



Clinical trial results:

Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety, and Immunogenicity of Wilate in Previously Treated Patients with Severe Hemophilia A

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-003681-34 |
| Trial protocol | HU BG PL |
| Global end of trial date | 29 March 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 02 May 2019 |
| First version publication date | 02 May 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | WIL-27 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02954575 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Octapharma AG |
| Sponsor organisation address | Seidenstrasse 2, Lachen, Switzerland, CH-8853 |
| Public contact | Clinical Trial Manager, Octapharma AG, +41 554512180, Cristina.Solomon@octapharma.ch |
| Scientific contact | Clinical Trial Manager, Octapharma AG, +41 554512180, Cristina.Solomon@octapharma.ch |

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? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 August 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 March 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the efficacy of Wilate in the prophylactic treatment of previously treated patients (PTP) with severe hemophilia A.

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 and national regulatory requirements.

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 occurrence of AEs and concomitant medications.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 21 December 2016 |
| 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 | Russian Federation: 7 |
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Bulgaria: 27 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Worldwide total number of subjects | 55 |
| EEA total number of subjects | 48 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 5 |
| Adults (18-64 years) | 50 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with documented severe hemophilia A, who had previous treatment with a FVIII concentrate for at least 150 exposure days (EDs) 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:

All patients will received Wilate for prophylactic treatment according to the guidelines given in the clinical study protocol and the patient's clinical condition.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Wilate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dose and frequency of Wilate was determined according to detailed guidelines given in the clinical study protocol and to the patient's clinical condition.

The dose used for PK assessment, i.e., 50 ± 5 IU/kg, was in line with the current recommendations of the EMA, which recommends a dose of 25–50 IU/kg.

The doses for prophylaxis (20–40 IU/kg Wilate/kg BW given at intervals of 2 to 3 days), the treatment of bleeding episodes and perioperative prophylaxis, were given as indicated in the European Summary of Product Characteristics. The body weight measurement obtained at the visit prior to the prophylactic treatments was used in the calculations of dose.

| Number of subjects in period 1 | Wilate |
|--------------------------------|--------|
| Started | 55 |
| Completed | 54 |
| Not completed | 1 |
| Adverse event, non-fatal | 1 |

Baseline characteristics

Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|------------------------|---------------|-------|--|
| Number of subjects | 55 | 55 | |
| Age categorical | | | |
| Units: Subjects | | | |
| < 16 years | 5 | 5 | |
| >= 16 years | 50 | 50 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 35.0 | | |
| standard deviation | ± 12.3 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 55 | 55 | |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Wilate |
| Reporting group description: All patients will received Wilate for prophylactic treatment according to the guidelines given in the clinical study protocol and the patient's clinical condition. | |
| Subject analysis set title | Per-protocol population (PP) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per-protocol (PP) set, i.e. a subset of the full analysis set excludes subjects with major protocol deviations which may have an impact on the evaluation of the primary study outcome parameter (major protocol deviations as defined during the data review meeting. | |
| Subject analysis set title | Safety population (SAF) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety (SAF) set includes all subjects who received at least one infusion of IMP | |
| Subject analysis set title | Full analysis set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The full analysis set (FAS) defined according to the intention-to-treat (ITT) principle will include all enrolled subjects who received at least one infusion of IMP after the initial PK or at Non-PK Visit. | |
| Subject analysis set title | Pharmacokinetic population (PK) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The pharmacokinetic (PK) set will include all subjects for which at least one valid Wilate PK profile has been obtained. | |
| Subject analysis set title | N (BE) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Number of bleeding events (PP -data set) | |
| Subject analysis set title | % (BE) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Percentage of bleeding events (PP -data set) | |
| Subject analysis set title | Initial PK |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Initial PK Assessment of FVIII:C | |
| Subject analysis set title | PK completion 6 months |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: PK Assessment of FVIII:C at 6 months | |
| Subject analysis set title | Number of patients |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Number of patients | |
| Subject analysis set title | % of patients |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: percentage of patients | |
| Subject analysis set title | Overall efficacy assessment (n) |

| | |
|---|--|
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Result of overall efficacy assessment (n) | |
| Subject analysis set title | Overall efficacy assessment (%) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Overall efficacy assessment (%) | |
| Subject analysis set title | ABRs during Wilate Prophylaxis |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| ABRs during Wilate Prophylaxis | |
| Subject analysis set title | Incremental IVR (kg/dL) over time |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| IVR from FVIII:C plasma levels from all patients at each visit | |
| Subject analysis set title | ANOVA assessed association between blood group & IMP half-life |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| ANOVA assessed association between blood group and Wilate half-life | |
| Subject analysis set title | ANOVA assessed association between VWF:Ag and IMP half-life |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| ANOVA assessed association between VWF:Ag and Wilate half-life | |
| Subject analysis set title | Number of patients Pearson Clopper CI (2-sided) 95% |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| 95% Pearson Clopper interval | |

Primary: Reduction of total annualized bleeding rate (TABR) under Prophylaxis

| | |
|-----------------|---|
| End point title | Reduction of total annualized bleeding rate (TABR) under Prophylaxis ^[1] |
|-----------------|---|

End point description:

The efficacy of prophylactic treatment with Wilate was statistically evaluated by comparing the primary endpoint, i.e., TABR under prophylaxis, with a predefined threshold of 29 BEs per patient per year. This threshold corresponds to 50% of the TABR reported in GENA-01 study which had a TABR of 58.1 per patient per year. A confirmative one-sided, one-sample Poisson test was used to test whether the mean annualised bleeding rate (ABR) in patients treated prophylactically with Wilate was below the threshold of 29 BEs per patient year ($\alpha = 2.5\%$). A corresponding two-sided 95% CI for the TABR was also provided.

In the per-protocol population (N=52) the one-sample Poisson test estimate was 2.13 (95% CI 1.64, 2.76) $p < 0.0001$ vs mean TABR >29

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Trial includes one arm only. For specifying statistical analysis in the system at least 2 arms are required, so no statistical analysis can be entered. Therefore only results for this endpoint are provided.

84.2% of all BEs were treated successfully (95% CI 72.13%, 92.52%; $p = 0.0096$ for proportion of success $\leq 70\%$)

| End point values | ABRs during Wilate Prophylaxis | | | |
|---|--------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 52 | | | |
| Units: bleeding events | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Bleeding Rate | 2.13 (1.64 to 2.76) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous annualized bleeding rate (SABR)

| | |
|-----------------|---|
| End point title | Spontaneous annualized bleeding rate (SABR) |
|-----------------|---|

End point description:

SABR was analysed in the same way as TABR, the only exception being that, for the comparison of mean SABRs, a predefined threshold of 19.1 per patient per year was chosen; this threshold corresponds to 50% of the SABR in GENA-01.

For the spontaneous BEs in the PP population, the one-sample Poisson test estimate was 1.53 (95% CI 1.13, 2.08; $p < 0.0001$ vs mean SABR > 19.1).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months

| End point values | ABRs during Wilate Prophylaxis | | | |
|--|--------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 52 | | | |
| Units: Bleeding Events | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Bleeding Rate | 1.53 (1.13 to 2.08) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Wilate in the treatment of breakthrough bleeding events

| | |
|-----------------|---|
| End point title | Efficacy of Wilate in the treatment of breakthrough bleeding events |
|-----------------|---|

End point description:

The proportion of bleeding events (BEs) successfully treated with Wilate were documented by the

patient (together with the investigator in case of on-site treatments) in the patient diary for all BEs according to a 4 point hemostatic efficacy scales including the four items: 'excellent,' 'good,' moderate,' and 'none'.

All efficacy ratings assessed as either 'excellent' or 'good' were considered 'successfully treated.'

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| End point values | N (BE) | % (BE) | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25 ^[2] | 25 ^[3] | | |
| Units: Bleeding Events | | | | |
| number (not applicable) | | | | |
| Excellent | 16 | 28.1 | | |
| Good | 32 | 56.1 | | |
| Moderate | 9 | 15.8 | | |
| Treated sucessfully (all BEs) | 48 | 84.2 | | |

Notes:

[2] - Number of patients with BEs

[3] - Number of patients with BEs

Statistical analyses

No statistical analyses for this end point

Secondary: Wilate consumption for prophylaxis

| | |
|--|------------------------------------|
| End point title | Wilate consumption for prophylaxis |
| End point description: | |
| The total consumption of Wilate for all patients receiving prophylaxis (IU/kg) | |
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| End point values | Per-protocol population (PP) | | | |
|-----------------------------|------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 52 | | | |
| Units: Total Dose IU/kg | | | | |
| number (not applicable) | | | | |
| Prophylaxis | 1300017.1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) assessment area under the curve [AUCnorm] of FVIII:C

| | |
|--|---|
| End point title | Pharmacokinetic (PK) assessment area under the curve [AUCnorm] of FVIII:C |
| End point description: PK assessments of FVIII:C were conducted using the one-stage (OS) assay. The value of the area under the curve [AUC] of FVIII:C was calculated based on the FVIII:C values measured in the patients participating in the PK study. | |
| End point type | Secondary |
| End point timeframe: at baseline and 6 months | |

| End point values | Initial PK | PK completion 6 months | | |
|-------------------------------------|----------------------|------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: AUCnorm (h*kg*IU/dL/IU) | | | | |
| geometric mean (standard deviation) | | | | |
| AUCnorm | 28.61 (± 9.31) | 30.75 (± 11.32) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK OS assay assessment (in vivo half-life) of FVIII:C

| | |
|---|---|
| End point title | PK OS assay assessment (in vivo half-life) of FVIII:C |
| End point description: PK assessments of FVIII:C were conducted using the OS assay. The in vivo half-life of FVIII:C was calculated based on the FVIII:C values measured in the patients participating in the PK study | |
| End point type | Secondary |
| End point timeframe: at baseline and 6 months | |

| End point values | Initial PK | PK completion 6 months | | |
|-------------------------------------|----------------------|------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: Half-life (h) | | | | |
| geometric mean (standard deviation) | | | | |
| Half-life (h) | 10.82 (± 2.5) | 11.5 (± 2.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK assessment (Maximum plasma concentration [C_{max}]) of FVIII:C

| | |
|-----------------|---|
| End point title | PK assessment (Maximum plasma concentration [C _{max}]) of FVIII:C |
|-----------------|---|

End point description:

PK assessments of FVIII:C were conducted using the one-stage (OS) assay. The Maximum plasma concentration of FVIII:C was calculated based on the FVIII:C values measured in the patients participating in the PK study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

at baseline and 6 months

| End point values | Initial PK | PK completion 6 months | | |
|-------------------------------------|----------------------|------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: C _{max} (IU/dL) | | | | |
| geometric mean (standard deviation) | | | | |
| C _{max} (IU/dL) | 106.7 (± 22.45) | 103.49 (± 26.53) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental in vivo recovery (IVR) of Wilate over time

| | |
|-----------------|--|
| End point title | Incremental in vivo recovery (IVR) of Wilate over time |
|-----------------|--|

End point description:

IVR was determined from FVIII:C plasma levels from all patients at each visit using OS assay

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At baseline, and at 3 and 6 months of treatment

| End point values | Incremental IVR (kg/dL) over time | | | |
|-------------------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 55 | | | |
| Units: kg/dL | | | | |
| geometric mean (standard deviation) | | | | |
| First PK/non-PK visit | 2.14 (± 0.51) | | | |
| 3 months | 2.14 (± 0.49) | | | |
| PK/non-PK completion 6 months | 1.97 (± 0.64) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Association between ABO blood type and the FVIII:C half-life of Wilate

| | |
|-----------------|--|
| End point title | Association between ABO blood type and the FVIII:C half-life of Wilate |
|-----------------|--|

End point description:

Analysis of variance (ANOVA) was used in an exploratory sense to assess an association between ABO blood type and the FVIII:C half-life of Wilate.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | ANOVA assessed association between blood group &IMP half-life | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 21 | | | |
| Units: p-value | | | | |
| number (not applicable) | | | | |
| One-Stage Assay (OS assay) | 0.0346 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Association between VWF:Ag concentration and the FVIII:C half-life of Wilate

| | |
|-----------------|--|
| End point title | Association between VWF:Ag concentration and the FVIII:C half-life of Wilate |
|-----------------|--|

End point description:

ANOVA was used in an exploratory sense to assess an association between VWF:Ag with the FVIII:C half-life of Wilate.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | ANOVA assessed association between VWF:Ag and IMP half-life | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 21 | | | |
| Units: p-value | | | | |
| number (not applicable) | | | | |
| One-Stage Assay (OS assay) | 0.4244 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of Wilate by testing for FVIII inhibitors

| | |
|---|--|
| End point title | Immunogenicity of Wilate by testing for FVIII inhibitors |
| End point description: FVIII inhibitor activity was determined at each study visit before the injection of Wilate using the modified Bethesda assay (Nijmegen modification). | |
| End point type | Secondary |
| End point timeframe: 6 months | |

| | | | | |
|----------------------------------|---|--|--|--|
| End point values | Number of patients Pearson Clopper CI (2-sided) 95% | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 55 | | | |
| Units: patients | | | | |
| number (confidence interval 95%) | | | | |
| FVIII inhibitors developed | 0 (0 to 16.11) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Virus safety to be measured by the incidence of parvovirus B19 seroconversions between baseline (BL) and end of study

| | |
|-----------------|--|
| End point title | Virus safety to be measured by the incidence of parvovirus B19 |
|-----------------|--|

End point description:

Virus safety was evaluated by taking a plasma sample for parvovirus B19 antibody testing before the first injection of Wilate. All patients negative at screening were tested again at the study completion visit.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months

| End point values | Number of patients | % of patients | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 55 ^[4] | 55 ^[5] | | |
| Units: % of patients | | | | |
| number (not applicable) | | | | |
| Positive for parvovirus B19 IgG antibodies at BL | 53 | 96.4 | | |
| Positive for parvovirus B19 IgM antibodies at BL | 1 | 1.82 | | |
| Negative for B19 IgM&IgG at BL and end of study | 2 | 3.64 | | |

Notes:

[4] - refers to percentage from the total 55 subjects in SAF

[5] - refers to percentage from the total 55 subjects in SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Wilate in surgical prophylaxis assessed by surgeon and hematologist using predefined assessment criteria

| | |
|-----------------|--|
| End point title | Efficacy of Wilate in surgical prophylaxis assessed by surgeon and hematologist using predefined assessment criteria |
|-----------------|--|

End point description:

Hemostatic efficacy was assessed at the end of surgery by the surgeon and at end of the postoperative period by the haematologist, using 4 point hemostatic efficacy scales including the four items: 'excellent,' 'good,' 'moderate,' and 'none'. Overall efficacy was assessed by the investigator, taking both the intra and postoperative assessments into account, and using the 'excellent,' 'good,' 'moderate,' and 'none' scale.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months

| End point values | Overall efficacy assessment (n) | Overall efficacy assessment (%) | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 55 | 55 | | |
| Units: Efficacy Rating | | | | |
| number (not applicable) | | | | |

| | | | | |
|-----------|---|-----|--|--|
| Excellent | 0 | 0 | | |
| Good | 1 | 100 | | |
| Moderate | 0 | 0 | | |
| None | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the observation period until study completion.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | SAF Population |
|-----------------------|----------------|

Reporting group description: -

| Serious adverse events | SAF Population | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | SAF Population | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 55 (21.82%) | | |
| Injury, poisoning and procedural complications | | | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytosis | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|--|--|
| Pain subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | | |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | | |
| Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 5 | | |
| Infections and infestations Erysipelas subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 1 / 55 (1.82%) 1 1 / 55 (1.82%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 16 January 2017 | <p>Protocol amendment has been prepared in response to the FDA information request:</p> <ul style="list-style-type: none">- a second PK Assessment Phase after 6 months of prophylactic treatment which is included in the PK Study Completion Visit has been added- study duration for patients undergoing PK assessment has been corrected from 1 week to 2 days per PK Assessment Phase.- thromboembolic events have been defined as events subject to expedited reporting throughout the duration of the study. Also, to actively monitor patients for signs and symptoms of thromboembolic events after the end of study treatment, a Follow-up Contact 30 days after the end of study treatment has been included.- specification that, of the 20 patients undergoing PK assessment, 4 patients should be between ≥ 12 and < 17 years of age has been added- the time period for recording bleeding events that will count towards the primary and relevant secondary endpoint has been more clearly defined.- determination of VWF:Ag and VWF:Ac has been dropped from the Screening Visit- further instruction how to proceed in case the interval between screening and treatment initiation is longer than 30 days have been added- information on how to deal with patients who develop FVIII inhibitors have been specified- details which bleeding frequency during prophylactic treatment should be considered 'unacceptable' for a dose adjustment to be triggered have been added- a retention sample being taken for possible virus marker testing in addition to parvovirus B19 antibody testing- the use of Wilate in surgical prophylaxis has been defined as additional (i.e., exploratory) rather than a secondary endpoint.- continuous infusion of Wilate during surgical prophylaxis has been disallowed- The possibility of 'severe hemorrhage' during surgery was deleted as a defining criterion for major surgeries |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported