



Clinical trial results:

A Multicenter, OpenLabel Study to Evaluate the LongTerm Safety, Tolerability and Efficacy of Subcutaneous PF06741086 in Subjects With Severe Hemophilia

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-001255-31 |
| Trial protocol | PL ES BG HR |
| Global end of trial date | 05 August 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 02 June 2021 |
| First version publication date | 02 June 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | B7841003 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03363321 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer Inc |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Centre, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 19 January 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study was designed to evaluate the safety, tolerability and efficacy of long-term treatment with PF-06741086 in severe hemophilia A or B subjects with or without inhibitors to FVIII or FIX who participated in the 3-month Phase 1b/2 Study B7841002. Additionally, de novo subjects were recruited into this study.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 30 May 2018 |
| 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 | Brazil: 1 |
| Country: Number of subjects enrolled | Chile: 7 |
| Country: Number of subjects enrolled | Croatia: 1 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | South Africa: 7 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | United States: 1 |
| Worldwide total number of subjects | 20 |
| EEA total number of subjects | 3 |

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) | 0 |
| Adults (18-64 years) | 20 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Twenty-four individuals were screened and 4 failed at screening. All the 20 subjects who met the eligibility criteria were assigned to the study treatment and were treated with marstacimab. Among 20 subjects, 18 completed the study, and 2 discontinued from study due to withdrawal by subject, which were not related to safety.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------------------------------------|
| Arm title | Cohort 1: 300mg - 300mg Non-Inhibitor |
|------------------|---------------------------------------|

Arm description:

Subjects without inhibitors to Factor VIII (FVIII) or Factor IX (FIX) from Cohort 1 of Study 1002 (B7841002) continued to receive PF-06741086 300 mg subcutaneously (SC) once weekly (QW) from Day 1 to Day 365.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Marstacimab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Marstacimab 300 mg was administered SC every week.

| | |
|------------------|---|
| Arm title | Cohort 2: 300mg Loading (L)+150mg-300mg L+150mg Non-Inhibitor |
|------------------|---|

Arm description:

Subjects without inhibitors to FVIII or FIX from Cohort 2 of Study 1002 continued to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Marstacimab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Marstacimab 300 mg loading dose, followed by 150 mg was administered SC every week.

| | |
|------------------|---|
| Arm title | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
|------------------|---|

Arm description:

Subjects without inhibitors to FVIII or FIX from Cohort 3 (450 mg SC) of Study 1002 started to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|-----------------------------------|
| Investigational medicinal product name | Marstacimab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Marstacimab 300 mg loading dose, followed by 150 mg was administered SC every week. | |
| Arm title | Cohort 4: 300mg - 300mg Inhibitor |

Arm description:

Subjects with inhibitors to FVIII or FIX from Cohort 4 (300 mg SC) of Study 1002 continued to receive PF-06741086 300 mg SC QW from Day 1 to Day 365.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Marstacimab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Marstacimab 300 mg was administered SC every week. | |
| Arm title | Cohort 5: De Novo 300mg L + 150mg Inhibitors |

Arm description:

De Novo subjects with inhibitors to FVIII or FIX received a 300 mg SC loading dose on Day 1, and then followed by 150 mg SC QW to Day 365.

| | |
|---|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Marstacimab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Marstacimab 300 mg loading dose, followed by 150 mg was administered SC every week. | |

| Number of subjects in period 1 | Cohort 1: 300mg - 300mg Non-Inhibitor | Cohort 2: 300mg Loading (L)+150mg-300mg L+150mg Non-Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
|--------------------------------|---------------------------------------|---|---|
| | | | |
| Started | 5 | 4 | 4 |
| Completed | 5 | 3 | 4 |
| Not completed | 0 | 1 | 0 |
| Consent withdrawn by subject | - | 1 | - |

| Number of subjects in period 1 | Cohort 4: 300mg - 300mg Inhibitor | Cohort 5: De Novo 300mg L + 150mg Inhibitors |
|--------------------------------|-----------------------------------|--|
| | | |
| Started | 5 | 2 |
| Completed | 4 | 2 |
| Not completed | 1 | 0 |
| Consent withdrawn by subject | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Cohort 1: 300mg - 300mg Non-Inhibitor |
| Reporting group description: Subjects without inhibitors to Factor VIII (FVIII) or Factor IX (FIX) from Cohort 1 of Study 1002 (B7841002) continued to receive PF-06741086 300 mg subcutaneously (SC) once weekly (QW) from Day 1 to Day 365. | |
| Reporting group title | Cohort 2: 300mg Loading (L)+150mg-300mg L+150mg Non-Inhibitor |
| Reporting group description: Subjects without inhibitors to FVIII or FIX from Cohort 2 of Study 1002 continued to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365. | |
| Reporting group title | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
| Reporting group description: Subjects without inhibitors to FVIII or FIX from Cohort 3 (450 mg SC) of Study 1002 started to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365. | |
| Reporting group title | Cohort 4: 300mg - 300mg Inhibitor |
| Reporting group description: Subjects with inhibitors to FVIII or FIX from Cohort 4 (300 mg SC) of Study 1002 continued to receive PF-06741086 300 mg SC QW from Day 1 to Day 365. | |
| Reporting group title | Cohort 5: De Novo 300mg L + 150mg Inhibitors |
| Reporting group description: De Novo subjects with inhibitors to FVIII or FIX received a 300 mg SC loading dose on Day 1, and then followed by 150 mg SC QW to Day 365. | |

| Reporting group values | Cohort 1: 300mg - 300mg Non-Inhibitor | Cohort 2: 300mg Loading (L)+150mg-300mg L+150mg Non-Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
|---|---------------------------------------|---|---|
| Number of subjects | 5 | 4 | 4 |
| Age Categorical Units: Subjects | | | |
| <18 Years | 0 | 0 | 0 |
| 18-44 Years | 4 | 4 | 2 |
| 45-64 Years | 1 | 0 | 2 |
| >=65 Years | 0 | 0 | 0 |
| Unspecified Years | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 33.0 | 31.3 | 41.8 |
| standard deviation | ± 9.70 | ± 10.63 | ± 16.24 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 5 | 4 | 4 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 3 | 2 | 4 |
| Black or African American | 2 | 2 | 0 |
| Asian | 0 | 0 | 0 |
| American Indian or Alaska Native | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Multiracial | 0 | 0 | 0 |
| Not reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 3 | 2 | 1 |
| Not Hispanic or Latino | 2 | 2 | 3 |
| Unknown or Not Reported | 0 | 0 | 0 |

| Reporting group values | Cohort 4: 300mg - 300mg Inhibitor | Cohort 5: De Novo 300mg L + 150mg Inhibitors | Total |
|---|-----------------------------------|--|-------|
| Number of subjects | 5 | 2 | 20 |
| Age Categorical | | | |
| Units: Subjects | | | |
| <18 Years | 0 | 0 | 0 |
| 18-44 Years | 3 | 2 | 15 |
| 45-64 Years | 2 | 0 | 5 |
| >=65 Years | 0 | 0 | 0 |
| Unspecified Years | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 42.0 | 20.0 | |
| standard deviation | ± 5.24 | ± 1.41 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 5 | 2 | 20 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 3 | 2 | 14 |
| Black or African American | 2 | 0 | 6 |
| Asian | 0 | 0 | 0 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Multiracial | 0 | 0 | 0 |
| Not reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 7 |
| Not Hispanic or Latino | 4 | 2 | 13 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Cohort 1: 300mg - 300mg Non-Inhibitor |
| Reporting group description: Subjects without inhibitors to Factor VIII (FVIII) or Factor IX (FIX) from Cohort 1 of Study 1002 (B7841002) continued to receive PF-06741086 300 mg subcutaneously (SC) once weekly (QW) from Day 1 to Day 365. | |
| Reporting group title | Cohort 2: 300mg Loading (L)+150mg-300mg L+150mg Non-Inhibitor |
| Reporting group description: Subjects without inhibitors to FVIII or FIX from Cohort 2 of Study 1002 continued to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365. | |
| Reporting group title | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
| Reporting group description: Subjects without inhibitors to FVIII or FIX from Cohort 3 (450 mg SC) of Study 1002 started to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365. | |
| Reporting group title | Cohort 4: 300mg - 300mg Inhibitor |
| Reporting group description: Subjects with inhibitors to FVIII or FIX from Cohort 4 (300 mg SC) of Study 1002 continued to receive PF-06741086 300 mg SC QW from Day 1 to Day 365. | |
| Reporting group title | Cohort 5: De Novo 300mg L + 150mg Inhibitors |
| Reporting group description: De Novo subjects with inhibitors to FVIII or FIX received a 300 mg SC loading dose on Day 1, and then followed by 150 mg SC QW to Day 365. | |

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), TEAEs by Severity, and Serious Adverse Events (SAEs) (All Causality and Treatment-related)

| | |
|--|--|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), TEAEs by Severity, and Serious Adverse Events (SAEs) (All Causality and Treatment-related) ^[1] |
| End point description: An adverse event (AE) was any untoward medical occurrence in a clinical investigation subject administered a product; the event did not need to have a causal relationship with the treatment. An SAE was any untoward medical occurrence at any dose that resulted in death; was life threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect. AEs included both SAEs and non-serious AEs. TEAEs were AEs occurred following the start of treatment or AEs increasing in severity during treatment. Treatment-related TEAEs were determined by the investigator. The analysis population included all subjects who received at least 1 dose of investigational product. Here "Number of Subjects Analyzed" signifies number of subjects who were evaluable for this endpoint. | |
| End point type | Primary |
| End point timeframe: Day 1 up to Day 393 | |

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: No statistical analysis was planned for this endpoint

| End point values | Cohort 1: 300mg - 300mg Non- Inhibitor | Cohort 2: 300mg Loading (L)+150mg- 300mg L+150mg Non- Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non- Inhibitor | Cohort 4: 300mg - 300mg Inhibitor |
|-------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 4 | 4 | 5 |
| Units: Subjects | | | | |
| All-causalities TEAE | 5 | 2 | 4 | 2 |
| Treatment-related TEAE | 2 | 0 | 0 | 0 |
| All-causalities serious TEAE | 1 | 0 | 0 | 0 |
| Treatment-related serious TEAE | 0 | 0 | 0 | 0 |
| All-causalities Grade 3 or 4 TEAE | 1 | 0 | 0 | 0 |
| Treatment-related Grade 3 or 4 TEAE | 0 | 0 | 0 | 0 |

| End point values | Cohort 5: De Novo 300mg L + 150mg Inhibitors | | | |
|-------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: Subjects | | | | |
| All-causalities TEAE | 1 | | | |
| Treatment-related TEAE | 1 | | | |
| All-causalities serious TEAE | 0 | | | |
| Treatment-related serious TEAE | 0 | | | |
| All-causalities Grade 3 or 4 TEAE | 1 | | | |
| Treatment-related Grade 3 or 4 TEAE | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Laboratory Findings Without Regard to Baseline Abnormality (Including Hematology, Serum Chemistry, and Urinalysis)

| | |
|-----------------|--|
| End point title | Number of Subjects With Abnormal Laboratory Findings Without Regard to Baseline Abnormality (Including Hematology, Serum Chemistry, and Urinalysis) ^[2] |
|-----------------|--|

End point description:

Following parameters were analyzed for laboratory examination: hematology, clinical chemistry, and urinalysis. The hematology parameters and pre-defined criteria included: neutrophils ($10^3/\text{millimeter}[\text{mm}]^3$) $<0.8 \times \text{lower limit of normal (LLN)}$, and basophils ($10^3/\text{mm}^3$) $>1.2 \times \text{upper limit of normal (ULN)}$. The clinical chemistry parameter and pre-defined criteria included: biliirubin (milligrams [mg]/decilitre [dL]) $>1.5 \text{ ULN}$, aspartate aminotransferase (units [U]/liter [L]) $>3.0 \text{ ULN}$, glucose (mg/dL) $>1.5 \times \text{ULN}$. The urinalysis parameter and pre-defined criteria included: urine glucose ≥ 1 , ketones (scalar) ≥ 1 , urine protein ≥ 1 , urine hemoglobin (scalar) ≥ 1 , and hyaline casts per low power field (/LPF). The analysis population included all subjects who received at least 1 dose of investigational product. Here "Number of Subjects Analyzed" signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Hematology and serum chemistry: Baseline, Days 1, 29, 57, 85, 169, 253, and 365 visits. Urinalysis: Baseline, Days 1, 85, 169, 253, and 365 visits.

Notes:

[2] - 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: No statistical analysis was planned for this endpoint

| End point values | Cohort 1: 300mg - 300mg Non- Inhibitor | Cohort 2: 300mg Loading (L)+150mg- 300mg L+150mg Non- Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non- Inhibitor | Cohort 4: 300mg - 300mg Inhibitor |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 ^[3] | 3 ^[4] | 4 ^[5] | 5 ^[6] |
| Units: Subjects | | | | |
| Neutrophils (10 ³ /mm ³) <0.8*LLN | 1 | 1 | 0 | 0 |
| Basophils (10 ³ /mm ³) >1.2*ULN | 0 | 0 | 0 | 1 |
| Bilirubin (mg/dL) >1.5*ULN | 0 | 0 | 0 | 0 |
| Aspartate Aminotransferase (U/L) >3.0*ULN | 0 | 0 | 0 | 0 |
| Glucose (mg/dL) >1.5*ULN | 0 | 0 | 1 | 1 |
| Urine Glucose ≥1 | 0 | 0 | 1 | 0 |
| Ketones (Scalar) ≥1 | 1 | 0 | 0 | 0 |
| Urine Protein ≥1 | 0 | 1 | 0 | 0 |
| Urine Hemoglobin (Scalar) ≥1 | 0 | 0 | 1 | 0 |
| Hyaline Casts (/LPF) >1 | 0 | 1 | 0 | 1 |

Notes:

[3] - Number of Subjects Evaluable for Hyaline Casts was 0.

[4] - Number of Subjects Evaluable for Hyaline Casts was 1.

[5] - Number of Subjects Evaluable for Hyaline Casts was 0.

[6] - Number of Subjects Evaluable for Hyaline Casts was 1.

| End point values | Cohort 5: De Novo 300mg L + 150mg Inhibitors | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 ^[7] | | | |
| Units: Subjects | | | | |
| Neutrophils (10 ³ /mm ³) <0.8*LLN | 0 | | | |
| Basophils (10 ³ /mm ³) >1.2*ULN | 1 | | | |
| Bilirubin (mg/dL) >1.5*ULN | 1 | | | |
| Aspartate Aminotransferase (U/L) >3.0*ULN | 1 | | | |
| Glucose (mg/dL) >1.5*ULN | 0 | | | |
| Urine Glucose ≥1 | 0 | | | |
| Ketones (Scalar) ≥1 | 0 | | | |
| Urine Protein ≥1 | 0 | | | |
| Urine Hemoglobin (Scalar) ≥1 | 0 | | | |
| Hyaline Casts (/LPF) >1 | 0 | | | |

Notes:

[7] - Number of Subjects Evaluable for Hyaline Casts was 1.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Changes From Baseline in Vital Signs Measurements Meeting the Pre-defined Categorical Summarization Criteria

| | |
|-----------------|---|
| End point title | Number of Subjects With Changes From Baseline in Vital Signs Measurements Meeting the Pre-defined Categorical Summarization Criteria ^[8] |
|-----------------|---|

End point description:

Following parameters were analyzed for vital sign examination: blood pressure (BP), pulse rate (PR), temperature, respiration rate. Categorical vital signs: Temperature >38.5 degree(s) Celsius (°C), Supine PR: <40 or >120 beats per minute (BPM), Systolic BP: <90 millimeter of mercury (mm Hg), >=30 mm Hg change from baseline, Diastolic BP: <50 mm Hg, >=20 mm Hg change from baseline. The analysis population included all subjects who received at least 1 dose of investigational product.

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

End point timeframe:

Baseline, Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365 and 393 visits.

Notes:

[8] - 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: No statistical analysis was planned for this endpoint

| End point values | Cohort 1: 300mg - 300mg Non- Inhibitor | Cohort 2: 300mg Loading (L)+150mg- 300mg L+150mg Non- Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non- Inhibitor | Cohort 4: 300mg - 300mg Inhibitor |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 4 | 4 | 5 |
| Units: Subjects | | | | |
| Systolic BP (mmHg) < 90 | 0 | 0 | 0 | 0 |
| Systolic BP Change ≥30 mm Hg increase | 0 | 0 | 1 | 0 |
| Systolic BP Change ≥30 mm Hg decrease | 0 | 1 | 0 | 1 |
| Diastolic BP (mmHg) < 50 | 0 | 0 | 0 | 0 |
| Diastolic BP Change ≥20 mm Hg increase | 1 | 0 | 1 | 1 |
| Diastolic BP Change ≥20 mm Hg decrease | 0 | 1 | 1 | 1 |
| Supine PR (BPM) <40 | 0 | 0 | 0 | 0 |
| Supine PR (BPM) >120 | 0 | 0 | 0 | 0 |
| Temperature >38.5 | 0 | 0 | 0 | 0 |

| End point values | Cohort 5: De Novo 300mg L + 150mg Inhibitors | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: Subjects | | | | |
| Systolic BP (mmHg) < 90 | 0 | | | |

| | | | | |
|--|---|--|--|--|
| Systolic BP Change ≥ 30 mm Hg increase | 0 | | | |
| Systolic BP Change ≥ 30 mm Hg decrease | 0 | | | |
| Diastolic BP (mmHg) < 50 | 0 | | | |
| Diastolic BP Change ≥ 20 mm Hg increase | 0 | | | |
| Diastolic BP Change ≥ 20 mm Hg decrease | 0 | | | |
| Supine PR (BPM) <40 | 0 | | | |
| Supine PR (BPM) >120 | 0 | | | |
| Temperature >38.5 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Change From Baseline in Electrocardiogram (ECG) Parameters Meeting the Pre-defined Categorical Summarization Criteria

| | |
|-----------------|--|
| End point title | Number of Subjects With Change From Baseline in Electrocardiogram (ECG) Parameters Meeting the Pre-defined Categorical Summarization Criteria ^{[9][10]} |
|-----------------|--|

End point description:

ECG was only evaluated in de novo subjects. Baseline was defined as the average of triplicate ECG measurements collected prior to dosing on Day 1 in B7841003. Criteria for potentially clinically important changes in ECG were defined as: PR interval value ≥ 300 millisecond (msec); PR interval baseline >200 msec and change $\geq 25\%$; PR interval baseline ≤ 200 msec and change $\geq 50\%$; QRS complex value ≥ 140 msec and change $\geq 50\%$; QTcF value ≥ 450 msec and change ≥ 30 msec. Only the number of participants meeting pre-defined criteria was reported below.

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

End point timeframe:

Baseline, Days 1 and 29 visits.

Notes:

[9] - 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: No statistical analysis was planned for this endpoint

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was only planned for the arm identified

| | | | | |
|---|--|--|--|--|
| End point values | Cohort 5: De Novo 300mg L + 150mg Inhibitors | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: Subjects | | | | |
| PR interval value ≥ 300 msec | 0 | | | |
| PR interval baseline >200 msec and Change $\geq 25\%$ | 0 | | | |
| PR interval baseline ≤ 200 msec and change $\geq 50\%$ | 0 | | | |
| QRS complex value ≥ 140 msec | 0 | | | |
| QRS complex change $\geq 50\%$ | 0 | | | |

| | | | | |
|----------------------------------|---|--|--|--|
| 450 msec ≤ QTcF Value < 480 msec | 0 | | | |
| 480 msec ≤ QTcF Value < 500 msec | 0 | | | |
| QTcF Value ≥ 500 msec | 0 | | | |
| 30 msec ≤ QTcF Change < 60 msec | 0 | | | |
| QTcF Change ≥ 60 msec | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormalities in Physical Examination Findings

| | |
|-----------------|--|
| End point title | Number of Subjects With Abnormalities in Physical Examination Findings ^[11] |
|-----------------|--|

End point description:

Physical examination included head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The analysis population included all subjects who received at least 1 dose of investigational product.

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

End point timeframe:

Day 1 to Day 393

Notes:

[11] - 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: No statistical analysis was planned for this endpoint

| End point values | Cohort 1: 300mg - 300mg Non- Inhibitor | Cohort 2: 300mg Loading (L)+150mg- 300mg L+150mg Non- Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non- Inhibitor | Cohort 4: 300mg - 300mg Inhibitor |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 4 | 4 | 5 |
| Units: Subjects | 5 | 2 | 3 | 4 |

| End point values | Cohort 5: De Novo 300mg L + 150mg Inhibitors | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: Subjects | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Injection Site Reactions

| | |
|-----------------|--|
| End point title | Number of Subjects With Injection Site Reactions ^[12] |
|-----------------|--|

End point description:

Injection site reactions included but were not limited to: erythema, induration, ecchymosis, pain and pruritus. Grade of severity was defined as follows: Mild: Transient or mild discomfort (< 48 hours); no medical intervention/therapy required. Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required. Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible. The analysis population included all subjects who received at least 1 dose of investigational product.

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

End point timeframe:

Day 1 to Day 365, and Day 393 visit.

Notes:

[12] - 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: No statistical analysis was planned for this endpoint

| End point values | Cohort 1: 300mg - 300mg Non- Inhibitor | Cohort 2: 300mg Loading (L)+150mg- 300mg L+150mg Non- Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non- Inhibitor | Cohort 4: 300mg - 300mg Inhibitor |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 4 | 4 | 5 |
| Units: Subjects | | | | |
| Erythema (redness) Mild | 0 | 0 | 0 | 0 |
| Erythema (redness) Moderate | 0 | 0 | 0 | 0 |
| Erythema (redness) Severe | 0 | 0 | 0 | 0 |
| Induration (swelling) Mild | 1 | 0 | 0 | 0 |
| Induration (swelling) Moderate | 0 | 0 | 0 | 0 |
| Induration (swelling) Severe | 0 | 0 | 0 | 0 |
| Ecchymosis (bruising) Mild | 1 | 0 | 0 | 0 |
| Ecchymosis (bruising) Moderate | 0 | 0 | 0 | 0 |
| Ecchymosis (bruising) Severe | 0 | 0 | 0 | 0 |
| Pain (after injection) Mild | 1 | 0 | 0 | 0 |
| Pain (after injection) Moderate | 0 | 0 | 0 | 0 |
| Pain (after injection) Severe | 0 | 0 | 0 | 0 |
| Pruritus (itching) Mild | 1 | 0 | 0 | 0 |
| Pruritus (itching) Moderate | 0 | 0 | 0 | 0 |
| Pruritus (itching) Severe | 0 | 0 | 0 | 0 |
| Other Mild | 1 | 0 | 0 | 0 |
| Other Moderate | 0 | 0 | 0 | 0 |
| Other Severe | 0 | 0 | 0 | 0 |
| Any injection site reaction Mild | 2 | 0 | 0 | 0 |
| Any injection site reaction Moderate | 0 | 0 | 0 | 0 |
| Any injection site reaction Severe | 0 | 0 | 0 | 0 |

| | | | | |
|------------------|---|--|--|--|
| End point values | Cohort 5: De Novo 300mg L + 150mg Inhibitors | | | |
|------------------|---|--|--|--|

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: Subjects | | | | |
| Erythema (redness) Mild | 0 | | | |
| Erythema (redness) Moderate | 0 | | | |
| Erythema (redness) Severe | 1 | | | |
| Induration (swelling) Mild | 0 | | | |
| Induration (swelling) Moderate | 0 | | | |
| Induration (swelling) Severe | 1 | | | |
| Ecchymosis (bruising) Mild | 0 | | | |
| Ecchymosis (bruising) Moderate | 0 | | | |
| Ecchymosis (bruising) Severe | 0 | | | |
| Pain (after injection) Mild | 0 | | | |
| Pain (after injection) Moderate | 0 | | | |
| Pain (after injection) Severe | 0 | | | |
| Pruritus (itching) Mild | 0 | | | |
| Pruritus (itching) Moderate | 0 | | | |
| Pruritus (itching) Severe | 0 | | | |
| Other Mild | 0 | | | |
| Other Moderate | 0 | | | |
| Other Severe | 1 | | | |
| Any injection site reaction Mild | 0 | | | |
| Any injection site reaction Moderate | 0 | | | |
| Any injection site reaction Severe | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate (ABR)

| | |
|---|--------------------------------|
| End point title | Annualized Bleeding Rate (ABR) |
| End point description: | |
| The ABR was calculated as $([\text{number of bleeding events} \times 365.25] / \text{observed treatment period in days})$ | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to Day 365, and Day 393 visit. Pre-Treatment summarized the data up to 6 months prior to participation in B7841003 for de novo subjects and up to 6 months prior to participation in B7841002 for roll over subjects. | |

| End point values | Cohort 1: 300mg - 300mg Non- Inhibitor | Cohort 2: 300mg Loading (L)+150mg- 300mg L+150mg Non- Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non- Inhibitor | Cohort 4: 300mg - 300mg Inhibitor |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 4 | 4 | 5 |
| Units: Bleeding episodes per subject per year | | | | |

| | | | | |
|--------------------------------------|-------------------|-------------------|--------------------|-------------------|
| arithmetic mean (standard deviation) | | | | |
| Pre-Treatment | 22.000 (± 7.8740) | 14.000 (± 1.6330) | 22.000 (± 13.5647) | 18.400 (± 1.6733) |
| On-Study | 2.971 (± 2.7895) | 3.586 (± 7.1726) | 1.916 (± 1.4492) | 0.000 (± 0.0000) |

| | | | | |
|---|--|--|--|--|
| End point values | Cohort 5: De Novo 300mg L + 150mg Inhibitors | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: Bleeding episodes per subject per year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pre-Treatment | 15.000 (± 4.2426) | | | |
| On-Study | 2.488 (± 3.5187) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 393

Adverse event reporting additional description:

The same event may appear as both AE and SAE; however, what is presented are distinct events. An event may be categorized as serious in 1 subject and as non-serious in another subject, or 1 subject may have experienced both a serious and non-serious event during the study.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Cohort 1: 300mg - 300mg Non-Inhibitor |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects without inhibitors to FVIII or FIX from Cohort 1 of Study 1002 continued to receive PF-06741086 300 mg SC QW from Day 1 to Day 365.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: 300mg L+150mg-300mg L+150mg Non-Inhibitor |
|-----------------------|---|

Reporting group description:

Subjects without inhibitors to FVIII or FIX from Cohort 2 of Study 1002 continued to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365.

| | |
|-----------------------|---|
| Reporting group title | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
|-----------------------|---|

Reporting group description:

Subjects without inhibitors to FVIII or FIX from Cohort 3 (450 mg SC) of Study 1002 started to receive PF-06741086 300 mg loading dose on Day 1 and 150 mg SC QW from Day 29 to Day 365.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Cohort 4: 300mg - 300mg Inhibitor |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects with inhibitors to FVIII or FIX from Cohort 4 (300 mg SC) of Study 1002 continued to receive PF-06741086 300 mg SC QW from Day 1 to Day 365.

| | |
|-----------------------|--|
| Reporting group title | Cohort 5: De Novo 300mg Loading + 150mg Inhibitors |
|-----------------------|--|

Reporting group description:

De Novo subjects with inhibitors to FVIII or FIX received a 300 mg SC loading dose on Day 1, and then followed by 150 mg SC QW to Day 365.

| Serious adverse events | Cohort 1: 300mg - 300mg Non-Inhibitor | Cohort 2: 300mg L+150mg-300mg L+150mg Non-Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
|---|---------------------------------------|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |

| | | | |
|---|----------------|---------------|---------------|
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 4: 300mg - 300mg Inhibitor | Cohort 5: De Novo 300mg Loading + 150mg Inhibitors | |
|---|-----------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Cohort 1: 300mg - 300mg Non-Inhibitor | Cohort 2: 300mg L+150mg-300mg L+150mg Non-Inhibitor | Cohort 3: 450mg - 300mg L + 150mg Non-Inhibitor |
|---|---------------------------------------|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 5 (100.00%) | 2 / 4 (50.00%) | 4 / 4 (100.00%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Burns second degree subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Contusion subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Limb injury subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Skull fracture subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Soft tissue injury subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Vascular disorders Haematoma subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 4 (25.00%) 2 | 1 / 4 (25.00%) 1 |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Nervous system disorders Epilepsy subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Headache subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| General disorders and administration site conditions Injection site haematoma subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Injection site reaction subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 2 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Inflammation subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Gastrointestinal disorders Food poisoning, unspecified subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Skin harmorrhage subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 |
| Psychiatric disorders Disorientation subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Arthropathy subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Haemarthrosis subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 4 | 1 / 4 (25.00%) 2 | 0 / 4 (0.00%) 0 |
| Joint range of motion decreased | | | |

| | | | |
|---|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Joint swelling subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Joint warmth subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Synovitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Tonsillitis subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |

| | | | |
|---|--------------------------------------|--|--|
| Non-serious adverse events | Cohort 4: 300mg - 300mg Inhibitor | Cohort 5: De Novo 300mg Loading + 150mg Inhibitors | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 2 / 5 (40.00%) | 1 / 2 (50.00%) | |
| Investigations Weight increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 2 (0.00%) 0 | |

| | | | |
|--|----------------|----------------|--|
| Injury, poisoning and procedural complications | | | |
| Burns second degree | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 2 | |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Injection site haematoma | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injection site reaction | | | |

| | | | |
|---|--------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Inflammation subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Gastrointestinal disorders Food poisoning, unspecified subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Skin and subcutaneous tissue disorders Skin harmorrhage subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |
| Psychiatric disorders Disorientation subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 3 | |
| Arthropathy subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |
| Haemarthrosis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |

| | | | |
|---|--------------------|---------------------|--|
| Joint range of motion decreased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Joint swelling subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Joint warmth subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Synovitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 2 (50.00%) 1 | |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |
| Tonsillitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |
| Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 2 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 08 November 2018 | 1. Protocol Summary: Revised treatment duration from 6 months to up to 365 days; Revised visit day numbers to correspond to up to 365 days treatment duration. 3. Added clinic visits on Days 225, 253, 281, 309, 337, and 365; Revised Table 1 title and footnotes to correspond to additional clinic visits and extended treatment duration. 4. Revised treatment duration from 6 months to up to 365 days. 5. Study Duration: Revised maximum study duration to 15 months. 6. Revised Inclusion Criterion #2 for de novo subjects to add the requirement for episodic (on-demand) treatment prior to screening, as mandated by the FDA; Added Inclusion Criterion #3 for de novo subjects to add the requirement for 6 or more breakthrough bleeding episodes in the 6 month period prior to screening, as mandated by the FDA. 7. Preparation and Dispensing: Revised visit day numbers to correspond to up to 365 days treatment duration. 8. Added text to clarify that Day 57 hematology and serum chemistry samples are for de novo subjects only; Removed Day 29 PK sample collection as it is intended for de novo subjects only (referenced in Section 6.2.2). 9. Section 6.2.4 Day 393 – End of Study Visit: Revised section to add clinic visit on Day 393. 10. Blood Volume: Revised Table 4 to include additional samples. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported