Clinical trial results:
A Non-Controlled, Open-Label, Multicenter, Study of Immune Tolerance Induction Performed with rFVIIIFc within a Timeframe of 60 Weeks in Severe Haemophilia A Patients with Inhibitors who have Failed Previous Immune Tolerance Induction Therapies

Summary

EudraCT number	2017-000065-73
Trial protocol	DE IE GB BE FR SE SI IT
Global end of trial date	31 August 2020

Results information

Result version number	v1 (current)
This version publication date	12 March 2021
First version publication date	12 March 2021

Trial information

Trial identification

Sponsor protocol code	Sobi.Elocta-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03103542
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swedish Orphan Biovitrum AB
Sponsor organisation address	Tomtebodavägen 23A, Solna, Stockholm, Sweden, 11276
Public contact	Medical Information, Swedish Orphan Biovitrum AB , +468 6972000, medical.info@sobi.com
Scientific contact	Medical Information, Swedish Orphan Biovitrum AB , +468 6972000, medical.info@sobi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2019
Global end of trial reached?	Yes
Global end of trial date	31 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the outcome of ITI treatment performed with rFVIIIFc within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants

Protection of trial subjects:

This study was conducted in compliance with the protocol, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), applicable regulatory requirements, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki).

The volume of blood taken from the patients complied with the European Commission guidance,the protocol states that the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. Local and/or regional guidelines regarding blood draw volumes were also considered.

Background therapy:

None

Evidence for comparator:

NA

Actual start date of recruitment	17 October 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: 1
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Ireland: 3
Worldwide total number of subjects	16
EEA total number of subjects	9

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	11
Adolescents (12-17 years)	4
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was open at 18 sites in 9 countries in Northern America and Europe. 11 sites in 7 countries recruited patients. It was initially planned to enroll 20 patients but due to recruitment challenges and a changing treatment landscape the recruitment was stopped after enrolling 16 patients. Recruitment was open from Aug 2017 to Nov 2019.

Pre-assignment

Screening details:

After informed consent was provided, patients underwent study specific screening procedures. During the 4- to 6-week screening period, patients continued with their usual treatment regimen in accordance with the local standard of care. Patients who met all inclusion and no exclusion criteria specified by the protocol were enrolled into the study.

Pre-assignment period milestones

Number of subjects started	18[1]
Number of subjects completed	16

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening Failure: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 18 patients entered the screening period for the study although only 16 of these were eventually enrolled.

Period 1

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

Arms

Arm title	rFVIIIFc

Arm description:

All enrolled 16 patients

Arm type	Experimental
Investigational medicinal product name	rFVIIIFc
Investigational medicinal product code	EMEA/H/C/003964
Other name	Elocta, Eloctate
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

During the ITI period the initial rFVIIIFc dose administered was 200 IU/kg/day, which could be given as once daily, or divided in two doses per day. If FVIII:C levels rose above 200 IU/dL already at a low-titer inhibitor (< 5 BU/mL), and before all three tolerance criteria had been confirmed, the dose were to be decreased according to investigator judgment to maintain the peak FVIII:C levels between 100-200 IU/dL.

During the initial part of the tapering period the rFVIIIFc dose administered were to be adjusted according to investigator judgment based on the FVIII:C results to maintain the peak FVIII:C levels between 100-200 IU/dL, with an aim to taper the FVIII:C levels to reach prophylactic levels as judged by the investigator after 16 weeks.

During the follow-up period, the prophylaxis regimen were to be adjusted based on clinical response, and with an aim to keep FVIII:C levels ≥ 1 IU/dL at all time points according to

investigator judgment and local practice.

Number of subjects in period 1	rFVIIIFc
Started	16
Completed	9
Not completed	7
Physician decision	2
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Unspecified	2

Baseline characteristics

Reporting groups

Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	16	16	
Age categorical			
Age at baseline			
Units: Subjects			
Children (2-11 years)	11	11	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	1	1	
Age continuous			
Age at baseline			
Units: years			
median	7.5		
full range (min-max)	3 to 46	-	
Gender categorical			
Gender			
Units: Subjects			
Female	0	0	
Male	16	16	
Demography - Race Units: Subjects			
White	15	15	
Asian	0	0	
Black or African American	1	1	
American Indian or Alaska Native	0	0	
Hemophilia history - severity Units: Subjects			
Mild	0	0	
Moderate	0	0	
Severe	16	16	
Hemophilia history - Family history of Inhibitors Units: Subjects			
Yes	7	7	
No	5	5	
Unknown	4	4	
Number of previous ITI Treatments Units: Subjects			
1 Treatment	10	10	
2 Treatments	4	4	
3 Treatments	2	2	
Inhibitor History - Historical Peak Titre Level Units: BU/ml			

median	127.4		
full range (min-max)	8 to 3000	-	
Inhibitor history - Age at Inhibitor development			
Units: years			
arithmetic mean	1.9		
standard deviation	± 3.6	-	

End points

End points reporting groups

Reporting group title	rFVIIIFc
Reporting group description:	
All enrolled 16 patients	

Primary: ITI success

End point title	ITI success[1]

End point description:

ITI success, defined as achieving all 3 of the following criteria:
• Negative titer for inhibitor (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) at 2 consecutive visits
• FVIII incremental recovery (IR) >66% of the expected IR at 2 consecutive visits
• FVIII half-life (t½) ≥7 hours

End point type	Primary

End point timeframe:

60 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: This is an observational study presenting results using descriptive statistics

End point values	rFVIIIFc			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects				
ITI Success	1			
Partial Success	2			
ITI failure	6			
Not determinable due to withdrawal during the ITI	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ITI success

End point title	Time to ITI success

End point description:

Time to tolerization (i.e. ITI success) of ITI performed with rFVIIIFc within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants.

For the subset of patients who were classified as partial success at the end of the ITI period, the time to fulfillment of the criteria for partial success was also analyzed descriptively.

End point type	Secondary

End point timeframe:

60 weeks

End point values	rFVIIIFc			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: weeks				
arithmetic mean (standard deviation)				
Time to ITI Success Time to Partial Success	46.71 (± 0) 38.76 (± 15.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of relapse during a 48-week period following successful ITI treatment

End point title	Occurrence of relapse during a 48-week period following successful ITI treatment

End point description:

Relapse was defined as a positive inhibitor (≥0.6 BU/mL) on 2 consecutive assessments and incremental recovery ≤66 % of the expected incremental recovery on 2 consecutive assessments.

End point type	Secondary

End point timeframe:

48 weeks

End point values	rFVIIIFc			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects				
relaps criteria met	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events

End point title	Adverse Events

End point description:

All observed adverse events.

(AE=adverse event, SAE=serious adverse event, TEAE=treatment emergent adverse event)

End point type	Secondary

End point timeframe:

SAEs - approx 166 weeks
AEs - approx 110 weeks

End point values	rFVIIIFc			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Number of events				
TEAEs	188			
Serious AEs	21			
Serious TEAEs	18			
Non-serious TEAEs	170			
Related TEAEs	2			
Mild AEs	145			
Moderate AEs	42			
Severe AEs	4			
AEs Leading to Withdrawal	3			
AEs Leading to Death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: From signature of the informed consent form to the safety follow-up visit (approximately 116 weeks).
Non-serious AEs: From the time of first dose of IMP to the safety follow-up visit (approximately 110 weeks).

Adverse event reporting additional description:

The investigator were to report all directly observed adverse events, and all adverse events spontaneously reported by the patient. In addition, each patient were to be questioned about AEs at each study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Overall

Reporting group description:

AEs are reported on overall level. Please note the difference in the reporting period of SAEs and non-serious AEs (SAEs also collected during screening period). 18 patients entered screening, 16 patients were eventually enrolled and are included in the analysis.

188 TEAEs (18 serious; 170 non-serious) were reported in all 16 patients.
3 SAEs occurred during the screening period (PTs Tonsillitis, Vascular device infection and Hemarthrosis).
2 SAEs (PTs Brachiocephalic vein thrombosis and Vena cava thrombosis) were considered related to ITI treatment.
3 SAEs in 2 patients (PTs Device related infection, Haemorrhage and Haemarthrosis) led to withdrawal.

The most frequently reported AE was Infections and infestations (42 events in 11 patients), followed by Injury, poisoning and procedural complications (28 events in 7 patients), Musculoskeletal and connective tissue disorders (28 events in 11 patients) and Gastrointestinal disorders (15 events in 8 patient).

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Brachiocephalic vein thrombosis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
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			
Headache			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spontaneous haemorrhage			
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			
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			

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			
Haemarthrosis			
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			
Tonsillitis			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal 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			
Thrombosis in device			
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: 0 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events subjects affected / exposed	16 / 16 (100.00%)		
Vascular disorders Haemorrhage subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
General disorders and administration site conditions Catheter site irritation subjects affected / exposed occurrences (all) Gait disturbance subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all) pyrexia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1 1 / 16 (6.25%) 2 1 / 16 (6.25%) 1 1 / 16 (6.25%) 4 1 / 16 (6.25%) 2		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Respiratory, thoracic and mediastinal disorders Cough			

subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Autism spectrum disorder			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Device damage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Haematocrit decreased			

subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Haemoglobin decreased				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Human rhinovirus test positive				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Protein urine present				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	2			
Red blood cell count decreased				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Tri-iodothyronine free increased				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Urine ketone body present				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
White blood cell count decreased				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Injury, poisoning and procedural complications				
Arthropod bite				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Contusion				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	15			
Fall				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	4			
Skin abrasion				

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Skin laceration			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Tongue injury			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Traumatic haematoma			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Traumatic haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	7		
Jugular vein occlusion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Iron deficiency anaemia			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Spontaneous haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Anal incontinence			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Lip ulceration			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Loose tooth			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Tooth development disorder			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Onychomadesis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Red man syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	9		
Arthropathy			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Growing pains			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Haemarthrosis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Mobility decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Posture abnormal			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Soft tissue swelling			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Fungal skin infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	10		
Rhinitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Tinea infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Upper respiratory tract infection subjects affected / exposed occurrences (all) Varicella subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	 3 / 16 (18.75%) 4 1 / 16 (6.25%) 1 3 / 16 (18.75%) 5 1 / 16 (6.25%) 1		
Metabolism and nutrition disorders 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
26 February 2018	• to consolidate the feedback received from various regulatory authorities and ethics committees • to decrease the patient burden (for examples changes in the PK samplings schedule, visit schedule and the possibility of home visits and study medication home deliveries) • to adjust the definition of relapse to be more in line with clinical praxis and increase patient retention • to clarify the instructions for concomitant use of bypassing agents • add emicizumab as an exclusion criterion/criterion for withdrawal • to facilitate reading and avoid misinterpretation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported