Clinical trial results:
A Non-controlled, Open-Label, Multicenter, Study of Efficacy of rFVIIIFc for Immune Tolerance Induction (ITI) in Severe Hemophilia A Subjects With Inhibitors Undergoing the First ITI Treatment

Summary

EudraCT number	2017-000373-36
Trial protocol	ES DE BE GB FR BG IT Outside EU/EEA
Global end of trial date	16 February 2021

Results information

Result version number	v1 (current)
This version publication date	28 August 2021
First version publication date	28 August 2021

Trial information

Trial identification

Sponsor protocol code	LPS16473

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03093480
WHO universal trial number (UTN)	-
Other trial identifiers	Bioverativ Therapeutics Inc.: 997HA402

Notes:

Sponsors

Sponsor organisation name	Bioverativ, a Sanofi company
Sponsor organisation address	225 Second Avenue, Waltham, Massachusetts (MA), United States, 02451
Public contact	Trial Transparency Team, Bioverativ, a Sanofi company, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Bioverativ, a Sanofi company, 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-001114-PIP01-10
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	06 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to describe the time to tolerisation (i.e., immune tolerance induction [ITI] success) with Recombinant Coagulation Factor VIII Fc (rFVIIIFc) in subjects within a maximum of 48 weeks (12 months) of ITI treatment.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the subjects 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 age-appropriate language was provided and explained to the subject. 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. All 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 accordance with the trial subjects' written informed consent and applicable personal data protection laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2017
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	Canada: 3
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	16
EEA total number of subjects	7

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)	7
Children (2-11 years)	8
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 14 active centres in 7 countries between 08-Dec-2017 to 16-Feb-2021.

Pre-assignment

Screening details:

Total 16 paediatric subjects were screened, enrolled and received drug.

Period 1

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

Arms

Arm title	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)

Arm description:

Subjects were to receive rFVIIIFc at a dose of 200 international units (IU)/kilogram (kg) as once daily injections or divided on several injections per day at the discretion of the investigator, starting at baseline visit up to maximum of 48 Weeks in ITI Period. Subjects who met the criteria for ITI success entered the tapering period and received rFVIIIFc at a dose adjusted according to investigator judgment based on the FVIII activity levels and with the aim of tapering the rFVIIIFc dose to reach a prophylactic dosing regimen within 16 weeks (4 months). Follow-Up was for 32 weeks under an adjusted prophylactic regimen according to investigator judgment.

Arm type	Experimental
Investigational medicinal product name	rFVIIIFc
Investigational medicinal product code	
Other name	ELOCTATE/ELOCTA; BIIB031; efmoroctocog alfa; antihemophilic factor [recombinant]; Fc fusion protein
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

rFVIIIFc 200 IU/kg/day in ITI Period, 50 or 100 IU/kg (adjusted according to investigator judgement) in tapering period and prophylactic regimen in follow-up period intravenously.

Number of subjects in period 1	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)
Started	16
Tapering Period	10 [1]
Follow-up Period	10 [2]
Completed	16

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: Tapering Period Full Analysis Set: includes subjects entering the tapering phase of the

study.

[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: Follow-Up Period Full Analysis Set: includes all subjects entering the follow-up phase in the study.

Baseline characteristics

Reporting groups

Reporting group title	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)

Reporting group description:

Subjects were to receive rFVIIIFc at a dose of 200 international units (IU)/kilogram (kg) as once daily injections or divided on several injections per day at the discretion of the investigator, starting at baseline visit up to maximum of 48 Weeks in ITI Period. Subjects who met the criteria for ITI success entered the tapering period and received rFVIIIFc at a dose adjusted according to investigator judgment based on the FVIII activity levels and with the aim of tapering the rFVIIIFc dose to reach a prophylactic dosing regimen within 16 weeks (4 months). Follow-Up was for 32 weeks under an adjusted prophylactic regimen according to investigator judgment.

Reporting group values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 3.8 ± 4.06	 -	
Gender categorical			
Based on inclusion criteria, only male subjects were included.			
Units: Subjects			
Female	0	0	
Male	16	16	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	12	12	
More than one race	0	0	
Unknown or Not Reported	2	2	

End points

End points reporting groups

Reporting group title	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)

Reporting group description:

Subjects were to receive rFVIIIFc at a dose of 200 international units (IU)/kilogram (kg) as once daily injections or divided on several injections per day at the discretion of the investigator, starting at baseline visit up to maximum of 48 Weeks in ITI Period. Subjects who met the criteria for ITI success entered the tapering period and received rFVIIIFc at a dose adjusted according to investigator judgment based on the FVIII activity levels and with the aim of tapering the rFVIIIFc dose to reach a prophylactic dosing regimen within 16 weeks (4 months). Follow-Up was for 32 weeks under an adjusted prophylactic regimen according to investigator judgment.

Primary: Time to Tolerisation With rFVIIIFc

End point title	Time to Tolerisation With rFVIIIFc[1]

End point description:

Time required for subjects to achieve ITI success, where ITI success was defined as achieving all 3 of the following criteria: confirmed negative titers consisting of 2 consecutive negative inhibitor assessments within 2 weeks (less than [<] 0.6 Bethesda units/millilitre [mL] by the Nijmegen-modified Bethesda assay); incremental recovery (IR) greater than or equal to (>=) 66 percent (%) of the expected IR in 2 consecutive assessments; half-life (t½) >= 7 hours. Subjects who were in ITI full analysis set (includes all subjects receiving at least 1 infusion of rFVIIIFc) and achieved ITI success.

End point type	Primary

End point timeframe:

Up to 48 Weeks

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	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: weeks				
median (inter-quartile range (Q1-Q3))	11.7 (9.8 to 26.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Immune Tolerance Induction Success

End point title	Number of Subjects With Immune Tolerance Induction Success

End point description:

Number of subjects who achieved ITI success, where ITI success was defined as achieving all 3 of the following criteria: confirmed negative titers consisting of 2 consecutive negative inhibitor assessments within 2 weeks (<0.6 Bethesda units/mL by the Nijmegen-modified Bethesda assay); IR >= 66% of the expected IR at 2 consecutive assessments; t½ >=7 hours. ITI full analysis set.

End point type	Secondary

End point timeframe:

Up to 48 Weeks

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: subject				
number (not applicable)	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced Relapse

End point title	Number of Subjects Who Experienced Relapse

End point description:

Number of subjects with ITI success who reaches the criteria for relapse (defined as confirmed positive inhibitor titer >= 0.6 BU/mL or abnormal recovery after tolerance was achieved, and t½ < 7 hours) evaluated during the Tapering or Follow-Up Periods. Tapering Full analysis set.

End point type	Secondary

End point timeframe:

Up to 48 weeks (16 weeks Tapering period and 32 weeks follow-up period)

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Bleeding Rates During Immune Tolerance Induction Period

End point title	Annualised Bleeding Rates During Immune Tolerance Induction Period

End point description:

A bleeding episode started from the first sign of a bleed and ended no more than 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections less than or equal to 72 hours apart were considered the same bleeding episode. Annualised bleeding rate for a subject during the ITI period was defined as the number of bleeding episodes divided by the length of the ITI period in days* 365.25. ITI full analysis set which excludes subjects who were observed for less than 90 days during the period.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: episodes per subject per year				
arithmetic mean (standard deviation)	6.6 (± 9.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Bleeding Rates After Immune Tolerance Induction Period

End point title	Annualised Bleeding Rates After Immune Tolerance Induction Period

End point description:

A bleeding episode started from the first sign of a bleed and ended no more than 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections less than or equal to 72 hours apart were considered the same bleeding episode. Annualised bleeding rate for a subject after the ITT period (for tapering and follow-up period) was defined as the number of bleeding episodes divided by the length of the period after the ITI period in days* 365.25. Tapering period full analysis set excluding subjects who were observed for less than 90 days in the period.

End point type	Secondary

End point timeframe:

Up to 48 weeks (16 weeks Tapering period and 32 weeks follow-up period)

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: episodes per subject per year				
arithmetic mean (standard deviation)				
Tapering period	1.0 (± 1.27)			
Follow-up Period	1.2 (± 2.91)			

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 (TESAEs) as a Measure of Safety and Tolerability

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) as a Measure of Safety and Tolerability

End point description:

An adverse event (AE) was any untoward medical occurrence that does not necessarily have a causal relationship with this treatment. An SAE was any untoward medical occurrence that at any dose: resulted in death; in the view of the investigator, places the subject at immediate risk of death (a life-threatening event); required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; resulted in a congenital anomaly/birth defect; any other medically important event that, in the opinion of the investigator, may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition. ITI full analysis set.

End point type	Secondary

End point timeframe:

Up to 2 Years

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: subjects				
number (not applicable)				
At least one TEAE	16			
At least one TESAE	9			
Death	0			
Discontinuation of treatment and/or study dueto AE	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Number of Days Missed From Work or School Per Month During Immune Tolerance Induction Period

End point title	Average Number of Days Missed From Work or School Per Month During Immune Tolerance Induction Period

End point description:

Average number of days missed from school or work per month for a period (counting in non-missing diary days) was defined as number of the missing school/work days in the period divided by number of days with data entry in the period. Number of days per month missed from school or work was reported for those who attend school or have a job. Subjects of ITI full analysis set and who attend school or have a job.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: days				
arithmetic mean (standard deviation)	2.3 (± 1.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Number of Days Missed From Work or School Per Month After Immune Tolerance Induction Period

End point title	Average Number of Days Missed From Work or School Per Month After Immune Tolerance Induction Period

End point description:

Average number of days missed from school or work per month for a period (counting in non-missing diary days) was defined as number of the missing school/work days in the period divided by number of days with data entry in the period. Number of days per month missed from school or work was reported for those who attend school or have a job. Subjects of Tapering full analysis set and who attended school or have a job. Here, '99999' was used as a space filler and signifies that the standard deviation was not estimable because only 1 subject was available for the analysis.

End point type	Secondary

End point timeframe:

Up to 48 weeks (16 weeks Tapering period & 32 weeks Follow-up period)

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: days				
arithmetic mean (standard deviation)	0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Number of Hospitalisation Days During Immune Tolerance Induction Period

End point title	Annualised Number of Hospitalisation Days During Immune Tolerance Induction Period

End point description:

Annualised number of hospitalisation days during a period for a subject was defined as the number of hospitalisation days divided by the length of the period in days * 365.25. ITI Full analysis set but excluding subjects who were observed for less than 90 days in the period.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: days				
arithmetic mean (standard deviation)	15.4 (± 32.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Number of Hospitalisation Days After Immune Tolerance Induction Period

End point title	Annualised Number of Hospitalisation Days After Immune Tolerance Induction Period

End point description:

Annualised number of hospitalisation days during a period for a subjects was defined as the number of hospitalisation days divided by the length of the period in days * 365.25. Tapering Period Full analysis set but excluding subjects who were observed for less than 90 days in the period.

End point type	Secondary

End point timeframe:

Up to 48 weeks (16 weeks Tapering period & 32 weeks Follow-up period)

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: days				
arithmetic mean (standard deviation)	2.7 (± 8.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to Treatment Regimen Overall Study Period

End point title	Adherence to Treatment Regimen Overall Study Period

End point description:

Adherence to treatment was based on prescribed daily dose for the overall study period which was defined as the percentage of administered doses versus the prescribed doses to a subjects for the entire study duration. ITI full analysis set.

End point type	Secondary

End point timeframe:

Up to 2 Years

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percentage of doses				
arithmetic mean (standard deviation)	100.8 (± 7.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised rFVIIIFc Consumption for Overall Study Period

End point title	Annualised rFVIIIFc Consumption for Overall Study Period

End point description:

Annualised rFVIIIFc consumption for a treatment period was the total nominal rFVIIIFc (IU/kg) / length of period in days * 365.25. ITI Full analysis set.

End point type	Secondary

End point timeframe:
Up to 2 Years

End point values	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: IU/kg				
arithmetic mean (standard deviation)	42713.4 (± 20938.08)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to end of the study (up to 2 years) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs were TEAEs i.e. defined as AEs that developed, worsened, or became serious on or after the first administration of rFVIIIFc. Analysis performed on ITI full analysis set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)

Reporting group description:

Subjects were to receive rFVIIIFc at a dose of 200 IU/kg as once daily injections or divided on several injections per day at the discretion of the investigator, starting at baseline visit up to maximum of 48 Weeks in ITI Period. Subjects who met the criteria for ITI success entered the tapering period and received rFVIIIFc at a dose adjusted according to investigator judgment based on the FVIII activity levels and with the aim of tapering the rFVIIIFc dose to reach a prophylactic dosing regimen within 16 weeks (4 months). Follow-Up was for 32 weeks under an adjusted prophylactic regimen according to investigator judgment.

Serious adverse events	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 16 (56.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth injury			

subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural oedema				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Focal dyscognitive seizures				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Complication associated with device				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injection site haematoma				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 16 (6.25%)			
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 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemarthrosis				

subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Synovitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Vascular access site infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device breakage			
subjects affected / exposed	1 / 16 (6.25%)		
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	Recombinant Coagulation Factor VIII Fc (rFVIIIFc)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)		
General disorders and administration site conditions			

Administration site extravasation subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Asthenia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Catheter site extravasation subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Catheter site haematoma subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 4		
Catheter site swelling subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Fatigue subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Injection site pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Pyrexia subjects affected / exposed occurrences (all)	7 / 16 (43.75%) 23		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Food allergy subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 3		
Seasonal allergy subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 11		
Nasal congestion subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 10		
Pharyngeal erythema subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 4		
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 9		
Wheezing subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Product issues Device occlusion subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Serum ferritin decreased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Injury, poisoning and procedural complications Animal bite subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Arthropod sting subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		

Eye injury				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Face injury				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	2			
Fall				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	2			
Head injury				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Mouth injury				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	4			
Lip injury				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Muscle rupture				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Scratch				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Skin abrasion				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	2			
Skin laceration				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Soft tissue injury				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Traumatic haematoma				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			

Wound dehiscence subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Wrong product administered subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Nervous system disorders Migraine subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Blood and lymphatic system disorders Lymphocytosis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Iron deficiency anaemia subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 5		
Monocytosis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Neutropenia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Gastrointestinal disorders Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Diarrhoea			

subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Eczema infantile			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Red man syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Urticaria contact			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Arthralgia			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Joint effusion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Osteochondrosis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Synovial disorder			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Synovitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	16		
Gastritis viral			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Infectious mononucleosis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Myringitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 16 (31.25%) 7		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Rhinitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Vascular device infection subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 3		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Vitamin d deficiency subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2018	Following changes were made: Primary reason for this amendment was to provide clarifications, consistency, and a few corrections.
11 July 2019	Following changes were made: Text was added as appropriate: "this study would enroll up to 17 subjects", Or "approximately, 17 subjects would be treated." Specific changes for Canada from Protocol 1.1 and 2.1 were added - the primary reason for this amendment was to reduce the number of subjects to be enrolled. Given the rarity of the disease and coupled with a low enrollment rate, a decision was made by the Sponsor to end enrollment at a total of 16 subjects in all countries, effective 12 Dec 2019. No safety concerns contributed to this decision. Clarified the timing for subjects moving from interim ITI visits to ITI outcome assessment visits, and clarified sample collection schedules for anti-drug antibodies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported