



## 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 With Inhibitors

#### Summary

EudraCT number	2015-002866-21
Trial protocol	DE ES GB PL FR IT
Global end of trial date	01 December 2020

#### Results information

Result version number	v2 (current)
This version publication date	12 June 2021
First version publication date	04 November 2017
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	BH29884
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02622321
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
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Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001839-PIP01-15
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	01 December 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 December 2020
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 safety, efficacy and pharmacokinetics of prophylactic emicizumab treatment in participants previously treated with episodic or prophylactic bypassing agents.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Costa Rica: 5
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	113
EEA total number of subjects	37

Notes:

<b>Subjects enrolled per age group</b>	
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)	32
Adults (18-64 years)	76
From 65 to 84 years	5
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 113 participants were enrolled in this study: 109 participants prior to the primary completion date plus a further 4 participants to Arm D of the study after the primary completion date. Participants in Arm A and Arm B were randomized in a 2:1 ratio; participants in Arm C and 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
<b>Arm title</b>	Arm A: 1.5 mg/kg Emicizumab QW

Arm description:

Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm A started to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study.

<b>Arm title</b>	Arm B (Control): No Prophylaxis
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Arm description:

Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm B continued with their prior episodic treatment regimen for the first 24 weeks of the study; they did not receive emicizumab prophylaxis during that time. After completing at least 24 weeks on study, participants in Arm B were allowed to switch to emicizumab prophylaxis (as described for Arm A) up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study.

<b>Arm title</b>	Arm C: 1.5 mg/kg Emicizumab QW
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**Arm description:**

Participants who were receiving prophylactic bypassing agents prior to study entry were enrolled in Arm C to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

**Dosage and administration details:**

Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study.

<b>Arm title</b>	Arm D: 1.5 mg/kg Emicizumab QW
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**Arm description:**

Participants who were either: 1) Receiving episodic bypassing agents prior to study entry but were unable to enroll in Arms A or B; or 2) Receiving bypassing agent prophylaxis prior to study entry but were unable to enroll in Arm C, were enrolled in Arm D to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

**Dosage and administration details:**

Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study.

<b>Number of subjects in period 1</b>	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis	Arm C: 1.5 mg/kg Emicizumab QW
Started	35	18	49
Received at Least One Dose of Treatment	34	18	49
Completed 24 Weeks in the Study	31 <sup>[1]</sup>	18	49
Dose Up-Titrated to 3 mg/kg QW	2 <sup>[2]</sup>	0 <sup>[3]</sup>	3 <sup>[4]</sup>
Completed	32	18	48
Not completed	3	0	1
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	2	-	-
Physician decision	1	-	-

<b>Number of subjects in period 1</b>	Arm D: 1.5 mg/kg Emicizumab QW
Started	11

Received at Least One Dose of Treatment	11
Completed 24 Weeks in the Study	11
Dose Up-Titrated to 3 mg/kg QW	2 <sup>[5]</sup>
Completed	11
Not completed	0
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Physician decision	-

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: Participants who withdrew from treatment were still considered to have completed the study if they subsequently completed the safety follow-up visit 24 weeks after discontinuation. For up-titration: After at least 24 weeks on prophylactic emicizumab, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to increase their dose to 3 mg/kg weekly.

[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: Participants who withdrew from treatment were still considered to have completed the study if they subsequently completed the safety follow-up visit 24 weeks after discontinuation. For up-titration: After at least 24 weeks on prophylactic emicizumab, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to increase their dose to 3 mg/kg weekly.

[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: Participants who withdrew from treatment were still considered to have completed the study if they subsequently completed the safety follow-up visit 24 weeks after discontinuation. For up-titration: After at least 24 weeks on prophylactic emicizumab, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to increase their dose to 3 mg/kg weekly.

[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: Participants who withdrew from treatment were still considered to have completed the study if they subsequently completed the safety follow-up visit 24 weeks after discontinuation. For up-titration: After at least 24 weeks on prophylactic emicizumab, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to increase their dose to 3 mg/kg weekly.

[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: Participants who withdrew from treatment were still considered to have completed the study if they subsequently completed the safety follow-up visit 24 weeks after discontinuation. For up-titration: After at least 24 weeks on prophylactic emicizumab, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to increase their dose to 3 mg/kg weekly.

## Baseline characteristics

### Reporting groups

Reporting group title	Arm A: 1.5 mg/kg Emicizumab QW
Reporting group description:	
Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm A started to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.	
Reporting group title	Arm B (Control): No Prophylaxis
Reporting group description:	
Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm B continued with their prior episodic treatment regimen for the first 24 weeks of the study; they did not receive emicizumab prophylaxis during that time. After completing at least 24 weeks on study, participants in Arm B were allowed to switch to emicizumab prophylaxis (as described for Arm A) up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.	
Reporting group title	Arm C: 1.5 mg/kg Emicizumab QW
Reporting group description:	
Participants who were receiving prophylactic bypassing agents prior to study entry were enrolled in Arm C to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.	
Reporting group title	Arm D: 1.5 mg/kg Emicizumab QW
Reporting group description:	
Participants who were either: 1) Receiving episodic bypassing agents prior to study entry but were unable to enroll in Arms A or B; or 2) Receiving bypassing agent prophylaxis prior to study entry but were unable to enroll in Arm C, were enrolled in Arm D to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.	

Reporting group values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis	Arm C: 1.5 mg/kg Emicizumab QW
Number of subjects	35	18	49
Age Categorical Units: Subjects			
Adolescents (12-17 years)	4	2	26
Adults (18-64 years)	30	15	21
Elderly (From 65-84 years)	1	1	2
Age Continuous Units: years			
arithmetic mean	35.8	37.2	25.6
standard deviation	± 13.9	± 13.7	± 16.8
Gender Categorical Units: Subjects			
Female	0	0	0
Male	35	18	49
Number of Participants by the Number of Bleeds (<9 or ≥9) in the Last 24 Weeks Prior to Study Entry Units: Subjects			
<9 Bleeds	11	5	23
≥9 Bleeds	24	13	26

<b>Reporting group values</b>	Arm D: 1.5 mg/kg Emicizumab QW	Total	
Number of subjects	11	113	
Age Categorical Units: Subjects			
Adolescents (12-17 years)	0	32	
Adults (18-64 years)	10	76	
Elderly (From 65-84 years)	1	5	
Age Continuous Units: years			
arithmetic mean	39.0		
standard deviation	± 16.1	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	11	113	
Number of Participants by the Number of Bleeds (<9 or ≥9) in the Last 24 Weeks Prior to Study Entry Units: Subjects			
<9 Bleeds	6	45	
≥9 Bleeds	5	68	



## End points

### End points reporting groups

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

Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm A started to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

Reporting group title	Arm B (Control): No Prophylaxis
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#### Reporting group description:

Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm B continued with their prior episodic treatment regimen for the first 24 weeks of the study; they did not receive emicizumab prophylaxis during that time. After completing at least 24 weeks on study, participants in Arm B were allowed to switch to emicizumab prophylaxis (as described for Arm A) up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

Participants who were receiving prophylactic bypassing agents prior to study entry were enrolled in Arm C to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

Participants who were either: 1) Receiving episodic bypassing agents prior to study entry but were unable to enroll in Arms A or B; or 2) Receiving bypassing agent prophylaxis prior to study entry but were unable to enroll in Arm C, were enrolled in Arm D to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

Subject analysis set title	Arm A (NIS): Previous Episodic Bypassing Agents
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Subject analysis set type	Sub-group analysis
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#### Subject analysis set description:

This arm includes data collected before entry into this study (assessed prospectively in a non-interventional study [NIS]) from Arm A participants who previously participated in NIS BH29768 (NCT02476942) and had received episodic bypassing agents during the NIS.

Subject analysis set title	Arm C (NIS): Previous Prophylactic Bypassing Agents
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Subject analysis set type	Sub-group analysis
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#### Subject analysis set description:

This arm includes data collected before entry into this study (assessed prospectively in a non-interventional study [NIS]) from Arm C participants who previously participated in NIS BH29768 (NCT02476942) and had received prophylactic bypassing agents during the NIS.

Subject analysis set title	Arm B (Emi): 1.5 mg/kg Emicizumab QW
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Subject analysis set type	Sub-group analysis
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#### Subject analysis set description:

This arm includes Arm B participants who switched to emicizumab prophylaxis after having first completed at least 24 weeks on study of no prophylaxis. After Week 24, emicizumab was administered at a loading dose of 3 mg/kg once a week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study.

Subject analysis set title	All Participants: 1.5 mg/kg Emicizumab QW
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Subject analysis set type	Intention-to-treat
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#### Subject analysis set description:

This analysis set includes all enrolled participants on the study. For Arm B, it only includes participants starting after study Week 24 when they crossed over to first receive prophylactic treatment with emicizumab (i.e., Arm B (Emi): 1.5 mg/kg Emicizumab QW). Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) subcutaneously (SC) for the first 4 weeks

followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

## Primary: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[1]</sup>
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### End point description:

The number of treated bleeds over the efficacy period was assessed as an annualized bleed rate (ABR) using a negative binomial (NB) regression model, which accounts for different follow-up times. Treated bleeds were defined as a bleed that was directly followed by a hemophilia medication reported to be a "treatment for bleed". 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose. The Intent-to-treat (ITT) population was defined as all participants who were randomized to Arm A or Arm B.

End point type	Primary
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### End point timeframe:

From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)

### Notes:

[1] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: treated bleeds per year				
number (confidence interval 95%)	2.9 (1.69 to 5.02)	23.3 (12.33 to 43.89)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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### Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (less than [ $<$ ] 9 or greater than or equal to [ $\geq$ ] 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization.

Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$< 0.0001$ <sup>[2]</sup>
Method	Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.277

Notes:

[2] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

### Secondary: Model-Based Annualized Bleed Rate (ABR) for All Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Model-Based Annualized Bleed Rate (ABR) for All Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[3]</sup>
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End point description:

The number of all bleeds over the efficacy period was assessed as an annualized bleed rate (ABR) using a negative binomial (NB) regression model, which accounts for different follow-up times. 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose. The Intent-to-treat (ITT) population was defined as all participants who were randomized to Arm A or Arm B.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)

Notes:

[3] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: all bleeds per year				
number (confidence interval 95%)	5.5 (3.58 to 8.60)	28.3 (16.79 to 47.76)		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization.

Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
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Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.102
upper limit	0.375

Notes:

[4] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

### **Secondary: Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Arm A: Emicizumab Versus Previous Episodic Bypassing Agents**

End point title	Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Arm A: Emicizumab Versus Previous Episodic Bypassing Agents <sup>[5]</sup>
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End point description:

This was an intra-participant comparison of the annualized bleed rates (ABRs) for all bleeds in Arm A participants who had previously received episodic bypassing agents during the non-interventional study (NIS) BH29768 (NCT02476942) (Arm A NIS) prior to entry in this study versus emicizumab prophylaxis during this study (Arm A). The number of all bleeds over the efficacy period was assessed as an ABR using a negative binomial (NB) regression model, which accounts for different follow-up times. 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.

End point type	Secondary
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End point timeframe:

Median [min-max] efficacy observation periods: for Arm A, 1.5 mg/kg Emicizumab QW: 30.86 [0.1-48.9] weeks; for Arm A (NIS), Previous Episodic Bypassing Agents: 21.14 [10.6-33.9] weeks

Notes:

[5] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

<b>End point values</b>	Arm A: 1.5 mg/kg Emicizumab QW	Arm A (NIS): Previous Episodic Bypassing Agents		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	24		
Units: all bleeds per year				
number (confidence interval 95%)	4.1 (2.10 to 8.02)	37.7 (28.40 to 50.04)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: This intra-participant comparison of ABR for all bleeds was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm A NIS) and on study (Arm A).	
Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm A (NIS): Previous Episodic Bypassing Agents
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[6]</sup>
Method	Non-Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.218

Notes:

[6] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

### Secondary: Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Arm A: Emicizumab Versus Previous Episodic Bypassing Agents

End point title	Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Arm A: Emicizumab Versus Previous Episodic Bypassing Agents <sup>[7]</sup>
End point description: This was an intra-participant comparison of the ABRs for treated bleeds in Arm A participants who had previously received episodic bypassing agents during the non-interventional study (NIS) BH29768 (NCT02476942) (Arm A NIS) prior to entry in this study versus emicizumab prophylaxis during this study (Arm A). The number of treated 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 were defined as a bleed that was directly followed by a hemophilia medication reported to be a "treatment for bleed". 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 whose dose was up-titrated, efficacy period ended the day before the first day on the up-titrated dose.	
End point type	Secondary

End point timeframe:

Median [min-max] efficacy observation periods: for Arm A, 1.5 mg/kg Emicizumab QW: 30.86 [0.1-48.9] weeks; for Arm A (NIS), Previous Episodic Bypassing Agents: 21.14 [10.6-33.9] weeks

Notes:

[7] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

<b>End point values</b>	Arm A: 1.5 mg/kg Emicizumab QW	Arm A (NIS): Previous Episodic Bypassing Agents		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	24		
Units: treated bleeds per year				
number (confidence interval 95%)	1.7 (0.71 to 4.06)	21.6 (15.40 to 30.22)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
This intra-participant comparison of ABR for treated bleeds was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm A NIS) and on study (Arm A).	
Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm A (NIS): Previous Episodic Bypassing Agents
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[8]</sup>
Method	Non-Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.198

Notes:

[8] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

## Secondary: Model-Based Annualized Bleed Rate (ABR) for Treated Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Model-Based Annualized Bleed Rate (ABR) for Treated Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[9]</sup>
End point description:	
The number of treated joint 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 joint bleeds were defined as 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. Bleeds due to surgery/procedure were excluded. The Intent-to-treat (ITT) population was defined as all participants who were randomized to Arm A or Arm B.	
End point type	Secondary
End point timeframe:	
From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)	

Notes:

[9] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: treated joint bleeds per year				
number (confidence interval 95%)	0.8 (0.26 to 2.20)	6.7 (1.99 to 22.42)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization.

Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 <sup>[10]</sup>
Method	Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.52

Notes:

[10] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

## Secondary: Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Arm C: Emicizumab Versus Previous Prophylactic Bypassing Agents

End point title	Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Arm C: Emicizumab Versus Previous Prophylactic Bypassing Agents <sup>[11]</sup>
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End point description:

This was an intra-participant comparison of the annualized bleed rates (ABRs) for all bleeds in Arm C participants who had previously received prophylactic bypassing agents during the non-interventional study (NIS) BH29768 (NCT02476942) (Arm C NIS) prior to entry in this study versus emicizumab prophylaxis during this study (Arm C). The number of all bleeds over the efficacy period was assessed as an ABR using a negative binomial (NB) regression model, which accounts for different follow-up times. 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.

End point type	Secondary
End point timeframe:	
Median [min-max] efficacy observation periods: for Arm C, 1.5 mg/kg Emicizumab QW: 30.14 [6.9-45.3] weeks; for Arm C (NIS), Previous Prophylactic Bypassing Agents: 32.14 [8.1-49.3] weeks	

Notes:

[11] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm C: 1.5 mg/kg Emicizumab QW	Arm C (NIS): Previous Prophylactic Bypassing Agents		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	24		
Units: all bleeds per year				
number (confidence interval 95%)	5.5 (2.98 to 10.26)	24.3 (18.11 to 32.67)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

This intra-participant comparison of ABR for all bleeds was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm C NIS) and on study (Arm C).

Comparison groups	Arm C: 1.5 mg/kg Emicizumab QW v Arm C (NIS): Previous Prophylactic Bypassing Agents
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[12]</sup>
Method	Non-Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.119
upper limit	0.435

Notes:

[12] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

## Secondary: Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Arm C: Emicizumab Versus Previous Prophylactic Bypassing Agents



End point title	Intra-Participant Comparison of the Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Arm C: Emicizumab Versus Previous Prophylactic Bypassing Agents <sup>[13]</sup>
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#### End point description:

This was an intra-participant comparison of the ABRs for treated bleeds in Arm C participants who had previously received bypassing agent prophylaxis during the non-interventional study (NIS) BH29768 (NCT02476942) (Arm C NIS) prior to entry in this study versus emicizumab prophylaxis during this study (Arm C). The number of treated 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 were defined as a bleed that was directly followed by a hemophilia medication reported to be a "treatment for bleed". 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 whose dose was up-titrated, efficacy period ended the day before the first day on the up-titrated dose.

End point type	Secondary
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#### End point timeframe:

Median [min-max] efficacy observation periods: for Arm C, 1.5 mg/kg Emicizumab QW: 30.14 [6.9-45.3] weeks; for Arm C (NIS), Previous Prophylactic Bypassing Agents: 32.14 [8.1-49.3] weeks

#### Notes:

[13] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm C: 1.5 mg/kg Emicizumab QW	Arm C (NIS): Previous Prophylactic Bypassing Agents		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	24		
Units: treated bleeds per year				
number (confidence interval 95%)	3.3 (1.33 to 8.08)	15.7 (11.08 to 22.29)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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#### Statistical analysis description:

This intra-participant comparison of ABR for treated bleeds between arms was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm C NIS) and on study (Arm C).

Comparison groups	Arm C: 1.5 mg/kg Emicizumab QW v Arm C (NIS): Previous Prophylactic Bypassing Agents
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 <sup>[14]</sup>
Method	Non-Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.089
upper limit	0.486

Notes:

[14] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

## Secondary: Model-Based Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Model-Based Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[15]</sup>
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End point description:

The number of treated spontaneous bleeds over the efficacy period was assessed as an annualized bleed rate (ABR) using a negative binomial (NB) regression model, which accounts for different follow-up times. 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose. The Intent-to-treat (ITT) population was defined as all participants who were randomized to Arm A or Arm B.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)

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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: treated spontaneous bleeds per year				
number (confidence interval 95%)	1.3 (0.73 to 2.19)	16.8 (9.94 to 28.30)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization

Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
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Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[16]</sup>
Method	Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.154

Notes:

[16] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

### Secondary: Model-Based Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Model-Based Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[17]</sup>
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End point description:

The number of treated target joint bleeds over the efficacy period was assessed as an annualized bleed rate (ABR) using a negative binomial (NB) regression model, which accounts for different follow-up times. Treated target joint bleeds included treated (with coagulation factors) joint bleeds in a target joint, defined as a joint in which greater than or equal to ( $\geq$ ) 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose. The Intent-to-treat (ITT) population was defined as all participants who were randomized to Arm A or Arm B.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)

Notes:

[17] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: treated target joint bleeds per year				
number (confidence interval 95%)	0.1 (0.03 to 0.58)	3.0 (0.96 to 9.13)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization.	
Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 <sup>[18]</sup>
Method	Stratified Wald Test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.227

Notes:

[18] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

### **Secondary: Mean Calculated Annualized Bleed Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis**

End point title	Mean Calculated Annualized Bleed Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[19]</sup>
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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 were excluded. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)

Notes:

[19] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: bleeds per year				
arithmetic mean (confidence interval 95%)				
Treated Bleeds	3.5 (0.83 to 9.46)	26.2 (17.17 to 38.37)		
All Bleeds	6.3 (2.37 to 13.45)	30.8 (20.89 to 43.76)		
Treated Spontaneous Bleeds	1.5 (0.11 to 6.42)	18.1 (10.74 to 28.57)		
Treated Joint Bleeds	1.0 (0.03 to 5.57)	8.1 (3.55 to 15.95)		
Treated Target Joint Bleeds	0.4 (0.00 to 4.48)	6.2 (2.32 to 13.34)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Median Calculated Annualized Bleed Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Median Calculated Annualized Bleed Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[20]</sup>
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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 were excluded. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)

Notes:

[20] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: bleeds per year				
median (inter-quartile range (Q1-Q3))				
Treated Bleeds	0.0 (0.00 to 3.73)	18.8 (12.97 to 35.08)		
All Bleeds	2.0 (0.00 to 9.87)	30.2 (18.26 to 39.37)		
Treated Spontaneous Bleeds	0.0 (0.00 to 3.28)	15.2 (6.64 to 30.44)		
Treated Joint Bleeds	0.0 (0.00 to 0.00)	1.0 (0.00 to 14.44)		
Treated Target Joint Bleeds	0.0 (0.00 to 0.00)	1.0 (0.00 to 6.52)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with 0 Bleeds for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Percentage of Participants with 0 Bleeds for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[21]</sup>
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End point description:

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 ( $\geq$ ) 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 were excluded. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks (median [min-max] efficacy observation periods in Arm A vs. Arm B: 29.29 [0.1-48.9] weeks vs. 24.14 [23.0-26.0] weeks)

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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

<b>End point values</b>	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: Percentage of participants				
number (confidence interval 95%)				
Treated Bleeds	62.9 (44.9 to 78.5)	5.6 (0.1 to 27.3)		
All Bleeds	37.1 (21.5 to 55.1)	5.6 (0.1 to 27.3)		
Treated Spontaneous Bleeds	68.6 (50.7 to 83.1)	11.1 (1.4 to 34.7)		
Treated Joint Bleeds	85.7 (69.7 to 95.2)	50.0 (26.0 to 74.0)		
Treated Target Joint Bleeds	94.3 (80.8 to 99.3)	50.0 (26.0 to 74.0)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hemophilia-Specific Quality of Life (Haem-A-QoL) Questionnaire Physical Health Score at Week 25 in Adult Participants (>/=18 Years Old), Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Hemophilia-Specific Quality of Life (Haem-A-QoL) Questionnaire Physical Health Score at Week 25 in Adult Participants (>/=18 Years Old), Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[22]</sup>
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End point description:

Haem-A-QoL questionnaire has been developed and used in hemophilia A participants. As a hemophilia-specific questionnaire, this measure assesses very specific aspects of dealing with hemophilia. This questionnaire consists of items pertaining to 10 domains specific to living with hemophilia. The 10 domains are: 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 range from 0 to 100 with lower scores reflective of better quality of life. Physical Health domain score is reported. Physical Health domain score is reported (range 0 to 100, with lower scores reflective of better physical health). ITT population. Number of subjects analyzed=adult participants with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Week 25

Notes:

[22] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

<b>End point values</b>	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26 <sup>[23]</sup>	14 <sup>[24]</sup>		
Units: score on a scale				
arithmetic mean (standard deviation)	30.19 (± 26.59)	57.14 (± 23.35)		

Notes:

[23] - Adult participants (≥18 years old) who responded to the questionnaire at Week 25

[24] - Adult participants (≥18 years old) who responded to the questionnaire at Week 25

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
Actual number of participants included for inferential statistics in Arm A is 25. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term. Analysis was performed using Analysis of Covariance (ANCOVA).	
Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029 <sup>[25]</sup>
Method	ANCOVA
Parameter estimate	Adjusted Mean Difference
Point estimate	21.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.89
upper limit	35.22

Notes:

[25] - Statistical significance was controlled at a two-sided alpha level of 0.05.

## Secondary: Haem-A-QoL Questionnaire Total Score at Week 25 in Adult Participants (≥18 Years Old), Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	Haem-A-QoL Questionnaire Total Score at Week 25 in Adult Participants (≥18 Years Old), Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[26]</sup>
End point description:	
Haem-A-QoL questionnaire has been developed and used in hemophilia A participants. As a hemophilia-specific questionnaire, this measure assesses very specific aspects of dealing with hemophilia. This questionnaire consists of items pertaining to 10 domains specific to living with hemophilia. The 10 domains are: 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 range from 0 to 100 with lower scores reflective of better quality of life. Haem-A-QoL Questionnaire Total Score is the average of the all domain scores and range from 0 to 100, with lower scores reflective of better quality of life. ITT population. Number of subjects analyzed=adult participants with available data for this endpoint.	
End point type	Secondary
End point timeframe:	
Week 25	



Notes:

[26] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26 <sup>[27]</sup>	14 <sup>[28]</sup>		
Units: score on a scale				
arithmetic mean (standard deviation)	26.465 (± 18.666)	47.504 (± 17.435)		

Notes:

[27] - Adult participants (≥18 years old) who responded to the questionnaire at Week 25

[28] - Adult participants (≥18 years old) who responded to the questionnaire at Week 25

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Actual number of participants included for inferential statistics in Arm A is 25. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term.	
Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019 <sup>[29]</sup>
Method	ANCOVA
Parameter estimate	Adjusted Mean Difference
Point estimate	14.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.56
upper limit	22.45

Notes:

[29] - Statistical significance was controlled at a two-sided alpha level of 0.05.

## Secondary: European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analog Scale Score at Week 25, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analog Scale Score at Week 25, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[30]</sup>
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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 Visual Analog Scale. The Visual Analogue Scale 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. ITT population. Number of subjects analyzed=participants with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Week 25

Notes:

[30] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30 <sup>[31]</sup>	16 <sup>[32]</sup>		
Units: score on a scale				
arithmetic mean (standard deviation)	83.8 (± 12.9)	76.4 (± 15.7)		

Notes:

[31] - Participants who responded to the questionnaire at Week 25

[32] - Participants who responded to the questionnaire at Week 25

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Actual number of participants included for inferential statistics in Arm A is 29. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term.

Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0171 <sup>[33]</sup>
Method	ANCOVA
Parameter estimate	Adjusted Mean Difference
Point estimate	-9.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.62
upper limit	-1.82

Notes:

[33] - Statistical significance was controlled at a two-sided alpha level of 0.05.

## Secondary: EQ-5D-5L Index Utility Score at Week 25, Arm A: Emicizumab Versus Arm B: No Prophylaxis

End point title	EQ-5D-5L Index Utility Score at Week 25, Arm A: Emicizumab Versus Arm B: No Prophylaxis <sup>[34]</sup>
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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 Visual Analog Scale. The EQ-5D-5L health state profile is designed to record the participant's current health state in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses from the five domains are used to calculate a single utility index value ranging from 1 to 5, where 1 indicates better health state (no problems) and 5 indicates worst health

state (confined to bed). ITT population. Number of subjects analyzed=participants with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Week 25

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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30 <sup>[35]</sup>	16 <sup>[36]</sup>		
Units: score on a scale				
arithmetic mean (standard deviation)	0.83 (± 0.22)	0.60 (± 0.35)		

Notes:

[35] - Participants who responded to the questionnaire at Week 25

[36] - Participants who responded to the questionnaire at Week 25

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Actual number of participants included for inferential statistics in Arm A is 29. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term.

Comparison groups	Arm A: 1.5 mg/kg Emicizumab QW v Arm B (Control): No Prophylaxis
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 <sup>[37]</sup>
Method	ANCOVA
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	-0.07

Notes:

[37] - Statistical significance was controlled at a two-sided alpha level of 0.05.

## Secondary: Hemophilia-Specific Quality of Life – Short Form (Haemo-QoL-SF) Questionnaire Total Score at Baseline and Week 25 in Adolescent Participants (12-17 Years Old)

End point title	Hemophilia-Specific Quality of Life – Short Form (Haemo-QoL-SF) Questionnaire Total Score at Baseline and Week 25 in Adolescent Participants (12-17 Years Old)
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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. Baseline was defined as the last assessment prior to treatment. Because participants in Arm B switched from episodic bypassing agents to start receiving emicizumab prophylaxis after Week 24, the timepoints for Arm B (Emi) are expressed relative to first emicizumab dose.

End point type	Secondary
End point timeframe:	
Baseline and Week 25 (for Arm B (Emi), Study Weeks are relative to first emicizumab dose)	

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis	Arm C: 1.5 mg/kg Emicizumab QW	Arm D: 1.5 mg/kg Emicizumab QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 <sup>[38]</sup>	2 <sup>[39]</sup>	26 <sup>[40]</sup>	0 <sup>[41]</sup>
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2,2,25,2)	34.643 (± 22.728)	37.143 (± 12.122)	30.714 (± 15.625)	()
Week 25 (n=3,2,22,2)	33.095 (± 17.559)	30.000 (± 14.142)	19.286 (± 14.507)	()

Notes:

[38] - Adolescent participants (12-17 years old)

[39] - Adolescent participants (12-17 years old)

[40] - Adolescent participants (12-17 years old)

[41] - None of the participants in Arm D were adolescents (12-17 years old).

End point values	Arm B (Emi): 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	2 <sup>[42]</sup>			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2,2,25,2)	30.000 (± 14.142)			
Week 25 (n=3,2,22,2)	12.143 (± 7.071)			

Notes:

[42] - Adolescent participants (12-17 years old)

## Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Model-Based Annualized Bleed Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target
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## 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 ( $\geq$ ) 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 were excluded.

End point type	Secondary
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## End point timeframe:

From start of emicizumab treatment to study completion (median [min-max] efficacy observation period for all participants: 109.29 [0.1-249.1] weeks)

## Notes:

[43] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm C: 1.5 mg/kg Emicizumab QW	Arm D: 1.5 mg/kg Emicizumab QW	Arm B (Emi): 1.5 mg/kg Emicizumab QW
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	35	49	11	18
Units: bleeds per year				
number (confidence interval 95%)				
Treated Bleeds	1.9 (1.02 to 3.53)	3.2 (1.51 to 6.65)	1.5 (0.20 to 11.72)	0.6 (0.22 to 1.36)
All Bleeds	3.5 (2.11 to 5.74)	4.3 (2.43 to 7.77)	2.3 (0.79 to 6.77)	1.3 (0.66 to 2.39)
Treated Spontaneous Bleeds	0.6 (0.33 to 1.26)	2.1 (0.89 to 4.80)	0.8 (0.07 to 9.16)	0.1 (0.06 to 0.29)
Treated Joint Bleeds	0.5 (0.16 to 1.69)	0.4 (0.14 to 0.96)	0.4 (0.05 to 3.41)	0.1 (0.04 to 0.31)
Treated Target Joint Bleeds	0.1 (0.01 to 0.31)	0.3 (0.09 to 0.84)	0.3 (0.04 to 2.36)	0.01 (0.01 to 0.18)

End point values	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: bleeds per year				
number (confidence interval 95%)				
Treated Bleeds	2.4 (1.50 to 3.82)			
All Bleeds	3.6 (2.55 to 5.13)			
Treated Spontaneous Bleeds	1.3 (0.76 to 2.18)			

Treated Joint Bleeds	0.4 (0.21 to 0.82)			
Treated Target Joint Bleeds	0.2 (0.10 to 0.57)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Efficizumab: Mean Calculated Annualized Bleed Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Enrolled Participants <sup>[44]</sup>
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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 were excluded.

End point type	Secondary
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End point timeframe:

From start of emicizumab treatment to study completion (median [min-max] efficacy observation period for all participants: 109.29 [0.1-249.1] weeks)

Notes:

[44] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Efficizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Efficizumab QW	Arm C: 1.5 mg/kg Efficizumab QW	Arm D: 1.5 mg/kg Efficizumab QW	Arm B (Emi): 1.5 mg/kg Efficizumab QW
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	35	49	11	18
Units: bleeds per year				
arithmetic mean (confidence interval 95%)				
Treated Bleeds	2.9 (0.58 to 8.63)	3.3 (0.77 to 9.28)	1.6 (0.14 to 6.61)	0.6 (0.00 to 4.85)
All Bleeds	4.8 (1.49 to 11.33)	4.6 (1.40 to 11.09)	2.5 (0.42 to 8.02)	1.3 (0.07 to 6.11)
Treated Spontaneous Bleeds	1.2 (0.06 to 5.99)	2.2 (0.32 to 7.59)	0.9 (0.01 to 5.33)	0.2 (0.00 to 4.01)
Treated Joint Bleeds	0.9 (0.02 to 5.42)	0.4 (0.00 to 4.53)	0.4 (0.00 to 4.56)	0.1 (0.00 to 3.95)
Treated Target Joint Bleeds	0.4 (0.00 to 4.44)	0.3 (0.00 to 4.35)	0.4 (0.00 to 4.40)	0.1 (0.00 to 3.79)

<b>End point values</b>	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: bleeds per year				
arithmetic mean (confidence interval 95%)				
Treated Bleeds	2.6 (0.46 to 8.16)			
All Bleeds	3.9 (1.05 to 10.13)			
Treated Spontaneous Bleeds	1.5 (0.10 to 6.35)			
Treated Joint Bleeds	0.5 (0.00 to 4.73)			
Treated Target Joint Bleeds	0.3 (0.00 to 4.30)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleed Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Enrolled Participants <sup>[45]</sup>
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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 were excluded.

End point type	Secondary
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End point timeframe:

From start of emicizumab treatment to study completion (median [min-max] efficacy observation period for all participants: 109.29 [0.1-249.1] weeks)

Notes:

[45] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm C: 1.5 mg/kg Emicizumab QW	Arm D: 1.5 mg/kg Emicizumab QW	Arm B (Emi): 1.5 mg/kg Emicizumab QW
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	35	49	11	18
Units: bleeds per year				
median (inter-quartile range (Q1-Q3))				
Treated Bleeds	0.3 (0.00 to 2.05)	0.0 (0.00 to 1.13)	0.0 (0.00 to 0.67)	0.0 (0.00 to 0.48)
All Bleeds	1.9 (0.22 to 5.13)	0.6 (0.00 to 2.25)	0.5 (0.00 to 4.41)	0.5 (0.00 to 2.18)
Treated Spontaneous Bleeds	0.0 (0.00 to 0.87)	0.0 (0.00 to 0.47)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.24)
Treated Joint Bleeds	0.0 (0.00 to 0.24)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)
Treated Target Joint Bleeds	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)

End point values	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: bleeds per year				
median (inter-quartile range (Q1-Q3))				
Treated Bleeds	0.0 (0.00 to 1.09)			
All Bleeds	0.6 (0.00 to 3.34)			
Treated Spontaneous Bleeds	0.0 (0.00 to 0.51)			
Treated Joint Bleeds	0.0 (0.00 to 0.00)			
Treated Target Joint Bleeds	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 Bleed Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Enrolled Participants

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

The number of treated bleeds over the efficacy period was calculated as:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.

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, and 229-240 weeks	

End point values	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: treated bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 110)	3.9 (1.05 to 10.12)			
13 to 24 Weeks (n = 109)	2.2 (0.31 to 7.53)			
25 to 36 Weeks (n = 102)	0.9 (0.01 to 5.31)			
37 to 48 Weeks (n = 101)	0.3 (0.00 to 4.38)			
49 to 60 Weeks (n = 99)	0.4 (0.00 to 4.56)			
61 to 72 Weeks (n = 98)	0.5 (0.00 to 4.73)			
73 to 84 Weeks (n = 92)	0.6 (0.00 to 4.80)			
85 to 96 Weeks (n = 79)	0.4 (0.00 to 4.46)			
97 to 108 Weeks (n = 67)	0.5 (0.00 to 4.71)			
109 to 120 Weeks (n = 50)	0.0 (0.0 to 3.69)			
121 to 132 Weeks (n = 44)	0.4 (0.00 to 4.48)			
133 to 144 Weeks (n = 37)	0.5 (0.00 to 4.62)			
145 to 156 Weeks (n = 31)	0.4 (0.00 to 4.53)			
157 to 168 Weeks (n = 28)	0.2 (0.00 to 4.01)			
169 to 180 Weeks (n = 23)	0.2 (0.00 to 4.08)			
181 to 192 Weeks (n = 19)	0.0 (0.0 to 3.69)			
193 to 204 Weeks (n = 13)	0.0 (0.0 to 3.69)			
205 to 216 Weeks (n = 9)	0.0 (0.0 to 3.69)			
217 to 228 Weeks (n = 4)	0.0 (0.0 to 3.69)			
229 to 240 Weeks (n = 2)	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 Bleed Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Enrolled Participants

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

The number of treated bleeds over the efficacy period was calculated as:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.

End point type	Secondary
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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, and 229-240 weeks

End point values	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: treated bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 110)	0.0 (0.00 to 4.35)			
13 to 24 Weeks (n = 109)	0.0 (0.00 to 0.00)			
25 to 36 Weeks (n = 102)	0.0 (0.00 to 0.00)			
37 to 48 Weeks (n = 101)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 99)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 98)	0.0 (0.00 to 0.00)			
73 to 84 Weeks (n = 92)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 79)	0.0 (0.00 to 0.00)			

97 to 108 Weeks (n = 67)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 50)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 44)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 37)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 31)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 28)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 23)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 19)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 13)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 9)	0.0 (0.00 to 0.00)			
217 to 228 Weeks (n = 4)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 2)	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 Bleed Rates (ABR) for All Bleeds per 12-Week Intervals Over Time, All Enrolled Participants

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

The number of all bleeds over the efficacy period was calculated as:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.

End point type	Secondary
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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, and 229-240 weeks

End point values	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: all bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 110)	6.2 (2.35 to 13.40)			
13 to 24 Weeks (n = 109)	3.4 (0.78 to 9.29)			
25 to 36 Weeks (n = 102)	1.5 (0.11 to 6.40)			
37 to 48 Weeks (n = 101)	1.4 (0.09 to 6.29)			
49 to 60 Weeks (n = 99)	1.1 (0.04 to 5.74)			
61 to 72 Weeks (n = 98)	1.0 (0.02 to 5.53)			
73 to 84 Weeks (n = 92)	1.3 (0.07 to 6.12)			
85 to 96 Weeks (n = 79)	1.0 (0.02 to 5.56)			
97 to 108 Weeks (n = 67)	1.2 (0.05 to 5.86)			
109 to 120 Weeks (n = 50)	0.9 (0.01 to 5.34)			
121 to 132 Weeks (n = 44)	0.8 (0.01 to 5.20)			
133 to 144 Weeks (n = 37)	0.5 (0.00 to 4.62)			
145 to 156 Weeks (n = 31)	0.8 (0.01 to 5.20)			
157 to 168 Weeks (n = 28)	0.3 (0.00 to 4.31)			
169 to 180 Weeks (n = 23)	0.8 (0.01 to 5.14)			
181 to 192 Weeks (n = 19)	0.2 (0.00 to 4.15)			
193 to 204 Weeks (n = 13)	0.0 (0.0 to 3.69)			
205 to 216 Weeks (n = 9)	0.0 (0.0 to 3.69)			
217 to 228 Weeks (n = 4)	0.0 (0.0 to 3.69)			
229 to 240 Weeks (n = 2)	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 Bleed Rates (ABR) for All Bleeds per 12-Week Intervals Over Time, All Enrolled Participants

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleed Rates (ABR) for All Bleeds per 12-Week Intervals Over Time, All Enrolled Participants
End point description:	
The number of all bleeds over the efficacy period was calculated as: $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . 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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.	
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, and 229-240 weeks	

End point values	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: all bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 110)	0.0 (0.00 to 8.70)			
13 to 24 Weeks (n = 109)	0.0 (0.00 to 4.35)			
25 to 36 Weeks (n = 102)	0.0 (0.00 to 0.00)			
37 to 48 Weeks (n = 101)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 99)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 98)	0.0 (0.00 to 0.00)			
73 to 84 Weeks (n = 92)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 79)	0.0 (0.00 to 0.00)			
97 to 108 Weeks (n = 67)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 50)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 44)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 37)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 31)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 28)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 23)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 19)	0.0 (0.00 to 0.00)			

193 to 204 Weeks (n = 13)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 9)	0.0 (0.00 to 0.00)			
217 to 228 Weeks (n = 4)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 2)	0.0 (0.00 to 0.00)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Efficizumab: Mean Calculated Annualized Bleed Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time, All Enrolled Participants
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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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.

End point type	Secondary
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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, and 229-240 weeks

<b>End point values</b>	All Participants: 1.5 mg/kg Efficizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: treated spontaneous bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 110)	2.2 (0.31 to 7.56)			
13 to 24 Weeks (n = 109)	1.3 (0.06 to 6.04)			
25 to 36 Weeks (n = 102)	0.4 (0.00 to 4.45)			
37 to 48 Weeks (n = 101)	0.2 (0.00 to 4.04)			
49 to 60 Weeks (n = 99)	0.1 (0.00 to 3.96)			

61 to 72 Weeks (n = 98)	0.2 (0.00 to 4.05)			
73 to 84 Weeks (n = 92)	0.2 (0.00 to 4.08)			
85 to 96 Weeks (n = 79)	0.1 (0.00 to 3.92)			
97 to 108 Weeks (n = 67)	0.3 (0.00 to 4.34)			
109 to 120 Weeks (n = 50)	0.0 (0.0 to 3.69)			
121 to 132 Weeks (n = 44)	0.1 (0.00 to 3.89)			
133 to 144 Weeks (n = 37)	0.0 (0.0 to 3.69)			
145 to 156 Weeks (n = 31)	0.4 (0.00 to 4.53)			
157 to 168 Weeks (n = 28)	0.2 (0.00 to 4.01)			
169 to 180 Weeks (n = 23)	0.2 (0.00 to 4.08)			
181 to 192 Weeks (n = 19)	0.0 (0.0 to 3.69)			
193 to 204 Weeks (n = 13)	0.0 (0.0 to 3.69)			
205 to 216 Weeks (n = 9)	0.0 (0.0 to 3.69)			
217 to 228 Weeks (n = 4)	0.0 (0.0 to 3.69)			
229 to 240 Weeks (n = 2)	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 Bleed Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time, All Enrolled Participants

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleed Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time, All Enrolled Participants
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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 whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose.

End point type	Secondary
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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, and 229-240 weeks

<b>End point values</b>	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: treated spontaneous bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 110)	0.0 (0.00 to 0.00)			
13 to 24 Weeks (n = 109)	0.0 (0.00 to 0.00)			
25 to 36 Weeks (n = 102)	0.0 (0.00 to 0.00)			
37 to 48 Weeks (n = 101)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 99)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 98)	0.0 (0.00 to 0.00)			
73 to 84 Weeks (n = 92)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 79)	0.0 (0.00 to 0.00)			
97 to 108 Weeks (n = 67)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 50)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 44)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 37)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 31)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 28)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 23)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 19)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 13)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 9)	0.0 (0.00 to 0.00)			
217 to 228 Weeks (n = 4)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 2)	0.0 (0.00 to 0.00)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Safety Summary of the Overall Percentage of Participants with at Least One Adverse Event, Severity Assessed According to the WHO Toxicity Grading Scale



End point title	Safety Summary of the Overall Percentage of Participants with at Least One Adverse Event, Severity Assessed According to the WHO Toxicity Grading Scale
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, only data before up-titration is included. aPCC = activated prothrombin complex concentrate; Hypersens.= hypersensitivity	
End point type	Secondary
End point timeframe:	
From Baseline until study completion (median [min-max] safety observation period for all participants: 133.97 [0.1-249.1] weeks)	

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis	Arm C: 1.5 mg/kg Emicizumab QW	Arm D: 1.5 mg/kg Emicizumab QW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	18	49	11
Units: Percentage of participants				
number (not applicable)				
Any Adverse Event (AE)	100.0	50.0	93.9	81.8
AE with Fatal Outcome	0	0	2.0	0
Serious AE	29.4	22.2	18.4	18.2
AE Leading to Withdrawal from Treatment	5.9	0	2.0	0
AE Leading to Dose Mod./Interruption	2.9	0	10.2	0
Grade $\geq 3$ AE	29.4	22.2	14.3	27.3
Related AE	44.1	0	26.5	36.4
Local Injection Site Reaction	26.5	0	14.3	36.4
Systemic Hypersens./Anaphylac(tic/toid) Reaction	0	0	0	0
Thrombotic Microangiopathy (TMA)	2.9	0	4.1	0
TMA Event Related to aPCC and Emicizumab	2.9	0	4.1	0
Thromboembolic Event (TE)	2.9	5.6	2.0	0
TE Event Related to aPCC and Emicizumab	2.9	0	2.0	0

End point values	Arm B (Emi): 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage of participants				
number (not applicable)				
Any Adverse Event (AE)	83.3			

AE with Fatal Outcome	0			
Serious AE	22.2			
AE Leading to Withdrawal from Treatment	0			
AE Leading to Dose Mod./Interruption	0			
Grade $\geq 3$ AE	16.7			
Related AE	22.2			
Local Injection Site Reaction	16.7			
Systemic	0			
Hypersens./Anaphylac(tic/toid) Reaction				
Thrombotic Microangiopathy (TMA)	0			
TMA Event Related to aPCC and Emicizumab	0			
Thromboembolic Event (TE)	5.6			
TE Event Related to aPCC and Emicizumab	0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Testing Negative or Positive for the Presence of Anti-Drug Antibodies (ADAs), Including Neutralizing ADAs, During the Study

End point title	Percentage of Participants Testing Negative or Positive for the Presence of Anti-Drug Antibodies (ADAs), Including Neutralizing ADAs, During the Study <sup>[46]</sup>
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End point description:

'Total ADA Negative' is the sum of all subjects who tested negative for ADA in the 2 following categories: 'ADA Negative', those who are pre-dose ADA negative or are missing pre-dose ADA data and who have all negative post-dose ADA results; and 'ADA Negative (Treatment Unaffected)', a subset who are pre-dose ADA positive but do not have a  $\geq 4$ -fold increase in post-dose ADA levels compared to baseline measurement. '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  $\geq 4$ -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. ADA-positive samples were further analyzed for neutralizing capacity using a modified FVIII chromogenic assay; if also positive, they were considered neutralizing ADAs.

End point type	Secondary
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End point timeframe:

From Baseline until study completion (median [min-max] safety observation period for all participants: 133.97 [0.1-249.1] weeks)

Notes:

[46] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm C: 1.5 mg/kg Emicizumab QW	Arm D: 1.5 mg/kg Emicizumab QW	Arm B (Emi): 1.5 mg/kg Emicizumab QW
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	33	49	11	18
Units: Percentage of participants				

number (not applicable)				
Total ADA Negative (Neg+Neg Unaffected)	100	95.9	100	100
ADA Negative, Negative	100	93.9	100	94.4
ADA Negative, Negative (Treatment Unaffected)	0	2.0	0	5.6
Total ADA Positive (Boosted + Induced)	0	4.1	0	0
ADA Positive, Positive (Treatment Boosted)	0	0	0	0
ADA Positive, Positive (Treatment Induced)	0	4.1	0	0
ADA Positive with Neutralizing ADAs	0	4.1	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Trough Concentrations of Emicizumab at Specified Timepoints

End point title	Plasma Trough Concentrations of Emicizumab at Specified Timepoints <sup>[47]</sup>
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End point description:

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). 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 for each arm (Arms A, C, D, B (Emi), and All Participants, respectively). Because Arm B (Emi) participants switched to emicizumab prophylaxis after Week 24, Study Weeks for Arm B (Emi) are expressed relative to first emicizumab dose in the results table. Here, '99999' represents no data available because the measurements were all below the LLOQ; '999999' represents data not available because standard deviation not calculable for a single participant; '9999999' represents data not available because no samples were collected.

End point type	Secondary
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End point timeframe:

Pre-dose (0 hour [hr]) on Weeks 1-5, 7, 9, 13, 17, 21, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, and 169 (For Arm B (Emi), Study Weeks are relative to first emicizumab dose)

Notes:

[47] - 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: The main efficacy comparisons were planned for the randomized participants in Arm A: 1.5 mg/kg Emicizumab QW and Arm B: No Prophylaxis (control arm; prior to switch to emicizumab after 24 weeks).

End point values	Arm A: 1.5 mg/kg Emicizumab QW	Arm C: 1.5 mg/kg Emicizumab QW	Arm D: 1.5 mg/kg Emicizumab QW	Arm B (Emi): 1.5 mg/kg Emicizumab QW
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	34	49	11	18
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=33,48,11,18,110)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Week 2 (n=34,46,10,17,107)	16.2 (± 4.4)	15.8 (± 5.5)	18.3 (± 6.5)	21.7 (± 10.6)
Week 3 (n=34,47,11,18,110)	31.6 (± 7.3)	31.7 (± 8.3)	32.7 (± 13.0)	32.3 (± 10.4)

Week 4 (n=32,46,11,18,107)	43.8 (± 12.2)	44.7 (± 11.5)	49.0 (± 13.5)	44.6 (± 18.6)
Week 5 (n=33,46,11,18,108)	53.5 (± 15.1)	54.0 (± 13.2)	59.1 (± 14.6)	52.2 (± 14.2)
Week 7 (n=33,46,11,17,107)	52.8 (± 16.2)	53.6 (± 14.3)	54.9 (± 9.2)	53.3 (± 18.0)
Week 9 (n=32,46,11,17,106)	50.4 (± 12.4)	52.6 (± 15.7)	53.7 (± 13.8)	48.9 (± 16.7)
Week 13 (n=32,46,11,17,106)	49.3 (± 13.4)	52.6 (± 15.0)	53.4 (± 14.0)	45.2 (± 16.2)
Week 17 (n=32,46,11,17,106)	50.7 (± 15.0)	51.2 (± 14.9)	57.5 (± 16.9)	46.5 (± 17.4)
Week 21 (n=32,44,11,17,104)	52.6 (± 17.4)	51.6 (± 17.1)	55.0 (± 13.7)	44.5 (± 15.4)
Week 25 (n=31,45,11,17,104)	54.6 (± 19.1)	50.4 (± 16.8)	52.8 (± 14.1)	45.8 (± 18.6)
Week 33 (n=27,41,10,17,95)	50.7 (± 17.2)	54.8 (± 16.7)	57.1 (± 15.2)	48.1 (± 21.1)
Week 41 (n=27,40,10,17,94)	45.3 (± 13.7)	54.8 (± 23.4)	63.3 (± 19.4)	49.3 (± 25.9)
Week 49 (n=27,40,9,15,91)	48.0 (± 12.3)	56.1 (± 22.2)	55.1 (± 18.7)	54.6 (± 27.6)
Week 61 (n=27,40,10,15,92)	52.2 (± 16.3)	60.9 (± 27.7)	53.2 (± 13.8)	51.8 (± 33.4)
Week 73 (n=27,39,9,12,87)	55.5 (± 14.9)	62.9 (± 24.9)	51.9 (± 13.0)	45.6 (± 26.2)
Week 85 (n=27,36,5,10,78)	56.9 (± 18.3)	56.6 (± 22.7)	50.9 (± 12.5)	42.5 (± 34.4)
Week 97 (n=25,27,5,9,66)	53.2 (± 15.2)	54.6 (± 20.0)	53.8 (± 16.9)	34.4 (± 26.4)
Week 109 (n=23,15,3,6,47)	49.6 (± 15.9)	47.4 (± 12.4)	49.3 (± 12.8)	32.8 (± 31.4)
Week 121 (n=19,11,2,7,39)	53.8 (± 16.3)	46.3 (± 12.5)	53.1 (± 5.0)	36.1 (± 33.6)
Week 133 (n=15,7,1,6,29)	50.5 (± 15.9)	49.0 (± 18.5)	52.0 (± 999999)	48.7 (± 29.4)
Week 145 (n=13,5,2,4,24)	51.3 (± 16.6)	44.0 (± 21.7)	49.5 (± 10.3)	38.2 (± 19.0)
Week 157 (n=15,4,2,0,21)	58.0 (± 16.5)	45.5 (± 17.0)	55.4 (± 19.2)	9999999 (± 9999999)
Week 169 (n=12,3,1,0,16)	55.0 (± 19.3)	43.2 (± 20.2)	50.8 (± 999999)	9999999 (± 9999999)

End point values	All Participants: 1.5 mg/kg Emicizumab QW			
Subject group type	Subject analysis set			
Number of subjects analysed	112			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=33,48,11,18,110)	99999 (± 99999)			
Week 2 (n=34,46,10,17,107)	17.1 (± 6.6)			
Week 3 (n=34,47,11,18,110)	31.9 (± 8.8)			
Week 4 (n=32,46,11,18,107)	44.9 (± 13.2)			
Week 5 (n=33,46,11,18,108)	54.1 (± 14.0)			
Week 7 (n=33,46,11,17,107)	53.4 (± 14.9)			
Week 9 (n=32,46,11,17,106)	51.5 (± 14.7)			
Week 13 (n=32,46,11,17,106)	50.5 (± 14.7)			
Week 17 (n=32,46,11,17,106)	51.0 (± 15.6)			
Week 21 (n=32,44,11,17,104)	51.1 (± 16.6)			
Week 25 (n=31,45,11,17,104)	51.2 (± 17.6)			
Week 33 (n=27,41,10,17,95)	52.7 (± 17.5)			
Week 41 (n=27,40,10,17,94)	52.0 (± 21.6)			
Week 49 (n=27,40,9,15,91)	53.3 (± 20.5)			
Week 61 (n=27,40,10,15,92)	56.0 (± 24.8)			
Week 73 (n=27,39,9,12,87)	57.1 (± 22.0)			

Week 85 (n=27,36,5,10,78)	54.5 (± 22.7)			
Week 97 (n=25,27,5,9,66)	51.3 (± 19.9)			
Week 109 (n=23,15,3,6,47)	46.7 (± 17.6)			
Week 121 (n=19,11,2,7,39)	48.5 (± 19.7)			
Week 133 (n=15,7,1,6,29)	49.8 (± 18.8)			
Week 145 (n=13,5,2,4,24)	47.4 (± 17.4)			
Week 157 (n=15,4,2,0,21)	55.3 (± 16.7)			
Week 169 (n=12,3,1,0,16)	52.5 (± 18.7)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline until study completion (median [min-max] safety observation period for all participants: 133.97 [0.1-249.1] weeks)

Adverse event reporting additional description:

Safety Population: All treated subjects grouped by treatment (including after up-titration). For Arm B, data collected with episodic bypassing agents (no prophylaxis) for first 24 weeks and with 1.5 mg/kg emicizumab QW after Week 24 are reported separately under Arm B (Control): No Prophylaxis and Arm B (Emi): 1.5 mg/kg Emicizumab QW, respectively.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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### Reporting groups

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

Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm A started to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once a week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

Participants who were receiving episodic treatment with bypassing agents prior to study entry and were randomized to study Arm B continued with their prior episodic treatment regimen for the first 24 weeks of the study; they did not receive emicizumab prophylaxis during that time. The safety data reported here represents data collected from all Arm B participants during the first 24 weeks of 'no prophylaxis'; safety data from Arm B participants who switched to emicizumab after Week 24 are reported separately under Arm B (Emi): 1.5 mg/kg Emicizumab QW.

Reporting group title	Arm B (Emi): 1.5 mg/kg Emicizumab QW
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Reporting group description:

This arm includes Arm B participants who switched to emicizumab prophylaxis after having first completed at least 24 weeks on study of no prophylaxis. After Week 24, emicizumab was administered at a loading dose of 3 mg/kg once a week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Safety data reported here represents data collected during emicizumab treatment only.

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

Participants who were receiving prophylactic bypassing agents prior to study entry were enrolled in Arm C to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

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

Participants who were either: 1) Receiving episodic bypassing agents prior to study entry but were unable to enroll in Arms A or B; or 2) Receiving bypassing agent prophylaxis prior to study entry but were unable to enroll in Arm C, were enrolled in Arm D to receive emicizumab prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg QW SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC up to the end of study. Participants continued to receive bypassing agent therapy to treat any breakthrough bleeds.

<b>Serious adverse events</b>	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis	Arm B (Emi): 1.5 mg/kg Emicizumab QW
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 34 (32.35%)	5 / 18 (27.78%)	4 / 18 (22.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			

subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device loosening			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer haemorrhage			



subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
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 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Tooth development disorder			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Subcapsular renal haematoma			

subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Haemarthrosis			
subjects affected / exposed	2 / 34 (5.88%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
Cavernous sinus thrombosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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

Device related infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Device related sepsis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Gastroenteritis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Meningitis bacterial			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Sepsis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Urinary tract infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (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 device infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (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

<b>Serious adverse events</b>	Arm C: 1.5 mg/kg	Arm D: 1.5 mg/kg	
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	Emicizumab QW	Emicizumab QW	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 49 (18.37%)	2 / 11 (18.18%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (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	2 / 49 (4.08%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional self-injury			

subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (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 / 49 (0.00%)	0 / 11 (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			
Road traffic accident			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer haemorrhage			

subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (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	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tooth development disorder			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcapsular renal haematoma			

subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Cavernous sinus thrombosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device related infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	



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

<b>Non-serious adverse events</b>	Arm A: 1.5 mg/kg Emicizumab QW	Arm B (Control): No Prophylaxis	Arm B (Emi): 1.5 mg/kg Emicizumab QW
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 34 (97.06%)	9 / 18 (50.00%)	15 / 18 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 34 (14.71%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Catheter site pain			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Device related thrombosis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	3 / 34 (8.82%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	4	0	2
Influenza like illness			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	9 / 34 (26.47%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences (all)	18	0	3

Pain			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	2	1	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 34 (14.71%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Nasal congestion			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	4 / 34 (11.76%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Product issues			

Device occlusion subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Investigations			
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Body temperature increased subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Indeterminable ABO blood type subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Prothrombin fragment 1.2 increased subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Fall subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Fibula fracture subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Incision site swelling subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Ligament sprain			

subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Post procedural constipation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Procedural nausea			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	1	1	2
Rib fracture			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Skin abrasion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin laceration			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Thermal burn			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Tibia fracture			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Procedural hypotension			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Arrhythmia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 4	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	6 / 34 (17.65%) 9	1 / 18 (5.56%) 1	4 / 18 (22.22%) 4
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Migraine subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 2
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Ear and labyrinth disorders			
Ear discomfort subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Dental caries			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences (all)	3	0	4
Diarrhoea			
subjects affected / exposed	4 / 34 (11.76%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	4	0	1
Enteritis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Large intestine polyp			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Food poisoning			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	4 / 34 (11.76%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Toothache			
subjects affected / exposed	4 / 34 (11.76%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	4	0	2
Vomiting			
subjects affected / exposed	3 / 34 (8.82%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			

Drug-induced liver injury subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 2
Ecchymosis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Hair growth abnormal subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Hand dermatitis subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Neurodermatitis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 2
Rash subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	1 / 18 (5.56%) 1	1 / 18 (5.56%) 1
Urticaria subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	9 / 34 (26.47%)	0 / 18 (0.00%)	6 / 18 (33.33%)
occurrences (all)	17	0	9
Arthropathy			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Groin pain			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Pain in extremity			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Plantar fasciitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Synovitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			



subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Cellulitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Device related infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	3 / 34 (8.82%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Herpes virus infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 34 (2.94%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	2
Lower respiratory tract infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	11 / 34 (32.35%)	2 / 18 (11.11%)	7 / 18 (38.89%)
occurrences (all)	29	2	14
Rhinitis			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Upper respiratory tract infection			
subjects affected / exposed	8 / 34 (23.53%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	21	2	2
Urinary tract infection			

subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 18 (5.56%) 1	1 / 18 (5.56%) 1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Dehydration			
subjects affected / exposed	1 / 34 (2.94%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Electrolyte imbalance			
subjects affected / exposed	0 / 34 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0

<b>Non-serious adverse events</b>	Arm C: 1.5 mg/kg Emicizumab QW	Arm D: 1.5 mg/kg Emicizumab QW	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 49 (85.71%)	9 / 11 (81.82%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Skin papilloma			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 49 (6.12%)	2 / 11 (18.18%)	
occurrences (all)	3	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Catheter site pain			

subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Device related thrombosis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Influenza like illness			
subjects affected / exposed	1 / 49 (2.04%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Injection site reaction			
subjects affected / exposed	8 / 49 (16.33%)	4 / 11 (36.36%)	
occurrences (all)	21	5	
Pain			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Peripheral swelling			
subjects affected / exposed	1 / 49 (2.04%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	8 / 49 (16.33%)	1 / 11 (9.09%)	
occurrences (all)	10	1	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 49 (6.12%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Nasal congestion			

subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	2 / 11 (18.18%) 2	
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 3	0 / 11 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2	1 / 11 (9.09%) 1	
Product issues Device occlusion subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4	1 / 11 (9.09%) 1	
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Body temperature increased subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 11 (9.09%) 1	
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 11 (9.09%) 1	
Indeterminable ABO blood type subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3	0 / 11 (0.00%) 0	
Prothrombin fragment 1.2 increased subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 11 (9.09%) 2	
Injury, poisoning and procedural complications			

Contusion		
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)
occurrences (all)	1	0
Fall		
subjects affected / exposed	1 / 49 (2.04%)	1 / 11 (9.09%)
occurrences (all)	1	2
Fibula fracture		
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0
Incision site swelling		
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0
Ligament sprain		
subjects affected / exposed	1 / 49 (2.04%)	1 / 11 (9.09%)
occurrences (all)	1	1
Limb injury		
subjects affected / exposed	1 / 49 (2.04%)	1 / 11 (9.09%)
occurrences (all)	1	1
Post procedural constipation		
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0
Procedural nausea		
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0
Procedural pain		
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)
occurrences (all)	2	0
Rib fracture		
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0
Skin abrasion		
subjects affected / exposed	0 / 49 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	2
Skin laceration		
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)
occurrences (all)	1	0

Thermal burn subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 11 (9.09%) 1	
Tibia fracture subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Tooth fracture subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 11 (9.09%) 1	
Procedural hypotension subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 11 (9.09%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 11 (9.09%) 1	
Headache subjects affected / exposed occurrences (all)	13 / 49 (26.53%) 22	3 / 11 (27.27%) 3	
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Migraine subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 11 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 11 (0.00%) 0	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3	0 / 11 (0.00%) 0	
Ear and labyrinth disorders			

Ear discomfort subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	1 / 11 (9.09%) 1	
Vision blurred subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 2	0 / 11 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2	0 / 11 (0.00%) 0	
Dental caries subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	1 / 11 (9.09%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 8	0 / 11 (0.00%) 0	
Enteritis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Large intestine polyp subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Food poisoning subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Gastritis subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 11 (0.00%) 0	
Nausea			

subjects affected / exposed	3 / 49 (6.12%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Toothache			
subjects affected / exposed	2 / 49 (4.08%)	2 / 11 (18.18%)	
occurrences (all)	3	2	
Vomiting			
subjects affected / exposed	4 / 49 (8.16%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Ecchymosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hair growth abnormal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Hand dermatitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Neurodermatitis			



subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 49 (24.49%)	3 / 11 (27.27%)	
occurrences (all)	33	5	
Arthropathy			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Groin pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Myalgia			

subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	4 / 49 (8.16%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Plantar fasciitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Synovitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 49 (4.08%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Folliculitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Device related infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	10 / 49 (20.41%)	0 / 11 (0.00%)	
occurrences (all)	10	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	

Nasopharyngitis			
subjects affected / exposed	16 / 49 (32.65%)	2 / 11 (18.18%)	
occurrences (all)	27	2	
Rhinitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	7 / 49 (14.29%)	2 / 11 (18.18%)	
occurrences (all)	8	2	
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Dehydration			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Electrolyte imbalance			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2016	The main changes were as follows: - The planned number of participants to be enrolled in Arm C was increased from approximately 10-20 to 30-50, to enable the collection of additional safety and efficacy data from participants previously treated with prophylactic bypassing agents; - An additional emicizumab treatment arm (Arm D) was added, to enroll participants on episodic bypassing agents who had participated in NIS BH29768 but were unable to enroll in time to either Arm A or Arm B. This arm enabled the collection of additional efficacy, safety, pharmacokinetic, and pharmacodynamic data and plasma samples for the development and validation of in vitro diagnostic assay(s) suitable for participants receiving emicizumab treatment; - A secondary endpoint was added to compare all bleeds (i.e., treated with coagulation factors or not treated) as an additional assessment of efficacy given that some participants might have reported bleeds they did not treat; A planned interim analysis by the independent Data Monitoring Committee (iDMC), scheduled to occur during the execution of the primary efficacy period, was removed. This was due to the anticipated rapid completion of enrollment (i.e., approximately 7 months) and the very short time interval between the interim and primary analyses; - An option was provided for participants who were approved to up-titrate their dose to potentially combine emicizumab volumes from more than 1 vial into 1 syringe to reduce the number of subcutaneous injections they required.
30 November 2016	The main changes were as follows: - The permitted treatment for breakthrough bleeds was specified with guidance regarding the use of concomitant bypassing agents in participants being treated with emicizumab, as well as additional local and central laboratory assessments, in order to minimize the risk and monitor for thromboembolic and thrombotic microangiopathy events; - The use of short-term prophylaxis with aPCC concomitantly with emicizumab was prohibited, in order to minimize the risk of thromboembolic and thrombotic microangiopathy events; Microangiopathic hemolytic anemia/ thrombotic microangiopathy was newly classified as an adverse event of special interest (AESI), and an exclusion criterion to exclude participants at high risk to experience thrombotic microangiopathy was added; - A new efficacy objective to evaluate the clinical effect of emicizumab prophylaxis on the number of spontaneous bleeds over time (spontaneous bleed rate) was added, because this is a bleed category that is impacted by an effective treatment.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 October 2016	4 participants experienced serious adverse events (2 participants experienced thromboembolic events and 2 participants experienced thrombotic microangiopathy) that resulted in temporary enrollment halt until further evaluation of these safety events, implementation of adequate mitigation measures and discussion with iDMC.	28 November 2016

Notes:

## Limitations and caveats

None reported