Clinical trial results:
An open-label, non-investigational product, multi-center, lead-in study to evaluate prospective efficacy and selected safety data of current factor IX (FIX) or factor VIII (FVIII) prophylaxis replacement therapy in the usual care setting of moderately severe to severe adult hemophilia B participants (FIX:C less than or equal to [<=]2percentage [%]) who are negative for neutralizing antibodies to adeno-associated virus vector-spark100 (BENEGENE-1) and moderately severe to severe hemophilia A adult participants (FVIII:C <=1%) who are negative for neutralizing antibodies to adeno-associated virus vector 6 (AAV6), prior to the respective therapeutic phase 3 gene therapy studies.

Summary

EudraCT number	2017-001271-23
Trial protocol	SE GB IE DE FR ES NL
Global end of trial date	12 December 2024

Results information

Result version number	v1 (current)
This version publication date	12 November 2025
First version publication date	12 November 2025

Trial information

Trial identification

Sponsor protocol code	C0371004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03587116
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 Hudson Boulevard East, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 April 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to establish prospective efficacy data of FIX or FVIII prophylaxis replacement therapy, in the usual care setting of hemophilia B participants who are negative for neutralizing antibodies (nAb) to adeno-associated virus vector (AAV)-Spark100 or hemophilia A participants who are negative for nAb to AAV6.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines; applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines; applicable laws and regulations, including applicable privacy laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 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	Australia: 11
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Saudi Arabia: 11
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Türkiye: 52

Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	212
EEA total number of subjects	62

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)	212
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 212 participants were enrolled in this study.

Pre-assignment

Screening details:

Participants with moderately severe to severe adult hemophilia B or hemophilia A who received FIX and FVIII standard prophylaxis replacement therapy in the usual care setting were enrolled in the study.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard of Care FIX Replacement Therapy (Hemophilia B)

Arm description:

Participants with moderately severe to severe hemophilia B who administered their own current FIX replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.

Arm type	No investigational product
Investigational medicinal product name	FIX replacement therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hemophilia B participants remained on their current FIX replacement therapy using their usual prophylaxis regimen.

Arm title	Standard of Care FVIII Replacement Therapy (Hemophilia A)

Arm description:

Participants with moderately severe to severe hemophilia A who administered their own current FVIII replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.

Arm type	No investigational product
Investigational medicinal product name	FVIII replacement therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hemophilia A participants remained on their current FVIII replacement therapy using their usual prophylaxis regimen.

Number of subjects in period 1	Standard of Care FIX Replacement Therapy (Hemophilia B)	Standard of Care FVIII Replacement Therapy (Hemophilia A)
Started	111	101
Completed	107	99
Not completed	4	2
Consent withdrawn by subject	4	-
No Longer Met Eligibility Criteria	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Standard of Care FIX Replacement Therapy (Hemophilia B)
Reporting group description:	
Participants with moderately severe to severe hemophilia B who administered their own current FIX replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.	
Reporting group title	Standard of Care FVIII Replacement Therapy (Hemophilia A)
Reporting group description:	
Participants with moderately severe to severe hemophilia A who administered their own current FVIII replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.	

Reporting group values	Standard of Care FIX Replacement Therapy (Hemophilia B)	Standard of Care FVIII Replacement Therapy (Hemophilia A)	Total
Number of subjects	111	101	212
Age categorical Units: Subjects			
In Utero	0	0	0
Preterm newborn infants (gestional age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2 - 11 years)	0	0	0
12 - 17 years	0	0	0
Adults (18 - 64 years)	111	101	212
From 65 - 84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.5	31.8	
standard deviation	± 11.25	± 11.21	-
Gender categorical Units: Subjects			
Male	111	101	212
Female	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	18	17	35
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	6	8
White	90	78	168
More than one race	1	0	1
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			

Hispanic or Latino	4	4	8
Not Hispanic or Latino	91	76	167
Unknown or Not Reported	16	21	37

End points

End points reporting groups

Reporting group title	Standard of Care FIX Replacement Therapy (Hemophilia B)

Reporting group description:

Participants with moderately severe to severe hemophilia B who administered their own current FIX replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.

Reporting group title	Standard of Care FVIII Replacement Therapy (Hemophilia A)

Reporting group description:

Participants with moderately severe to severe hemophilia A who administered their own current FVIII replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.

Primary: Annualized Bleeding Rate (ABR) for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set

End point title	Annualized Bleeding Rate (ABR) for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set[1][2]

End point description:

ABR per participant calculated as number of bleeds over number of days from baseline visit (Day 1 of study) to end of study*365.25 days. All bleeds=treated and untreated bleeds. Treated bleed: event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Untreated bleed: event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Efficacy analysis set included participants who signed an informed consent form (ICF), had their blood sample collected and assayed for bioengineered AAV capsid, derived from a naturally occurring AAV serotype (AAV-Spark100) or adeno-associated virus 6(AAV6) immunity testing, who were subsequently identified as nAb negative(negative for nAb to AAV-Spark100 for hemophilia B cohort), met inclusion/exclusion criteria and who participated in prospective data collection phase as part of their usual healthcare setting.

End point type	Primary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

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: Only descriptive data was planned to be analyzed for this endpoint.

[2] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	3.61 (± 7.634)			
All bleeds	4.46 (± 9.446)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set

End point title	ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set[3][4]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study *365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for hemophilia B cohort), met inclusion/ exclusion criteria and who participated and completed at least 6 months of prospective data collection phase as part of their usual healthcare setting.

End point type	Primary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

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: Only descriptive data was planned to be analyzed for this endpoint.

[4] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	3.71 (± 7.717)			
All bleeds	4.56 (± 9.557)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set

End point title	ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set[5][6]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. In this outcome measure, ABR for all and treated bleeds during prospective data collection period in hemophilia B participants per protocol amendment 5 analysis set was reported. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Primary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

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: Only descriptive data was planned to be analyzed for this endpoint.

[6] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds All bleeds	4.21 (± 10.609) 4.78 (± 10.887)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds During Retrospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set

End point title	ABR for Treated Bleeds and All Bleeds During Retrospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set[7][8]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. In this outcome measure, ABR for all and treated bleeds during retrospective data collection period in hemophilia B participants per

protocol amendment 5 analysis set was reported. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected. Here, “Subjects Analyzed” signifies number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

During retrospective data collection period (12 months before screening collected in the hemophilia history case report form [CRF])

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: Only descriptive data was planned to be analyzed for this endpoint.

[8] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	5.42 (± 8.163)			
All bleeds	6.79 (± 10.390)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds From the Combined Retrospective and Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set

End point title	ABR for Treated Bleeds and All Bleeds From the Combined Retrospective and Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set[9][10]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. In this outcome measure, ABR for all and treated bleeds during retrospective and prospective data collection period in hemophilia B participants per protocol amendment 5 analysis set was reported. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected. Here, "Subjects Analyzed” signifies number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

From start of retrospective data collection period (12 months before screening collected in hemophilia history CRF) up to end of prospective data collection follow-up of period (maximum follow-up:1269 days), for a total of approximately 4.5 years

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: Only descriptive data was planned to be analyzed 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	4.65 (± 7.589)			
All bleeds	5.48 (± 8.284)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set

End point title	ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set[11][12]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds=treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for the hemophilia A cohort), met the inclusion/ exclusion criteria and who participated in the prospective data collection phase as part of their usual healthcare setting.

End point type	Primary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

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: Only descriptive data was planned to be analyzed for this endpoint.

[12] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds All bleeds	4.87 (± 7.246) 6.10 (± 10.578)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set

End point title	ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set[13][14]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for the hemophilia A cohort), met the inclusion/ exclusion criteria and who participated and completed at least 6 months of the prospective data collection phase as part of their usual healthcare setting.

End point type	Primary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[13] - 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: Only descriptive data was planned to be analyzed for this endpoint.

[14] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	3.82 (± 5.665)			

All bleeds	4.33 (± 6.700)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set

End point title	ABR for Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set[15][16]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. In this outcome measure, ABR for all and treated bleeds during prospective data collection period in hemophilia A participants per protocol amendment 5 analysis set was reported. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Primary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[15] - 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: Only descriptive data was planned to be analyzed for this endpoint.

[16] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	7.62 (± 9.907)			
All bleeds	10.86 (± 16.692)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds During Retrospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set

End point title	ABR for Treated Bleeds and All Bleeds During Retrospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set[17][18]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. In this outcome measure, ABR for all and treated bleeds during retrospective data collection period in hemophilia A participants per protocol amendment 5 analysis set was reported. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Primary

End point timeframe:

During retrospective data collection period (12 months before screening collected in the hemophilia history CRF)

Notes:

[17] - 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: Only descriptive data was planned to be analyzed for this endpoint.

[18] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	9.83 (± 13.656)			
All bleeds	14.29 (± 18.208)			

Statistical analyses

No statistical analyses for this end point

Primary: ABR for Treated Bleeds and All Bleeds From the Combined Retrospective and Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set

End point title	ABR for Treated Bleeds and All Bleeds From the Combined Retrospective and Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set[19][20]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. All bleeds included treated and untreated bleeds. A treated bleed was defined as an event necessitating administration of coagulation factor within 72 hours of signs

or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. In this outcome measure, ABR for all and treated bleeds during retrospective and prospective data collection period in hemophilia A participants per protocol amendment 5 analysis set was reported. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Primary

End point timeframe:

From start of retrospective data collection period (12 months before screening collected in hemophilia history CRF) up to end of prospective data collection follow-up of period (maximum follow-up:948 days), for a total of approximately 3.6 years

Notes:

[19] - 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: Only descriptive data was planned to be analyzed for this endpoint.

[20] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	9.01 (± 11.908)			
All bleeds	12.77 (± 16.290)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Infusion Rate (AIR) During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set

End point title	Annualized Infusion Rate (AIR) During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set[21]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for the hemophilia B cohort), met the inclusion/ exclusion criteria and who participated in the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[21] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Infusions per year				
arithmetic mean (standard deviation)	62.81 (± 33.250)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set

End point title	AIR During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set[22]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for the hemophilia B cohort), met the inclusion/ exclusion criteria and who participated and completed at least 6 months of the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[22] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: Infusions per year				
arithmetic mean (standard deviation)	62.82 (± 33.213)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR During Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set

End point title	AIR During Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set[23]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[23] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Infusions per year				
arithmetic mean (standard deviation)	56.97 (± 20.987)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR During Retrospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set

End point title	AIR During Retrospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set[24]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

During retrospective data collection period (12 months before screening collected in the hemophilia history CRF)

Notes:

[24] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Infusions per year				
arithmetic mean (standard deviation)	66.97 (± 30.535)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR From the Combined Retrospective and Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set

End point title	AIR From the Combined Retrospective and Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set[25]

End point description:

AIR combining retrospective and prospective data was calculated as (number of infusions from baseline visit (Day 1) to end of study + number of infusions collected in the Hemophilia History form) / (number of days from baseline visit (Day 1) to end of study + 365.25) / 365.25. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

From start of retrospective data collection period (12 months before screening collected in hemophilia history CRF) up to end of prospective data collection follow-up of period (maximum follow-up:1269 days), for a total of approximately 4.5 years

Notes:

[25] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Infusions per year				
arithmetic mean (standard deviation)	60.98 (± 23.130)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set

End point title	AIR During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set[26]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for the hemophilia A cohort), met the inclusion/ exclusion criteria and who participated in the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[26] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Infusions per year				
arithmetic mean (standard deviation)	127.07 (± 51.784)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set

End point title	AIR During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set[27]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for the hemophilia A cohort), met the inclusion/ exclusion criteria and who participated and completed at least 6 months of the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[27] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Infusions per year				
arithmetic mean (standard deviation)	127.12 (± 55.418)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR During Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set

End point title	AIR During Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set[28]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[28] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Infusions per year				
arithmetic mean (standard deviation)	133.19 (± 56.725)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set

End point title	Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set[29]

End point description:

Annualized factor consumption was calculated as the total factor replacement therapy consumption (in international unit [IU] and dose) *365.25 days/number of days during the observation time period while the participant received factor prophylaxis replacement therapy in the usual care setting from baseline visit (Day 1) to end of study. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for the hemophilia B cohort), met the inclusion/ exclusion criteria and who participated in the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[29] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: International units per year				
arithmetic mean (standard deviation)	238312 (± 127817)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR From the Combined Retrospective and Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set

End point title	AIR From the Combined Retrospective and Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set[30]

End point description:

AIR combining retrospective and prospective data was calculated as (number of infusions from baseline visit (Day 1) to end of study + number of infusions collected in the Hemophilia History form) / (number of days from baseline visit (Day 1) to end of study + 365.25) / 365.25. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

From start of retrospective data collection period (12 months before screening collected in hemophilia

history CRF) up to end of prospective data collection follow-up of period (maximum follow-up:948 days), for a total of approximately 3.6 years

Notes:

[30] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Infusions per year				
arithmetic mean (standard deviation)	139.88 (± 52.490)			

Statistical analyses

No statistical analyses for this end point

Secondary: AIR During Retrospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set

End point title	AIR During Retrospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set[31]

End point description:

AIR per participant was calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study * 365.25 days. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

During retrospective data collection period (12 months before screening collected in the hemophilia history CRF)

Notes:

[31] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Infusions per year				
arithmetic mean (standard deviation)	141.88 (± 50.487)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set

End point title	Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set[32]

End point description:

Annualized factor consumption was calculated as the total factor replacement therapy consumption (in IU and dose) *365.25 days/number of days during the observation time period while the participant received factor prophylaxis replacement therapy in the usual care setting from baseline visit (Day 1) to end of study. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for the hemophilia B cohort), met the inclusion/ exclusion criteria and who participated and completed at least 6 months of the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[32] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: International units per year				
arithmetic mean (standard deviation)	240501 (± 128676)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set

End point title	Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia B Participants: Protocol Amendment 5 Analysis set[33]

End point description:

Annualized factor consumption was calculated as the total factor replacement therapy consumption (in IU and dose) *365.25 days/number of days during the observation time period while the participant received factor prophylaxis replacement therapy in the usual care setting from baseline visit (Day 1) to end of study. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[33] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: International units per year				
arithmetic mean (standard deviation)	223408 (± 85995)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set

End point title	Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set[34]

End point description:

Annualized factor consumption was calculated as the total factor replacement therapy consumption (in IU and dose) *365.25 days/number of days during the observation time period while the participant received factor prophylaxis replacement therapy in the usual care setting from baseline visit (Day 1) to end of study. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for the hemophilia A cohort), met the inclusion/ exclusion criteria and who participated in the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[34] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: International units per year				
arithmetic mean (standard deviation)	304998 (± 153932)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set

End point title	Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set[35]

End point description:

Annualized factor consumption was calculated as the total factor replacement therapy consumption (in IU and dose) *365.25 days/number of days during the observation time period while the participant received factor prophylaxis replacement therapy in the usual care setting from baseline visit (Day 1) to end of study. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for the hemophilia A cohort), met the inclusion/ exclusion criteria and who participated and completed at least 6 months of the prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[35] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: International units per year				
arithmetic mean (standard deviation)	314195 (± 163786)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set

End point title	Annualized Total Factor IX Replacement Therapy Consumption During Prospective Data Collection Period in Hemophilia A Participants: Protocol Amendment 5 Analysis set[36]

End point description:

Annualized factor consumption was calculated as the total factor replacement therapy consumption (in IU and dose) *365.25 days/number of days during the observation time period while the participant received factor prophylaxis replacement therapy in the usual care setting from baseline visit (Day 1) to end of study. Protocol Amendment 5 analysis set included all participants enrolled under Protocol Amendment 5 and afterwards, who fulfilled the inclusion/exclusion criteria and had retrospective and prospective data collected.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[36] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: International units per year				
arithmetic mean (standard deviation)	235097 (± 67977)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set

End point title	ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set[37]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1) to end of study*365.25 days. Spontaneous bleeds: bleeding for no apparent or known reason particularly into the joints, muscles, and soft tissues. All bleeds included treated and untreated bleeds. Treated bleed: event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Untreated bleed: event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for hemophilia B cohort), met inclusion/ exclusion criteria and who participated in prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[37] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	2.11 (± 3.835)			
All bleeds	2.79 (± 6.411)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set

End point title	ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Efficacy Analysis set[38]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1 of the study) to end of study*365.25 days. Traumatic bleeds were defined as bleeding event occurring for an apparent or known reason. All bleeds included treated and untreated bleeds. Treated bleed: event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Untreated bleed: event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for hemophilia B cohort), met inclusion/exclusion criteria and who participated in prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[38] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	1.50 (± 6.380)			
All bleeds	1.68 (± 6.623)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set

End point title	ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set[39]

End point description:

ABR per participant calculated as number of bleeds over number of days from baseline visit (Day 1) to end of study*365.25days. Spontaneous bleeds: bleeding for no apparent or known reason particularly into joints, muscles, soft tissues. All bleeds=treated and untreated bleeds. Treated bleed:event necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Untreated bleed:event not necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Per-Protocol analysis set: all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative(negative for nAb to AAV-Spark100 for hemophilia B cohort),met inclusion/exclusion criteria and who participated and completed at least 6 months of prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[39] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	2.17 (± 3.872)			
All bleeds	2.84 (± 6.490)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set

End point title	ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia B Participants: Per-protocol Analysis set[40]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1) to end of study*365.25 days. Traumatic bleeds were defined as bleeding event occurring for an apparent or known reason. All bleeds=treated and untreated bleeds. Treated bleed: event necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Untreated bleed: event not necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative(negative for nAb to AAV-Spark100 for hemophilia B cohort),met inclusion/exclusion criteria and who participated and completed at least 6 months of prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Notes:

[40] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	1.54 (± 6.465)			
All bleeds	1.72 (± 6.710)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set

End point title	ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set[41]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1) to end of study*365.25 days. Spontaneous bleeds: bleeding for no apparent or known reason particularly into the joints, muscles, and soft tissues. All bleeds included treated and untreated bleeds. Treated bleed: event necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Untreated bleed: event not necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for hemophilia A cohort), met inclusion/ exclusion criteria and who participated in prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[41] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	3.15 (± 5.948)			
All bleeds	3.89 (± 7.552)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set

End point title	ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Efficacy Analysis set[42]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1) to end of study*365.25 days. Traumatic bleeds were defined as bleeding event occurring for an apparent or known reason. All bleeds included treated and untreated bleeds. A treated bleed: event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. An untreated bleed was defined as an event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Efficacy analysis set included participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for hemophilia A cohort), met inclusion/exclusion criteria and who participated in prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[42] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	1.78 (± 3.893)			
All bleeds	2.27 (± 5.503)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set

End point title	ABR for Spontaneous Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set[43]

End point description:

ABR per participant calculated as number of bleeds over number of days from baseline visit (Day 1) to end of study*365.25days. Spontaneous bleeds: bleeding for no apparent or known reason particularly into joints,muscles, soft tissues. All bleeds=treated and untreated bleeds. Treated bleed: event necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Untreated bleed: event not necessitating administration of coagulation factor within 72hours of signs or symptoms of bleeding. Per-Protocol analysis set: all participants who signed an ICF,had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing,who were subsequently identified as nAb negative(negative for nAb to AAV6 for hemophilia A cohort),met inclusion/exclusion criteria and who participated and completed at least 6 months of prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[43] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	2.37 (± 4.101)			
All bleeds	2.73 (± 5.143)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set

End point title	ABR for Traumatic Treated Bleeds and All Bleeds During Prospective Data Collection Period in Hemophilia A Participants: Per-protocol Analysis set[44]

End point description:

ABR per participant was calculated as number of bleeds over number of days from baseline visit (Day 1) to end of study*365.25 days. Traumatic bleeds were defined as bleeding event occurring for an apparent or known reason. All bleeds=treated and untreated bleeds. Treated bleed: event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Untreated bleed: event not necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding. Per-Protocol analysis set included all participants who signed an ICF, had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing, who were subsequently identified as nAb negative (negative for nAb to AAV6 for hemophilia A cohort), met inclusion/exclusion criteria and who participated and completed at least 6 months of prospective data collection phase as part of their usual healthcare setting.

End point type	Secondary

End point timeframe:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 948 days])

Notes:

[44] - 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: This endpoint was planned to be analysed only for the specified reporting arms.

End point values	Standard of Care FVIII Replacement Therapy (Hemophilia A)			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Treated bleeds	1.45 (± 3.467)			
All bleeds	1.60 (± 3.608)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Serious Adverse Events (SAEs)

End point title	Number of Participants With Serious Adverse Events (SAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An SAE was any untoward medical occurrence at any dose that met 1 of the following criteria: 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; other important medical events per protocol of the study. Safety analysis set (SAS) included all enrolled participants (negative for nAb to AAV-Spark100 for the hemophilia B cohort, or negative for nAb to AAV6 for the hemophilia A cohort) who entered the prospective data collection phase.

End point type	Other pre-specified

End point timeframe:

During prospective data collection period: Day 1 through end of study visit (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)	Standard of Care FVIII Replacement Therapy (Hemophilia A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	101		
Units: Participants	9	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Adverse Events of Special Interest (AESIs)

End point title	Number of Participants With Adverse Events of Special Interest (AESIs)

End point description:

An AE was any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Adverse events of special interest were FIX/FVIII inhibitor development, thrombotic events, and FIX hypersensitivity events for this study. SAS included all enrolled participants (negative for nAb to AAV-Spark100 for the hemophilia B cohort, or negative for nAb to AAV6 for the hemophilia A cohort) who entered the prospective data collection phase.

End point type	Other pre-specified

End point timeframe:

During prospective data collection period: Day 1 through end of study visit (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

End point values	Standard of Care FIX Replacement Therapy (Hemophilia B)	Standard of Care FVIII Replacement Therapy (Hemophilia A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	101		
Units: Participants	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During prospective data collection period (from baseline visit of the study [Day 1] up to end of study follow-up [maximum follow-up: 1269 days])

Adverse event reporting additional description:

Same event may occur as both non-SAE and SAE but are distinct events. An event may be categorised as serious in 1 participant and non-serious in another, or a participant may have experienced both SAE and non-SAE. Safety analysis set was evaluated.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Standard of Care FIX Replacement Therapy (Hemophilia B)

Reporting group description:

Participants with moderately severe to severe hemophilia B who administered their own current FIX replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.

Reporting group title	Standard of Care FVIII Replacement Therapy (Hemophilia A)

Reporting group description:

Participants with moderately severe to severe hemophilia A who administered their own current FVIII replacement therapy in the usual healthcare setting were included. No investigational product was administered as a part of this study.

Serious adverse events	Standard of Care FIX Replacement Therapy (Hemophilia B)	Standard of Care FVIII Replacement Therapy (Hemophilia A)	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 111 (8.11%)	4 / 101 (3.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	0 / 111 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint injury	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		

subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth fracture	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	2 / 111 (1.80%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	0 / 111 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	0 / 111 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemophilic arthropathy	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	1 / 111 (0.90%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	0 / 111 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Standard of Care FIX Replacement Therapy (Hemophilia B)	Standard of Care FVIII Replacement Therapy (Hemophilia A)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 111 (3.60%)	0 / 101 (0.00%)	
Vascular disorders			
Haematoma	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		

subjects affected / exposed	2 / 111 (1.80%)	0 / 101 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: MedDRA v27.1 was used for Hemophilia B cohort. MedDRA v26.0 was used for Hemophilia A cohort.		
subjects affected / exposed	2 / 111 (1.80%)	0 / 101 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2019	Including an additional cohort (hemophilia A population) as part of the 6-month lead-in study, to support the initiation of the hemophilia A gene therapy Phase 3 study. Incorporate administrative changes from the 6 previous protocol administrative change letters (PACLs).
17 May 2022	Clarified that participant with a history of a neoplasm (including hepatic malignancy) that required treatment (e.g., chemotherapy, radiotherapy, immunotherapy), is excluded, except for adequately treated basal or squamous cell carcinoma of the skin or a surgically removed benign neoplasm not requiring chemotherapy, radiotherapy and/or immunotherapy. Any other neoplasm that has been cured by resection should be discussed between the investigator and sponsor. Clarified that participants with conditions associated with increased thromboembolic risk such as known inherited or acquired thrombophilia, or a history of thrombotic events, including venous thromboembolism, should be excluded so that it is not open to investigator discretion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported