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

Summary

EudraCT number	2018-004675-13
Trial protocol	BG HU HR
Global end of trial date	23 April 2022

Results information

Result version number	v1 (current)
This version publication date	03 March 2023
First version publication date	03 March 2023

Trial information

Trial identification

Sponsor protocol code	WIL-31

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04052698
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 011303

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, 8853
Public contact	Sigurd Knaub, Octapharma AG, sigurd.knaub@octapharma.com
Scientific contact	Sylvia Werner, Octapharma AG, sylvia.werner@octapharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki, national regulatory requirements and FDA Code of Federal Regulations. Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as monitoring of AEs, SAEs and concomitant medication.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	05 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Belarus: 2
Country: Number of subjects enrolled	Lebanon: 16
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	43
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	10
Adolescents (12-17 years)	14
Adults (18-64 years)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients aged ≥6 years with diagnose of Von Willebrand Disease VWD type 1, 2A, 2B, 2M, or 3 according to medical history and requiring substitution therapy with a VWF-containing product to control bleeding were screened according to predefined in- and exclusion criteria.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Wilate

Arm description:

The FVIII/VWF concentrate Wilate, produced from plasma of human donors, was presented as a powder and solvent for intravenous injection containing nominally 500 IU or 1000 IU human VWF and human FVIII per vial. The prophylactic dose for each patient was determined by the Principal Investigator based on each patient's clinical condition.

Arm type	Experimental
Investigational medicinal product name	Wilate
Investigational medicinal product code	
Other name	Wilate , Factor VIII (plasma derived)
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

For the PK assessment in patients (6–16 years), a single dose of 60 ± 10 IU/kg BW was to be administered. For prophylactic treatment, IMP was to be administered 2–3 x/week (20–40 IU/kg BW for 12 months). The prophylactic dose was determined by the Investigator based on the patient's clinical condition and at following time points: In patients (≥17 years), first prophylactic dose was to be administered at time of the baseline IVR assessment, in patients (6–16 years) after completion of the PK phase. In case of unacceptably frequent spontaneous breakthrough BEs (i.e., more than 2 spontaneous BEs or 1 major spontaneous BE within a 30-day period), the dose of Wilate was to be increased by approx. 5 IU/kg (depending on the entire content of the additional vials that need to be reconstituted). If, after a dose increase, patients still experienced more than 2 spontaneous bleeding episodes, the dosing interval was to be shortened from 2 x/week to 3 x/week.

Number of subjects in period 1	Wilate
Started	43
Completed	30
Not completed	13
Protocol violation	10
Adverse event, non-fatal	2
permanently left country for job	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	43	43	
Age categorical Units: Subjects			
6-<12 yrs	10	10	
12-<17 yrs	8	8	
≥17 yrs	25	25	
Age continuous Units: years			
median	17		
full range (min-max)	7.0 to 61.0	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	26	26	

End points

End points reporting groups

Reporting group title	Wilate
Reporting group description:	
The FVIII/VWF concentrate Wilate, produced from plasma of human donors, was presented as a powder and solvent for intravenous injection containing nominally 500 IU or 1000 IU human VWF and human FVIII per vial. The prophylactic dose for each patient was determined by the Principal Investigator based on each patient's clinical condition.	
Subject analysis set title	Patients 6-<12 years
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pediatric patients 6-<12	
Subject analysis set title	Patients 12-<17 years
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients aged 12-<17 years	
Subject analysis set title	Patients ≥17
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Adult patients aged ≥17 years	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled patients who received at least one dose of IMP after the Baseline IVR Visit in adults or the Baseline PK Visit in children.	
Subject analysis set title	Modified full analysis set (mFAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The modified full analysis set (mFAS) was a subset of the FAS excluding all patients for whom laboratory results did not confirm the patient's VWD status, i.e., severe VWD Type 1, 2A, 2B, 2M or 3. These patients seem to have had mild VWD, Hemophilia A, or an unknown bleeding disorder, and were excluded from the mFAS as they were not a true representation of the target population.	
Subject analysis set title	Estimated Rate WIL-29
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
For the efficacy assessment the individual annualized bleeding rates under prophylactic treatment in this study was compared to the annualized bleeding rates recorded for the same patient during the previous, non-interventional study WIL-29	
Subject analysis set title	Estimated Rate WIL-31
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Annualized bleeding rates under prophylactic treatment in study WIL-31 , which was compared to the annualized bleeding rates recorded for the same patient during the previous, non-interventional study WIL-29	
Subject analysis set title	6-<12 years (mFAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Population of mFAS Set aged 6-<12 years	
Subject analysis set title	12-<17 yrs (mFAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Population from mFAS Set aged 12-<17 years	
Subject analysis set title	≥17 yrs (mFAS)

Subject analysis set type	Sub-group analysis
Subject analysis set description: Population from mFAS Seit aged ≥17 years	
Subject analysis set title	Type 1 VWD (mFAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Type 1 VWD	
Subject analysis set title	Type 2 VWD (mFAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Type 2 VWD	
Subject analysis set title	Type 3 VWD (mFAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Type 3 VWD	

Primary: Total annualized bleeding rate (TABR)

End point title	Total annualized bleeding rate (TABR)

End point description:

The primary endpoint of this study was to demonstrate that prophylactic treatment with Wilate lowers the patients' total annualized bleeding rate (TABR) observed during on-demand treatment by more than 50%.
The individual annualized bleeding rates under prophylactic treatment in this study was compared to the annualized bleeding rates recorded for the same patient during a previous, non-interventional study (WIL-29).

End point type	Primary

End point timeframe:

Time period between first prophylactic dose of IMP at baseline and the day of the last dose at 12 months.

End point values	Estimated Rate WIL-29	Estimated Rate WIL-31		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	33		
Units: bleeding events per year				
number (not applicable)	33.3751	5.4914		

Statistical analyses

Statistical analysis title	Ratio of TABR in WIL-31 and WIL-29

Statistical analysis description:

Ratio calculated as the ABR during the prophylaxis period in WIL-31 vs the corresponding ABR during the On-Demand Period in WIL-29.

Comparison groups	Estimated Rate WIL-29 v Estimated Rate WIL-31

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001 [2]
Method	Regression, Linear
Parameter estimate	mean ratio
Point estimate	0.1645
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.10194
upper limit	0.26558

Notes:

[1] - Ratio calculated as the ABR during the prophylaxis period in WIL-31 vs the corresponding ABR during the On-Demand Period in WIL-29

[2] - p-value from a 1-sided test whether the mean ratio is less than 0.5 utilizing a negative binomial counting regression model.

Secondary: Spontaneous annualized bleeding rate (SABR)

End point title	Spontaneous annualized bleeding rate (SABR)

End point description:

The individual spontanoeaous annualized bleeding rates under prophylactic treatment in this study was compared to the spontaneous annualized bleeding rates recorded for the same patient during a previous, non-interventional study (WIL-29) using a negative binomial counting regression model.

End point type	Secondary

End point timeframe:

Time period between first prophylactic dose of IMP at baseline and the day of the last dose at 12 months.

End point values	Estimated Rate WIL-29	Estimated Rate WIL-31		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	33		
Units: bleeding events per year				
number (not applicable)	24.4168	3.3925		

Statistical analyses

Statistical analysis title	Ratio of SABR in WIL-31 and WIL-29

Statistical analysis description:

Ratio calculated as the ABR during the prophylaxis period in WIL-31 vs the corresponding ABR during the On-Demand Period in WIL-29.

Comparison groups	Estimated Rate WIL-31 v Estimated Rate WIL-29

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001 [4]
Method	Regression, Linear
Parameter estimate	mean ratio
Point estimate	0.1389
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07664
upper limit	0.25187

Notes:

[3] - Ratio calculated as the ABR during the prophylaxis period in WIL-31 vs the corresponding ABR during the On-Demand Period in WIL-29

[4] - p-value from a 1-sided test whether the mean ratio is less than 0.5 utilizing a negative binomial counting regression model

Secondary: Wilate consumption for prophylaxis

End point title	Wilate consumption for prophylaxis

End point description:

Wilate consumption (VWF/FVIII IU/kg per week per patient) for prophylaxis.

End point type	Secondary

End point timeframe:

From Baseline to end of study at month 12.

End point values	Modified full analysis set (mFAS)	6-<12 years (mFAS)	12-<17 yrs (mFAS)	≥17 yrs (mFAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	9	6	18
Units: IU/kg				
median (full range (min-max))	58.28 (28.2 to 113.7)	66.34 (42.6 to 113.7)	64.44 (52.6 to 101.0)	53.46 (28.2 to 109.6)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs have been elicited at each visit (Baseline up to Study Completion Visit) , whether scheduled or unscheduled.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Safety Set

Reporting group description:

The safety (SAF) set included all patients who received at least one dose of IMP.

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 43 (9.30%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 pneumonia			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.7 %

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 43 (60.47%)		
Investigations			
Parvovirus B19 test positive			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	20		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Pain in extremity			

subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2019	Protocol Version 2 (Amendment 1) - Refinement of Exclusion criteria 1 and 6 - The 1-Month and 2-Month Contacts were changed into formal study visits that also include an IVR assessment. - Between the 3- and 6-Month Visits, the 6- and 9-Month Visits, and the 9- and 12-Month Visits, monthly telephone contacts were added. - The Wilate dose for the first IVR assessment at the time of the Baseline IVR Visit was changed from 60±10 IU/kg BW to being each patient's individually assigned prophylactic dose as used for subsequent visits. - Obtaining female patients' history of heavy menstrual bleeding was added at screening. - The PROMIS-29 was added as an additional QoL assessment. - Assessment of joint status using the Hemophilia Joint Health Score (HJHS) and the documentation of target joints were added. - The Pictorial Blood Loss Assessment Chart was implemented and the PBAC score was added as a tool to estimate menstrual blood loss. - The minimum number of patients aged ≥6 to <17 years was increased from 2 to 4. - The methods of VWF:Ac determination to be used were clearly specified as being VWF:RCo and VWF:GpIbM. - A clarification was added that, if no mutation was identified in the VWF gene for patients with VWD Type 2B, additional genetic testing was to be performed to exclude pseudo-VWD.
22 August 2019	Protocol Version 3 (Amendment 2): The protocol was amended to comply with FDA requests. - A PK assessment in pediatric patients was added as a secondary objective and a secondary endpoint. - The number of pediatric patients was increased from 4 to 10. - Patients with body weight <20 kg were excluded. - The protocol author and contact for SAE reporting was changed. - The possible interval between the Screening Visit and the Baseline IVR Visit was reduced from 30 days to 2 weeks. - The estimated start date of the study was changed from Q4 2019 to Q1 2020. - The definition of target joint assessment was extended to the Study Completion Visit. - In this protocol, seroconversion for Parvovirus B19 was to be reported as an AE.

25 February 2020	Protocol Version 5 (Amendment 3) - VWF:Ag testing was removed - FVIII:C was added as a parameter in IVR assessments. - Inclusion criterion 3 was updated to allow for patients that switched to prophylaxis within the past 2 years and had reliable documentation of on-demand treatment before switching. - Menstrual bleeds excluded from calculation of TABR. -The annual rate of heavy (i.e., major) menstrual bleeds was added as an exploratory endpoint. -Clarification that the Screening and Baseline Visits could coincide in adults, but-must not coincide in children was added. - Standard anesthetic medication was not to be collected as concomitant medications. - The patient diary was handed out at screening, NOT baseline. - All patients were to use their previous product between screening and baseline. - Previous product was to be documented as concomitant medication. - BEs were to be documented under BEs. - Number of pregnancy tests were reduced. - Number of blood draws for hematology/chemistry were reduced. - Wilate consumption data added as secondary endpoint.
01 March 2021	Protocol Version 7 (Amendment 4) - Increased number of patients to be enrolled, in order to get 25 evaluable patients, from 28 to 40. Increased number of pediatric patients from 4 to 6. -The following sentence added: If, after a dose increase, patients still experience more than 2 spontaneous bleeding episodes, the dosing interval should be shortened from 2 times per week to 3 times per week. - Added forbidden medication in Section 4.2 (consistent with other protocols). - Added that BUN or urea could be tested. - Corrected the “within 60 -/+5 min before infusion time point” to “within 60 min before infusion”.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported