



## Clinical trial results:

### A Phase 3b/4, Prospective, Multicenter, Open-label, Randomized, Crossover Study of Tolerability and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and of Faster Infusion Rates in Patients With Hemophilia A or B With Inhibitors

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-005781-39   |
| Trial protocol           | HR RO            |
| Global end of trial date | 27 December 2021 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 05 January 2023 |
| First version publication date | 05 January 2023 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 091501 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02764489 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Takeda   |
| Sponsor organisation address | 95 Hayden Avenue, Lexington, United States, MA 02421 |
| Public contact               | Study Director, Takeda, TrialDisclosures@takeda.com  |
| Scientific contact           | Study Director, Takeda, TrialDisclosures@takeda.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                       | 27 December 2021 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 27 December 2021 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the tolerability and safety of infusing reduced volume Factor Eight Inhibitor Bypassing Activity (FEIBA) at the standard infusion rate of 2 U/kg/min and to evaluate the tolerability and safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/kg/min, in comparison to the standard rate of 2 U/kg/min at the regular volume.

Protection of trial subjects:

Study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 12 February 2019 |
| 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 | Thailand: 7 |
| Country: Number of subjects enrolled | Malaysia: 2 |
| Country: Number of subjects enrolled | Algeria: 4  |
| Country: Number of subjects enrolled | Croatia: 2  |
| Country: Number of subjects enrolled | India: 8    |
| Country: Number of subjects enrolled | Poland: 1   |
| Country: Number of subjects enrolled | Turkey: 4   |
| Country: Number of subjects enrolled | Ukraine: 5  |
| Worldwide total number of subjects   | 33          |
| 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)      | 33 |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 18 investigative sites in Thailand, Malaysia, Algeria, Croatia, India, Poland, Turkey, and Ukraine from 12 February 2019 to 27 December 2021. Participants with a diagnosis of Congenital Hemophilia A were enrolled.

### Pre-assignment

Screening details:

Participants received factor eight inhibitor bypassing activity (FEIBA) reconstituted in regular volume and FEIBA reconstituted in 50% reduced volume in a crossover fashion for Part 1 and FEIBA reconstituted in 50% reduced volume at escalated infusion rates for Part 2. Participants who completed Part 1 entered Part 2 of the study.

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 45 <sup>[1]</sup> |
| Number of subjects completed | 33                |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Discontinued Before First Infusion: 12 |
|----------------------------|--|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 12 participants of 45 participants were enrolled but discontinued before the first infusion.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Part 1:Screening (Day -35) up to Day 19 |
| Is this the baseline period? | Yes                                     |
| Allocation method            | Randomised - controlled                 |
| Blinding used                | Not blinded                             |

### Arms

|           |   |
|-----------|---|
| Arm title | Part 1:FEIBA 85±15 U/kg 2 U/kg/min Rate or Vice Versa |
|-----------|---|

Arm description:

Participants who were eligible were randomized to receive: 3 infusions (infusions 1, 2 and 3) of factor eight inhibitor bypassing activity (FEIBA) 85 ± 15 U/kg, reconstituted in regular volume sterile water for injection (SWFI) followed by 3 infusions (infusions 4, 5 and 6) of FEIBA 85 ± 15 U/kg reconstituted in 50% reduced volume SWFI (Sequence A) or: 3 infusions (infusions 1, 2 and 3) of FEIBA 85 ± 15 U/kg, reconstituted in 50% reduced volume SWFI, followed by 3 infusions of FEIBA 85 ± 15 U/kg, reconstituted in regular volume SWFI (Sequence B).

All infusions in Part 1 were given at the standard infusion rate of 2 U/kg/min.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | FEIBA  |
| Investigational medicinal product code |  |
| Other name                             | FEIBA NF, AICC, anti-inhibitor coagulant complex, Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]), FEIBA NF.

|  |   |
|--|---|
| <b>Number of subjects in period 1</b>      | Part 1:FEIBA 85±15 U/kg 2 U/kg/min Rate or Vice Versa |
| Started                                    | 33  |
| Completed                                  | 30  |
| Not completed                              | 3   |
| Withdrawal by Subject (After 1st Infusion) | 1   |
| Adverse Event (After 1st Infusion)         | 2   |

## Period 2

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 2 title               | Part 2:Approximately Day 20 to Day 43 |
| Is this the baseline period? | No                                    |
| Allocation method            | Non-randomised - controlled           |
| Blinding used                | Not blinded                           |

## Arms

|                  |   |
|------------------|---|
| <b>Arm title</b> | Part 2:FEIBA 85±15U/kg 50% Reduce Volume at 4 Then 10U/kg/min |
|------------------|---|

### Arm description:

Participants who completed Part 1, received FEIBA 85 ± 15 U/kg, reconstituted in 50% reduced volume SWFI at an increased rate of 4 U/kg/min for infusions 7, 8, and 9, followed by FEIBA 85 ± 15 U/kg, reconstituted in 50% reduced volume SWFI at an increased rate of 10 U/kg/min for infusions 10, 11, and 12.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | FEIBA  |
| Investigational medicinal product code |  |
| Other name                             | FEIBA NF, AICC, anti-inhibitor coagulant complex, Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Intravenous use  |

### Dosage and administration details:

Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]), FEIBA NF.

|                                       |   |
|---------------------------------------|---|
| <b>Number of subjects in period 2</b> | Part 2:FEIBA 85±15U/kg 50% Reduce Volume at 4 Then 10U/kg/min |
| Started                               | 30  |
| Completed                             | 28  |
| Not completed                         | 2   |
| Physician decision                    | 1   |
| Adverse event, non-fatal              | 1   |



## Baseline characteristics

### Reporting groups

|   |   |
|---|---|
| Reporting group title   | Part 1:FEIBA 85±15 U/kg 2 U/kg/min Rate or Vice Versa |
| Reporting group description:<br>Participants who were eligible were randomized to receive: 3 infusions (infusions 1, 2 and 3) of factor eight inhibitor bypassing activity (FEIBA) 85 ± 15 U/kg, reconstituted in regular volume sterile water for injection (SWFI) followed by 3 infusions (infusions 4, 5 and 6) of FEIBA 85 ± 15 U/kg reconstituted in 50% reduced volume SWFI (Sequence A) or: 3 infusions (infusions 1, 2 and 3) of FEIBA 85 ± 15 U/kg, reconstituted in 50% reduced volume SWFI, followed by 3 infusions of FEIBA 85 ± 15 U/kg, reconstituted in regular volume SWFI (Sequence B).<br>All infusions in Part 1 were given at the standard infusion rate of 2 U/kg/min. |   |

| Reporting group values  | Part 1:FEIBA 85±15 U/kg 2 U/kg/min Rate or Vice Versa | Total |  |
|---|---|-------|--|
| Number of subjects  | 33  | 33    |  |
| Age Categorical<br>Units: Subjects                                      |   |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 35.4<br>± 11.92                                       | -     |  |
| Gender categorical<br>Units: Subjects                                   |   |       |  |
| Male  | 33  | 33    |  |
| Female  | 0   | 0     |  |
| Race<br>Units: Subjects   |   |       |  |
| American Indian or Alaska Native  | 0   | 0     |  |
| Asian   | 17  | 17    |  |
| Native Hawaiian or Other Pacific Islander                               | 0   | 0     |  |
| Black or African American   | 0   | 0     |  |
| White   | 16  | 16    |  |
| More than one race  | 0   | 0     |  |
| Unknown or Not Reported   | 0   | 0     |  |
| Ethnicity<br>Units: Subjects  |   |       |  |
| Hispanic or Latino  | 2   | 2     |  |
| Not Hispanic or Latino  | 31  | 31    |  |
| Unknown or Not Reported   | 0   | 0     |  |

### Subject analysis sets

|  |   |
|--|---|
| Subject analysis set title   | Part 1:FEIBA 85 ± 15 U/kg Regular Volume at 2 U/kg/min Rate |
| Subject analysis set type  | Full analysis   |
| Subject analysis set description:<br>Participants were randomized to receive 3 infusions of FEIBA 85 ± 15 U/kg, IV reconstituted in regular volume SWFI at the standard rate of 2 U/kg/min, every 48 hours (Participants in Sequence A: infusions 1, 2, and 3 and Participants in Sequence B: infusions 4, 5 and 6). |   |

|  |  |
|--|--|
| Subject analysis set title   | Part 1:FEIBA 85±15 U/kg 50% Reduced Volume at 2 U/kg/min Rate  |
| Subject analysis set type  | Full analysis  |
| Subject analysis set description:<br>Participants were randomized to receive 3 infusions of FEIBA 85 ± 15 U/kg, IV reconstituted in 50% reduced volume SWFI, at the standard rate of 2 U/kg/min, every 48 hours (Participants in Sequence A: infusions 4, 5, and 6 and Participants in Sequence B: infusions 1, 2 and 3).                                  |  |
| Subject analysis set title   | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 4 U/kg/min Rate  |
| Subject analysis set type  | Full analysis  |
| Subject analysis set description:<br>Participants who completed Part 1 of the study received up to 3 infusions of FEIBA 85 ± 15 U/kg IV reconstituted in 50% reduced volume SWFI at an increased rate of 4 U/kg/min, every 48 hours (infusions 7, 8, and 9).   |  |
| Subject analysis set title   | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 U/kg/min Rate |
| Subject analysis set type  | Full analysis  |
| Subject analysis set description:<br>Participants who completed Part 1 of the study and received up to 3 infusions (infusions 7, 8, and 9) at the rate of 4 U/kg/min in Part 2 received up to 3 infusions (10, 11, and 12) of FEIBA 85 ± 15 U/kg IV reconstituted in 50% reduced volume SWFI at an increased infusion rate of 10 U/kg/min, every 48 hours. |  |

| Reporting group values             | Part 1:FEIBA 85 ± 15 U/kg Regular Volume at 2 U/kg/min Rate | Part 1:FEIBA 85±15 U/kg 50% Reduced Volume at 2 U/kg/min Rate | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 4 U/kg/min Rate |
|------------------------------------|---|---|---|
| Number of subjects                 | 33  | 30  | 30  |
| Age Categorical<br>Units: Subjects |   |   |   |

|   |        |        |        |
|---|--------|--------|--------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 0<br>± | 0<br>± | 0<br>± |
| Gender categorical<br>Units: Subjects                                   |        |        |        |
| Male  | 0      | 0      | 0      |
| Female  | 0      | 0      | 0      |
| Race<br>Units: Subjects   |        |        |        |
| American Indian or Alaska Native  | 0      | 0      | 0      |
| Asian   | 0      | 0      | 0      |
| Native Hawaiian or Other Pacific Islander                               | 0      | 0      | 0      |
| Black or African American   | 0      | 0      | 0      |
| White   | 0      | 0      | 0      |
| More than one race  | 0      | 0      | 0      |
| Unknown or Not Reported   | 0      | 0      | 0      |
| Ethnicity<br>Units: Subjects  |        |        |        |
| Hispanic or Latino  | 0      | 0      | 0      |
| Not Hispanic or Latino  | 0      | 0      | 0      |
| Unknown or Not Reported   | 0      | 0      | 0      |

|                        |                    |  |  |
|------------------------|--------------------|--|--|
| Reporting group values | Part 2:FEIBA 85±15 |  |  |
|------------------------|--------------------|--|--|



U/kg 50% Reduced  
Volume at 10  
U/kg/min Rate

|   |    |  |  |
|---|----|--|--|
| Number of subjects                        | 28 |  |  |
| Age Categorical                           |    |  |  |
| Units: Subjects                           |    |  |  |
| Age continuous                            |    |  |  |
| Units: years                              |    |  |  |
| arithmetic mean                           | 0  |  |  |
| standard deviation                        | ±  |  |  |
| Gender categorical                        |    |  |  |
| Units: Subjects                           |    |  |  |
| Male                                      | 0  |  |  |
| Female                                    | 0  |  |  |
| Race                                      |    |  |  |
| Units: Subjects                           |    |  |  |
| American Indian or Alaska Native          | 0  |  |  |
| Asian                                     | 0  |  |  |
| Native Hawaiian or Other Pacific Islander | 0  |  |  |
| Black or African American                 | 0  |  |  |
| White                                     | 0  |  |  |
| More than one race                        | 0  |  |  |
| Unknown or Not Reported                   | 0  |  |  |
| Ethnicity                                 |    |  |  |
| Units: Subjects                           |    |  |  |
| Hispanic or Latino                        | 0  |  |  |
| Not Hispanic or Latino                    | 0  |  |  |
| Unknown or Not Reported                   | 0  |  |  |

## End points

### End points reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Part 1:FEIBA 85±15 U/kg 2 U/kg/min Rate or Vice Versa |
|-----------------------|---|

#### Reporting group description:

Participants who were eligible were randomized to receive: 3 infusions (infusions 1, 2 and 3) of factor eight inhibitor bypassing activity (FEIBA) 85 ± 15 U/kg, reconstituted in regular volume sterile water for injection (SWFI) followed by 3 infusions (infusions 4, 5 and 6) of FEIBA 85 ± 15 U/kg reconstituted in 50% reduced volume SWFI (Sequence A) or: 3 infusions (infusions 1, 2 and 3) of FEIBA 85 ± 15 U/kg, reconstituted in 50% reduced volume SWFI, followed by 3 infusions of FEIBA 85 ± 15 U/kg, reconstituted in regular volume SWFI (Sequence B).

All infusions in Part 1 were given at the standard infusion rate of 2 U/kg/min.

|                       |   |
|-----------------------|---|
| Reporting group title | Part 2:FEIBA 85±15U/kg 50% Reduce Volume at 4 Then 10U/kg/min |
|-----------------------|---|

#### Reporting group description:

Participants who completed Part 1, received FEIBA 85 ± 15 U/kg, reconstituted in 50% reduced volume SWFI at an increased rate of 4 U/kg/min for infusions 7, 8, and 9, followed by FEIBA 85 ± 15 U/kg, reconstituted in 50% reduced volume SWFI at an increased rate of 10 U/kg/min for infusions 10, 11, and 12.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Part 1:FEIBA 85 ± 15 U/kg Regular Volume at 2 U/kg/min Rate |
|----------------------------|---|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

#### Subject analysis set description:

Participants were randomized to receive 3 infusions of FEIBA 85 ± 15 U/kg, IV reconstituted in regular volume SWFI at the standard rate of 2 U/kg/min, every 48 hours (Participants in Sequence A: infusions 1, 2, and 3 and Participants in Sequence B: infusions 4, 5 and 6).

|                            |   |
|----------------------------|---|
| Subject analysis set title | Part 1:FEIBA 85±15 U/kg 50% Reduced Volume at 2 U/kg/min Rate |
|----------------------------|---|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

#### Subject analysis set description:

Participants were randomized to receive 3 infusions of FEIBA 85 ± 15 U/kg, IV reconstituted in 50% reduced volume SWFI, at the standard rate of 2 U/kg/min, every 48 hours (Participants in Sequence A: infusions 4, 5, and 6 and Participants in Sequence B: infusions 1, 2 and 3).

|                            |   |
|----------------------------|---|
| Subject analysis set title | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 4 U/kg/min Rate |
|----------------------------|---|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

#### Subject analysis set description:

Participants who completed Part 1 of the study received up to 3 infusions of FEIBA 85 ± 15 U/kg IV reconstituted in 50% reduced volume SWFI at an increased rate of 4 U/kg/min, every 48 hours (infusions 7, 8, and 9).

|                            |  |
|----------------------------|--|
| Subject analysis set title | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 U/kg/min Rate |
|----------------------------|--|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

#### Subject analysis set description:

Participants who completed Part 1 of the study and received up to 3 infusions (infusions 7, 8, and 9) at the rate of 4 U/kg/min in Part 2 received up to 3 infusions (10, 11, and 12) of FEIBA 85 ± 15 U/kg IV reconstituted in 50% reduced volume SWFI at an increased infusion rate of 10 U/kg/min, every 48 hours.

### Primary: Number of Participants With Any Treatment Emergent Adverse Event (TEAE)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Any Treatment Emergent Adverse Event (TEAE) <sup>[1]</sup> |
|-----------------|--|

#### End point description:

An AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. SAS included all participants who received at least one dose of IP (i.e., FEIBA).

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

End point timeframe:

From first dose of study drug up to end of study (up to Day 43)

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            | Part 1:FEIBA<br>85 ± 15 U/kg<br>Regular<br>Volume at 2<br>U/kg/min Rate | Part 1:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 2<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 4<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 10<br>U/kg/min Rate |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed | 33  | 30  | 30  | 28   |
| Units: participants         | 8   | 7   | 1   | 4  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants With Any Hypersensitivity Reaction

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Any Hypersensitivity Reaction <sup>[2]</sup> |
|-----------------|--|

End point description:

Number of participants with AEs particular to allergic-type hypersensitivity reactions were assessed. Clinical manifestations of hypersensitivity reactions included, but was not limited to Skin rash, Pruritus (itching), Urticaria (hives), Angioedema (for example, swelling of the lips and/or tongue) and Anaphylactic reaction. SAS included all participants who received at least one dose of IP (i.e., FEIBA).

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

End point timeframe:

From first dose of study drug up to end of study (up to Day 43)

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            | Part 1:FEIBA<br>85 ± 15 U/kg<br>Regular<br>Volume at 2<br>U/kg/min Rate | Part 1:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 2<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 4<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 10<br>U/kg/min Rate |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed | 33  | 30  | 30  | 28   |
| Units: participants         | 3   | 1   | 0   | 0  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants With Any Thromboembolic Event

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Any Thromboembolic Event <sup>[3]</sup> |
|-----------------|---|

End point description:

Participants with adverse events related to thromboembolic event were reported. Clinical manifestations of thromboembolic events included, but was not limited to myocardial infarction, deep vein thrombosis, pulmonary embolism, stroke and transitory ischemic attack. SAS included all participants who received at least one dose of IP (i.e., FEIBA).

End point type Primary

End point timeframe:

From first dose of study drug up to end of study (up to Day 43)

Notes:

[3] - 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            | Part 1:FEIBA<br>85 ± 15 U/kg<br>Regular<br>Volume at 2<br>U/kg/min Rate | Part 1:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 2<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 4<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 10<br>U/kg/min Rate |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed | 33  | 30  | 30  | 28   |
| Units: participants         | 0   | 0   | 0   | 0  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants With Any Infusion Site Reaction

End point title Number of Participants With Any Infusion Site Reaction<sup>[4]</sup>

End point description:

Infusion sites were monitored for pain, tenderness, erythema, and swelling. Infusion site evaluations were made by clinical staff or by the participant or caregiver. SAS included all participants who received at least one dose of IP (i.e., FEIBA).

End point type Primary

End point timeframe:

From first dose of study drug up to end of study (up to Day 43)

Notes:

[4] - 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            | Part 1:FEIBA<br>85 ± 15 U/kg<br>Regular<br>Volume at 2<br>U/kg/min Rate | Part 1:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 2<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 4<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 10<br>U/kg/min Rate |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed | 33  | 30  | 30  | 28   |
| Units: participants         | 2   | 1   | 0   | 0  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants With AEs Leading to Study Discontinuation

|                 |   |
|-----------------|---|
| End point title | Number of Participants With AEs Leading to Study Discontinuation <sup>[5]</sup> |
|-----------------|---|

End point description:

SAS included all participants who received at least one dose of IP (i.e., FEIBA).

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

End point timeframe:

From first dose of study drug up to end of study (up to Day 43)

Notes:

[5] - 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            | Part 1:FEIBA<br>85 ± 15 U/kg<br>Regular<br>Volume at 2<br>U/kg/min Rate | Part 1:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 2<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 4<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 10<br>U/kg/min Rate |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed | 33  | 30  | 30  | 28   |
| Units: participants         | 2   | 1   | 0   | 0  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants With Vital Signs considered as AEs

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Vital Signs considered as AEs <sup>[6]</sup> |
|-----------------|--|

End point description:

Number of participants with vital signs considered as AEs were assessed. Vital signs included body temperature (degree Celsius or degrees Fahrenheit [°C or °F]), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (millimeter of mercury [mmHg]). SAS included all participants who received at least one dose of IP (i.e., FEIBA). Participants were counted more than once in the arm groups.

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

End point timeframe:

From first dose of study drug up to end of study (up to Day 43)

Notes:

[6] - 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            | Part 1:FEIBA<br>85 ± 15 U/kg<br>Regular<br>Volume at 2<br>U/kg/min Rate | Part 1:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 2<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 4<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 10<br>U/kg/min Rate |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed | 33  | 30  | 30  | 28   |
| Units: participants         | 0   | 0   | 0   | 1  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants With Laboratory Assessments considered as AEs

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Laboratory Assessments considered as AEs <sup>[7]</sup> |
|-----------------|---|

End point description:

Number of participants with Laboratory Assessments considered as AEs were assessed. Laboratory assessments included hematology, clinical chemistry, coagulation testing, serological testing, pregnancy testing, cluster differentiation 4 (CD4). SAS included all participants who received at least one dose of IP (i.e., FEIBA). Participants were counted more than once in the arm groups.

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

End point timeframe:

From first dose of study drug up to end of study (up to Day 43)

Notes:

[7] - 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            | Part 1:FEIBA<br>85 ± 15 U/kg<br>Regular<br>Volume at 2<br>U/kg/min Rate | Part 1:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 2<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 4<br>U/kg/min Rate | Part 2:FEIBA<br>85±15 U/kg<br>50% Reduced<br>Volume at 10<br>U/kg/min Rate |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed | 33  | 30  | 30  | 28   |
| Units: participants         | 2   | 2   | 0   | 0  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to end of study (up to Day 43)

Adverse event reporting additional description:

At each visit investigator documented occurrence of adverse events (untoward medical occurrence in participant administered IP that does not necessarily have a causal relationship with treatment).

SAS=participants receiving at least one dose of IP (FEIBA).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Part 1:FEIBA 85 ± 15 U/kg Regular Volume at 2 U/kg/min Rate |
|-----------------------|---|

Reporting group description:

Participants were randomized to receive 3 infusions of FEIBA 85 ± 15 U/kg, IV reconstituted in regular volume SWFI at the standard rate of 2 U/kg/min, every 48 hours (Participants in Sequence A: infusions 1, 2, and 3 and Participants in Sequence B: infusions 4, 5 and 6).

|                       |   |
|-----------------------|---|
| Reporting group title | Part 1:FEIBA 85±15 U/kg 50% Reduced Volume at 2 U/kg/min Rate |
|-----------------------|---|

Reporting group description:

Participants were randomized to receive 3 infusions of FEIBA 85 ± 15 U/kg, IV reconstituted in 50% reduced volume SWFI, at the standard rate of 2 U/kg/min, every 48 hours (Participants in Sequence A: infusions 4, 5, and 6 and Participants in Sequence B: infusions 1, 2 and 3).

|                       |   |
|-----------------------|---|
| Reporting group title | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 4 U/kg/min Rate |
|-----------------------|---|

Reporting group description:

Participants who completed Part 1 of the study received up to 3 infusions of FEIBA 85 ± 15 U/kg IV infusions reconstituted in 50% reduced volume SWFI at an increased rate of 4 U/kg/min, every 48 hours (infusions 7, 8, and 9).

|                       |  |
|-----------------------|--|
| Reporting group title | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 U/kg/min Rate |
|-----------------------|--|

Reporting group description:

Participants who completed Part 1 of the study and received up to 3 infusions (infusions 7, 8, and 9) at the rate of 4 U/kg/min in Part 2 received up to 3 infusions (10, 11, and 12) of FEIBA 85 ± 15 U/kg IV reconstituted in 50% reduced volume SWFI at an increased infusion rate of 10 U/kg/min, every 48 hours.

| Serious adverse events                            | Part 1:FEIBA 85 ± 15 U/kg Regular Volume at 2 U/kg/min Rate | Part 1:FEIBA 85±15 U/kg 50% Reduced Volume at 2 U/kg/min Rate | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 4 U/kg/min Rate |
|---|---|---|---|
| Total subjects affected by serious adverse events |   |   |   |
| subjects affected / exposed                       | 3 / 33 (9.09%)  | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| number of deaths (all causes)                     | 0   | 0   | 0   |
| number of deaths resulting from adverse events    | 0   | 0   | 0   |
| Nervous system disorders                          |   |   |   |
| Epilepsy  |   |   |   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 33 (3.03%) | 0 / 30 (0.00%) | 0 / 30 (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          |
| Immune system disorders                         |                |                |                |
| Drug hypersensitivity                           |                |                |                |
| subjects affected / exposed                     | 1 / 33 (3.03%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypersensitivity                                |                |                |                |
| subjects affected / exposed                     | 1 / 33 (3.03%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Muscle haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 30 (3.33%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |  |  |  |
|---|--|--|--|
| <b>Serious adverse events</b>                     | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 U/kg/min Rate |  |  |
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 0 / 28 (0.00%)   |  |  |
| number of deaths (all causes)                     | 0  |  |  |
| number of deaths resulting from adverse events    | 0  |  |  |
| Nervous system disorders                          |  |  |  |
| Epilepsy  |  |  |  |
| subjects affected / exposed                       | 0 / 28 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Immune system disorders                           |  |  |  |
| Drug hypersensitivity                             |  |  |  |
| subjects affected / exposed                       | 0 / 28 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Hypersensitivity                                  |  |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 28 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Muscle haemorrhage                              |                |  |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Part 1:FEIBA 85 ± 15 U/kg Regular Volume at 2 U/kg/min Rate | Part 1:FEIBA 85±15 U/kg 50% Reduced Volume at 2 U/kg/min Rate | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 4 U/kg/min Rate |
|---|---|---|---|
| Total subjects affected by non-serious adverse events |   |   |   |
| subjects affected / exposed                           | 2 / 33 (6.06%)  | 5 / 30 (16.67%)   | 0 / 30 (0.00%)  |
| Nervous system disorders                              |   |   |   |
| Headache  |   |   |   |
| subjects affected / exposed                           | 1 / 33 (3.03%)  | 2 / 30 (6.67%)  | 0 / 30 (0.00%)  |
| occurrences (all)                                     | 2   | 2   | 0   |
| Musculoskeletal and connective tissue disorders       |   |   |   |
| Arthralgia  |   |   |   |
| subjects affected / exposed                           | 1 / 33 (3.03%)  | 3 / 30 (10.00%)   | 0 / 30 (0.00%)  |
| occurrences (all)                                     | 1   | 4   | 0   |

| <b>Non-serious adverse events</b>                     | Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 U/kg/min Rate |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 2 / 28 (7.14%)   |  |  |
| Nervous system disorders                              |  |  |  |
| Headache  |  |  |  |
| subjects affected / exposed                           | 0 / 28 (0.00%)   |  |  |
| occurrences (all)                                     | 0  |  |  |
| Musculoskeletal and connective tissue disorders       |  |  |  |
| Arthralgia  |  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 28 (7.14%) |  |  |
| occurrences (all)           | 2              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 02 March 2016     | -EudraCT Number was updated. -Criteria for participants with hemophilia A was changed from $\geq 0.4$ to $\geq 0.6$ BU. -All references of data monitoring committee (DMC) were removed and updated to ISMC. -Inclusion criteria were added to synopsis. -Text was added to describe how the sites will receive FEIBA and SWFI within a kit. -The duration of time the participants will be on study was clarified by Part 1 and Part 2. -The occurrence of thromboembolic events was added to the primary objectives and endpoints, and allergic reactions were renamed to allergic-type hypersensitivity reactions. -The outcome measure of evaluating product-related AEs was updated to all AEs and SAEs, outcome measure of evaluating the occurrence of AEs leading to discontinuation was added, and evaluating the occurrence of thromboembolic AEs was deleted. -Additional text was added to describe the washout period depending on whether the participant is treated with FEIBA or rFVIIa, and for management of bleeding episodes. -Thromboembolic events were added as a special treatment consideration. -The planned statistical analysis of the primary analysis was updated. -Review of participant diary and diary collection was removed and replaced with breakthrough bleeds monitoring and concomitant medication monitoring. -A standard of care medication for bleeding episodes was introduced into the protocol to allow for this change in study design. -Additional text was added to describe the scenario of bleeding during times other than washout periods and PK collection periods. -Severe allergic reaction was added as a reason for completion/discontinuation. -PK timepoints were updated. -The sample size calculation was reworded and clarified, adding in the coefficient of variation and the margins of equivalence. -Blood sample for thrombotic marker analysis will be collected at either the 30-minute or 24-hour timepoint. Was updated to just the 30 minutes timepoint. |
| 04 August 2017    | -The phase of the study was changed from 3b to 3b/4. -The words "two-part" and "the safety" were removed from the title and PK was changed to Tolerability. -SAE reporting via eCRF removed -Updated timelines for initiation, primary completion, study completion and duration. -Updated study purpose, primary objectives and exploratory objectives to include Tolerability and Safety and remove PK and secondary objectives. -Study design changed to Tolerability and Safety from PK comparability, pharmacokinetic and safety. -Changed Primary and Exploratory Outcome Measure(s). -Removed secondary outcome measures. -Anaphylaxis was removed as an example from primary objective 2. -From clinically symptomatic liver disease changed to Advanced liver disease and prothrombin time [PT] 5 seconds above upper limit of normal was included. -Herbal supplements containing anti-platelet activity was added as an exclusion criteria. -Updated sample size calculation and Planned Statistical Analysis. -Updated Part 1 and 2 as per design change from PK to tolerability and safety evaluation. -Updated bleeding episode to be resolved in 48 hours and washout period removed during screening. -Updated to exclude need for samples to be used for retesting, further evaluation of an AE, or follow-up of other results. -Updated infusion sites monitoring by participants from 72 to 48 hours. -The entire statistics section was revised in line with the change in study design from PK to tolerability and safety.   |
| 14 September 2017 | -Product Insert changed to Investigator's Brochure.   |

|               |   |
|---------------|---|
| 06 March 2018 | <p>-“Concentration” of Factor II was changed to “activity” of Factor II throughout. - Primary outcome measure rephrased. -Exclusion criterion added. -Clarification that vital signs and lab results considered AEs was listed in summary tables. - Addition of Emicuzimab as a product not permitted as a concomitant therapy. Also, addition of rFVIIa as a product not permitted for concomitant/sequential therapy that should not be used unless FEIBA does not work to treat breakthrough bleeding. -Addition of text. -Slight changes to timing of blood draws, specifically addition of a pre-infusion blood draw for coagulation parameters to add a control to compare to post-infusion blood draw findings, and removal of a blood draw at 12 hours to make the study less strenuous for the patient. Also added a blood draw for FII at screening. -Removal of hepatitis B virus antibody from testing. - Addition of Xs to clarify when blood would be drawn to monitor FII levels, and to clarify that pre-infusion blood draws will be considered as 48 hour post-infusion time point for prior infusion. -Removal of HBVantibody from the testing schedule. -Clarification of the FII blood draw schedule in Table 5.</p> |
|---------------|---|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported