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STUDY PROTOCOL FOR A NON-INTERVENTIONAL STUDY

A Prospective, Multicentre, Non-Interventional Study Evaluating the Bleeding Incidence in Patients with Von Willebrand Disease Undergoing On-Demand Treatment (WIL-29)

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EU PAS register number	EUPAS29946
Active substances	VWF concentrates VWF/FVIII concentrates Cryoprecipitate
Medicinal products	VWF-containing products
Product references	VWF-containing products licensed in each participating country
Procedure number	n/a
Marketing authorisation holders	All marketing authorizations holders for VWF-containing products used as per local practice
Joint PASS	No
Research question and objectives	The primary objective of this study is to characterise the bleeding and treatment pattern of patients with type 3, type 2 (except 2N), or severe type 1 von Willebrand disease receiving routine on-demand treatment with a von Willebrand factor-containing product.
Countries of study	Belarus, Bulgaria, Croatia, Hungary, Lebanon, Russia, Ukraine, and USA

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PROTOCOL SIGNATURES

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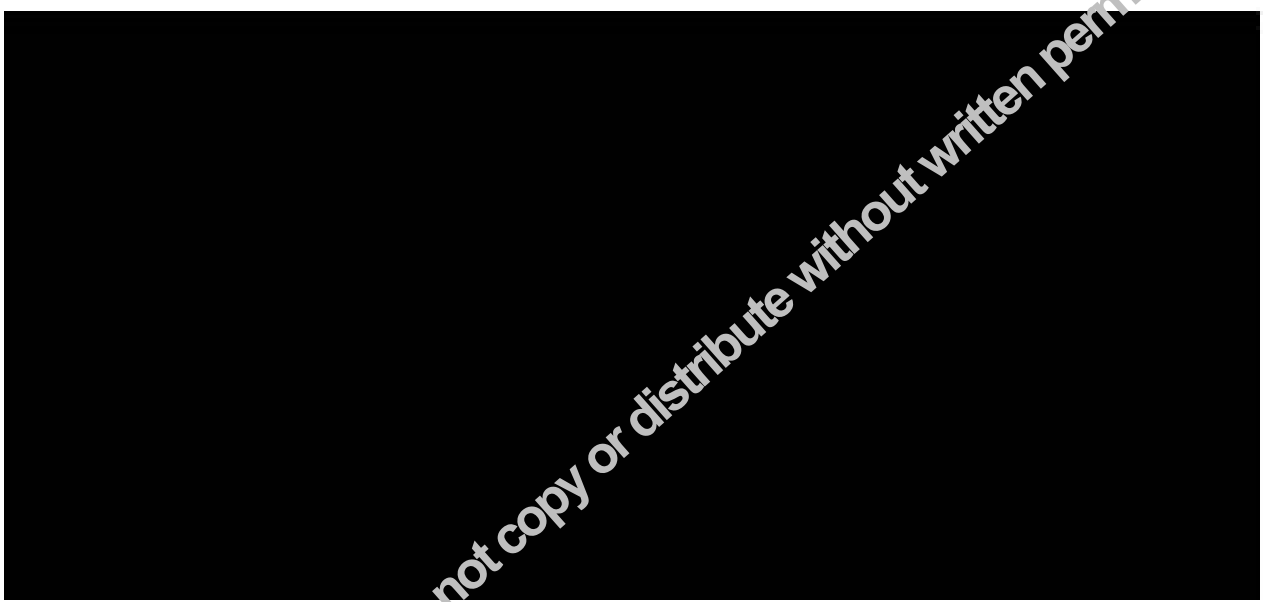

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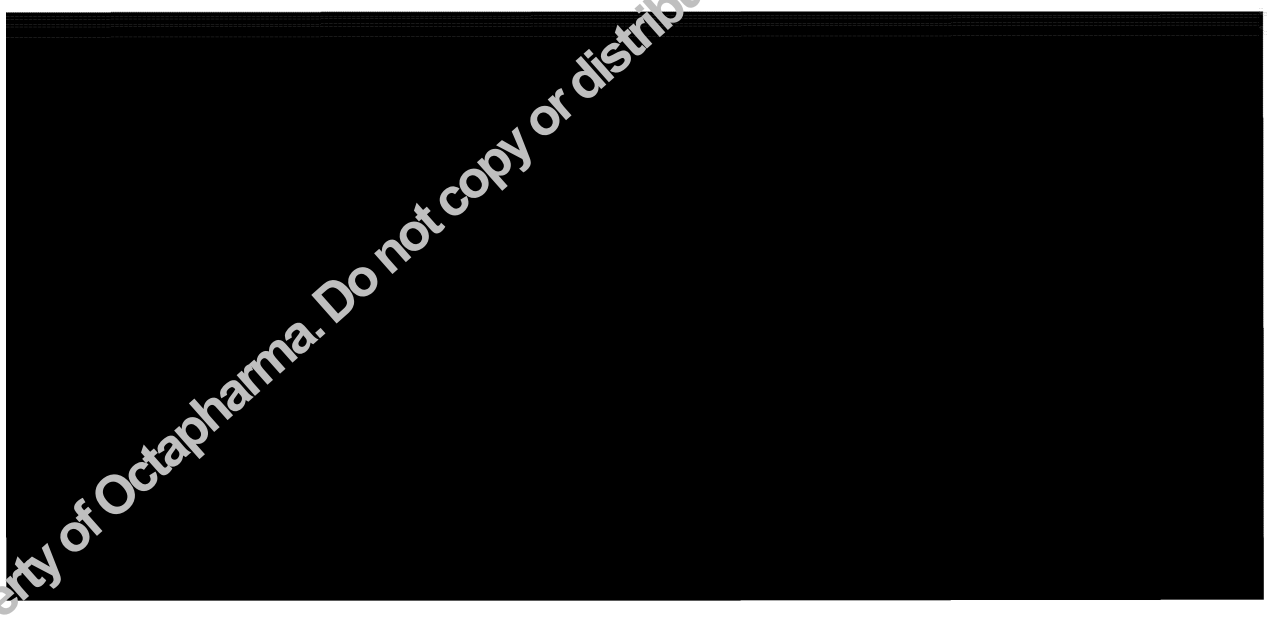

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1 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BE	Bleeding Event
CRO	Contract Research Organization
DDVAP	Desmopressin (1-deamino-8-D-arginine vasopressin)
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FVIII	Factor VIII
GPP	Good Pharmacoepidemiologic Practices
HCP	Health-Care Provider
ICH	International Conference of Harmonization
IEC/IRB	Independent Ethics Committee/Institutional Review Board
NIS	Non-Interventional Study
PROMIS	Patient-Reported Outcomes Measurement Information System
PTP	Previously Treated Patients
QoL	Quality of Life
SABR	Spontaneous Annualised Bleeding Rate
SADR	Serious Adverse Drug Reaction
SF-10	10-Item Short Form Health Survey
SF-36v2	36-Item Short Form Health Survey, version 2
SmPC	Summary of Product Characteristics
TABR	Total Annualised Bleeding Rate
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
VWF:Ac	Von Willebrand Factor Activity
VWF:RCo	VWF Ristocetin Cofactor
VWF:Gp1bM	Assay to Determine VWF:Ac Based on Spontaneous Binding of VWF to a Gain-of-Function Mutant Gp1b Fragment
VWF:GP1bR	Assay to Determine VWF:Ac Based on Ristocetin-Induced Binding of VWF to a Recombinant Wild-Type Gp1b Fragment

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2 RESPONSIBLE PARTIES

The key parties responsible for the conduct of this study are listed in **Table 1**. A complete list of study sites and treating physicians enrolling patients into this study will be provided in the final study report.

Table 1 Key Parties Responsible for the Conduct of Study WIL-29

Co-ordinating Investigator	[redacted]
Clinical Trial Manager	[redacted]
Clinical Project Manager	[redacted]
Data Management and Statistical Analysis	[redacted]

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3 ABSTRACT

Title of Study:

A Prospective, Multicentre, Non-Interventional Study Evaluating the Bleeding Incidence in Patients with Von Willebrand Disease Undergoing On-Demand Treatment (WIL-29)

Rationale and Background:

The purpose of this study is to prospectively obtain reliable data on the bleeding and treatment pattern of patients with VWD undergoing on-demand treatment with a VWF-containing product over a period of 6 months. The data obtained will be used as a basis for historical comparisons with the bleeding and treatment pattern obtained from a clinical study on the efficacy of prophylactic treatment with a VWF/FVIII concentrate.

Research Question and Objectives:

The primary objective of this study is to characterise the bleeding and treatment pattern of patients with type 3, type 2 (except 2N), or severe type 1 VWD undergoing routine on-demand treatment with a VWF-containing product.

The secondary objectives of this study are to:

- Determine the effectiveness of the VWF-containing product used in the treatment of bleeding episodes (BEs)
- Determine the effectiveness of the VWF-containing product used in surgical prophylaxis
- Assess the quality of life (QoL) of VWD patients undergoing on-demand treatment with a VWF-containing product
- Assess the safety of the VWF-containing product used for on-demand VWD treatment

Study Design:

This is a prospective, multicentre, international, non-controlled non-interventional study.

Population:

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

1. Male or female patients aged ≥5.5 years at the time of enrolment
2. VWD type 1 (baseline von Willebrand factor activity [VWF:RCo, <30 IU/dL), 2A, 2B, 2M, or 3 according to medical history requiring substitution therapy with a VWF-containing product to control bleeding
3. Currently receiving on-demand treatment with a VWF-containing product
4. In female patients of child-bearing potential using hormonal contraception, the medication class should remain unchanged during the period of participation in the study

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5. Voluntarily given, fully informed written and signed consent before collection of any patient data

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

1. Patients currently on prophylaxis for VWD (except for perioperative prophylaxis) as well as patients having received treatment once a month for menstrual bleeding, but not for any other bleeds
2. Patients whose VWD treatment is planned to be switched from on-demand to prophylactic treatment in the next 6 months
3. History, or current suspicion, of VWF or FVIII inhibitors
4. Medical history of a thromboembolic event within 6 months before enrolment
5. Severe liver or kidney diseases as described in the medical records
6. Female patients with an existing or suspected pregnancy or who are breast-feeding at the time of enrolment
7. Change in hormonal contraception within 6 months before enrolment
8. Cervical or uterine conditions causing abnormal uterine bleeding (including infection or dysplasia)
9. Other coagulation disorders or bleeding disorders due to anatomical reasons
10. Participation in an interventional clinical study during the 6-month of study period
11. Inability to complete the patient diary to reliably evaluate the type, frequency, and treatment of BEs during the 6-month study period

Variables:

Collected variables comprise:

- Demographic and baseline characteristics
- Medical history and prior medications
- Hemophilia Joint Health Score (HJHS)
- Bleeding episode data
  - BE type (spontaneous, traumatic, postoperative, menstrual, other)
  - BE site
  - BE severity (minor, major)
  - Date and time the BE first occurred or was first noticed
  - Date and time the BE ended
  - BE treated or not treated
  - Data on the administration of the VWF-containing product
  - Assessment of the effectiveness of treatment at the end of the BE
- Data on the administration of the VWF-containing product
  - Name and batch number of VWF-containing product
  - Dates and times of injections of VWF-containing product
  - Doses of VWF-containing product in IU and IU/kg

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  - Purpose of injection with VWF-containing product (treatment of BE, prophylaxis of recurrent bleeding, surgery, prophylaxis after surgery)

- Assessment of the effectiveness of the treatment of BEs
- PBAC data and scores (for female patients of child-bearing potential)
- Data on surgical prophylaxis
- Assessment of the effectiveness of surgical prophylaxis
- Quality of life using the PROMIS-29, the 36-Item Short Form Health Survey, version 2 (SF-36v2) for patients ≥16 years, and the SF-10 for patients ≥5.5 and <16 years of age

Data Sources:

The data source for the calculation of the bleeding rate will be the information documented in the patient diaries as well as the information collected based on the review of the patient's medical records.

Study Size:

Overall, around 55 PTPs aged ≥5.5 years at the time of enrolment will be included into this NIS. Of the 55 patients, at least 6 patients should have type 3 VWD and at least 6 patients should be ≥5.5 to <16 years of age.

Data Analysis:

All data will be analysed descriptively.

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4 AMENDMENTS AND UPDATES

Any amendments will be submitted to the competent independent ethics committees (IECs) or institutional review boards (IRBs) as well as to competent regulatory authorities as required by national regulations (see **Section 9.2**).

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5 MILESTONES

The milestones of this study are summarized in **Table 2**.

Table 2 Study Milestones and Planned Dates

Milestone	Planned date
Start of data collection	Q3 2019
End of data collection	Q1 2021
Final study report	Q2 2021

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6 RATIONALE AND BACKGROUND

6.1 VON WILLEBRAND DISEASE

Inherited von Willebrand disease (VWD) is the most common inherited haemorrhagic disorder, with an estimated prevalence of 1 in every 1000 individuals of either sex. There is wide geno- and phenotypic variability of the disease, and not all patients with VWD require treatment.

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

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

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

The appropriate treatment for the patients in whom DDAVP is ineffective or contraindicated are VWF/factor VIII (FVIII) concentrates, which have become the mainstay of VWD treatment. Cryoprecipitate, which is screened for viruses but not treated to inactivate them, is also rich in VWF, but is likely to be less safe than the viral-attenuated concentrates [2].

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

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6.2 RATIONALE FOR CONDUCTING THE STUDY

Bleeding disorders are a disease area in which good record-keeping is an essential component of home-based care. Complete bleeding and treatment records are an essential tool of communication between patients and their health-care providers (HCPs), and they help HCPs monitor patients and medication use to ensure optimal treatment [4–6]. However, record-keeping varies considerably between treatment centres and countries, posing a challenge when retrospectively estimating bleeding rates in a reliable manner.

The purpose of this study is to prospectively obtain reliable data on the bleeding and treatment pattern of patients with VWD undergoing on-demand treatment with a VWF-containing product over a period of 6 months. The data obtained will be used as a basis for historical comparisons with the bleeding and treatment pattern obtained in a clinical study on the efficacy of prophylactic treatment with a VWF/FVIII concentrate.

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7 RESEARCH QUESTION AND OBJECTIVES

7.1 PRIMARY OBJECTIVE

The primary objective of this study is to characterise the bleeding and treatment pattern of patients with type 3, type 2 (except 2N), or severe type 1 VWD undergoing routine on-demand treatment with a VWF-containing product.

7.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to:

- Determine the effectiveness of the VWF-containing product used in the treatment of bleeding episodes (BEs)
- Determine the effectiveness of the VWF-containing product used in surgical prophylaxis
- Assess the quality of life (QoL) of VWD patients undergoing on-demand treatment with a VWF-containing product
- Assess the patients' joint status using the Hemophilia Joint Health Score (HJHS)
- Assess the menstrual bleeding intensity of female patients of child-bearing potential
- Assess the safety of the VWF-containing product used for on-demand VWD treatment

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8 RESEARCH METHODS

8.1 STUDY DESIGN

This is a prospective, multicentre, international, non-controlled non-interventional study (NIS).

8.2 STUDY ENDPOINTS

8.2.1 Primary Endpoint

The primary endpoint of this NIS is to characterise the total annualised bleeding rate (TABR) of patients with type 3, type 2 (except 2N), or severe type 1 VWD undergoing routine on-demand treatment with a VWF-containing product.

The TABR will be calculated as the total number of spontaneous, traumatic and other BEs in the time period between the start of data collection for each patient and the Study Completion Visit, divided by the duration (in years) between the start of data collection and the Study Completion Visit. Surgery periods, and BEs occurring within these surgery periods, as well as menstrual bleeds will be excluded from the calculation of TABR.

8.2.2 Secondary Endpoints

The secondary endpoints of this study are the:

- Spontaneous annualised bleeding rate (SABR), calculated in analogy with TABR
- Data on the consumption of the VWF-containing product (VWF/FVIII IU/kg per month per patient) used for routine on-demand treatment
- Effectiveness of VWF-containing product in the treatment of BEs based on the proportion of successfully treated BEs
- Effectiveness of surgical prophylaxis with VWF-containing product based on the proportion of successfully treated surgeries
- QoL based on the PROMIS-29 for all patients, SF-36v2 for patients ≥16 years, and SF-10 for patients ≥5.5 and <16 years of age.
- Hemophilia Joint Health Score (HJHS)
- Pictorial Blood Loss Assessment Chart (PBAC) score
- Safety of the patient's VWF-containing product by monitoring adverse drug reactions (ADRs) throughout the study

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8.3 STUDY POPULATION

8.3.1 Number of Patients

Overall, around 55 PTPs aged ≥5.5 years at the time of enrolment will be included into this NIS. Of the 55 patients, at least 6 patients should have type 3 VWD and at least 6 patients should be ≥5.5 to <16 years of age.

8.3.2 Inclusion Criteria

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

1. Male or female patients aged ≥5.5 years at the time of enrolment
2. VWD type 1 (baseline von Willebrand factor activity [VWF:RCo], <30 IU/dL), 2A, 2B, 2M, or 3 according to medical history requiring substitution therapy with a VWF-containing product to control bleeding
3. Currently receiving frequent on-demand treatment with a VWF-containing product
4. In female patients of child-bearing potential using hormonal contraception, the medication class should remain unchanged for the duration of their study participation
5. Voluntarily given, fully informed written and signed consent obtained before collection of any patient data

8.3.3 Exclusion Criteria

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

1. Patients currently on prophylaxis for VWD (except for perioperative prophylaxis) as well as patients having received treatment once a month for menstrual bleeding, but not for any other bleeds
2. Patients whose VWD treatment is planned to be switched from on-demand to prophylactic treatment in the next 6 months
3. History, or current suspicion, of VWF or FVIII inhibitors
4. Medical history of a thromboembolic event within 6 months before enrolment
5. Severe liver or kidney diseases as described in the medical records
6. Female patients with an existing or suspected pregnancy or who are breast-feeding at the time of enrolment
7. Change in hormonal contraception within 6 months before enrolment
8. Cervical or uterine conditions causing abnormal uterine bleeding (including infection or dysplasia)
9. Other coagulation disorders or bleeding disorders due to anatomical reasons
10. Participation in an interventional clinical study during the 6-month of study period
11. Inability to complete the patient diary to reliably evaluate the type, frequency, and treatment of BEs during the 6-month study period

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8.4 STUDY CONDUCT

8.4.1 Study Setting and Centres

This study will be conducted in about 20 centres for the treatment of bleeding disorders world-wide.

8.4.2 Study Duration

The overall study duration will be approximately 2 years. Each patient will be followed for around 6 months from the time of enrolment. The study will be considered completed at the time of database lock.

8.4.3 Patient Codes

Each patient enrolled into this NIS will be uniquely identifiable by a patient code consisting of the study code, centre code, and patient number. The centre code is assigned to the study site by Octapharma. At each site, enrolled patients will be numbered consecutively. Once assigned to a patient, a patient number will not be reused.

8.4.4 Study Conduct

Male or female patients aged ≥5.5 years at the time of enrolment with VWD type 1 (baseline von Willebrand factor activity [VWF:RCo], <30 IU/dL), 2A, 2B, 2M, or 3 according to medical history having been prescribed on-demand therapy with a VWF-containing product to control their bleeding will be included into this study after written informed consent has been obtained (see **Section 9.1**).

Patient eligibility for enrolment will be determined at the Screening Visit, during which demographic and baseline data, the medical history, and prior medications will be recorded (see **Section 8.5.1** and **Section 8.5.2**). Quality of life will also be assessed during the Screening Visit (see **Section 8.5.8**).

Patients and/or their parents or legal guardians will be asked to keep a patient diary to document any bleedings and treatment details as well as information on the patients' medical condition, treatment side effects, other noteworthy medical events, and concomitant medications throughout the study (see **Section 8.4.5**). In addition, treating physicians should enquire, during each follow-up visit, about any safety-relevant events and concomitant medications taken. The treating physicians will assess the causal relationship of any safety-relevant events and report these as ADRs or other relevant safety information as required.

For women of child-bearing potential, bleeding information from each menstrual period in this study will be collected using the Pictorial Blood Assessment Chart (PBAC) (see **Section 8.5.10**).

Details on any surgical interventions patients may be undergoing while participating in this study will also be collected (see **Section 8.5.6**).

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Patient treatment as well as all follow-up visits will take place as per the routine standard of care of each study site. The recommended schedule is for follow-up visits to take place at 1, 3, and 6 months after the Screening Visit.

The recommended flow chart of study visits and the variables that should be collected in this study are given in **Table 3**. The variables are described in detail in **Section 8.5**.

Table 3 Recommended Flow Chart of Study Visits and Data Collected During On-Demand Treatment with a VWF-Containing Product

	For more information, see Section	Screening Visit	Follow-up visits at 1, 3, and 6 months
Informed consent		x	
Inclusion and exclusion criteria	**8.3**	x	
Demographic & baseline data, including pregnancy status and HJHS	**8.5.1**	x	
Medical history and prior medications, including VWD treatments and genetic testing history, if available	**8.5.2**	x	
Family history of VWD		x	
Bleeding history in the previous 6 months in PTPs		x	
History of VWF and FVIII inhibitors		x	
Quality of life using PROMIS-29 and SF-36v2 or SF-10, as applicable	**8.5.8**	x	
Handing out patient diaries and PBAC instruction	**8.4.5, 8.5.10**	x	
Possible VWF/FVIII inhibitor testing, if inhibitors suspected*			x
Collection of patient diary pages	**8.4.5**		x
Obtaining PBAC data and scores	**8.5.10**		x
Details on potential surgical interventions	**8.5.6, 8.5.7**		x
Adverse drug reaction (ADR) monitoring	**10**		x
Concomitant medications			x

HJHS = Hemophilia Joint Health Score, PBAC = Pictorial Blood Assessment Chart
*As per routine standard of care at each treatment centre.

8.4.5 Patient Diaries

Documenting treatment and bleeding data is an integral part of home treatment for VWD. In this study, enrolled patients will be provided with a patient diary during the Screening Visit. Patients will be asked to complete their diaries and to bring them along to each follow-up visit. The completed diary pages will be collected by the treating physician, and the information recorded will be transcribed to the electronic Case Report Forms (eCRFs). The patient diaries are considered source data, and the original diary pages will be included in the patient's medical record.

The following data should be recorded in the patient diary:

- Bleeding episode data (see **Section 8.5.3**)
- Data on the administration of the VWF-containing product (see **Section 8.5.4**)
- Assessment of the effectiveness of the treatment of BEs (see **Section 8.5.5**)
- Any medications taken, or other treatments received (e.g., physical therapy, blood transfusions), by the patient throughout the duration of the study

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8.5 VARIABLES

8.5.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics are age, ethnic origin, height, weight, AB0 blood group (if derivable from the patient's medical history), and pregnancy and breast-feeding status.

In addition, the Hemophilia Joint Health Score (HJHS, see **Section 8.5.9**) will be obtained. Also, target joint(s), defined as having had 3 or more spontaneous BEs into a single joint in 6 consecutive months before the Screening Visit, will be recorded, if available.

8.5.2 Medical History and Prior Medications

The medical history as well as prior and concomitant medications will be obtained by patient interview. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files, if available.

VWF activity using VWF:RCo, VWF:Gp1bM, VWF:Gp1bR, or any other pertinent method will be recorded, as will VWF:Ag, the VWF multimer pattern for VWD type 2A, and the genotype for VWD type 2B, if available.

In addition, the age at first treatment for VWD and information on on-demand treatment with VWF-containing product in the previous 6 months before enrolment will be collected. Patients should preferably have a record of at least 6 spontaneous BEs requiring treatment in the past 3 months before screening. If this is not the case, the investigator should assess whether the patient experiences frequent enough bleedings to be included in the study.

For female patients of child-bearing potential, the birth control measures used within 6 months before enrolment will be documented. For all female patients, any history of heavy menstrual bleeding will be recorded.

8.5.3 Bleeding Episode (BE) Data

Study participants will be instructed by the investigator on recording BEs in their patient diaries. For any BE occurring during the study, whether treated or not, the following data will be recorded:

- BE type (spontaneous, traumatic, postoperative, menstrual, other)
- BE site
- BE severity (minor, major) (see **Table 4**)
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended
- BE treated or not treated
- Data on the administration of the VWF-containing product (see **Section 8.5.4**)
- Assessment of the effectiveness of treatment at the end of the BE (see **Section 8.5.5**)

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All of these parameters will be documented by the patient (together with the treating physician in case of on-site treatments) in the patient diary. Patients who experience a major BE should be treated at the treatment centre, if possible.

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

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

The severity of menstrual bleeding will be categorized as either 'minor or 'major'. Thus, menstrual bleeding of regular intensity classified as minor will be considered normal. Heavy menstrual bleeding will be regarded as a BE of 'major' severity (see **Table 4**).

BE severity will be assessed using the criteria given in **Table 4**.

Table 4 Definition of the Severity of Bleeding

Type of bleeding	Description
Minor bleeding	▪ **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) ▪ **Most nose bleeds** (i.e., those causing distress or interference with daily or social activities)
Major bleeding	Generally, ▪ requires hospitalization ▪ causes incapacity, significant pain, and substantial decrease in range of motion of affected joint (in case of joint bleeds) ▪ includes **symptomatic bleeding in a critical area or organ** (such as intracranial, intraspinal, intraocular, retroperitoneal, intraabdominal, intraarticular, or pericardial bleeds), **intramuscular bleeds** with compartment syndrome, **bleeds of the pelvic muscles**, **periorbital bleeds**, **gastrointestinal bleeds**, **other central nervous system bleeds**, **heavy menstrual bleeding**,* bleeding in the **area of the neck, throat, or pharynx**, **major trauma**, or **bleeding causing a decrease in haemoglobin levels by 20 g/L** (1.24 mmol/L) or more. *Heavy menstrual bleeding qualifies as 'major bleeding' and is defined as any menstrual bleeding that – interferes with daily activities such as work, housework, exercise, or social activities, – requires changing pads/tampons more frequently than hourly (referred to as 'flooding'), – lasts 7 or more days, – includes the presence of clots >1 cm combined with a history of flooding, or – yields a PBAC score ≥185.

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8.5.4 Data on the Administration of VWF-Containing Product

The following parameters will be documented:

- Name and batch number of VWF-containing product
- Dates and times of injections of VWF-containing product
- Doses of VWF-containing product in IU and IU/kg
- Purpose of injection with VWF-containing product (treatment of BE, prophylaxis of recurrent bleeding, surgery, prophylaxis after surgery)

8.5.5 Assessment of the Effectiveness of Treatment of BEs

At the end of a BE, treatment effectiveness will be assessed by the patient (together with the treating physician in case of on-site treatment) using the predefined criteria detailed in **Table 5**. The assessment of the treatment effectiveness is not required for menstrual bleedings.

Table 5 Effectiveness Assessment of the Treatment of BEs

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

The **proportion of BEs successfully treated with VWF-containing product** will be evaluated for all BEs taken together and by BE severity. All effectiveness ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated.'

8.5.6 Data on Surgical Prophylaxis

Any surgeries taking place during the patients' study participation should be reported and documented as outlined in the recommended flow chart of data collected during surgical prophylaxis (**Table 6**).

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Table 6 Recommended Flow Chart of Data Recorded During Surgical Prophylaxis

Parameters	For more information, see Section	Any time before surgery	Within 3 hours before surgery	Surgery		Post-operatively		
				Intra-operatively	End [1]	POP day 1	Any POP day	End of POP period [4]
Body weight		x						
Type of surgery (planned or emergency)		x						
Location of surgery		x						
Severity of surgery	**8.5.6.1**	x						
Duration of surgery					x			
Blood loss & transfusions during surgery					x			
Administration of VWF-containing product	**8.5.4**		x	(x)	(x)	(x)	(x)	(x)
FVIII:C plasma levels			#	(#)	(#) [2]	(#) [3]	(#)	(#)
VWF:Ac and VWF:Ag plasma levels			#	(#)	(#) [2]	(#) [3]	(#)	(#)
Vitals		x		x	x			
Presence of wound haematomas						x	x	x
Efficacy assessment by treating physician	**8.5.7**							x
Adverse drug reaction (ADR) monitoring	**10**	Throughout observation period						
Concomitant medications		Throughout observation period						

POP = postoperative, FVIII:C = factor VIII procoagulant activity, VWF:Ac = VWF activity (VWF:RCo, VWF:Gp1bM, or VWF:GP1bR), VWF:Ag = von Willebrand factor antigen

( ) Optional

Preferably before (≤30 min) and 30±15 minutes after administration of VWF-containing product, if these data are obtained as per standard of care

[1] Defined as the time after the last surgical suture

[2] Preferably obtained within an hour after the last surgical suture, if these data are obtained as per standard of care

[3] For major surgeries, levels documented for first 3 postoperative doses, if these data obtained as per standard of care

[4] Defined as the time when patient returns to regular on-demand treatment

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8.5.6.1 Severity of Surgery

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

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

All other surgeries are classified as **minor**.

8.5.6.2 Definitions of Surgery Periods and Time Points

- **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 on-demand treatment.
- The **end of the postoperative period** is the time the patient returns to on-demand treatment.

8.5.7 Assessment of the Effectiveness of Surgical Prophylaxis

An overall assessment of effectiveness will be made at the end of the postoperative period by the treating physician (**Table 7**).

Table 7 Effectiveness Assessment of Surgical Prophylaxis by Treating Physician

Excellent	Haemostasis similar to that of a haemostatically normal patient
Good	Mildly abnormal haemostasis in terms of quantity and/or quality (e.g., slight oozing)
Moderate/poor	Moderately abnormal haemostasis in terms of quantity and/or quality (e.g., moderate, controllable bleeding)
None	Severely abnormal haemostasis in terms of quantity and/or quality (e.g., severe haemorrhage that is difficult to control)

All effectiveness ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated' surgeries.

8.5.8 Quality of Life

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

- Patient-Reported Outcomes Measurement Information System (PROMIS)-29 [7–9] for patients of all ages. For patients aged ≥5.5 to <8 years, the questionnaires will be completed by the patient's parent/legal guardian. For patients ≥8 years, self-reporting will be used, if possible.
- 36-Item Short Form Health Survey, version 2 (SF-36v2, [10]) for patients ≥16 years
- 10-Item Short From Health Survey (SF-10, [11]) for patients ≥5.5 and <16 years of age

The completeness of the questionnaire will be checked by the treating physician, and the data will be entered in the eCRF.

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8.5.9 Joint Health Status

Joint health will be assessed using the Hemophilia Joint Health Score (HJHS) [12], which has been specifically validated for the assessment of clinical outcome in VWD [13]. Also, target joint(s), defined as having had 3 or more spontaneous BEs into a single joint in 6 consecutive months before the Screening Visit, will be recorded, if available.

8.5.10 Pictorial Blood Assessment Chart

Bleeding information from each menstrual period in this study will be collected using the Pictorial Blood Assessment Chart (PBAC) [14, 15]. The PBAC will be provided to all female patients of child-bearing potential.

The investigator will train all relevant patients on how to complete the PBAC. At each study visit, the investigator will review the completed PBAC and also calculate the PBAC score. The data documented in the PBAC and the investigator-calculated final score will be recorded in the eCRF.

8.6 DATA SOURCES

The data source for the calculation of the bleeding rate will be the information documented in the patient diaries as well as the information collected based on the review of the patient's medical records.

8.7 DATA MANAGEMENT

The treating physician will document clinical data as per routine practice in the patients' medical records and transfer information to the study-specific eCRF as required.

If any errors in the eCRFs are found during data review, queries will be generated and submitted to the site personnel. Once the query has been answered, Data Management will review the new or changed data to ensure an appropriate response and close the query.

8.8 DATA ANALYSIS

No formal sample size calculations were performed. The sample size of 55 patients was chosen based on feasibility and to allow data summaries to be produced. However, with a sample size of 55, a two-sided 95% confidence interval for the mean ABR will extend ±0.8 from the observed mean, assuming that the standard deviation is 3 or less and the confidence interval is based on the large sample z statistic.

The data will be analysed using descriptive statistical methods. Full details of the planned analyses will be given in a Statistical Analysis Plan, which will be completed before data analysis.

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8.9 QUALITY CONTROL

To ensure data quality, the treating physician should review the patient diaries returned by the patient for completeness. Whenever any information is missing, the treating physician will contact the patient to obtain the information and document the contact and the information obtained from the patient in the patient records.

The data entered into the eCRF by the treating physician or delegated person will be verified against the source documents by study monitors.

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9 PROTECTION OF HUMAN SUBJECTS

9.1 PATIENT INFORMATION AND INFORMED CONSENT

Freely given written informed consent for participation in this study will be obtained from all patients after the aims, methods, and other important aspects of this NIS that are relevant to the patient's decision to participate have been adequately explained.

The informed consent form must be signed, with the name and date noted by the patient, before the patient is exposed to any study-related procedure, including screening for eligibility. For patients not qualified to give legal consent, written consent must be obtained from the patient's parent(s) or legal guardian(s). Children old enough to understand the risks and benefits of the observational programme should also be informed and provide their written assent.

The treating physician will explain that the patients are 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. Also, the treating physician will complete the informed consent section of the eCRF for each patient enrolled.

Patients and/or their parents or legal guardians will be informed that they are free to withdraw their consent for participation in this NIS at any time during the study without any consequences for their further medical care and without the need to justify their decision.

Also, patients and/or their parents or legal guardians will be informed that their medical (source) records may be reviewed by study monitors or other personnel involved in the conduct of the study, and that these persons are bound by strict confidentiality obligations.

Patients will also be instructed as to the importance of cooperating with their treating physicians throughout the observational programme by carefully documenting any BEs and treatments in their study diaries and by attending all follow-up visits scheduled in agreement with their treating physicians.

9.2 SUBMISSION OF STUDY DOCUMENTS TO IECS/IRBS, REGULATORY AUTHORITIES, AND OTHER STAKEHOLDERS

In accordance with Good Pharmacoepidemiological Practices (GPP), the study will be approved by the competent IECs/IRBs. Also, the study protocol as well as any protocol amendments, a sample of the patient information and informed consent/assent forms, materials provided to the patients and/or their parents or legal guardians, and further requested information will be submitted to the appropriate IECs/IRB, regulatory authorities, and other stakeholders as required by national regulations. Before the first patient is enrolled into the study, any party (e.g., sponsor, treating physician, CRO) involved in notifying the relevant stakeholders should confirm in writing that all ethical and legal requirements have been met.

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9.3 CONFIDENTIALITY OF PATIENT DATA

The treating physician will ensure that the patient's confidentiality is preserved. In eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient code.

Documents not intended for submission to the Sponsor, i.e., a confidential patient identification code list, original consent forms, and patient records, will be maintained by the treating physician in strict confidence.

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10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1 SAFETY MONITORING

Throughout this NIS, all adverse drug reactions and other relevant safety information becoming known or arising during treatment with any of the VWF-containing products used in this study and as defined below have to be documented and reported to Octapharma.

10.1.1 Definition of Adverse Drug Reaction and Other Safety Information

Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended [Directive 2001/83/EC Art. 1(11)].

'Response' here means that a causal relationship between a medicinal product and an adverse event (AE) is at least a reasonable possibility [Guideline ICH-E2A].

ADRs may arise from the use of a product within or outside the terms of the marketing authorisation or from occupational exposure [Directive 2001/83/EC Art 101(1)]. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.

Serious Adverse Drug Reaction

A serious ADR (SADR) is an ADR that fulfils at least one of the following criteria:

- Results in death
- Is life-threatening (this implies that the patient was at risk of death at the time of the event; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing in-patient hospitalisation (hospitalisation does not refer to the treatment of an ADR on an out-patient status)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event, e.g.,
  - Suspected transmission of an infectious agent via a medicinal product
  - Inhibitor development
  - Thromboembolic event
  - Other reactions that should be reported in an expedited manner, although they did not immediately result in one of the above seriousness criteria, e.g., intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation

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Other Relevant Safety Information

Other relevant safety information is any information relating to:

- Pregnancies or breast-feeding
- Drug abuse (persistent, sporadic, or intentional excessive use of a medicinal product inconsistent with the product's summary of product characteristics (SmPC) or prescribing information, or acceptable medical practice)
- Misuse (situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information)
- Overdose (administration of a dose of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information)
- Medication errors (prescribing or dispensing error)
- Interactions with other medicinal products or devices
- Occupational exposure (an exposure to a medicinal product as a result of one's professional or non-professional occupation) associated with any VWF concentrate used during this study, even if no ADR occurred.

10.1.2 Reporting of Adverse Drug Reactions and Other Relevant Safety Information

For information about possible ADRs and other relevant safety information associated with each product used during this study, refer to the local summary of product characteristics or prescribing information.

Patients who carry out home treatment should be asked to inform their treating physicians about any relevant safety information as soon as they become aware of it. The treating physician will then assess the causal relationship of any events for ADRs and report these and other relevant drug safety information as required.

***ADRs in patients treated with* Wilate**

All suspected (serious and non-serious) ADRs and other relevant safety information associated with the **administration of *Wilate*** have to be reported in the Case Safety Report Form (CSRF) (see **Section 13**, **Annex 1**), which should be sent, by email, to the local safety units within one business day. The contact details of the local safety units are given in **Section 13**, **Annex 2**.

Quarterly a reconciliation shall be made between study team and local safety units to ensure all ADR and other safety relevant information have been completely forwarded to local safety units.

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Information on all **pregnancies** occurring during the study period **in patients treated with *Wilate*** is to be collected in the *Pregnancy Form* (see **Section 13**, **Annex 3**) and sent to the local safety units (in **Section 13**, **Annex 2**.)

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:

***ADRs in patients treated with VWF-containing product other than* Wilate**

All suspected (serious and non-serious) ADRs and other relevant safety information associated with the **administration of any VWF-containing product other than *Wilate*** used during this study have to be reported to the responsible parties in accordance with local regulations.

All **pregnancies** occurring during the study period **in patients treated with any VWF-containing product other than *Wilate*** have to be reported to the responsible party in accordance with local regulations.

10.1.3 Method and Duration of Observation of the Study Areas after the Occurrence of ADRs

After an ADR is discovered, it should be monitored until it is resolved or until it is regarded as permanent. The outcome of the ADR should be documented and classified in one of the following categories: “Recovered, resolved,” ”Recovering, resolving,” “Not recovered, not resolved,” “Recovered, resolved with sequelae,” “Fatal,” or “Unknown.”

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11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1 FINAL STUDY REPORT

A final study report will be prepared after completion of the study and submitted to relevant study stakeholders as required locally.

11.2 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is envisaged by a physician, the physician 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 author.

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

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13 ANNEXES

Annex 1 Case Safety Report Form 39
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Annex 3 Pregnancy Form 50

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Annex 1 Case Safety Report Form

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Case Safety Report Form

Local Log Number _____

1. GENERAL INFORMATION

Local Log Number _____

1.1 Report version and dates

◯ Initial Date initially received: (dd/mm/yyyy) _____

◯ Additional information Date of additional information received: (dd/mm/yyyy) _____

1.2 Report source

◯ Health care professional ◯ Consumer (e.g. patient) ◯ Health Authority ◯ Literature

◯ Non-Interventional study, please enter Study ID: _____

◯ Other, please specify: _____

1.3 Special Situation

*If "Pregnancy/breast feeding" is ticked, please complete also the Pregnancy Report form.

◯ Pregnancy/breast feeding* ◯ Misuse/abuse/overdose ◯ Off-label-use ◯ Lack of efficacy ◯ Medication error ◯ Other, please specify: _____

1.4 Country

Country of occurrence _____

2. REPORTER

2.1 Primary Source

#1

Given name: _____ Family name: _____ Organisation: _____

Street: _____ Country: _____

Postcode: _____ City: _____ State: _____

Telephone number: _____ Fax number: _____ E-mail address: _____

Qualification: ◯ Physician ◯ Pharmacist ◯ Nurse ◯ Health care professional (unspecified) ◯ Patient ◯ Other non-health care professional

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Case Safety Report Form

Local Log Number _____

#2	Given name:_____ Family name:_____ Organisation:_____
	Street:_____ Country: _____
	Postcode:_____ City: _____ State:_____
	Telephone number:_____ Fax number:_____ E-mail address:_____
	Qualification: ◯ Physician ◯ Pharmacist ◯ Nurse ◯ Health care professional (unspecified) ◯ Patient ◯ Other non-health care professional

3. PATIENT INFORMATION

3.1 Patient Details

Initials: First letter of Firstname and first letter of Surname

Initials: Date of birth: (dd/mm/yyyy) Age: Age Unit: Sex: ◯ Female ◯ Male ☐ Pregnant Week of gestation: _____

_____ _____ _____ _____

Height: (cm) Weight: (kg) Blood Group: Rhesus Factor: Patient Study ID or any medical record number:

_____ _____ _____ _____

Ethnic group: ◯ Caucasoid ◯ Mongoloid ◯ Negroid ◯ Australoid

◯ Other, please specify: _____

3.2 Patient history of illnesses and diseases (e.g. allergies, medical history, alcohol abuse, etc.)

◯ Yes (please specify below) ◯ None ◯ Unknown

	Illness or disease (please add each illness/disease in a separate line)

3.3 Concomitant medication (other medication the patient received prior to the adverse reaction(s) or at the time of suspect drug(s) administered)

◯ Yes (please specify below) ◯ None ◯ Unknown

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Concomitant Medication 1

Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 2

Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 3

Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 4

Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 5

Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

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Concomitant Medication 6					
Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 7					
Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 8					
Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 9					
Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

Concomitant Medication 10					
Trade name				Active ingredient	
Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route
Indication					

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Local Log Number _____

4. SUSPECT PRODUCT(S) (Information on treatment that led to the adverse reaction(s))

4.1 Overall treatment regimen of suspect product(s)

Suspect Product 1

Product/Generic (incl. strength)	Batch number(s)	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)

Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route

Infusion rate	Duration (#)	Duration (unit)	Indication

Suspect Product 2

Product/Generic (incl. strength)	Batch number(s)	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)

Dosage (#)	Dosage (unit)	Frequency (#)	Interval (#)	Interval (unit)	Route

Infusion rate	Duration (#)	Duration (unit)	Indication

Suspect Product 3

Product/Generic (incl. strength)	Batch number(s)	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)

Dosage (#):	Dosage (unit):	Frequency (#)	Interval (#)	Interval (unit):	Route

Infusion rate	Duration (#)	Duration (unit)	Indication

4.2 Previous Treatment with suspect product(s)

Did the patient receive previous treatment with suspect product(s) and/or similar product(s)? ◯ Yes ◯ No ◯ unknown

Name of product_____ Treatment date (approx. period):_____

Did the patient experience adverse reaction in previous treatment? ◯ Yes ◯ No ◯ Unknown

Adverse reaction_____ Reaction date (dd/mm/yyyy)_____ Outcome_____

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Local Log Number _____

Name of product_____ Treatment date (approx. period) _____

Did the patient experience adverse reaction in previous treatment? ○ Yes ○ No ○ Unknown

Adverse reaction_____ Reaction date (dd/mm/yyyy) _____ Outcome_____

Name of product_____ Treatment date (approx. period) _____

Did the patient experience adverse reaction in previous treatment? ○ Yes ○ No ○ Unknown

Adverse reaction_____ Reaction date (dd/mm/yyyy) _____ Outcome_____

5. ADVERSE REACTION(S) (Adverse reaction(s) according to the primary reporter's words and/or phrases)

* Latency: Time since the treatment with suspect drug(s)

Adverse Reaction 1

Adverse reaction/ diagnosis:			Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)
Duration:	Duration (unit):	Latency* (incl. units):	Outcome:	

Adverse Reaction 2

Adverse reaction/ diagnosis:			Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)
Duration:	Duration (unit):	Latency* (incl. units):	Outcome:	

Adverse Reaction 3

Adverse reaction/ diagnosis:			Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)
Duration:	Duration (unit):	Latency* (incl. units):	Outcome	

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Local Log Number _____

1. Action taken with respect to suspect product(s)? (state product for resp action in case different actions were taken for different products)	Product	Action
2. If product was withdrawn, did reaction(s) stop/improve after stopping suspect product without patient receiving remedial therapy?	○ Yes ○ No ○ Unknown ○ NA	
3. Did reaction(s) reappear after reintroduction?	○ Yes ○ No ○ Unknown ○ NA	
Remedial Therapy (Information on therapy to treat the adverse reaction(s).	If yes, please specify:	

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6. LABORATORY TEST			
Laboratory tests performed (Any tests relating to the adverse reaction(s) including results, units, and normal range.)			◯ Yes ◯ No ◯ Unknown
Lab Test 1			
Test name / Which test was performed?			
Test date (dd/mm/yyyy)	Test result	Test result unit	
Comment			
Lab Test 2			
Test name / Which test was performed?			
Test date (dd/mm/yyyy)	Test result	Test result unit	
Comment			
Lab Test 3			
Test name / Which test was performed?			
Test date (dd/mm/yyyy)	Test result	Test result unit	
Comment			

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Case Safety Report Form

Local Log Number _____

Lab Test 4		
Test name / Which test was performed?		
Test date (dd/mm/yyyy)	Test result	Test result unit
Comment		

7. CASE REPORT ASSESSMENT (Provided by the primary reporter)

7.1 Seriousness Assessment

○ Non-Serious ○ Not provided by the primary source

○ Serious

IF SERIOUS, please choose at least one of the following criteria (defined by the primary reporter):

☐ Patient hospitalized From:* _____ To:* _____

☐ Hospitalization prolonged From:* _____ To:* _____

☐ Life threatening

*Date format: (dd/mm/yyyy)

☐ Resulting in persistent or significant disability/incapacity

☐ Resulting in congenital anomaly or birth defect

☐ Medically significant _____

☐ Fatal (please complete section below)

☐ Other, please specify:

IF FATAL, please complete:

Date of death: _____ Autopsy performed: ○ Yes ○ No ○ Unknown
(dd/mm/yyyy)

Cause of death:

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7.2 Causality Assessment
Relatedness of the observed symptoms/reactions to the administration of suspected Octapharma product: ○ Probably related ○ Possibly related ○ Unlikely related ○ Not related ○ Unclassifiable/Unknown Comment:

Other possible cause(s) of the adverse reaction(s):

☐ Underlying disease ☐ Concomitant medication ☐ Other suspected product (non-Octapharma)

☐ Other, please specify:

8. NARRATIVE / DETAILED DESCRIPTION OF EVENT
(A detailed description of the chronology and outcome of the adverse reaction(s))

9. OTHER COMMENTS

Was Competent Authority(ies) informed?	If yes, please enter Authority reference #:
Comment	

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Annex 2 Contact Addresses of Local Safety Offices

Country	Address	Email
Belarus	[redacted]	
Bulgaria		
Croatia		
Hungary		
Lebanon		
Russia		
Ukraine		
United States of America		

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Annex 3 Pregnancy Form

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CDSU Ref:

Pregnancy Form

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Reporter Details

Surname		Firstname	
Qualification	☐general practitioner physician ☐obstetrician / gynaecologist ☐consumer ☐other		
Address			
Tel		Fax	
Email			

Please complete the form as appropriate and accurately as possible, date, sign and return as soon as possible to the Octapharma Local Safety Office (refer to the protocol Section 13, Annex 2)
WE THANK YOU FOR YOUR CO-OPERATION

Section A Maternal Information

Patient (initials)	Date of birth (dd/mm/yyyy)	Age	Height (cm)	Weight (kg)

A.1 Obstetrical history

No of previous pregnancies		No of live-births	

Result of previous pregnancies (tick as appropriate and please specify gestational age)

☐Miscarriage	
☐Elective termination	
☐Late foetal death	
☐Ectopic pregnancy	
☐Molar pregnancy	
☐Other	

Did any OTHER complication occur during previous pregnancies?	☐ No ☐ Yes ->	
Or were there any foetal/ neonatal abnormalities?	☐ No ☐ Yes ->	
History of subfertility and treatment	☐ No ☐ Yes ->	

A.2 Maternal Medical History

☐ Hypertension	☐ Allergic disease	☐ Hepatitis
☐ Diabetes	☐ Heart disease	☐ AIDS
☐ Seizure disorder	☐ Depression	☐ Other
☐ Thyroid disorder	☐ Psychiatric disorder	
☐ Asthma	☐ Sexually transmitted disorder	

A.3 Current Pregnancy

Date of last menstrual period (LMP) (dd/mm/yyyy)	Gestational age at the time of this report (weeks)	Estimated date of delivery (dd / mm / yyyy)

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Pregnancy Form

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A.3 Current Pregnancy

Date of last menstrual period (LMP) (dd/mm/yyyy)	Gestational age at the time of this report (weeks)	Estimated date of delivery (dd / mm / yyyy)

No of foetuses?		Treatment for infertility?	☐ No ☐ Yes	

Medications taken during pregnancy (incl. OTC products and pregnancy supplements)

Drug & Batch	Dose/Unit	Route	From	To	Indication

Recreational Drug Use

Tobacco	☐ No ☐ Yes	Amount:	
Alcohol	☐ No ☐ Yes	Amount:	
Illicit drugs	☐ No ☐ Yes	Amount:	

Previous Immunity to

☐ Rubella	☐ Toxoplasmosis	☐ Cytomegalo virus	☐ Listeria

Antenatal Check-Up

	Date	Significant observations
☐ Ultrasound		
☐ Amniocentesis		
☐ Maternal Serum Alpha-Fetoprotein (AFP)		

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☐ Chorionic Villi Biopsy		
☐ Umbilical Blood Sampling		
☐ Biophysical Electrical Monitoring		
☐ Other		

A.4 Familial History

Spontaneous abortion	☐ Mother (Maternal) ☐ Father (Maternal)	☐ Mother (Paternal) ☐ Father (Paternal)

☐ Hereditary disease ->

☐ Anomalies / Malformation ->

☐ Psychomotor retardation ->

A.5 Additional Comments

Reporter Name:	**Date of report:**	**Signature:**

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Pregnancy Form

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Section B Paternal Information (If appropriate)

Patient (initials)	Date of birth (dd/mm/yyyy)	Age	Height (cm)	Weight (kg)

B.1 Medical History

			From	To

B.2 Medications around time of conception

Drug & Batch	Dose/Unit	Route	From	To	Indication

B.3 Additional Comments

Reporter Name:	**Date of report:**	**Signature:**

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Pregnancy Form

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Reporter Details

Surname		Firstname	
Qualification	☐general practitioner physician ☐obstetrician / gynaecologist ☐consumer ☐other		
Address			
Tel		Fax	
Email			

Please complete the form as appropriate and accurately as possible, date, sign and return as soon as possible to the Octapharma Local Safety Office (refer to the protocol Section 13, Annex 2)

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Section C Neonatal Information

Neonatal (initials)	Date of birth (dd/mm/yyyy)	Gestational age (LMP)at birth	Gender
			☐ Male ☐ Female

Height (cm)	Weight (kg)	Head circumference (cm)	Apgar score (1 min)	Apgar score (5 min)

☐ Live birth ☐ Foetal death (please complete C2) ☐ Elective termination (please complete C2)

C.1 Delivery details

Mode of delivery	☐ Natural ☐ Caesarean section	
Labour / delivery complications (e.g. foetal distress, amniotic fluid abnormal)	☐ No ☐ Yes ->	
Abnormal placenta	☐ No ☐ Yes ->	
Malformations/ anomalies / diseases diagnosed at birth	☐ No ☐ Yes ->	
Dysmaturity	☐ No ☐ Yes ->	
Need for resuscitation/ admission in ICU	☐ No ☐ Yes ->	
Other treatments	☐ No ☐ Yes ->	

C.2 Foetal Information

Foetal examination performed ☐ No ☐ Yes ->	Results if available (eg gender, anomalies, identified cause of death):

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C.3 Additional Comments		
Reporter Name:	**Date of report:**	**Signature:**

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Reporter Details

Surname		Firstname	
Qualification	☐general practitioner physician ☐obstetrician / gynaecologist ☐consumer ☐other		
Address			
Tel		Fax	
Email			

Please complete the form as appropriate and accurately as possible, date, sign and return as soon as possible to the Octapharma Local Safety Office (refer to the protocol Section 13, Annex 2)

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Section D Infant Information

Infant (initials)	Date of birth (dd/mm/yyyy)	Age	Height (cm)	Weight (kg)

Breast-fed?	☐ No ☐ Yes	Until:
Developmental assessment performed?	☐ No ☐ Yes ->	Test & Results:

D.1 Medical

Significant Illnesses/hospitalizations	From	To	Treatment(s)
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes

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D.2 Drug Therapies

Drug & Batch	Dose/Unit	Route	From	To	Indication

D.3 Additional Comments

Reporter Name:	**Date of report:**	**Signature:**

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