



Clinical trial results:

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

Summary

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

Results information

Result version number	v1
This version publication date	30 September 2018
First version publication date	30 September 2018

Trial information

Trial identification

Sponsor protocol code	BH30071
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02847637
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	15 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Costa Rica: 9
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	152
EEA total number of subjects	67

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	8
Adults (18-64 years)	139
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	C: No Prophylaxis
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Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial; they were given the opportunity to switch to emicizumab prophylaxis after completing 24 weeks no prophylaxis.

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

Dosage and administration details:

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

Arm title	A: Emicizumab 1.5 mg/kg/week
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Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram per week (mg/kg/week) subcutaneously (SC) for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study.

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

Dosage and administration details:

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

Arm title	B: Emicizumab 3 mg/kg/2 weeks
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Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 3 mg/kg/2 weeks emicizumab SC until the end of study.

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

Dosage and administration details:

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

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

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study.

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

Dosage and administration details:

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

Number of subjects in period 1	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks
Started	18	36	35
Completed 24 weeks on No Prophylaxis	16	0 ^[1]	0
Switched to emicizumab 3 mg/kg/2 weeks	16	0 ^[2]	0
Completed 24 weeks emicizumab treatment	1	35	34
Completed	1	1	0
Not completed	17	35	35
Withdrew from treatment due to AE	-	-	1
First emicizumab dose delayed	1	-	-
Ongoing treatment with emicizumab	16	35	34

Number of subjects in period 1	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Started	63
Completed 24 weeks on No Prophylaxis	0
Switched to emicizumab 3 mg/kg/2 weeks	0
Completed 24 weeks emicizumab treatment	58
Completed	0
Not completed	63

Withdrew from treatment due to AE	-
First emicizumab dose delayed	-
Ongoing treatment with emicizumab	63

Notes:

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

Justification: The milestone of "Switched to emicizumab 3 mg/kg/2 weeks" is only applicable to Arm C: No Prophylaxis.

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

Justification: The milestone of "Completed 24 weeks on No Prophylaxis" is only applicable to Arm C: No Prophylaxis.

Baseline characteristics

Reporting groups

Reporting group title	C: No Prophylaxis
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Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial; they were given the opportunity to switch to emicizumab prophylaxis after completing 24 weeks no prophylaxis.

Reporting group title	A: Emicizumab 1.5 mg/kg/week
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Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram per week (mg/kg/week) subcutaneously (SC) for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study.

Reporting group title	B: Emicizumab 3 mg/kg/2 weeks
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Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 3 mg/kg/2 weeks emicizumab SC until the end of study.

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

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study.

Reporting group values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks
Number of subjects	18	36	35
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	1	0	0
Adults (18-64 years)	17	34	34
From 65-84 years	0	2	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	37.8	39.8	40.4
standard deviation	± 12.9	± 14.0	± 11.4
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	18	36	35
Number of Participants with <9 or ≥9 Bleeds in the Last 24 Weeks Prior to Study Entry Units: Subjects			
Less Than (<) 9 Bleeds	4	9	5

Greater Than or Equal To (\geq) 9 Bleeds	14	27	30
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Number of Target Joints in the Last 24 Weeks Prior to Study Entry			
A target joint was defined as at least 3 bleeds into the same joint over the last 24 weeks prior to study entry.			
Units: target joints			
arithmetic mean	2.2	2.1	2.2
standard deviation	± 1.4	± 1.4	± 1.7

Reporting group values	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)	Total	
Number of subjects	63	152	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	7	8	
Adults (18-64 years)	54	139	
From 65-84 years	2	5	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	36.4		
standard deviation	± 14.4	-	
Sex: Female, Male			
Units: Subjects			
Female	0	0	
Male	63	152	
Number of Participants with <9 or \geq 9 Bleeds in the Last 24 Weeks Prior to Study Entry			
Units: Subjects			
Less Than (<) 9 Bleeds	53	71	
Greater Than or Equal To (\geq) 9 Bleeds	10	81	
Number of Target Joints in the Last 24 Weeks Prior to Study Entry			
A target joint was defined as at least 3 bleeds into the same joint over the last 24 weeks prior to study entry.			
Units: target joints			
arithmetic mean	1.0		
standard deviation	± 1.6	-	

End points

End points reporting groups

Reporting group title	C: No Prophylaxis
Reporting group description: Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial; they were given the opportunity to switch to emicizumab prophylaxis after completing 24 weeks no prophylaxis.	
Reporting group title	A: Emicizumab 1.5 mg/kg/week
Reporting group description: Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram per week (mg/kg/week) subcutaneously (SC) for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study.	
Reporting group title	B: Emicizumab 3 mg/kg/2 weeks
Reporting group description: Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 3 mg/kg/2 weeks emicizumab SC until the end of study.	
Reporting group title	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Reporting group description: Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study.	
Subject analysis set title	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)
Subject analysis set type	Sub-group analysis
Subject analysis set description: This sub-group includes all participants from Arm C who switched to emicizumab prophylaxis after having completed at least 24 weeks on No Prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks (after at least 24 weeks) followed by a maintenance dose of 3 mg/kg/2 weeks SC up to the end of study. The data reported was collected only during emicizumab prophylaxis treatment.	
Subject analysis set title	Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768
Subject analysis set type	Sub-group analysis
Subject analysis set description: This sub-group includes historical data from participants in the non-interventional study (NIS) BH29768 who had received FVIII prophylaxis and were followed for a minimum of 24 weeks on the NIS prior to enrollment in Arm D of this study.	
Subject analysis set title	Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis)
Subject analysis set type	Sub-group analysis
Subject analysis set description: This sub-group includes data from the same participants who had received FVIII prophylaxis in NIS BH29768 prior to study entry and then enrolled in Arm D of this study to receive emicizumab prophylaxis at a dose of 3 mg/kg/week subcutaneously (SC) for 4 weeks, followed by emicizumab 1.5 mg/kg/week SC until the end of study. The data reported was collected only during emicizumab prophylaxis treatment.	
Subject analysis set title	A+Bnise: Pre-Study Episodic FVIII in NIS BH29768
Subject analysis set type	Sub-group analysis
Subject analysis set description: This sub-group includes historical data from participants in the non-interventional study (NIS) BH29768 who had received episodic FVIII treatment and were followed for a minimum of 24 weeks on the NIS prior to enrollment in Arms A or B of this study. A pooled analysis, as opposed to two separate analyses, was performed due to the small number of NIS episodic patients (NISE) randomized to either Arm A or B.	
Subject analysis set title	A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This sub-group includes data from the same participants who had received episodic FVIII treatment in NIS BH29768 prior to study entry and then enrolled in Arms A or B of this study to receive emicizumab prophylaxis at a dose of 3 mg/kg/week subcutaneously (SC) for 4 weeks, followed by either emicizumab 1.5 mg/kg/week SC (Arm A) or emicizumab 3 mg/kg/2 weeks SC (Arm B) until the end of study. A pooled analysis, as opposed to two separate analyses, was performed due to the small number of NIS episodic patients (NISE) randomized to either Arm A or B. The data reported was collected only during emicizumab prophylaxis treatment.

Primary: Annualized Bleeding Rate (ABR) for Treated Bleeds

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

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

End point type	Primary
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End point timeframe:

From Baseline to at least 24 weeks

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated bleed rate per year				
number (confidence interval 95%)	38.2 (22.86 to 63.76)	1.5 (0.89 to 2.47)	1.3 (0.75 to 2.25)	1.6 (1.07 to 2.44)

Statistical analyses

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

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

Comparison groups	A: Emicizumab 1.5 mg/kg/week v C: No Prophylaxis
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.075

Notes:

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

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

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

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

Notes:

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

Secondary: Annualized Bleeding Rate (ABR) for All Bleeds

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

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

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: all bleed rate per year				
number (confidence interval 95%)	47.6 (28.45 to 79.59)	2.5 (1.63 to 3.90)	2.6 (1.63 to 4.29)	3.3 (2.22 to 4.83)

Statistical analyses

Statistical analysis title	ABR Ratio for Arm A versus Arm C
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C \neq 1.	
Comparison groups	C: No Prophylaxis v A: Emicizumab 1.5 mg/kg/week
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.099

Notes:

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

Statistical analysis title	ABR Ratio for Arm B versus Arm C
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C \neq 1.	
Comparison groups	C: No Prophylaxis v B: Emicizumab 3 mg/kg/2 weeks
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.103

Notes:

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

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

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

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

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated joint bleed rate per year				
number (confidence interval 95%)	26.5 (14.67 to 47.79)	1.1 (0.59 to 1.89)	0.9 (0.44 to 1.67)	1.2 (0.70 to 2.01)

Statistical analyses

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

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

Comparison groups	C: No Prophylaxis v A: Emicizumab 1.5 mg/kg/week
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Number of subjects included in analysis	54
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.0001 ^[5]
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Method	Stratified Wald test
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Parameter estimate	ABR Ratio
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Point estimate	0.04
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Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.085

Notes:

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

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

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

Comparison groups	C: No Prophylaxis v B: Emicizumab 3 mg/kg/2 weeks
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.07

Notes:

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

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

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

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

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated spontaneous bleed rate per year				
number (confidence interval 95%)	15.6 (7.60 to 31.91)	1.0 (0.48 to 1.91)	0.3 (0.11 to 0.75)	0.5 (0.23 to 0.94)

Statistical analyses

Statistical analysis title	ABR Ratio for Arm A versus Arm C
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C \neq 1.	
Comparison groups	C: No Prophylaxis v A: Emicizumab 1.5 mg/kg/week
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[7]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.151

Notes:

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

Statistical analysis title	ABR Ratio for Arm B versus Arm C
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C \neq 1.	
Comparison groups	C: No Prophylaxis v B: Emicizumab 3 mg/kg/2 weeks
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[8]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.056

Notes:

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

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

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

The number of treated target joint bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was assessed using a NB regression model, which accounts for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor. A "target joint bleed" is defined as a bleed reported as a joint bleed into a target joint, defined as at least 3 bleeds into the same joint during the last 24 weeks prior to study entry. It is considered a "treated target joint bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed". Bleeds due to surgery/procedure are excluded.

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: treated target joint bleed rate per year				
number (confidence interval 95%)	13.0 (5.22 to 32.33)	0.6 (0.28 to 1.42)	0.7 (0.27 to 1.64)	0.6 (0.26 to 1.53)

Statistical analyses

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

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

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

Notes:

[9] - Not controlled for type I error

Statistical analysis title	ABR Ratio for Arm B versus Arm C
Statistical analysis description:	
H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C ≠ 1.	
Comparison groups	C: No Prophylaxis v B: Emicizumab 3 mg/kg/2 weeks
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[10]
Method	Stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.147

Notes:

[10] - Not controlled for type I error

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

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

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

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

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

Statistical analyses

Statistical analysis title	ABR Ratio - Dnisp: Emicizumab vs FVIII Prophylaxis
Statistical analysis description: H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio \neq 1. This is an intra-participant analysis of the ABR Ratio for a total of 48 participants (not 96) over two different periods: on study while receiving emicizumab prophylaxis (Dnisp: Emicizumab Prophylaxis) versus before study entry while receiving FVIII prophylaxis in NIS BH29768 (Dnisp: Pre-Study FVIII Prophylaxis).	
Comparison groups	Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis) v Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[11]
Method	Non-stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.195
upper limit	0.514

Notes:

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

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

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

This is an intra-participant comparison of the annualized bleeding rate (ABR) for all bleeds on study versus historical ABR in the NIS population previously treated with FVIII prophylaxis in NIS BH29768.

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

End point type	Secondary
End point timeframe:	
From Baseline to at least 24 weeks	

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

Statistical analyses

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

H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio \neq 1.

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

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

Notes:

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

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

FVIII (NISE)

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

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

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

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

Statistical analyses

Statistical analysis title	ABR Ratio Emicizumab Prophylaxis vs Episodic FVIII
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Statistical analysis description:

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

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

Notes:

[13] - Not controlled for type I error

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

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

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

End point type	Secondary
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End point timeframe:

From Baseline to at least 24 weeks

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

Statistical analyses

Statistical analysis title	ABR Ratio Emicizumab Prophylaxis vs Episodic FVIII
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Statistical analysis description:

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

Comparison groups	A+Bnise: Pre-Study Episodic FVIII in NIS BH29768 v A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[14]
Method	Non-stratified Wald test
Parameter estimate	ABR Ratio
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.068

Notes:

[14] - Not controlled for type I error

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

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

The Haem-A-QoL questionnaire is rated by 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 score for each domain ranges from 0 to 100; 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 ANCOVA model and have been adjusted for the following co-variables: baseline score, treatment group, and treatment by baseline interaction term. Analysis includes all adult participants who provided responses at Baseline and Week 25.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

Notes:

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

Justification: Only participants in Arms A, B, and C were randomized in this study.

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	44.32 (± 17.15)	31.81 (± 27.86)	28.35 (± 25.57)	

Statistical analyses

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm A)
Comparison groups	C: No Prophylaxis v A: Emicizumab 1.5 mg/kg/week
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0891 ^[16]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	12.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	26.98

Notes:

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

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm B)
Comparison groups	C: No Prophylaxis v B: Emicizumab 3 mg/kg/2 weeks
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0349 ^[17]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	15.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	30.78

Notes:

[17] - Not controlled for type I error

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

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

The Haem-A-QoL questionnaire is rated by 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 score for each domain ranges from 0 to 100; lower scores reflective of better quality of life. Haem-A-QoL Total Score is the average of all domain scores (range 0 to 100, lower scores reflective of better quality of life). The means were derived via an ANCOVA model and have been adjusted for the following co-variables: baseline score, treatment group, and treatment by baseline interaction term. Analysis includes all adult participants who provided responses at Baseline and Week 25.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

Notes:

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

Justification: Only participants in Arms A, B, and C were randomized in this study.

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	29.95 (\pm 13.56)	24.04 (\pm 15.26)	21.39 (\pm 12.64)	

Statistical analyses

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm A)
Comparison groups	C: No Prophylaxis v A: Emicizumab 1.5 mg/kg/week
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1269 ^[19]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.72
upper limit	13.55

Notes:

[19] - Not controlled for type I error

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

Notes:

[20] - Not controlled for type I error

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

End point title	European Quality of Life 5-Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score in the
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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 ANCOVA model and have been adjusted for the following co-variables: baseline score, treatment group, and treatment by baseline interaction term. Analysis includes all participants who provided responses at Baseline and Week 25.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

Notes:

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

Justification: Only participants in Arms A, B, and C were randomized in this study.

End point values	C: No Prophylaxis	A: Efficizumab 1.5 mg/kg/week	B: Efficizumab 3 mg/kg/2 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	72.57 (± 8.20)	76.61 (± 20.99)	81.72 (± 15.55)	

Statistical analyses

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

Notes:

[22] - Not controlled for type I error

Statistical analysis title	Difference in Adjusted Means (Arm C vs. Arm B)
Comparison groups	C: No Prophylaxis v B: Efficizumab 3 mg/kg/2 weeks

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0373 ^[23]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.74
upper limit	-0.55

Notes:

[23] - Not controlled for type I error

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

End point title	EQ-5D-5L Questionnaire Index Utility Score in the Randomized Population at Week 25 ^[24]
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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: EQ-5D-5L health state profile (descriptive system) and 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. This analysis includes all participants who provided responses at Baseline and Week 25.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

Notes:

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

Justification: Only participants in Arms A, B, and C were randomized in this study.

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	34	29	
Units: units on a scale				
arithmetic mean (standard deviation)	0.63 (± 0.20)	0.76 (± 0.24)	0.76 (± 0.18)	

Statistical analyses

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

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 ^[25]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	-0.04

Notes:

[25] - Not controlled for type I error

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

Notes:

[26] - Not controlled for type I error

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

End point title	Hemophilia-Specific Quality of Life - Short Form (Haemo-QoL-SF) Questionnaire Score in Adolescent Participants (12 to 17 Years of Age) at Week 25
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End point description:

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

End point type	Secondary
End point timeframe:	
Week 25	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[27]	0 ^[28]	0 ^[29]	0 ^[30]
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

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

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

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

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

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[31]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Adverse Event

End point title	Percentage of Participants With at Least One Adverse Event
End point description:	
The percentage of participants experiencing at least one adverse event, including all non-serious and serious adverse events, is reported here. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.	
End point type	Secondary
End point timeframe:	
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	33.3	94.4	85.7	87.3

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	50.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Grade ≥ 3 Adverse Events

End point title	Percentage of Participants With Grade ≥ 3 Adverse Events
End point description:	
The World Health Organization (WHO) toxicity grading scale will be used for assessing adverse event severity. For adverse events that are not specifically listed in the WHO toxicity grading scale, a grade 3 adverse event is defined as: severe, marked limitation in activity, some assistance usually required, medical intervention or therapy required, hospitalization possible; and a grade 4 adverse event is defined as: life-threatening, extreme limitation in activity, significant assistance required, significant medical intervention or therapy required, hospitalization or hospice care probable. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.	
End point type	Secondary
End point timeframe:	
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	5.6	8.3	11.4	9.3

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
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Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events Leading to Withdrawal From Treatment

End point title	Percentage of Participants With Adverse Events Leading to Withdrawal From Treatment
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End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	2.9	0

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

Secondary: Percentage of Participants With Adverse Events of Changes from Baseline in Vital Signs

End point title	Percentage of Participants With Adverse Events of Changes from Baseline in Vital Signs
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End point description:

The percentage of participants with adverse events of changes from baseline in vital signs is reported here. Vital signs measurements consisted of heart and respiratory rate, temperature, and systolic and diastolic blood pressures, with an abnormal vital sign value being outside of the normal range. An abnormal vital sign result is reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); results in a medical intervention or a change in concomitant therapy; or is clinically significant in the investigator's judgment. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events of Changes from Baseline in Physical Examination Findings

End point title	Percentage of Participants With Adverse Events of Changes from Baseline in Physical Examination Findings
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End point description:

Post-baseline physical examination abnormalities that were not present at baseline or worsened were reported as adverse events. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.

End point type	Secondary
End point timeframe:	
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events of Abnormal Laboratory Values

End point title	Percentage of Participants With Adverse Events of Abnormal Laboratory Values
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End point description:

The percentage of participants with adverse events of abnormal laboratory values is reported here. An abnormal laboratory value is defined as a laboratory test result outside of the normal range for hematology or serum chemistries. It is reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); results in a medical intervention or a change in concomitant therapy; or is clinically significant in the investigator's judgment. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.

End point type	Secondary
End point timeframe:	
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Local Injection-Site Reactions

End point title	Percentage of Participants With Local Injection-Site Reactions
End point description:	
Local adverse events that occurred within 24 hours after study drug administration and, in the investigator's opinion, were judged to be related to study drug injection, were captured as an "injection-site reaction" on the Adverse Event electronic Case Report Form (eCRF). An injection-related reaction that was localized was marked as a "local injection-site reaction." At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.	
End point type	Secondary
End point timeframe:	
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	25.0	20.0	33.3

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	12.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Thromboembolic Events

End point title	Percentage of Participants With Thromboembolic Events
End point description:	
At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.	
End point type	Secondary
End point timeframe:	
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Thrombotic Microangiopathy

End point title	Percentage of Participants With Thrombotic Microangiopathy
End point description: At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.	
End point type	Secondary
End point timeframe: From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)	

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reactions

End point title	Percentage of Participants With Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reactions
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End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.

End point type	Secondary
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End point timeframe:

From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)

End point values	C: No Prophylaxis	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	36	35	63
Units: percentage of participants				
number (not applicable)	0	0	0	0

End point values	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Emicizumab Antibodies

End point title	Percentage of Participants With Anti-Emicizumab Antibodies ^[32]
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End point description:

A validated ELISA method was used to analyze the levels of anti-emicizumab antibodies in plasma. A sample was considered positive for anti-emicizumab antibodies if the test result reached or exceeded a pre-determined threshold. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.

End point type	Secondary			
End point timeframe:				
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)				
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: Samples were collected at baseline and only during treatment with emicizumab.				
Participants in Arm C: No Prophylaxis did not receive emicizumab for the first 24 weeks they were on the study; after completing 24 weeks, they were given the opportunity to cross over to Arm Cemi: Emicizumab 3 mg/kg/2 weeks (Switch from No Prophylaxis).				
End point values	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	35	32	60	6
Units: percentage of participants				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With De Novo Development of Factor VIII (FVIII) Inhibitors ^[33]			
End point description:				
Levels of anti-FVIII antibodies (inhibitors) were analyzed using a validated FVIII activity assay. A participant was considered to have developed de novo FVIII inhibitors if the inhibitor levels detected in a post-baseline sample reached or exceeded a pre-determined threshold. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.				
End point type	Secondary			
End point timeframe:				
From Baseline up to 24 weeks after last dose of study drug (up to 2.5 years)				
Notes:				
[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.				
Justification: Samples were collected at baseline and only during treatment with emicizumab. Participants in Arm C: No Prophylaxis did not receive emicizumab for the first 24 weeks they were on the study; after completing 24 weeks, they were given the opportunity to cross over to Arm Cemi: Emicizumab 3 mg/kg/2 weeks (Switch from No Prophylaxis).				
End point values	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	16
Units: percentage of participants				

number (not applicable)	0	0	0	0
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Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (C_{trough}) of Emicizumab

End point title	Trough Plasma Concentration (C _{trough}) of Emicizumab ^[34]
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End point description:

Plasma concentrations of emicizumab were analyzed using a validated Enzyme Linked Immunosorbent Assay (ELISA). The lower limit of quantitation (LLOQ) was 0.1 micrograms per milliliter (µg/mL). The pharmacokinetic (PK) evaluable population included all participants who received at least one dose of emicizumab and had at least one post-dose emicizumab concentration result. Here, n=participants with available data for this endpoint at specified timepoints in each arm (A, B, D, Cemi), respectively. Here, '99999' represents data not calculable due to single participant; '9999' represents data collection not planned for this arm at this timepoint; and '999' represents no data available because either the measurements were below LLOQ or no patient samples were available at that timepoint. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of approximately 1 year.

End point type	Secondary
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End point timeframe:

Predose (Hour 0) on every week during Weeks 1-4, every 2 weeks during Weeks 5-8, every 4 weeks during Weeks 9-24, every 8 weeks during Weeks 25-48, every 12 weeks thereafter up to the end of the study (up to 2 years)

Notes:

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

Justification: Samples were collected at baseline and only during treatment with emicizumab.

Participants in Arm C: No Prophylaxis did not receive emicizumab for the first 24 weeks they were on the study; after completing 24 weeks, they were given the opportunity to cross over to Arm Cemi: Emicizumab 3 mg/kg/2 weeks (Switch from No Prophylaxis).

End point values	A: Emicizumab 1.5 mg/kg/week	B: Emicizumab 3 mg/kg/2 weeks	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)	Cemi: Emicizumab 3 mg/kg/2 weeks (Switch From No Prophylaxis)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	35	63	16
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=35, 33, 61, 0)	999 (± 999)	999 (± 999)	999 (± 999)	9999 (± 9999)
Week 2 (n=36, 35, 61, 0)	16.3 (± 6.1)	16.8 (± 5.9)	17.4 (± 5.4)	9999 (± 9999)
Week 3 (n=36, 35, 62, 0)	29.1 (± 9.3)	29.2 (± 6.5)	30.5 (± 8.7)	9999 (± 9999)
Week 4 (n=35, 34, 60, 0)	41.6 (± 11.9)	41.8 (± 9.5)	42.2 (± 9.4)	9999 (± 9999)
Week 5 (n=34, 35, 62, 0)	48.0 (± 13.7)	48.8 (± 12.3)	54.5 (± 12.5)	9999 (± 9999)
Week 7 (n=32, 33, 60, 0)	47.9 (± 16.1)	48.4 (± 11.4)	52.4 (± 13.4)	9999 (± 9999)
Week 9 (n=33, 33, 63, 0)	49.0 (± 16.4)	47.1 (± 13.7)	55.1 (± 16.1)	9999 (± 9999)
Week 13 (n=33, 31, 59, 0)	48.7 (± 18.3)	48.7 (± 15.6)	56.0 (± 15.7)	9999 (± 9999)
Week 17 (n=31, 32, 56, 0)	51.7 (± 18.8)	49.6 (± 17.2)	55.4 (± 16.8)	9999 (± 9999)
Week 21 (n=29, 33, 58, 0)	48.0 (± 17.7)	46.7 (± 15.3)	55.8 (± 16.3)	9999 (± 9999)

Week 25 (n=28, 26, 47, 13)	51.0 (± 22.2)	46.3 (± 18.0)	55.0 (± 17.5)	999 (± 999)
Week 26 (n=0, 0, 0, 13)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	19.4 (± 9.2)
Week 27 (n=0, 0, 0, 12)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	32.9 (± 14.5)
Week 28 (n=0, 0, 0, 9)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	46.7 (± 17.4)
Week 29 (n=0, 0, 0, 9)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	59.2 (± 25.3)
Week 31 (n=0, 0, 0, 9)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	52.9 (± 17.3)
Week 33 (n=12, 15, 29, 7)	61.8 (± 30.4)	47.6 (± 19.5)	59.9 (± 19.3)	47.0 (± 17.9)
Week 37 (n=0, 0, 0, 7)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	39.2 (± 17.6)
Week 41 (n=6, 10, 10, 4)	45.2 (± 17.9)	47.1 (± 19.7)	54.9 (± 13.4)	40.3 (± 6.4)
Week 45 (n=0, 0, 0, 4)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	43.8 (± 9.4)
Week 49 (n=2, 2, 1, 0)	62.3 (± 30.8)	43.6 (± 13.2)	54.1 (± 99999)	999 (± 999)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to the clinical cut-off date (15 Sep 2017) for primary analysis (approximately 1 year)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	A: Emicizumab 1.5 mg/kg/week
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Reporting group description:

Participants who received episodic treatment with FVIII prior to study entry will receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram per week (mg/kg/week) subcutaneously (SC) for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study (maximum up to 2 years).

Reporting group title	C: No Prophylaxis
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Reporting group description:

Participants who received episodic treatment with FVIII prior to study entry will be randomized to continue episodic FVIII treatment when they start the trial; they will have the opportunity to switch to emicizumab prophylaxis after 24 weeks on-study.

Reporting group title	Cemi: Emicizumab 3 mg/kg/2 weeks (From No Prophylaxis)
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Reporting group description:

This arm includes Arm C participants who switched to emicizumab prophylaxis after completing at least 24 weeks on No Prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks (after at least 24 weeks) followed by a maintenance dose of 3 mg/kg/2 weeks SC up to the end of study. Data reported represents data collected during emicizumab treatment only.

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

Participants who received FVIII prophylaxis prior to study entry will receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week emicizumab SC until the end of study (maximum up to 2 years).

Reporting group title	B: Emicizumab 3 mg/kg/2 weeks
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Reporting group description:

Participants who received episodic treatment with FVIII prior to study entry will receive emicizumab prophylaxis at a dose of 3 mg/kg/week SC for 4 weeks, followed by 3 mg/kg/2 weeks emicizumab SC until the end of study (maximum up to 2 years).

Serious adverse events	A: Emicizumab 1.5 mg/kg/week	C: No Prophylaxis	Cemi: Emicizumab 3 mg/kg/2 weeks (From No Prophylaxis)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 36 (2.78%)	1 / 18 (5.56%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Putamen haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (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			
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Groin pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (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
Synovitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (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
Product issues			
Device loosening			
subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subperiosteal abscess			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (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
Wound infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)	B: Emicizumab 3 mg/kg/2 weeks	
Total subjects affected by serious adverse events			

subjects affected / exposed number of deaths (all causes) number of deaths resulting from adverse events	8 / 63 (12.70%) 0	3 / 35 (8.57%) 0	
Injury, poisoning and procedural complications Femur fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 63 (0.00%) 0 / 0 0 / 0	 1 / 35 (2.86%) 0 / 1 0 / 0	
Vascular disorders Haematoma subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 63 (0.00%) 0 / 0 0 / 0	 0 / 35 (0.00%) 0 / 0 0 / 0	
Cardiac disorders Acute coronary syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 63 (1.59%) 0 / 1 0 / 0	 0 / 35 (0.00%) 0 / 0 0 / 0	
Nervous system disorders Putamen haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 63 (0.00%) 0 / 0 0 / 0	 1 / 35 (2.86%) 0 / 1 0 / 0	
Gastrointestinal disorders Mallory-Weiss syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 63 (1.59%) 0 / 1 0 / 0	 0 / 35 (0.00%) 0 / 0 0 / 0	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 63 (1.59%) 0 / 1 0 / 0	 1 / 35 (2.86%) 0 / 1 0 / 0	
Psychiatric disorders Suicidal ideation			

subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	0 / 63 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subperiosteal abscess			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (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 %

Non-serious adverse events	A: Emicizumab 1.5 mg/kg/week	C: No Prophylaxis	Cemi: Emicizumab 3 mg/kg/2 weeks (From No Prophylaxis)
Total subjects affected by non-serious adverse events subjects affected / exposed	26 / 36 (72.22%)	5 / 18 (27.78%)	8 / 16 (50.00%)
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Papilloma subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Injury, poisoning and procedural complications			
Bite subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 14	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0
Excoriation subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0
Muscle strain			

subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0
Laceration subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Ligament sprain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Tooth fracture subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 6	1 / 18 (5.56%) 1	1 / 16 (6.25%) 1
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	9 / 36 (25.00%) 35	0 / 18 (0.00%) 0	2 / 16 (12.50%) 2
Pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 18 (0.00%) 0	2 / 16 (12.50%) 3
Diarrhoea subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 18 (5.56%) 2	1 / 16 (6.25%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0

Vomiting subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 18 (5.56%) 2	0 / 16 (0.00%) 0
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 19	1 / 18 (5.56%) 1	1 / 16 (6.25%) 3
Back pain subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 18 (5.56%) 2	0 / 16 (0.00%) 0
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 18 (0.00%) 0	0 / 16 (0.00%) 0
Gastric infection subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 18 (0.00%) 0	1 / 16 (6.25%) 1
Localised infection			

subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 36 (5.56%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Pharyngitis			
subjects affected / exposed	3 / 36 (8.33%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Sinusitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 36 (11.11%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	4	2	0

Non-serious adverse events	D: Emicizumab 1.5 mg/kg/week (Pre-study FVIII Prophylaxis)	B: Emicizumab 3 mg/kg/2 weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 63 (68.25%)	23 / 35 (65.71%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 63 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 63 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 63 (4.76%)	2 / 35 (5.71%)	
occurrences (all)	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papilloma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			

Bite			
subjects affected / exposed	0 / 63 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Contusion			
subjects affected / exposed	4 / 63 (6.35%)	1 / 35 (2.86%)	
occurrences (all)	5	2	
Excoriation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	4 / 63 (6.35%)	0 / 35 (0.00%)	
occurrences (all)	5	0	
Tooth fracture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 63 (12.70%)	4 / 35 (11.43%)	
occurrences (all)	17	19	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	20 / 63 (31.75%)	7 / 35 (20.00%)	
occurrences (all)	29	17	
Pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 63 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	

Gastrointestinal disorders	Abdominal pain			
	subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
	occurrences (all)	1	0	
	Diarrhoea			
	subjects affected / exposed	1 / 63 (1.59%)	2 / 35 (5.71%)	
	occurrences (all)	1	3	
	Nausea			
	subjects affected / exposed	3 / 63 (4.76%)	2 / 35 (5.71%)	
	occurrences (all)	3	2	
	Vomiting			
	subjects affected / exposed	0 / 63 (0.00%)	0 / 35 (0.00%)	
	occurrences (all)	0	0	
Skin and subcutaneous tissue disorders				
	Pruritus			
	subjects affected / exposed	1 / 63 (1.59%)	1 / 35 (2.86%)	
	occurrences (all)	1	1	
Psychiatric disorders				
	Insomnia			
	subjects affected / exposed	0 / 63 (0.00%)	2 / 35 (5.71%)	
	occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders				
	Arthralgia			
	subjects affected / exposed	14 / 63 (22.22%)	6 / 35 (17.14%)	
	occurrences (all)	35	13	
	Back pain			
	subjects affected / exposed	0 / 63 (0.00%)	1 / 35 (2.86%)	
	occurrences (all)	0	1	
	Musculoskeletal stiffness			
	subjects affected / exposed	0 / 63 (0.00%)	0 / 35 (0.00%)	
	occurrences (all)	0	0	
	Pain in extremity			
	subjects affected / exposed	3 / 63 (4.76%)	3 / 35 (8.57%)	
	occurrences (all)	3	3	
Infections and infestations				

Conjunctivitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	5 / 63 (7.94%)	3 / 35 (8.57%)	
occurrences (all)	5	3	
Gastric infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	10 / 63 (15.87%)	6 / 35 (17.14%)	
occurrences (all)	13	8	
Pharyngitis			
subjects affected / exposed	2 / 63 (3.17%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Sinusitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	8 / 63 (12.70%)	4 / 35 (11.43%)	
occurrences (all)	8	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported