportion of spontaneous and traumatic BEs successfully treated with *wilat*e as assessed by the use of a 4-point ordinal haemostatic efficacy scale (excellent – good – moderate – none), respectively
- The overall efficacy of *wilate* in perioperative prophylaxis against excessive bleeding as assessed at the end of the postoperative period by the responsible treating Investigator. A 4-point ordinal haemostatic efficacy scale (excellent – good – moderate – none) will be used
- *wilate* consumption data for prophylactic treatment, for on-demand treatment and during surgical prophylaxis

Safety Parameters:

Secondary Endpoints:

- Incidence of VWF and FVIII inhibitors
- Incidence of thromboembolic events
- Joint Health Status determination by the use of the HJHS, given the patient's age and constitutional development allow this assessment
- Safety and tolerability of *wilate* by monitoring adverse events (AEs) throughout the study

Exploratory Endpoint:

The exploratory endpoint of this study, which is solely investigated in the hereditary type 3 VWD patients with ≥14.5 kg body weight, is a VWF multimer analysis from the PK samples taken at 15 minutes, and 24 hours after *wilate* injection, by using multimer analysis using low- and high resolution electrophoresis gels.

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Study Procedures:

Patients will participate in the following visits:

Study Visits:

Visit 1: Screening Visit

At the Screening Visit, the following assessments will be performed:

- Obtain voluntarily given signed and dated informed consent
- Inclusion and exclusion criteria
- Collect demographic characteristics and medical history, incl. target joints
- Physical examination, collect vital signs and Haemophilia Joint Health Score (HJHS)
- Collect haematology blood samples for the local laboratory and blood samples for the central laboratory tests which include VWF:Ac (VWF:RCo), VWF and FVIII inhibitor testing and VWF multimer analysis, as well as the retention sample for possible virus testing
- During the Screening Visit, the patient's parents will receive a patient diary. The Investigator will explain how to fill in the diary and emphasise the importance of carefully documenting any BEs, treatment details, AEs, and concomitant medication.

Patients may continue treatment with their previous VWF-containing product for up to four weeks, awaiting confirmation of the VWD diagnosis from the central laboratory. The PK visit must be initiated within four weeks after the Screening Visit.

Visit 2: PK Visit

During the PK Visit, patients will receive *wilate* at a dose of 80 IU/kg BW after a washout period of at least 72 hours from the patient's previous administration of a VWF-containing product. The exact dose calculated according to the nominal potency should be administered, with 70–85 IU/kg BW as the acceptable range. Blood samples will be taken pre-dose (baseline), 15 minutes, 3, 9, 24, 48 and 72 hours after administration of *wilate*.

During the PK Visit the following assessments will be performed:

- Confirmation of inclusion and exclusion criteria
- Before injection: measure body weight
- Before injection and at 15 min (±5 min) after injection: vital signs

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- Within 60 min before and 15 min (±5 min), 3 (±1 hour) and 9, 24, 48, and 72 hours (each ±2 hours) after injection: PK blood samples – VWF:Ac (VWF:RCo), FVIII:C (OS)
- At 15 min (±5 min) and 24 hours (±2 hours) after injection: VWF multimer analysis in type 3 VWD patients with ≥14.5 kg body weight
- During the visit: patient diary review, bleeding episodes monitoring, AE monitoring, concomitant medication

Patients must not be experiencing acute bleeding during the course of the PK visit.

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

The patient's parents will be trained in how to correctly prepare and administer *wilate*, which will be re-supplied whenever necessary during the study. The Investigator will discuss *wilate* dose and frequency of administration with the patients' parents, both for regular prophylaxis and for treatment of BEs.

The first prophylactic dose will be administered after completion of the PK Assessment, i.e. after the 72-hour sample has been collected), and should be administered at the study site before patients return to home treatment. Where applicable, external home-care companies with experience in conducting clinical studies will be contracted, with trained nurses supporting patients' parents by providing training, re-training, and oversight through home-care visit support throughout the study.

Visit 3: 1-Month IVR Visit

The 1-Month IVR Visit will take place 1 month (±3 days) after the first prophylactic injection of *wilate* has been received. The following assessments will be performed:

- Before injection: measure body weight
- Within 60 min before and 15 min after (±5 min) injection: IVR blood sampling (VWF:Ac [VWF:RCo] and FVIII:C [OS]) and vital signs
- During the visit: patient diary review, review of compliance, bleeding episodes monitoring, AE monitoring, concomitant medication, AB0 blood group testing (if unknown, can also be shifted to a later timepoint)

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Visit 4: 2-Month IVR Visit

The 2-Month IVR Visit will take place 2 months (±3 days) after the first prophylactic injection of *wilate* has been received. The following assessments will be performed:

- Before injection: measure body weight
- Within 60 min before and 15 min after (±5 min) injection: IVR blood sampling (VWF:Ac [VWF:RCo] and FVIII:C [OS]) and vital signs
- During the visit: patient diary review, review of compliance, bleeding episodes monitoring, AE monitoring, concomitant medication

Visits 5–7: 3-Monthly IVR Visits

The 3-Monthly IVR Visits will take place after 3 (±1 week), 6 (±2 weeks), and 9 months (±2 weeks) after the first prophylactic injection of *wilate* has been received. The following assessments will be performed:

- Before injection: measure body weight, blood sampling for VWF and FVIII inhibitor testing
- Within 60 min before and 15 min after (±5 min) injection: IVR blood sampling (VWF:Ac [VWF:RCo] and FVIII:C [OS]) and vital signs
- During the visit: patient diary review, review of compliance, bleeding episodes monitoring, AE monitoring, concomitant medication

Visit 8: Study Completion (12-Month) Visit

The Study Completion Visit will take place 12 months (+2 weeks) after the first prophylactic injection of *wilate.* The following assessments will be performed:

- Before injection: measure body weight, blood sampling for VWF and FVIII inhibitor testing, and for haematology parameters at local laboratory.
- Within 60 min before and 15 min after (±5 min) injection: IVR blood sampling (VWF:Ac [VWF:RCo] and FVIII:C [OS]) and vital signs
- During the visit: patient diary review, review of compliance, HJHS, physical examination, bleeding episodes monitoring, AE monitoring, concomitant medication, target joints.

Compliance calls

Parents should be contacted by telephone every 5–7 weeks after the 3-monthly IVR visits at 3, 6, and 9 months. The compliance calls will check the following:

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- Patient's overall condition and wellbeing
- Adherence to the treatment regimen (dose and frequency)
- Bleeding episodes and their treatment
- Requirement of any prophylactic treatment adjustment
- Adverse events
- Concomitant medication
- Answer parents' questions or concerns, if any

Unscheduled Visits and Additional Measures

If an inhibitor development is suspected (e.g. based on an unexplained need to increase the dose, a lack of efficacy of *wilate* injections seen in more frequent spontaneous bleeds, or prolonged bleeding), VWF and FVIII inhibitor tests will be performed at the central laboratory. In case of positive inhibitor results, inhibitor re-testing 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.

Statistical Analysis Plan:

No formal sample size calculation was performed for the study. The sample size of up to 12 patients, including at least four patients with type 3 VWD, is based on a communication with the FDA and on EU guideline CPMP/BPWG/220/02 calling for a trial in at least eight children with VWD under the age of 6 years, three of whom should have type 3 VWD and was selected to accommodate for drop-outs.

The tABR will be evaluated over all types of VWD. The frequency and severity of BEs and the total, traumatic and spontaneous ABR will be calculated from patients' dosing and treatment frequency in different VWD types.

The haemostatic efficacy of *wilate* in the treatment of BEs will be assessed, and a frequency distribution of all successfully treated BEs will be presented overall and by severity, along with an exploratory 95% confidence interval (CI). Statistical analyses of other secondary endpoints will be descriptive, including exploratory 95% CIs.

The PK and recovery assessments will be summarised using descriptive statistics and the presentation of concentration vs. time plots. The results of IVR assessments over time will be

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presented per time point and as differences to baseline, along with 95% CIs for the mean differences.

Safety analysis will be based on the occurrence of AEs, e.g. results of immunogenicity screening, thrombogenicity monitoring for sustained excessive FVIII plasma levels (and an increased risk of thrombotic events), and safety laboratory testing. 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.

FLOW CHART FOR PK ASSESSMENT AND PROPHYLACTIC TREATMENT

Table 1 Flow Chart of Assessments Performed Throughout the Study

ASSESSMENTS	Screening Visit	PK Visit (within 4 weeks after Screening)	1-Month Visit (±3 days)	2-Month Visit (±3 days)	3-Month Visit (±1 week)	Compliance Call 1 [1] (5–7 weeks after 3-Month Visit)	6-Month Visit (±2 weeks)	Compliance Call 2 [1] (5–7 weeks after 6-Month Visit)	9-Month Visit (±2 weeks)	Compliance Call 3 [1] (5–7 weeks after 9-Month Visit)	Study Completion (12-Month) Visit (+2 weeks)
Informed consent	X										
Eligibility criteria	X	X									
Demographics	X										
Body weight	X	X	X	X	X		X		X		X
Height	X										
Medical history and prior medication	X										
Family history of VWD	X										
Vital signs (blood pressure, heart rate, body temperature, respiratory rate) [2]	X	X	X	X	X		X		X		X
Physical examination	X										X
Injections at study site											
PK injection (80 IU/kg BW) [10]		X									
IVR injection			X	X	X		X		X		X
Start of prophylactic treatment phase [8]		X									
Local laboratory assessments											
Routine safety laboratory (haematology)	X										X [3]
Determination of AB0 blood group			X [4]								
Central laboratory assessments											
VWF:Ac (VWF:RCo)	X	X [6]	X [2]	X [2]	X [2]		X [2]		X [2]		X [2]
FVIII:C (OS)		X [6]	X [2]	X [2]	X [2]		X [2]		X [2]		X [2]
VWF and FVIII inhibitors [5]	X				X [3]		X [3]		X [3]		X [3]
Retention samples for virus marker testing	X										
VWF multimer analysis	X	X [7]									
Haemophilia Joint Health Score (HJHS) [9]	X										X
Assessment of compliance and adherence to treatment regimen		X	X	X	X	X	X	X	X	X	X

ASSESSMENTS	Screening Visit	PK Visit (within 4 weeks after Screening)	1-Month Visit (±3 days)	2-Month Visit (±3 days)	3-Month Visit (±1 week)	Compliance Call 1 [1] (5–7 weeks after 3-Month Visit)	6-Month Visit (±2 weeks)	Compliance Call 2 [1] (5–7 weeks after 6-Month Visit)	9-Month Visit (±2 weeks)	Compliance Call 3 [1] (5–7 weeks after 9-Month Visit)	Study Completion (12-Month) Visit (+2 weeks)
Bleeding Episodes monitoring	Throughout the study										
Concomitant Medication monitoring	Throughout the study										
Adverse event monitoring	Throughout the study										

VWD = von Willebrand disease, FVIII = factor VIII, FVIII:C = factor VIII procoagulant activity, OS = one-stage assay

[1] Parents should be contacted by telephone 5–7 weeks after the 3-monthly IVR visits at 3, 6, and 9 months.to check the patient's status of bleedings, AEs, concomitant medications, compliance and adherence with treatment regimen, including the evaluation of the need to adjust the prophylactic treatment, completing diary.

[2] Within 60 min before and 15 ±5 min after *wilate* injection.

[3] Before injection.

[4] To be determined unless known.

[5] At the given time-points and at any time if inhibitor development is suspected.

[6] Blood samples for PK and recovery assessment to be taken before injection, and after 15 minutes, 3, 9, 24, 48 and 72 hours after injection (central laboratory). At least three different *wilate* batches should be used.

[7] Multimer analysis will be performed in all patients at Screening. At the PK Visit, the VWF multimer analysis will only be performed in type 3 VWD patients with ≥14.5 kg body weight: the samples taken at 15 minutes, and 24 hours after the injection will be used to investigate the VWF multimer distribution of the VWF by multimeric sizing analysis using low- and high resolution electrophoreses gels.

[8] Start of prophylactic treatment phase: first IMP injection after collection of the last PK sample (i.e. the 72-hour sample), which is administered at the study site before patients return to home treatment

[9] Given the patient's age and constitutional development allow this assessment.

[10] The exact dose calculated according to the nominal potency should be administered, with 70– 85 IU/kg BW as the acceptable range.

PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

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

[redacted] [redacted] 14.12.2022

Signature Date

[redacted]

Octapharma AG
Seidenstrasse 2
8853 Lachen, Switzerland

Signature of the Author of the Protocol/Clinical Project Manager

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

[redacted]

05-DEC-2022

Date

[redacted]

Octapharma Pharmazeutika Produtionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Signature of the Study Medical Expert

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

[redacted]

15-DEC-2022

Signature Date

[redacted]

Octapharma AG
Seidenstrasse 2
8853 Lachen, Switzerland

Signature of the Biostatistician

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

[redacted] [redacted] 2022-12-15

[redacted] Signature Date

Ergomed CDS
Im Mediapark 2
D-50670 Cologne, Germany

Signature of the Coordinating Investigator

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

[redacted]

12/6/2022

Signature Date

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San Bernandino
CA 92408, United States

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABR	Annualised Bleeding Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
Ag	Antigen
BE	Bleeding Episode
BW	Body Weight
CI	Confidence Interval
CRF	Clinical Report Form
CRO	Contract Research Organisation
DDAVP	Desmopressin (1-deamino-8-D-arginine vasopressin)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
FAS	Full Analysis Set
FVIII	Factor VIII
FVIII:C	Factor VIII procoagulant activity
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HJHS	Haemophilia Joint Health Score
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
PP	Per Protocol
RBC	Red Blood Count
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SURG	Surgery (Population)
TABR	Total Annualised Bleeding Rate
TEAE	Treatment-Emergent Adverse Event
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
VWF:Ac	Von Willebrand Factor Activity
VWF:RCo	Von Willebrand ristocetin cofactor activity
WBC	White blood cell count

1 INTRODUCTION

Von Willebrand Disease

Inherited von Willebrand disease (VWD) is the most common inherited haemorrhagic disorder, and many cases are diagnosed in childhood, with an estimated prevalence of 1 in every 100 individuals of either sex [1]. 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. 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. Von Willebrand disease 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]. Clinical symptoms of VWD include predominantly mild mucosal bleeding; surgical bleeding may occur with specific challenges and joint bleeding can occur in the most severe forms [3].

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), this approach 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. Immediate potential complications of DDAVP include flushing, hypotension/hypertension, gastrointestinal upset, and headache. Repeated dosing of this antidiuretic-hormone mimicking drug can lead to hyponatremia and seizures [3]. Although some responses have been seen in other type 2 patients, they are usually either too small or not sufficiently sustained to be effective. DDAVP is not effective in type 3 patients and is usually contraindicated in type 2B patients because it may promote thrombocytopenia, although it has been effective in selected type 2B patients [4]. DDAVP is not recommended for patients under the age of 2 due to poor response [5].

The appropriate treatments for 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 viral-attenuated concentrates [6].

wilate

wilate is a plasma-derived, stable, highly purified, double virus inactivated concentrate of freeze-dried active VWF and FVIII prepared from cryoprecipitate 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, 16 prospective clinical studies with *wilate* have been completed, eight in patients with VWD and eight in patients with haemophilia A. A summary of findings from nonclinical and clinical studies with *wilate*, including in paediatric patients, is provided in the product's Investigator's Brochure (IB) [7].

wilate received its first marketing authorisation in Germany in February 2005; to date, *wilate* has been licensed in 72 countries worldwide.

1.1 Rationale for Conducting the Study

The purpose of this study is to obtain additional data on the efficacy, PK, immunogenicity, and safety of *wilate* in paediatric patients below the age of 6 years with severe VWD undergoing regular prophylaxis, thus supplementing the existing body of data to obtain approval of *wilate* in the prophylactic treatment of severe VWD in this patient population. Other studies have demonstrated a beneficial effect of prophylaxis with VWF treatment in patients with severe VWD, including paediatric patients. These reported reduced mucosal and joint bleeding rates, decreased median ABR, a reduced incidence of major bleeds, and good tolerability:

- Treatment of mucosal bleeding (epistaxis and gastrointestinal bleeding) and joint bleeding remains problematic in clinically severe VWD. Patients are often unresponsive to treatment (e.g. desmopressin or antifibrinolytic therapy) and may require VWF replacement therapy. A prospective, treatment escalation design study evaluated the effect of escalating dose prophylaxis in 11 patients with severe VWD (median age 34.6 years). Use of prophylaxis with VWF concentrates reduced mucosal and joint bleeding rates. The median ABR decreased from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7) [8].
- A recent phase 3, multi-centre, open-label trial included 17 previously treated children <12 years old with severe type 1, 2A, or 3 VWD (VWF:RCo <20% at screening or a documented history of VWF:RCo <10%), for whom DDAVP treatment had been ineffective, contraindicated, or unavailable. Participants received on-demand treatment of nonsurgical bleeds, were undergoing a surgical procedure, or were treated on a predefined prophylactic regimen with a plasma-derived VWF/FVIII concentrate. The duration of study participation ranged from 12 to 13 months. Pharmacokinetic parameters for VWF markers were generally comparable to adults but showed lower VWF:RCo exposure, as indicated by a lower incremental recovery, shorter half-life, and faster clearence. Incidence of major bleeds was lower for prophylaxis (3.3%) than on-demand therapy (27.1%); joint bleeds were also lower (3.3% vs 11.5%, respectively). Investigator-reported excellent/good haemostatic efficacy against nonsurgical bleeds was 100%. No clinically relevant differences in PK, haemostatic efficacy, or safety were observed between age groups (<6 years and 6 to <12 years). The treatment was well tolerated. Adverse events were mild to moderate and consistent with the adult safety profile. No cases of anaphylactic reactions or angioedema, development of FVIII/VWF inhibitors, thromboembolic events, or viral infections were reported [9].
- A study found that 23% (184/804) of VWD patients self-reported joint bleeds. These 184 patients reported joint damage more often (54% vs. 18%, $p<0.001$) and had lower health-related QoL (SF-36, $p<0.05$) compared to VWD patients not reporting joint bleeds. Of 55 patients with available joint bleed data, 65% had the first joint bleed in childhood. These 55 patients used more clotting factor concentrate ($p<0.001$), more often had X-ray joint damage (44% vs. 11%, $p=0.001$] and chronic joint pain (44% vs. 18%, $p=0.008$) compared to 55 control VWD patients without joint bleeds [10]. Therefore, it was considered valuable to measure the HJHS score in the enrolled paediatric patients, because although the HJHS score has been validated in adult patients [11], there are no validated tools to determine QoL or disease-specific tools to assess the musculoskeletal status in paediatric patients with severe VWD.

Since there are insufficient data on use of *wilate* in paediatric patients with severe VWD below the age of 6 years, Octapharma plans to evaluate the efficacy of *wilate* in bleeding prophylaxis in these patients.

1.2 Dose Rationale

Doses of *wilate* vary based on the indication. The doses for prophylaxis (30–50 IU/kg BW administered 2–3 times per week), the treatment of BEs, and perioperative prophylaxis are detailed in Section 5.2. Because there are currently insufficient data to recommend the use of *wilate* in children under 6 years of age, the dose rationale was based on recommended doses in adults and children over 6 years of age [12, 13], with some adjustments allowing for the fact that, contrary to adults, 1 IU/kg BW VWF:Ac and FVIII:C may not raise the plasma level by as much as 1.5–2% of normal activity for the respective proteins in children below the age of 6 years.

1.3 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* [7]:

- **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:Ac 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 also applies to pathogens of hitherto unknown origin. The manufacturing process of *wilate*, which includes two 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, including paediatric patients.

1.4 COVID-19 Benefit-Risk Statement

For the WIL-33 study, patients and their parents are required to come into the treatment centre for 8 visits over a period of approximately 12 months in order to participate in the study. There is therefore a risk that the parents may become exposed to COVID-19 and potentially even infected. The standard safety measures will be in place at the treatment centres in line with the local requirements.

Potential COVID-19 related risks for site management and project management will be evaluated in advance and options such as alternative monitoring approaches will be implemented. In addition, for the support of the study processes (e.g. provision of the study medication and transport of the blood samples), only well-established service providers are selected which have strong regional expertise and strict risk and quality guidelines in place, including with regards to potential COVID-19-related risks. The current regulations regarding transport and logistics will be continuously monitored for the countries participating in the study, and flexible solutions and longer lead times will be implemented wherever appropriate. In order to address the risk of delays in study visits, exceeding the permitted time windows for visits on grounds of COVID-19-infection on the part of patients/parents or study staff at the sites is excluded from classification as major protocol deviation in all cases. Also, the number of patients as required by the EU guideline CPMP/BPWG/2220/02 [15], which requires at least 8 patients with severe VWD under the age of 6 years, has been increased by 150% to 12 patients, not least to counteract possible COVID-19-related drop-outs.

The potential impact of COVID-19 on the patients, the patient's parents and the study performance was weighed up against the negative impact of not doing the study, i.e. that *wilate* treatment will not be adequately assessed for use in paediatric patients. Overall, the benefit-risk evaluation of *wilate* and of performing this study is positive.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to determine the efficacy of *wilate* in the prophylactic treatment of up to 12 paediatric patients (eight evaluable) with severe VWD (defined as screening von Willebrand factor ristocetin cofactor activity [VWF:RCo] <20%) under the age of 6 years, for a period of 12 months.

2.2 Secondary Objective(s)

The secondary objectives of this study are to:

- Determine the pharmacokinetics (PK) of *wilate* for VWF:Ac (VWF:RCo) and FVIII:C (one-stage [OS])
- Determine incremental in-vivo recovery (IVR) of *wilate* over time
- Evaluate the rate of traumatic and spontaneous breakthrough bleeds under prophylactic treatment, including the corresponding treatment efficacy
- Assess the treatment response in minor and major bleeds and surgeries
- Determine *wilate* consumption data for prophylactic treatment, on-demand treatment, and surgeries
- Investigate the immunogenic potential of *wilate* by screening for VWF and FVIII inhibitors
- Investigate the thrombogenic potential of *wilate*
- Assess the patients' joint status with the Haemophilia Joint Health Score (HJHS)
- Assess the safety and tolerability of *wilate*

2.3 Exploratory Objective(s)

The exploratory objective of this study is to investigate the VWF multimer composition in the hereditary type 3 VWD paediatric patient group.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary endpoint of this study is to determine the total annualised bleeding rate (tABR) during prophylactic treatment with *wilate.*

3.1.2 Secondary Endpoints

The secondary endpoints of this study are to determine:

- PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS) based on blood samples taken pre-dose (baseline), 15 minutes, 3, 9, 24, 48 and 72 hours after dosing of 80 IU/kg BW *wilate*
- Incremental in-vivo recovery (IVR) of *wilate* for VWF:Ac (VWF:RCo) and FVIII:C (OS) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- Efficacy of *wilate* in the prevention and treatment of spontaneous and traumatic breakthrough BEs based on on their rate the proportion of spontaneous and traumatic BEs successfully treated with *wilat*e as assessed by the use of a 4-point ordinal haemostatic efficacy scale (excellent – good – moderate – none), respectively
- The overall efficacy of *wilate* in perioperative prophylaxis against excessive bleeding as assessed at the end of the postoperative period by the responsible treating Investigator. A 4-point ordinal haemostatic efficacy scale (excellent – good – moderate – none) will be used
- *wilate* consumption data for prophylactic treatment, for on-demand treatment and during surgical prophylaxis

3.1.3 Safety Parameters

Secondary Endpoints

- Incidence of VWF and FVIII inhibitors
- Incidence of thromboembolic events
- Joint Health Status determination by the use of the HJHS, given the patient's age and constitutional development allow this assessment
- Safety and tolerability of *wilate* assessed by monitoring AEs throughout the study

3.1.4 Exploratory Endpoint

The exploratory endpoint of this study, which is solely investigated in the hereditary type 3 VWD patient group with ≥14.5 kg body weight, is a VWF multimer analysis from the PK samples taken at 15 minutes, and 24 hours after *wilate* injection, by using multimer analysis using low- and high resolution electrophoresis gels.

3.2 Overall Study Design and Plan

This is an open, prospective, non-controlled, international, multi-centre phase 3 study investigating the efficacy, pharmacokinetics, immunogenicity, and safety of *wilate* in paediatric

patients below the age of 6 years at the time of screening with severe VWD (defined as VWF:RCo <20%, regardless of prior treatment) undergoing regular prophylaxis. The study is estimated to start in Q3 2021 and to be completed by Q2 2024 resulting in an overall duration of 2 years and 6 months.

"Regardless of prior treatment" in this context means that both subjects previously treated with VWF/FVIII-containing products (either on-demand treatment or regular prophylactic treatment) and previously untreated patients (PUPs) can be included in the study.

Overall, 12 patients (eight evaluable) will be enrolled by up to 15 sites worldwide. At least four of these patients should be suffering from hereditary type 3 VWD. The remaining patients can be diagnosed with severe type 2 (except 2N) or severe type 1 VWD.

Of the 12 patients, at least eight patients should be evaluable for the primary endpoint.

The planned prophylactic treatment duration per patient is 12 months.

Patients will participate in the following visits: Screening Visit, PK Visit, 1-Month, 2-Month, 3-Month, 6-Month, and 9-Month Visits, and a Study Completion (12-Month) Visit. Moreover, "Compliance Calls" will be performed every 5–7 weeks after the 3-monthly IVR visits at 3, 6, and 9 months (detailed in **Section 6.1** and in the flow chart of assessments by study visit [**Table 1**]).

The start of the prophylactic treatment phase is defined as the first IMP injection after collection of the last PK sample (i.e. the 72-hour sample), which is administered at the study site before patients return to home treatment. Parents will receive product for home treatment and will be instructed on proper storage and administration. Involvement of a physician or a study nurse will be documented.

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

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

This open-label, prospective, non-controlled, international, multi-centre phase 3 study is designed to evaluate the efficacy of *wilate* in bleeding prophylaxis in paediatric patients below 6 years of age with severe VWD.

There is currently no data available on the tABR of patients <6 years of age with VWD undergoing regular prophylaxis. Description of the effect of prophylaxis on the tABR of patients with inherited coagulation disorders has been used as an efficacy endpoint to evaluate the clinical benefit of this intervention.

3.3.2 Control Group(s)

Not applicable.

3.3.3 Study Parameters

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

1. wilate Consumption Data

- Dates and times of *wilate* injections
- Doses of *wilate* in IU and *wilate* batch numbers. IU/kg BW per injection, per month, and per year will be calculated.
- Purpose of *wilate* injection (PK/incremental in vivo recovery [IVR], prophylaxis, prophylaxis to avoid re-bleeding, treatment of BE, surgical prophylaxis)

2. Assessment of Adherence with the Treatment Regimen

Adherence with the treatment regimen will be assessed throughout the study. Any change of the prophylactic dose as determined by the responsible treating Investigator during the PK Visit will be documented in the patient records and electronic Case Report Form (eCRF), including start and end dates of each dose and the reason for dose change.

3. Efficacy Assessment in Treatment of BEs

Details of each (treated and not treated) BE will be recorded:

- BE type (spontaneous, traumatic, postoperative, other)
- BE location
- BE severity (minor or major) (Table 2**)**
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended
- *wilate* administration data, if applicable
- Assessment of the efficacy of treatment at the end of the BE, if applicable

All parameters will be documented in a patient diary by the patient's parent(s)/legal guardian(s) (hereafter referred to as "parents"), or in the case of on-site treatments with the responsible treating Investigator, and in the case of use of a home-care service together with the nurse.

Table 2 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).

Bleeding severity	Description
Major	Generally requires hospitalisation; 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, 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.

The amount of *wilate* needed and the number of injections necessary to stop the bleed will be documented. The required IU/kg BW per bleeding event will be calculated.

Efficacy of *wilate* will be assessed for all treated BEs, using a 4-point objective haemostatic efficacy scale (i.e. excellent – good – moderate – none) detailed in **Table 3**. In case of minor bleeds treated at home, the assessment should be made by the patients' parents. Major BEs should preferably be treated at the study site. An efficacy assessment will be made by the responsible treating Investigator after the end of the bleeding event, based on the 4-point objective haemostatic efficacy scale.

Table 3 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

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

The proportion of BEs successfully treated with *wilate* will be evaluated for all BEs in total and further differentiated by BE severity. All efficacy ratings assessed as either "excellent" or "good" according to the 4-point objective haemostatic efficacy scale will be considered successfully treated.

4. Efficacy Assessment in Perioperative Prophylaxis

The following surgery-related parameters will be documented for major surgeries (parameters marked with * are obligatory also for minor surgeries, while the unmarked parameters can be collected for minor surgeries depending on availability).

- 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 *wilate* administration data*
- Pre-, intra-, and postoperative VWF:Ac (VWF:RCo) and FVIII plasma levels
- Routine safety laboratory
- Presence of wound haematomas
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Details on concomitantly administered medications (except standard anaesthetics)*
- Blood transfusion requirements
- Brief narrative describing the outcome of the intervention*
- Overall efficacy assessment at the end of the postoperative period by the responsible treating Investigator. Predefined assessment criteria will be used*
- Monitoring of AEs*

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)
- 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**.

4 STUDY POPULATION

4.1 Population Base

Overall, 12 patients (eight evaluable) with VWD under the age of 6 years suffering from severe VWD defined as screening VWF:RCo <20%, regardless of prior treatment will be enrolled into this study. At least four of these patients should be suffering from hereditary type 3 VWD. The remaining patients can be diagnosed with severe type 2 (except 2N) or severe type 1 VWD.

"Regardless of prior treatment" in this context means that both subjects previously treated with VWF/FVIII-containing products (either on-demand treatment or regular prophylactic treatment) and previously untreated patients (PUPs) can be included in the study.

4.1.1 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. Type 3 (at least four patients), severe type 2 (except 2N) or severe type 1 VWD (any of which with VWF:RCo <20%) according to medical history, requiring substitution therapy with a VWF-containing product
3. Minimum body weight 12.5 kg at the time of screening
4. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted (obtained from the patient's parent(s)/legal guardian(s)

4.1.2 Exclusion Criteria

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

1. History, or current suspicion of VWF or FVIII inhibitors
2. Injection of DDAVP or VWF-containing product within 72 hours prior to inclusion
3. Medical history of a thromboembolic event
4. Platelet count <100,000/µL at screening (except for VWD type 2B)
5. Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar drugs
6. Treatment with any IMP in another interventional clinical study currently or within four weeks before enrolment
7. Other coagulation disorders or bleeding disorders
8. Known hypersensitivity to any of the components of the study drug

4.2 Prior and Concomitant Therapy

4.2.1 Permitted Concomitant Therapy

Vaccination against hepatitis A and B (or the presence of antibodies resulting from a previous infection, or other evidence of immunisation) is strongly recommended before repeated treatment with a VWF/FVIII concentrate such as *wilate*.

Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar drugs may not be enrolled.

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

4.2.2 Forbidden Concomitant Therapy

No VWF/FVIII concentrates other than *wilate* must be administered (except for emergency situations). Patients permanently switching to other VWF/FVIIII products 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: in the case of an accident causing a bleeding that requires treatment with VWF concentrate but without access to the IMP, a different concentrate may be used instead)
- the IMP was not available for the patient in time (example: patient experiences a severe bleed but parents do not have enough product available).

4.3 Withdrawal and Replacement of Subjects/Patients

4.3.1 Premature Subject/Patient Withdrawal

Parents have the right to withdraw their children from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw subjects/patients in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study noninterpretable, any unnecessary withdrawal of subjects/patients should be avoided.

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 Subject/Patient Replacement Policy

Patients withdrawn from the study for safety reasons will not be replaced.

4.4 Assignment of Subjects/Patients to Treatment Groups

The Investigator will enter a unique identifier (consisting of the study code (SC), centre code (CC), and patient number (PN), in the format "SC-CC-PN") of each patient in both the CRF and the confidential patient identification list. The Investigator will inform the monitor of new patients enrolled.

Under no circumstances are patients who enrol in the study permitted to re-enrol.

4.5 Relevant Protocol Deviations

Deviations from the protocol should be avoided at all times throughout the study. If deviations occur, the Investigator should promptly inform the monitor, and the implication of the deviation must be assessed and discussed. Any deviation must be documented, stating the reason and date and the action taken. The documentation must be kept in the Investigator's study file and the Sponsor's study master file. A complete list of all critical, major and minor deviations will be compiled and regularly updated by the Project Manager and provided for preparation of the Clinical Study Report (CSR).

All cases where the time windows for visits to the study centres are exceeded due to COVID-19-related illness on the part of patients/parents or study staff will be defined as a minor deviation.

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

Examples of critical/major protocol deviations are:

- Patients who entered the study even though they did not satisfy the eligibility criteria.
- Patients who received the wrong treatment or incorrect dose (also see **Section 5.4**).
- Patients with substantial deviations from the prophylactic treatment regimen.
- Patients who received forbidden concomitant medication.

4.6 Subsequent Therapy

All patients who leave the study – be it prematurely or per protocol (PP) – will continue VWD treatment as per the discretion of the responsible treating Investigator.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterisation of Investigational Product(s)

The VWF/FVIII 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. 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 of the IMP 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.

As an accepted exception to the storage conditions, the product can be stored at room temperature (max. +25°C or 77°F) for a maximum of 2 months.

After reaching room temperature, however, no return to refrigerated conditions is permitted.

2 months after the product is taken out of the refrigerator for the first time it must not be used any more and must be destroyed following local rules.

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

For the PK Assessment, a single dose of 80 IU/kg BW will be administered, based on the weight measured at the beginning of the visit. The exact dose calculated according to the nominal potency should be administered, with 70–85 IU/kg BW as the acceptable range. The injection or infusion rate should not exceed 2–3 mL per minute. At least three different *wilate* batches will be used.

As regards determining incremental in-vivo recovery over time, a single dose of *wilate* is administered at the dose of regular prophylactic treatment.

5.4.2 *wilate* Dosage for Prophylactic Treatment

For prophylactic treatment, *wilate* should be administered 2–3 times per week at a recommended dose of 30–50 IU/kg BW over 12 months. The prophylactic dose and frequency

for each patient will be determined by the responsible treating Investigator, based on the individual patient's clinical condition.

After each body weight measurement during the study, dose adjustments based on the patient's actual weight should be considered.

The first prophylactic dose will be administered after completion of the PK Assessment, i.e. after the 72-hour sample has been collected), and should be administered at the study site before patients return to home treatment. The same venipuncture as that used to collect the sample can be used for administration (taking into account prior rinsing with NaCl).

It is recommended to aim for a dose that supports the administration of full vials of *wilate* during home treatment. However, the administration of partial vials is permitted if clinically indicated, as long as the recommended dose range is respected. Such cases must be carefully discussed and explained in detail with the patients' parents and must be accurately documented in the patient's diary and in the eCRF. Parents should be trained in the administration of partial vials and their return after use.

In case of unacceptably frequent breakthrough BEs (i.e. two or more BEs within a 30-day period or one major BE), the dose of *wilate* should be increased by approximately 5 IU/kg BW (depending on the vial size of the additional vial(s) that need(s) to be injected) and/or the treatment frequency can be increased. This rule applies irrespective of whether one or more bleeding sites are affected, and for BEs that occur on the same day.

5.4.3 *wilate* Dose for the Treatment of Bleeding Episodes (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 and FVIII:C raises the plasma level by 1.5–2% of normal activity for the respective protein, but this increase may be lower in children below the age of 6 years. Usually, about 20–50 IU/kg BW *wilate* are necessary to achieve adequate haemostasis. This will raise the VWF:Ac and FVIII:C in the patients by approximately 30–100% [12].

Recommendations for the dosing in the treatment of BEs in paediatric patients under 6 years of age has been adapted from the US Package Insert [13] and is shown in **Table 4**.

Table 4 *wilate* Dosage Recommendations for the Treatment of BEs

Dose Type	Minor haemorrhage	Major haemorrhage
Loading dose	30–50 IU/kg BW	50–80 IU/kg BW
Maintenance dose	30–40 IU/kg BW every 12–24 hours	30–50 IU/kg BW every 12–24 hours
Therapeutic goal	Maintain VWF:Ac and FVIII:C trough levels >30%	Maintain VWF:Ac and FVIII:C trough levels >50%

After the initial treatment phase of a BE, any further treatment to avoid re-bleeding is to be documented as "prophylactic treatment to avoid re-bleeding" until the transition to the regular prophylactic treatment schedule.

5.4.4 *wilate* Dose for Surgical Prophylaxis

For prevention of bleeding in case of surgery, VWF:Ac peak levels of 50% should be achieved for minor surgeries and VWF:Ac peak level of 100% should be achieved for major surgeries.

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, VWF:Ac 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. Accordingly, FVIII activity levels should not exceed 200%.

Recommendations for the dosing in in surgical prophylaxis in paediatric patients under 6 years of age has been adapted from the US Package Insert [13] and is shown in **Table 5**.

Table 5 *wilate* Dosage Recommendations for Surgical Prophylaxis

Dose type	Minor surgeries (including tooth extractions)	Major surgeries
Loading dose	40–60 IU/kg BW	60–80 IU/kg BW
Maintenance dose	20–30 IU/kg BW, or half the loading dose, every 12–24 hours for up to 3 days	30–40 IU/kg BW, or half the loading dose, every 12–24 hours for up to 6 days or longer
Therapeutic goal	Achieve VWF:Ac peak levels of 50% after loading dose and trough levels of >30% during maintenance doses	Achieve VWF:Ac 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 [12].

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 *wilate* provided to the site will be accounted for. This includes *wilate* received at the site, *wilate* dispensed to patients, and *wilate* returned used or unused by the patient's parents.

Supplies and re-supplies of *wilate* for home treatment of patients are carefully calculated and should suffice for the next home treatment period, before the patients return to the study site for their next visit. The agreed number of vials will be handed out to the patient's parents, who

will be advised that all used, partially used and expired vials must be returned on the next visit. During the completion visit, all unused vials must also be returned to the study centre for accountability of the IMP.

A Drug Inventory and Dispensing Log will be kept current by the Investigator, detailing the dates and quantities of *wilate* 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.

Used and partially used vials which were either kept at site or returned by patients' parents need to be verified and counted by the study monitor who will in turn approve their destruction after completion of the accountability process.

Unused *wilate* should be destroyed at the study site in accordance with local regulations. If this is not possible, arrangements shall be made to return them to the Sponsor for destruction. Destruction of unused vials can be initiated only after accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written permission for destruction.

5.7.2 Assessment of Treatment Compliance

For all IVR and PK Assessments, *wilate* will be administered at the study site, with compliance under the control of the treating Investigator.

Adherence with the treatment regimen will be assessed throughout the study. Any change of the prophylactic dose as determined by the responsible treating Investigator during the Baseline Visit will be documented in the patient records and eCRF, including start and end dates of each dose and the reason for dose change.

Parents should be conducted by telephone every 5–7 weeks after the start of the prophylactic treatment phase, and every 5–7 weeks after the 3-monthly IVR visits at 3, 6, and 9 months.

6 STUDY CONDUCT

The flow chart of assessments by study visit is given in **Table 1**. Details on the individual assessments and methods are provided in **Section 7.**

6.1 Observations by Visit

All enrolled patients will participate in the following study visits:

- Screening Visit (Visit 1)
- PK Visit (Visit 2)
- 1-Month Visit (Visit 3)
- 2-Month Visit (Visit 4)
- 3-Month Visit (Visit 5)
- 6-Month Visit (Visit 6)
- 9-Month Visit (Visit 7)
- Study Completion (12-Month) Visit (Visit 8)
- "Compliance Calls" will be performed every 5–7 weeks after the 3-monthly IVR visits at 3, 6, and 9 months.

Parents will receive product for home treatment and will be instructed on proper storage and administration. Involvement of a physician or a study nurse will be documented.

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

6.1.1 Screening Visit (Visit 1)

The following assessments will be performed during the Screening Visit, which should take place within 4 weeks before the first administration of IMP:

- Obtaining voluntarily given, written (signed and dated) informed consent
- Inclusion and exclusion criteria
- Demographic and baseline characteristics
- Medical history and prior medication, including VWD type (including e.g. historical values of VWF:Ac (VWF:RCo), VWF:Ag, multimer analyses, FVIII-binding tests), prior VWD specific treatment, and family history of VWD
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Physical examination
- Blood samples
    - Routine safety laboratory [local laboratory]
    - VWF:Ac (VWF:RCo) [central laboratory]
    - VWF and FVIII inhibitor testing [central laboratory]
    - VWF multimer analysis [central laboratory]
    - Retention samples for possible virus marker testing [central laboratory]

- Assess the patients' joint status using the Haemophilia Joint Health Score (HJHS) and any target joints (defined as three or more sponatenouos BEs in a single joint within six consecutive months preceding the Screening Visit).
- Documentation of concomitant medication

During the Screening Visit, the patients' parents will receive a patient diary. The Investigator will explain how to fill in the diary and emphasise the importance of carefully documenting any BEs, treatment details, AEs, and concomitant medication.

Patients may continue treatment with their previous VWF-containing product for up to four weeks, awaiting confirmation of the VWD diagnosis from the central laboratory.

The PK visit must be initiated within four weeks after the Screening Visit.

Any treatment with previously used VWF-containing product, any BEs and AEs occurring between the Screening Visit and the PK Visit will be documented in the patient diary.

6.1.2 PK Visit (Visit 2)

During the PK Visit, patients will receive *wilate* at a dose of 80 IU/kg BW after a washout period of at least 72 hours from the patient's previous administration of a VWF-containing product. The exact dose calculated according to the nominal potency should be administered, with 70–85 IU/kg BW as the acceptable range. Patients must be bleed-free when visiting the study site for PK. Blood samples will be taken pre-dose (baseline), 15 minutes, 3, 9, 24, 48 and 72 hours after dosing of 80 IU/kg BW *wilate*.

The following assessments will be performed:

- Before any other assessments
  - Confirmation of inclusion and exclusion criteria
- Before injection
  - Body weight
  - Vital signs (blood pressure, heart rate, body temperature, and respiratory rate should be monitored during the PK assessment: at baseline and at 15 min [±5 min] after injection)
- Within 60 min before and 15 min (±5 min), 3 (± 1 hour) and 9, 24, 48, and 72 hours (each ±2 hours) after injection
  - PK blood samples:
    - VWF:Ac (VWF:RCo) [central laboratory]
    - FVIII:C (OS) [central laboratory]
- At 15 min (±5min) and 24 hours (±2hours) after injection
  - VWF multimer analysis in type 3 VWD patients ≥14.5 kg body weight by using the PK samples taken at 15 minutes and 24 hours after the injection [central laboratory]

- During the visit
  - Patient diary review
  - Bleeding episodes monitoring
  - Monitoring of AEs
  - Concomitant medication

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

The patients' parents will be trained in how to correctly prepare and administer *wilate*, which will be re-supplied whenever necessary during the study. The Investigator will discuss *wilate* dose and frequency of administration with the patients' parents, both for regular prophylaxis and for treatment of BEs.

The first prophylactic dose will be administered after completion of the PK Assessment, i.e. after the 72-hour samples have been collected), and should be administered at the study site before patients return to home treatment.

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

6.1.3 1-Month Visit (Visit 3)

The 1-Month IVR visit will take place 1 month (±3 days) after the first prophylactic injection of *wilate* has been received.

The following assessments will be performed:

- Before injection
  - Body weight
  - Vital signs (blood pressure, heart rate, body temperature, and respiratory rate should be monitored during the IVR Assessment: baseline, 15±5 min after injection)
- Within 60 min before and 15 min after (±5 min) injection
  - VWF:Ac (VWF:RCo) [central laboratory]
  - FVIII:C (OS) [central laboratory]
- During the visit
  - Patient diary review
  - Review of compliance and adherence to the treatment regimen
  - Bleeding episodes monitoring
  - AE monitoring
  - Concomitant medication
  - AB0 blood group testing, unless already known, and if blood volume restrictions allow (otherwise sample to be drawn at any further time point during the study [local laboratory]

During this visit, a prophylactic injection of *wilate* will be administered.

6.1.4 2-Month Visit (Visit 4)

The 2-Month IVR visit will take place 2 months (±3 days) after the first prophylactic injection of *wilate* has been received.

The following assessments will be performed:

- Before injection
  - Body weight
  - Vital signs (blood pressure, heart rate, body temperature, and respiratory rate should be monitored during the IVR Assessment: baseline, 15±5 min after injection)
- Within 60 min before and 15 min after (±5 min) injection
  - VWF:Ac (VWF:RCo) [central laboratory]
  - FVIII:C (OS) [central laboratory]
- During the visit
  - Patient diary review
  - Review of compliance and adherence to the treatment regimen
  - Bleeding episodes monitoring
  - AE monitoring
  - Concomitant medication

During this visit, a prophylactic injection of *wilate* will be administered.

6.1.5 3-Month Visit (Visit 5)

The first of the 3-Monthly Visits will take place 3 months (±1 week) after the first prophylactic injection of *wilate* has been received.

The following assessments will be performed:

- Before injection
  - Body weight
  - Vital signs (blood pressure, heart rate, body temperature, and respiratory rate should be monitored during the IVR Assessment: at baseline, and at 15±5 min after injection)
  - Blood samples
    - VWF and FVIII inhibitor testing [central laboratory]
- Within 60 min before and 15 min after (±5 min) injection
  - VWF:Ac (VWF:RCo) [central laboratory]
  - FVIII:C (OS) [central laboratory]
- During the visit
  - Patient diary review
  - Review of compliance and adherence to the treatment regimen

- Bleeding episodes monitoring
- Monitoring of AEs
- Concomitant medication

During this visit, a prophylactic injection of *wilate* will be administered.

6.1.6 6-Month and 9-Month Visit (Visit 6 and 7)

The following 3-Monthly visits will take place 6 (±2 weeks), and 9 months (±2 weeks) after the first prophylactic injection of *wilate* was received.

The following assessments will be performed:

- Before injection
  - Body weight
  - Vital signs (blood pressure, heart rate, body temperature, and respiratory rate should be monitored during the IVR Assessment: at baseline, and at 15±5 min after injection)
  - Blood samples
    - VWF and FVIII inhibitor testing [central laboratory]
- Within 60 min before and 15 min after (±5 min) injection
  - VWF:Ac (VWF:RCo) [central laboratory]
  - FVIII:C (OS) [central laboratory]
- During the visit
  - Patient diary review
  - Review of compliance and adherence to the treatment regimen
  - Bleeding episodes monitoring
  - Monitoring of AEs
  - Concomitant medication

During these visits, a prophylactic injection of *wilate* will be administered.

6.1.7 Study Completion (12-Month) Visit (Last visit)

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

The following assessments will be performed:

- During the visit
  - Before injection
    - Body weight
    - Vital signs (blood pressure, heart rate, body temperature, and respiratory rate should be monitored during the IVR Assessment: baseline, 15±5 min after injection)

        - Blood sampling
            - Routine safety laboratory [local laboratory]
            - VWF and FVIII inhibitor testing [central laboratory]
    - Within 60 min before and 15 min after (±5 min) injection
        - IVR blood sampling
            - VWF:Ac (VWF:RCo) [central laboratory]
            - FVIII:C (OS) [central laboratory]
    - During the visit
        - Patient diary review
        - Review of compliance and adherence to the treatment regimen
        - HJHS
        - Target Joints (three or more sponatenouos BEs in a single joint within six consecutive months preceding the Completion Visit)
        - Physical examination
        - Bleeding episodes monitoring
        - Monitoring of AEs
        - Concomitant medication

All used and unused *wilate* vials will be returned by the parents or their home-care providers.

Patients prematurely withdrawing from the study for any reason will be invited to attend the Study Completion Visit at the time of withdrawal.

After the final examination, the clinical study is considered completed for the subject/patient. No further study-related assessments will be performed, unless safety concerns (e.g. ongoing AEs) require follow-up.

6.1.8 Compliance Calls

Parents should be contacted by telephone every 5–7 weeks after the 3-monthly IVR visits at 3, 6, and 9 months.

The compliance calls will check the following:

- Patient's overall condition and wellbeing
- Adherence to the treatment regimen (dose and frequency)
- Bleeding episodes and their treatment
- Requirement of any prophylactic treatment adjustment
- Adverse events
- Concomitant medication
- Answer parents' questions or concerns, if any

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.

6.1.9 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 *wilate* injections seen in more frequent spontaneous bleeds, or prolonged bleeding), VWF and FVIII inhibitor tests will be performed at the central laboratory and will be documented accordingly (see **Section 7.4.5.1**).

In case of positive inhibitor result, inhibitor re-testing using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result, and further measures will need to be discussed on an individual basis. If the result is confirmed, the patient will be discontinued from the study.

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

6.1.10 Surgical Visits

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

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 details on the surgery data to be documented and the surgical efficacy assessments to be performed, see **Section 7.2.2.**

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Subject/Patient

The duration of the planned prophylactic treatment for each patient will be 12 months (+2-weeks).

6.2.2 Planned Duration for the Study as a Whole

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

The estimated start of the study (enrolment of first patient) is Q3 2021, and the estimated end of the study (last visit of last patient) is Q2 2024.

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.

Patients prematurely withdrawing from the study for any reason will be invited to attend the Study Completion Visit at the time of withdrawal (see **Section 6.1.7**).

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 following reasons:

6.2.3.1 Early Termination of the Entire Clinical Study

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

6.2.3.2 Early Termination at an Individual Study 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, partially completed, and blank CRFs, etc.) must be returned to the Sponsor. Unused *wilate* will be destroyed at the study site in accordance with local requirements, following completion of the appropriate drug account and after release by the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

Demographic and baseline information will be recorded during the Screening Visit

7.1.1 Demographic and baseline characteristics

The demographic and baseline characteristics are age, ethnic origin, height, weight, and AB0 blood group.

7.1.2 Medical history and prior/concomitant medications

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

Prior and concomitant medications will be obtained by interview.

The history or presence of VWF or FVIII inhibitor activity is an exclusion criterion (see **Section 4.1.2**).

7.2 Efficacy Assessments

This section summarises the assessments to be performed for the calculation of the primary, secondary and exploratory endpoints of this study (see **Section 3.1**).

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

7.2.1 Assessments for Primary Efficacy Endpoint(s)

The primary endpoint of this study is to determine the total annualised bleeding rate (tABR) during prophylactic treatment with *wilate*. BEs will be monitored throughout the study. The parents of study participants will be instructed by the Investigator on recording all BEs and in how to record them. The following details of each (treated and not treated) bleeding episode will be recorded:

- BE type (spontaneous, traumatic, postoperative, other)
- BE location
- BE severity (minor or major)
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended
- *wilate* administration data, if applicable
- Assessment of the efficacy of treatment at the end of the BE, if applicable

All of these parameters will be documented in the patient diary by the patient's parents, together with the responsible treating Investigator in case of on-site treatments, or with the nurse in case a home-care service is used.

The amount of *wilate* needed and the number of injections necessary to stop the bleed will be documented. The required IU/kg BW per bleeding event will be calculated.

7.2.2 Assessments for Secondary Efficacy Endpoint(s)

Consumption of *wilate*

The following parameters will be documented:

- Dates and times of *wilate* injections
- Doses of *wilate* in IU and *wilate* batch numbers. IU/kg BW per injection, per month and per year will be calculated.
- Purpose of *wilate* injection (PK/IVR, prophylaxis, prophylaxis to avoid re-bleeding, treatment of BE, surgical prophylaxis)

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.

Efficacy of *wilate* for treatment of BEs

Efficacy of *wilate* will be assessed for all treated BEs, using a 4-point objective haemostatic efficacy scale (i.e. excellent – good – moderate – none) using the predefined criteria detailed in **Section 3.3.3.** In case of minor bleeds treated at home, the assessment should be made by the patients' parents. For major bleeds, which should preferably be treated at the study site, an efficacy assessment will made by the responsible treating Investigator after the end of the bleeding event, based on the objective haemostatic efficacy scale.

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

The proportion of BEs successfully treated with *wilate* will be evaluated for all BEs in total, and further differentiated by BE severity. All efficacy ratings assessed as either "excellent" or "good" will be considered successfully treated.

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

Treatment of Surgeries

The following surgery-related parameters will be documented for major surgeries (parameters marked with * are obligatory also for minor surgeries, while the unmarked parameters can be collected for minor surgeries depending on availability):

- 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 *wilate* administration data (see definitions under **(b)** below)*
- Pre-, intra-, and postoperative VWF:Ac (VWF:RCo) and FVIII plasma levels (see definitions under **(b)** below)
- Routine safety laboratory
- Presence of wound haematomas
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Details on concomitantly administered medications (except standard anaesthetics)*
- Blood transfusion requirements
- Brief narrative describing the outcome of the intervention*
- Overall efficacy assessment at the end of the postoperative period by the responsible treating Investigator. Predefined assessment criteria will be used (see below)*
- Monitoring of AEs*

Details regarding the time points of data collection and assessments for surgical prophylaxis are described below in **Table 6**.

The efficacy of *wilate* will be assessed at end of the postoperative period by the responsible treating Investigator, using predefined assessment criteria.

(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)
- 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.

Table 6 Assessments for Perioperative 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	7.2.2	x						
Location of surgery	7.2.2	x						
Severity of surgery	7.2.2	x						
Expected duration of surgery	7.2.2	x						
Actual duration of surgery	7.2.2				x			
Expected average/maximum blood loss during surgery	7.2.2	x						
Actual blood loss and transfusions during surgery	7.2.2				x			
Administration of *wilate*	5.4		x	(x)	(x)	(x)	(x)	(x)
FVIII:C	7.4.5		# L	(#) L	(#) L	(#) [2] L	(#) L	(#) L
VWF:Ac (VWF:RCo)	7.4.5		# L	(#) L	(#) L	(#) [2] L	(#) L	(#) L
Routine safety laboratory	7.4.5	x				(x)	(x)	(x)
Presence of wound haematomas	7.4.2					x	x	x
Vital signs	7.4.7	x		x		x		
Efficacy assessments	7.2.2				S			H
Overall efficacy assessment	7.2.2							I
Brief narrative of outcome of the intervention	7.2.2							x
Concomitant medications	7.4.2	Throughout observation period						
Adverse event monitoring	7.4.2	Throughout observation period						

POP = postoperative, FVIII:C = factor VIII procoagulant activity, VWF:Ac = VWF activity, VWF:RCo= von Willebrand ristocetin cofactor 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 *wilate* administration

[1] Immediately after the last surgical suture

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

Efficacy in Perioperative Prophylaxis

Following **major surgeries**, efficacy will be assessed at the end of surgery by the Surgeon and at the end of the postoperative period by the responsible Haematologist/Investigator (see above). In both cases, predefined assessment criteria will be used.

In addition, an overall assessment of efficacy will be made for all minor and major surgeries at the end of the postoperative period by the Investigator.

At the End of Surgery

At the end of surgery (defined as the time immediately after the last surgical suture), the haemostatic efficacy of *wilate* will be assessed by the responsible Investigator using the criteria listed in **Table** 7.

Table 7 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

At the end of the postoperative period (defined as the time the patient returns to his or her regular VWF treatment regimen), the haemostatic efficacy of *wilate* will be assessed by the responsible Investigator using the criteria listed in **Table 8.**

Table 8 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

As for major surgeries, the overall efficacy will be assessed by the responsible Investigator using the excellent, good, moderate, and none scale, taking both the intra- and postoperative assessments into account, based on the following algorithm in **Table 9**.

Table 9 Algorithm for the Overall Efficacy Assessment for Surgical Prophylaxis

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

For minor surgeries, the overall assessment of perioperative prophylaxis will be assessed by the responsible Investigator using the excellent, good, moderate, and none scale, taking the postoperative assessment in to account as shown in **Table 8.**

Joint Health Status

Joint health will be assessed using the Haemophilia Joint Health Score (HJHS) [16], which has been specifically validated for the assessment of clinical outcome in adult patients with VWD (mean age 46 years [range 18–80]) [11].

The HJHS has shown excellent reliability and good validity in both adults and children with haemophilia [16-18].

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

7.3 Pharmacokinetic Assessments

Pharmacokinetic parameters will be assessed for VWF:Ac (VWF:RCo) and FVIII:C (one-stage, OS) assays based on actual *wilate* potencies.

The following PK parameters will be assessed:

- Area under the curve (AUC) and AUC normalised 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)

To account for residual VWF:Ac and FVIII:C levels the listed parameters will be computed on pre-dose-adjusted concentration vs. time profiles.

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

7.4 Safety Assessments

7.4.1 Assessments for Safety Endpoints

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP, comparator, or placebo
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs

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

7.4.2.2 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 nonleading question such as "How have you been since the last visit/during the previous study period?" In addition, the Investigator will check the subject/patient diaries (if applicable) for any documented event.

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

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

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

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

7.4.2.3 Severity of AEs

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

7.4.2.5 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 Investigator's Brochure or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, 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 well being of the subject/patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action 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 subject/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.

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 subject/patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should 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.

Hospitalisation is *not* considered an SAE in the case where:

- the hospitalization takes place because of study-related procedure (e.g. PK assessment)
- of any planned surgical procedure (e.g. for the implementation of a port-a-cath)

7.4.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee:

[redacted]
Clinical Resarch & Development Haematology
Fax: [redacted]
Email: [redacted]

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

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

Octapharma's Central Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
[redacted]

24 hours emergency telephone number: [redacted]

Waivers the from SAE Reporting Requirement

Waivers from the SAE reporting requirement include hospitalisation for the treatment of a (disease related) BE assessd as unrelated to IMP treatment, and 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 laboratory parameters shown in **Table 10** will be investigated during the study at the time points specified in **Section 6.1**.

Table 10 Laboratory Sampling Flowchart

Laboratory Assessments	Screening Visit	PK Visits	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 [1]					
Routine safety laboratory	x							x [2]
CENTRAL LAB								
VWF:Ac (VWF:RCo)	x	x [3]	x [4]	x [4]	x [4]	x [4]	x [4]	x [4]
FVIII:C (OS)		x [3]	x [4]	x [4]	x [4]	x [4]	x [4]	x [4]
VWF and FVIII inhibitors	x				x [2]	x [2]	x [2]	x [2]
VWF multimer analysis	x	x [5]						
Retention samples for possible virus marker testing	x							

[1] If unknown, can also be shifted to a later timepoint
[2] Before injection
[3] Before injection and at 15 min, 3 hr, 9 hr, 24 hr, 48 hr and 72 hrs after injection
[4] Within 60 min before and 15±5 min after injection
[5] For VWD type 3 patients ≥14.5 kg BW, samples from 15 min and 24 hrs will be used for additional multimer analysis

An effort was made in this study to avoid invasive procedures and repeated blood sampling in paediatric patients, in agreement with EU guidelines. The *Ethical Considerations for Clinical Trials on Medicinal Products conducted with the Paediatric Population* will be followed during the conduct of WIL-33.

For sampling, the Committee recommends that per individual, trial-related blood loss should not exceed 3% of the total blood volume during a period of four weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 90 ml/kg BW; in mean 3% is around 2.7 mL blood per kg BW [19].

Blood Sampling

The *actual* date and time of any blood sampling must be recorded in the eCRF, on the label of the laboratory tubes and on the corresponding laboratory shipment forms. The exact sampling volumes needed, and further specific processes will be desribed in the laboratory manual.

EDTA Blood

Around 2 mL (or less, as required by the local laboratory) of EDTA blood will be collected for the measurement of haematology parameters (RBC count, WBC count, haemoglobin, haematocrit, platelet count) at the screening and at completion visit. All haematology tests are to be done at the local laboratory in accordance with local requirements.

Citrated Plasma

For the analysis of FVIII:C, VWF:Ac, FVIII inhibitor screen, and VWF inhibitor screen citrated blood is collected and sent to the main central laboratory, from where it is further distributed as required. As the only exception, samples collected for multimer analysis must be sent separately to the specialised laboratory as indicated below.

After collection and centrifugation, the plasma will be aliquoted into cryo-resistant tubes. Samples will be stored at ≤-70°C and shipped to the central laboratory on dry-ice. The samples from the screening visit must be sent to the laboratories within 2 working days. The frequency of further shipments depends on the number of patients and other local factors, and will be individually specified.

The blood volumes needed for the regular study visits range from a minimum of approximately 5.6 mL per visit day (at Visits 3-4: Monthly IVR Visits) to 9.7 mL (at Visits 5–7: 3-Monthly IVR Visits).

As for the PK Visit, the needed volumes per day range from approximately 2.8 mL (at PK days 3 and 4) to 11.2 mL (at PK day 1), whereas additional multimer analysis in severe VWD Type 3 patients requires sampling volumes of up to 13.0 mL on one day (VWD Type 3 patients with ≥14.5 kg body weight).

These assumptions are based on the smallest possible collection tube volumes, details of which are provided in the laboratory manual that will be made available to all participating study centres.

For analysis performed locally, e.g. at screening and pre-, intra, and post-surgery, citrated blood as required by the local laboratory will be collected and processed in accordance with local requirements.

Serum

AB0 blood group analysis is only indicated in cases where the blood group is not known from medical history at the time of screening, and can be done at the 1-Month visit or at any other time during the study by the local laboratory.

For retention samples for possible later virus testing, a serum sample of another approximately 2.5 mL is taken (at Screening Visit only) and sent frozen to the central main blood sample reception laboratory.

All collection tubes and materials required as well as exact shipping information are provided by the central laboratory in advance.

Laboratory Abnormalities

The Investigator must assess the clinical significance of abnormal laboratory values outside the normal range as specified by the reference laboratory. Any clinically significant abnormalities should be fully investigated.

Only laboratory abnormalities that have been rated as being clinically significant will be documented as AEs/ADRs. Clinically significant is defined as any laboratory abnormality that the Investigator feels is of clinical concern, and/or requires medical intervention and/or follow-up. Additional tests and other evaluations required to establish the significance, or aetiology of an abnormal result or to monitor the course of an AE should be obtained if clinically indicated. Any abnormal laboratory value that persists should be followed until resolution or for 14 days after the final study visit, whichever occurs first. Preferably, clinically significant laboratory abnormalities should be medically diagnosed and entered as a diagnosis into the AE form, if not already present at baseline.

All remaining serum and plasma volumes will be labelled and stored as retention samples at the central laboratory for at least 2 years after the completion of the study and until Octapharma's written authorisation to destroy these samples.

7.4.5.1 Central Laboratory

The following laboratory parameters will be determined in accordance with the time points specified in **Table 1** and in **Section 6,** and as shown in the Laboratory Sampling Flowchart in **Table 10**:

- **FVIII:C (one-stage)** in *wilate* batches used for PK/IVR evaluations will be determined (for VWF:Ac (VWF:RCo), potency will be obtained from the Certificates of Analysis).
- **FVIII:C** will be measured in plasma at pre-specified time points using the OS assay.
- **VWF:Ac** will be measured in plasma at pre-specified time points by VWF:RCo.
- For **VWF** and **FVIII inhibitor titre testing,** a sample will be analysed at the central laboratory. In addition, VWF and FVIII inhibitor testing will be performed testing at baseline, every 3 months, and in case of inhibitor suspicion.
- A retention sample is to be drawn for possible virus marker testing.
- Multimer distribution of the VWF by multimer analysis using low- and high resolution electrophoresis gels (preferably 1% and >2% gels) in paediatric patients with VWD type 3 and a body weight ≥14.5 kg; VWF multimers will be determined by a quantitative method.

Central laboratory facilities:

Main blood sample reception laboratory for EMEA countries:
Labcorp Central Laboratory Services S.à.r.l.
7, rue Moïse-Marcinhes
1217 Meyrin, Geneva, Switzerland

Main blood sample reception laboratory for US / CA:
Labcorp Central Laboratory Services
Limited Partnership
8211 SciCorDrive
Indianapolis, IN, 46214, US

Analysis of central laboratory parameters:
VWF:Ac (RCo), FVIII (OS), VWF Inhibitors, FVIII Inhibitors;
LabCorp Esoterix Coagulation Laboratory
8490 Upland Drive
Suite 100
Englewood, Colorado 80112, US

Analysis of central laboratory parameter:
VWF Multimer Analysis
MEDILYS Laborgesellschaft mbH
Paul-Ehrlich-Straße 1
22763 Hamburg, Germany

Laboratory kits for all required central laboratory tests are provided by Labcorp Central Laboratory Services in Indianapolis, US.

7.4.5.2 Local Laboratory

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

- **Haematology:** red blood cell count, white blood cell count, haemoglobin, haematocrit, and platelet count
- **AB0 blood-group testing**, if unknown. Should the blood group not have been previously determined, this can be done at any time during the study, by however respecting blood volume restrictions.
- **VWF:Ac** (VWF:RCo) **and FVIII:C** measurements in case of BEs or surgeries will also be done by the local laboratories, if clinically indicated.
- **VWF / FVIII inhibitor** determination if an inhibitor is suspected, and if laboratory facilities allow.

The analyses of the local laboratories are carried out according to local regulations.

7.4.6 Virus Safety Tests

Retention samples will be taken for possible virus marker testing in the central laboratory.

7.4.7 Vital Signs and Physical Examination

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

Physical examinations will be performed at the visits specified in **Section 6**. Both height and weight will be measured at screening. In addition, weight will be measured at all visits prior to *wilate* dosing and serve as a basis for continuous dose adjustments, if appropriate.

7.4.8 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.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report and transmit it to the Clinical Trial Manager and to Octopharma'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.

Overdose, interaction, medication error and lack of efficacy

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

b) Drug overdose

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

c) Drug interaction

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

d) Medication error

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

e) 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 previous studies with *wilate.*

Evaluation of the tABR 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 (see **Section 1.2**).

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 subject/patient files for each subject/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 and document any further study-related details, such as patient information and consent process (whose signature was retrieved, date and time of consent), any details communicated regarding IMP administration and IMP handling (i.e. training of parents for home-treatment, including any potential external home-treatment planned).

All data entered in the eCRF must be supported by source data in the subject/patient records, with exceptions listed in Section 8.1.2.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

Patients will usually be treated at home by their parents or by their home physician. Parents will, therefore, be provided with a sufficient amount of *wilate* and a patient diary, which should also be documented in the patient's source data records on an ongoing basis.

The patient diary will be handed to the patient during the Screening Visit after inclusion into the study. The Investigator will explain to the patients' parents how to fill in the diary and emphasise the importance of careful documentation.

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

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

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.

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 electronic Case Report Form (eCRF) 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 to Investigators

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

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

The Investigator will be informed about the methods for rating relevant study outcomes and for completing CRFs 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 forms, site copies of all CRFs, 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 subject/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 subject's/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 subject's/patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

Not applicable.

9 STATISTICAL METHODS AND SAMPLE SIZE

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

9.1 Determination of Sample Size

No formal sample size calculation was performed for the study.

The sample size of up to 12 patients, including at least four patients with VWD type 3, is based on a communication from the FDA and on EU guideline CPMP/BPWG/220/02 calling for a trial in at least eight children with VWD under the age of six years, three of whom should have type 3 VWD and was selected to accommodate for drop-outs.

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. Geometric means and standard deviations will presented in addition for PK concentrations and parameters. This will be complemented by the presentation of exploratory CIs for means or proportions.

A formal statistical analysis plan 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** will include all patients who received at least one dose of *wilate*.

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

The **per-protocol (PP) set**, i.e., a subset of the full analysis set, will exclude patients with major protocol deviations which may have an impact on the evaluation of the primary study outcome parameter(s). Examples of major and minor protocol deviations will be described in the Statistical Analysis Plan.

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 SAF, containing all patients for whom a valid PK profile was obtained at the PK Visit.

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 safety set.

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

For secondary and explarotary endpoints, ITT and PP analyses will be carried out, unless the two analysis sets differ by no more than 1 patient.

Analysis and efficacy 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 (*wilate* 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.

9.2.2.1 Efficacy of wilate in Prophylactic Treatment

The haemostatic efficacy of *wilate* will be assessed by evaluating tABR over all types of VWD.

The frequency and severity of BEs and the total, traumatic and spontaneous ABR will be calculated from patients' dosing and treatment frequency in different VWD types. Efficacy of prophylactic treatment with *wilate* will be statistically evaluated by analysing the primary endpoint.

The tABR will be calculated as the total number of spontaneous bleeds, traumatic bleeds, and other bleeds occurring in the time period between first prophylactic dose of *wilate* and the Study Completion Visit, divided by the duration (in years) between first prophylactic dose of *wilate* and the Study Completion Visit. Bleeding episodes occurring within surgery periods will be excluded from the calculation of tABR.

9.2.2.2 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.

9.2.2.3 Pharmacokinetic Analysis/Recovery Assessments

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} (normalised for the administered dose)
- In vivo half-life ($T_{1/2}$)
- Maximum plasma concentration (C_{max})
- Time to reach maximum plasma concentration (T_{max})
- Mean residence time (MRT)
- Volume of distribution (Vd)
- Clearance (CL)
- Incremental in vivo recovery (IVR)

Pharmacokinetic parameters will be computed for VWF:Ac and FVIII:C. The one-stage (OS) assay for FVIII, actual *wilate* potencies, and actual sampling times will be used in the calculations. Pharmacokinetic parameters will be derived by non-compartmental methods.

To account for residual VWF:Ac and FVIII:C levels, the listed parameters will be computed on pre-dose-adjusted concentration vs. time profiles.

The PK profiles of VWF:Ac and FVIII:C, the PK parameters derived and recovery assessments will be summarised using descriptive statistics (including geometric means and standard deviations) as well as the presentation of concentration vs time plots (individual values and means). 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.

9.2.2.4 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, *wilate* consumption) will be presented descriptively.

9.2.2.5 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, e.g. results of immunogenicity screening, thrombogenicity monitoring for sustained excessive FVIII plasma levels (and an increased risk of thrombotic events), and safety laboratory testing. Analysis of AEs will focus on TEAEs.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) in the version current at the clinical start of the study. The analysis will include only treatment-emergent adverse events (TEAEs), i.e., AEs that started or worsened after the first IMP injection. 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 frequency tables for positive findings, along with 95% Pearson-Clopper CIs.

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.

Other safety parameters (e.g., changes in physical examination findings) will be analysed by 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 (if Applicable)

Not applicable

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in in compliance with the protocol and its amendments, the *ICH Guideline for Good Clinical Practice (GCP) E6 (R2) (EMA/CHMP/ICH/135/1995),* the *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, applicable regulatory requirements, and 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, the Investigator, 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 subject/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 subject/patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each patient's legal parent/guardian 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's legal parent/guardian, before the patient is exposed to any study-related procedure, including screening tests for eligibility. If the children are old enough to understand the risks and benefits of the study, they should also be informed and provide their written consent.

The Investigator will explain that the patients'legal parents/guardians 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 CRF for each patient enrolled.

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

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-centre studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent 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 subjects/patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of subjects/patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Subject/Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential subject identification code list, original consent 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 CRF 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 subject/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 CRFs, 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 subjects/patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

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

12.2 Publication Policy

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

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

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-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 subject/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.