EU Clinical Trials Register

Clinical trial results:
A Randomized, Multicenter, Open-Label, Phase III Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus No Prophylaxis in Hemophilia A Patients Without Inhibitors

Summary

EudraCT number	2016-000072-17
Trial protocol	GB IE ES DE PL FR IT
Global end of trial date	12 May 2022

Results information

Result version number	v2 (current)
This version publication date	05 November 2022
First version publication date	30 September 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BH30071

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02847637
WHO universal trial number (UTN)	-
Other trial identifiers	Study Acronym: HAVEN 3

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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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	12 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of prophylactic emicizumab (1.5 mg/kg/week or 3 mg/kg/2weeks) compared with no prophylaxis in patients with haemophilia A without Factor VIII (FVIII) inhibitors on the basis of the number of bleeds over time.

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Costa Rica: 9
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	152
EEA total number of subjects	60

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)	8
Adults (18-64 years)	139
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 161 participants were screened; 9 failed screening, and 152 participants, who had previously received either episodic or prophylactic treatment with FVIII agents, were enrolled in this study. Participants in Arms C, A, and B were randomized in a 1:2:2 ratio, respectively; participants in Arm D were enrolled without randomization.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm C (Control): No Prophylaxis

Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial. After completing 24 weeks of no prophylaxis (i.e., episodic FVIII treatment) on study, then they were given the opportunity to switch to emicizumab prophylaxis of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Arm type	Active comparator
Investigational medicinal product name	Emicizumab
Investigational medicinal product code	RO5534262
Other name	Hemlibra, ACE910
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

After having completed 24 weeks of episodic factor VIII (FVIII) treatment (no prophylaxis), participants were given the opportunity to switch to emicizumab prophylaxis. Emicizumab was administered subcutaneously (SC) at a loading dose of 3 milligrams per kilogram per week (mg/kg/week) for the first 4 weeks, followed by a maintenance dose of 3 mg/kg/2 weeks.

Arm title	Arm A: Emicizumab 1.5 mg/kg QW

Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Arm type	Experimental
Investigational medicinal product name	Emicizumab
Investigational medicinal product code	RO5534262
Other name	Hemlibra, ACE910
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Emicizumab was administered subcutaneously (SC) at a loading dose of 3 milligrams per kilogram per week (mg/kg/week) for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg/week.

Arm title	Arm B: Emicizumab 3 mg/kg Q2W

Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Arm type	Experimental
Investigational medicinal product name	Emicizumab
Investigational medicinal product code	RO5534262
Other name	Hemlibra, ACE910
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Emicizumab was administered subcutaneously (SC) at a loading dose of 3 milligrams per kilogram per week (mg/kg/week) for the first 4 weeks, followed by a maintenance dose of 3 mg/kg/2 weeks.

Arm title	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)

Arm description:

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Arm type	Experimental
Investigational medicinal product name	Emicizumab
Investigational medicinal product code	RO5534262
Other name	Hemlibra, ACE910
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Emicizumab was administered subcutaneously (SC) at a loading dose of 3 milligrams per kilogram per week (mg/kg/week) for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg/week.

Number of subjects in period 1	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W
Started	18	36	35
Completed First 24 Weeks of Treatment	16 [1]	35	34
Emicizumab Dose Was Up-Titrated	0 [2]	1 [3]	1 [4]
Changed Emicizumab Dosing Regimen	1 [5]	3 [6]	1 [7]
Completed	17	34	34
Not completed	1	2	1

Consent withdrawn by subject	-	1	1
Lost to follow-up	1	1	-

Number of subjects in period 1	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Started	63
Completed First 24 Weeks of Treatment	63
Emicizumab Dose Was Up-Titrated	7 [8]
Changed Emicizumab Dosing Regimen	1 [9]
Completed	63
Not completed	0
Consent withdrawn by subject	-
Lost to follow-up	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A total of 17 participants switched from No Prophylaxis to emicizumab prophylaxis after 24 weeks and completed the study, but 1 of those participants did so after having completed just 23.5 weeks on No Prophylaxis.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

Baseline characteristics

Reporting groups

Reporting group title	Arm C (Control): No Prophylaxis
Reporting group description:	

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial. After completing 24 weeks of no prophylaxis (i.e., episodic FVIII treatment) on study, then they were given the opportunity to switch to emicizumab prophylaxis of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm A: Emicizumab 1.5 mg/kg QW
Reporting group description:	

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm B: Emicizumab 3 mg/kg Q2W
Reporting group description:	

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Reporting group description:	

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects	18	36	35
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	1	0	0
Adults (18-64 years)	17	34	34
From 65-84 years	0	2	1

85 years and over	0	0	0

Age Continuous Units: years			
arithmetic mean	37.8	39.8	40.4
standard deviation	± 12.9	± 14.0	± 11.4
Sex: Female, Male Units: participants			
Female	0	0	0
Male	18	36	35
Number of Participants with <9 or ≥9 Bleeds in the Last 24 Weeks Prior to Study Entry Units: Subjects			
Less Than (<) 9 Bleeds	4	9	5
Greater Than or Equal To (≥) 9 Bleeds	14	27	30
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	6	10
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	3	3	1
White	11	24	20
More than one race	0	0	0
Unknown or Not Reported	0	2	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	4	5
Not Hispanic or Latino	17	32	30
Unknown or Not Reported	1	0	0
Number of Target Joints in the Last 24 Weeks Prior to Study Entry			
A target joint was defined as at least 3 bleeds into the same joint over the last 24 weeks prior to study entry.			
Units: target joints			
arithmetic mean	2.2	2.1	2.2
standard deviation	± 1.4	± 1.4	± 1.7

Reporting group values	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Total	
Number of subjects	63	152	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	

Adolescents (12-17 years)	7	8	
Adults (18-64 years)	54	139	
From 65-84 years	2	5	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	36.4		
standard deviation	± 14.4	-	
Sex: Female, Male Units: participants			
Female	0	0	
Male	63	152	
Number of Participants with <9 or ≥9 Bleeds in the Last 24 Weeks Prior to Study Entry Units: Subjects			
Less Than (<) 9 Bleeds	53	71	
Greater Than or Equal To (≥) 9 Bleeds	10	81	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	12	32	
Native Hawaiian or Other Pacific Islander	0	1	
Black or African American	1	8	
White	47	102	
More than one race	0	0	
Unknown or Not Reported	3	9	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	16	
Not Hispanic or Latino	53	132	
Unknown or Not Reported	3	4	
Number of Target Joints in the Last 24 Weeks Prior to Study Entry			
A target joint was defined as at least 3 bleeds into the same joint over the last 24 weeks prior to study entry.			
Units: target joints			
arithmetic mean	1.0		
standard deviation	± 1.6	-	

End points

End points reporting groups

Reporting group title	Arm C (Control): No Prophylaxis

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial. After completing 24 weeks of no prophylaxis (i.e., episodic FVIII treatment) on study, then they were given the opportunity to switch to emicizumab prophylaxis of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm A: Emicizumab 1.5 mg/kg QW

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm B: Emicizumab 3 mg/kg Q2W

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)

Reporting group description:

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Subject analysis set title	Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm includes historical data from participants in the non-interventional study (NIS) BH29768 who had received FVIII prophylaxis and were followed for a minimum of 24 weeks on the NIS prior to enrollment in Arm D of this study.

Subject analysis set title	Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm includes data from the same participants who had received FVIII prophylaxis in NIS BH29768 prior to study entry and then enrolled in Arm D of this study to receive emicizumab prophylaxis at a dose of 3 mg/kg once per week (QW) subcutaneously (SC) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW until the end of study. The data reported was collected only during emicizumab prophylaxis treatment.

Subject analysis set title	A+Bnise: Pre-Study Episodic FVIII in NIS BH29768
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm includes historical data from participants in the non-interventional study (NIS) BH29768 who

had received episodic FVIII treatment and were followed for a minimum of 24 weeks on the NIS prior to randomization to Arms A or B of this study. A pooled analysis, as opposed to two separate analyses, was performed due to the small number of NIS episodic patients (NISE) randomized to either Arm A or B.

Subject analysis set title	A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This arm includes data from the same participants who had received episodic FVIII treatment in NIS BH29768 prior to study entry and then were randomized to Arms A or B of this study to receive emicizumab prophylaxis at a dose of 3 mg/kg subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of either 1.5 mg/kg emicizumab SC QW (Arm A) or 3 mg/kg emicizumab SC Q2W (Arm B). A pooled analysis, as opposed to two separate analyses, was performed due to the small number of NIS episodic patients (NISE) randomized to either Arm A or B. The data reported was collected only during emicizumab prophylaxis treatment.

Subject analysis set title	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes all participants from Arm C who had switched to emicizumab prophylaxis up to the primary completion date (PCD; i.e., analysis cutoff) after having completed 24 weeks on No Prophylaxis. The data reported was collected only during emicizumab prophylaxis treatment up to the PCD. Emicizumab was administered at a loading dose of 3 mg/kg SC once per week (QW) for the first 4 weeks, followed by maintenance dosing of 3 mg/kg emcizumab SC Q2W.

Subject analysis set title	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes all participants from Arm C who switched to emicizumab prophylaxis during the entire study after completing 24 weeks on No Prophylaxis. The data reported was collected only during emicizumab prophylaxis treatment. Emicizumab was administered at a loading dose of 3 mg/kg SC once per week (QW) for the first 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC Q2W. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Subject analysis set title	All Emicizumab Participants
Subject analysis set type	Safety analysis

Subject analysis set description:

This analysis set included all participants who received emicizumab on the study. For Arm C, it only includes participants starting after Week 24 on study when they crossed over to first receive prophylactic treatment with emicizumab.

Subject analysis set title	Arms A and D: Emicizumab 1.5 mg/kg QW
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set is a combination of all emicizumab-treated participants from Arms A and D who received the same emicizumab prophylaxis dosing regimen at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW.

Subject analysis set title	Arms B and C (Emi): Emicizumab 3 mg/kg Q2W
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set is a combination of all emicizumab-treated participants from Arms B and C (Emi) who received the same emicizumab prophylaxis dosing regimen at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W).

Primary: Annualized Bleeding Rate (ABR) for Treated Bleeds

End point title	Annualized Bleeding Rate (ABR) for Treated Bleeds

End point description:

The number of treated bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was assessed using a negative binomial (NB) regression model, which accounts for different follow-up times, with the number of bleeds as a function of randomization and the time that each participant

stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor. A bleed is considered a "treated bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed", irrespective of the time between treatment and the preceding bleed. Bleeds due to surgery/procedure are excluded.

End point type	Primary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated bleed rate per year				
number (confidence interval 95%)	38.2 (22.86 to 63.76)	1.5 (0.89 to 2.47)	1.3 (0.75 to 2.25)	1.6 (1.07 to 2.44)

Statistical analyses

Statistical analysis title	ABR Ratio for Arm A versus Arm C

Statistical analysis description:

H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.075

Notes:

[1] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value was obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Statistical analysis title	ABR Ratio for Arm B versus Arm C

Statistical analysis description:

H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.066

Notes:

[2] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value was obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Secondary: Annualized Bleeding Rate (ABR) for All Bleeds

End point title	Annualized Bleeding Rate (ABR) for All Bleeds

End point description:

The number of all bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was assessed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor. "All bleeds" comprises both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: all bleed rate per year				
number (confidence interval 95%)	47.6 (28.45 to 79.59)	2.5 (1.63 to 3.90)	2.6 (1.63 to 4.29)	3.3 (2.22 to 4.83)

Statistical analyses

Statistical analysis title	ABR Ratio for Arm B versus Arm C

Statistical analysis description:

H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.103

Notes:

[3] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value was obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Statistical analysis title	ABR Ratio for Arm A versus Arm C

Statistical analysis description:

H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.099

Notes:

[4] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value was obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Secondary: Annualized Bleeding Rate (ABR) for Treated Joint Bleeds

End point title	Annualized Bleeding Rate (ABR) for Treated Joint Bleeds

End point description:

The number of treated joint bleeds over the efficacy period is presented as an ABR that was assessed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor. A "joint bleed" is defined as a bleed reported as "joint" and with at least one of the following symptoms: increasing swelling or warmth of the skin over the joint; and/or increasing pain, decreased range of motion, or difficulty using the joint compared with baseline. It is considered a "treated joint bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed". Bleeds due to

surgery/procedure are excluded.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated joint bleed rate per year				
number (confidence interval 95%)	26.5 (14.67 to 47.79)	1.1 (0.59 to 1.89)	0.9 (0.44 to 1.67)	1.2 (0.70 to 2.01)

Statistical analyses

Statistical analysis title	ABR Ratio for Arm B versus Arm C

Statistical analysis description:

H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.07

Notes:

[5] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value is obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Statistical analysis title	ABR Ratio for Arm A versus Arm C

Statistical analysis description:

H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.085

Notes:

[6] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value is obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Secondary: Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds

End point title	Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was assessed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor. A bleed is classified as "spontaneous" if there is no other known contributing factor such as trauma or procedure/surgery. A "treated spontaneous bleed" is a spontaneous bleed that is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed". Bleeds due to surgery/procedure are excluded.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated spontaneous bleed rate per year				
number (confidence interval 95%)	15.6 (7.60 to 31.91)	1.0 (0.48 to 1.91)	0.3 (0.11 to 0.75)	0.5 (0.23 to 0.94)

Statistical analyses

Statistical analysis title	ABR Ratio for Arm B versus Arm C
Statistical analysis description:	

H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.056

Notes:

[7] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value is obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Statistical analysis title	ABR Ratio for Arm A versus Arm C
Statistical analysis description:	

H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.151

Notes:

[8] - Statistical significance is controlled at the 2-sided, 0.05 alpha level. The p-value is obtained via a global model with a 3-level categorical effect for treatment (emicizumab 1.5 mg/kg/week, emicizumab 3 mg/kg/2 weeks, or no prophylaxis).

Secondary: Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds

End point title	Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds
End point description:	

The number of treated target joint bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was assessed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor. A "target joint bleed" is defined as a bleed reported as a joint bleed into a target joint, defined as at least 3 bleeds into the same joint during the last 24 weeks prior to study entry. It is

considered a "treated target joint bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed". Bleeds due to surgery/procedure are excluded.

End point type	Secondary
End point timeframe:	

From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated target joint bleed rate per year				
number (confidence interval 95%)	13.0 (5.22 to 32.33)	0.6 (0.28 to 1.42)	0.7 (0.27 to 1.64)	0.6 (0.26 to 1.53)

Statistical analyses

Statistical analysis title	ABR Ratio for Arm A versus Arm C
Statistical analysis description:	

H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.143
Notes:	

[9] - Not controlled for type I error

Statistical analysis title	ABR Ratio for Arm B versus Arm C
Statistical analysis description:	

H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C ≠ 1.

Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg

	Q2W
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.147

Notes:

[10] - Not controlled for type I error

Secondary: Intra-Participant Comparison of ABR for Treated Bleeds on Study Versus Pre-Study in Participants from the Non-Interventional Study Population Previously Treated with Factor VIII (FVIII) Prophylaxis (NISP)

End point title	Intra-Participant Comparison of ABR for Treated Bleeds on Study Versus Pre-Study in Participants from the Non-Interventional Study Population Previously Treated with Factor VIII (FVIII) Prophylaxis (NISP)

End point description:

This is an intra-participant comparison of the annualized bleeding rate (ABR) for treated bleeds on study versus pre-study in the NIS population previously treated with FVIII prophylaxis in NIS BH29768. The number of treated bleeds over the efficacy period is presented as an ABR that was assessed using a NB regression model, which accounts for different follow-up times, with the number of bleeds as a function of treatment and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes a repeated statement to account for intra-participant comparison. A bleed is considered a "treated bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed", irrespective of the time between treatment and the preceding bleed. Bleeds due to surgery/procedure are excluded.

End point type	Secondary

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for Dnisp-FVIII Prophylaxis: 30.07 [5.0-45.1] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for Dnisp-Emicizumab Prophylaxis: 33.71 [20.1-48.6] weeks)

End point values	Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768	Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: treated bleed rate per year				
number (confidence interval 95%)	4.8 (3.22 to 7.09)	1.5 (0.98 to 2.33)		

Statistical analyses

Statistical analysis title	ABR Ratio - Dnisp: Emicizumab vs FVIII Prophylaxis

Statistical analysis description:

H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio ≠ 1. This is an intra-participant analysis of the ABR Ratio for a total of 48 participants (not 96) over two different periods: on study while receiving emicizumab prophylaxis (Dnisp: Emicizumab Prophylaxis) versus before study entry while receiving FVIII prophylaxis in NIS BH29768 (Dnisp: Pre-Study FVIII Prophylaxis).

Comparison groups	Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768 v Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Non-stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.195
upper limit	0.514

Notes:

[11] - Statistical significance is controlled at the 2-sided, 0.05 alpha level.

Secondary: Intra-Participant Comparison of ABR for All Bleeds on Study Versus Pre-Study in Participants from the Non-Interventional Study Population Previously Treated with FVIII Prophylaxis (NISP)

End point title	Intra-Participant Comparison of ABR for All Bleeds on Study Versus Pre-Study in Participants from the Non-Interventional Study Population Previously Treated with FVIII Prophylaxis (NISP)

End point description:

This is an intra-participant comparison of the annualized bleeding rate (ABR) for all bleeds on study versus pre-study in the NIS population previously treated with FVIII prophylaxis in NIS BH29768. The number of all bleeds over the efficacy period is presented as an ABR that was assessed using a NB regression model, which accounts for different follow-up times, with the participant's number of bleeds as a function of treatment and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes a repeated statement to account for intra-participant comparison. "All bleeds" comprises both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded.

End point type	Secondary

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for Dnisp-FVIII Prophylaxis: 30.07 [5.0-45.1] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for Dnisp-Emicizumab Prophylaxis: 33.71 [20.1-48.6] weeks)

End point values	Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768	Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: all bleed rate per year				
number (confidence interval 95%)	8.9 (5.72 to 13.87)	3.3 (2.17 to 5.06)		

Statistical analyses

Statistical analysis title	ABR Ratio - Dnisp: Emicizumab vs FVIII Prophylaxis
Statistical analysis description:	

H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio ≠ 1. This is an intra-participant analysis of the ABR Ratio for a total of 48 participants (not 96) over two different periods: on study while receiving emicizumab prophylaxis (Dnisp: Emicizumab Prophylaxis) versus before study entry while receiving FVIII prophylaxis in NIS BH29768 (Dnisp: Pre-Study FVIII Prophylaxis).

Comparison groups	Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768 v Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [12]
Method	Non-stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.626

Notes:

[12] - Statistical significance is controlled at the 2-sided, 0.05 alpha level.

Secondary: Intra-Participant Comparison of ABR for Treated Bleeds on Study Versus Pre-Study in Participants from the NIS Population Previously Treated with Episodic FVIII (NISE)

End point title	Intra-Participant Comparison of ABR for Treated Bleeds on Study Versus Pre-Study in Participants from the NIS Population Previously Treated with Episodic FVIII (NISE)
End point description:	

This is an intra-participant comparison of the annualized bleeding rate (ABR) for treated bleeds on study versus pre-study in the NIS population previously treated with episodic FVIII in NIS BH29768. The number of treated bleeds over the efficacy period is presented as an ABR that was assessed using a NB regression model, which accounts for different follow-up times, with the number of bleeds as a function of treatment and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes a repeated statement to account for intra-participant comparison. A bleed is considered a "treated bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed", irrespective of the time between treatment and the preceding bleed. Bleeds due to surgery/procedure are excluded.

End point type	Secondary

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for A+Bnise-FVIII Episodic: 25.71 [15.4-40.9] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for A+Bnise-Emicizumab: 34.71 [24.1-50.6] weeks)

End point values	A+Bnise: Pre-Study Episodic FVIII in NIS BH29768	A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: treated bleed rate per year				
number (confidence interval 95%)	34.4 (27.45 to 43.14)	1.0 (0.43 to 2.54)		

Statistical analyses

Statistical analysis title	ABR Ratio Emicizumab Prophylaxis vs Episodic FVIII

Statistical analysis description:

H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio ≠ 1. This is an intra-participant analysis of the ABR Ratio for a total of 20 participants (not 40) over two different periods: on study while receiving emicizumab prophylaxis (A+Bnise: Emicizumab Prophylaxis) versus before study entry while receiving episodic FVIII in NIS BH29768 (A+Bnise: Pre-Study Episodic FVIII).

Comparison groups	A+Bnise: Pre-Study Episodic FVIII in NIS BH29768 v A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Non-stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.067

Notes:

[13] - Not controlled for type I error

Secondary: Intra-Participant Comparison of ABR for All Bleeds on Study Versus Pre-Study in Participants from the NIS Population Previously Treated with Episodic FVIII (NISE)

End point title	Intra-Participant Comparison of ABR for All Bleeds on Study Versus Pre-Study in Participants from the NIS Population Previously Treated with Episodic FVIII (NISE)

End point description:

This is an intra-participant comparison of the annualized bleeding rate (ABR) for all bleeds on study versus pre-study in the NIS population previously treated with episodic FVIII in NIS BH29768. The number of all bleeds over the efficacy period is presented as an ABR that was assessed using a NB

regression model, which accounts for different follow-up times, with the participant's number of bleeds as a function of treatment and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes a repeated statement to account for intra-participant comparison. "All bleeds" comprises both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded.

End point type	Secondary

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for A+Bnise-FVIII Episodic: 25.71 [15.4-40.9] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for A+Bnise-Emicizumab: 34.71 [24.1-50.6] weeks)

End point values	A+Bnise: Pre-Study Episodic FVIII in NIS BH29768	A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: all bleed rate per year				
number (confidence interval 95%)	39.6 (31.94 to 49.04)	1.6 (0.85 to 2.92)		

Statistical analyses

Statistical analysis title	ABR Ratio Emicizumab Prophylaxis vs Episodic FVIII

Statistical analysis description:

H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio ≠ 1. This is an intra-participant analysis of the ABR Ratio for a total of 20 participants (not 40) over two different periods: on study while receiving emicizumab prophylaxis (A+Bnise: Emicizumab Prophylaxis) versus before study entry while receiving episodic FVIII in NIS BH29768 (A+Bnise: Pre-Study Episodic FVIII).

Comparison groups	A+Bnise: Pre-Study Episodic FVIII in NIS BH29768 v A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Non-stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.068

Notes:

[14] - Not controlled for type I error

Secondary: Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Physical Health Subscore for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25

End point title	Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Physical Health Subscore for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25[15]

End point description:

The Haem-A-QoL questionnaire has been developed and used in hemophilia A participants, assessing very specific aspects of dealing with hemophilia. The questionnaire consists of items pertaining to 10 domains: physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain ranges from 0 to 100 with lower scores reflective of better quality of life. Physical Health domain score is reported (range 0 to 100, with lower scores reflective of better physical health). The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variates: baseline score, treatment group, and treatment by baseline interaction term.

End point type	Secondary

End point timeframe:

Baseline, Week 25

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint applies to adults in the randomized population, and only participants in Arms A, B, and C were randomized in this study.

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	44.32 (± 17.15)	31.81 (± 27.86)	28.35 (± 25.57)	

Statistical analyses

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm B)
Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0349 [16]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	15.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	30.78

Notes:

[16] - Not controlled for type I error

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm A)
Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5

	mg/kg QW
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0891 [17]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	12.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	26.98

Notes:

[17] - Statistical significance is controlled at the 2-sided, 0.05 alpha level.

Secondary: Haem-A-QoL Questionnaire Total Score for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25

End point title	Haem-A-QoL Questionnaire Total Score for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25[18]

End point description:

The Haem-A-QoL questionnaire has been developed and used in hemophilia A participants, assessing very specific aspects of dealing with hemophilia. The questionnaire consists of items pertaining to 10 domains: physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain ranges from 0 to 100 with lower scores reflective of better quality of life. Haem-A-QoL Total Score is the average of all domain scores and it ranges from 0 to 100, with lower scores reflective of better quality of life. The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variates: baseline score, treatment group, and treatment by baseline interaction term.

End point type	Secondary

End point timeframe:

Baseline, Week 25

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint applies to adults in the randomized population, and only participants in Arms A, B, and C were randomized in this study.

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	29.95 (± 13.56)	24.04 (± 15.26)	21.39 (± 12.64)	

Statistical analyses

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm A)
Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5

	mg/kg QW
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1269 [19]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.72
upper limit	13.55

Notes:

[19] - Not controlled for type I error

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm B)
Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0317 [20]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	16.35

Notes:

[20] - Not controlled for type I error

Secondary: European Quality of Life 5-Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score in the Randomized Population at Week 25

End point title	European Quality of Life 5-Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score in the Randomized Population at Week 25[21]

End point description:

EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L VAS. The VAS is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variates: baseline score, treatment group, and treatment by baseline interaction term.

End point type	Secondary

End point timeframe:

Baseline, Week 25

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint applies to the randomized population, and only participants in Arms A, B, and C were randomized in this study.

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	72.57 (± 8.20)	76.61 (± 20.99)	81.72 (± 15.55)	

Statistical analyses

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm A)
Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3402 [22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.43
upper limit	4.35

Notes:

[22] - Not controlled for type I error

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm B)
Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0373 [23]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.74
upper limit	-0.55

Notes:

[23] - Not controlled for type I error

Secondary: EQ-5D-5L Questionnaire Index Utility Score in the Randomized Population at Week 25

End point title	EQ-5D-5L Questionnaire Index Utility Score in the Randomized Population at Week 25[24]

End point description:

EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L VAS. The EQ-5D-5L health state profile is designed to record the participant's current health state in 5 domains: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Responses from the five domains are used to calculate a single index utility score on a scale of 0 to 1, with higher scores reflective of better quality of life. The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variates: baseline score, treatment group, and treatment by baseline interaction term.

End point type	Secondary

End point timeframe:

Baseline, Week 25

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to the randomized population, and only participants in Arms A, B, and C were randomized in this study.

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	0.63 (± 0.20)	0.76 (± 0.24)	0.76 (± 0.18)	

Statistical analyses

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm A)
Comparison groups	Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [25]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	-0.04

Notes:

[25] - Not controlled for type I error

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm B)
Comparison groups	Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059 [26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	-0.04

Notes:

[26] - Not controlled for type I error

Secondary: Hemophilia-Specific Quality of Life - Short Form (Haemo-QoL-SF) Questionnaire Score in Adolescent Participants (12 to 17 Years of Age) in the Randomized Population at Week 25

End point title	Hemophilia-Specific Quality of Life - Short Form (Haemo-QoL-SF) Questionnaire Score in Adolescent Participants (12 to 17 Years of Age) in the Randomized Population at Week 25[27]

End point description:

The Haemo-QoL-SF contains 35 items, which cover nine domains considered relevant for the children's health-related quality of life (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated with five respective response options: never, seldom, sometimes, often, and always. Haemo-QoL-SF total score range from 0 to 100, where lower scores reflect better health-related quality of life. The analysis was not performed due to the small number of adolescents randomized or enrolled in this study.

End point type	Secondary

End point timeframe:

Week 25

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint applies to adolescents in the randomized population, and only participants in Arms A, B, and C were randomized in this study.

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[28]	0[29]	0[30]	
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[28] - Analysis was not performed due to small number of adolescents randomized to this study.

[29] - Analysis was not performed due to small number of adolescents randomized to this study.

[30] - Analysis was not performed due to small number of adolescents randomized to this study.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Adverse Event During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Adverse Event During the First 24 Weeks of the Study, Primary Analysis

End point description:

The percentage of participants experiencing at least one adverse event, including all non-serious and serious adverse events, is reported here. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	33.3	94.4	85.7	87.3

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	50.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Grade ≥3 Adverse Event During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Grade ≥3 Adverse Event During the First 24 Weeks of the Study, Primary Analysis

End point description:

The World Health Organization (WHO) toxicity grading scale will be used for assessing adverse event severity. For adverse events that are not specifically listed in the WHO toxicity grading scale, a grade 3 adverse event is defined as: severe, marked limitation in activity, some assistance usually required, medical intervention or therapy required, hospitalization possible; and a grade 4 adverse event is defined as: life-threatening, extreme limitation in activity, significant assistance required, significant medical intervention or therapy required, hospitalization or hospice care probable. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	5.6	8.3	11.4	9.3

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Adverse Event Leading to Withdrawal From Treatment During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Adverse Event

Leading to Withdrawal From Treatment During the First 24 Weeks of the Study, Primary Analysis

End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	2.9	0

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Vital Signs During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Vital Signs During the First 24 Weeks of the Study, Primary Analysis

End point description:

The percentage of participants with adverse events of changes from baseline in vital signs is reported here. Vital signs measurements consisted of heart and respiratory rate, temperature, and systolic and diastolic blood pressures, with an abnormal vital sign value being outside of the normal range. An abnormal vital sign result is reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); results in a medical intervention or a change in concomitant therapy; or is clinically significant in the investigator's judgment. At the clinical cut-off date for primary

analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at Least One Adverse Event of Abnormal Laboratory Values During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants with at Least One Adverse Event of Abnormal Laboratory Values During the First 24 Weeks of the Study, Primary Analysis

End point description:

The percentage of participants with adverse events of abnormal laboratory values is reported here. An abnormal laboratory value is defined as a laboratory test result outside of the normal range for hematology or serum chemistries. It is reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); results in a medical intervention or a change in concomitant therapy; or is clinically significant in the investigator's judgment. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	5.6	17.1	4.8

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	6.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Physical Examination Findings During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Physical Examination Findings During the First 24 Weeks of the Study, Primary Analysis

End point description:

Post-baseline physical examination abnormalities that were not present at baseline or worsened were reported as adverse events. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Local Injection-Site Reaction During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Local Injection-Site Reaction During the First 24 Weeks of the Study, Primary Analysis

End point description:

Local adverse events that occurred within 24 hours after study drug administration and, in the investigator's opinion, were judged to be related to study drug injection, were captured as an "injection-site reaction" on the Adverse Event electronic Case Report Form (eCRF). An injection-related reaction that was localized was marked as a "local injection-site reaction." At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63

Units: percentage of participants				
number (not applicable)	0	25.0	20.0	33.3

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	12.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Thrombotic Microangiopathy During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Thrombotic Microangiopathy During the First 24 Weeks of the Study, Primary Analysis

End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to			

	PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Thromboembolic Event During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Thromboembolic Event During the First 24 Weeks of the Study, Primary Analysis

End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction During the First 24 Weeks of the Study, Primary Analysis

End point title	Percentage of Participants With at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction During the First 24 Weeks of the Study, Primary Analysis

End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type	Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

End point values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Summary of the Percentage of Emicizumab-Treated Participants With at Least One Adverse Event During the Study

End point title	Safety Summary of the Percentage of Emicizumab-Treated Participants With at Least One Adverse Event During the Study[31]

End point description:

Investigators sought information on adverse events (AEs) at each contact with participants. The WHO toxicity grading scale was used for assessing AE severity (i.e., intensity of an AE); any AEs not specifically listed in the WHO toxicity grading scale were assessed for severity according to the following grades: Grade 1 is mild; Grade 2 is moderate, Grade 3 is severe; Grade 4 is life-threatening; and Grade 5 is death. Regardless of severity, some AEs may have also met seriousness criteria. The terms "severe" and "serious" are not synonymous; severity and seriousness were independently assessed for each AE. For participants whose emicizumab dose was up-titrated and those who opted for a change in dosing regimen (after implementation of protocol v4), only AEs that occurred before either one of those events are included. Hypersens.= hypersensitivity; Mod. = modification

End point type	Secondary

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

End point values	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	17
Units: percentage of participants				
number (not applicable)				
Any Adverse Event (AE)	100.0	97.1	100.0	88.2
AE with Fatal Outcome	0.0	0.0	0.0	0.0
Serious AE	27.8	22.9	25.4	5.9
AE Leading to Withdrawal from Treatment	0.0	2.9	0.0	0.0
AE Leading to Dose Mod./Interruption	2.8	0.0	1.6	0.0
Grade ≥3 AE	36.1	28.6	20.6	5.9
Related AE	30.6	34.3	47.6	23.5
Local Injection Site Reaction	27.8	22.9	39.7	23.5
Systemic Hypersens./Anaphylac(tic/toid) Reaction	0.0	0.0	0.0	0.0
Thromboembolic Event (TE)	0.0	2.9	1.6	0.0
Thrombotic Microangiopathy (TMA)	0.0	0.0	0.0	0.0

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: percentage of participants				
number (not applicable)				
Any Adverse Event (AE)	98.0			
AE with Fatal Outcome	0.0			
Serious AE	23.2			

AE Leading to Withdrawal from Treatment	0.7			
AE Leading to Dose Mod./Interruption	1.3			
Grade ≥3 AE	24.5			
Related AE	37.7			
Local Injection Site Reaction	31.1			
Systemic Hypersens./Anaphylac(tic/toid) Reaction	0.0			
Thromboembolic Event (TE)	1.3			
Thrombotic Microangiopathy (TMA)	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Model-Based Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Model-Based Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants[32]

End point description:

The number of bleeds over the efficacy period was assessed as an ABR using a negative binomial (NB) regression model, which accounts for different follow-up times. Treated bleeds: a bleed for which coagulation factors were administered. All bleeds included both treated and non-treated bleeds. Treated spontaneous bleeds: treated bleeds with no known contributing factor (e.g., trauma, surgery). Treated joint bleeds: treated bleeds in a joint associated with unusual sensation (aura) in a joint, in combination with another symptom: swelling/warmth, pain/decreased range of motion (RoM), or difficulty moving the joint. Treated target joint bleeds: treated joint bleeds in a target joint, defined as a joint in which greater than or equal to (≥) 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. For all types of bleeds: the 72-hour rule was implemented, and bleeds due to surgery/procedure and bleeds after up-titration or change of dosing regimen were excluded.

End point type	Secondary

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

End point values	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	17
Units: bleeds per year				
number (confidence interval 95%)				
Treated Bleeds	0.8 (0.48 to 1.29)	0.7 (0.40 to 1.08)	1.5 (1.02 to 2.34)	1.2 (0.47 to 3.19)

All Bleeds	1.1 (0.72 to 1.66)	1.1 (0.73 to 1.73)	2.4 (1.68 to 3.43)	2.2 (1.16 to 4.15)
Treated Spontaneous Bleeds	0.5 (0.23 to 1.03)	0.2 (0.10 to 0.45)	0.5 (0.30 to 0.78)	0.4 (0.12 to 1.35)
Treated Joint Bleeds	0.4 (0.24 to 0.73)	0.4 (0.21 to 0.68)	1.0 (0.60 to 1.76)	0.7 (0.25 to 1.66)
Treated Target Joint Bleeds	0.2 (0.11 to 0.43)	0.2 (0.08 to 0.39)	0.6 (0.26 to 1.42)	0.4 (0.13 to 1.31)

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: bleeds per year				
number (confidence interval 95%)				
Treated Bleeds	1.2 (0.92 to 1.56)			
All Bleeds	1.8 (1.46 to 2.29)			
Treated Spontaneous Bleeds	0.4 (0.29 to 0.58)			
Treated Joint Bleeds	0.7 (0.53 to 1.00)			
Treated Target Joint Bleeds	0.4 (0.29 to 0.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants[33]

End point description:

The number of bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated bleeds: a bleed for which coagulation factors were administered. All bleeds included both treated and non-treated bleeds. Treated spontaneous bleeds: treated bleeds with no known contributing factor (e.g., trauma, surgery). Treated joint bleeds: treated bleeds in a joint associated with unusual sensation (aura) in a joint, in combination with another symptom: swelling/warmth, pain/decreased range of motion (RoM), or difficulty moving the joint. Treated target joint bleeds: treated joint bleeds in a target joint, defined as a joint in which greater than or equal to (≥) 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. For all types of bleeds: the 72-hour rule was implemented, and bleeds due to surgery/procedure and bleeds after up-titration or change of dosing regimen were excluded.

End point type	Secondary

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

End point values	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	17
Units: bleeds per year				
arithmetic mean (confidence interval 95%)				
Treated Bleeds	1.2 (0.04 to 5.83)	0.8 (0.01 to 5.23)	1.7 (0.15 to 6.69)	1.2 (0.05 to 5.95)
All Bleeds	1.4 (0.09 to 6.29)	1.3 (0.07 to 6.10)	2.6 (0.45 to 8.15)	2.2 (0.32 to 7.58)
Treated Spontaneous Bleeds	0.7 (0.00 to 4.97)	0.3 (0.00 to 4.22)	0.6 (0.00 to 4.81)	0.4 (0.00 to 4.48)
Treated Joint Bleeds	0.6 (0.00 to 4.94)	0.5 (0.00 to 4.64)	1.1 (0.04 to 5.78)	0.6 (0.00 to 4.95)
Treated Target Joint Bleeds	0.4 (0.00 to 4.54)	0.3 (0.00 to 4.28)	0.6 (0.00 to 4.92)	0.4 (0.00 to 4.50)

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: bleeds per year				
arithmetic mean (confidence interval 95%)				
Treated Bleeds	1.3 (0.07 to 6.07)			
All Bleeds	2.0 (0.23 to 7.19)			
Treated Spontaneous Bleeds	0.5 (0.00 to 4.68)			
Treated Joint Bleeds	0.8 (0.01 to 5.23)			
Treated Target Joint Bleeds	0.5 (0.00 to 4.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants[34]

End point description:

The number of bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated bleeds: a bleed for which coagulation factors were administered. All bleeds included both treated and non-treated bleeds. Treated spontaneous bleeds: treated bleeds with no known contributing factor (e.g., trauma, surgery). Treated joint bleeds: treated bleeds in a joint associated with unusual sensation (aura) in a joint, in combination with another symptom: swelling/warmth, pain/decreased range of motion (RoM), or difficulty moving the joint. Treated target joint bleeds: treated joint bleeds in a target joint, defined as a joint in which greater than or equal to (≥) 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. For all types of bleeds: the 72-hour rule was implemented, and bleeds due to surgery/procedure and bleeds after up-titration or change of dosing regimen were excluded.

End point type	Secondary

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

End point values	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	17
Units: bleeds per year				
median (inter-quartile range (Q1-Q3))				
Treated Bleeds	0.4 (0.00 to 1.28)	0.4 (0.00 to 1.06)	0.5 (0.00 to 1.07)	0.0 (0.00 to 2.48)
All Bleeds	0.5 (0.09 to 1.77)	0.8 (0.23 to 1.92)	1.0 (0.38 to 2.70)	1.6 (0.20 to 3.8)
Treated Spontaneous Bleeds	0.0 (0.00 to 0.51)	0.0 (0.00 to 0.23)	0.0 (0.00 to 0.48)	0.0 (0.00 to 0.65)
Treated Joint Bleeds	0.2 (0.00 to 0.89)	0.2 (0.00 to 0.49)	0.0 (0.00 to 0.59)	0.0 (0.00 to 1.09)
Treated Target Joint Bleeds	0.1 (0.00 to 0.55)	0.0 (0.00 to 0.37)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.81)

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: bleeds per year				
median (inter-quartile range (Q1-Q3))				
Treated Bleeds	0.4 (0.00 to 1.15)			
All Bleeds	1.0 (0.19 to 2.37)			

Treated Spontaneous Bleeds	0.0 (0.00 to 0.40)			
Treated Joint Bleeds	0.2 (0.00 to 0.72)			
Treated Target Joint Bleeds	0.0 (0.00 to 0.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point description:

The number of treated bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated bleeds: a bleed for which coagulation factors were administered. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Treated bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 150)	1.9 (0.21 to 7.04)			
13 to 24 Weeks (n = 148)	1.9 (0.20 to 6.99)			
25 to 36 Weeks (n = 144)	1.0 (0.02 to 5.57)			
37 to 48 Weeks (n = 144)	0.9 (0.01 to 5.35)			
49 to 60 Weeks (n = 142)	1.0 (0.02 to 5.54)			
61 to 72 Weeks (n = 140)	1.1 (0.04 to 5.72)			
73 to 84 Weeks (n = 140)	0.7 (0.01 to 5.12)			

85 to 96 Weeks (n = 131)	1.1 (0.03 to 5.68)				
97 to 108 Weeks (n = 117)	0.9 (0.01 to 5.32)				
109 to 120 Weeks (n = 104)	0.6 (0.00 to 4.83)				
121 to 132 Weeks (n = 99)	0.5 (0.00 to 4.72)				
133 to 144 Weeks (n = 94)	1.1 (0.03 to 5.68)				
145 to 156 Weeks (n = 93)	1.1 (0.03 to 5.70)				
157 to 168 Weeks (n = 89)	1.1 (0.04 to 5.78)				
169 to 180 Weeks (n = 85)	1.3 (0.06 to 6.05)				
181 to 192 Weeks (n = 83)	1.0 (0.02 to 5.56)				
193 to 204 Weeks (n = 82)	1.6 (0.13 to 6.57)				
205 to 216 Weeks (n = 80)	0.8 (0.01 to 5.15)				
217 to 228 Weeks (n = 76)	0.5 (0.00 to 4.59)				
229 to 240 Weeks (n = 72)	0.8 (0.01 to 5.30)				
241 to 252 Weeks (n = 67)	0.3 (0.00 to 4.21)				
253 to 264 Weeks (n = 58)	0.5 (0.00 to 4.72)				
265 to 276 Weeks (n = 22)	0.2 (0.00 to 4.09)				
277 to 288 Weeks (n = 5)	0.0 (0.0 to 3.69)				

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point description:

The number of treated bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated bleeds: a bleed for which coagulation factors were administered. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Treated bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 150)	0.0 (0.00 to 4.35)			
13 to 24 Weeks (n = 148)	0.0 (0.00 to 2.17)			
25 to 36 Weeks (n = 144)	0.0 (0.00 to 0.00)			
37 to 48 Weeks (n = 144)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 142)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 140)	0.0 (0.00 to 0.00)			
73 to 84 Weeks (n = 140)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 131)	0.0 (0.00 to 0.00)			
97 to 108 Weeks (n = 117)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 104)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 99)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 94)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 93)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 89)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 85)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 83)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 82)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 80)	0.0 (0.00 to 0.00)			
217 to 228 Weeks (n = 76)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 72)	0.0 (0.00 to 0.00)			
241 to 252 Weeks (n = 67)	0.0 (0.00 to 0.00)			
253 to 264 Weeks (n = 58)	0.0 (0.00 to 0.00)			
265 to 276 Weeks (n = 22)	0.0 (0.00 to 0.00)			
277 to 288 Weeks (n = 5)	0.0 (0.00 to 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for All Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for All Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point description:

The number of all bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. All bleeds included both treated bleeds (with coagulation factors) and non-treated bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: All bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 150)	3.8 (0.97 to 9.91)			
13 to 24 Weeks (n = 148)	2.8 (0.53 to 8.45)			
25 to 36 Weeks (n = 144)	1.8 (0.17 to 6.83)			
37 to 48 Weeks (n = 144)	1.4 (0.10 to 6.33)			
49 to 60 Weeks (n = 142)	1.5 (0.10 to 6.37)			
61 to 72 Weeks (n = 140)	1.6 (0.14 to 6.66)			
73 to 84 Weeks (n = 140)	1.2 (0.05 to 5.88)			
85 to 96 Weeks (n = 131)	1.4 (0.09 to 6.30)			

97 to 108 Weeks (n = 117)	1.3 (0.06 to 6.02)				
109 to 120 Weeks (n = 104)	0.8 (0.01 to 5.21)				
121 to 132 Weeks (n = 99)	0.8 (0.01 to 5.20)				
133 to 144 Weeks (n = 94)	1.2 (0.04 to 5.84)				
145 to 156 Weeks (n = 93)	1.3 (0.06 to 6.02)				
157 to 168 Weeks (n = 89)	1.4 (0.09 to 6.28)				
169 to 180 Weeks (n = 85)	1.7 (0.15 to 6.72)				
181 to 192 Weeks (n = 83)	1.4 (0.08 to 6.19)				
193 to 204 Weeks (n = 82)	1.7 (0.16 to 6.74)				
205 to 216 Weeks (n = 80)	1.1 (0.04 to 5.72)				
217 to 228 Weeks (n = 76)	0.6 (0.00 to 4.91)				
229 to 240 Weeks (n = 72)	0.9 (0.02 to 5.41)				
241 to 252 Weeks (n = 67)	0.4 (0.00 to 4.47)				
253 to 264 Weeks (n = 58)	0.6 (0.00 to 4.86)				
265 to 276 Weeks (n = 22)	0.2 (0.00 to 4.09)				
277 to 288 Weeks (n = 5)	0.0 (0.0 to 3.69)				

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for All Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for All Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point description:

The number of all bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. All bleeds included both treated bleeds (with coagulation factors) and non-treated bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: All bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 150)	0.0 (0.00 to 4.35)			
13 to 24 Weeks (n = 148)	0.0 (0.00 to 4.35)			
25 to 36 Weeks (n = 144)	0.0 (0.00 to 4.35)			
37 to 48 Weeks (n = 144)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 142)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 140)	0.0 (0.00 to 0.00)			
73 to 84 Weeks (n = 140)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 131)	0.0 (0.00 to 0.00)			
97 to 108 Weeks (n = 117)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 104)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 99)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 94)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 93)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 89)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 85)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 83)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 82)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 80)	0.0 (0.00 to 0.00)			
217 to 228 Weeks (n = 76)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 72)	0.0 (0.00 to 0.00)			
241 to 252 Weeks (n = 67)	0.0 (0.00 to 0.00)			
253 to 264 Weeks (n = 58)	0.0 (0.00 to 0.00)			
265 to 276 Weeks (n = 22)	0.0 (0.00 to 0.00)			
277 to 288 Weeks (n = 5)	0.0 (0.00 to 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point description:

The number of treated spontaneous bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated spontaneous bleeds were defined as treated (with coagulation factors) bleeds with no known contributing factor (e.g., trauma, surgery). The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Treated spontaneous bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 150)	0.7 (0.00 to 4.98)			
13 to 24 Weeks (n = 148)	0.7 (0.00 to 5.00)			
25 to 36 Weeks (n = 144)	0.3 (0.00 to 4.30)			
37 to 48 Weeks (n = 144)	0.4 (0.00 to 4.53)			
49 to 60 Weeks (n = 142)	0.5 (0.00 to 4.60)			
61 to 72 Weeks (n = 140)	0.3 (0.00 to 4.25)			
73 to 84 Weeks (n = 140)	0.1 (0.00 to 3.95)			
85 to 96 Weeks (n = 131)	0.4 (0.00 to 4.48)			

97 to 108 Weeks (n = 117)	0.2 (0.00 to 4.14)				
109 to 120 Weeks (n = 104)	0.2 (0.00 to 4.03)				
121 to 132 Weeks (n = 99)	0.1 (0.00 to 3.96)				
133 to 144 Weeks (n = 94)	0.6 (0.00 to 4.78)				
145 to 156 Weeks (n = 93)	0.6 (0.00 to 4.87)				
157 to 168 Weeks (n = 89)	0.2 (0.00 to 4.09)				
169 to 180 Weeks (n = 85)	0.4 (0.00 to 4.50)				
181 to 192 Weeks (n = 83)	0.2 (0.00 to 4.01)				
193 to 204 Weeks (n = 82)	0.1 (0.00 to 3.80)				
205 to 216 Weeks (n = 80)	0.3 (0.00 to 4.24)				
217 to 228 Weeks (n = 76)	0.1 (0.00 to 3.81)				
229 to 240 Weeks (n = 72)	0.1 (0.00 to 3.94)				
241 to 252 Weeks (n = 67)	0.1 (0.00 to 3.82)				
253 to 264 Weeks (n = 58)	0.3 (0.00 to 4.29)				
265 to 276 Weeks (n = 22)	0.2 (0.00 to 4.09)				
277 to 288 Weeks (n = 5)	0.0 (0.0 to 3.69)				

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants

End point description:

The number of treated spontaneous bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated spontaneous bleeds were defined as treated (with coagulation factors) bleeds with no known contributing factor (e.g., trauma, surgery). The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Treated spontaneous bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 150)	0.0 (0.00 to 0.00)			
13 to 24 Weeks (n = 148)	0.0 (0.00 to 0.00)			
25 to 36 Weeks (n = 144)	0.0 (0.00 to 0.00)			
37 to 48 Weeks (n = 144)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 142)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 140)	0.0 (0.00 to 0.00)			
73 to 84 Weeks (n = 140)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 131)	0.0 (0.00 to 0.00)			
97 to 108 Weeks (n = 117)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 104)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 99)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 94)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 93)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 89)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 85)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 83)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 82)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 80)	0.0 (0.00 to 0.00)			
217 to 228 Weeks (n = 76)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 72)	0.0 (0.00 to 0.00)			
241 to 252 Weeks (n = 67)	0.0 (0.00 to 0.00)			
253 to 264 Weeks (n = 58)	0.0 (0.00 to 0.00)			
265 to 276 Weeks (n = 22)	0.0 (0.00 to 0.00)			
277 to 288 Weeks (n = 5)	0.0 (0.00 to 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Emicizumab Antibodies at Any Time Post-Baseline During the Study

End point title	Percentage of Participants With Anti-Emicizumab Antibodies at Any Time Post-Baseline During the Study[35]

End point description:

A validated enzyme-linked immunosorbent assay (ELISA) method was used to analyze the levels of anti-drug antibodies (ADAs) against emicizumab in plasma. A sample was considered positive for anti-emicizumab antibodies if the test result reached or exceeded a pre-determined threshold. 'Total ADA Positive' is the sum of all subjects who tested positive for ADA in the 2 following categories: 'ADA Positive (Treatment Boosted)', those who are pre-dose ADA positive and have a ≥4-fold increase in post-dose ADA levels compared to baseline measurement; and 'ADA Positive (Treatment Induced)', those who are pre-dose ADA negative or missing data and who have at least one post-dose ADA positive sample.

End point type	Secondary

End point timeframe:

From Baseline to discontinuation from study (median [min-max] observation period for all emicizumab participants: 262.3 [14.4-288.3] weeks)

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

End point values	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	17
Units: percentage of participants				
number (not applicable)				
Total ADA Positive (Boosted+Induced)	8.3	5.7	1.6	0.0
ADA Positive (Treatment Boosted)	0.0	2.9	0.0	0.0
ADA Positive (Treatment Induced)	8.3	2.9	1.6	0.0

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: percentage of participants				
number (not applicable)				

Total ADA Positive (Boosted+Induced)	4.0			
ADA Positive (Treatment Boosted)	0.7			
ADA Positive (Treatment Induced)	3.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With De Novo Development of Factor VIII (FVIII) Inhibitors

End point title	Percentage of Participants With De Novo Development of Factor VIII (FVIII) Inhibitors[36]

End point description:

Levels of anti-FVIII antibodies (inhibitors) were analyzed using a validated FVIII activity assay. A participant was considered to have developed de novo FVIII inhibitors if the inhibitor levels detected in a post-baseline sample reached or exceeded a pre-determined threshold.

End point type	Secondary

End point timeframe:

From Baseline to discontinuation from study (median [min-max] observation period for all emicizumab participants: 262.3 [14.4-288.3] weeks)

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

End point values	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	17
Units: percentage of participants				
number (not applicable)	0.0	0.0	0.0	0.0

End point values	All Emicizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of Emicizumab

End point title	Trough Plasma Concentration (Ctrough) of Emicizumab[37]

End point description:

Trough plasma concentrations of emicizumab were analyzed using a validated Enzyme Linked Immunosorbent Assay (ELISA). The lower limit of quantification (LLOQ) was 100 nanograms per milliliter (ng/mL). Because participants in Arm C (Control) switched from no prophylaxis to start receiving emicizumab prophylaxis after Week 24, the timepoints for Arm C (Emi) are expressed relative to first emicizumab dose. The pharmacokinetic (PK) evaluable population included all participants who received at least one dose of emicizumab and had at least one post-dose emicizumab concentration result. Here, n=participants with available data for this endpoint at specified timepoints in each arm (A, B, D, Cemi), respectively. Here, '999999' represents no data available because no patient samples were taken at that timepoint.

End point type	Secondary

End point timeframe:

Predose at Weeks 1, 2, 3, 4, 5, 7, 9, 13, 17, 21, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, 229, 241, 253, 265, and 277

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

End point values	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	17
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=35,35,61,17,96,52)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Week 2 (n=36,35,62,17,98,52)	16.3 (± 6.1)	16.8 (± 5.9)	17.3 (± 5.4)	19.6 (± 8.2)
Week 3 (n=36,35,62,17,98,52)	29.1 (± 9.3)	29.2 (± 6.5)	30.5 (± 8.7)	33.0 (± 12.6)
Week 4 (n=36,35,62,17,98,52)	41.9 (± 11.8)	41.4 (± 9.7)	42.4 (± 9.4)	47.9 (± 15.0)
Week 5 (n=34,35,62,17,96,52)	48.0 (± 13.7)	48.8 (± 12.3)	54.5 (± 12.5)	59.6 (± 20.7)
Week 7 (n=32,33,61,17,93,50)	47.9 (± 16.1)	48.4 (± 11.4)	52.4 (± 13.3)	55.2 (± 16.2)
Week 9 (n=33,34,63,17,96,51)	49.0 (± 16.4)	46.4 (± 14.1)	55.1 (± 16.1)	53.1 (± 15.7)
Week 13 (n=33,34,63,17,96,51)	48.7 (± 18.3)	47.6 (± 16.0)	55.0 (± 15.9)	47.9 (± 18.1)
Week 17 (n=33,34,62,17,95,51)	54.3 (± 24.0)	48.9 (± 17.7)	55.0 (± 16.5)	43.4 (± 16.2)
Week 21 (n=32,34,61,16,93,50)	50.7 (± 20.2)	47.3 (± 15.5)	55.1 (± 16.2)	45.6 (± 18.8)
Week 25 (n=31,34,58,17,89,51)	50.5 (± 21.7)	47.6 (± 18.9)	54.8 (± 16.8)	51.8 (± 23.4)
Week 33 (n=30,34,58,16,88,50)	56.3 (± 25.3)	52.9 (± 22.4)	59.1 (± 18.5)	52.0 (± 21.3)
Week 41 (n=31,34,58,17,89,51)	54.8 (± 24.2)	48.4 (± 18.8)	59.6 (± 21.4)	50.7 (± 24.4)
Week 49 (n=31,32,58,17,89,49)	55.4 (± 22.9)	52.2 (± 20.2)	60.2 (± 19.9)	54.3 (± 21.3)
Week 61 (n=31,33,57,17,88,50)	55.3 (± 21.4)	52.0 (± 21.1)	61.1 (± 22.5)	52.5 (± 19.8)
Week 73 (n=31,32,57,15,88,47)	54.4 (± 21.5)	51.6 (± 21.3)	58.5 (± 19.2)	47.8 (± 18.4)
Week 85 (n=31,32,55,13,86,45)	48.8 (± 17.4)	46.4 (± 20.4)	56.7 (± 18.5)	47.7 (± 17.9)
Week 97 (n=28,29,48,11,76,40)	52.6 (± 20.0)	50.9 (± 21.0)	58.5 (± 18.7)	51.7 (± 28.3)
Week 109 (n=26,26,39,11,65,37)	53.9 (± 19.2)	52.3 (± 19.5)	59.0 (± 19.1)	46.4 (± 27.0)
Week 121 (n=23,24,37,10,60,34)	58.8 (± 21.1)	55.0 (± 22.0)	57.1 (± 18.2)	50.0 (± 25.2)
Week 133 (n=23,23,34,10,57,33)	55.3 (± 26.0)	54.7 (± 18.5)	59.3 (± 19.2)	54.6 (± 26.9)
Week 145 (n=23,22,33,6,56,28)	54.1 (± 23.7)	51.3 (± 17.7)	55.7 (± 20.4)	44.8 (± 11.6)
Week 157 (n=19,21,30,9,49,30)	57.6 (± 27.8)	52.2 (± 21.4)	55.9 (± 23.7)	46.8 (± 24.0)

Week 169 (n=16,16,22,8,38,24)	53.9 (± 21.8)	50.3 (± 19.6)	56.4 (± 18.0)	45.8 (± 20.6)
Week 181 (n=15,11,17,8,32,19)	59.8 (± 24.8)	48.8 (± 22.1)	57.5 (± 21.3)	43.5 (± 26.2)
Week 193 (n=17,18,21,7,38,25)	53.9 (± 21.0)	52.4 (± 24.6)	60.5 (± 19.6)	42.1 (± 19.1)
Week 205 (n=18,20,23,8,41,28)	53.5 (± 20.8)	51.9 (± 22.4)	58.6 (± 24.1)	54.2 (± 31.1)
Week 217 (n=16,19,26,9,42,28)	54.4 (± 20.8)	55.0 (± 20.6)	60.8 (± 23.2)	50.8 (± 26.1)
Week 229 (n=17,17,26,9,43,26)	54.9 (± 20.9)	47.9 (± 18.9)	54.4 (± 19.3)	53.5 (± 30.4)
Week 241 (n=16,18,24,6,40,24)	51.9 (± 19.3)	50.2 (± 16.8)	60.1 (± 23.3)	52.0 (± 36.1)
Week 253 (n=15,15,22,4,37,19)	58.6 (± 28.7)	46.5 (± 17.8)	58.4 (± 24.7)	40.3 (± 43.9)
Week 265 (n=10,13,17,0,27,13)	58.7 (± 25.8)	47.3 (± 14.5)	60.0 (± 23.9)	999999 (± 999999)
Week 277 (n=6,5,2,0,8,5)	71.9 (± 34.2)	49.0 (± 16.2)	61.3 (± 17.2)	999999 (± 999999)

End point values	Arms A and D: Emicizumab 1.5 mg/kg QW	Arms B and C (Emi): Emicizumab 3 mg/kg Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	52		
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=35,35,61,17,96,52)	0 (± 0)	0 (± 0)		
Week 2 (n=36,35,62,17,98,52)	16.9 (± 5.7)	17.7 (± 6.8)		
Week 3 (n=36,35,62,17,98,52)	30.0 (± 8.9)	30.5 (± 9.0)		
Week 4 (n=36,35,62,17,98,52)	42.2 (± 10.3)	43.6 (± 11.9)		
Week 5 (n=34,35,62,17,96,52)	52.2 (± 13.2)	52.4 (± 16.2)		
Week 7 (n=32,33,61,17,93,50)	50.9 (± 14.4)	50.7 (± 13.5)		
Week 9 (n=33,34,63,17,96,51)	53.0 (± 16.4)	48.7 (± 14.9)		
Week 13 (n=33,34,63,17,96,51)	52.8 (± 16.9)	47.7 (± 16.5)		
Week 17 (n=33,34,62,17,95,51)	54.7 (± 19.3)	47.0 (± 17.2)		
Week 21 (n=32,34,61,16,93,50)	53.6 (± 17.7)	46.7 (± 16.4)		
Week 25 (n=31,34,58,17,89,51)	53.3 (± 18.7)	49.0 (± 20.4)		
Week 33 (n=30,34,58,16,88,50)	58.1 (± 20.9)	52.6 (± 21.9)		
Week 41 (n=31,34,58,17,89,51)	57.9 (± 22.4)	49.2 (± 20.6)		
Week 49 (n=31,32,58,17,89,49)	58.5 (± 21.0)	52.9 (± 20.4)		
Week 61 (n=31,33,57,17,88,50)	59.1 (± 22.1)	52.2 (± 20.5)		
Week 73 (n=31,32,57,15,88,47)	57.1 (± 20.0)	50.4 (± 20.3)		
Week 85 (n=31,32,55,13,86,45)	53.8 (± 18.5)	46.8 (± 19.5)		
Week 97 (n=28,29,48,11,76,40)	56.3 (± 19.3)	51.1 (± 22.9)		
Week 109 (n=26,26,39,11,65,37)	57.0 (± 19.1)	50.5 (± 21.7)		
Week 121 (n=23,24,37,10,60,34)	57.7 (± 19.2)	53.5 (± 22.7)		
Week 133 (n=23,23,34,10,57,33)	57.7 (± 22.1)	54.7 (± 20.9)		
Week 145 (n=23,22,33,6,56,28)	55.0 (± 21.6)	49.9 (± 16.6)		
Week 157 (n=19,21,30,9,49,30)	56.6 (± 25.1)	50.6 (± 21.9)		
Week 169 (n=16,16,22,8,38,24)	55.3 (± 19.4)	48.8 (± 19.6)		
Week 181 (n=15,11,17,8,32,19)	58.6 (± 22.7)	46.5 (± 23.4)		
Week 193 (n=17,18,21,7,38,25)	57.5 (± 20.2)	49.5 (± 23.3)		
Week 205 (n=18,20,23,8,41,28)	56.4 (± 22.6)	52.6 (± 24.6)		
Week 217 (n=16,19,26,9,42,28)	58.3 (± 22.2)	53.6 (± 22.1)		
Week 229 (n=17,17,26,9,43,26)	54.6 (± 19.7)	49.8 (± 23.1)		
Week 241 (n=16,18,24,6,40,24)	56.8 (± 21.9)	50.6 (± 22.2)		

Week 253 (n=15,15,22,4,37,19)	58.5 (± 26.0)	45.2 (± 23.9)			
Week 265 (n=10,13,17,0,27,13)	59.5 (± 24.2)	47.3 (± 14.5)			
Week 277 (n=6,5,2,0,8,5)	69.2 (± 30.1)	49.0 (± 16.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Total observation time for all participants: From enrollment until study completion (median [min-max] 262.3 [14.4-288.3] weeks); Arm C (Control): From enrollment to 24 weeks on no prophylaxis (median [min-max]: 24.00 [14.4-25.0] weeks)

Adverse event reporting additional description:

Adverse events (AEs) in emicizumab-treated subjects are reported from first dose until study completion, including after dose up-titration or change of dosing regimen. AEs in Arm C are reported in 2 groups: Arm C (Control) for the first 24 weeks on no prophylaxis; Arm C (Emi) for those who switched after 24 weeks to receive emicizumab prophylaxis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Arm C (Control): No Prophylaxis

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial; they were given the opportunity to switch to emicizumab prophylaxis after completing 24 weeks of no prophylaxis. The results for this control arm represent data collected during the first 24 weeks on study while receiving their usual care of episodic treatment with FVIII.

Reporting group title	Arm A: Emicizumab 1.5 mg/kg QW

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)

Reporting group description:

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)

Reporting group description:

This arm includes all participants from Arm C who switched to emicizumab prophylaxis after completing 24 weeks on No Prophylaxis. The data reported was collected only during emicizumab prophylaxis treatment. Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) SC QW for the first 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC Q2W. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Arm B: Emicizumab 3 mg/kg Q2W

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once

every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

Serious adverse events	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	10 / 36 (27.78%)	16 / 63 (25.40%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PARATHYROID TUMOUR BENIGN			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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
BONE GIANT CELL TUMOUR BENIGN			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAPILLARY THYROID CANCER			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALIVARY GLAND NEOPLASM			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	1 / 18 (5.56%)	1 / 36 (2.78%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE			

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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			
ASTHENIA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
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			
EPISTAXIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
SUICIDAL IDEATION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
DEVICE LOOSENING			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
Injury, poisoning and procedural complications			
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCLE STRAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
MUSCLE RUPTURE			

subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DURAL TEAR			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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
POISONING			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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			
ATRIAL FLUTTER			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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
ACUTE MYOCARDIAL INFARCTION			

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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

ACUTE CORONARY SYNDROME

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ARRHYTHMIA

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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

CEREBROSPINAL FLUID LEAKAGE

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

HEADACHE

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PUTAMEN HAEMORRHAGE

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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

SEIZURE

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CEREBRAL HAEMORRHAGE

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders

FISTULA OF SMALL INTESTINE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MELAENA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
GASTRIC HAEMORRHAGE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPLENIC ARTERY ANEURYSM			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATEMESIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHEZIA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL HAEMORRHAGE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETROPERITONEAL HAEMORRHAGE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALLORY-WEISS SYNDROME			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATURIA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETEROLITHIASIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL HAEMATOMA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

HYPERPARATHYROIDISM			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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			
GROIN PAIN			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNOVITIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
ABSCESS LIMB			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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

APPENDICITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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
ARTHRITIS BACTERIAL			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GINGIVAL ABSCESS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (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
SUBPERIOSTEAL ABSCESS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TONSILLITIS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DIABETES MELLITUS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (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

Serious adverse events	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)	Arm B: Emicizumab 3 mg/kg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	8 / 35 (22.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PARATHYROID TUMOUR BENIGN			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE GIANT CELL TUMOUR BENIGN			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAPILLARY THYROID CANCER			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SALIVARY GLAND NEOPLASM			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

ASTHENIA				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory, thoracic and mediastinal disorders				
EPISTAXIS				
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Psychiatric disorders				
SUICIDAL IDEATION				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Product issues				
DEVICE LOOSENING				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Injury, poisoning and procedural complications				
POST PROCEDURAL HAEMATOMA				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
MUSCLE STRAIN				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
MUSCLE RUPTURE				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
FEMORAL NECK FRACTURE				

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

DURAL TEAR

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

FEMUR FRACTURE

subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

POISONING

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

ROAD TRAFFIC ACCIDENT

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

TENDON RUPTURE

subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Cardiac disorders

ATRIAL FLUTTER

subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

ACUTE MYOCARDIAL INFARCTION

subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

ACUTE CORONARY SYNDROME

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARRHYTHMIA			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBROSPINAL FLUID LEAKAGE			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PUTAMEN HAEMORRHAGE			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
FISTULA OF SMALL INTESTINE			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			

subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
GASTRIC HAEMORRHAGE				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
SPLENIC ARTERY ANEURYSM				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
HAEMATEMESIS				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
HAEMATOCHEZIA				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
RECTAL HAEMORRHAGE				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
ANAL HAEMORRHAGE				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
PANCREATITIS				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
RETROPERITONEAL HAEMORRHAGE				

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
MALLORY-WEISS SYNDROME				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
UPPER GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal and urinary disorders				
NEPHROLITHIASIS				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
HAEMATURIA				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
URETEROLITHIASIS				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
RENAL HAEMATOMA				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Endocrine disorders				
HYPERPARATHYROIDISM				
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Musculoskeletal and connective tissue disorders			
GROIN PAIN			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNOVITIS			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS LIMB			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ARTHRITIS BACTERIAL		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
GINGIVAL ABSCESS		
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
SUBPERIOSTEAL ABSCESS		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
TONSILLITIS		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
WOUND INFECTION		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
INFECTION		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolism and nutrition disorders		
DIABETES MELLITUS		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	35 / 36 (97.22%)	61 / 63 (96.83%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PAPILLOMA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
HYPERTENSION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	4 / 63 (6.35%)
occurrences (all)	0	1	4
General disorders and administration site conditions			
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	2 / 63 (3.17%)
occurrences (all)	0	0	2
PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	2 / 63 (3.17%)
occurrences (all)	0	1	2
PYREXIA			
subjects affected / exposed	0 / 18 (0.00%)	4 / 36 (11.11%)	6 / 63 (9.52%)
occurrences (all)	0	4	7
ASTHENIA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
INJECTION SITE REACTION			
subjects affected / exposed	0 / 18 (0.00%)	10 / 36 (27.78%)	24 / 63 (38.10%)
occurrences (all)	0	37	42
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	2 / 63 (3.17%)
occurrences (all)	0	1	2
DRUG HYPERSENSITIVITY			

subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
HYPERSENSITIVITY			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
ERECTILE DYSFUNCTION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
NASAL CONGESTION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	2 / 63 (3.17%)
occurrences (all)	0	0	2
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	6 / 63 (9.52%)
occurrences (all)	0	1	12
COUGH			
subjects affected / exposed	0 / 18 (0.00%)	4 / 36 (11.11%)	7 / 63 (11.11%)
occurrences (all)	0	7	9
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	4 / 63 (6.35%)
occurrences (all)	0	0	4
SLEEP DISORDER			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0
INSOMNIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	2 / 63 (3.17%)
occurrences (all)	0	1	2
ANXIETY			
subjects affected / exposed	0 / 18 (0.00%)	4 / 36 (11.11%)	4 / 63 (6.35%)
occurrences (all)	0	4	7
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0

BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	5 / 63 (7.94%)
occurrences (all)	0	2	5
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	3 / 63 (4.76%)
occurrences (all)	0	1	3
BLOOD PRESSURE DIASTOLIC INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	4 / 63 (6.35%)
occurrences (all)	0	2	4
Injury, poisoning and procedural complications			
BITE			
subjects affected / exposed	1 / 18 (5.56%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences (all)	1	0	2
LIMB INJURY			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	3 / 63 (4.76%)
occurrences (all)	0	2	5
TOOTH FRACTURE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	2 / 63 (3.17%)
occurrences (all)	0	0	2
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	10 / 63 (15.87%)
occurrences (all)	0	2	17
ARTHROPOD BITE			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	5
LIGAMENT INJURY			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
CONTUSION			
subjects affected / exposed	0 / 18 (0.00%)	3 / 36 (8.33%)	6 / 63 (9.52%)
occurrences (all)	0	15	13

JOINT INJURY			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	5 / 63 (7.94%)
occurrences (all)	0	0	9
MUSCLE STRAIN			
subjects affected / exposed	0 / 18 (0.00%)	3 / 36 (8.33%)	2 / 63 (3.17%)
occurrences (all)	0	3	2
SKIN ABRASION			
subjects affected / exposed	1 / 18 (5.56%)	0 / 36 (0.00%)	3 / 63 (4.76%)
occurrences (all)	1	0	3
BACK INJURY			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
FALL			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	8 / 63 (12.70%)
occurrences (all)	0	2	9
SKIN LACERATION			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	3 / 63 (4.76%)
occurrences (all)	0	1	3
TONGUE INJURY			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
HYDROCELE			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 18 (5.56%)	7 / 36 (19.44%)	14 / 63 (22.22%)
occurrences (all)	1	13	33
PARAESTHESIA			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	3 / 63 (4.76%)
occurrences (all)	0	1	3
DIZZINESS			

subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
SCIATICA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	2
CONSTIPATION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	5 / 63 (7.94%)
occurrences (all)	0	0	6
GASTRITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	1 / 63 (1.59%)
occurrences (all)	0	1	1
DIARRHOEA			
subjects affected / exposed	1 / 18 (5.56%)	4 / 36 (11.11%)	6 / 63 (9.52%)
occurrences (all)	2	4	6
VOMITING			
subjects affected / exposed	1 / 18 (5.56%)	1 / 36 (2.78%)	3 / 63 (4.76%)
occurrences (all)	2	1	5
DENTAL CARIES			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	3 / 63 (4.76%)
occurrences (all)	0	7	3
ABDOMINAL PAIN			
subjects affected / exposed	0 / 18 (0.00%)	3 / 36 (8.33%)	2 / 63 (3.17%)
occurrences (all)	0	5	3
NAUSEA			

subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	7 / 63 (11.11%)
occurrences (all)	0	1	9
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	4 / 63 (6.35%)
occurrences (all)	0	0	4
DYSPEPSIA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
LARGE INTESTINE POLYP			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	1 / 63 (1.59%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 18 (0.00%)	5 / 36 (13.89%)	9 / 63 (14.29%)
occurrences (all)	0	7	9
ECZEMA			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	3 / 63 (4.76%)
occurrences (all)	0	2	3
PRURITUS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	4 / 63 (6.35%)
occurrences (all)	0	1	5
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
ALOPECIA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

GROIN PAIN			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	4 / 63 (6.35%)
occurrences (all)	0	1	5
ARTHRITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
JOINT SWELLING			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	8 / 63 (12.70%)
occurrences (all)	0	0	10
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 18 (5.56%)	5 / 36 (13.89%)	6 / 63 (9.52%)
occurrences (all)	1	6	7
SYNOVITIS			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	7 / 63 (11.11%)
occurrences (all)	0	3	9
MUSCLE SPASMS			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	2 / 63 (3.17%)
occurrences (all)	0	3	2
MUSCLE CONTRACTURE			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	2 / 63 (3.17%)
occurrences (all)	0	1	2
MUSCULOSKELETAL STIFFNESS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences (all)	1	0	1
TENOSYNOVITIS			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0
TENDONITIS			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	2 / 63 (3.17%)
occurrences (all)	0	2	3
BACK PAIN			
subjects affected / exposed	1 / 18 (5.56%)	6 / 36 (16.67%)	8 / 63 (12.70%)
occurrences (all)	1	11	10
HAEMOPHILIC ARTHROPATHY			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	1 / 63 (1.59%)
occurrences (all)	0	1	1

MYALGIA			
subjects affected / exposed	0 / 18 (0.00%)	4 / 36 (11.11%)	6 / 63 (9.52%)
occurrences (all)	0	4	7
ARTHRALGIA			
subjects affected / exposed	1 / 18 (5.56%)	16 / 36 (44.44%)	25 / 63 (39.68%)
occurrences (all)	1	41	78

Infections and infestations

SINUSITIS			
subjects affected / exposed	1 / 18 (5.56%)	0 / 36 (0.00%)	4 / 63 (6.35%)
occurrences (all)	3	0	4
BRONCHITIS			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	3 / 63 (4.76%)
occurrences (all)	0	4	4
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
BACTERIAL INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
GASTRIC INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
INFLUENZA			
subjects affected / exposed	0 / 18 (0.00%)	7 / 36 (19.44%)	9 / 63 (14.29%)
occurrences (all)	0	8	10
NASOPHARYNGITIS			
subjects affected / exposed	1 / 18 (5.56%)	9 / 36 (25.00%)	20 / 63 (31.75%)
occurrences (all)	1	16	35
EAR INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
CONJUNCTIVITIS			
subjects affected / exposed	1 / 18 (5.56%)	1 / 36 (2.78%)	0 / 63 (0.00%)
occurrences (all)	1	1	0
LOCALISED INFECTION			

subjects affected / exposed	1 / 18 (5.56%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	1	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 18 (5.56%)	8 / 36 (22.22%)	14 / 63 (22.22%)
occurrences (all)	2	11	19
GASTROENTERITIS			
subjects affected / exposed	0 / 18 (0.00%)	3 / 36 (8.33%)	1 / 63 (1.59%)
occurrences (all)	0	3	1
PHARYNGITIS			
subjects affected / exposed	0 / 18 (0.00%)	4 / 36 (11.11%)	3 / 63 (4.76%)
occurrences (all)	0	4	10
RHINITIS			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0
DIARRHOEA INFECTIOUS			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 18 (0.00%)	3 / 36 (8.33%)	7 / 63 (11.11%)
occurrences (all)	0	3	7
BODY TINEA			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0
PERIODONTITIS			
subjects affected / exposed	0 / 18 (0.00%)	1 / 36 (2.78%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
ABSCESS LIMB			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0
CORONAVIRUS INFECTION			
subjects affected / exposed	0 / 18 (0.00%)	0 / 36 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
HYPERURICAEMIA			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	0 / 63 (0.00%)
occurrences (all)	0	2	0
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	0 / 18 (0.00%)	2 / 36 (5.56%)	1 / 63 (1.59%)
occurrences (all)	0	2	1

Non-serious adverse events	Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis)	Arm B: Emicizumab 3 mg/kg Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)	33 / 35 (94.29%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PAPILLOMA			
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
HYPERTENSION			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
PAIN			
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
PYREXIA			
subjects affected / exposed	1 / 17 (5.88%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
ASTHENIA			
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	1	2	

INJECTION SITE REACTION			
subjects affected / exposed	4 / 17 (23.53%)	8 / 35 (22.86%)	
occurrences (all)	4	25	
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
HYPERSENSITIVITY			
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
ERECTILE DYSFUNCTION			
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
NASAL CONGESTION			
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
COUGH			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	2	
SLEEP DISORDER			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
INSOMNIA			

subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
ANXIETY		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Investigations		
BLOOD CREATININE INCREASED		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
BLOOD CREATINE PHOSPHOKINASE INCREASED		
subjects affected / exposed	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	4
ASPARTATE AMINOTRANSFERASE INCREASED		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	3
BLOOD PRESSURE DIASTOLIC INCREASED		
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0
ALANINE AMINOTRANSFERASE INCREASED		
subjects affected / exposed	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	3
Injury, poisoning and procedural complications		
BITE		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
LIMB INJURY		
subjects affected / exposed	1 / 17 (5.88%)	3 / 35 (8.57%)
occurrences (all)	1	5
TOOTH FRACTURE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0
LIGAMENT SPRAIN		
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences (all)	1	1

ARTHROPOD BITE

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0

LIGAMENT INJURY

subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0

CONTUSION

subjects affected / exposed	2 / 17 (11.76%)	2 / 35 (5.71%)
occurrences (all)	3	3

JOINT INJURY

subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	5

MUSCLE STRAIN

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0

SKIN ABRASION

subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1

BACK INJURY

subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0

FALL

subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences (all)	1	1

SKIN LACERATION

subjects affected / exposed	2 / 17 (11.76%)	1 / 35 (2.86%)
occurrences (all)	2	1

TONGUE INJURY

subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0

ROAD TRAFFIC ACCIDENT

subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences (all)	1	1

Congenital, familial and genetic
disorders

HYDROCELE				
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)		
occurrences (all)	1	0		
Nervous system disorders				
HEADACHE				
subjects affected / exposed	2 / 17 (11.76%)	7 / 35 (20.00%)		
occurrences (all)	2	30		
PARAESTHESIA				
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)		
occurrences (all)	1	1		
DIZZINESS				
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)		
occurrences (all)	1	2		
SCIATICA				
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)		
occurrences (all)	3	1		
Ear and labyrinth disorders				
TINNITUS				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences (all)	0	0		
Eye disorders				
CATARACT				
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)		
occurrences (all)	0	0		
Gastrointestinal disorders				
GASTROOESOPHAGEAL REFLUX DISEASE				
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)		
occurrences (all)	0	1		
CONSTIPATION				
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)		
occurrences (all)	0	1		
GASTRITIS				
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)		
occurrences (all)	0	3		
DIARRHOEA				

subjects affected / exposed	2 / 17 (11.76%)	5 / 35 (14.29%)
occurrences (all)	3	6
VOMITING		
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences (all)	1	1
DENTAL CARIES		
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
ABDOMINAL PAIN		
subjects affected / exposed	3 / 17 (17.65%)	0 / 35 (0.00%)
occurrences (all)	4	0
NAUSEA		
subjects affected / exposed	0 / 17 (0.00%)	4 / 35 (11.43%)
occurrences (all)	0	4
ABDOMINAL PAIN UPPER		
subjects affected / exposed	0 / 17 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	3
DYSPEPSIA		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
LARGE INTESTINE POLYP		
subjects affected / exposed	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences (all)	1	1
Skin and subcutaneous tissue disorders		
RASH		
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
ECZEMA		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
PRURITUS		
subjects affected / exposed	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	2
RASH MACULO-PAPULAR		
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0

ALOPECIA		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Renal and urinary disorders		
NEPHROLITHIASIS		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	3
Endocrine disorders		
HYPOTHYROIDISM		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Musculoskeletal and connective tissue disorders		
GROIN PAIN		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
ARTHRITIS		
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0
JOINT SWELLING		
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
PAIN IN EXTREMITY		
subjects affected / exposed	0 / 17 (0.00%)	4 / 35 (11.43%)
occurrences (all)	0	4
SYNOVITIS		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
MUSCLE SPASMS		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
MUSCLE CONTRACTURE		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
MUSCULOSKELETAL STIFFNESS		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0

TENOSYNOVITIS			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
TENDONITIS			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
BACK PAIN			
subjects affected / exposed	2 / 17 (11.76%)	3 / 35 (8.57%)	
occurrences (all)	3	4	
HAEMOPHILIC ARTHROPATHY			
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
MYALGIA			
subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
ARTHRALGIA			
subjects affected / exposed	3 / 17 (17.65%)	11 / 35 (31.43%)	
occurrences (all)	5	26	
Infections and infestations			
SINUSITIS			
subjects affected / exposed	2 / 17 (11.76%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
BRONCHITIS			
subjects affected / exposed	2 / 17 (11.76%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
BACTERIAL INFECTION			
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
GASTRIC INFECTION			
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
INFLUENZA			

subjects affected / exposed	2 / 17 (11.76%)	4 / 35 (11.43%)
occurrences (all)	2	4

NASOPHARYNGITIS

subjects affected / exposed	3 / 17 (17.65%)	8 / 35 (22.86%)
occurrences (all)	4	19

EAR INFECTION

subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0

CONJUNCTIVITIS

subjects affected / exposed	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	2

LOCALISED INFECTION

subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2

UPPER RESPIRATORY TRACT INFECTION

subjects affected / exposed	3 / 17 (17.65%)	6 / 35 (17.14%)
occurrences (all)	4	9

GASTROENTERITIS

subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2

PHARYNGITIS

subjects affected / exposed	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1

RHINITIS

subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2

DIARRHOEA INFECTIOUS

subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0

COVID-19

subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0

BODY TINEA

subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0

RESPIRATORY TRACT INFECTION		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
PERIODONTITIS		
subjects affected / exposed	2 / 17 (11.76%)	1 / 35 (2.86%)
occurrences (all)	2	1
ABSCESS LIMB		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0
CORONAVIRUS INFECTION		
subjects affected / exposed	1 / 17 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	0
Metabolism and nutrition disorders		
HYPERURICAEMIA		
subjects affected / exposed	0 / 17 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
HYPERCHOLESTEROLAEMIA		
subjects affected / exposed	0 / 17 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2016	The main changes to the protocol are as follows: - The specific factor VIII (FVIII) prophylactic dose and frequency was removed from the definition for FVIII prophylaxis regimen for the inclusion criterion for patients previously treated with FVIII prophylaxis to be enrolled in Arm D.; - Modified dose escalation criteria to more precisely define the subpopulation who may benefit from an increased dose of emicizumab; - Added clarification regarding the efficacy analyses that will be performed for treated bleeds (i.e., treated with coagulation factors) and all bleeds (i.e., both treated and not treated with coagulation factors) given that some patients may report bleeds that they did not treat. In addition, rate of spontaneous bleeds was added as a secondary endpoint.; - Added safety updates regarding a case of atypical hemolytic uremic syndrome (aHUS) and a patient who developed cavernous sinus thrombosis. Both occurred in patients with hemophilia A with FVIII inhibitors receiving bypassing agents.; - The optional interim analysis section was removed based on the anticipated study timelines, as no interim analyses are expected for this study.; - Provided the option for patients to potentially combine emicizumab volumes (if necessary) from up to two vials into 1 syringe to reduce the number of subcutaneous injections they may require.
30 November 2016	The main changes to the protocol are as follows: - The safety sections were updated with the most recent safety information regarding 2 cases of thrombotic microangiopathy (TMA) and 2 patients who developed thromboembolic events in Study BH29884. Both occurred in patients with hemophilia A with FVIII inhibitors receiving bypassing agents. The section for risks associated with emicizumab was updated accordingly, and microangiopathic hemolytic anemia/TMA is newly classified as an adverse event of special interest.; - Although factor VIII (FVIII) and activated prothrombin complex concentrate (aPCC) are fundamentally different in their potential interaction with emicizumab, the amended protocol points investigators to the fact that circulating emicizumab increases patients' coagulation potential and provides suggestions about the use of FVIII in conjunction with emicizumab.; - The van Elteren test will be used as back-up statistical method for the primary analysis instead of the Wilcoxon rank sum test to allow a stratified analysis to be performed.; - Although the use of bypassing agents is unlikely in patients without inhibitors, for completeness and clarity, the amended protocol includes guidelines for their use in patients receiving emicizumab, including dosage and requirements for laboratory monitoring.
20 December 2019	Protocol v4 (dated 20 December 2019): Upon implementation of this amendment, treatment duration was extended until 5 years after the last patient was enrolled to enable the collection of additional long-term safety and efficacy data. During this study prolongation, each patient chose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg every 4 weeks [Q4W]) and continued on that dosing regimen until discontinuation from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported