Clinical trial results:
A Multi-Centre Trial Evaluating Efficacy and Safety of Prophylactic Administration of Concizumab in Patients with Severe Haemophilia A without Inhibitors

Summary

EudraCT number	2016-000614-29
Trial protocol	SE DE ES FR GB IT
Global end of trial date	03 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	NN7415-4255

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03196297
WHO universal trial number (UTN)	U1111-1179-3872
Other trial identifiers	Japanese trial registration number: JapicCTI-173682

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Transparency and Medical Writing (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Transparency and Medical Writing (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2018
Global end of trial reached?	Yes
Global end of trial date	03 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the efficacy of concizumab administered subcutaneously (s.c.) once daily in preventing bleeding episodes in patients with severe haemophilia A without

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th World Medical Association [WMA] 2013) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents (2016), and Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	16 August 2017
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	France: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Ukraine: 2
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	36
EEA total number of subjects	15

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	34
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 26 sites in 11 countries: France(3), Germany(2), Italy(1), Japan(3), Spain(3), Sweden(2), Thailand(1), Turkey(3), the United Kingdom(4), Ukraine(1) and the United States(3). In addition, 5 sites were approved by the IRB/IEC and/or local health authority but did not screen or assign any participants to treatment.

Pre-assignment

Screening details:

The trial consisted of two treatment periods: main part which lasted at least 24 weeks for all participants in the trial and an extension part which was up to 102 weeks.

Period 1

Period 1 title	Main part
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Concizumab- Main part

Arm description:

Subjects were to receive subcutaneous (s.c.) injection of concizumab once daily for at least 24 weeks. The initial dose was 0.15 milligrams per kilogram (mg/kg) and then the dose was escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the participants during the trial were treated with turoctocog at home.

Arm type	Experimental
Investigational medicinal product name	Concizumab B 100 mg/mL
Investigational medicinal product code	
Other name	concizumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive a s.c. injection of concizumab once daily. At the first treatment visit (week 0) concizumab was administered at the trial site supervised by medically trained trial staff. After visit 2, the subject self administered concizumab daily preferably at the same time in the morning, at home.

Number of subjects in period 1	Concizumab- Main part
Started	36
Full Analysis set (FAS)	36
Subject analysis set (SAS)	36
Completed	32
Not completed	4
Consent withdrawn by subject	4

Period 2

Period 2 title	Extension part
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Concizumab- Extension part

Arm description:

Patients continued the extension phase at the same dose of concizumab once daily they have reached at the end of main part for 52-102 weeks with the potential dose escalation based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the patients during the trial were treated with turoctocog at home.

Arm type	Experimental
Investigational medicinal product name	Concizumab B 100 mg/mL
Investigational medicinal product code	
Other name	concizumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who received concizumab during the main part were to continue with their treatment at last dose by the end of main part with s.c. injection of concizumab once daily for 52-102 weeks with the potential dose escalation based on the number of spontaneous bleeding episodes.

Number of subjects in period 2	Concizumab-Extension part
Started	32
FAS	32
SAS	32
Completed	29
Not completed	3
Consent withdrawn by subject	1
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Concizumab- Main part

Reporting group description:

Subjects were to receive subcutaneous (s.c.) injection of concizumab once daily for at least 24 weeks. The initial dose was 0.15 milligrams per kilogram (mg/kg) and then the dose was escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the participants during the trial were treated with turoctocog at home.

Reporting group values	Concizumab- Main part	Total	
Number of subjects	36	36	
Age Categorical Units:			

Age Continuous			
Full analysis set (FAS) included all randomised subjects.			
Units: years arithmetic mean standard deviation	 36.9 ± 12.9	 -	
Gender Categorical Units: Subjects			
Female	0	0	
Male	36	36	

End points

End points reporting groups

Reporting group title	Concizumab- Main part

Reporting group description:

Subjects were to receive subcutaneous (s.c.) injection of concizumab once daily for at least 24 weeks. The initial dose was 0.15 milligrams per kilogram (mg/kg) and then the dose was escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the participants during the trial were treated with turoctocog at home.

Reporting group title	Concizumab- Extension part

Reporting group description:

Patients continued the extension phase at the same dose of concizumab once daily they have reached at the end of main part for 52-102 weeks with the potential dose escalation based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the patients during the trial were treated with turoctocog at home.

Subject analysis set title	Concizumab 0.15 mg/kg- Main part
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received s.c. injection of 0.15 mg/kg concizumab once daily for at least 24 weeks. Breakthrough bleeding episodes occurring to the participants during the trial were treated with turoctocog at home.

Subject analysis set title	Concizumab 0.20 mg/kg- Main part
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received s.c. injection of concizumab once daily for at least 24 weeks. The initial dose was 0.15 mg/kg which was then escalated to 0.20 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the participants during the trial were treated with turoctocog at home.

Subject analysis set title	Concizumab 0.25 mg/kg- Main part
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received s.c. injection of concizumab once daily for at least 24 weeks. The initial dose was 0.15 mg/kg which was then escalated 0.25 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the participants during the trial were treated with turoctocog at home.

Primary: The number of bleeding episodes

End point title	The number of bleeding episodes[1]

End point description:

The number of bleeding episodes that were treated during at least 24 weeks from treatment onset are presented. The data is presented while on last dose level when the bleed occurred. Results are based on the FAS which included all randomised subjects.

End point type	Primary

End point timeframe:

During at least 24 weeks from treatment onset

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: The primary endpoint was evaluated using descriptive statistics. Thus, no statistical analysis was performed.

End point values	Concizumab 0.15 mg/kg-Main part	Concizumab 0.20 mg/kg-Main part	Concizumab 0.25 mg/kg-Main part	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	8	
Units: Episodes	43	13	14	

Statistical analyses

No statistical analyses for this end point

Secondary: The number of spontaneous bleeding episodes

End point title	The number of spontaneous bleeding episodes

End point description:

Bleeds that were not linked to a specific, known action or event are called spontaneous bleeding episodes. The number of spontaneous bleeding episodes that were treated during at least 24 weeks from treatment onset are presented. The data is presented while on last dose level when the bleed occurred. Results are based on the FAS which included all randomised subjects.

End point type	Secondary

End point timeframe:

During at least 24 weeks from treatment onset

End point values	Concizumab 0.15 mg/kg-Main part	Concizumab 0.20 mg/kg-Main part	Concizumab 0.25 mg/kg-Main part	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	7	8	
Units: episodes	16	8	2	

Statistical analyses

No statistical analyses for this end point

Secondary: The number of treatment emergent adverse events (TEAEs)

End point title	The number of treatment emergent adverse events (TEAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily had a causal relationship with this treatment. A TEAE was defined as an event that had onset from the first exposure to treatment until the last visit in the trial. Number of TEAEs that occurred during at least 24 weeks from treatment onset (week 0) are presented. The data is presented per dose level subjects were on at the time of onset of the adverse event. Results are based on the safety analysis set (SAS) which included all randomised subjects.

End point type	Secondary

End point timeframe:

During at least 24 weeks from treatment onset

End point values	Concizumab 0.15 mg/kg-Main part	Concizumab 0.20 mg/kg-Main part	Concizumab 0.25 mg/kg-Main part	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36	15	8	
Units: events	105	16	9	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration (week 0) up to 134 weeks.
All presented adverse events are treatment emergent adverse events (TEAEs). TEAE is an event that had onset from the first exposure to treatment until the last visit in the trial.

Adverse event reporting additional description:

Results are based on the safety analysis set which included all dosed subjects. The data is presented per dose level subjects were on at the time of onset of the adverse event.

MedDRA versions 21.0 and 22.1 were used for the main and extension phases respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Concizumab 0.15 mg/kg - Main part

Reporting group description:

Subjects received s.c. injection of 0.15 mg/kg concizumab once daily for 24 weeks. Breakthrough bleeding episodes occurring to the subjects during the trial were treated with turoctocog at home.

Reporting group title	Concizumab 0.20 mg/kg - Main part

Reporting group description:

Subjects received s.c. injection of concizumab once daily for 24 weeks. The initial dose was 0.15 mg/kg which was then escalated to 0.20 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the subjects during the trial were treated with turoctocog at home.

Reporting group title	Concizumab 0.25 mg/kg - Main part

Reporting group description:

Subjects received s.c. injection of concizumab once daily for 24 weeks. The initial dose was 0.15 mg/kg which was then escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the subjects during the trial were treated with turoctocog at home.

Reporting group title	Concizumab 0.15 mg/kg - Extension part

Reporting group description:

Subjects were to receive s.c. injection of 0.15 mg/kg of concizumab once daily. Subjects who completed the main part (24 weeks) of the study were continued the same dose regimen for concizumab once daily for 52-102 weeks with the potential dose escalation based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the subjects during the trial were treated with turoctocog at home

Reporting group title	Concizumab 0.20 mg/kg - Extension part

Reporting group description:

Subjects were to receive s.c. injection of concizumab once daily. Subjects who completed the main part (24 weeks) of the study were continued the same dose regimen for concizumab once daily for 52-102 weeks. The initial dose was 0.15 mg/kg which was then escalated to 0.20 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the subjects during the trial were treated with turoctocog at home.

Reporting group title	Concizumab 0.25 mg/kg - Extension part

Reporting group description:

Subjects were to receive s.c. injection of concizumab once daily. Subjects who completed the main part (24 weeks) of the study were continued the same dose regimen for concizumab once daily for 52-102 weeks. The initial dose was 0.15 mg/kg which was then escalated to 0.25 mg/kg based on the number of spontaneous bleeding episodes. Breakthrough bleeding episodes occurring to the subjects during the trial were treated with turoctocog at home.

Serious adverse events	Concizumab 0.15 mg/kg - Main part	Concizumab 0.20 mg/kg - Main part	Concizumab 0.25 mg/kg - Main part
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Concizumab 0.15 mg/kg - Extension part	Concizumab 0.20 mg/kg - Extension part	Concizumab 0.25 mg/kg - Extension part
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 19 (10.53%)	1 / 14 (7.14%)	2 / 10 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Concizumab 0.15 mg/kg - Main part	Concizumab 0.20 mg/kg - Main part	Concizumab 0.25 mg/kg - Main part
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 36 (72.22%)	7 / 15 (46.67%)	3 / 8 (37.50%)
Surgical and medical procedures			
Tooth repair			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration			

site conditions			
Exercise tolerance decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Granuloma			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	2 / 36 (5.56%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Injection site bruising			
subjects affected / exposed	5 / 36 (13.89%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	8	0	0
Injection site haematoma			
subjects affected / exposed	4 / 36 (11.11%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	5	0	0
Injection site haemorrhage			
subjects affected / exposed	3 / 36 (8.33%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	6	0	0
Injection site induration			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injection site pruritus			
subjects affected / exposed	2 / 36 (5.56%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			

subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Product issues			
Device physical property issue			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Antithrombin III decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Basophil count increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood fibrinogen decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			

subjects affected / exposed	3 / 36 (8.33%)	2 / 15 (13.33%)	2 / 8 (25.00%)
occurrences (all)	4	2	2
Hepatic enzyme increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Prothrombin fragment 1.2 increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Prothrombin level increased			
subjects affected / exposed	3 / 36 (8.33%)	2 / 15 (13.33%)	2 / 8 (25.00%)
occurrences (all)	4	2	3
Soluble fibrin monomer complex increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thrombin-antithrombin III complex increased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 36 (2.78%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Limb injury			

subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Muscle rupture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin injury			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 36 (19.44%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	7	1	0
Presyncope			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Pinguecula			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Retinal detachment			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Anal fistula			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic gastritis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastric polyps			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lip discolouration			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Penile ulceration			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Crystalluria			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Arthropathy			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Back pain			

subjects affected / exposed	4 / 36 (11.11%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Groin pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Haemophilic arthropathy			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Neck pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Fungal skin infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Gastrointestinal infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gingivitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	9 / 36 (25.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	11	1	0
Otitis externa			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Periodontitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pyoderma			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Upper respiratory tract infection			
subjects affected / exposed	2 / 36 (5.56%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 36 (0.00%)	0 / 15 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Concizumab 0.15 mg/kg - Extension part	Concizumab 0.20 mg/kg - Extension part	Concizumab 0.25 mg/kg - Extension part
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 19 (84.21%)	9 / 14 (64.29%)	7 / 10 (70.00%)
Surgical and medical procedures			
Tooth repair			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Exercise tolerance decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Granuloma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Injection site haematoma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Injection site haemorrhage			

subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Injection site induration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 14 (14.29%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	2 / 19 (10.53%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Haemoptysis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Product issues			
Device physical property issue			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Antithrombin III decreased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Basophil count increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood fibrinogen decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Fibrin D dimer increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 14 (7.14%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Hepatic enzyme increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Prothrombin fragment 1.2 increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Prothrombin level increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Soluble fibrin monomer complex increased			

subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Thrombin-antithrombin III complex increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Vitamin D decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	7
Fall			
subjects affected / exposed	0 / 19 (0.00%)	2 / 14 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Ligament sprain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Muscle rupture			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Radius fracture			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 19 (10.53%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Presyncope			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eye disorders			
Pinguecula			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Retinal detachment			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Anal fistula			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Chronic gastritis			
subjects affected / exposed	2 / 19 (10.53%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Dental caries			
subjects affected / exposed	1 / 19 (5.26%)	1 / 14 (7.14%)	1 / 10 (10.00%)
occurrences (all)	1	4	1

Diarrhoea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastric polyps			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Lip discolouration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Penile ulceration			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rash			

subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Crystalluria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 14 (14.29%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Arthropathy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 19 (5.26%)	2 / 14 (14.29%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Groin pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haemophilic arthropathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Muscle tightness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			

subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	8	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gingivitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	2 / 19 (10.53%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Laryngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	6 / 19 (31.58%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	8	1	0

Otitis externa			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Periodontitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Pyoderma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	2 / 19 (10.53%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Tooth abscess			
subjects affected / exposed	0 / 19 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	2 / 14 (14.29%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 19 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 19 (10.53%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2017	This protocol amendment was prepared to address VHP1081 requirements to clarify individual discontinuation criteria, holding rules for the trial and protocol deviations in order to improve safety and rights of the patients.
20 October 2017	This protocol amendment was prepared to obtain 24 hours pharmacokinetic (PK)-profile under daily dosing with concizumab after initiation of multiple dosing.
02 March 2018	This protocol amendment was finalised to prolong the extension part of trial ensuring additional safety data and providing the option for the patients to be enrolled into a subsequent trial if eligible. Furthermore, patients who permanently prematurely discontinue trial product due to a safety concern can now be followed after completion of visit 17 (end of trial) by unscheduled visits until Last Patient Last Visit (LPLV) (global).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	The decision to pause the trial was a result of the occurrence of non-fatal thrombotic events in three patients enrolled in the ongoing phase 3 programme. The trial was completed as planned.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31444162