



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)

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|---|---------------------------------------|
| 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 spontaneous 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

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 13 June 2019 | <p>Protocol Version 2 (Amendment 1)</p> <ul style="list-style-type: none">- 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 | <p>Protocol Version 3 (Amendment 2): The protocol was amended to comply with FDA requests.</p> <ul style="list-style-type: none">- 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 | <p>Protocol Version 5 (Amendment 3)</p> <ul style="list-style-type: none"> - 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 | <p>Protocol Version 7 (Amendment 4)</p> <ul style="list-style-type: none"> - 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