ISRCTN11217735 https://doi.org/10.1186/ISRCTN11217735

Clinical study to assess how well wilate works in the regular treatment of young children with severe von Willebrand disease

Submission date
12/07/2021

Recruitment status
No longer recruiting

Registration date
23/08/2021

Overall study status
Completed

Last Edited
08/03/2024

Condition category
Haematological Disorders

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Von Willebrand disease (VWD) is a blood disorder in which the blood does not clot properly due to low levels of the clotting protein von Willebrand factor (VWF). Medicines such as wilate can be used to replace the missing factor. The aim of this study is to determine the effectiveness of wilate in the prophylactic (preventative) treatment of up to 12 paediatric patients with severe VWD under the age of 6 years, for a period of 12 months.

Who can participate?
Patients under the age of 6 years suffering from severe VWD, regardless of previous treatment, with a minimum body weight of 12.5 kg at screening, requiring treatment with a VWF-containing product.

What does the study involve?
Patients are asked to visit the study site for a screening visit, which will include collecting data on medical history and demographic characteristics, a general physical examination and a blood sample.
The next visit will take place after the first administration of the study drug at the investigational site, with blood samples taken before, after 15 minutes, and after 3, 9, 24, 48 and 72 hours later. Additional samples are taken for VWD type 3 patients with a minimum body weight of 14.5 kg.
After drawing the 72 hours blood sample, the first treatment will be administered, with the dose based on the patient's body weight, and a 2-3 times per week home administration schedule over 12 months. Additional visits to the site are foreseen at 1, 2, 3, 6, 9 and 12 months after the start of treatment.

What are the possible benefits and risks of participating?
For patients with VWD, the replacement of VWF using a VWF concentrate is one common method to normalize the blood’s ability to clot and to avoid or stop bleeding episodes, especially in cases where desmopressin cannot be used or is not effective. Medical experts agree that replacement treatment with VWF concentrates in VWD is of benefit to patients. Several studies

suggest that prophylaxis may be the optimal treatment, particularly in patients with severe bleeds due to VWD. However, prophylactic treatment in VWD is still not very common, and will be offered to the study patients for a period of 12 months. Participation will provide information about the study drug which may have a future benefit to others.

Where is the study from?
Octapharma (Austria)

When is the study starting and how long is it expected to run for?
March 2020 to December 2024

Who is funding the study?
Octapharma (Austria)

Who is the main contact?
1. Cristina Solomon, cristina.solomon@octapharma.com
2. Tarja-Elina Weisz, tarja-elina.weisz@ocpharma.com

Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-004344-28

ClinicalTrials.gov (NCT)
NCT04953884

Protocol serial number
WIL-33 / doc ID 3534

Study information

Scientific Title
Clinical study to investigate the efficacy, pharmacokinetics, immunogenicity and safety of wilate in severe von Willebrand disease patients under the age of 6 years

Acronym
WIL-33

Study objectives
Prophylactic treatment with von Willebrand factor concentrate may be beneficial to paediatric patients with severe von Willebrand disease (VWD). Well standardized PK data, as well as efficacy data in the long-term prevention of breakthrough bleeds, is not available for wilate so far. The WIL-33 study aims 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.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 14/04/2021, National Committee for Ethical Expertise of Clinical Trials (str. A. Cosmescu, 3; MD 2009, mun. Chişinău, Moldova; +373 (0)22205414; comitetetica@msmps.gov.md), ref: 1067
2. Approved 05/05/2021, Ethics Committee for Clinical Trials Related to Medicinal Products and Medical Devices at Agency for Medicines and Medical Devises (ul. Sv. Kiril i Metodij 54, kat 1; 1000 Skopje; Republic of North Macedonia; +389 (0)2 5112-394; email: not available), ref: 12-2264
3. Approved 15/06/2021, Moscow City Independent Ethics Committee (MGEK, Minskaya str., 12, bld. 2, Moscow, 121096, Russia; +7 (0)499 144 0028; email: not available), ref: Meeting no. 89
4. Approved 29/06/2021, Loma Linda University, Office of the Vice President of Research Affairs (24887 Taylor Street, Suite 202, Loma Linda, CA 92350, USA; +1 (0)909 558 4531; irb@llu.edu), ref: IRB# 5210168
5. Approved 14/07/2021, Ethics committee within the Belarusian Research Center for Pediatric

Oncology, Hematology and Immunology (Borovlyanskiy S/S, v. Borovlyany, Frunzenskaya str., 43, 223053 Minsk region, Republic of Belarus; +375 (0)29 624 36 54; email: not available), ref: not applicable
6. Approved 15/07/2021, Independent Ethics Committee within FGBU “NMITs DGOI n.a.Dmitriy Rogachev" Ministry of Health of the Russian Federation (Samory Mashela str., 1, Moscow, 117997, Russia; +7 (0)495 287 65 70 EXT. 5522; info@fnkc.ru), ref: 7e/7-21
7. Approved 20/07/2021, Ethics Committee of Western Ukrainian Specialized Children’s Medical Centre (27, Dnisterska Street, Lviv, 79035, Ukraine; +38 (0)67 303 03 21; email: not available), ref: 80/b
8. Approved 29/10/2021, Ethics Committee of National Children's Specialized Hospital "Okhmatdyt" (28/1, Viacheslava Chornovola St, Kyiv, Ukraine, 01135; +38 (0)44 236 06 12; email: not available), ref: not available
9. Approved 05/01/2023, Ethics Committee of the Medical Faculty of Rheinische Friedrich Wilhelm-Universität Bonn (Venusberg-Campus 1, Gebäude C 74/4 OG, 53127 Bonn, Germany; +49 228 287 51562; ethik@ukbonn.de), ref: 347/22-AMG-ff
10. Approved 05/01/2023, Ethics Committee of Ärztekammer Nordrhein (Tersteegenstraße 9, 40474 Düsseldorf; 0211/4302-0; aerztekammer@aekno.de), ref: 347/22-AMG-ff
11. Approved 24/01/2023, Tulane University Biomedical IRB, Tulane Human Research Protection Office Institutional Review Boards (1440 Canal Street, Suite 1705, TW-8436; New Orleans, LA 70112, USA; +1 (504) 988-2665; irbmain@tulane.edu), ref: 2022-1488

Study design
Open-label prospective non-controlled international multi-centre phase III study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Von Willebrand disease

Interventions
Patients will be treated with the VWF/FVIII concentrate wilate, produced from the plasma of human donors, which is presented as a powder and solvent for intravenous injection containing nominally 500 IU or 1000 IU human VWF and human FVIII per vial.

Treatments will be administered in the course of
1. Pharmacokinetic investigation (PK visit) - within 4 weeks after screening
2. Incremental recovery (IVR) visits to the study site (after 1, 2, 3, 6, 9, 12 months after the start of the prophylactic treatment phase)
3. Regular prophylactic treatment over 12 months (2-3 times per week)
4. Treatment of bleeding episodes on demand
5. Surgical interventions as surgical prophylaxis

Wilate dosage for PK assessment:
Single dose of 80 IU/kg body-weight (BW) - exact dose calculated according to the nominal potency, with 70–85 IU/kg BW as the acceptable range

Wilate dosage recommendations for IVR visits and prophylactic treatment:
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 will 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.

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:
Minor haemorrhage: loading dose 30–50 IU/kg BW; maintenance dose 30–40 IU/kg BW every 12–24 hours; therapeutic goal to maintain VWF:Ac and FVIII:C trough levels >30%;
Major haemorrhage: loading dose: 50–80 IU/kg BW; maintenance dose: 30–50 IU/kg BW every 12–24 hours; therapeutic goal to maintain VWF:Ac and FVIII:C trough levels >50%

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

Intervention Type
Biological/Vaccine

Phase
Phase III

Drug/device/biological/vaccine name(s)
Wilate (von Willebrand Factor [VWF] and Factor VIII [FVIII])

Primary outcome(s)
The total annualised bleeding rate (tABR) during prophylactic treatment with wilate: the tABR will be calculated as the total number of spontaneous bleeds, traumatic bleeds, and other bleeds occurring in the time period between the first prophylactic dose of wilate and the Study Completion Visit, divided by the duration (in years) between the first prophylactic dose of wilate and the Study Completion Visit. Bleeding episodes occurring within surgery periods will be excluded from the calculation of tABR. In addition to the estimates of the tABR exploratory 95% CIs will be calculated from a Poisson regression model

Key secondary outcome(s))
1. PK profile characteristics of VWF:Ac (by measuring the Ristocetin Co-Factor [VWF:RCo]) and FVIII:C (measured using the one-stage assay [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. Pharmacokinetic parameters will be computed for VWF:Ac and FVIII:C vs time profiles. 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 based on pre-dose-adjusted concentration vs. time profiles.
2. Incremental in-vivo recovery (IVR) of wilate for VWF:Ac (VWF:RCo) and FVIII:C (OS) at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment
3. Efficacy of wilate in the treatment of spontaneous and traumatic breakthrough BEs based on the proportion of spontaneous and traumatic BEs successfully treated with wilate as assessed by the use of a 4-point ordinal haemostatic efficacy scale (excellent – good – moderate – none) throughout the study (whenever a BE is treated)
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. Primarily, all obtained data on treatment characteristics (wilate dosages, frequencies, total consumption) and BEs (duration, frequency, efficacy assessment) will be described by providing summary statistics and supporting figures where appropriate.
In general, the efficacy of wilate in the treatment of bleeding episodes will also be presented by type (spontaneous, traumatic, postoperative, other), sites (nose, oral cavity, knee, ankle, elbow, arm, leg, intestinal and other. In addition, knee, ankle and elbow sites will be summarized as site 'joint') and severity (minor, moderate, major, life-threatening).
4. The overall efficacy of wilate in perioperative prophylaxis against excessive bleeding as assessed by the responsible treating Investigator using a 4-point ordinal haemostatic efficacy scale (excellent – good – moderate – none) at the end of the postoperative period
5. Wilate consumption data for prophylactic treatment, for on-demand treatment and during surgical prophylaxis through individual documentation of each treatment in the patient diary throughout the study

Completion date
31/12/2024

Eligibility

Key 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 (and 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))

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Upper age limit
6 years

Sex
All

Total final enrolment
12

Key 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
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

Date of first enrolment
22/09/2021

Date of final enrolment
13/11/2023

Locations

Countries of recruitment
Belarus

Germany

Moldova

North Macedonia

Russian Federation

Ukraine

United States of America

Study participating centre
Loma Linda University Health
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United States of America
92408

Study participating centre
Morozovskaya Children's Hospital
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Study participating centre
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Study participating centre
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Study participating centre
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Institut für Experimentelle Hämatologie und Transfusionsmedizin (IHT)
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Bonn
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53127

Study participating centre
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Sponsor information

Organisation
Octapharma (Austria)

ROR
https://ror.org/022k50n33

Funder(s)

Funder type
Industry

Funder Name
Octapharma

Alternative Name(s)
Octapharma AG

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available as this is an industry-sponsored clinical trial. Upon completion of the clinical study report data will be held at Octapharma Pharmazeutika Produktionsges.m.b.H. and results are planned to be published in a peer-reviewed journal.

IPD sharing plan summary

Not expected to be made available