



## 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

#### Summary

EudraCT number	2026-000042-29
Trial protocol	Outside EU/EEA
Global end of trial date	29 August 2025

#### Results information

Result version number	v1 (current)
This version publication date	15 March 2026
First version publication date	15 March 2026

#### Trial information

##### Trial identification

Sponsor protocol code	YO39309
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03315455
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	F. Hoffmann-La Roche Ltd
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4058
Public contact	F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche Ltd, 41 616878333, global.trial_information@roche.com
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Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 August 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 August 2022
Global end of trial reached?	Yes
Global end of trial date	29 August 2025
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To evaluate the efficacy of prophylactic emicizumab (i.e., administered on a scheduled basis with the intent to prevent bleeds) compared with no prophylaxis in patients with hemophilia A
- To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds in pediatric patients

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

The control group for the primary efficacy endpoint will be a concurrent, no prophylaxis "usual care" arm, in which patients who were on episodic therapy prior to study entry will be randomized (2:2:1 prophylactic emicizumab 1.5 mg/kg QW:prophylactic emicizumab 6 mg/kg Q4W:no prophylaxis), which will enable an inter-patient comparison of the treatment and control groups.

A second comparison will be a comparison to an individual patient's bleed rate calculated over the 24 weeks prior to study entry, from the medical record. This will enable inpatient analyses of bleed rates to be performed.

All patients, whether assigned to receive prophylactic emicizumab or no prophylaxis, will continue to receive FVIII or rFVIIa on an episodic basis for the treatment of breakthrough bleeds during the study. Specific doses of FVIII or rFVIIa will not be mandated in the study but investigators should review with patients and approve the appropriate dose to be used to treat breakthrough bleeds. For patients receiving emicizumab, breakthrough bleeds should be treated with the lowest FVIII or rFVIIa dose expected to achieve hemostasis, which may be lower than the patients' prior FVIII or rFVIIa dose.

Actual start date of recruitment	26 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	China: 70
Worldwide total number of subjects	85
EEA total number of subjects	0

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)	15
Adolescents (12-17 years)	11
Adults (18-64 years)	58
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 76 patients were screened for eligibility, 6 of whom were deemed ineligible, and 70 participants were randomized to this study to Arms A, B, and C. Arm D was added later in a protocol amendment (Version 4) after the study had already started. For Arm D, a total of 16 were screened and 15 eligible pediatric patients were enrolled.

### Pre-assignment

Screening details:

Patients with hemophilia A who previously received episodic treatment with FVIII or bypassing agents were recruited for the study at 13 sites across 4 countries/regions. The majority of patients were enrolled from mainland China.

### 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 C: No Prophylaxis (Control), Then Emicizumab

Arm description:

Participants  $\geq 12$  years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm C did not receive any prophylactic treatment for at least 24 weeks (Control). After 24 weeks, participants had the opportunity to switch to receive emicizumab prophylaxis at 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

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

Dosage and administration details:

After 24 weeks of no prophylaxis (i.e., episodic standard-of-care treatment for bleeds), participants randomized to Arm C had the opportunity to switch to receive emicizumab prophylaxis at 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until the end of the study.

<b>Arm title</b>	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW
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Arm description:

Participants  $\geq 12$  years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm A received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

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

**Dosage and administration details:**

Participants randomized to Arm A received emicizumab prophylaxis at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW until the end of the study.

<b>Arm title</b>	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W
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**Arm description:**

Participants  $\geq 12$  years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm B received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 6 mg/kg via SC injection Q4W for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

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

**Dosage and administration details:**

Participants randomized to Arm B received emicizumab prophylaxis at a dose of 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until the end of the study.

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

Participants  $< 12$  years old with hemophilia A and FVIII inhibitors who were enrolled to Arm D received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

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

**Dosage and administration details:**

Pediatric participants  $< 12$  years old who enrolled in Arm D received emicizumab prophylaxis at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW until the end of the study.

<b>Number of subjects in period 1</b>	Arm C: No Prophylaxis (Control), Then Emicizumab	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W
Started	14	29	27
Completed 24 Weeks in the Study	14	29	27
Completed Treatment with Emicizumab	14	27	27
Completed	14	27	27
Not completed	0	2	0

Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	1	-

<b>Number of subjects in period 1</b>	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW
Started	15
Completed 24 Weeks in the Study	15
Completed Treatment with Emicizumab	15
Completed	15
Not completed	0
Adverse event, serious fatal	-
Consent withdrawn by subject	-

## Baseline characteristics

### Reporting groups

Reporting group title	Arm C: No Prophylaxis (Control), Then Emicizumab
Reporting group description:	
Participants ≥12 years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm C did not receive any prophylactic treatment for at least 24 weeks (Control). After 24 weeks, participants had the opportunity to switch to receive emicizumab prophylaxis at 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	
Reporting group title	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW
Reporting group description:	
Participants ≥12 years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm A received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	
Reporting group title	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W
Reporting group description:	
Participants ≥12 years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm B received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 6 mg/kg via SC injection Q4W for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	
Reporting group title	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW
Reporting group description:	
Participants <12 years old with hemophilia A and FVIII inhibitors who were enrolled to Arm D received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	

Reporting group values	Arm C: No Prophylaxis (Control), Then Emicizumab	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W
Number of subjects	14	29	27
Age Categorical Units: Participants			
<18 Years Old	2	3	6
≥18 to <65 Years Old	12	26	20
≥65 Years Old	0	0	1
Age Continuous Units: Years			
arithmetic mean	27.5	32.2	28.6
standard deviation	± 10.9	± 12.0	± 13.5
Sex: Female, Male Units: Participants			
Female	0	0	0

Male	14	29	27
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Race/Ethnicity, Customized Units: Subjects			
Asian	14	29	27
Race/Ethnicity, Customized Units: Subjects			
Not Hispanic or Latino	14	29	27
Factor VIII (FVIII) Inhibitor Status at Study Entry Units: Subjects			
FVIII Inhibitor Positive	3	5	7
FVIII Inhibitor Negative (Non- Inhibitor)	11	24	20
Categorical Number of Bleeds (<9 or ≥9) in the Past 24 Weeks Prior to Study Entry Units: Subjects			
<9 Bleeds	3	7	6
≥9 Bleeds	11	22	21

<b>Reporting group values</b>	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Total	
Number of subjects	15	85	
Age Categorical Units: Participants			
<18 Years Old	15	26	
≥18 to <65 Years Old	0	58	
≥65 Years Old	0	1	
Age Continuous Units: Years			
arithmetic mean	7.5		
standard deviation	± 2.2	-	
Sex: Female, Male Units: Participants			
Female	0	0	
Male	15	85	
Race/Ethnicity, Customized Units: Subjects			
Asian	15	85	
Race/Ethnicity, Customized Units: Subjects			
Not Hispanic or Latino	15	85	
Factor VIII (FVIII) Inhibitor Status at Study Entry Units: Subjects			
FVIII Inhibitor Positive	15	30	
FVIII Inhibitor Negative (Non- Inhibitor)	0	55	
Categorical Number of Bleeds (<9 or ≥9) in the Past 24 Weeks Prior to Study Entry			



Units: Subjects			
<9 Bleeds	5	21	
≥9 Bleeds	10	64	

## End points

### End points reporting groups

Reporting group title	Arm C: No Prophylaxis (Control), Then Emicizumab
Reporting group description: Participants ≥12 years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm C did not receive any prophylactic treatment for at least 24 weeks (Control). After 24 weeks, participants had the opportunity to switch to receive emicizumab prophylaxis at 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	
Reporting group title	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW
Reporting group description: Participants ≥12 years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm A received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	
Reporting group title	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W
Reporting group description: Participants ≥12 years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm B received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 6 mg/kg via SC injection Q4W for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	
Reporting group title	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW
Reporting group description: Participants <12 years old with hemophilia A and FVIII inhibitors who were enrolled to Arm D received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.	
Subject analysis set title	Arm C (Control): No Prophylaxis
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants ≥12 years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm C did not receive any prophylactic treatment for the first 24 weeks of the study (Control). Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of bleeds during the study.	
Subject analysis set title	A+B NIS: Previous Episodic Therapy Pre-Study
Subject analysis set type	Per protocol
Subject analysis set description: The NIS population includes all patients who participated in NIS BH29768 prior to enrollment in Study YO39309 (pooled from Arms A and B). It consists of patients previously treated with episodic FVIII or bypassing agents. This previous episodic therapy analysis group includes historical bleed data during participation in NIS BH29768 prior to enrollment in this study from 2 patients enrolled in Arm A who had FVIII inhibitors and had received episodic therapy with bypassing agents and 2 patients enrolled in Arm B who did not have FVIII inhibitors and had received episodic therapy with FVIII.	
Subject analysis set title	A+B NIS: Emicizumab Prophylaxis On-Study
Subject analysis set type	Per protocol
Subject analysis set description: The NIS population includes all patients who participated in NIS BH29768 prior to enrollment in Study YO39309 (pooled from Arms A and B). It consists of patients previously treated with episodic FVIII or bypassing agents. On this study, the participants received prophylactic emicizumab at a dose of 3	

mg/kg via SC injection QW for the first 4 weeks, followed by either 1.5 mg/kg (in Arm A) or 6 mg/kg (in Arm B) via SC injection Q4W for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

Subject analysis set title	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject analysis set type	Safety analysis

Subject analysis set description:

This Arm C (Emi) is part of Safety Population 2, which includes all patients who switched to receive emicizumab and received at least one dose of emicizumab. After 24 weeks in Arm C (Control) on no prophylaxis, participants were given the opportunity to switch to receive emicizumab prophylaxis at 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until marketing authorization as part of this study or a separate extension study, as long as they derive clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

Subject analysis set title	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject analysis set type	Per protocol

Subject analysis set description:

This Arm C (Emi) is part of the PK-Evaluable Population which includes all patients who received at least one dose of emicizumab and had at least one post-baseline emicizumab concentration result. After 24 weeks in Arm C (Control) on no prophylaxis, participants were given the opportunity to switch to receive emicizumab prophylaxis at 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until marketing authorization as part of this study or a separate extension study, as long as they derive clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

### Primary: Model-Based Annualized Bleeding Rate for Treated Bleeds

End point title	Model-Based Annualized Bleeding Rate for Treated Bleeds <sup>[1]</sup>
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End point description:

The number of treated bleeds over the efficacy period was estimated as an annualized bleeding rate (ABR) using a negative binomial regression model, which accounts for different follow-up times. A treated bleed was 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.

End point type	Primary
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End point timeframe:

From Baseline to at least 24 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated bleeds per year				
number (confidence interval 95%)	1.0 (0.53 to 1.85)	1.0 (0.50 to 1.84)	1.2 (0.48 to 3.13)	27.0 (13.29 to 54.91)

### Statistical analyses

<b>Statistical analysis title</b>	Arm A vs. Arm C for Treated Bleeds
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio $\neq$ 1	
Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[2]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.084

Notes:

[2] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

<b>Statistical analysis title</b>	Arm B vs. Arm C for Treated Bleeds
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio $\neq$ 1	
Comparison groups	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[3]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.082

Notes:

[3] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

### Primary: Mean Calculated Annualized Bleeding Rate for Treated Bleeds

End point title	Mean Calculated Annualized Bleeding Rate for Treated
End point description:	
<p>The number of treated bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula: <math>ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25</math>. A treated bleed was 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.</p>	
End point type	Primary

End point timeframe:

From Baseline to at least 24 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis of the primary endpoint was conducted only on the results of the model-based ABR for treated bleeds; the calculated ABR is only a supportive analysis.

[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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated bleeds per year				
arithmetic mean (confidence interval 95%)	1.4 (0.09 to 6.29)	1.5 (0.10 to 6.38)	1.2 (0.05 to 5.94)	43.7 (31.71 to 58.71)

## Statistical analyses

No statistical analyses for this end point

## Primary: Median Calculated Annualized Bleeding Rate for Treated Bleeds

End point title	Median Calculated Annualized Bleeding Rate for Treated
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End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . A treated bleed was 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.

End point type	Primary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis of the primary endpoint was conducted only on the results of the model-based ABR for treated bleeds; the calculated ABR is only a supportive analysis.

[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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated bleeds per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 1.23)	0.0 (0.00 to 2.26)	0.0 (0.00 to 2.08)	45.3 (21.74 to 70.49)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Model-Based Annualized Bleeding Rate for All Bleeds

End point title	Model-Based Annualized Bleeding Rate for All Bleeds <sup>[8]</sup>
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End point description:

The number of all bleeds over the efficacy period was estimated as an annualized bleeding rate (ABR) using a negative binomial regression model, which accounts for different follow-up times. In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule meant that 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. For non-treated bleeds, the 72-hour rule was implemented by calculating a treatment-free period of 72 hours from the bleed itself.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

[8] - 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: All bleeds per year				
number (confidence interval 95%)	1.9 (1.23 to 2.97)	2.1 (1.33 to 3.26)	3.8 (2.21 to 6.69)	41.1 (26.37 to 64.19)

## Statistical analyses

Statistical analysis title	Arm A vs. Arm C for All Bleeds
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Statistical analysis description:

H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio  $\neq$  1

Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C
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	(Control): No Prophylaxis
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[9]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.084

Notes:

[9] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

<b>Statistical analysis title</b>	Arm B vs. Arm C for All Bleeds
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio $\neq$ 1	
Comparison groups	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[10]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.092

Notes:

[10] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

## Secondary: Mean Calculated Annualized Bleeding Rate for All Bleeds

End point title	Mean Calculated Annualized Bleeding Rate for All Bleeds <sup>[11]</sup>
End point description:	
<p>The number of all bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula: <math>ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25</math>. In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule meant that 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. For non-treated bleeds, the 72-hour rule was implemented by calculating a treatment-free period of 72 hours from the bleed itself.</p>	
End point type	Secondary
End point timeframe:	
From Baseline to at least 24 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: All bleeds per year				
arithmetic mean (confidence interval 95%)	2.7 (0.51 to 8.37)	3.1 (0.67 to 8.94)	3.8 (1.01 to 10.01)	53.0 (39.71 to 69.33)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Median Calculated Annualized Bleeding Rate for All Bleeds

End point title	Median Calculated Annualized Bleeding Rate for All Bleeds <sup>[12]</sup>
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End point description:

The number of all bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule meant that 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. For non-treated bleeds, the 72-hour rule was implemented by calculating a treatment-free period of 72 hours from the bleed itself.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

[12] - 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: All bleeds per year				
median (inter-quartile range (Q1-Q3))	1.5 (0.00 to 4.21)	1.9 (0.00 to 5.62)	2.1 (0.00 to 5.77)	56.7 (26.09 to 70.81)



## Statistical analyses

No statistical analyses for this end point

### Secondary: Model-Based Annualized Bleeding Rate for Treated Spontaneous Bleeds

End point title	Model-Based Annualized Bleeding Rate for Treated Spontaneous Bleeds <sup>[13]</sup>
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End point description:

The number of treated spontaneous bleeds over the efficacy period was estimated as an annualized bleeding rate (ABR) using a negative binomial regression model, which accounts for different follow-up times. A treated spontaneous bleed was defined as a treated bleed (bleed directly followed by a hemophilia medication reported to be a "treatment for bleed") with no other known contributing factor such as trauma or procedure/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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated spontaneous bleeds per year				
number (confidence interval 95%)	0.4 (0.18 to 0.96)	0.5 (0.20 to 1.12)	0.6 (0.18 to 2.16)	23.6 (9.28 to 60.03)

## Statistical analyses

Statistical analysis title	Arm A vs. Arm C for Treated Spontaneous Bleeds
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Statistical analysis description:

H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio  $\neq$  1

Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis
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Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[14]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.053

Notes:

[14] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

<b>Statistical analysis title</b>	Arm B vs. Arm C for Treated Spontaneous Bleeds
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio ≠ 1	
Comparison groups	Arm B: 6 mg/kg Efficizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[15]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.007
upper limit	0.059

Notes:

[15] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

## Secondary: Mean Calculated Annualized Bleeding Rate for Treated Spontaneous Bleeds

End point title	Mean Calculated Annualized Bleeding Rate for Treated Spontaneous Bleeds <sup>[16]</sup>
End point description:	
<p>The number of treated spontaneous bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula: <math>ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25</math>. A treated spontaneous bleed was defined as a treated bleed (bleed directly followed by a hemophilia medication reported to be a "treatment for bleed") with no other known contributing factor such as trauma or procedure/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.</p>	
End point type	Secondary
End point timeframe:	
From Baseline to at least 24 weeks	

Notes:

[16] - 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated spontaneous bleeds per year				
arithmetic mean (confidence interval 95%)	0.5 (0.00 to 4.66)	0.6 (0.00 to 4.88)	0.6 (0.00 to 4.92)	30.9 (20.95 to 43.85)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Median Calculated Annualized Bleeding Rate for Treated Spontaneous Bleeds

End point title	Median Calculated Annualized Bleeding Rate for Treated Spontaneous Bleeds <sup>[17]</sup>
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End point description:

The number of treated spontaneous bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . A treated spontaneous bleed was defined as a treated bleed (bleed directly followed by a hemophilia medication reported to be a "treatment for bleed") with no other known contributing factor such as trauma or procedure/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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated spontaneous bleeds per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.96)	0.0 (0.00 to 0.00)	21.8 (6.48 to 52.18)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Model-Based Annualized Bleeding Rate for Treated Joint Bleeds

End point title	Model-Based Annualized Bleeding Rate for Treated Joint
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End point description:

The number of treated joint bleeds over the efficacy period was estimated as an annualized bleeding rate (ABR) using a negative binomial regression model, which accounts for different follow-up times. A treated joint bleed was defined as a bleed with type reported as "joint" based on at least one of the following symptoms: increasing swelling or warmth of the skin over the joint and/or increasing pain, decreased range of motion, or difficulty using the joint compared with baseline, and the bleed 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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

Justification: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated joint bleeds per year				
number (confidence interval 95%)	0.7 (0.36 to 1.46)	0.6 (0.28 to 1.22)	0.1 (0.02 to 0.88)	17.7 (8.33 to 37.57)

## Statistical analyses

Statistical analysis title	Arm A vs. Arm C for Treated Joint Bleeds
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Statistical analysis description:

H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio  $\neq$  1

Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis
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Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[19]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.102

Notes:

[19] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

<b>Statistical analysis title</b>	Arm B vs. Arm C for Treated Joint Bleeds
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio = 1; versus, H1 (alternative hypothesis): ABR Ratio ≠ 1	
Comparison groups	Arm B: 6 mg/kg Efficizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[20]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.084

Notes:

[20] - Statistical significance was controlled at a 2-sided alpha level of 0.05. Hierarchical testing was used to account for multiple comparisons.

## Secondary: Mean Calculated Annualized Bleeding Rate for Treated Joint Bleeds

End point title	Mean Calculated Annualized Bleeding Rate for Treated Joint Bleeds <sup>[21]</sup>
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End point description:

The number of treated joint bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . A treated joint bleed was defined as a bleed with type reported as "joint" based on at least one of the following symptoms: increasing swelling or warmth of the skin over the joint and/or increasing pain, decreased range of motion, or difficulty using the joint compared with baseline, and the bleed 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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated joint bleeds per year				
arithmetic mean (confidence interval 95%)	1.0 (0.02 to 5.57)	0.8 (0.01 to 5.20)	0.1 (0.00 to 3.93)	25.5 (16.62 to 37.56)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Median Calculated Annualized Bleeding Rate for Treated Joint Bleeds

End point title	Median Calculated Annualized Bleeding Rate for Treated Joint Bleeds <sup>[22]</sup>
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End point description:

The number of treated joint bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . A treated joint bleed was defined as a bleed with type reported as "joint" based on at least one of the following symptoms: increasing swelling or warmth of the skin over the joint and/or increasing pain, decreased range of motion, or difficulty using the joint compared with baseline, and the bleed 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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated joint bleeds per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)	0.0 (0.00 to 1.40)	0.0 (0.00 to 0.00)	10.9 (8.70 to 50.00)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Model-Based Annualized Bleeding Rate for Treated Target Joint Bleeds

End point title	Model-Based Annualized Bleeding Rate for Treated Target Joint Bleeds <sup>[23]</sup>
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End point description:

The number of treated target joint bleeds over the efficacy period was estimated as an annualized bleeding rate (ABR) using a negative binomial regression model, which accounts for different follow-up times. A treated target joint bleed was defined as a joint bleed in a target joint, which is a joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry or an unresolved target joint (target joint that does not fulfil  $\leq 2$  bleeds into this joint within a consecutive 12-month period), and the bleed 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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

[23] - 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated target joint bleeds per year				
number (confidence interval 95%)	0.4 (0.18 to 1.09)	0.3 (0.12 to 0.85)	0 (0 to 0)	8.6 (3.15 to 23.42)

## Statistical analyses

Statistical analysis title	Arm B vs. Arm C for Treated Target Joint Bleeds
Comparison groups	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[24]</sup>
Method	ABR Ratio
Parameter estimate	ABR Ratio
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.122

Notes:

[24] - Not controlled for Type I error

<b>Statistical analysis title</b>	Arm A vs. Arm C for Treated Target Joint Bleeds
Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[25]</sup>
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.163

Notes:

[25] - Not controlled for Type I error

## Secondary: Median Calculated Annualized Bleeding Rate for Treated Target Joint Bleeds

End point title	Median Calculated Annualized Bleeding Rate for Treated Target Joint Bleeds <sup>[26]</sup>
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End point description:

The number of treated target joint bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . A treated target joint bleed was defined as a joint bleed in a target joint, which is a joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry or an unresolved target joint (target joint that does not fulfil  $\leq 2$  bleeds into this joint within a consecutive 12-month period), and the bleed 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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks



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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated target joint bleeds per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)	0.0 (0.00 to 1.13)	0.0 (0.00 to 0.00)	6.5 (0.00 to 19.68)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Calculated Annualized Bleeding Rate for Treated Target Joint Bleeds

End point title	Mean Calculated Annualized Bleeding Rate for Treated Target Joint Bleeds <sup>[27]</sup>
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End point description:

The number of treated target joint bleeds over the efficacy period is presented here as a calculated annualized bleeding rate (ABR) that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . A treated target joint bleed was defined as a joint bleed in a target joint, which is a joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry or an unresolved target joint (target joint that does not fulfil  $\leq 2$  bleeds into this joint within a consecutive 12-month period), and the bleed 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.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

Justification: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Control): No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Treated target joint bleeds per year				
arithmetic mean (confidence interval)	0.7 (0.00 to	0.5 (0.00 to	0.0 (0.0 to	15.6 (8.83 to

95%)	5.06)	4.76)	3.69)	25.47)
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## Statistical analyses

No statistical analyses for this end point

### Secondary: Intra-Participant Comparison of the Calculated Annualized Bleeding Rate for Treated Bleeds with Emicizumab Prophylaxis On-Study Versus with Previous Episodic Therapy Pre-Study

End point title	Intra-Participant Comparison of the Calculated Annualized Bleeding Rate for Treated Bleeds with Emicizumab Prophylaxis On-Study Versus with Previous Episodic Therapy Pre-Study
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End point description:

This is an intra-participant comparison of the annualized bleeding rate (ABR) for treated bleeds pre-study versus on-study in the non-interventional study (NIS) population previously treated with episodic therapy in NIS BH29768. The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . A treated bleed was 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.

End point type	Secondary
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End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (mean [min-max] for A+B NIS-Previous Episodic Therapy: 183 [169-221] days); and From Baseline to at least 24 weeks on study (mean [min-max] for A+B NIS-Emicizumab: 363 [324-422] days)

End point values	A+B NIS: Previous Episodic Therapy Pre- Study	A+B NIS: Emicizumab Prophylaxis On-Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	4		
Units: Treated bleeds per year				
arithmetic mean (full range (min-max))	13.02 (4.96 to 21.61)	0.24 (0.00 to 0.97)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Arms A, B, and C: Adjusted Mean Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Physical Health Domain Score at Week 25 in Participants ≥18 Years of Age

End point title	Arms A, B, and C: Adjusted Mean Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Physical Health Domain Score at
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## End point description:

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

End point type	Secondary
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End point timeframe:

Baseline and Week 25

## Notes:

[28] - 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: Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the participants were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	21	8	
Units: score on a scale				
arithmetic mean (standard deviation)	27.85 (± 19.82)	24.20 (± 16.09)	42.53 (± 14.00)	

## Statistical analyses

Statistical analysis title	Arm B vs. Arm C for Haem-A-QoL PH Score
Comparison groups	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0204 <sup>[29]</sup>
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	18.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.97
upper limit	33.68

## Notes:

[29] - Type I error controlled

Statistical analysis title	Arm A vs. Arm C for Haem-A-QoL PH Score
Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0515 <sup>[30]</sup>
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	14.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	29.46

Notes:

[30] - Type I error controlled

## Secondary: Intra-Participant Comparison of the Calculated Annualized Bleeding Rate for All Bleeds with Emicizumab Prophylaxis On-Study Versus with Previous Episodic Therapy Pre-Study

End point title	Intra-Participant Comparison of the Calculated Annualized Bleeding Rate for All Bleeds with Emicizumab Prophylaxis On-Study Versus with Previous Episodic Therapy Pre-Study
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End point description:

This is an intra-participant comparison of the annualized bleeding rate (ABR) for all bleeds pre-study versus on-study in the non-interventional study (NIS) population previously treated with episodic therapy in NIS BH29768. The ABR was calculated for each participant using the following formula:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . All bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. "All bleeds" comprises both treated and non-treated bleeds, and the 72-hour rule was implemented separately for each type. For treated bleeds, the 72-hour rule meant that 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. For non-treated bleeds, the 72-hour rule was calculated as a treatment-free period of 72 hours from the bleed itself.

End point type	Secondary
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End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (mean [min-max] for A+B NIS-Previous Episodic Therapy: 183 [169-221] days); and From Baseline to at least 24 weeks on study (mean [min-max] for A+B NIS-Emicizumab: 363 [324-422] days)

End point values	A+B NIS: Previous Episodic Therapy Pre- Study	A+B NIS: Emicizumab Prophylaxis On-Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	4		
Units: All bleeds per year				
arithmetic mean (full range (min-max))	39.67 (15.13 to 92.55)	2.04 (1.10 to 3.38)		

## Statistical analyses

## Secondary: Arms A, B, and C: Change from Baseline to Week 25 in Haem-A-QoL Questionnaire Physical Health Domain Score for Participants ≥18 Years of Age

End point title	Arms A, B, and C: Change from Baseline to Week 25 in Haem-A-QoL Questionnaire Physical Health Domain Score for Participants ≥18 Years of Age <sup>[31]</sup>
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### End point description:

The Haem-A-QoL questionnaire has been developed and used in hemophilia A participants, assessing very specific aspects of dealing with hemophilia. The questionnaire consists of items pertaining to 10 domains: physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain ranges from 0 to 100 with lower scores reflective of better quality of life. Physical Health domain score is reported (range 0 to 100, with lower scores reflective of better physical health).

End point type	Secondary
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### End point timeframe:

Baseline and Week 25

### Notes:

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

Justification: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	21	8	
Units: score on a scale				
arithmetic mean (standard deviation)				
Value at Baseline (BL)	50.60 (± 20.38)	42.14 (± 14.10)	51.25 (± 23.41)	
Change from BL to Week 25	-20.20 (± 19.82)	-22.14 (± 16.09)	-5.63 (± 14.00)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Arms A, B, and C: Adjusted Mean Haem-A-QoL Questionnaire Total Score at Week 25 in Participants ≥18 Years of Age

End point title	Arms A, B, and C: Adjusted Mean Haem-A-QoL Questionnaire Total Score at Week 25 in Participants ≥18 Years of Age <sup>[32]</sup>
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### End point description:

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

End point type	Secondary
End point timeframe:	
Baseline and Week 25	
Notes:	
[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.	
Justification: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.	

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	21	8	
Units: score on a scale				
arithmetic mean (standard deviation)	37.26 ( $\pm$ 16.17)	29.30 ( $\pm$ 14.60)	43.32 ( $\pm$ 7.47)	

## Statistical analyses

<b>Statistical analysis title</b>	Arm B vs. Arm C for Haem-A-QoL Total Score
Comparison groups	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0297 <sup>[33]</sup>
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	14.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	26.59

Notes:

[33] - Not controlled for Type I error

<b>Statistical analysis title</b>	Arm A vs. Arm C for Haem-A-QoL Total Score
Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3281 <sup>[34]</sup>
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	6.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.27
upper limit	18.4

Notes:

[34] - Not controlled for Type I error

### Secondary: Arms A, B, and C: Change from Baseline to Week 25 in Haem-A-QoL Questionnaire Total Score for Participants ≥18 Years of Age

End point title	Arms A, B, and C: Change from Baseline to Week 25 in Haem-A-QoL Questionnaire Total Score for Participants ≥18 Years of Age <sup>[35]</sup>
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End point description:

The Haem-A-QoL questionnaire has been developed and used in hemophilia A participants, assessing very specific aspects of dealing with hemophilia. The questionnaire consists of items pertaining to 10 domains: physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain ranges from 0 to 100 with lower scores reflective of better quality of life. Haem-A-QoL Total Score is the average of all domain scores and it ranges from 0 to 100, with lower scores reflective of better quality of life.

End point type	Secondary
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End point timeframe:

Baseline and Week 25

Notes:

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

Justification: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	21	8	
Units: score on a scale				
arithmetic mean (standard deviation)				
Value at Baseline (BL)	49.15 (± 16.04)	46.59 (± 12.58)	42.05 (± 17.89)	
Change from BL to Week 25	-10.14 (± 16.17)	-17.61 (± 14.60)	-2.50 (± 7.47)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Arms A, B, and C: Hemophilia-Specific Quality of Life Short Form (Haemo-QoL-SF) Questionnaire Total Score at Baseline and Week 25 in Participants 12 to 17 Years of Age

End point title	Arms A, B, and C: Hemophilia-Specific Quality of Life Short Form (Haemo-QoL-SF) Questionnaire Total Score at Baseline
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## End point description:

The Haemo-QoL-SF contains 35 items covering nine dimensions considered relevant for the adolescent's (aged 12-17 years) health-related quality of life (HRQoL). Items are rated with five respective response options: never, seldom, sometimes, often, and always. The score ranges from 0 to 100, and a higher score is indicative of poorer HRQoL. According to the pre-specified statistical analysis plan, no statistical analyses were performed on the protocol-defined endpoints for the Haemo-QoL-SF due to the small number of adolescents randomized to Arms A, B and C.

End point type	Secondary
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End point timeframe:

Baseline and Week 25

## Notes:

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

Justification: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	5	2	
Units: score on a scale				
arithmetic mean (full range (min-max))				
Value at Baseline (BL)	44.5 (35.7 to 58.6)	35.7 (20.0 to 50.7)	44.7 (35.0 to 54.3)	
Value at Week 25	32.9 (27.9 to 39.3)	27.6 (10.0 to 40.0)	21.5 (13.6 to 29.3)	

## Statistical analyses

No statistical analyses for this end point

**Secondary: Arms A, B, and C: Adjusted Mean European Quality of Life 5-Dimensions-5 Levels Questionnaire (EQ-5D-5L) Questionnaire Visual Analog Scale (VAS) Score at Week 25**

End point title	Arms A, B, and C: Adjusted Mean European Quality of Life 5-Dimensions-5 Levels Questionnaire (EQ-5D-5L) Questionnaire Visual Analog Scale (VAS) Score at Week 25 <sup>[37]</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 VAS. The VAS is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variables: baseline score, treatment group, and treatment by baseline interaction term.

End point type	Secondary
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End point timeframe:

Baseline and Week 25



Notes:

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

Justification: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	25	9	
Units: score on a scale				
arithmetic mean (standard deviation)	81.82 ( $\pm$ 23.19)	85.94 ( $\pm$ 15.20)	78.36 ( $\pm$ 20.68)	

### Statistical analyses

Statistical analysis title	Arm C vs. Arm A for EQ-5D-5L VAS
Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6165 [38]
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	-3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.23
upper limit	10.31

Notes:

[38] - Not controlled for Type I error

Statistical analysis title	Arm C vs. Arm B for EQ-5D-5L VAS
Comparison groups	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2797 [39]
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	-7.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.48
upper limit	6.33

Notes:

[39] - Not controlled for Type I error

### Secondary: Arms A, B, and C: Change from Baseline in EQ-5D-5L Questionnaire VAS Score at Week 25

End point title	Arms A, B, and C: Change from Baseline in EQ-5D-5L Questionnaire VAS Score at Week 25 <sup>[40]</sup>
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End point description:

The European Quality of Life 5-Dimensions-5 Levels Questionnaire (EQ-5D-5L) is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L VAS. The VAS is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state.

End point type	Secondary
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End point timeframe:

Baseline and Week 25

Notes:

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

Justification: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Efficizumab Prophylaxis QW	Arm B: 6 mg/kg Efficizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	29	25	10	
Units: score on a scale				
arithmetic mean (standard deviation)				
Value at Baseline (BL) (n=29,25,10)	74.59 (± 16.91)	78.96 (± 12.91)	84.50 (± 15.07)	
Change from BL to Week 25 (n=28,25,9)	4.82 (± 19.13)	7.40 (± 16.67)	-2.00 (± 13.27)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Arms A, B, and C: Adjusted Mean EQ-5D-5L Index Utility Score at Week 25

End point title	Arms A, B, and C: Adjusted Mean EQ-5D-5L Index Utility Score at Week 25 <sup>[41]</sup>
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End point description:

The European Quality of Life 5-Dimensions-5 Levels Questionnaire (EQ-5D-5L) is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2

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

End point type	Secondary
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End point timeframe:

Baseline and Week 25

Notes:

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

Justification: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	25	9	
Units: score on a scale				
arithmetic mean (standard deviation)	0.79 (± 0.27)	0.82 (± 0.17)	0.74 (± 0.35)	

## Statistical analyses

Statistical analysis title	Arm C vs. Arm A for EQ-5D-5L Index Utility
Comparison groups	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW v Arm C (Control): No Prophylaxis
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.489 <sup>[42]</sup>
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.09

Notes:

[42] - Not controlled for Type I error

Statistical analysis title	Arm C vs. Arm B for EQ-5D-5L Index Utility
Comparison groups	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W v Arm C (Control): No Prophylaxis

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2454 <sup>[43]</sup>
Method	ANCOVA
Parameter estimate	Difference in Adjusted Means
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.06

Notes:

[43] - Not controlled for Type I error

## Secondary: Arms A, B, and C: Change from Baseline in EQ-5D-5L Index Utility Score at Week 25

End point title	Arms A, B, and C: Change from Baseline in EQ-5D-5L Index Utility Score at Week 25 <sup>[44]</sup>
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End point description:

The European Quality of Life 5-Dimensions-5 Levels Questionnaire (EQ-5D-5L) is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L VAS. The EQ-5D-5L health state profile is designed to record the participant's current health state in 5 domains: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Responses from the five domains are used to calculate a single index utility score on a scale of 0 to 1, with higher scores reflective of better quality of life.

End point type	Secondary
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End point timeframe:

Baseline and Week 25

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: This is a comparison between the randomized arms only (Arms A, B, and C). Arm C: No Prophylaxis is presented as an analysis set because it only includes data from the first 24 weeks while the patients were not receiving prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	29	25	10	
Units: score on a scale				
arithmetic mean (standard deviation)				
Value at Baseline (BL) (n=29,25,10)	0.68 (± 0.27)	0.75 (± 0.20)	0.76 (± 0.27)	
Change from BL to Week 25 (n=28,25,9)	0.08 (± 0.22)	0.08 (± 0.21)	0.02 (± 0.09)	

## Statistical analyses

**Secondary: Arm D: Change from Baseline in Haemo-QoL-SF Questionnaire Physical Health and Total Scores at Week 25 in Participants 8 to 12 Years of Age**

End point title	Arm D: Change from Baseline in Haemo-QoL-SF Questionnaire Physical Health and Total Scores at Week 25 in Participants 8 to 12 Years of Age <sup>[45]</sup>
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## End point description:

The Hemophilia-Specific Quality of Life Short Form (Haemo-QoL-SF) questionnaire contains 35 items covering nine dimensions considered relevant for the children's health-related quality of life (HRQoL). Items are rated with five respective response options: never, seldom, sometimes, often, and always. The scores range from 0 to 100, and higher scores are indicative of poorer HRQoL.

End point type	Secondary
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## End point timeframe:

Baseline and Week 25

## 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: This is a single-group descriptive analysis of Arm D that only includes a subset of patients (8-12 years old) from this arm.

<b>End point values</b>	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: score on a scale				
arithmetic mean (standard deviation)				
PH Score: Baseline (BL) - Value at Visit (n=6)	67.71 (± 30.98)			
PH Score: Change from BL at Week 25 (n=5)	-53.75 (± 37.66)			
Total Score: BL - Value at Visit (n=6)	54.40 (± 19.68)			
Total Score: Change from BL at Week 25 (n=5)	-23.86 (± 17.84)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Arm D: Caregiver-Reported Adapted Health-Related Quality of Life for Hemophilia Patients With Inhibitors (Adapted Inhib-QoL) Including Aspects of Caregiver Burden Questionnaire Transformed Total Score Over Time**

End point title	Arm D: Caregiver-Reported Adapted Health-Related Quality of Life for Hemophilia Patients With Inhibitors (Adapted Inhib-QoL) Including Aspects of Caregiver Burden Questionnaire Transformed Total Score Over Time <sup>[46]</sup>
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## End point description:

Proxy assessment of HRQoL and aspects of caregiver burden for all children, regardless of age, were collected using the Adapted Inhib-QoL with Aspects of Caregiver Burden questionnaire. The questionnaire comprises two parts. The first part asks the caregiver for his/her opinion on the child's HRQoL (proxy HRQoL). The second part asks the caregiver to rate how the child's situation is for them (i.e., the impact of the child's disease and treatment on the caregiver). Items are rated with 5

respective response options: never, seldom, sometimes, often, and all the time. Scores range from 0 to 100, with lower scores reflective of better HRQoL. A total score is calculated as the sum of all of the items in the scale.

End point type	Secondary
End point timeframe:	
Baseline (Week 1) and Weeks 13 and 25	

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: This is a single-group descriptive analysis of Arm D only.

<b>End point values</b>	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 10)	51.04 (± 10.47)			
Week 13 (n = 6)	29.85 (± 10.71)			
Week 25 (n = 1)	11.29 (± 0)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with at Least One Adverse Event, Severity According to the World Health Organization (WHO) Toxicity Grading Scale, Primary Analysis of Randomized Comparison Arms

End point title	Number of Participants with at Least One Adverse Event, Severity According to the World Health Organization (WHO) Toxicity Grading Scale, Primary Analysis of Randomized Comparison Arms <sup>[47]</sup>
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End point description:

The number of participants experiencing at least one adverse event (AE), including all non-serious and serious AEs, is reported here. According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as 1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE.

End point type	Secondary
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End point timeframe:

From Baseline until primary cutoff date (at least 24 weeks): Arm C (Control) No Prophylaxis, median (range): 24.0 (23.9-28.0) weeks; Arms A & B Emicizumab, median (range): Arm A: 43.7 (28.1-60.3) weeks; Arm B: 46.1 (24.0-58.7) weeks

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: This is a comparison of the adverse events that occurred in the randomized arms only

(Arms A, B, and C) at the time of the primary data cutoff date.

<b>End point values</b>	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm C (Control): No Prophylaxis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	29	27	14	
Units: Participants				
Any AE, Any WHO Grade	25	19	2	
AEs by Highest WHO Grade: Grade 1	10	6	2	
AEs by Highest WHO Grade: Grade 2	12	12	0	
AEs by Highest WHO Grade: Grade 3	3	1	0	
AEs by Highest WHO Grade: Grade 4	0	0	0	
AE with Fatal Outcome	0	0	0	
Serious AE	2	1	0	
AE Related to Treatment	12	10	0	
Local Injection Site Reaction	4	5	0	
Systemic Hypersens./Anaphylac(tic/toid) Reaction	0	1	0	
Thromboembolic Event	0	0	0	
Thrombotic Microangiopathy	0	0	0	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with at Least One Adverse Event, Severity According to the World Health Organization (WHO) Toxicity Grading Scale, Final Analysis

End point title	Number of Participants with at Least One Adverse Event, Severity According to the World Health Organization (WHO) Toxicity Grading Scale, Final Analysis <sup>[48]</sup>
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End point description:

The number of participants experiencing at least one adverse event (AE), including all non-serious and serious AEs, is reported here. According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as 1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE.

End point type	Secondary
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End point timeframe:

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

Notes:

[48] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after

participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

<b>End point values</b>	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants				
Any Adverse Event (AE), Any WHO Grade	29	24	15	14
AEs by Highest WHO Grade: Grade 1	5	3	4	2
AEs by Highest WHO Grade: Grade 2	14	14	9	9
AEs by Highest WHO Grade: Grade 3	6	5	2	2
AEs by Highest WHO Grade: Grade 4	4	2	0	1
AE with Fatal Outcome	1	0	0	0
Serious AE	9	6	2	4
AE Related to Treatment	15	12	1	6

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with at Least One Adverse Event Leading to Study Drug Discontinuation, Final Analysis

End point title	Number of Participants with at Least One Adverse Event Leading to Study Drug Discontinuation, Final Analysis <sup>[49]</sup>
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End point description:

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as 1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE.

End point type	Secondary
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End point timeframe:

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

Notes:

[49] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.



End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction, Severity According to the WHO Toxicity Grading Scale, Final Analysis

End point title	Number of Participants with at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction, Severity According to the WHO Toxicity Grading Scale, Final Analysis <sup>[50]</sup>
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End point description:

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as 1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE.

End point type	Secondary
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End point timeframe:

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

Notes:

[50] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants				
Any Sys.Hypersens./Anaphylaxis Reaction, Any Grade	0	1	0	0
Event by Highest WHO Grade: Grade 1	0	1	0	0

## Statistical analyses

### Secondary: Number of Participants with at Least One Thromboembolic Event, Severity According to the WHO Toxicity Grading Scale, Final Analysis

End point title	Number of Participants with at Least One Thromboembolic Event, Severity According to the WHO Toxicity Grading Scale, Final Analysis <sup>[51]</sup>
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#### End point description:

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as 1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE.

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

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

#### Notes:

[51] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants				
Any Thromboembolic Event (TE), Any WHO Grade	1	0	0	0
TEs by Highest WHO Grade: Grade 4	1	0	0	0

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with at Least One Thrombotic Microangiopathy, Severity According to the WHO Toxicity Grading Scale, Final Analysis

End point title	Number of Participants with at Least One Thrombotic Microangiopathy, Severity According to the WHO Toxicity Grading Scale, Final Analysis <sup>[52]</sup>
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#### End point description:

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as 1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each

reported AE.

End point type	Secondary
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End point timeframe:

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

Notes:

[52] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with at Least One Injection-Site Reaction, Severity According to the WHO Toxicity Grading Scale, Final Analysis

End point title	Number of Participants with at Least One Injection-Site Reaction, Severity According to the WHO Toxicity Grading Scale, Final Analysis <sup>[53]</sup>
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End point description:

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as 1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE.

End point type	Secondary
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End point timeframe:

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

Notes:

[53] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants				
Any Injection-Site Reaction (ISR), Any WHO Grade	4	5	0	0
ISR by Highest WHO Grade: Grade 1	3	5	0	0
ISR by Highest WHO Grade: Grade 2	1	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Serum Chemistry Laboratory Abnormalities by Shift from Baseline to Highest WHO Grade Post-Baseline

End point title	Number of Participants with Serum Chemistry Laboratory Abnormalities by Shift from Baseline to Highest WHO Grade Post-Baseline <sup>[54]</sup>
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End point description:

The number of participants with abnormal shifts in laboratory chemistry parameters while on emicizumab throughout the study are provided below as shifts from baseline to the highest WHO grade post-baseline (1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening). Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria: Is accompanied by clinical symptoms; Results in a change in study treatment; Results in a medical intervention or a change in concomitant therapy; Is clinically significant in the investigator's judgment. It was the investigator's responsibility to review all laboratory findings. SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT = serum glutamic-pyruvic transaminase/alanine aminotransferase

End point type	Secondary
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End point timeframe:

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

Notes:

[54] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants				
Corrected Calcium (Low), Normal to Grade 3	0	0	0	1
Corrected Calcium (Low), Normal to Grade 4	0	0	3	0
Glucose (Low), Normal to Grade 4	0	0	0	1

Glucose (High), Normal to Grade 3	1	0	0	0
Phosphorus (Low), Normal to Grade 3	0	1	0	0
Potassium (Low), Normal to Grade 4	0	0	1	0
Potassium (High), Normal to Grade 3	0	1	0	0
SGOT/AST (High), Normal to Grade 3	1	1	0	0
SGPT/ALT (High), Normal to Grade 3	0	1	2	0
Sodium (Low), Normal to Grade 4	1	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Hematology Laboratory Abnormalities by Shift from Baseline to Highest WHO Grade Post-Baseline

End point title	Number of Participants with Hematology Laboratory Abnormalities by Shift from Baseline to Highest WHO Grade Post-Baseline <sup>[55]</sup>
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End point description:

The number of participants with abnormal shifts in laboratory hematology parameters while on emicizumab throughout the study are provided below as shifts from baseline to the highest WHO grade post-baseline (1 = mild, 2 = moderate, 3 = severe, or 4 = potentially life-threatening). Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria: Is accompanied by clinical symptoms; Results in a change in study treatment; Results in a medical intervention or a change in concomitant therapy; Is clinically significant in the investigator's judgment. It was the investigator's responsibility to review all laboratory findings.

End point type	Secondary
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End point timeframe:

From first dose of emicizumab until end of study: Arms A to C: up to 88 months; Arm D: up to 52.4 months

Notes:

[55] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Participants				
Hemoglobin (Low), Normal to Grade 4	2	0	0	0
Hemoglobin (Low), Normal to Grade 2	1	0	2	1
Platelet (Low), Normal to Grade 2	0	0	0	1

## Statistical analyses

**Secondary: Change from Baseline in Body Temperature Over Time**

End point title	Change from Baseline in Body Temperature Over Time <sup>[56]</sup>
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End point description:

The data for Arm C are from the emicizumab prophylaxis period and are labelled to correspond to the visit schedule of the other study arms. For Arm C, this is relative to the point at which participants switched to start receiving emicizumab (after having completed 24 weeks of no prophylaxis). Safety Population 2 included all participants from all arms who received at least one dose of emicizumab. The number analyzed (n=) indicates those with evaluable data at a given timepoint. There is no recorded data for Arm C participants at Week 73 because they spent the first 24 weeks of the study on no prophylaxis (i.e., before receiving emicizumab). The value '9999' means there are no results to report (i.e., 0 patients with data).

End point type	Secondary
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End point timeframe:

Baseline and Weeks 5, 25, 49, and 73

Notes:

[56] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: Celsius (C)				
arithmetic mean (standard deviation)				
Baseline (BL) - Value at Visit (n=29,27,14,15)	36.48 (± 0.43)	36.57 (± 0.38)	36.59 (± 0.33)	36.45 (± 0.40)
Change from BL at Week 5 (n=29,27,14,15)	-0.04 (± 0.46)	-0.01 (± 0.40)	0.09 (± 0.35)	-0.11 (± 0.32)
Change from BL at Week 25 (n=29,27,14,15)	-0.12 (± 0.53)	0.04 (± 0.40)	-0.03 (± 0.44)	-0.12 (± 0.58)
Change from BL at Week 49 (n=29,26,13,12)	-0.11 (± 0.47)	-0.07 (± 0.43)	-0.27 (± 0.27)	-0.04 (± 0.37)
Change from BL at Week 73 (n=29,26,0,11)	-0.10 (± 0.43)	0.04 (± 0.43)	-0.01 (± 0.35)	9999 (± 9999)

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline in Pulse Rate Over Time**

End point title	Change from Baseline in Pulse Rate Over Time <sup>[57]</sup>
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End point description:

The data for Arm C are from the emicizumab prophylaxis period and are labelled to correspond to the visit schedule of the other study arms. For Arm C, this is relative to the point at which participants switched to start receiving emicizumab (after having completed 24 weeks of no prophylaxis). Safety Population 2 included all participants from all arms who received at least one dose of emicizumab. The number analyzed (n=) indicates those with evaluable data at a given timepoint. There is no recorded

data for Arm C participants at Week 73 because they spent the first 24 weeks of the study on no prophylaxis (i.e., before receiving emicizumab). The value '9999' means there are no results to report (i.e., 0 patients with data).

End point type	Secondary
End point timeframe:	
Baseline, Weeks 5, 25, 49, and 73	

Notes:

[57] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline (BL) - Value at Visit (n=29,27,14,15)	81.7 (± 10.3)	78.9 (± 11.5)	94.1 (± 11.7)	88.1 (± 10.5)
Change from BL at Week 5 (n=29,27,14,15)	1.6 (± 11.4)	3.5 (± 11.3)	-4.3 (± 11.0)	-4.4 (± 9.6)
Change from BL at Week 25 (n=29,27,14,15)	-2.0 (± 11.0)	4.8 (± 13.6)	-8.6 (± 12.7)	-5.0 (± 8.7)
Change from BL at Week 49 (n=29,26,13,11)	2.1 (± 12.2)	5.0 (± 10.1)	-8.4 (± 15.3)	-7.6 (± 12.8)
Change from BL at Week 73 (n=27,26,0,10)	2.4 (± 13.2)	2.0 (± 13.5)	-8.7 (± 14.9)	9999 (± 9999)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Respiratory Rate Over Time

End point title	Change from Baseline in Respiratory Rate Over Time <sup>[58]</sup>
End point description:	
The data for Arm C are from the emicizumab prophylaxis period and are labelled to correspond to the visit schedule of the other study arms. For Arm C, this is relative to the point at which participants switched to start receiving emicizumab (after having completed 24 weeks of no prophylaxis). Safety Population 2 included all participants from all arms who received at least one dose of emicizumab. The number analyzed (n=) indicates those with evaluable data at a given timepoint. There is no recorded data for Arm C participants at Week 73 because they spent the first 24 weeks of the study on no prophylaxis (i.e., before receiving emicizumab). The value '9999' means there are no results to report (i.e., 0 patients with data).	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 5, 25, 49, and 73	

Notes:

[58] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: breaths per minute				
arithmetic mean (standard deviation)				
Baseline (BL) - Value at Visit (n=29,27,14,15)	19.9 (± 2.2)	19.5 (± 2.5)	20.4 (± 1.7)	19.2 (± 2.6)
Change from BL at Week 5 (n=29,27,14,15)	0.2 (± 2.3)	-0.1 (± 1.7)	-0.7 (± 1.7)	-0.3 (± 1.8)
Change from BL at Week 25 (n=29,27,14,15)	-0.6 (± 2.4)	-0.3 (± 1.8)	-0.4 (± 1.7)	-0.2 (± 1.9)
Change from BL at Week 49 (n=29,26,13,8)	-0.1 (± 2.7)	0.1 (± 2.0)	-0.3 (± 2.5)	-0.2 (± 2.5)
Change from BL at Week 73 (n=27,26,0,10)	-0.2 (± 2.6)	-0.5 (± 2.1)	-1.0 (± 2.4)	9999 (± 9999)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Systolic Blood Pressure Over Time

End point title	Change from Baseline in Systolic Blood Pressure Over Time <sup>[59]</sup>
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End point description:

The data for Arm C are from the emicizumab prophylaxis period and are labelled to correspond to the visit schedule of the other study arms. For Arm C, this is relative to the point at which participants switched to start receiving emicizumab (after having completed 24 weeks of no prophylaxis). Safety Population 2 included all participants from all arms who received at least one dose of emicizumab. The number analyzed (n=) indicates those with evaluable data at a given timepoint. There is no recorded data for Arm C participants at Week 73 because they spent the first 24 weeks of the study on no prophylaxis (i.e., before receiving emicizumab). The value '9999' means there are no results to report (i.e., 0 patients with data).

End point type	Secondary
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End point timeframe:

Baseline, Weeks 5, 25, 49, and 73

Notes:

[59] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.



End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: millimetres of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (BL) - Value at Visit (n=29,27,14,15)	123.6 (± 16.6)	120.1 (± 12.4)	96.3 (± 10.0)	124.9 (± 11.3)
Change from BL at Week 5 (n=29,27,14,15)	1.7 (± 12.4)	0.6 (± 10.6)	1.5 (± 12.5)	-2.4 (± 10.7)
Change from BL at Week 25 (n=29,27,14,15)	-1.1 (± 13.5)	-0.8 (± 8.4)	-0.7 (± 11.1)	-0.4 (± 8.7)
Change from BL at Week 49 (n=29,26,13,10)	-0.4 (± 12.6)	-0.2 (± 8.4)	2.4 (± 12.9)	-2.0 (± 10.5)
Change from BL at Week 73 (n=27,26,0,12)	0.2 (± 11.8)	2.7 (± 9.2)	4.3 (± 9.4)	9999 (± 9999)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Diastolic Blood Pressure Over Time

End point title	Change from Baseline in Diastolic Blood Pressure Over Time <sup>[60]</sup>
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End point description:

The data for Arm C are from the emicizumab prophylaxis period and are labelled to correspond to the visit schedule of the other study arms. For Arm C, this is relative to the point at which participants switched to start receiving emicizumab (after having completed 24 weeks of no prophylaxis). Safety Population 2 included all participants from all arms who received at least one dose of emicizumab. The number analyzed (n=) indicates those with evaluable data at a given timepoint. There is no recorded data for Arm C participants at Week 73 because they spent the first 24 weeks of the study on no prophylaxis (i.e., before receiving emicizumab). The value '9999' means there are no results to report (i.e., 0 patients with data).

End point type	Secondary
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End point timeframe:

Baseline, Weeks 5, 25, 49, and 73

Notes:

[60] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: millimetres of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (BL) - Value at Visit (n=29,27,14,15)	82.6 (± 14.5)	79.1 (± 9.8)	65.8 (± 7.7)	82.4 (± 9.7)

Change from BL at Week 5 (n=29,27,14,15)	1.1 (± 11.6)	1.7 (± 9.0)	-0.1 (± 10.2)	-1.9 (± 9.2)
Change from BL at Week 25 (n=29,27,14,15)	-0.4 (± 12.7)	-2.4 (± 9.1)	3.0 (± 9.5)	-3.6 (± 8.1)
Change from BL at Week 49 (n=29,26,13,10)	0.6 (± 8.9)	-0.8 (± 8.8)	-0.7 (± 11.8)	0.6 (± 10.2)
Change from BL at Week 73 (n=27,26,0,12)	1.5 (± 12.3)	-0.5 (± 8.7)	1.5 (± 11.9)	9999 (± 9999)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants by Post-Baseline Anti-Emicizumab Antibody (ADA) Status

End point title	Number of Participants by Post-Baseline Anti-Emicizumab Antibody (ADA) Status <sup>[61]</sup>
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End point description:

Participants were considered anti-drug antibody (ADA)-positive if they were ADA-negative at baseline but developed an ADA response following study drug administration, or if they were ADA-positive at baseline and the titer of one or more post-baseline samples was at least 4-fold greater than the titer of the baseline sample. Participants were considered ADA-negative if they were ADA-negative at baseline and all post-baseline samples were negative following drug administration, or if they were ADA-positive at baseline but did not have any post-baseline (following drug administration) samples with a titer that was at least 4-fold greater than the titer of the baseline sample.

End point type	Secondary
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End point timeframe:

Samples taken at Baseline and at prespecified times post-baseline from first dose of emicizumab until data cutoff date, median (range) time of exposure to emicizumab: All Arms: 196.14 (20.1-222.1) weeks; Arm D only: 64.14 (61.1-67.3) weeks

Notes:

[61] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	14
Units: participants				
ADA-Positive Status	4	4	0	0
ADA-Negative Status	25	23	15	14

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Trough Concentration (Ctrough) of Emicizumab

End point title	Plasma Trough Concentration (Ctrough) of Emicizumab <sup>[62]</sup>
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End point description:

The data for Arm C are from the emicizumab prophylaxis period and are labelled to correspond to the visit schedule of the other study arms. For Arm C, this is relative to the point at which participants switched to start receiving emicizumab (after having completed 24 weeks of no prophylaxis). The Pharmacokinetics Population included all participants from all arms who received at least one dose of emicizumab. One participant from Arm C was excluded from analysis due to a dosing protocol deviation. The number analyzed (n=) indicates those with evaluable data at a given timepoint. The value '9999' means there are no results to report (i.e., 0 patients with data).

End point type	Secondary
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End point timeframe:

Arms A & D, QW (up to Week 49 for Arm D only): Weeks 2, 3, 4, 5, 7, 9, 13, 17, 21, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121, and 133; Arms B & C, Q4W: Weeks 2, 3, 4, 5, 9, 13, 17, 21, 25, 37, 49, 61, 73, 85, 97, 109, 121, and 133

Notes:

[62] - 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: Arm C: Emicizumab is presented as an analysis set because it only includes data after participants completed the first 24 weeks of no prophylaxis and switched to receiving emicizumab prophylaxis.

End point values	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	15	13
Units: microgram per millilitre (µg/mL)				
geometric mean (geometric coefficient of variation)				
Week 2 (n=29,27,13,15)	12.5 (± 36.1)	13.0 (± 29.1)	16.0 (± 13.9)	13.9 (± 37.4)
Week 3 (n=29,27,13,15)	22.9 (± 31.9)	24.1 (± 31.3)	32.6 (± 15.7)	28.2 (± 29.4)
Week 4 (n=28,27,13,15)	32.5 (± 31.7)	34.2 (± 32.2)	47.3 (± 16.5)	39.6 (± 26.5)
Week 5 (n=28,27,13,15)	39.8 (± 30.0)	41.5 (± 30.9)	55.1 (± 13.3)	41.7 (± 35.1)
Week 7 (n=28,0,0,14)	38.8 (± 30.6)	9999 (± 9999)	55.4 (± 17.3)	9999 (± 9999)
Week 9 (n=28,27,13,15)	38.2 (± 31.6)	35.1 (± 31.8)	48.7 (± 19.9)	37.6 (± 26.9)
Week 13 (n=28,27,12,15)	37.0 (± 34.3)	30.6 (± 41.4)	47.4 (± 24.2)	33.2 (± 35.4)
Week 17 (n=28,27,13,12)	38.2 (± 31.3)	30.5 (± 35.2)	47.2 (± 23.6)	30.0 (± 28.7)
Week 21 (n=28,27,13,13)	37.8 (± 28.6)	31.0 (± 40.2)	46.7 (± 16.5)	31.9 (± 25.7)
Week 25 (n=28,27,13,15)	36.4 (± 32.7)	32.1 (± 45.7)	46.2 (± 25.3)	32.9 (± 28.2)
Week 33 (n=28,0,0,9)	37.1 (± 32.7)	9999 (± 9999)	43.4 (± 17.5)	9999 (± 9999)
Week 37 (n=0,24,13,0)	9999 (± 9999)	31.4 (± 33.5)	9999 (± 9999)	34.7 (± 32.0)
Week 41 (n=27,0,0,6)	40.4 (± 30.6)	9999 (± 9999)	46.4 (± 25.5)	9999 (± 9999)
Week 49 (n=27,26,12,5)	41.8 (± 31.1)	33.0 (± 48.0)	60.2 (± 11.2)	34.5 (± 39.0)
Week 61 (n=25,26,10,0)	42.8 (± 29.3)	36.0 (± 49.0)	9999 (± 9999)	36.3 (± 32.2)
Week 73 (n=24,24,11,0)	45.7 (± 41.6)	37.5 (± 40.5)	9999 (± 9999)	34.5 (± 32.3)
Week 85 (n=22,22,13,0)	42.7 (± 41.2)	38.4 (± 45.1)	9999 (± 9999)	35.9 (± 36.4)
Week 97 (n=23,26,11,0)	42.4 (± 31.1)	35.6 (± 34.8)	9999 (± 9999)	39.4 (± 36.9)
Week 109 (n=25,26,3,0)	45.4 (± 36.8)	36.5 (± 35.3)	9999 (± 9999)	38.4 (± 15.1)
Week 121 (n=18,18,0,0)	41.6 (± 36.0)	35.8 (± 38.2)	9999 (± 9999)	9999 (± 9999)
Week 133 (n=8,10,0,0)	50.3 (± 25.9)	35.6 (± 29.7)	9999 (± 9999)	9999 (± 9999)

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the date of randomization or enrollment until the end of study (Arm C [Control] No Prophylaxis: up to 28 weeks; Arms A to C Emicizumab: up to 88 months; Arm D Emicizumab: up to 52.4 months)

Adverse event reporting additional description:

After randomization (randomized arms A, B, and C) or initiation of study drug (non-randomized arm D), all adverse events were reported until the patient completed their last study visit. After this period, the investigator reported any serious adverse events that were believed to be related to prior study drug treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	28.0

### Reporting groups

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

Participants  $\geq 12$  years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm C did not receive any prophylactic treatment for the first 24 weeks of the study (Control).

Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of bleeds during the study.

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

Participants  $\geq 12$  years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm A received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

Reporting group title	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
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Reporting group description:

After 24 weeks on no prophylaxis, participants were given the opportunity to switch to receive emicizumab prophylaxis at 3 mg/kg QW via SC injection for 4 weeks, followed by 6 mg/kg Q4W until marketing authorization as part of this study or a separate extension study, as long as they derive clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

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

Participants  $< 12$  years old with hemophilia A and FVIII inhibitors who were enrolled to Arm D received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 1.5 mg/kg via SC injection QW for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

Reporting group title	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W
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Reporting group description:

Participants  $\geq 12$  years old with hemophilia A (with or without FVIII inhibitors) who were randomized to Arm B received prophylactic emicizumab at a dose of 3 mg/kg via SC injection QW for the first 4 weeks, followed by 6 mg/kg via SC injection Q4W for at least 24 weeks. After 24 weeks of treatment, participants were allowed to continue receiving emicizumab until marketing authorization, as part of this study or a separate extension study, as long as they derived clinical benefit. Participants continued to receive standard-of-care treatments on an episodic basis for the treatment of breakthrough bleeds during the study.

<b>Serious adverse events</b>	Arm C (Control): No Prophylaxis	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	9 / 29 (31.03%)	4 / 14 (28.57%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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			
Haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mass			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (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
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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
Injury, poisoning and procedural			

complications			
Limb fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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
Fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (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
Bone contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (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
Iron deficiency anaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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
Eye disorders			
Cataract			

subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileal ulcer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (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
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			



subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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
Mouth haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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
Rectal ulcer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric dilatation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (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
Ureterolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (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
Haemophilic arthropathy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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 respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (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 D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	6 / 27 (22.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (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			
Mass			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Limb fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone contusion			

subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileal ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (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 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			

subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (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			
Ureteric dilatation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemophilic arthropathy subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (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 C (Control): No Prophylaxis	Arm A: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm C (Emi): 6 mg/kg Emicizumab Prophylaxis Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	28 / 29 (96.55%)	14 / 14 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	5 / 29 (17.24%)	1 / 14 (7.14%)
occurrences (all)	0	5	1
Haematoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	5 / 29 (17.24%)	0 / 14 (0.00%)
occurrences (all)	0	10	0
Injection site reaction			
subjects affected / exposed	0 / 14 (0.00%)	4 / 29 (13.79%)	0 / 14 (0.00%)
occurrences (all)	0	7	0
Influenza like illness			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 29 (6.90%) 2	1 / 14 (7.14%) 1
Asthenia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Chest discomfort subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Reproductive system and breast disorders Breast hyperplasia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	4 / 29 (13.79%) 5	0 / 14 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 29 (3.45%) 2	0 / 14 (0.00%) 0
Bronchiectasis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Pulmonary mass subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	4 / 29 (13.79%) 8	0 / 14 (0.00%) 0
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	3 / 29 (10.34%) 7	0 / 14 (0.00%) 0



Blood uric acid increased			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	2 / 14 (14.29%)
occurrences (all)	0	2	3
Alanine aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	5 / 29 (17.24%)	6 / 14 (42.86%)
occurrences (all)	0	9	14
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	5 / 29 (17.24%)	4 / 14 (28.57%)
occurrences (all)	0	9	7
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Blood ketone body increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Blood potassium decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Differential white blood cell count abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
White blood cell count abnormal			

subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Neutrophil count abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	4
Ligament sprain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Arthropod bite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Animal bite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Meniscus injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Closed globe injury			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Muscle strain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Skin abrasion subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Soft tissue injury subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	0 / 14 (0.00%) 0
Palipitations subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 29 (3.45%) 1	1 / 14 (7.14%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	5 / 29 (17.24%) 5	1 / 14 (7.14%) 1
Dizziness subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	3 / 29 (10.34%) 4	1 / 14 (7.14%) 3
Head discomfort subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Syncope subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	0 / 14 (0.00%) 0
Anaemia			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	4 / 29 (13.79%) 4	1 / 14 (7.14%) 1
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	0 / 14 (0.00%) 0
Splenomegaly subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 29 (3.45%) 1	1 / 14 (7.14%) 1
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	4 / 29 (13.79%) 7	3 / 14 (21.43%) 5
Constipation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	3 / 29 (10.34%) 4	1 / 14 (7.14%) 1
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	1 / 14 (7.14%) 1
Dyspepsia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	0 / 14 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	3 / 29 (10.34%) 3	0 / 14 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 29 (0.00%) 0	2 / 14 (14.29%) 2
Vomiting			

subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Dental caries			
subjects affected / exposed	0 / 14 (0.00%)	3 / 29 (10.34%)	1 / 14 (7.14%)
occurrences (all)	0	3	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Gastritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Colitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Chronic gastritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Aphthous ulcer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tooth impacted			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	2 / 14 (14.29%)
occurrences (all)	0	2	3
Gallbladder polyp			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hepatic steatosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	4 / 14 (28.57%)
occurrences (all)	0	1	4

Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Nephrolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Arthralgia			

subjects affected / exposed	0 / 14 (0.00%)	5 / 29 (17.24%)	0 / 14 (0.00%)
occurrences (all)	0	5	0
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Haemarthrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haemophilic arthropathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	11 / 29 (37.93%)	8 / 14 (57.14%)
occurrences (all)	3	18	20
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 29 (10.34%)	1 / 14 (7.14%)
occurrences (all)	0	5	1
Pharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Viral infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Varicella			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	2 / 29 (6.90%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Suspected COVID-19			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	2 / 14 (14.29%)
occurrences (all)	0	1	3
COVID-19			
subjects affected / exposed	0 / 14 (0.00%)	6 / 29 (20.69%)	5 / 14 (35.71%)
occurrences (all)	0	6	5
Appendicitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	0 / 14 (0.00%)	10 / 29 (34.48%)	4 / 14 (28.57%)
occurrences (all)	0	17	8
Electrolyte imbalance			



subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 29 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hyperlipidaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Iron deficiency			
subjects affected / exposed	0 / 14 (0.00%)	1 / 29 (3.45%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

<b>Non-serious adverse events</b>	Arm D: 1.5 mg/kg Emicizumab Prophylaxis QW	Arm B: 6 mg/kg Emicizumab Prophylaxis Q4W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	24 / 27 (88.89%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Haematoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 15 (33.33%)	2 / 27 (7.41%)	
occurrences (all)	7	2	
Injection site reaction			
subjects affected / exposed	0 / 15 (0.00%)	5 / 27 (18.52%)	
occurrences (all)	0	29	
Influenza like illness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Chest discomfort			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 27 (3.70%) 1	
Reproductive system and breast disorders Breast hyperplasia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)  Bronchiectasis subjects affected / exposed occurrences (all)  Pulmonary mass subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0  1 / 15 (6.67%) 1  0 / 15 (0.00%) 0  0 / 15 (0.00%) 0	0 / 27 (0.00%) 0  0 / 27 (0.00%) 0  0 / 27 (0.00%) 0  0 / 27 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)  Blood glucose increased subjects affected / exposed occurrences (all)  Blood uric acid increased subjects affected / exposed occurrences (all)  Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2  0 / 15 (0.00%) 0  4 / 15 (26.67%) 8  1 / 15 (6.67%) 1	0 / 27 (0.00%) 0  1 / 27 (3.70%) 1  1 / 27 (3.70%) 2  7 / 27 (25.93%) 14	

Aspartate aminotransferase increased		
subjects affected / exposed	0 / 15 (0.00%)	6 / 27 (22.22%)
occurrences (all)	0	12
Alanine aminotransferase abnormal		
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0
Blood ketone body increased		
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)
occurrences (all)	1	0
Aspartate aminotransferase abnormal		
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0
Weight decreased		
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0
Blood potassium decreased		
subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	2
Bilirubin conjugated increased		
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0
Differential white blood cell count abnormal		
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0
White blood cells urine positive		
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)
occurrences (all)	1	0
White blood cell count abnormal		
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0
Neutrophil count abnormal		
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0
Weight increased		

subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Neutrophil count increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	2	
Ligament sprain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Limb injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Arthropod bite			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Animal bite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Meniscus injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Closed globe injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Skin abrasion			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 27 (7.41%) 2	
Soft tissue injury subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 27 (3.70%) 1	
Palipitations subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 27 (3.70%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 27 (7.41%) 2	
Dizziness subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 27 (3.70%) 1	
Head discomfort subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 27 (0.00%) 0	
Anaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 27 (3.70%) 1	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 27 (0.00%) 0	
Splenomegaly			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 27 (3.70%) 1	
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	4 / 27 (14.81%) 4	
Constipation subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 27 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Abdominal distension subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 27 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 27 (7.41%) 2	
Dental caries subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 27 (7.41%) 2	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Colitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Chronic gastritis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Haemorrhoids			
subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Tooth impacted			
subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	2 / 15 (13.33%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
Gallbladder polyp			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Hepatic steatosis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Dermatitis			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 27 (3.70%) 3	
Renal and urinary disorders Ureterolithiasis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 27 (3.70%) 1	
Haematuria subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 27 (0.00%) 0	
Musculoskeletal and connective tissue disorders Groin pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Muscular weakness subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Arthralgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	4 / 27 (14.81%) 4	
Back pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 27 (0.00%) 0	
Haemarthrosis			



subjects affected / exposed	0 / 15 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Haemophilic arthropathy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 15 (66.67%)	11 / 27 (40.74%)	
occurrences (all)	40	26	
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
Otitis media			
subjects affected / exposed	1 / 15 (6.67%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	1 / 15 (6.67%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Tonsillitis			
subjects affected / exposed	2 / 15 (13.33%)	1 / 27 (3.70%)	
occurrences (all)	4	2	
Gingivitis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Viral infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Laryngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Suspected COVID-19			
subjects affected / exposed	3 / 15 (20.00%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
COVID-19			
subjects affected / exposed	3 / 15 (20.00%)	7 / 27 (25.93%)	
occurrences (all)	3	8	
Appendicitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	2 / 15 (13.33%)	10 / 27 (37.04%)	
occurrences (all)	3	13	
Electrolyte imbalance			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Hyperlipidaemia			

subjects affected / exposed	0 / 15 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Iron deficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2017	<p>Protocol v2, the main changes to the protocol were as follows:</p> <ul style="list-style-type: none"><li>- Update of the safety sections with the most recent safety information regarding 2 patients who developed thrombotic microangiopathy and 2 patients who developed thromboembolic events in Study BH29884. Both occurred in patients with hemophilia A with FVIII inhibitors receiving bypassing agents. Information on the requirements for laboratory monitoring of coagulation status following bypassing agent use was also updated. The section for risks associated with emicizumab was updated accordingly, and microangiopathic hemolytic anemia/thrombotic microangiopathy was newly classified as an AESI. An exclusion criterion to exclude patients at high risk to experience thrombotic microangiopathy was added.</li><li>- Addition of guidance on the use of FVIII in conjunction with emicizumab.</li><li>- Prohibition of the use of short-term prophylaxis with aPCC or PCC concomitantly with emicizumab in order to minimize the risk of thromboembolic and thrombotic microangiopathy events.</li><li>- Replacement of the Wilcoxon rank sum test with the Van Elteren test as a back-up statistical method for the primary analysis to allow a stratified analysis to be performed.</li><li>- The permitted treatment for breakthrough bleeds was specified with guidance regarding the use of concomitant bypassing agents in patients being treated with emicizumab, including dosage and requirements for laboratory monitoring, to minimize the risk of thromboembolic and thrombotic microangiopathy events.</li></ul>
30 October 2017	<p>Protocol v3, the main changes to the protocol were as follows:</p> <ul style="list-style-type: none"><li>- Safety findings related to thrombotic microangiopathy observed in Study BH29884 were updated.</li><li>- Laboratory testing of prothrombin fragment 1+2 for monitoring of patients treated with emicizumab receiving bypassing agents concomitantly was removed.</li><li>- Sample collection for the Research Biosample Repository was removed.</li></ul>
19 July 2019	<p>Protocol v4, the main changes to the protocol were as follows:</p> <ul style="list-style-type: none"><li>- An additional arm (Arm D) was added to the study to characterize the pharmacokinetics, efficacy, and safety of emicizumab prophylaxis in pediatric patients (aged &lt;12 years) who have hemophilia A with inhibitors and previously receiving bypassing agent treatment. Arm D was planned to enroll approximately 15 patients. A schedule of activities was added. The study design and other applicable sections of the protocol were amended to reflect the addition of Arm D.</li><li>- Efficacy, PK, PD, and safety information was added based on available data from Studies ACE002JP, BH29884, BH29992, BH30071, BO39182, and JO39881 to align with Emicizumab IB, Version 12.</li><li>- Patients who were enrolled in Study BH29768 were eligible to enroll in this study, provided they met the eligibility criteria and were able to enroll at a participating site while the study was open for enrollment.</li></ul>
22 April 2023	<p>Protocol v5 has been primarily amended to extend the study. The study will end 3 years after the last Arm D patient completes 1 year treatment and patients still having clinical benefit are transferred to a post-trial continued access solution per Roche Global Policy on Continued Access to Investigational Medicinal Products (see Sections 3.1 and 4.3.4). The study will end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should the post-trial continued access solution be available earlier. Language has been added to clarify that collection of pharmacokinetic (PK)/anti-drug antibody (ADA)/Biomarker samples from Arm D patients will stop when the patient completes the study or after Week 49, whichever occurs first.</p>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported