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[1]
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.

Number of subjects in period 1	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

Arm title	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.

Number of subjects in period 2	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:

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 values	Part 1:FEIBA 85±15 U/kg 2 U/kg/min Rate or Vice Versa	Total	
Number of subjects	33	33	
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	35.4		
standard deviation	± 11.92	-	
Gender categorical Units: Subjects			
Male	33	33	
Female	0	0	
Race 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 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:

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.

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			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	0	0	0
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Male	0	0	0
Female	0	0	0
Race			
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			
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)[1]

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 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	Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 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[2]

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 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	Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 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[3]

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 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	Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 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[4]

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 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	Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 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[5]

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 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	Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 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 [6]

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 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	Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 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[7]

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 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	Part 2:FEIBA 85±15 U/kg 50% Reduced Volume at 10 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

Serious adverse events	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 %

Non-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 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

Non-serious adverse events	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 occurrences (all)	2 / 28 (7.14%) 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 ≥0.4 to ≥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	-"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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported