Clinical trial results:
Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients >=12 Years of Age With Severe Hemophilia A

Summary

EudraCT number	2019-002023-15
Trial protocol	DE GB FR BG BE GR HU NL ES Outside EU/EEA IT
Global end of trial date	03 February 2022

Results information

Result version number	v1
This version publication date	17 August 2022
First version publication date	17 August 2022

Trial information

Trial identification

Sponsor protocol code	EFC16293

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04161495
WHO universal trial number (UTN)	U1111-1223-4867
Other trial identifiers	Short title: XTEND-1

Notes:

Sponsors

Sponsor organisation name	Bioverativ, a Sanofi Company
Sponsor organisation address	225 Second Avenue, Waltham, Massachusetts, United States, 02451
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002501-PIP01-18
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of BIVV001 as a prophylaxis treatment.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adults and paediatric subjects. The parent(s) or guardian(s) as well as children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. Adult subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Brazil: 4

Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Korea, Republic of: 6
Worldwide total number of subjects	159
EEA total number of subjects	71

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)	25
Adults (18-64 years)	129
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 51 active sites in 19 countries. A total of 170 subjects were screened between 21 November 2019 to 19 March 2021, of which 11 had screen failure due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 159 subjects were enrolled in this current study (EFC16293), of which 92 subjects were rolled over from study OBS16221 and then subsequently enrolled and received BIVV001 in current study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Prophylaxis

Arm description:

Subjects who were on a prophylaxis treatment with a FVIII product prior to study EFC16293 including subjects who rolled over from study OBS16221, received BIVV001 50 international units per kilogram (IU/kg) intravenous (IV) injection once-weekly (QW) for 52 weeks in the current study. Study OBS16221 subjects with 6 months historical data on prophylaxis treatment with a marketed FVIII product prior to enrollment were analysed as a subgroup (named as: Arm A: Historical Prophylaxis (OBS16221) in the endpoint analysis.

Arm type	Experimental
Investigational medicinal product name	Efanesoctocog alfa
Investigational medicinal product code	BIVV001
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

BIVV001 50 IU/kg, IV injection QW for up to 52 weeks.

Arm title	Arm B: On-Demand Then Prophylaxis

Arm description:

Subjects who were on an on-demand treatment regimen with a FVIII product prior to study EFC16293, including subjects who rolled over from study OBS16221, received BIVV001 50 IU/kg IV injection as an on-demand treatment (as needed for the treatment of bleeding episodes) from Week 1 to Week 26 in current study. At Week 26, subjects in Arm B were switched to prophylaxis treatment, and received BIVV001 50 IU/kg, IV injection QW until Week 52.

Arm type	Experimental
Investigational medicinal product name	Efanesoctocog alfa
Investigational medicinal product code	BIVV001
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

BIVV001 50 IU/kg, IV injection for 52 weeks (On-demand followed by QW Prophylaxis - each of 26 weeks).

Number of subjects in period 1	Arm A: Prophylaxis	Arm B: On-Demand Then Prophylaxis
Started	133	26
Historical Prophylaxis in OBS16221	82 [1]	10 [2]
Arm B: On-demand	0 [3]	26
Arm B: Prophylaxis	0 [4]	26
Completed	124	25
Not completed	9	1
Consent withdrawn by subject	3	-
Protocol violation	1	-
Other - Unspecified	1	-
Death	-	1
Adverse event	1	-
Prohibited concomitant medication	3	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of subjects rolled over from study OBS16221 who were on prophylactic treatment with a marketed FVIII product for at least 6 months.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of subjects rolled over from study OBS16226 and were on prophylactic treatment with a marketed FVIII product for at least 6 months.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is not applicable to Arm A: Prophylaxis and is applicable only to Arm B: On-Demand Then Prophylaxis.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is not applicable to Arm A: Prophylaxis and is applicable only to Arm B: On-Demand Then Prophylaxis.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Prophylaxis
Reporting group description:	
Subjects who were on a prophylaxis treatment with a FVIII product prior to study EFC16293 including subjects who rolled over from study OBS16221, received BIVV001 50 international units per kilogram (IU/kg) intravenous (IV) injection once-weekly (QW) for 52 weeks in the current study. Study OBS16221 subjects with 6 months historical data on prophylaxis treatment with a marketed FVIII product prior to enrollment were analysed as a subgroup (named as: Arm A: Historical Prophylaxis (OBS16221) in the endpoint analysis.	
Reporting group title	Arm B: On-Demand Then Prophylaxis
Reporting group description:	
Subjects who were on an on-demand treatment regimen with a FVIII product prior to study EFC16293, including subjects who rolled over from study OBS16221, received BIVV001 50 IU/kg IV injection as an on-demand treatment (as needed for the treatment of bleeding episodes) from Week 1 to Week 26 in current study. At Week 26, subjects in Arm B were switched to prophylaxis treatment, and received BIVV001 50 IU/kg, IV injection QW until Week 52.	

Reporting group values	Arm A: Prophylaxis	Arm B: On-Demand Then Prophylaxis	Total
Number of subjects	133	26	159
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.9	42.8	
standard deviation	± 15.3	± 11.7	-
Gender categorical Units: Subjects			
Female	1	0	1
Male	132	26	158
Race Units: Subjects			
Asian	29	0	29
Black or African American	3	0	3
White	71	26	97
Not reported due to confidentiality regulations	26	0	26
Other	4	0	4

End points

End points reporting groups

Reporting group title	Arm A: Prophylaxis

Reporting group description:

Subjects who were on a prophylaxis treatment with a FVIII product prior to study EFC16293 including subjects who rolled over from study OBS16221, received BIVV001 50 international units per kilogram (IU/kg) intravenous (IV) injection once-weekly (QW) for 52 weeks in the current study. Study OBS16221 subjects with 6 months historical data on prophylaxis treatment with a marketed FVIII product prior to enrollment were analysed as a subgroup (named as: Arm A: Historical Prophylaxis (OBS16221) in the endpoint analysis.

Reporting group title	Arm B: On-Demand Then Prophylaxis

Reporting group description:

Subjects who were on an on-demand treatment regimen with a FVIII product prior to study EFC16293, including subjects who rolled over from study OBS16221, received BIVV001 50 IU/kg IV injection as an on-demand treatment (as needed for the treatment of bleeding episodes) from Week 1 to Week 26 in current study. At Week 26, subjects in Arm B were switched to prophylaxis treatment, and received BIVV001 50 IU/kg, IV injection QW until Week 52.

Subject analysis set title	Arm A: Historical Prophylaxis (OBS16221)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who had 6 months historical data on prophylaxis treatment (with marketed FVIII products) in study OBS16221 prior to enrollment in current study.

Subject analysis set title	Arm A: BIVV001 Prophylaxis in EFC16293
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received BIVV001 50 IU/kg (prophylaxis treatment regimen) for at least 6 months in current study (EFC16293) and had at least 6 months prophylaxis treatment regimen (with marketed FVIII products) in study OBS16221 prior to enrollment in the current study.

Subject analysis set title	Arm B: On-Demand
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were on an On-demand treatment regimen with a FVIII product prior to study EFC16293 including subjects who rolled over from study OBS16221, received BIVV001 50 IU/kg IV injection as an On-demand treatment (as needed for the treatment of bleeding episodes) from Week 1 to Week 26 in current study.

Subject analysis set title	Arm B: Prophylaxis
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received BIVV001 50 IU/kg IV injection as an on-demand treatment from Week 1 to Week 26 and were switched to prophylaxis dosing and received BIVV001 50 IU/kg, IV injection QW until Week 52 in the current study.

Subject analysis set title	Subjects With Surgery
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (who had at least 6 days of exposure to BIVV001) from any arm (Arm A or Arm B) who underwent major surgery (defined as any invasive operative procedure that required any of the following: opening into a major body cavity [e.g., abdomen, thorax, skull]; operation on a joint; removal of an organ; dental extraction of any molar teeth or greater than or equal to (>=) 3 non-molar teeth; operative alteration of normal anatomy; crossing of a mesenchymal barrier [e.g., pleura, peritoneum, dura]) after the first dose of study drug during the current study.

Subject analysis set title	BIVV001 (efanesoctocog alfa)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were enrolled in study and received BIVV001 in either Arm A or B.

Primary: Estimated Annualised Bleeding Rate (ABR) in Arm A: Prophylaxis

End point title	Estimated Annualised Bleeding Rate (ABR) in Arm A: Prophylaxis[1][2]

End point description:

ABR is annualised number of treated bleeding episodes (BE) per subject per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered less than or equal to (<=) 72 hours apart from previous injection were considered same bleeding episode. ABR=number of treated BE during efficacy period (EP)/number of days during EP*365.25. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. This endpoint presents estimated results (i.e., results estimated by fitting negative binomial [NB] regression model on data collected during EP). Full analysis set (FAS): all subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline to Week 52

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: As the endpoint was descriptive in nature, no statistical analysis was provided.

[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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)	0.71 (0.52 to 0.97)			

Statistical analyses

No statistical analyses for this end point

Primary: Observed Annualised Bleeding Rate in Arm A: Prophylaxis

End point title	Observed Annualised Bleeding Rate in Arm A: Prophylaxis[3][4]

End point description:

ABR is annualised number of treated bleeding episodes per subject per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. ABR=number of treated bleeding episodes during EP/number of days during EP*365.25. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. This endpoint presents observed results (i.e., descriptive statistics values based on the data which was collected during EP). Analysis was performed on FAS population.

End point type	Primary

End point timeframe:

Baseline to Week 52

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: As the endpoint was descriptive in nature, no statistical analysis was provided.

[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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: episodes per subject per year				
arithmetic mean (standard deviation)	0.71 (± 1.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Bleeding Rate During the Efficacy Period in Arm A: Prophylaxis - Non-inferiority Analysis

End point title	Estimated Annualised Bleeding Rate During the Efficacy Period in Arm A: Prophylaxis - Non-inferiority Analysis

End point description:

ABR is annualised number of treated bleeding episodes per subject per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. ABR=number of treated bleeding episodes during EP/number of days during EP*365.25. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. This endpoint presents estimated results (i.e., results received estimated by fitting NB regression model on data collected during EP). Analysed on per protocol set which included all subjects who had received at least one dose of study drug and did not had important protocol deviations potentially impacting efficacy.

End point type	Secondary

End point timeframe:

From 6 months (prior to entry into study EFC16293) until the day before enrollment in EFC16293 - for Historical prophylaxis; Baseline up to Week 52 of current study EFC16293 for BIVV001 Prophylaxis

End point values	Arm A: Historical Prophylaxis (OBS16221)	Arm A: BIVV001 Prophylaxis in EFC16293		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)	2.99 (2.03 to 4.42)	0.69 (0.43 to 1.12)		

Statistical analyses

Statistical analysis title	Historical Prophylaxis Versus BIVV001 Prophylaxis

Statistical analysis description:

Hierarchical testing framework was used to control type I error for secondary endpoint analyses. Statistical testing of Arm A intra-patient comparison non-inferiority continued only when estimation of previous endpoint was statistically significant at 0.05 level. For Arm A intra-patient comparison, mean difference and 95% confidence interval were estimated by NB regression model in which treatment (BIVV001 prophylaxis vs historical prophylaxis vs historical prophylaxis) was treated as covariate.

Comparison groups	Arm A: Historical Prophylaxis (OBS16221) v Arm A: BIVV001 Prophylaxis in EFC16293
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Mean difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.49
upper limit	-1.11

Notes:

[5] - Non-inferiority would be established if the upper bound of the one-sided 97.5% CI was less than 4. 'Number of subjects included in analysis' field: total number of subjects included in analysis were 77 instead of 154.

Secondary: Observed Annualised Bleeding Rate During the Efficacy Period in Prophylaxis - Non-inferiority Analysis

End point title	Observed Annualised Bleeding Rate During the Efficacy Period in Prophylaxis - Non-inferiority Analysis

End point description:

ABR is annualised number of treated bleeding episodes per subject per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. ABR=number of treated bleeding episodes during EP/number of days during EP*365.25. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. This endpoint presents observed results (i.e., descriptive statistics values based on the data which was collected during EP). Analysis was performed on per protocol set.

End point type	Secondary

End point timeframe:

From 6 months (prior to entry into study EFC16293) until the day before enrollment in EFC16293 - for Historical prophylaxis; Baseline up to Week 52 of current study EFC16293 for BIVV001 Prophylaxis

End point values	Arm A: Historical Prophylaxis (OBS16221)	Arm A: BIVV001 Prophylaxis in EFC16293		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	77		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	2.98 (± 5.21)	0.69 (± 1.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Bleeding Rate During the Efficacy Period in Arm A: Prophylaxis - Superiority Analysis

End point title	Estimated Annualised Bleeding Rate During the Efficacy Period in Arm A: Prophylaxis - Superiority Analysis

End point description:

ABR is annualised number of treated bleeding episodes per subject per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. ABR=number of treated bleeding episodes during EP/number of days during EP*365.25. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. This endpoint presents estimated results (i.e., results received estimated by fitting NB regression model on data collected during EP). Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From 6 months (prior to entry into study EFC16293) until the day before enrollment in EFC16293 - for Historical Prophylaxis; Baseline up to Week 52 of current study EFC16293 - for BIVV001 Prophylaxis

End point values	Arm A: Historical Prophylaxis (OBS16221)	Arm A: BIVV001 Prophylaxis in EFC16293		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78	78		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)	2.96 (2.00 to 4.37)	0.69 (0.43 to 1.11)		

Statistical analyses

Statistical analysis title	Historical Prophylaxis Versus BIVV001 Prophylaxis

Statistical analysis description:

Tested according to hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen). For test about Arm A intra-patient comparison superiority, mean difference and 95% CI were estimated using NB regression model in which treatment (BIVV001 prophylaxis vs historical prophylaxis) was treated as covariate. 'Number of subjects included in analysis' field: total number of subjects included in analysis were 77 instead of 156.

Comparison groups	Arm A: Historical Prophylaxis (OBS16221) v Arm A: BIVV001 Prophylaxis in EFC16293

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority[6]
Method	Negative binomial regression mode
Parameter estimate	Mean difference
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.42

Notes:

[6] - Superiority would be declared if the upper bound of the one-sided 97.5% confidence interval was less than 1.

Secondary: Observed Annualised Bleeding Rate During the Efficacy Period in Arm A: Prophylaxis - Superiority Analysis

End point title	Observed Annualised Bleeding Rate During the Efficacy Period in Arm A: Prophylaxis - Superiority Analysis

End point description:

ABR is annualised number of treated bleeding episodes per subject per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. ABR=number of treated bleeding episodes during EP/number of days during EP*365.25. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. This endpoint presents observed results (i.e., descriptive statistics values based on the data which was collected during EP). Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From 6 months (prior to entry into study EFC16293) until the day before enrollment in EFC16293 - for Historical Prophylaxis; Baseline up to Week 52 of current study EFC16293 - for BIVV001 Prophylaxis

End point values	Arm A: Historical Prophylaxis (OBS16221)	Arm A: BIVV001 Prophylaxis in EFC16293		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78	78		
Units: episodes per subject per year				
arithmetic mean (standard deviation)	2.95 (± 5.19)	0.68 (± 1.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes Measurements Information Systems (PROMIS) Pain Intensity 3a First Item at Week 52 in Arm A: Prophylaxis

End point title	Change From Baseline in Patient Reported Outcomes

	Measurements Information Systems (PROMIS) Pain Intensity 3a First Item at Week 52 in Arm A: Prophylaxis[7]

End point description:

PROMIS is a system of reliable and precise measures of subject-reported heath status. PROMIS measures cover physical, mental and social health and can be used for many chronic conditions. PROMIS - Pain Intensity - Short Form 3a consisted of 3 questions, subjects reported on the intensity of pain experienced in the past 7 days. Each question had 5 responses scored between 1 (had no pain) to 5 (very severe pain). Total score range was from 3 (no pain) to 15 (very severe pain), where higher score indicated more intense pain. Total raw score was converted into a T-score which rescaled raw score into standardised score with mean of 50 and standard deviation (SD) of 10. Higher PROMIS T-score represented worst outcome. For PROMIS pain intensity 3a, T-score of 60 was one SD worse than average. FAS population. Here, number of subjects analysed = subjects evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Baseline, Week 52

Notes:

[7] - 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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: T-score				
arithmetic mean (standard deviation)	-1.97 (± 7.86)			

Attachments (see zip file)	Statistical data:PROMIS Pain Intensity 3a 1st Item/Statistical

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Haemophilia A Quality of Life Questionnaire (Haem-A-QOL) Physical Health Score at Week 52 in Arm A: Prophylaxis

End point title	Change From Baseline in Haemophilia A Quality of Life Questionnaire (Haem-A-QOL) Physical Health Score at Week 52 in Arm A: Prophylaxis[8]

End point description:

Haem-A-QoL is a subject-reported questionnaire designed for adult subjects >=17 years of age) with hemophilia; and consisted of 46 items comprising 10 domains (physical health [5 items], feelings [4 items], view of self [5 items], sports and leisure [5 items], work and school [4 items], dealing with hemophilia [3 items], treatment [8 items], future [5 items], family planning [4 items], partnership and sexuality [3 items]). Items were rated along five response options: never, rarely, sometimes, often, or all the time. Raw score for physical health domain were transformed to a scale ranged from 0 to 100, where lower scores denoted better physical health. Change from baseline in physical Health domain score was reported in this endpoint. Analysis was performed on FAS population. Here, number of subjects analysed = subjects evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Baseline, Week 52

Notes:

[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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: score on a scale				
arithmetic mean (standard deviation)	-6.79 (± 18.59)			

Attachments (see zip file)	Statistical data: Haem-A-QOL Physical Health Score/Statistical

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hemophilia Joint Health Score (HJHS) Total Score at Week 52 in Arm A: Prophylaxis

End point title	Change from Baseline in Hemophilia Joint Health Score (HJHS) Total Score at Week 52 in Arm A: Prophylaxis[9]

End point description:

HJHS is a validated 11-item scoring tool developed for the assessment of joint health in subjects with hemophilia. It comprised an evaluation of the elbows, knee and ankle joints: swelling (0 to 3), duration of swelling (0 and 1), muscle atrophy (0 to 2), crepitus on motion (0 to 2), flexion loss (0 to 3), extension loss (0 to 3), joint pain (0 to 2) and strength (0 to 4), in each item 0 = none and higher score = severe damage and global gait (walking, stairs, running, hopping on 1 leg) scored on scale 0 to 4, where 0 = all skills in normal limit and 4 = no skills within normal limits). Total HJHS score = sum of joint totals (0 to 120) + general gait (1 to 4) and ranged from 0 (no joint damage) to 124 (severe joint damage), where higher score indicated severe joint damage. Analysis was performed on FAS population. Here, number of subjects analysed = subjects evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Baseline, Week 52

Notes:

[9] - 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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: score on a scale				
arithmetic mean (standard deviation)	-1.5 (± 6.4)			

Attachments (see zip file)	Statistical data: HJHS Total Score/Statistical data-HJHS Total

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Bleeding Rate by Type of Bleed (Spontaneous, Traumatic and Unknown Type)

End point title	Annualised Bleeding Rate by Type of Bleed (Spontaneous, Traumatic and Unknown Type)[10]

End point description:

ABR: annualised number of treated bleeding episodes per subject per year. EP reflects sum of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. Treated bleeding episode: episode that started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Spontaneous bleeding: bleeding episode without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic bleeding: bleeding episode with known/believed reason for bleed. FAS. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on-demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Spontaneous	0.00 (0.00 to 0.00)	16.69 (8.64 to 23.76)	0.00 (0.00 to 0.00)	
Traumatic	0.00 (0.00 to 0.00)	3.95 (0.00 to 6.48)	0.00 (0.00 to 0.00)	
Unknown type	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Bleeding Rate by Location of Bleed (Joint, Muscle, Internal and Skin/Mucosa)

End point title	Annualised Bleeding Rate by Location of Bleed (Joint, Muscle, Internal and Skin/Mucosa)[11]

End point description:

ABR:annualised number of treated bleeding episodes per subject per year. Efficacy period reflects sum

of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. Treated bleeding episode:episode that started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Spontaneous bleeding:bleeding episode without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic bleeding:bleeding episode with known/believed reason for bleed. FAS. Data for this endpoint: planned to be collected and analysed separately in Arm B for subjects during on-demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[11] - 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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Joint	0.00 (0.00 to 1.02)	18.42 (10.80 to 23.90)	0.00 (0.00 to 0.00)	
Muscle	0.00 (0.00 to 0.00)	0.00 (0.00 to 4.15)	0.00 (0.00 to 0.00)	
Internal	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	
Skin/mucosa	0.00 (0.00 to 0.00)	0.00 (0.00 to 2.09)	0.00 (0.00 to 0.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Bleeding Rate for all Bleeding Episodes

End point title	Annualised Bleeding Rate for all Bleeding Episodes[12]

End point description:

ABR: annualised number of all bleeding (treated and untreated) episodes/subject/year. ABR=number of all bleeding episodes during EP/number of days in EP*365.25. EP reflects sum of all time intervals during which subjects were treated with BIVV001 according to study arms and treatment regimens. Bleeding episode: episode started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. Any bleed at different location: considered as separate bleeding episode, regardless of time from last injection. Spontaneous: bleeding without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic: bleeding with known/believed reason. FAS population. Data for this endpoint: planned to be collected and analysed separately in Arm B for subjects during on-demand and prophylaxis post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 1.15)	21.13 (16.80 to 27.13)	0.00 (0.00 to 1.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Bleeding Rate: Intra-subject Comparison of Arm B Subjects

End point title	Annualised Bleeding Rate: Intra-subject Comparison of Arm B Subjects

End point description:

ABR is annualised number of treated bleeding episodes per subject per year. Treated Bleeding episode: any occurrence of hemorrhage that required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same bleeding episode. ABR=(Number of treated bleeding episodes during EP/number of days during EP*365.25. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. Analysis was performed on FAS population. In this endpoint, ABR of Arm B: separately for subjects during prophylaxis treatment versus On-Demand treatment was reported.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Arm B: On-Demand	Arm B: Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))	21.13 (15.12 to 27.13)	0.00 (0.00 to 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Factor VIII (FVIII) Activity Levels

Above 1%, 5%, 10%, 15%, and 20% in Arm A: Prophylaxis

End point title	Percentage of Subjects Achieving Factor VIII (FVIII) Activity Levels Above 1%, 5%, 10%, 15%, and 20% in Arm A: Prophylaxis[13]

End point description:

FVIII activity level was measured using activated partial thromboplastin time (aPTT)-based one stage clotting assay. Percentage of subjects who achieved steady-state trough FVIII activity levels above (>) 1%, 5%, 10%, 15%, and 20% were reported for Arm A: Prophylaxis in this endpoint. Analysis was performed on PK analysis set which included subjects who had completed adequate blood sample collection to assess key PK parameters. Here, number of subjects analysed = subjects evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[13] - 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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	131			
Units: percentage of subjects				
number (not applicable)				
>1%	100			
>5%	99.0			
>10%	83.5			
>15%	40.8			
>20%	17.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections of BIVV001 Required to Treat a Bleeding Episode

End point title	Number of Injections of BIVV001 Required to Treat a Bleeding Episode[14]

End point description:

The number of injections required to resolve each bleeding episode was averaged across all bleeding episodes per subject. A bleeding episode was defined as an episode that started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location or injections administered <=72 hours apart from previous injection were considered same bleeding episode. Analysis was performed on FAS population. Here, number of subjects analysed = subjects evaluable for this endpoint. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	26	6	
Units: injections per subject				
median (inter-quartile range (Q1-Q3))	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose of BIVV001 Required to Treat Bleeding Episode

End point title	Total Dose of BIVV001 Required to Treat Bleeding Episode[15]

End point description:

The total dose (IU/kg) used to resolve each bleeding episode was averaged across all bleeding episodes per subject. A bleeding episode was defined as an episode that started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location or injections administered <=72 hours apart from previous injection were considered same bleeding episode. Analysis was performed on FAS population. Here, number of subjects analysed = subjects evaluable for this endpoint. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[15] - 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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	47[16]	26[17]	6[18]	
Units: IU/kg				
median (inter-quartile range (Q1-Q3))	50.85 (41.69 to 52.08)	50.96 (50.10 to 51.83)	49.79 (40.54 to 50.60)	

Notes:

[16] - 86 = total number of treated bleeding episodes in Arm A: Prophylaxis.

[17] - 268 = total number of treated bleeding episodes in Arm B: On-Demand.

[18] - 8 = total number of treated bleeding episodes in Arm B: Prophylaxis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Bleeding Episodes Treated With a Single Injection of BIVV001

End point title	Percentage of Bleeding Episodes Treated With a Single Injection of BIVV001[19]

End point description:

A bleeding episode was defined as an episode that started from 1st sign of bleed and ended no more than 72 hours after last injection to treat bleeding episode, any subsequent bleeding at same location or injections administered <=72 hours apart from previous injection were considered same bleeding episode. Percentage of bleeding episodes (of all bleeding episodes occurred) which were treated with single injection was reported in this endpoint. Analysis was performed on FAS population. Here, number of subjects analysed field represents the total number of bleeding episodes. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[19] - 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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133[20]	26[21]	26[22]	
Units: percentage of bleeding episodes				
number (not applicable)	94.2	97.4	100	

Notes:

[20] - 86 = total number of treated bleeding episodes in Arm A: Prophylaxis.

[21] - 268 = total number of treated bleeding episodes in Arm B: On-Demand.

[22] - 8 = total number of treated bleeding episodes in Arm B: Prophylaxis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Response to BIVV001 Treatment Based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point Response Scale

End point title	Percentage of Subjects With Response to BIVV001 Treatment Based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point Response Scale[23]

End point description:

The subject's response related to each injection of BIVV001 treatment for treating a bleed was evaluated using ISTH 4-point response scale categorised as: Excellent (complete pain relief/complete resolution of signs of bleeding), Good (significant pain relief/improvement in signs of bleeding), Moderate (modest pain relief/improvement in signs of bleeding) and none (no or minimal improvement/condition worsened). Assessment was performed approximately 72 hours after the initial treatment for the bleeding episode. Bleeding episode was defined as an episode that started from first sign of a bleed and ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location or injections less than or equal to (<=) 72 hours apart were considered same bleeding episode. FAS population. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: percentage of subjects				
number (not applicable)				
Excellent or Good	82.2	98.4	100	
Excellent	53.4	76.5	83.3	
Good	28.8	22.0	16.7	
Moderate	13.7	1.6	0	
None	4.1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Physicians' Global Assessment of Subject's Response to BIVV001 Treatment

End point title	Physicians' Global Assessment of Subject's Response to BIVV001 Treatment[24]

End point description:

Physicians assessed subject's response to BIVV001 treatment using 4-point response scale: Excellent=bleeding episodes (BE) responded to fewer than/usual number of injections/less than/usual dose of FVIII/rate of breakthrough bleeding during prophylaxis was <= that usually observed; Effective=most BE responded to same number of injections and dose, but some required more injections/higher doses/there was minor increase in rate of breakthrough bleeding; partially effective=BE most often required more injections and/or higher doses than expected/adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses; Ineffective=routine failure to control hemostasis or hemostatic control required additional agents. Percentages were based on total number of responses. FAS population. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on-demand and prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133[25]	26[26]	26[27]	
Units: percentage of responses				
number (not applicable)				
Excellent	95.7	96.1	93.2	
Effective	4.3	3.9	6.8	
Partially effective	0	0	0	
Ineffective	0	0	0	

Notes:

[25] - 622 = Total responses in Arm A: Prophylaxis.

[26] - 77 = Total responses in Arm B: On-Demand.

[27] - 44 = Total responses Arm B: Prophylaxis.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Annualised BIVV001 Consumption Per Subject

End point title	Total Annualised BIVV001 Consumption Per Subject[28]

End point description:

Total annualised BIVV001 consumption (in IU/kg) was calculated for each subject as: Total IU/kg of BIVV001 during EP divided by total number of days during EP*365.25. Efficacy period reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to the study arms and treatment regimens. Analysis was performed on FAS population. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: IU/kg per subject per year				
median (full range (min-max))	2756.99 (2385.1 to 50171.7)	1212.27 (435.9 to 2023.8)	2737.53 (2486.4 to 2924.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hemophilia Joint Health Score (HJHS) Domain Score at Week 52 in Arm A: Prophylaxis

End point title	Change from Baseline in Hemophilia Joint Health Score (HJHS) Domain Score at Week 52 in Arm A: Prophylaxis[29]

End point description:

HJHS is a validated 11-item scoring tool developed for the assessment of joint health in subjects with hemophilia. Following domains were assessed for elbows, knee and ankle joints: swelling (score 0=no swelling to 3=severe), duration of swelling (score 0=no swelling and 1=>=6 months), muscle atrophy (score 0=none to 2=severe), crepitus on motion (score 0=none to 2=severe), flexion loss (score 0=<5" to 3=>20"), extension loss (score 0=<5" to 3=>20"), joint pain (score 0=no pain through active range of motion to 2=pain through active range) and strength (score 0=holds test position with maximum resistance to 4=trace/no muscle contraction), in each item 0 = none and higher score = severe damage. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Baseline, Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: score on scale				
arithmetic mean (standard deviation)				
Swelling (n = 114)	-0.3 (± 1.2)			
Duration Of Swelling (n = 113)	-0.2 (± 0.8)			
Muscle Atrophy (n = 116)	-0.3 (± 1.2)			
Crepitus On Motion (n = 114)	-0.3 (± 1.2)			
Flexion Loss (n = 112)	-0.3 (± 1.6)			
Extension Loss (n = 113)	-0.2 (± 1.5)			
Joint Pain (n = 114)	-0.1 (± 1.2)			
Strength (n = 113)	0.3 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Annualised Joint Bleeding Rate (AJBR)

End point title	Estimated Annualised Joint Bleeding Rate (AJBR)[30]

End point description:

AJBR: annualised number of joint bleeding/subject/year. ABR= number of treated joint bleeding episodes during EP divided by total number of days during EP*365.25. Joint bleeding episode: an unusual sensation in joint ("aura") in combination with 1) increasing swelling/warmth over skin, joint; 2) increasing pain or 3) progressive loss of range of motion or difficulty in using limb as compared with Baseline. Bleeding episode: episode that started from first sign of bleed and ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location/injections <= 72 hours apart were considered same bleeding episode. EP reflects the sum of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. Analysed on FAS population. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: joint bleeding episodes per subject year				
arithmetic mean (confidence interval 95%)	0.51 (0.36 to 0.72)	17.48 (14.88 to 20.54)	0.62 (0.25 to 1.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Annualised Joint Bleeding Rate (AJBR)

End point title	Observed Annualised Joint Bleeding Rate (AJBR)[31]

End point description:

AJBR: annualised number of joint bleeding/subject/year. ABR= number of treated joint bleeding episodes during EP divided by total number of days during EP*365.25. Joint bleeding episode: unusual sensation in joint ("aura") with 1) in combination with increasing swelling/warmth over skin, joint; 2) increasing pain or 3) progressive loss of range of motion or difficulty in using limb as compared with Baseline. Bleeding episode: episode that started from first sign of bleed and ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location/injections <= 72 hours apart were considered same bleeding episode. EP reflects sum of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. FAS population. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: joint bleeding episodes per subject year				
arithmetic mean (standard deviation)	0.52 (± 1.09)	17.45 (± 7.31)	0.61 (± 1.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Target Joint Resolved in Subjects at Week 52 in Arm A: Prophylaxis

End point title	Total Number of Target Joint Resolved in Subjects at Week 52 in Arm A: Prophylaxis[32]

End point description:

A target joint at baseline was defined as a major joint with >=3 spontaneous bleeding episodes in a consecutive 6 month period prior to entry to the study, captured at Baseline. A target joint resolved was defined as <=2 spontaneous bleeds into that joint during 12 months of continuous exposure. Total number of target joints resolved at Week 52 were reported. Analysis was performed on FAS population. Here, number of subjects analysed detail indicates total number of target joints with >=3 spontaneous bleeding at Baseline. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	133[33]			
Units: Target joints				
number (not applicable)	45			

Notes:

[33] - 80 = Total number of target joints with >=3 spontaneous bleeding at Baseline in Arm A: Prophylaxis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes Measurements Information Systems Short Form (PROMIS-SF) Physical Function (PF) 6b at Week 52 in Arm A: Prophylaxis

End point title	Change From Baseline in Patient Reported Outcomes Measurements Information Systems Short Form (PROMIS-SF) Physical Function (PF) 6b at Week 52 in Arm A: Prophylaxis[34]

End point description:

PROMIS-SF v2.0 PF 6b consisted of 2-items from item-improved Health Assessment Questionnaire (HAQ) and 4-items from item-improved Physical Function-10 (PF-10) instruments. Both of these instruments assessed subject's present abilities and had 5-response options: HAQ: 1=without any difficulty, 2=with little difficulty, 3=with some difficulty, 4=with much difficulty,5=unable to do and PF-10: 1=not at all, 2=very little, 3=somewhat, 4=quite a lot, 5=cannot do. Total score: average scores of

component items, which ranged from 0 (no disability) to 100 (worst disability). T-score rescales raw scale score (sum of scores from all questions answered) into a standardised score with a mean of 50 and standard deviation of 10, based on scoring tables provided in PROMIS Scoring Manuals. Higher PROMIS T-score=more of concept being measured. FAS. Here, number of subjects analysed = subjects evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Baseline, Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: T-score				
arithmetic mean (standard deviation)	0.62 (± 4.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Haemophilia A Quality of Life Questionnaire Total Score at Week 52 in Arm A: Prophylaxis

End point title	Change From Baseline in Haemophilia A Quality of Life Questionnaire Total Score at Week 52 in Arm A: Prophylaxis[35]

End point description:

Haem-A-QoL: subject-reported questionnaire designed for adult subjects (>=17 years of age) with hemophilia; and consisted of 46 items comprising 10 domains (physical health [5 items], feelings [4 items], view of self [5 items], sports and leisure [5 items], work and school [4 items], dealing with hemophilia [3 items], treatment [8 items], future [5 items], family planning [4 items], partnership and sexuality [3 items]). Items were rated along 5 response options: 1=never, 2=rarely, 3=sometimes,4=often, and 5=all the time and higher scores represent greater impairment. Raw score for each domain were transformed to a scale ranged between 0 and 100, where lower scores denoted better physical health. Haem-A-QoL Total Score was average of all domain scores and ranged from 0 to 100, where lower scores = better quality of life. FAS population. Here, number of subjects analysed=subjects evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for Arm B.

End point type	Secondary

End point timeframe:

Baseline, Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: score on scale				
arithmetic mean (standard deviation)	-4.56 (± 11.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigators' or Surgeons' Assessment of Subject's Hemostatic Response to BIVV001 Treatment

End point title	Investigators' or Surgeons' Assessment of Subject's Hemostatic Response to BIVV001 Treatment

End point description:

The Investigators/Surgeons who complete the surgical procedures assess the subject’s response to surgery with BIVV001 treatment using a 4-point scale, where responses were categorised as worst response: 1 = Excellent, 2 = Good, 3 = Fair, and 4 = Poor/none. Higher score indicated worst response. This assessment was performed 24 hours after the surgery. Analysis was performed on surgery subgroup population which included all subjects who had undergone major surgery (defined as any invasive operative procedure that required any of the following: opening into major body cavity [e.g., abdomen, thorax, skull]; operation on a joint; removal of an organ; dental extraction of any molar teeth or >=3 non-molar teeth; operative alteration of normal anatomy; crossing of a mesenchymal barrier [e.g., pleura, peritoneum, dura]) after the first dose of study drug. Here, number of subjects analysed field detail indicates number of major surgeries.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Subjects With Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	13[36]			
Units: response to major surgeries				
Excellent or Good	12			
Excellent	12			
Good	0			
Fair	0			
Poor/none	0			

Notes:

[36] - 12 = number of major surgeries in arm 'Subjects with surgery'.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required to Maintain Hemostasis During

Perioperative Period for Major Surgery

End point title	Number of Injections Required to Maintain Hemostasis During Perioperative Period for Major Surgery

End point description:

Perioperative period was time lapse surrounding the surgical act which was divided into 3 stages: preoperative (4 weeks prior to surgery), operative (during the surgery) and post-operative (24-hour post-surgery). The number of injections to maintain hemostasis (a process to prevent and stop bleeding from a blood vessel) during surgery included all injections from loading dose (i.e., the preoperative injection, administered either on the day of surgery or one day prior to the surgery), to the end of surgery. Major surgery: defined as any invasive operative procedure that required any of the following: opening into major body cavity (e.g., abdomen, thorax, skull); operation on a joint; removal of an organ; dental extraction of any molar teeth or >=3 non-molar teeth; operative alteration of normal anatomy; crossing of a mesenchymal barrier (e.g., pleura, peritoneum, dura). Surgery subgroup population. Here, number of subjects analysed field detail indicates number of major surgeries.

End point type	Secondary

End point timeframe:

During the perioperative period (any time from Baseline up to Week 52)

End point values	Subjects With Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	13[37]			
Units: injections				
Zero injection	0			
One injection	11			
Two injection	0			
Three injection	0			
Four injection	0			
>Four injection	0			

Notes:

[37] - 12 = number of major surgeries in arm 'Subjects with Surgery'.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose Required to Maintain Hemostasis During Perioperative Period for Major Surgery

End point title	Total Dose Required to Maintain Hemostasis During Perioperative Period for Major Surgery

End point description:

Perioperative period was time lapse surrounding surgical act which was divided into 3 stages: preoperative (4 weeks prior to surgery), operative (during the surgery) and post-operative (24-hour post-surgery). Total dose (IU/kg) was the sum across all injections per major surgery (including loading dose) needed to maintain hemostasis (a process to prevent and stop bleeding from a blood vessel) during surgery. The analysis was based on the major surgeries conducted during the treatment regimen. Major surgery: defined as any invasive operative procedure that required any of the following: opening into major body cavity (e.g., abdomen, thorax, skull); operation on a joint; removal of an organ; dental extraction of any molar teeth or >=3 non-molar teeth; operative alteration of normal anatomy; crossing of a mesenchymal barrier (e.g., pleura, peritoneum, dura). Analysis was performed on surgery subgroup population. Here, number of subjects analysed field detail indicates number of surgeries

End point type	Secondary

End point timeframe:

During the perioperative period (any time from Baseline up to Week 52)

End point values	Subjects With Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	13[38]			
Units: IU/kg				
arithmetic mean (standard deviation)	41.65 (± 15.21)			

Notes:

[38] - 11 = number of surgeries in arm 'Subjects with Surgery'.

Statistical analyses

No statistical analyses for this end point

Secondary: Total BIVV001 Consumption During Perioperative Period for Major Surgery

End point title	Total BIVV001 Consumption During Perioperative Period for Major Surgery

End point description:

Perioperative period: time lapse surrounding surgical act which was divided into 3 stages: preoperative (4 weeks prior to surgery), operative (during the surgery) and post-operative (24-hour post-surgery). Total consumption (IU/kg) per major surgery on day of surgery, for first 2 weeks following surgery and for overall surgical/rehabilitation period were summarised using all major surgeries conducted during treatment regimen. Day of surgery (Day 0): calendar day of surgery, included loading dose given for that surgery. First 2 weeks following surgery began day after surgery and extended for 14 calendar days. Surgical/rehabilitation period: time from 1st dose of BIVV001 given for surgery (i.e., pre-surgery dose) up to 1 minute before 1st regular prophylactic dose after last day of postoperative care/rehabilitation. Total BIVV001 consumption was determined as sum of all doses administered during referenced time period: Day -1 (day prior to surgery) to 14. Surgery subgroup population.

End point type	Secondary

End point timeframe:

Day -1 to Day 14

End point values	Subjects With Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	13[39]			
Units: IU/kg per major surgery				
arithmetic mean (standard deviation)	166.71 (± 72.48)			

Notes:

[39] - 12 = Number of major surgeries in arm 'Subjects with Surgery'.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Blood Component Transfusions Used During Perioperative Period for Major Surgery

End point title	Number of Blood Component Transfusions Used During Perioperative Period for Major Surgery

End point description:

The perioperative period was the time lapse surrounding the surgical act which was divided into 3 stages: preoperative (4 weeks prior to surgery), operative (during the surgery) and post-operative (24-hour post-surgery). The number of blood component transfusions used during perioperative period were summarised categorically (0, 1, 2, 3 and >3) for all major surgeries for the surgery subgroup. Major surgery: defined as any invasive operative procedure that required any of the following: opening into major body cavity (e.g., abdomen, thorax, skull); operation on a joint; removal of an organ; dental extraction of any molar teeth or >=3 non-molar teeth; operative alteration of normal anatomy; crossing of a mesenchymal barrier (e.g., pleura, peritoneum, dura). Analysis was performed on surgery subgroup population. Here, number of subjects analysed field detail indicates number of major surgeries.

End point type	Secondary

End point timeframe:

During the perioperative period (any time from Baseline up to Week 52)

End point values	Subjects With Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	13[40]			
Units: transfusions per surgery				
Zero	12			
One	0			
Two	0			
Three	0			
> Three	0			

Notes:

[40] - 12 = Number of major surgeries in arm 'Subjects with Surgery'.

Statistical analyses

No statistical analyses for this end point

Secondary: Type of Blood Component Transfusions Used During Perioperative Period for Major Surgery

End point title	Type of Blood Component Transfusions Used During Perioperative Period for Major Surgery

End point description:

The perioperative period was the time lapse surrounding the surgical act which was divided into 3 stages: preoperative (4 weeks prior to surgery), operative (during the surgery) and post-operative (24-hour post-surgery). The type of blood component (Red blood cell, platelet, fresh frozen plasma, whole blood and other) transfusions used were summarised for all major surgeries. Post-operative referred to the day following the end of surgery to the date of hospital discharge. Major surgery: defined as any invasive operative procedure that required any of the following: opening into major body cavity (e.g., abdomen, thorax, skull); operation on a joint; removal of an organ; dental extraction of any molar teeth or >=3 non-molar teeth; operative alteration of normal anatomy; crossing of a mesenchymal barrier (e.g., pleura, peritoneum, dura). Analysis was performed on surgery subgroup population. Here, number of subjects analysed field detail indicates number of major surgeries.

End point type	Secondary

End point timeframe:

During the perioperative period (any time from Baseline up to Week 52)

End point values	Subjects With Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	12[41]			
Units: transfusions per surgery				
Red Blood Cell	0			
Platelet	0			
Fresh Frozen Plasma	0			
Whole Blood	0			
Other	0			

Notes:

[41] - 12 = Number of major surgeries in arm 'Subjects with Surgery'.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAE)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAE)[42]

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject who received study drug which did not necessarily have a causal relationship with the treatment. A serious AE (SAE) was defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was a medically important event. Treatment-emergent AEs were AEs that developed, worsened or became serious from Baseline (Day 1) up to 3 weeks post last dose of BIVV001. Analysis was performed on safety population which included all subjects who received at least one dose of study drug. Analysis was performed separately for subjects in Arm B when they were on On-demand and prophylaxis treatment.

End point type	Secondary

End point timeframe:

Arm A: From Baseline (Day 1) up to 3 weeks post last dose of BIVV001 (i.e., up to Week 55); Arm B: On-demand: Baseline to Week 26 and Arm B: Prophylaxis: From Week 26 up to 3 weeks post last dose of BIVV001 in Week 52 (i.e., up to Week 55)

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: subjects				
TEAE	108	12	8	
TESAE	13	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Blood Loss During Perioperative Period for Major Surgery

End point title	Estimated Blood Loss During Perioperative Period for Major Surgery

End point description:

The perioperative period was the time lapse surrounding the surgical act which was divided into 3 stages: preoperative (4 weeks prior to surgery), operative (during the surgery) and post-operative (24-hour post-surgery). The estimated total blood loss (in milliliters) during perioperative period was summarised for all major surgeries. Major surgery: defined as any invasive operative procedure that required any of the following: opening into major body cavity (e.g., abdomen, thorax, skull); operation on a joint; removal of an organ; dental extraction of any molar teeth or >=3 non-molar teeth; operative alteration of normal anatomy; crossing of a mesenchymal barrier (e.g., pleura, peritoneum, dura). Analysis was performed on surgery subgroup population. Here, number of subjects analysed field detail indicates number of major surgeries with blood loss estimation.

End point type	Secondary

End point timeframe:

During the perioperative period (any time from Baseline up to Week 52)

End point values	Subjects With Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	13[43]			
Units: millilitres				
arithmetic mean (standard deviation)	143.33 (± 189.38)			

Notes:

[43] - 6 = Number of major surgeries with blood loss estimation in arm 'Subjects with Surgery'.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Neutralising Antibodies (Development of Inhibitors) Directed Against Factor VIII

End point title	Number of Subjects With Neutralising Antibodies (Development of Inhibitors) Directed Against Factor VIII[44]

End point description:

Development of inhibitors was defined as an inhibitor result of ≥0.6 BU/mL that was confirmed by a second test result of ≥0.6 BU/mL from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. Both tests must have been
performed by the central laboratory using the Nijmegen-modified Bethesda assay. Analysis was performed on safety population. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post

switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Occurrence of Embolic and Thrombotic Events

End point title	Number of Subjects With Occurrence of Embolic and Thrombotic Events[45]

End point description:

Embolic and thrombotic events were defined as arterial or venous thrombosis, confirmed by imaging. Analysis was performed on safety population. Data for this endpoint was planned to be collected and analysed separately in Arm B for subjects during on demand treatment and during prophylaxis treatment post switch.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[45] - 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: Data were planned to be collected and analysed for specified arm only.

End point values	Arm A: Prophylaxis	Arm B: On-Demand	Arm B: Prophylaxis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	133	26	26	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Maximum FVIII Activity (Cmax)

End point title	Pharmacokinetics (PK): Maximum FVIII Activity (Cmax)

End point description:

Cmax was defined as the maximum observed plasma FVIII Activity. Analysis was performed on PK population which included all subjects who had completed adequate blood sample collection to assess key PK parameters. Here, "n"= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (15 minutes post-dose on Day 1) and 15 minutes post-dose on Week 52

End point values	Arm A: Prophylaxis	Arm B: On-Demand Then Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	26		
Units: IU per decilitre				
arithmetic mean (standard deviation)				
Baseline (n = 133, 26)	125.05 (± 31.72)	138.36 (± 48.66)		
Week 52 (n = 125, 23)	144.72 (± 36.65)	149.42 (± 29.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination Half-life (t1/2z)

End point title	Pharmacokinetics: Elimination Half-life (t1/2z)

End point description:

Plasma t1/2z was the time measured for the plasma concentration of drug to decrease by one half. Analysis was performed on PK population. Here, "n"= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

pre-dose and 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline); pre-dose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	159			
Units: hours				
median (full range (min-max))				
Baseline (n = 159)	46.5 (29.1 to 104)			
Week 26 (n = 17)	46.7 (29.4 to 63.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Clearance (CL)

End point title	Pharmacokinetics: Clearance (CL)

End point description:

CL is defined as the rate at which the drug is removed from the body. Analysis was performed on PK population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline)

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	153			
Units: millilitre per hour per kilogram				
arithmetic mean (standard deviation)	0.508 (± 0.124)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Total Clearance at Steady State (CLss)

End point title	Pharmacokinetics: Total Clearance at Steady State (CLss)

End point description:

CLss is defined as the rate at which the drug is removed from the body at steady state. Analysis was performed on PK population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: millilitre per hour per kilogram				
arithmetic mean (standard deviation)	0.449 (± 0.101)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Area Under the Plasma FVIII Activity Versus Time Curve (AUC0-tau)

End point title	Pharmacokinetics: Area Under the Plasma FVIII Activity Versus Time Curve (AUC0-tau)

End point description:

AUCtau was defined as area under the plasma concentration-time profile from time zero (pre-dose) to dosing interval (AUC0-tau), where dosing interval was 7 days. Analysis was performed on PK population. Here, "n" = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline); pre-dose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26 (Day 183)

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	159			
Units: hour*IU/decilitre				
arithmetic mean (standard deviation)				
Baseline (n = 153) Week 26 (n = 17)	9600 (± 2010) 11800 (± 2720)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Accumulation Index (AI)

End point title	Pharmacokinetics: Accumulation Index (AI)

End point description:

AI is the ratio of accumulation of a drug under steady state conditions (i.e., after repeated administration) as compared to a single dose. AI was calculated as ratio of area under the curve (AUC) of Week 26 (Day 183) divided by AUC of Day 1, where AUC is the area under the plasma concentration versus time curve from time 0 to infinity. Analysis was performed on PK population. Here, number of

subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: ratio				
arithmetic mean (standard deviation)	1.17 (± 0.160)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Volume of Distribution at Steady State (Vss)

End point title	Pharmacokinetics: Volume of Distribution at Steady State (Vss)

End point description:

Volume of distribution (Vd) is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Vss is the apparent volume of distribution at steady-state. Analysis was performed on PK population. Here, "n" = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline); pre-dose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26 (Day 183)

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	159			
Units: millilitre per kilogram				
arithmetic mean (standard deviation)				
Baseline (n = 153)	31.7 (± 7.44)			
Week 26 (n = 17)	29.6 (± 8.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Mean Residence Time (MRT)

End point title	Pharmacokinetics: Mean Residence Time (MRT)

End point description:

MRT is the average total time a drug molecule spends in the body. Analysis was performed on PK population. Here, "n"= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline); pre-dose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26 (Day 183)

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	159			
Units: hours				
median (full range (min-max))				
Baseline (n = 153) Week 26 (n = 17)	61.9 (34.3 to 111) 66.1 (46.7 to 92.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Incremental Recovery (IR)

End point title	Pharmacokinetics: Incremental Recovery (IR)

End point description:

IR was calculated as (Peak activity [in IU/dL] - Trough activity [in IU/dL])/Actual Dose (in IU/kg), and peak activity at each visit was the highest activity level after the dosing, and trough activity at each visit was the activity level prior to the dosing. Analysis was performed on PK population. Here, "n"= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline); pre-dose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-dose on Week 26 (Day 183)

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	159			
Units: kg*IU/dL/IU				
arithmetic mean (standard deviation)				

Baseline (n = 159)	2.60 (± 0.648)			
Week 26 (n = 17)	3.05 (± 0.592)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Trough Concentration for BIVV001 (Ctrough)

End point title	Pharmacokinetics: Trough Concentration for BIVV001 (Ctrough)

End point description:

Ctrough is the pre-dose concentration of a drug. Analysis was performed on PK population. Here, "n"= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

pre-dose at Baseline (Day 1) and Week 52

End point values	Arm A: Prophylaxis	Arm B: On-Demand Then Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	26		
Units: IU/dL				
arithmetic mean (standard deviation)				
Baseline	0.00 (± 0.00)	0.00 (± 0.00)		
Week 52	15.70 (± 10.72)	21.14 (± 29.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Time Above Predefined (1%) FVIII Activity Levels

End point title	Pharmacokinetics: Time Above Predefined (1%) FVIII Activity Levels

End point description:

Time above predefined (1%) FVIII activity levels means time which BIVV001 maintains above 10 IU/dL and 40 IU/dL with single dose of 50 IU/kg. Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 3, 24, 72, 168, 240 and 336 hours post-dose on Day 1 (Baseline)

End point values	BIVV001 (efanesoctocog alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	159			
Units: hours				
median (full range (min-max))				
Time to 10 IU/dL	185 (111 to 330)			
Time to 40 IU/dL	85.1 (44.4 to 156)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Arm A: From Baseline (Day 1) up to 3 weeks post last dose of BIVV001 (i.e., up to Week 55); Arm B: On-demand: Baseline to Week 26 and Arm B: Prophylaxis: From Week 26 to 3 weeks post last dose of BIVV001 in Week 52 (i.e., up to Week 55)

Adverse event reporting additional description:

Reported AEs and deaths were treatment-emergent AEs that developed, worsened or became serious from Baseline (Day 1) up to 3 weeks post last dose of BIVV001. Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Arm A: Prophylaxis

Reporting group description:

Subjects who were on a prophylaxis treatment with a FVIII product prior to study EFC16293 including subjects who rolled over from study OBS16221, received BIVV001 50 international units per kilogram (IU/kg) intravenous (IV) injection once-weekly (QW) for 52 weeks in the current study. Study OBS16221 subjects with 6 months historical data on prophylaxis treatment with a marketed FVIII product prior to enrollment were analysed as a subgroup (named as: Arm A: Historical Prophylaxis (OBS16221) in the endpoint analysis.

Reporting group title	Arm B: On-demand

Reporting group description:

Subjects who were on an On-demand treatment regimen with a FVIII product prior to study EFC16293 including subjects who rolled over from study OBS16221, received BIVV001 50 IU/kg IV injection as an On-demand treatment (as needed for the treatment of bleeding episodes) from Week 1 to Week 26 in current study.

Reporting group title	Arm B: Prophylaxis

Reporting group description:

Subjects who received BIVV001 50 IU/kg IV injection as an on-demand treatment from Week 1 to Week 26 and were switched to prophylaxis dosing and received BIVV001 50 IU/kg, IV injection QW until Week 52 in the current study.

Reporting group title	BIVV001 (efanesoctocog alfa)

Reporting group description:

All subjects who were enrolled in study and received BIVV001 in either Arm A or B.

Serious adverse events	Arm A: Prophylaxis	Arm B: On-demand	Arm B: Prophylaxis
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 133 (9.77%)	2 / 26 (7.69%)	0 / 26 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Investigations			
Blood Glucose Increased			

subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Cd4 Lymphocytes Decreased			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	0 / 133 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Combined Tibia-Fibula Fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Traumatic Haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Surgical and medical procedures			
Central Venous Catheter Removal			

subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Nervous system disorders			
Cubital Tunnel Syndrome			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Status Epilepticus			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulnar Tunnel Syndrome			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Haemophilic Arthropathy			
subjects affected / exposed	2 / 133 (1.50%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility Decreased			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (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
Infections and infestations			
Covid-19 Pneumonia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 26 (3.85%)	0 / 26 (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

Product issues			
Device Breakage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BIVV001 (efanesoctocog alfa)		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 159 (9.43%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Investigations			
Blood Glucose Increased			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cd4 Lymphocytes Decreased			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Combined Tibia-Fibula Fracture			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic Haemorrhage			

subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Central Venous Catheter Removal			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cubital Tunnel Syndrome			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status Epilepticus			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ulnar Tunnel Syndrome			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemophilic Arthropathy			

subjects affected / exposed	2 / 159 (1.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mobility Decreased			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Covid-19 Pneumonia			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device Breakage			
subjects affected / exposed	1 / 159 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A: Prophylaxis	Arm B: On-demand	Arm B: Prophylaxis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 133 (42.11%)	7 / 26 (26.92%)	1 / 26 (3.85%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	10 / 133 (7.52%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	11	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 133 (19.55%)	5 / 26 (19.23%)	1 / 26 (3.85%)
occurrences (all)	40	5	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 133 (5.26%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	8	0	0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 133 (18.80%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	31	1	0
Back Pain			
subjects affected / exposed	8 / 133 (6.02%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	9	1	0

Non-serious adverse events	BIVV001 (efanesoctocog alfa)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 159 (40.25%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	10 / 159 (6.29%)		
occurrences (all)	11		
Nervous system disorders			
Headache			
subjects affected / exposed	32 / 159 (20.13%)		
occurrences (all)	46		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 159 (4.40%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 159 (16.35%)		
occurrences (all)	32		
Back Pain			
subjects affected / exposed	9 / 159 (5.66%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2019	The following changes were made: - Dose regimen changed from 65 IU/kg to 50 IU/kg with modified justification. - Designated "key secondary efficacy endpoint" and added rationale & statistical analysis methods. - Updated safety endpoints: "vascular thrombotic events" to "embolic and thrombotic events" and definition. - Added sample size justification to enroll 75 subjects of Arm A who would have at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline for assessment of key secondary efficacy endpoint and to define End of Study. - Modified Benefit/Risk assessment. - Modified "vascular thrombotic event" to "embolic or thrombotic event", statistical hypotheses with modified key secondary efficacy endpoint.
13 May 2020	The following changes were made: - Modified requirements for washout of FVIII products before screening and allow inclusion of subjects based on historical FVIII results or documented genotype known to produce severe hemophilia A. - Allowed flexibility in washout of FVIII products before the Baseline visit in subjects participating in the abbreviated PK group. - Updated inclusion criteria: severe hemophilia A definition, prophylactic treatment regimen and On-demand regimen with a FVIII product and contraceptive use condition by female subjects. - Updated exclusion criteria: Added acetylsalicylic acid or Non-non-steroidal anti-inflammatory drug (non-NSAID) antiplatelet agent treatment. - Allowed faster infusion rate for the BIVV001 injection performed at home. - Added option for drug delivery from sites directly to subject's home in exceptional circumstances. - Added non-NSAID anti-platelet therapy to prohibited medication. - Added definitions of Grade 3, 4 and 5 allergic reactions.
20 August 2021	The following changes were made: - Added international nonproprietary name (INN), efanesoctocog alfa. - Revised secondary efficacy endpoint analysis was revised to allow formal statistical testing and update the multiplicity adjustment for the Haem-A-QoL (≥17 years old) Physical Health score, PROMIS Pain Intensity 3a and Hemophilia Joint Health Score (HJHS) total score measures. - Added statistical testing for some secondary efficacy endpoints and added sections – multiplicity issue and immunogenicity analysis. - Added an exit interview for subjects from selected countries. - Revised text of PROMIS-SF Physical Function – SF 6b. - Added "Patient Global Impression of Severity – Physical activity" instrument.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported