Clinical trial results:
A Multi-Centre, Randomised, Open-Label, Controlled Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients with Inhibitors

Summary

EudraCT number	2016-000510-30
Trial protocol	SE DK GB GR ES AT HR IT
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	14 February 2021
First version publication date	14 February 2021

Trial information

Trial identification

Sponsor protocol code	NN7415-4310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03196284
WHO universal trial number (UTN)	U1111-1179-2925
Other trial identifiers	Japanese trial registration number: JapicCTI-173681

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, 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	24 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 September 2018
Global end of trial reached?	Yes
Global end of trial date	31 January 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 haemophilia A and B patients with inhibitors.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 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	Austria: 2
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	26
EEA total number of subjects	14

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)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 17 sites in 12 countries as follows: Austria (1), Croatia (1), Denmark (1), Italy (2), Spain (2), Sweden (1), the United Kingdom (1), Israel (1), Malaysia (2), Ukraine (1), Japan (2) and the United States (2).

Pre-assignment

Screening details:

The trial consisted of two treatment periods: main part which lasted 24 weeks for participants randomised to eptacog alfa and at least 24 weeks for patients randomised to concizumab and an extension part which lasted up to 94 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Concizumab- Main part

Arm description:

Subjects were to receive a subcutaneous (s.c.) injection of concizumab once daily for 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. A loading dose of 0.5 mg/kg was given as the first concizumab dose. A single injection of 90 micrograms per kilogram (µg/kg) eptacog alfa (rFVIIa) was administered in a non-bleeding state one week after dosing with concizumab had initiated.

Arm type	Experimental
Investigational medicinal product name	Eptacog alfa (activated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A single injection of 90 µg/kg eptacog alfa (rFVIIa) was administered in a non-bleeding state one week after dosing with concizumab had initiated.

Investigational medicinal product name	Concizumab B 100 mg/mL
Investigational medicinal product code	
Other name	
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 for 24 weeks. The initial dose was 0.15 mg/kg and then the dose was escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

Arm title	Eptacog alfa- Main part

Arm description:

Subjects were to receive eptacog alfa on-demand treatment for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Eptacog alfa (activated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were to receive eptacog alfa on-demand treatment for 24 weeks.

Number of subjects in period 1	Concizumab- Main part	Eptacog alfa- Main part
Started	17	9
Completed	17	8
Not completed	0	1
Consent withdrawn by subject	-	1

Period 2

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

Arms

Arm title	Concizumab- Extension part

Arm description:

Subjects who completed main part treatment were to receive a s.c. injection of concizumab once daily for 52-94 weeks. Subjects who received concizumab during the main part were to continue with their treatment at last dose by the end of main part and those received eptacog alfa during the main part were to start their treatment with 0.15 mg/kg of concizumab. The dose was then escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

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

Dosage and administration details:

Subjects who completed main part treatment were to receive a s.c. injection of concizumab once daily for 52-94 weeks. Subjects who received concizumab during the main part were to continue with their treatment at last dose by the end of main part and those received eptacog alfa during the main part were to start their treatment with 0.15 mg/kg of concizumab. The dose was then escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

Number of subjects in period 2	Concizumab-Extension part
Started	25
Completed	22
Not completed	3
Consent withdrawn by subject	1
Physician decision	1
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Concizumab- Main part
Reporting group description:	
Subjects were to receive a subcutaneous (s.c.) injection of concizumab once daily for 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. A loading dose of 0.5 mg/kg was given as the first concizumab dose. A single injection of 90 micrograms per kilogram (µg/kg) eptacog alfa (rFVIIa) was administered in a non-bleeding state one week after dosing with concizumab had initiated.	
Reporting group title	Eptacog alfa- Main part
Reporting group description:	
Subjects were to receive eptacog alfa on-demand treatment for 24 weeks.	

Reporting group values	Concizumab- Main part	Eptacog alfa- Main part	Total
Number of subjects	17	9	26
Age Categorical Units: Subjects			
Age Continuous			
Full analysis set (FAS) included all randomised subjects.			
Units: years			
arithmetic mean	34.1	41.1	
standard deviation	± 11.1	± 15.0	-
Gender Categorical Units: Subjects			
Female	0	0	0
Male	17	9	26

End points

End points reporting groups

Reporting group title	Concizumab- Main part

Reporting group description:

Subjects were to receive a subcutaneous (s.c.) injection of concizumab once daily for 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. A loading dose of 0.5 mg/kg was given as the first concizumab dose. A single injection of 90 micrograms per kilogram (µg/kg) eptacog alfa (rFVIIa) was administered in a non-bleeding state one week after dosing with concizumab had initiated.

Reporting group title	Eptacog alfa- Main part

Reporting group description:

Subjects were to receive eptacog alfa on-demand treatment for 24 weeks.

Reporting group title	Concizumab- Extension part

Reporting group description:

Subjects who completed main part treatment were to receive a s.c. injection of concizumab once daily for 52-94 weeks. Subjects who received concizumab during the main part were to continue with their treatment at last dose by the end of main part and those received eptacog alfa during the main part were to start their treatment with 0.15 mg/kg of concizumab. The dose was then escalated to 0.20 and 0.25 mg/kg based on the number of spontaneous bleeding episodes. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

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

Subject analysis set description:

Subjects received s.c. injection of 0.15 mg/kg concizumab once daily for 24 weeks. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

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

Subject analysis set 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. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

Subject analysis set title	Eptacog alfa- Main part
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects were to receive eptacog alfa on-demand treatment for 24 weeks.

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 (week 0) are presented. 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: Inferential statistics was not performed.

End point values	Concizumab-Main part	Eptacog alfa-Main part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	9		
Units: Count of episodes	47	77		

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 (week 0) are presented. The data is presented per the last dose level which the subjects have reached at the time of assessment. 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	Eptacog alfa-Main part	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	2	9	
Units: Count of episodes	19	5	69	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events (TEAEs)

End point title	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 the last dose level which the subjects have reached at the time of event. Results are based on the safety analysis set (SAS) 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	Eptacog alfa-Main part	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	2	9	
Units: Count of events	39	4	18	

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 126 weeks

Adverse event reporting additional description:

Results are based on the safety analysis set which included all randomized subjects.

All presented adverse events are treatment emergent adverse events (TEAEs). TEAE was defined as an event that had onset from the first exposure to treatment (randomisation date, in case of on-demand arm) until the last visit in the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Eptacog alfa - Main part

Reporting group description:

Subjects were to receive eptacog alfa on-demand treatment for 24 weeks.

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. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

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. A loading dose of 0.5 mg/kg was given as the first concizumab dose.

Reporting group title	Concizumab 0.15 mg/kg - Extension part

Reporting group description:

Subjects who were on treatment with concizumab once daily at the end of main part of the study continued their treatment in the extension part. Subjects who received eptacog alfa in the main part switched to treatment with concizumab in the extension part (a loading dose of 0.5 mg/kg was given as the first concizumab dose). The dose of concizumab was 0.15 mg/kg.

Reporting group title	Concizumab 0.20 mg/kg - Extension part

Reporting group description:

Subjects who were on treatment with concizumab once daily at the end of main part of the study continued their treatment in the extension part. Subjects who received eptacog alfa in the main part switched to treatment with concizumab in the extension part (a loading dose of 0.5 mg/kg was given as the first concizumab dose). The initial dose of concizumab was 0.15 mg/kg which was then escalated to 0.20 mg/kg based on the number of spontaneous bleeding episodes.

Reporting group title	Concizumab 0.25 mg/kg - Extension part

Reporting group description:

Subjects who were on treatment with concizumab once daily at the end of main part of the study continued their treatment in the extension part. Subjects who received eptacog alfa in the main part switched to treatment with concizumab in the extension part (a loading dose of 0.5 mg/kg was given as the first concizumab dose). The initial dose of concizumab was 0.15 mg/kg which was then escalated to 0.25 mg/kg based on the number of spontaneous bleeding episodes.

Serious adverse events	Eptacog alfa - Main part	Concizumab 0.15 mg/kg - Main part	Concizumab 0.20 mg/kg - Main part
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	1 / 17 (5.88%)	0 / 2 (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			
Hand fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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
Subdural haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (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
Cardiac disorders			
Congestive cardiomyopathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (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
General disorders and administration site conditions			
Puncture site haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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			
Sleep apnoea syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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
Muscle haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (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			
Hordeolum			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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	3 / 23 (13.04%)	1 / 13 (7.69%)	0 / 4 (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			
Hand fracture			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (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
Subdural haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (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
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (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
Cardiac disorders			
Congestive cardiomyopathy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (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
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (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
General disorders and administration site conditions			

Puncture site haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (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
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (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
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (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
Muscle haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (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			
Hordeolum			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (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

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

Non-serious adverse events	Eptacog alfa - Main part	Concizumab 0.15 mg/kg - Main part	Concizumab 0.20 mg/kg - Main part
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	13 / 17 (76.47%)	2 / 2 (100.00%)
Investigations			
Eosinophil count increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			

subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Prothrombin fragment 1.2 increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Prothrombin level increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 9 (22.22%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Overdose			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Congestive cardiomyopathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 9 (0.00%)	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Ulnar nerve palsy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Injection site erythema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Injection site haematoma			
subjects affected / exposed	0 / 9 (0.00%)	3 / 17 (17.65%)	0 / 2 (0.00%)
occurrences (all)	0	6	0
Injection site haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Flatulence			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Food poisoning			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			

subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haemophilic arthropathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Osteoporosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Synovitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 9 (11.11%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	3 / 17 (17.65%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Pharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Skin infection			

subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 9 (0.00%)	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	0	1	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	13 / 23 (56.52%)	9 / 13 (69.23%)	2 / 4 (50.00%)
Investigations			
Eosinophil count increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Prothrombin fragment 1.2 increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Prothrombin level increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Overdose			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Cardiac disorders			
Congestive cardiomyopathy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ulnar nerve palsy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	2 / 23 (8.70%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Injection site erythema			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injection site haematoma			
subjects affected / exposed	1 / 23 (4.35%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Injection site haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Constipation			

subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Flatulence			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Food poisoning			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	1 / 23 (4.35%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Haemorrhoids			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin ulcer			

subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Groin pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haemophilic arthropathy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Synovitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Influenza			

subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 23 (4.35%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 23 (13.04%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	5	1	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 23 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 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.
22 November 2017	This protocol amendment was prepared to obtain pharmacokinetic (PK)-profile of daily dosing with concizumab after initiation of multiple dosing.
12 September 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).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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