Clinical trial results:
A 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 Pediatric Patients <12 Years of Age With Severe Hemophilia A

Summary

EudraCT number	2020-000769-18
Trial protocol	DE FR IE GB BE SE HU NL IT Outside EU/EEA
Global end of trial date	18 January 2023

Results information

Result version number	v2 (current)
This version publication date	19 April 2024
First version publication date	30 July 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	EFC16295

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04759131
WHO universal trial number (UTN)	U1111-1244-0558
Other trial identifiers	IND: 017464

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the safety of BIVV001 in previously treated pediatric subjects with hemophilia A.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric patients. The parent(s) or guardian(s) as well as the 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. A topical anesthesia may have been used to minimise distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Türkiye: 8
Country: Number of subjects enrolled	Switzerland: 3

Worldwide total number of subjects	74
EEA total number of subjects	22

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)	2
Children (2-11 years)	72
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 40 active sites in 15 countries. A total of 79 pediatric subjects were screened between 19 February 2021 to 09 February 2022, of which 5 subjects had screen failure due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

The study comprised of 2 age cohorts of children with severe hemophilia A: less than (<) 6 years and 6 to <12 years. A total of 74 subjects were enrolled in this 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	BIVV001: Subjects aged <6 Years

Arm description:

Subjects aged <6 years received BIVV001 at a dose of 50 international units per kilogram (IU/kg) intravenous (IV) injection once-weekly (QW) prophylaxis for 52 weeks.

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	BIVV001: Subjects aged 6 to <12 Years

Arm description:

Subjects aged 6 to <12 years received BIVV001 at a dose of 50 IU/kg IV injection QW prophylaxis for 52 weeks.

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.

Number of subjects in period 1	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years
Started	38	36
Completed	36	36
Not completed	2	0
Investigator’s discretion	1	-
Subject withdrawal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	BIVV001: Subjects aged <6 Years
Reporting group description:	
Subjects aged <6 years received BIVV001 at a dose of 50 international units per kilogram (IU/kg) intravenous (IV) injection once-weekly (QW) prophylaxis for 52 weeks.	
Reporting group title	BIVV001: Subjects aged 6 to <12 Years
Reporting group description:	
Subjects aged 6 to <12 years received BIVV001 at a dose of 50 IU/kg IV injection QW prophylaxis for 52 weeks.	

Reporting group values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years	Total
Number of subjects	38	36	74
Age categorical			
Baseline characteristics analysis was performed on full analysis set (FAS) which included all subjects who took at least 1 dose of study intervention.			
Units: Subjects			
Children (1 to 5 years)	38	0	38
Children (>=6 to 11 years))	0	36	36
Age continuous			
Units: years			
arithmetic mean	3.69	8.42	
standard deviation	± 1.21	± 2.08	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	38	36	74
Race			
Units: Subjects			
White	30	25	55
Black or African American	1	2	3
Asian	4	4	8
Other or Not Reported	3	5	8

End points

End points reporting groups

Reporting group title	BIVV001: Subjects aged <6 Years

Reporting group description:

Subjects aged <6 years received BIVV001 at a dose of 50 international units per kilogram (IU/kg) intravenous (IV) injection once-weekly (QW) prophylaxis for 52 weeks.

Reporting group title	BIVV001: Subjects aged 6 to <12 Years

Reporting group description:

Subjects aged 6 to <12 years received BIVV001 at a dose of 50 IU/kg IV injection QW prophylaxis for 52 weeks.

Subject analysis set title	Subjects With Major Surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects from any arm (BIVV001: subjects aged <6 Years or BIVV001: subjects aged 6 to <12 Years) who had at least 6 days of exposure to BIVV001 and a negative inhibitor test within 4 weeks prior to surgery and 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 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 'BIVV001: subjects aged <6 years' or 'BIVV001: subjects aged 6 to <12 years'.

Primary: 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[1]

End point description:

Inhibitor development was defined as an inhibitor result of greater than or equal to (>=0.6) Bethesda units (BU/mL) that was confirmed by a second test result 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 analysis set which included all subjects who took at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

Baseline up 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.

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Bleeding Rate (ABR): For Treated Bleeds

End point title	Annualised Bleeding Rate (ABR): For Treated Bleeds

End point description:

ABR: annualised number of treated bleeding episodes (BE) per subject per year. ABR=number of treated BE during efficacy period (EP)/total number of days during EP*365.25. Treated BE: any occurrence of hemorrhage required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat BE, any subsequent bleeding at same location/injections administered less than or equal to (<=) 72 hours apart from previous injection were considered same BE. Any injection after >72 hours post preceding one=considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. EP=sum of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. ABR: by negative binomial model with total number of treated BE during EP as response variable and log-transformed EP duration (years) as offset variable. FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)	0.48 (0.30 to 0.77)	1.33 (0.64 to 2.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity Analysis: Annualised Bleeding Rate: For Treated Bleeds

End point title	Sensitivity Analysis: Annualised Bleeding Rate: For Treated Bleeds

End point description:

ABR: annualised number of treated BE per subject per year. ABR = number of treated BE during EP/total number of days during EP*365.25. Treated BE: 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 BE, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same BE. Any injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new bleeding episode in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. EP reflects sum of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. ABR: using NB model with total number of treated BE during EP as response variable and log-transformed EP duration (years) as offset variable. FAS population.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35[2]		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)	0.48 (0.30 to 0.77)	0.75 (0.41 to 1.40)		

Notes:

[2] - Excluded 1 subject who did not receive weekly prophylaxis treatment for an extended period of time.

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity Analysis: Annualised Bleeding Rate for All Bleeding Episodes

End point title	Sensitivity Analysis: Annualised Bleeding Rate for All Bleeding Episodes

End point description:

ABR: annualised number of all BE (treated & untreated)/subject/year. ABR=number of all BE during EP/total number of days during EP*365.25. BE: any hemorrhage occurrence required administration of BIVV001. It started from 1st sign of bleed & ended no more than 72 hours after last injection to treat BE, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same BE. Any bleed at different location: considered as separate BE, regardless of time from last injection. EP: sum of all intervals of time during which subjects treated with BIVV001 according to study arms and treatment regimens. ABR: estimated by NB model with total number of treated BE during EP as response variable and log-transformed EP duration (years) as offset variable. Spontaneous: bleeding without contributing factor (definite trauma/antecedent strenuous activity). Traumatic: bleeding with known/believed reason. FAS population.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35[3]		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)	2.78 (1.39 to 5.58)	2.32 (1.30 to 4.13)		

Notes:

[3] - Excluded 1 subject who did not receive weekly prophylaxis treatment for an extended period of time.

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

End point description:

ABR:annualised number of all BE (treated and untreated)/subject/year. ABR=number of all BE during EP/total number of days during EP*365.25. BE:any occurrence of hemorrhage required administration of BIVV001. It started from 1st sign of bleed and ended no more than 72 hours after last injection to treat BE, any subsequent bleeding at same location/injections administered <=72 hours apart from previous injection were considered same BE. Any injection after >72 hours post preceding one=considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. EP:sum of all intervals of time during which subjects treated with BIVV001 according to study arms & treatment regimens. ABR:NB model with total number of treated BE during EP as response variable and log-transformed EP duration (years) as offset variable. Spontaneous:bleeding without contributing factor, Traumatic:bleeding with known reason. FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)	2.78 (1.39 to 5.58)	2.85 (1.59 to 5.12)		

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)

End point description:

ABR: annualised number of treated bleeding episodes per subject per year. ABR = number of all BE during EP/total number of days during EP*365.25. EP reflects sum of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. Treated BE: 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 injection to treat bleed, taken >72 hours after preceding one was considered 1st injection to treat new BE in same location. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Spontaneous bleeding: BE without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic bleeding: BE with known/believed reason for bleed. Analysed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)				
Spontaneous	0.17 (0.08 to 0.38)	0.14 (0.04 to 0.53)		
Traumatic	0.28 (0.14 to 0.55)	0.59 (0.31 to 1.14)		
Unknown type	0.03 (0.00 to 0.20)	0.59 (0.12 to 3.02)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Sensitivity Analysis: Annualised Bleeding Rate by Type of Bleed (Spontaneous, Traumatic and Unknown Type)

End point description:

ABR: annualised number of treated bleeding episodes per subject per year. ABR = number of all BE during EP/total number of days during EP*365.25. EP reflects sum of all intervals of time during which subjects were treated with BIVV001 according to study arms and treatment regimens. Treated BE: 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 injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Spontaneous bleeding: BE without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic bleeding: BE with known/believed reason for bleed. Analysed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35[4]		
Units: episodes per subject per year				
arithmetic mean (confidence interval 95%)				
Spontaneous	0.17 (0.08 to 0.38)	0.15 (0.04 to 0.55)		
Traumatic	0.28 (0.14 to 0.55)	0.52 (0.26 to 1.04)		
Unknown type	0.03 (0.00 to 0.20)	0.09 (0.03 to 0.27)		

Notes:

[4] - Excluded 1 subject who did not receive weekly prophylaxis treatment for an extended period of time.

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)

End point description:

ABR: annualised number of treated bleeding episodes per subject per year. ABR = number of all BE during EP/total number of days during EP*365.25. 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 injection >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Spontaneous bleeding: BE without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic bleeding: BE with known/believed reason for bleed. Analysed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: episodes per subject per year				
arithmetic mean (standard deviation)				
Joint	0.19 (± 0.63)	0.99 (± 3.62)		
Muscle	0.03 (± 0.16)	0.17 (± 0.51)		
Internal	0.08 (± 0.28)	0.06 (± 0.35)		
Skin/mucosa	0.16 (± 0.38)	0.25 (± 0.60)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Sensitivity Analysis: Annualised Bleeding Rate by Location of Bleed (Joint, Muscle, Internal and Skin/Mucosa)

End point description:

ABR: annualised number of treated bleeding episodes per subject per year. ABR = number of all BE during EP/total number of days during EP*365.25. EP reflects sum of all intervals of time during which subjects were treated with BIVV001 according to study arms & treatment regimens. Treated BE: 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 injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Spontaneous bleeding: BE without contributing factor (definite trauma/antecedent "strenuous" activity). Traumatic bleeding: BE with known/believed reason for bleed. Analysed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35[5]		
Units: episodes per subject per year				
arithmetic mean (standard deviation)				
Joint	0.19 (± 0.63)	0.40 (± 0.93)		
Muscle	0.03 (± 0.16)	0.17 (± 0.52)		
Internal	0.08 (± 0.28)	0.06 (± 0.35)		
Skin/mucosa	0.16 (± 0.38)	0.26 (± 0.61)		

Notes:

[5] - Excluded 1 subject who did not receive weekly prophylaxis treatment for an extended period of time.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving FVIII Activity Levels Above 1%, 3%, 5%, 10%, 15%, and 20%

End point title	Percentage of Subjects Achieving FVIII Activity Levels Above 1%, 3%, 5%, 10%, 15%, and 20%

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%, 3%, 5%, 10%, 15%, and 20% were reported in this endpoint. Subjects were counted in more than one category, as applicable. Analysis was performed on full analysis set (FAS) which included all subjects who took at least 1 dose of study intervention. Here, 'number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	29		
Units: percentage of subjects				
number (not applicable)				
>1%	100	100		
>3%	100	100		
>5%	75.0	100		
>10%	18.8	51.7		
>15%	9.4	6.9		
>20%	3.1	6.9		

Statistical analyses

No statistical analyses for this end point

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

End point title	Sensitivity Analysis: Number of Injections of BIVV001 Required to Treat a Bleeding Episode

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. Any injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. Analysis was performed on FAS excluding 1 subject who did not receive weekly prophylaxis treatment for an extended period of time.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[6]	35[7]		
Units: injections per bleeding episode				
arithmetic mean (standard deviation)	1.12 (± 0.33)	1.00 (± 0.00)		

Notes:

[6] - 17 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged <6 Years'.

[7] - 26 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged 6 to <12 Years'.

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

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. Any injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location was considered as separate bleeding episode, regardless of time from last injection. Analysis was performed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[8]	36[9]		
Units: injections per bleeding episode				
arithmetic mean (standard deviation)	1.12 (± 0.33)	1.30 (± 0.69)		

Notes:

[8] - 17 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged <6 Years'.

[9] - 47 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged 6 to <12 Years'.

Statistical analyses

No statistical analyses for this end point

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

End point title	Sensitivity Analysis: Percentage of Bleeding Episodes Treated With a Single Injection of BIVV001

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. Any injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. 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, excluding the subject who did not receive the weekly prophylaxis treatment as per protocol for an extended period of time.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[10]	25[11]		
Units: percentage of bleeding episodes				
number (not applicable)	88.2	100		

Notes:

[10] - 17 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged <6 Years'.

[11] - 26 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged 6 to <12 Years'.

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

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. Any injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. 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.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[12]	36[13]		
Units: percentage of bleeding episodes				
number (not applicable)	88.2	78.7		

Notes:

[12] - 17 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged <6 Years'.

[13] - 47 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged 6 to <12 Years'.

Statistical analyses

No statistical analyses for this end point

Secondary: Physicians' Global Assessment (PGA) of Subject's Response to BIVV001 Treatment Based on a 4-point Response Scale

End point title	Physicians' Global Assessment (PGA) of Subject's Response to BIVV001 Treatment Based on a 4-point Response Scale

End point description:

Physicians assessed subject's response to BIVV001 treatment using 4-point response scale categorised as: Excellent= 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. Analysis was performed on FAS. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Week 13 and Week 52/End of study (EOS)/Early termination (ET)

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: subjects				
Week 13: Excellent	37	34		
Week 13: Effective	0	2		
Week 13: Partially effective	0	0		
Week 13: Ineffective	0	0		
Week 52/EOS/ET: Excellent	37	36		
Week 52/EOS/ET: Effective	0	0		
Week 52/EOS/ET: Partially effective	0	0		
Week 52/EOS/ET: Ineffective	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity Analysis: Total Dose of BIVV001 Required to Treat Bleeding Episode

End point title	Sensitivity Analysis: Total Dose of BIVV001 Required to Treat Bleeding Episode

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. Any injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any injection after >72 hours post preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. Total dose was expressed in unit: IU/kg. Analysis was performed on FAS, excluding 1 subject who did not receive weekly prophylaxis treatment for an extended period of time.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[14]	35[15]		
Units: IU/kg				
arithmetic mean (standard deviation)	52.29 (± 15.84)	50.39 (± 6.71)		

Notes:

[14] - 17 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged <6 Years'.

[15] - 26 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged 6 to <12 Years'.

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

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. Any injection to treat bleed, taken >72 hours after preceding one, was considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. Total dose was expressed in unit: International units per kilogram (IU/kg). Analysis was performed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[16]	36[17]		
Units: IU/kg				
arithmetic mean (standard deviation)	52.29 (± 15.84)	66.90 (± 37.01)		

Notes:

[16] - 17 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged <6 Years'.

[17] - 47 = total number of treated bleeding episodes in 'BIVV001: Subjects Aged 6 to <12 Years'.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's Response to BIVV001 Treatment Based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point Response Scale

End point title	Subject's Response to BIVV001 Treatment Based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point Response Scale

End point description:

Subject's response to 1st injection of BIVV001 treatment for treating bleed was evaluated by ISTH 4-point response scale categorised as: Excellent (complete pain relief [PR]/complete resolution of signs of

bleeding [SoB]), Good (significant PR/improvement in SoB), Moderate (modest PR/improvement in SoB) and none (no or minimal improvement/condition worsened). Assessed approximately 72 hours after initial treatment for BE. Bleeding episode: an episode that started from 1st 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 BE. Any injection after >72 hours post preceding one=considered 1st injection to treat new BE in same location. Any bleed at different location: considered as separate BE, regardless of time from last injection. Subjects were counted in more than one category, as applicable. Analysed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[18]	36[19]		
Units: Injections with a response				
Excellent	14	22		
Good	1	2		
Moderate	1	0		
None	0	0		

Notes:

[18] - 16 = number of injections with a response.

[19] - 24 = number of injections with a response.

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

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. 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.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: IU/kg per subject per year				
arithmetic mean (standard deviation)	3115.57 (± 488.64)	2884.67 (± 207.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Joint Bleeding Rate (AJBR)

End point title	Annualised Joint Bleeding Rate (AJBR)

End point description:

AJBR: annualised number of joint bleeding/subject/year. ABR = number of treated joint BE during EP divided by total number of days during EP*365.25. Joint BE: unusual sensation in joint ('aura') along with 1) increasing swelling/warmth over skin, joint; 2) increasing pain or 3) progressive loss of range of motion/difficulty in using limb compared to Baseline. BE: episode started from 1st sign of bleed & ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location/injections <=72 hours apart considered same BE. Any injection after >72 hours post preceding one=1st injection to treat new BE in same location. Any bleed at different location=separate BE, regardless of time from last injection. EP: sum of all intervals of time during which subjects treated with BIVV001 per study arms and treatment regimens. ABR: NB model with total number of treated BE during EP (response variable) & log-transformed EP duration (offset variable). FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: joint BE per subject per year				
arithmetic mean (confidence interval 95%)	0.19 (0.06 to 0.62)	0.99 (0.38 to 2.60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemophilia Joint Health Score Domain Score at Week 52

End point title	Change From Baseline in Hemophilia Joint Health Score Domain Score at Week 52

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), for each item 0 = no damage and higher score = severe damage. Analysis was performed on FAS. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: score on a scale				
arithmetic mean (standard deviation)				
Swelling (n = 19, 35)	0.0 (± 0.0)	-0.1 (± 0.6)		
Duration Of Swelling (n = 19, 35)	0.1 (± 0.2)	-0.0 (± 0.2)		
Muscle Atrophy (n = 19, 35)	0.0 (± 0.0)	-0.1 (± 0.4)		
Crepitus On Motion (n = 19, 35)	0.1 (± 0.2)	-0.1 (± 0.5)		
Flexion Loss (n = 19, 35)	-0.9 (± 4.1)	-0.1 (± 0.6)		
Extension Loss (n = 19, 35)	-0.2 (± 1.0)	0.2 (± 0.9)		
Joint Pain (n = 19, 35)	0.0 (± 0.0)	0.0 (± 0.4)		
Strength (n = 18, 33)	1.3 (± 10.0)	-0.8 (± 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity Analysis: Annualised Joint Bleeding Rate (AJBR)

End point title	Sensitivity Analysis: Annualised Joint Bleeding Rate (AJBR)

End point description:

AJBR: annualised number of joint bleeding/subject/year. ABR = number of treated joint BE during EP divided by total number of days during EP*365.25. Joint BE: unusual sensation in joint ('aura') along with 1) increasing swelling/warmth over skin, joint; 2) increasing pain or 3) progressive loss of range of motion/difficulty in using limb compared to Baseline. BE: episode started from 1st sign of bleed & ended no more than 72 hours after last treatment for bleed, within which any symptoms of bleeding at same location/injections <=72 hours apart considered same BE. Any injection after >72 hours post preceding one=1st injection to treat new BE in same location. Any bleed at different location=separate BE, regardless of time from last injection. EP: sum of all intervals of time during which subjects treated with BIVV001 per study arms and treatment regimens. ABR: NB model with total number of treated BE during EP (response variable) & log-transformed EP duration (offset variable). FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35[20]		
Units: joint BE per subject per year				
arithmetic mean (confidence interval 95%)	0.19 (0.06 to 0.62)	0.41 (0.19 to 0.89)		

Notes:

[20] - Excluded 1 subject who did not receive weekly prophylaxis treatment for an extended period of time.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemophilia Quality of Life Questionnaire (Haemo-QoL) Kids Short Version Total Score at Week 52 for Children Subjects (Aged 4 to 7 and 8 to <12 Years)

End point title	Change From Baseline in Hemophilia Quality of Life Questionnaire (Haemo-QoL) Kids Short Version Total Score at Week 52 for Children Subjects (Aged 4 to 7 and 8 to <12 Years)

End point description:

Haemo-QoL kids short version: used to measure physical and emotional impacts on quality of life in children & adolescent with hemophilia. It was administered to children & their caregivers. Short version for children containing 16 items (4 to 7 years) and 35 items (8 to <12 years) were selected in this study. This version covers 9 dimensions relevant for children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia & treatment). Items were rated along 5 response options: never, seldom, sometimes, often and always, higher scores=greater impairment. Raw score for each domain were transformed to scale ranged between 0 to 100, where lower score=better HRQoL. Haem-A-QoL total Score=average of all domain scores and ranged from 0 to 100, where lower scores=better QoL. FAS. n=subjects with available data, n=0 signifies that no subjects were aged 8 to <12 years in 1st arm. 99999=space filler, no subjects were evaluable.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: score on a scale				
arithmetic mean (standard deviation)				
4 to 7 years (n = 10, 4)	-5.31 (± 10.83)	4.69 (± 5.41)		
8 to <12 years (n = 0, 10)	99999 (± 99999)	-9.79 (± 12.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemophilia Quality of Life Questionnaire Parent Proxy Short Version Total Score at Week 52 for Children Subjects (Aged 4 to 7 and 8 to <12 Years): Parent's Evaluation

End point title	Change From Baseline in Hemophilia Quality of Life Questionnaire Parent Proxy Short Version Total Score at Week 52 for Children Subjects (Aged 4 to 7 and 8 to <12 Years): Parent's Evaluation

End point description:

Haemo-QoL parent proxy short version: used to measure physical and emotional impacts on quality of life in children and adolescent with hemophilia. It was administered to children & their caregivers. Short version for children's caregivers containing 16 items (subjects 4 to 7 years) and 35 items (subjects 8 to <12 years) were selected in this study. This version covers 9 dimensions relevant for children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated along 5 response options: never, seldom, sometimes, often and always, higher scores=greater impairment. Raw score for each domain: transformed to scale ranged between 0 to 100, lower score=better HRQoL. Haem-A-QoL total Score=average of all domain scores and ranged from 0 to 100, lower scores=better quality of life. FAS. n=subjects with available data for each specified category, n=0 signifies that no subjects were evaluable.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[21]	13		
Units: score on a scale				
arithmetic mean (standard deviation)				
4 to 7 years (n = 19, 4)	-3.21 (± 12.23)	-1.17 (± 11.08)		
8 to <12 years (n = 0, 9)	99999 (± 99999)	-4.05 (± 10.77)		

Notes:

[21] - 99999 = space filler which signifies that no subjects were evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemophilia Quality of Life Questionnaire Parent Proxy Short Version Physical Health Domain Score at Week 52 for Children Subjects (Aged 8 to <12 years): Parent's Evaluation

End point title	Change From Baseline in Hemophilia Quality of Life Questionnaire Parent Proxy Short Version Physical Health Domain Score at Week 52 for Children Subjects (Aged 8 to <12 years): Parent's Evaluation[22]

End point description:

Haemo-QoL parent proxy short version: used to measure physical & emotional impacts on quality of life in children & adolescent with hemophilia. It was administered to children & their caregivers. Short version for children's caregivers containing 35 items (subjects 8 to <12 years) were selected and it covers 9 dimensions relevant for children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia & treatment). Items are rated along 5

response options:never, seldom, sometimes, often and always, higher scores=greater impairment. Raw score for physical health domain were transformed to scale ranged between 0 and 100; lower score=better HRQoL. FAS. Number of subjects analysed=subjects with available data. Change from baseline in physical Health domain score per parent's evaluation was reported in this endpoint. Data for this endpoint was not planned to be collected & analysed for arm 'BIVV001:Subjects aged <6 years'.

End point type	Secondary

End point timeframe:

Baseline, Week 52

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be collected and analysed for specified arm only.

End point values	BIVV001: Subjects aged 6 to <12 Years			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: score on a scale				
arithmetic mean (standard deviation)	-7.64 (± 11.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemophilia Quality of Life Questionnaire Kids Short Version Physical Health Domain Score at Week 52 for Children Subjects (Aged 8 to <12 years)

End point title	Change From Baseline in Hemophilia Quality of Life Questionnaire Kids Short Version Physical Health Domain Score at Week 52 for Children Subjects (Aged 8 to <12 years)[23]

End point description:

Haemo-QoL kids short version: used to measure physical & emotional impacts on quality of life in children & adolescent with hemophilia. It was administered to children & their caregivers. Short version for children containing 35 items (8 to <12 years) were selected in this study. This version covers 9 dimensions considered relevant for children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated along 5 response options: never, seldom, sometimes, often and always, higher scores=greater impairment. Raw score for physical health domain were transformed to scale ranged between 0 to 100, where lower score=better HRQoL. FAS. Number of subjects analysed=subjects with available data this endpoint. Change from baseline in physical Health domain score was reported in this endpoint. Data for this endpoint was not planned to be collected and analysed for 'BIVV001: Subjects aged <6 years'.

End point type	Secondary

End point timeframe:

Baseline, 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	BIVV001: Subjects aged 6 to <12 Years			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: score on a scale				
arithmetic mean (standard deviation)	-10.63 (± 14.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Target Joints Resolved in Subjects at Week 52

End point title	Total Number of Target Joints Resolved in Subjects at Week 52

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 (defined as treatment regimen period >=52 weeks). Total number of target joints resolved at Week 52 were reported. Analysis was performed on FAS population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and had at least 12 months of continuous exposure.

End point type	Secondary

End point timeframe:

Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	1[25]		
Units: Target joints resolved				
number (not applicable)		2		

Notes:

[24] - None of the subject had at least 12 months of continuous exposure.

[25] - 2=Total number of target joints (Baseline) from subjects with at least 12 months continuous exposure

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemophilia Joint Health Score (HJHS) Total Score at Week 52

End point title	Change From Baseline in Hemophilia Joint Health Score (HJHS) Total Score at Week 52

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 to 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 ranged from 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. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	33		
Units: score on a scale				
arithmetic mean (standard deviation)	0.2 (± 8.3)	-1.1 (± 4.3)		

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: 1 = Excellent, 2 = Good, 3 = Fair, and 4 = Poor/none. Higher score indicated worst response. This assessment was performed 24 hours after the surgery. A surgery can be counted in more than one response category. Analysed on a surgery subgroup population which included all subjects who had undergone major surgery after the 1st dose of study drug. Here, number of subjects analysed' = subjects with major surgeries during the specified period (defined as the date and time of the first dose of study drug up to the last dose of study drug).

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Subjects With Major Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	2[26]			
Units: major surgeries				
number (not applicable)				
Excellent or Good	2			
Excellent	2			
Good	0			
Fair	0			

Poor/none	0			

Notes:

[26] - Number of major surgeries during the specified period occurred in subjects analysed = 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Per Surgery Required to Maintain Hemostasis During Perioperative Period for Major Surgery

End point title	Number of Injections Per Surgery 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 (process to prevent and stop bleeding from blood vessel) per 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 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). Analysed on surgery subgroup population. Number of subjects analysed = subjects with major surgeries during specified period.

End point type	Secondary

End point timeframe:

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

End point values	Subjects With Major Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	2[27]			
Units: Major surgeries				
One injection	2			
Two injection	0			
Three injection	0			
Four injection	0			
>Four injection	0			

Notes:

[27] - Number of major surgeries during the specified period occurred in subjects analysed = 2.

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. Number of subjects analysed = subjects with major surgeries during specified period.

End point type	Secondary

End point timeframe:

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

End point values	Subjects With Major Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	2[28]			
Units: Major surgeries				
Zero	2			
One	0			
Two	0			
Three	0			
>Three	0			

Notes:

[28] - Number of major surgeries during the specified period occurred in subjects analysed = 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Total BIVV001 Consumption From Day -1 to 14 During Perioperative Period for Major Surgery

End point title	Total BIVV001 Consumption From Day -1 to 14 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 BIVV001 consumption were summarised from the loading dose (the day before surgery, i.e., on Day -1) up to 2 weeks following the surgery (i.e., Day 14) and were reported in this endpoint. Analysis was performed on surgery subgroup population. Here, Number of subjects analysed = subjects with major surgeries during specified period.

End point type	Secondary

End point timeframe:

Day -1 to Day 14

End point values	Subjects With Major Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	2[29]			
Units: IU/kg per major surgery				
arithmetic mean (standard deviation)	201.97 (± 29.42)			

Notes:

[29] - Number of major surgeries with BIVV001 administration within Day -1 to Day 14 = 2

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. Number of subjects analysed = subjects with major surgeries during specified period.

End point type	Secondary

End point timeframe:

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

End point values	Subjects With Major Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	2[30]			
Units: Major surgeries				
Red Blood Cell	0			
Platelet	0			
Fresh Frozen Plasma	0			
Whole Blood	0			
Other	0			

Notes:

[30] - Number of major surgeries during the specified period occurred in subjects analysed = 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Blood Loss During Major Surgery

End point title	Estimated Blood Loss During Major Surgery

End point description:

The estimated total blood loss (in millilitres) during major surgeries were summarised. 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 = subjects with reported blood loss during major surgery.

End point type	Secondary

End point timeframe:

Day 0 (i.e., day of surgery)

End point values	Subjects With Major Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	2[31]			
Units: millilitres				
arithmetic mean (standard deviation)	25.00 (± 35.36)			

Notes:

[31] - Major surgeries with blood loss report during treatment regimen occurred in subjects analysed = 2

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose Required to Maintain Hemostasis From Day -1 to Day 0 During Perioperative Period for Major Surgery

End point title	Total Dose Required to Maintain Hemostasis From Day -1 to Day 0 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 surgery) and post-operative (24-hour post-surgery). Total dose (IU/kg) was sum across all injections per major surgery (including loading dose) needed to maintain hemostasis (process to prevent and stop bleeding from blood vessel) during surgery. Major surgery: any invasive operative procedure that required any of following: opening into major body cavity (e.g., abdomen, thorax, skull); operation on joint; removal of organ; dental extraction of any molar teeth or >=3 non-molar teeth; operative alteration of normal anatomy; crossing of mesenchymal barrier (e.g., pleura, peritoneum, dura). Day 0=surgery day. Loading dose for given surgery was preoperative injection, administered either on day of surgery or one day prior to surgery (i.e., Day -1). Surgery subgroup population. Number of subjects analysed=subjects with major surgeries.

End point type	Secondary

End point timeframe:

Day -1 to Day 0 (day of surgery)

End point values	Subjects With Major Surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	2[32]			
Units: IU/kg				
arithmetic mean (standard deviation)	61.13 (± 1.06)			

Notes:

[32] - Number of major surgeries with loading dose given on day of surgery/1 day prior to surgery (Day -1).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse (TESAEs)

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. Analysis was performed on safety analysis set.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to 3 weeks post last dose of BIVV001 (i.e., up to Week 55)

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: subjects				
TEAE	33	29		
TESAE	5	4		

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

End point description:

Embolic and thrombotic events were defined as arterial or venous thrombosis, confirmed by imaging. Analysis was performed on safety analysis set.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	BIVV001: Subjects aged <6 Years	BIVV001: Subjects aged 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: subjects	0	0		

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 analysis set. Here, 'number of subjects analysed = subjects with available data for this endpoint. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: hours				
arithmetic mean (standard deviation)	40.2 (± 4.29)			

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. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: IU per decilitre				
arithmetic mean (standard deviation)	128 (± 46.4)			

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 analysis set. Here, 'number of subjects analysed = subjects with available data for this endpoint. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: millilitres per hour per kilogram				
arithmetic mean (standard deviation)	0.711 (± 0.132)			

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 analysis set. Here, 'number of subjects analysed = subjects with available data for this endpoint. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: millilitres per kilogram				
arithmetic mean (standard deviation)	37.3 (± 6.19)			

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:

AUC0-tau was defined as area under the plasma concentration-time profile from time zero (pre-dose) to dosing interval. Analysis was performed on PK analysis set. Here, 'number of subjects analysed = subjects with available data for this endpoint. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: hour*IU per decilitre				
arithmetic mean (standard deviation)	7000 (± 1300)			

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. Data for this endpoint is not reported because samples were not collected to estimate CLss.

End point type	Secondary

End point timeframe:

0 hour - 168 hour at week 26, 39 or 52

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[33]			
Units: millilitres per hour per kilogram				
arithmetic mean (standard deviation)	()			

Notes:

[33] - No data available.

Statistical analyses

No statistical analyses for this end point

Secondary: Time Above Predefined (10% and 40%) FVIII Activity Levels

End point title	Time Above Predefined (10% and 40%) FVIII Activity Levels

End point description:

Time above predefined (10% and 40%) FVIII activity levels mean time which BIVV001 maintains above 10 IU/dL and 40 IU/dL with single doses of 50 IU/kg. Analysis was performed on PK analysis set. Here, n=subjects with available data for each specified category. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: hours				
arithmetic mean (standard deviation)				
Time to 10 IU/dL	160 (± 18.7)			
Time to 40 IU/dL	72.2 (± 12.5)			

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 analysis set. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: IU/dL per IU/kg				
arithmetic mean (standard deviation)	2.53 (± 0.880)			

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. Ctrough was measured by apTT-Baseline-OSC assay. Analysis was performed on FAS. Here, 'n' = subjects with available data for each specified category. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

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

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	74			
Units: IU/dL				
arithmetic mean (standard deviation)				
Baseline (n = 69) Week 52 (n = 72)	0.00 (± 0.00) 13.68 (± 21.84)			

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 analysis set. Here, 'number of subjects analysed = subjects with available data for this endpoint. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: hours				
arithmetic mean (standard deviation)	53.0 (± 6.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Dose-normalised Area Under the Activity-time Curve (DNAUC0-tau)

End point title	Pharmacokinetics: Dose-normalised Area Under the Activity-time Curve (DNAUC0-tau)

End point description:

AUC0-tau was defined as the area under the activity-time curve over the dosing interval. AUC was normalised by dose. Analysis was performed on PK analysis set. Here, 'number of subjects analysed = subjects with available data for this endpoint. Data was planned to be collected and analysed for combined population of both arm groups with the available PK data.

End point type	Secondary

End point timeframe:

pre-dose, 0.25, 3, 24, 72, and 168 hours post-dose on Day 1

End point values	BIVV001 (Efanesoctocog Alfa)			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: hour*kilogram*IU/decilitre/IU				
arithmetic mean (standard deviation)	139 (± 25.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline (Day 1) up to 3 weeks post last dose of BIVV001 (i.e., up to Week 55)	
Adverse event reporting additional description:	
Analysis was performed on safety analysis set.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	BIVV001: Subjects aged <6 years
Reporting group description:	
Subjects aged <6 years received BIVV001 at a dose of 50 IU/kg IV injection QW prophylaxis for 52 weeks.	
Reporting group title	BIVV001: Subjects aged 6 to <12 years
Reporting group description:	
Subjects aged 6 to <12 years received BIVV001 at a dose of 50 IU/kg IV injection QW prophylaxis for 52 weeks.	

Serious adverse events	BIVV001: Subjects aged <6 years	BIVV001: Subjects aged 6 to <12 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 38 (13.16%)	4 / 36 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head Injury			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Circumcision			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Vascular Device Occlusion			

subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Eosinophilic Oesophagitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Malfunction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BIVV001: Subjects aged <6 years	BIVV001: Subjects aged 6 to <12 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 38 (81.58%)	28 / 36 (77.78%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Sars-Cov-2 Test Positive			
subjects affected / exposed	7 / 38 (18.42%)	4 / 36 (11.11%)	
occurrences (all)	7	6	
Injury, poisoning and procedural complications			
Joint Injury			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Limb Injury			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	
Contusion			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Head Injury			
subjects affected / exposed	1 / 38 (2.63%)	4 / 36 (11.11%)	
occurrences (all)	1	4	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 38 (7.89%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Iron Deficiency Anaemia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	8 / 38 (21.05%)	1 / 36 (2.78%)	
occurrences (all)	17	1	
Peripheral Swelling			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	3 / 38 (7.89%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	4 / 38 (10.53%)	1 / 36 (2.78%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Oropharyngeal Pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	3 / 38 (7.89%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 38 (0.00%)	5 / 36 (13.89%)	
occurrences (all)	0	7	
Pain In Extremity			

subjects affected / exposed	2 / 38 (5.26%)	3 / 36 (8.33%)	
occurrences (all)	2	4	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 38 (15.79%)	5 / 36 (13.89%)	
occurrences (all)	7	7	
Respiratory Tract Infection Viral			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Pharyngitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	3 / 38 (7.89%)	3 / 36 (8.33%)	
occurrences (all)	6	3	
Influenza			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Gastroenteritis Viral			
subjects affected / exposed	5 / 38 (13.16%)	1 / 36 (2.78%)	
occurrences (all)	6	2	
Ear Infection			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Covid-19			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Viral Infection			
subjects affected / exposed	3 / 38 (7.89%)	1 / 36 (2.78%)	
occurrences (all)	4	1	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 38 (7.89%)	1 / 36 (2.78%)	
occurrences (all)	4	2	
Asymptomatic Covid-19			

subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	5 / 36 (13.89%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported