



Clinical trial results:

A Multicenter, Open-Label, Phase III Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Emicizumab Given Every 4 Weeks (Q4W) in Patients with Hemophilia A

Summary

EudraCT number	2016-001094-33
Trial protocol	ES PL BE
Global end of trial date	

Results information

Result version number	v1
This version publication date	20 December 2018
First version publication date	20 December 2018

Trial information

Trial identification

Sponsor protocol code	BO39182
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03020160
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 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the Pharmacokinetics (PK) Run-In and the Expansion Parts of this study are the following:

PK Run-In Part Objectives:

- To investigate the pharmacokinetics (PK) of emicizumab after single and multiple (every 4 weeks [Q4W]) subcutaneous (SC) administration of 6 milligrams per kilogram (mg/kg)
- To assess the safety and tolerability of emicizumab after 6 mg/kg Q4W SC administration

Expansion Part Objectives:

- To evaluate the clinical effect of prophylactic emicizumab on the number of treated bleeds over time, all bleeds over time, joint bleeds over time, target joint bleeds over time, and spontaneous bleeds over time
- To evaluate the health-related quality of life, health status, and patient preference for treatment regimen
- To evaluate the overall safety of emicizumab given Q4W in patients with hemophilia A
- To characterize the pharmacokinetics of multiple Q4W doses of 6mg/kg emicizumab

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. Each study subject or their legally authorized representative was required to read and sign an Informed Consent Form or an Informed Assent Form (ages 12-17), as applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	48
EEA total number of subjects	24

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)	4
Adults (18-64 years)	41
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 7 patients were screened and enrolled in the PK run-in cohort of the study. For the expansion cohort, a total of 44 patients were screened, of whom 41 were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Emicizumab: PK Run-In Part

Arm description:

Subjects will received SC emicizumab at a dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Emicizumab
Investigational medicinal product code	B02BX06
Other name	Hemlibra, RO5534262
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects will received SC emicizumab at a dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.

Arm title	Emicizumab: Expansion Part
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Arm description:

Subjects will receive SC emicizumab at a loading dose of 3 mg/kg every week for initial 4 weeks followed by a maintenance dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Emicizumab
Investigational medicinal product code	B02BX06
Other name	Hemlibra, RO5534262
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects will receive SC emicizumab at a loading dose of 3 mg/kg every week for initial 4 weeks followed by a maintenance dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.

Number of subjects in period 1	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part
Started	7	41
Completed 24 weeks in the study	7	41
Completed	0	0
Not completed	7	41

Continuing to receive emicizumab	7	41
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Baseline characteristics

Reporting groups

Reporting group title	Emicizumab: PK Run-In Part
Reporting group description:	
Subjects will received SC emicizumab at a dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.	
Reporting group title	Emicizumab: Expansion Part
Reporting group description:	
Subjects will receive SC emicizumab at a loading dose of 3 mg/kg every week for initial 4 weeks followed by a maintenance dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.	

Reporting group values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part	Total
Number of subjects	7	41	48
Age Categorical			
Units: Subjects			
Adolescents (12-17 years)	1	3	4
Adults (18-64 years)	6	35	41
Elderly (From 65-84 years)	0	3	3
Age continuous			
Units: years			
arithmetic mean	37.3	38.7	
standard deviation	± 13.3	± 15.7	-
Sex: Female, Male			
Units: Subjects			
Female	0	0	0
Male	7	41	48
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	8	10
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	5	31	36
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	6	38	44
Unknown or Not Reported	0	1	1
Number of Subjects with 0, 1, or >1 Target Joints in the Last 24 Weeks Prior to Study Entry			
A target joint was defined as a a joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry.			
Units: Subjects			
0 Target Joints	1	16	17
1 Target Joint	2	8	10
>1 Target Joints	4	17	21

End points

End points reporting groups

Reporting group title	Emicizumab: PK Run-In Part
Reporting group description:	
Subjects will received SC emicizumab at a dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.	
Reporting group title	Emicizumab: Expansion Part
Reporting group description:	
Subjects will receive SC emicizumab at a loading dose of 3 mg/kg every week for initial 4 weeks followed by a maintenance dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.	

Primary: Expansion Part: Annualized Bleeding Rate (ABR) for Treated Bleeds

End point title	Expansion Part: Annualized Bleeding Rate (ABR) for Treated Bleeds ^{[1][2]}
End point description:	
The number of treated bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times. 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 time between treatment and the preceding bleed. A bleed and the first treatment thereafter and before a new bleed starts, are considered to be pairs, with the following exception: if multiple bleeds occur on the same calendar day, the subsequent treatment is considered to apply for each of these multiple bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location are counted as one bleed if the second bleed occurs within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure are excluded.	
End point type	Primary
End point timeframe:	
From Baseline to at least 24 weeks	

Notes:

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

Justification: No formal hypothesis testing was planned for this study. All analyses are descriptive.

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: treated bleed rate per year				
number (confidence interval 95%)	2.4 (1.38 to 4.28)			

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Part: Annualized Bleeding Rate (ABR) for All Bleeds

End point title	Expansion Part: Annualized Bleeding Rate (ABR) for All
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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 analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., the time that each participant stays in the study). In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule was implemented exactly as defined for the "treated bleeds" outcome measure. For non-treated bleeds, the 72-hour rule was implemented by calculating a treatment-free period of 72 hours from the bleed itself.

End point type	Primary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

Justification: No formal hypothesis testing was planned for this study. All analyses are descriptive.

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: all bleed rate per year				
number (confidence interval 95%)	4.5 (3.10 to 6.60)			

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Part: Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds

End point title	Expansion Part: Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds ^{[5][6]}
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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 analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., the time that each participant stays in the study). 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 also fulfills the conditions of a treated bleed (see ABR for Treated Bleeds for the definition). Treated bleeds that fulfilled the 72-hour rule were included in the analysis of spontaneous bleeds. 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

Notes:

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

Justification: No formal hypothesis testing was planned for this study. All analyses are descriptive.

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: treated spontaneous bleed rate per year				
number (confidence interval 95%)	0.6 (0.27 to 1.53)			

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Part: Annualized Bleeding Rate (ABR) for Treated Joint Bleeds

End point title	Expansion Part: Annualized Bleeding Rate (ABR) for Treated Joint Bleeds ^[7] ^[8]
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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 analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., the time that each participant stays in the study). A "joint bleed" is defined as a bleed with type 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. A "treated joint bleed" is a joint bleed that also fulfills the conditions of a treated bleed (see ABR for Treated Bleeds for the definition). Treated bleeds that fulfilled the 72-hour rule were included in the analysis of joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Primary
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End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

Justification: No formal hypothesis testing was planned for this study. All analyses are descriptive.

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: treated joint bleed rate per year				
number (confidence interval 95%)	1.7 (0.82 to 3.68)			

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Part: Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds

End point title	Expansion Part: Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds ^{[9][10]}
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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 analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., the time that each participant stays in the study). A "target joint bleed" is defined as a joint bleed in a target joint, which is a joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry. A "treated target joint bleed" is a target joint bleed that also fulfills the conditions of a treated bleed (see ABR for Treated Bleeds for the definition). 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

Notes:

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

Justification: No formal hypothesis testing was planned for this study. All analyses are descriptive.

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: treated target joint bleed rate per year				
number (confidence interval 95%)	1.0 (0.31 to 3.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Change from Baseline to Week 25 in the Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Total Score for Adult Subjects (≥18 Years of Age)

End point title	Expansion Part: Change from Baseline to Week 25 in the Hemophilia A Quality of Life (Haem-A-QoL) Questionnaire Total Score for Adult Subjects (≥18 Years of Age) ^[11]
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End point description:

The Haem-A-QoL is a patient-reported questionnaire that was designed for adult participants with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feelings, relationships, treatment, view of yourself, and outlook for the future) and a scale representing Total Score. Items are rated along five response options: never, rarely, sometimes, often, or all the time; although for some items there is also a "not applicable" option. Scale scores range from 0 to 100 with lower scores reflective of better quality of life. A decrease of 7 points or more on the Total Score was defined as the threshold for a clinically meaningful improvement. The analysis included all adult subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline and Week 25.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-13.62 (-18.36 to -8.88)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Percentage of Adult Subjects (≥18 Years of Age) with a Clinically Meaningful Improvement from Baseline to Week 25 in the Haem-A-QoL Questionnaire Total Score

End point title	Expansion Part: Percentage of Adult Subjects (≥18 Years of Age) with a Clinically Meaningful Improvement from Baseline to Week 25 in the Haem-A-QoL Questionnaire Total Score ^[12]
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End point description:

The Haem-A-QoL is a patient-reported questionnaire that was designed for adult participants with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feelings, relationships, treatment, view of yourself, and outlook for the future) and a scale representing Total Score. Items are rated along five response options: never, rarely, sometimes, often, or all the time; although for some items there is also a "not applicable" option. Scale scores range from 0 to 100 with lower scores reflective of better quality of life. A decrease of 7 points or more on the Total Score was defined as the threshold for a clinically meaningful improvement. The analysis included all adult subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline

and Week 25.

End point type	Secondary
End point timeframe:	
Baseline, Week 25	

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percentage of subjects				
number (not applicable)	67.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Change from Baseline to Week 25 in the Haem-A-QoL Questionnaire Physical Health Score for Adult Subjects (≥18 Years of Age)

End point title	Expansion Part: Change from Baseline to Week 25 in the Haem-A-QoL Questionnaire Physical Health Score for Adult Subjects (≥18 Years of Age) ^[13]
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End point description:

The Haem-A-QoL is a patient-reported questionnaire that was designed for adult participants with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feelings, relationships, treatment, view of yourself, and outlook for the future) and a scale representing Total Score. Items are rated along five response options: never, rarely, sometimes, often, or all the time; although for some items there is also a "not applicable" option. Scale scores range from 0 to 100 with lower scores reflective of better quality of life. A decrease of 10 points or more on the Physical Health Score was defined as the threshold for a clinically meaningful improvement. The analysis included all adult subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline and Week 25.

End point type	Secondary
End point timeframe:	
Baseline, Week 25	

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-15.14 (-22.44 to -7.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Percentage of Adult Subjects (≥18 Years of Age) with a Clinically Meaningful Improvement from Baseline to Week 25 in the Haem-A-QoL Questionnaire Physical Health Score

End point title	Expansion Part: Percentage of Adult Subjects (≥18 Years of Age) with a Clinically Meaningful Improvement from Baseline to Week 25 in the Haem-A-QoL Questionnaire Physical Health Score ^[14]
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End point description:

The Haem-A-QoL is a patient-reported questionnaire that was designed for adult participants with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feelings, relationships, treatment, view of yourself, and outlook for the future) and a scale representing Total Score. Items are rated along five response options: never, rarely, sometimes, often, or all the time; although for some items there is also a "not applicable" option. Scale scores range from 0 to 100 with lower scores reflective of better quality of life. A decrease of 10 points or more on the Physical Health Score was defined as the threshold for a clinically meaningful improvement. The analysis included all adult subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline and Week 25.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percentage of subjects				
number (not applicable)	67.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Change from Baseline to Week 25 in the Hemophilia-Quality of Life-Short Form (Haemo-QoL-SF) Questionnaire Total Score for Adolescent Subjects (12-17 Years of Age)

End point title	Expansion Part: Change from Baseline to Week 25 in the Hemophilia-Quality of Life-Short Form (Haemo-QoL-SF) Questionnaire Total Score for Adolescent Subjects (12-17 Years of Age) ^[15]
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End point description:

The Haemo-QoL-SF was developed in a series of age-related questionnaires to measure health-related quality of life (HRQoL) in children and adolescents with hemophilia. The short version for older children containing 35 items was selected for adolescents in this study. Items are rated along five response options: never, rarely, sometimes, often, or all the time. This version covers nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia, and treatment). Scale scores range from 0 to 100, with lower scores indicating better HRQoL. The analysis included all adolescent subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline and Week 25. Given the small number of adolescent subjects, the results of the Haemo-QoL-SF questionnaire should be interpreted with caution.

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: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: units on a scale				
arithmetic mean (standard deviation)	-8.10 (± 6.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Change from Baseline to Week 25 in the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score

End point title	Expansion Part: Change from Baseline to Week 25 in the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score ^[16]
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End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score, as well as a visual analogue scale (VAS) that measures health state. The VAS is designed to rate the subject'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. An increase in the VAS score of 7 points or greater was defined as the threshold for a meaningful improvement. The analysis included all subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline

and Week 25.

End point type	Secondary
End point timeframe:	
Baseline, Week 25	

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: units on a scale				
arithmetic mean (confidence interval 95%)	5.53 (1.15 to 9.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Percentage of Subjects with a Meaningful Improvement from Baseline to Week 25 in the EQ-5D-5L Questionnaire VAS Score

End point title	Expansion Part: Percentage of Subjects with a Meaningful Improvement from Baseline to Week 25 in the EQ-5D-5L Questionnaire VAS Score ^[17]
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End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score, as well as a visual analogue scale (VAS) that measures health state. The VAS is designed to rate the subject'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. An increase in the VAS score of 7 points or greater was defined as the threshold for a meaningful improvement. The analysis included all subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline and Week 25.

End point type	Secondary
End point timeframe:	
Baseline, Week 25	

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of subjects				
number (not applicable)	35.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Change from Baseline to Week 25 in the EQ-5D-5L Questionnaire Index Utility Score

End point title	Expansion Part: Change from Baseline to Week 25 in the EQ-5D-5L Questionnaire Index Utility Score ^[18]
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End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single summary score for the Index Utility Score where overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction. An increase in the Index Utility Score of 0.07 points or greater was defined as the threshold for a meaningful improvement. The analysis included all subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire 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: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: units on a scale				
arithmetic mean (confidence interval 95%)	0.06 (0.03 to 0.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Percentage of Subjects with a Meaningful Improvement from Baseline to Week 25 in the EQ-5D-5L Questionnaire Index Utility Score

End point title	Expansion Part: Percentage of Subjects with a Meaningful Improvement from Baseline to Week 25 in the EQ-5D-5L Questionnaire Index Utility Score ^[19]
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End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single summary score for the Index Utility Score where overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction. An increase in the Index Utility Score of 0.07 points or greater was defined as the threshold for a meaningful improvement. The analysis included all subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline and Week 25.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of subjects				
number (not applicable)	47.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Proportion of Days Away from Work to Expected Days at Work in the Previous Four Weeks

End point title	Expansion Part: Proportion of Days Away from Work to Expected Days at Work in the Previous Four Weeks ^[20]
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End point description:

Subjects enrolled in the expansion part of the study reported at each time point the number of days away from work (i.e., days of work missed) and the expected number of days at work in the previous four weeks, which is reported here as the proportion of the number of days away from work to the expected number of days at work. The number of subjects who were working and completed the questionnaire at Baseline, Week 13, and Week 25 is reported in brackets.

End point type	Secondary
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End point timeframe:

Predose at Baseline, Weeks 13 and 25, and every 12 weeks thereafter up to study completion/early termination (up to approximately 4 years)

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on

subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: away/expected work days				
arithmetic mean (confidence interval 95%)				
Baseline (n = 28)	0.05 (0.01 to 0.10)			
Week 13 (n = 28)	0.00 (0.00 to 0.00)			
Week 25 (n = 27)	0.01 (0.00 to 0.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Proportion of Days Away from School to Expected Days at School in the Previous Four Weeks

End point title	Expansion Part: Proportion of Days Away from School to Expected Days at School in the Previous Four Weeks ^[21]
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End point description:

Subjects enrolled in the expansion part of the study reported at each time point the number of days away from school (i.e., days of school missed) and the expected number of days at school in the previous four weeks, which is reported here as the proportion of the number of days away from school to the expected number of days at school. The number of subjects who were enrolled in school and completed the questionnaire at Baseline, Week 13, and Week 25 is reported in brackets.

End point type	Secondary
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End point timeframe:

Predose at Baseline, Weeks 13 and 25, and every 12 weeks thereafter up to study completion/early termination (up to approximately 4 years)

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: away/expected school days				
arithmetic mean (confidence interval 95%)				
Baseline (n = 10)	0.12 (0.01 to 0.24)			

Week 13 (n = 8)	0.00 (0.00 to 0.00)			
Week 25 (n = 10)	0.03 (0.00 to 0.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Number of Days Hospitalized

End point title	Expansion Part: Number of Days Hospitalized ^[22]
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End point description:

At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks); all subjects had completed at least 24 weeks of treatment.

End point type	Secondary
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End point timeframe:

From Baseline until at least 24 weeks of treatment through to study completion (up to approximately 4 years)

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: days				
arithmetic mean (standard deviation)	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Percentage of Subjects Who Preferred Either the New Emicizumab Subcutaneous (SC) Treatment or Their Previous Hemophilia Intravenous (IV) Treatment, or Had No Preference, as Assessed Using the Emicizumab Preference Survey

End point title	Expansion Part: Percentage of Subjects Who Preferred Either the New Emicizumab Subcutaneous (SC) Treatment or Their Previous Hemophilia Intravenous (IV) Treatment, or Had No Preference, as Assessed Using the Emicizumab Preference Survey ^[23]
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End point description:

The Emicizumab Preference Survey is a fit-for-purpose questionnaire developed by the sponsor to record the subject's preference for treatment with intravenous (IV) factor VIII (FVIII) or subcutaneous (SC) emicizumab, or no preference.

End point type	Secondary
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End point timeframe:

Predose at Week 17

Notes:

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

Justification: The efficacy end points of this study were planned to be primarily evaluated based on subjects in the expansion cohort of the study. The overall sample size of 40 subjects in the expansion cohort was based on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 subjects would, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percentage of participants				
number (confidence interval 95%)				
Prefer the New Emicizumab SC Treatment	100 (91.40 to 100.00)			
Prefer My Old Hemophilia Treatment (IV)	0.0 (0.00 to 8.60)			
Have No Preference	0.0 (0.00 to 8.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Run-In Part: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Emicizumab

End point title	PK Run-In Part: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Emicizumab ^[24]
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End point description:

End point type	Secondary
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End point timeframe:

Predose (0 hr) and 8 hrs postdose on Day 1; Days

3,5,8,11,15,18,22,25,29,36,43,50,57,85,113,141,148,155,162,169, once between 2 emicizumab administrations between Weeks 9 and 21, and once every 12 weeks from Week 25 to study completion (up to 4 years)

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: The study plan was to evaluate Tmax only in the PK run-in cohort of the study.

End point values	Emicizumab: PK Run-In Part			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: day				
median (full range (min-max))				

After First Dose (Weeks 1-5)	6.95 (3.99 to 7.18)			
After Sixth Dose (Weeks 21-25)	6.98 (6.90 to 14.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Run-In Part: Maximum Observed Plasma Concentration (Cmax) of Emicizumab

End point title	PK Run-In Part: Maximum Observed Plasma Concentration (Cmax) of Emicizumab ^[25]
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End point description:

End point type	Secondary
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End point timeframe:

Predose (0 hr) and 8 hrs postdose on Day 1; Days 3,5,8,11,15,18,22,25,29,36,43,50,57,85,113,141,148,155,162,169, once between 2 emicizumab administrations between Weeks 9 and 21, and once every 12 weeks from Week 25 to study completion (up to 4 years)

Notes:

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

Justification: The study plan was to evaluate Cmax only in the PK run-in cohort of the study.

End point values	Emicizumab: PK Run-In Part			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
After First Dose (Weeks 1-5)	31.8 (± 19.3)			
After Sixth Dose (Weeks 21-25)	62.7 (± 17.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Run-In Part: Area Under the Plasma Concentration-Time Curve from Time Zero to End of Dosing Interval (AUC[0-tau]) of Emicizumab

End point title	PK Run-In Part: Area Under the Plasma Concentration-Time Curve from Time Zero to End of Dosing Interval (AUC[0-tau]) of Emicizumab ^[26]
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End point description:

End point type	Secondary
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End point timeframe:

Predose (0 hr) and 8 hrs postdose on Day 1; Days

3,5,8,11,15,18,22,25,29,36,43,50,57,85,113,141,148,155,162,169, once between 2 emicizumab administrations between Weeks 9 and 21, and once every 12 weeks from Week 25 to study completion (up to 4 years)

Notes:

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

Justification: The study plan was to evaluate AUC[0-tau] only in the PK run-in cohort of the study.

End point values	Emicizumab: PK Run-In Part			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: day*µg/mL				
geometric mean (geometric coefficient of variation)				
After First Dose (Weeks 1-5)	663 (± 19.6)			
After Sixth Dose (Weeks 21-25)	1420 (± 20.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Run-In Part: Area Under the Plasma Concentration-Time Curve from Time Zero to Extrapolated Infinite Time (AUC[0-inf]) of Emicizumab

End point title	PK Run-In Part: Area Under the Plasma Concentration-Time Curve from Time Zero to Extrapolated Infinite Time (AUC[0-inf]) of Emicizumab ^[27]
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End point description:

t_{1/2} was not properly estimated after the first dose due to sampling time and dosing schedule; hence, dependent PK parameters, such as AUC[0-inf], could not be estimated after the sixth dose of emicizumab (as indicated by the entered value '99999').

End point type	Secondary
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End point timeframe:

Predose (0 hr) and 8 hrs postdose on Day 1; Days

3,5,8,11,15,18,22,25,29,36,43,50,57,85,113,141,148,155,162,169, once between 2 emicizumab administrations between Weeks 9 and 21, and once every 12 weeks from Week 25 to study completion (up to 4 years)

Notes:

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

Justification: The study plan was to evaluate AUC[0-inf] only in the PK run-in cohort of the study.

End point values	Emicizumab: PK Run-In Part			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: day*µg/mL				
geometric mean (geometric coefficient of variation)				
After First Dose (Weeks 1-5)	1490 (± 27.2)			
After Sixth Dose (Weeks 21-25)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Run-In Part: Apparent Plasma Terminal Half-Life (t_{1/2}) of Emicizumab

End point title	PK Run-In Part: Apparent Plasma Terminal Half-Life (t _{1/2}) of Emicizumab ^[28]
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End point description:

t_{1/2} was not properly estimated after the first dose due to sampling time and dosing schedule; hence, t_{1/2} could not be determined after the sixth dose of emicizumab, as indicated by the entered value '99999'.

End point type	Secondary
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End point timeframe:

Predose (0 hr) and 8 hrs postdose on Day 1; Days

3,5,8,11,15,18,22,25,29,36,43,50,57,85,113,141,148,155,162,169, once between 2 emicizumab administrations between Weeks 9 and 21, and once every 12 weeks from Week 25 to study completion (up to 4 years)

Notes:

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

Justification: The study plan was to evaluate t_{1/2} only in the PK run-in cohort of the study.

End point values	Emicizumab: PK Run-In Part			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: day				
geometric mean (geometric coefficient of variation)				
After First Dose (Weeks 1-5)	29.5 (± 38.5)			
After Sixth Dose (Weeks 21-25)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Run-In Part: Apparent Clearance (CL/F) of Emicizumab

End point title	PK Run-In Part: Apparent Clearance (CL/F) of Emicizumab ^[29]
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End point description:

Only CL/F is reported after the first dose; the apparent clearance at steady state (CL_{ss}/F) is reported after the sixth dose instead. This is because t_{1/2} was not properly estimated after the first dose due to sampling time and dosing schedule, and dependent PK parameters, such as CL/F, could not be estimated.

End point type	Secondary
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End point timeframe:

Predose (0 hr) and 8 hrs postdose on Day 1; Days

3,5,8,11,15,18,22,25,29,36,43,50,57,85,113,141,148,155,162,169, once between 2 emicizumab administrations between Weeks 9 and 21, and once every 12 weeks from Week 25 to study completion (up to 4 years)

Notes:

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

Justification: The study plan was to evaluate CL/F only in the PK run-in cohort of the study.

End point values	Emicizumab: PK Run-In Part			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mL/h				
geometric mean (geometric coefficient of variation)				
After First Dose (Weeks 1-5)	10.7 (± 23.9)			
After Sixth Dose (Weeks 21-25)	11.1 (± 20.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Minimum Observed Plasma Concentration (Cmin) of Emicizumab

End point title	Expansion Part: Minimum Observed Plasma Concentration (Cmin) of Emicizumab ^[30]
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End point description:

The analysis included all subjects enrolled in the expansion part of the study. The value 'n =' represents the number of subjects with an evaluable sample at a given time point. '9999' indicates that Cmin could not be estimated because the value was lower than the quantifiable limit.

End point type	Secondary
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End point timeframe:

Predose at Weeks 1, 2, 3, 4, 5, 9, 13, 17, 21, 25, once every 12 weeks from Week 25 to study completion (up to approximately 4 years)

Notes:

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

Justification: The study plan was to evaluate Cmin only in the expansion cohort of the study.

End point values	Emicizumab: Expansion Part			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Week 1 (n = 41)	9999 (± 9999)			
Week 2 (n = 41)	16.0 (± 36.8)			
Week 3 (n = 41)	29.8 (± 30.5)			
Week 4 (n = 40)	41.3 (± 32.4)			

Week 5 (n = 41)	48.8 (± 32.2)			
Week 9 (n = 41)	40.4 (± 45.7)			
Week 13 (n = 40)	38.8 (± 48.8)			
Week 17 (n = 41)	36.1 (± 53.8)			
Week 21 (n = 41)	37.4 (± 48.5)			
Week 25 (n = 41)	37.7 (± 52.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with At Least One Adverse Event

End point title	Number of Subjects with At Least One Adverse Event
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End point description:

The number of subjects experiencing at least one adverse event, including all non-serious and serious adverse events, is reported here. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

End point type	Secondary
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End point timeframe:

From Baseline to study completion (up to approximately 4 years)

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	7	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Grade ≥3 Adverse Events

End point title	Number of Subjects with Grade ≥3 Adverse Events
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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. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

End point type	Secondary
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End point timeframe:

From Baseline to study completion (up to approximately 4 years)

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events Leading to Withdrawal from Treatment

End point title	Number of Subjects with Adverse Events Leading to Withdrawal from Treatment
End point description:	
The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).	
End point type	Secondary
End point timeframe:	
From Baseline to study completion (up to approximately 4 years)	

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events of Changes from Baseline in Vital Signs

End point title	Number of Subjects with Adverse Events of Changes from Baseline in Vital Signs
End point description:	
The number of subjects 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. The analysis included all subjects who received at	

least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

End point type	Secondary
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End point timeframe:

From Baseline to study completion (up to approximately 4 years)

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events of Changes from Baseline in Physical Examination Findings

End point title	Number of Subjects 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. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

End point type	Secondary
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End point timeframe:

From Baseline to study completion (up to approximately 4 years)

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events of Abnormal Laboratory Values

End point title	Number of Subjects with Adverse Events of Abnormal Laboratory Values
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End point description:

The number of subjects 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. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

End point type	Secondary
End point timeframe:	
From Baseline to study completion (up to approximately 4 years)	

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Local Injection-Site Reactions

End point title	Number of Subjects 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." The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).	
End point type	Secondary
End point timeframe:	
From Baseline to study completion (up to approximately 4 years)	

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	1	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Thromboembolic Events

End point title	Number of Subjects with Thromboembolic Events
End point description: The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).	
End point type	Secondary
End point timeframe: From Baseline to study completion (up to approximately 4 years)	

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Thrombotic Microangiopathy

End point title	Number of Subjects with Thrombotic Microangiopathy
End point description: The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).	
End point type	Secondary
End point timeframe: From Baseline to study completion (up to approximately 4 years)	

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reactions

End point title	Number of Subjects with Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reactions
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End point description:

The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

End point type	Secondary
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End point timeframe:

From Baseline to study completion (up to approximately 4 years)

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Anti-Drug Antibodies to Emicizumab

End point title	Number of Subjects with Anti-Drug Antibodies to Emicizumab
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End point description:

A validated enzyme-linked immunosorbent assay (ELISA) method was used to analyze the levels of anti-drug antibodies to emicizumab in blood plasma samples. A sample was considered positive for anti-drug antibodies if the test result reached or exceeded a pre-determined threshold. The analysis included all subjects who received at least one dose of emicizumab. The number of subjects analyzed indicates those with both baseline and post-baseline assessments. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

End point type	Secondary
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End point timeframe:

Baseline, Weeks 5, 9, 13, 17, 21, and 25, and every 12 weeks thereafter until study completion (up to approximately 4 years)

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	40		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With De Novo Development of Anti-Factor VIII (FVIII) Antibodies

End point title	Number of Subjects With De Novo Development of Anti-Factor VIII (FVIII) Antibodies
End point description: The levels of anti-FVIII antibodies (inhibitors) were analyzed using a validated FVIII activity assay. A subject 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. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).	
End point type	Secondary
End point timeframe: Baseline, Weeks 9 and 17 (for non-inhibitor subjects only), Week 25, and every 12 weeks thereafter until study completion (up to approximately 4 years)	

End point values	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until the clinical cut-off date (15-Dec-2017) for the primary analysis (median observation time was 43.71 weeks [range: 41.7-45.7 weeks])

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	Emicizumab: PK Run-In Part
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Reporting group description:

Participants will received SC emicizumab at a dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.

Reporting group title	Emicizumab: Expansion Part
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Reporting group description:

Participants will received SC emicizumab at a loading dose of 3 mg/kg every week for initial 4 weeks followed by a maintenance dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.

Serious adverse events	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 41 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (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			
Rhabdomyolysis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Emicizumab: PK Run-In Part	Emicizumab: Expansion Part	
Total subjects affected by non-serious adverse events subjects affected / exposed	7 / 7 (100.00%)	30 / 41 (73.17%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Aneurysm			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	1 / 7 (14.29%)	9 / 41 (21.95%)	
occurrences (all)	1	26	
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Injection site pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			

Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Genital tract inflammation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Cough subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 2	
Rhinorrhea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Sleep disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Investigations			
Glycosylated haemoglobin increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 41 (0.00%) 0	
Post procedural inflammation			

subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Tongue injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	2	
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Muscle strain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Venomous sting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	3	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			

subjects affected / exposed	2 / 7 (28.57%)	5 / 41 (12.20%)	
occurrences (all)	3	7	
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	3	
Hypoaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	3	
Presyncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Eye disorders			
Eczema eyelids			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Aphthous ulcer			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Dental caries			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Faeces discoloured subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 41 (0.00%) 0	
Liver disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Erythema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Erythema nodosum subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Psoriasis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Rash subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Hydronephrosis			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 41 (4.88%) 2	
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 8	8 / 41 (19.51%) 15	
Back pain subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 7	1 / 41 (2.44%) 1	
Myalgia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 41 (2.44%) 1	
Osteitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 41 (0.00%) 0	
Joint lock subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 41 (0.00%) 0	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 41 (0.00%) 0	
Osteoarthritis subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	0 / 41 (0.00%) 0	
Synovitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 41 (4.88%) 4	
Temporomandibular joint syndrome			

subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Tendon disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Muscle contracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Pain in jaw			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	3 / 41 (7.32%)	
occurrences (all)	3	3	
Chronic sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	

Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	11 / 41 (26.83%) 12	
Oral herpes subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Otitis media subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Iron deficiency subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 41 (2.44%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2016	Protocol amendment 1 (version 2) included safety information on thromboembolic and thrombotic microangiopathy events observed in Study BH29884, as well as refinement of the study efficacy objectives. All subject enrollment commenced under this version of the protocol.
25 July 2017	Protocol amendment 2 (version 3) included updated information on safety findings of thrombotic microangiopathy in Study BH29884 and ways to mitigate risks. Key changes to the protocol that modified the study design or analyses in this amendment, along with a rationale for each change, are summarized: -Updated safety findings of thrombotic microangiopathy observed in Study BH29884; - Clarification on activated prothrombin complex concentrate (aPCC) use was added: aPCC in combination with emicizumab were to be avoided completely in patients who had the option of using other bypassing agents to treat bleeds; - Clarification about anti-fibrinolytics use was added: Anti-fibrinolytics in combination with recombinant activated factor VII were to be used with caution and avoided in combination with aPCC or Byclot; -Clarification regarding laboratory monitoring of coagulation status after any bypassing agent use was added; -Definition of "joint bleeds" was modified from the ISTH definition because of lack of clarity. The previous definition of "joint bleed" required the reporting of a combination of an "unusual sensation (aura) in the joint" and another joint bleed symptom (e.g., decreased range of motion) as per the bleed/medication questionnaire. The definition of "joint bleed" was redefined as bleeds with bleed type "joint bleed" reported with at least one of the symptoms of joint bleed as per the questionnaire except for the symptom "unusual sensation (aura) in the joint" reported alone; -New safety risk associated with emicizumab was added for life-threatening bleeding due to unreliable standard coagulation tests and inhibitors assays in the setting of emicizumab; -The sample size section was aligned with the approved statistical analysis plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Given the small number of adolescent participants, the results of the Haemo-QoL-SF questionnaire should be interpreted with caution.

Notes: