EU Clinical Trials Register

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	29 June 2022

Results information

Result version number	v2 (current)
This version publication date	29 December 2022
First version publication date	20 December 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO39182

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03020160
WHO universal trial number (UTN)	-
Other trial identifiers	Study Acronym: HAVEN 4

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2022
Was the trial ended prematurely?	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 was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. 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	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Years
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, 41 of whom 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 Cohort

Arm description:

Participants received emicizumab subcutaneously (SC) at a dose of 6 mg/kg once every 4 weeks (Q4W), with no loading dose, for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W), and continue on that dosing regimen until discontinuation from the study.

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:

Participants received emicizumab subcutaneously (SC) at a dose of 6 mg/kg once every 4 weeks, with no loading dose, for a minimum of 24 weeks.

Arm title	Emicizumab: Expansion Cohort

Arm description:

Participants received emicizumab subcutaneously (SC) at a loading dose of 3 mg/kg once every week for the first 4 weeks followed by a maintenance dose of 6 mg/kg emicizumab SC once every 4 weeks (Q4W) for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W) and continue on that dosing regimen until discontinuation from the study.

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Dosage and administration details:

Participants received emicizumab subcutaneously (SC) at a loading dose of 3 mg/kg once every week for the first 4 weeks followed by a maintenance dose of 6 mg/kg emicizumab SC once every 4 weeks for a minimum of 24 weeks.

Number of subjects in period 1	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort
Started	7	41
Completed 24 Weeks in the Study	7	41
Emicizumab Dose Was Up-Titrated	0 [1]	4 [2]
Changed Emicizumab Dosing Regimen	0 [3]	1 [4]
Completed	6	41
Not completed	1	0
Consent withdrawn by subject	1	-

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: Emicizumab dose up-titration and change of dosing regimen were not study milestones that applied to all participants, but rather only to those who met the criteria for/opted for such changes to their dosing.

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

Justification: Emicizumab dose up-titration and change of dosing regimen were not study milestones that applied to all participants, but rather only to those who met the criteria for/opted for such changes to their dosing.

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

Justification: Emicizumab dose up-titration and change of dosing regimen were not study milestones that applied to all participants, but rather only to those who met the criteria for/opted for such changes to their dosing.

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

Justification: Emicizumab dose up-titration and change of dosing regimen were not study milestones that applied to all participants, but rather only to those who met the criteria for/opted for such changes to their dosing.

Baseline characteristics

Reporting groups

Reporting group title	Emicizumab: PK Run-In Cohort

Reporting group description:

Participants received emicizumab subcutaneously (SC) at a dose of 6 mg/kg once every 4 weeks (Q4W), with no loading dose, for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W), and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Emicizumab: Expansion Cohort

Reporting group description:

Participants received emicizumab subcutaneously (SC) at a loading dose of 3 mg/kg once every week for the first 4 weeks followed by a maintenance dose of 6 mg/kg emicizumab SC once every 4 weeks (Q4W) for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W) and continue on that dosing regimen until discontinuation from the study.

Reporting group values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort	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
Number of Subjects by Hemophilia A Severity at Baseline			
Units: Subjects			
Mild	0	1	1
Moderate	0	0	0
Severe	7	40	47
Number of Subjects by Factor VIII Inhibitor Status at Baseline			
Units: Subjects			
Factor VIII Inhibitor Positive	3	5	8
Factor VIII Inhibitor Negative	4	36	40

End points

End points reporting groups

Reporting group title	Emicizumab: PK Run-In Cohort

Reporting group description:

Participants received emicizumab subcutaneously (SC) at a dose of 6 mg/kg once every 4 weeks (Q4W), with no loading dose, for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W), and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Emicizumab: Expansion Cohort

Reporting group description:

Participants received emicizumab subcutaneously (SC) at a loading dose of 3 mg/kg once every week for the first 4 weeks followed by a maintenance dose of 6 mg/kg emicizumab SC once every 4 weeks (Q4W) for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W) and continue on that dosing regimen until discontinuation from the study.

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 Cohort			
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

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

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 Cohort			
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]

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

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 Cohort			
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]

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

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 Cohort			
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]

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

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 Cohort			
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: 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[11]

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:

[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 Cohort			
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 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)[12]

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 Cohort			
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: 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]

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 Cohort			
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: 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[14]

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:

[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 Cohort			
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 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[15]

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:

[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 Cohort			
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)[16]

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

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 Cohort			
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: 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]

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 Cohort			
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: 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[18]

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

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 Cohort			
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: 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[19]

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

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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: units on a scale				
arithmetic mean (confidence interval	0.06 (0.03 to			

95%)	0.10)

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]

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

End point timeframe:

Predose at Baseline, Weeks 13 and 25

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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	28			
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]

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

End point timeframe:

Predose at Baseline, Weeks 13 and 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: 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 Cohort			
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]

End point description:

End point type	Secondary

End point timeframe:

From Baseline until at least 24 weeks of treatment (median [min-max] observation time: 25.57 [24.1-29.4] weeks)

Notes:

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

Justification: 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 Cohort			
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]

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 VIIII (FVIII) or subcutaneous (SC) emicizumab, or no preference.

End point type	Secondary

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 Cohort			
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]

End point description:

End point type	Secondary

End point timeframe:

Week 1 Day 1 predose (0 hours) and 8 hours postdose, and Week 1 Days 3 and 5, Week 2 Days 8 and 11, Week 3 Days 15 and 18, Week 4 Days 22 and 25, and Day 1 of Weeks 5, 21, 22, 23, 24, and 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: The study plan was to evaluate pharmacokinetic (PK) parameters of emicizumab only in the PK Run-In cohort of the study.

End point values	Emicizumab: PK Run-In Cohort			
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]

End point description:

End point type	Secondary

End point timeframe:

Week 1 Day 1 predose (0 hours) and 8 hours postdose, and Week 1 Days 3 and 5, Week 2 Days 8 and 11, Week 3 Days 15 and 18, Week 4 Days 22 and 25, and Day 1 of Weeks 5, 21, 22, 23, 24, and 25

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 pharmacokinetic (PK) parameters of emicizumab only in the PK Run-In cohort of the study.

End point values	Emicizumab: PK Run-In Cohort			
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]

End point description:

End point type	Secondary

End point timeframe:

Week 1 Day 1 predose (0 hours) and 8 hours postdose, and Week 1 Days 3 and 5, Week 2 Days 8 and 11, Week 3 Days 15 and 18, Week 4 Days 22 and 25, and Day 1 of Weeks 5, 21, 22, 23, 24, and 25

Notes:

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

Justification: The study plan was to evaluate pharmacokinetic (PK) parameters of emicizumab only in the PK Run-In cohort of the study.

End point values	Emicizumab: PK Run-In Cohort			
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]

End point description:

t1/2 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

End point timeframe:

Week 1 Day 1 predose (0 hours) and 8 hours postdose, and Week 1 Days 3 and 5, Week 2 Days 8 and 11, Week 3 Days 15 and 18, Week 4 Days 22 and 25, and Day 1 of Weeks 5, 21, 22, 23, 24, and 25

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study plan was to evaluate pharmacokinetic (PK) parameters of emicizumab only in the PK Run-In cohort of the study.

End point values	Emicizumab: PK Run-In Cohort			
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 (t1/2) of Emicizumab

End point title	PK Run-In Part: Apparent Plasma Terminal Half-Life (t1/2) of Emicizumab[28]

End point description:

t1/2 was not properly estimated after the first dose due to sampling time and dosing schedule; hence, t1/2 could not be determined after the sixth dose of emicizumab, as indicated by the entered value '99999'.

End point type	Secondary

End point timeframe:

Week 1 Day 1 predose (0 hours) and 8 hours postdose, and Week 1 Days 3 and 5, Week 2 Days 8 and 11, Week 3 Days 15 and 18, Week 4 Days 22 and 25, and Day 1 of Weeks 5, 21, 22, 23, 24, and 25

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study plan was to evaluate pharmacokinetic (PK) parameters of emicizumab only in the PK Run-In cohort of the study.

End point values	Emicizumab: PK Run-In Cohort			
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]

End point description:

Only CL/F is reported after the first dose; the apparent clearance at steady state (CLss/F) is reported after the sixth dose instead. This is because t1/2 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

End point timeframe:

Week 1 Day 1 predose (0 hours) and 8 hours postdose, and Week 1 Days 3 and 5, Week 2 Days 8 and 11, Week 3 Days 15 and 18, Week 4 Days 22 and 25, and Day 1 of Weeks 5, 21, 22, 23, 24, and 25

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 pharmacokinetic (PK) parameters of emicizumab only in the PK Run-In cohort of the study.

End point values	Emicizumab: PK Run-In Cohort			
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: PK Run-In Part: Plasma Concentration of Emicizumab at Specified Timepoints

End point title	PK Run-In Part: Plasma Concentration of Emicizumab at Specified Timepoints[30]

End point description:

The analysis included all subjects enrolled in the PK run-in part of the study. The value 'n =' represents the number of subjects with an evaluable sample at a given time point. '999999' indicates that plasma concentration could not be estimated because samples were below the lower limit of quantification (BLQ).

End point type	Secondary

End point timeframe:

Week 1 Day 1 predose and 8 hours postdose, and Week 1 Days 3 and 5, Week 2 Days 8 and 11, Week 3 Days 15 and 18, Week 4 Days 22 and 25, and Day 1 of Weeks 5, 6, 7, 8, 9, 11, 13, 15, 17, 19, 21, 22, 23, 24, and 25, and every 12 weeks thereafter to Week 265

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 plasma concentrations of emicizumab over time for the PK Run-In and Expansion cohorts are reported under separate endpoints because of the differences in sampling schedules between the two cohorts.

End point values	Emicizumab: PK Run-In Cohort			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: micrograms per millilitre (µg/mL)				
geometric mean (geometric coefficient of variation)				
Week 1, Day 1 - Predose (n = 7)	999999 (± 999999)			
Week 1, Day 1 - 8 hours (n = 7)	7.0 (± 71.7)			
Week 1, Day 3 (n = 7)	20.6 (± 51.2)			
Week 1, Day 5 (n = 7)	26.5 (± 29.7)			
Week 2, Day 8 (n = 7)	29.4 (± 25.1)			
Week 2, Day 11 (n = 7)	27.7 (± 21.9)			
Week 3, Day 15 (n = 7)	26.3 (± 20.5)			
Week 3, Day 18 (n = 7)	24.1 (± 21.6)			
Week 4, Day 22 (n = 7)	22.0 (± 14.8)			
Week 4, Day 25 (n = 7)	20.6 (± 15.6)			
Week 5 (n = 7)	18.5 (± 18.2)			
Week 6 (n = 7)	47.4 (± 13.8)			
Week 7 (n = 7)	42.1 (± 18.3)			
Week 8 (n = 7)	35.4 (± 22.5)			
Week 9 (n = 7)	28.2 (± 18.6)			
Week 11 (n = 7)	55.9 (± 20.4)			
Week 13 (n = 7)	34.6 (± 24.1)			
Week 15 (n = 7)	52.0 (± 17.0)			
Week 17 (n = 7)	36.7 (± 16.1)			
Week 19 (n = 7)	50.8 (± 32.6)			
Week 21 (n = 7)	34.5 (± 25.1)			
Week 22 (n = 7)	62.2 (± 17.5)			
Week 23 (n = 7)	56.5 (± 19.0)			
Week 24 (n = 7)	47.9 (± 28.7)			
Week 25 (n = 7)	39.2 (± 25.3)			
Week 37 (n = 7)	34.0 (± 15.8)			
Week 49 (n = 7)	34.7 (± 23.2)			

Week 61 (n = 7)	41.1 (± 25.9)				
Week 73 (n = 7)	39.7 (± 22.8)				
Week 85 (n = 7)	38.0 (± 29.2)				
Week 97 (n = 7)	43.6 (± 17.1)				
Week 109 (n = 5)	37.7 (± 13.8)				
Week 121 (n = 5)	39.6 (± 19.8)				
Week 133 (n = 5)	37.5 (± 14.2)				
Week 145 (n = 5)	34.8 (± 13.1)				
Week 157 (n = 5)	35.0 (± 20.7)				
Week 181 (n = 5)	45.4 (± 14.6)				
Week 193 (n = 5)	37.9 (± 21.5)				
Week 205 (n = 5)	45.4 (± 21.0)				
Week 217 (n = 5)	45.3 (± 11.3)				
Week 229 (n = 5)	52.1 (± 18.6)				
Week 241 (n = 5)	45.6 (± 13.6)				
Week 253 (n = 5)	40.4 (± 13.8)				
Week 265 (n = 5)	42.4 (± 16.5)				

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Plasma Concentration of Emicizumab at Specified Timepoints

End point title	Expansion Part: Plasma Concentration of Emicizumab at Specified Timepoints[31]

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. '999999' indicates that plasma concentration could not be estimated because samples were below the lower limit of quantification (BLQ).

End point type	Secondary

End point timeframe:

Predose on Day 1 of Weeks 1, 2, 3, 4, 5, 9, 13, 17, 21, 25, 37, 49, 61, 73. 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, 229, 241, and 253

Notes:

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

Justification: The plasma concentrations of emicizumab over time for the PK Run-In and Expansion cohorts are reported under separate endpoints because of the differences in sampling schedules between the two cohorts.

End point values	Emicizumab: Expansion Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: micrograms per millilitre (µg/mL)				
geometric mean (geometric coefficient of variation)				
Week 1 (n = 41)	999999 (± 999999)			

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)	38.9 (± 49.1)				
Week 17 (n = 41)	36.1 (± 53.8)				
Week 21 (n = 41)	37.4 (± 48.3)				
Week 25 (n = 41)	37.6 (± 52.5)				
Week 37 (n = 38)	39.6 (± 49.9)				
Week 49 (n = 38)	40.2 (± 48.4)				
Week 61 (n = 37)	38.7 (± 51.7)				
Week 73 (n = 34)	42.1 (± 51.2)				
Week 85 (n = 26)	36.4 (± 50.8)				
Week 97 (n = 21)	35.6 (± 49.5)				
Week 109 (n = 20)	33.0 (± 63.6)				
Week 121 (n = 21)	32.5 (± 60.5)				
Week 133 (n = 21)	33.7 (± 49.0)				
Week 145 (n = 14)	36.5 (± 51.7)				
Week 157 (n = 15)	47.3 (± 36.0)				
Week 169 (n = 18)	41.7 (± 41.9)				
Week 181 (n = 15)	45.1 (± 47.9)				
Week 193 (n = 15)	48.6 (± 47.0)				
Week 205 (n = 16)	46.0 (± 48.2)				
Week 217 (n = 15)	43.9 (± 47.8)				
Week 229 (n = 14)	50.2 (± 43.1)				
Week 241 (n = 9)	36.2 (± 46.5)				
Week 253 (n = 9)	38.8 (± 46.6)				

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Adverse Event

End point title	Percentage of Subjects with at Least One Adverse Event

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)				
Any Adverse Event (AE)	100.0	95.1		
Serious AE	28.6	19.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Grade ≥3 Adverse Event

End point title	Percentage of Subjects with at Least One Grade ≥3 Adverse Event

End point description:

The World Health Organization (WHO) Toxicity Grading Scale was used for assessing adverse event (AE) severity. For AEs that are not specifically listed in the WHO Toxicity Grading Scale, a Grade 3 AE is defined as: severe, marked limitation in activity, some assistance usually required, medical intervention or therapy required, hospitalization possible; and a Grade 4 AE is defined as: life-threatening, extreme limitation in activity, significant assistance required, significant medical intervention or therapy required, hospitalization or hospice care probable. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE; the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE. The analysis included all subjects who received at least 1 dose of emicizumab

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	28.6	17.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Adverse Event Leading to Withdrawal from Treatment

End point title	Percentage of Subjects with at Least One Adverse Event Leading to Withdrawal from Treatment

End point description:

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. A serious AE is any AE that is a significant medical event meeting any of the standard criteria. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to the World Health Organization [WHO] toxicity grading scale); the event itself may be of relatively minor medical significance. Severity and seriousness were independently assessed by the investigator for each reported AE. The analysis included all subjects who received at least one dose of emicizumab.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Adverse Event Related to Study Treatment

End point title	Percentage of Subjects with at Least One Adverse Event Related to Study Treatment

End point description:

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. In order to assess the causality of an AE, investigators used their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The analysis included all subjects who received at least one dose of emicizumab.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: Percentage of subjects				
number (not applicable)				
Any Adverse Event Related to Study Treatment	28.6	34.2		
Injection Site Reaction	14.3	22.0		
Chills	0.0	2.4		
Presyncope	0.0	2.4		
Rash	0.0	2.4		
Erythema	0.0	2.4		
Incorrect Dose Administered	0.0	2.4		
Accidental Overdose	0.0	2.4		
Iron Deficiency Anaemia	14.3	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Adverse Event of Changes from Baseline in Vital Signs

End point title	Percentage of Subjects with at Least One Adverse Event of Changes from Baseline in Vital Signs

End point description:

The percentage 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 was reported as an adverse event if it met any of the following criteria: was accompanied by clinical symptoms; resulted in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); resulted in a medical intervention or a change in concomitant therapy; or was clinically significant in the investigator's judgment. All of the adverse events reported here were assessed independently by the investigator as not related to treatment with emicizumab. The analysis included all subjects who received at least one dose of emicizumab.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)				
Hypertension	28.6	9.8		
Pyrexia	14.3	9.8		
Tachycardia	0.0	2.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Adverse Event of Changes from Baseline in Physical Examination Findings

End point title	Percentage of Subjects with at Least One Adverse Event of Changes from Baseline in Physical Examination Findings

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.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Shift in Clinical Laboratory Parameters From Baseline World Health Organization (WHO) Toxicity Scale Grade 0-2 to Post-Baseline Grade 3 or 4

End point title	Percentage of Subjects with at Least One Shift in Clinical Laboratory Parameters From Baseline World Health Organization (WHO) Toxicity Scale Grade 0-2 to Post-Baseline Grade 3 or 4

End point description:

An abnormal laboratory value was defined as a laboratory test result outside of the normal range for hematology or serum chemistry parameters. The WHO toxicity grading scale, which ranges from Grades 1 to 4 (least severe to most severe, respectively; Grade 0 is within normal range), was used for assessing the severity of laboratory abnormalities and adverse events (WHO 2003). Not every laboratory abnormality qualified as an adverse event; an abnormality was reported as an adverse event if it met any of the following criteria: was accompanied by clinical symptoms; resulted in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); resulted in a medical intervention or a change in concomitant therapy; or was clinically significant in the

investigator's judgment. In this study, any laboratory value changes were transient and returned to baseline for all subjects. The analysis included all subjects who received at least 1 dose of emicizumab.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)				
Aspartate Aminotransferase (AST) - High	0.0	2.4		
Calcium, Corrected - Low	0.0	2.4		
Phosphorus - Low	0.0	4.9		
Sodium - High	0.0	2.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Local Injection-Site Reaction

End point title	Percentage of Subjects with at Least One Local Injection-Site Reaction

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.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	14.3	22.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Thromboembolic Event

End point title	Percentage of Subjects with at Least One Thromboembolic Event

End point description:

Hypercoagulation and thromboembolic events were to be reported as serious adverse events or adverse events of special interest. Healthcare providers educated patients/caregivers to recognize the signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain or swelling, etc.) and to ensure that they understood the importance of seeking appropriate medical attention. The analysis included all subjects who received at least one dose of emicizumab.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Thrombotic Microangiopathy

End point title	Percentage of Subjects with at Least One Thrombotic Microangiopathy

End point description:

Thrombotic microangiopathy is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, etc. Thrombotic microangiopathy events were to be reported as serious adverse events or adverse events of special interest. The analysis included all subjects who received at least one dose of emicizumab.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Anti-Drug Antibodies to Emicizumab at Any Time Post-Baseline During the Study

End point title	Percentage of Subjects with Anti-Drug Antibodies to Emicizumab at Any Time Post-Baseline During the Study

End point description:

A validated enzyme-linked immunosorbent assay (ELISA) method was used to analyze the levels of anti-drug antibodies (ADAs) to emicizumab in blood plasma samples. Subjects were considered ADA-positive if they were ADA-negative at baseline but developed an ADA response following study drug administration (treatment-induced ADA response), or if they were ADA-positive at baseline and the titer of one or more post-baseline samples was at least 4-fold greater (i.e., ≥0.60 titer units) than the titer of the baseline sample (treatment-enhanced ADA response). 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.

End point type	Secondary

End point timeframe:

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

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	14.3	2.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction

End point title	Percentage of Subjects with at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction

End point description:

Since emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. These events were to be reported as serious adverse events or adverse events of special interest. Healthcare providers (HCP) instructed patients and caregivers how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence. The analysis included all subjects who received at least one dose of emicizumab.

End point type	Secondary

End point timeframe:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	41		
Units: percentage of subjects				
number (not applicable)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage 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 were FVIII inhibitor-negative at baseline and had received at least one dose of emicizumab during the study.

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 5 years, 5 months)

End point values	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[32]	36[33]		
Units: percentage of subjects				
number (not applicable)	0.0	0.0		

Notes:

[32] - Only subjects who were FVIII inhibitor-negative at baseline were included.

[33] - Only subjects who were FVIII inhibitor-negative at baseline were included.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 191.14 [28.0-264.4] weeks)

Notes:

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

Justification: 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: bleeds per year				
number (confidence interval 95%)				
Treated Bleeds	1.9 (1.22 to 3.02)			
All Bleeds	2.9 (1.97 to 4.17)			
Treated Spontaneous Bleeds	0.5 (0.26 to 1.00)			
Treated Joint Bleeds	1.2 (0.69 to 2.17)			
Treated Target Joint Bleeds	0.5 (0.24 to 1.26)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds[35]

End point description:

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

End point type	Secondary

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 191.14 [28.0-264.4] weeks)

Notes:

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

Justification: 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: bleeds per year				
arithmetic mean (confidence interval 95%)				
Treated Bleeds	2.0 (0.25 to 7.28)			
All Bleeds	3.0 (0.63 to 8.82)			
Treated Spontaneous Bleeds	0.7 (0.00 to 4.95)			
Treated Joint Bleeds	1.3 (0.07 to 6.11)			
Treated Target Joint Bleeds	0.6 (0.00 to 4.77)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds[36]

End point description:

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

End point type	Secondary

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 191.14 [28.0-264.4] weeks)

Notes:

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

Justification: 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: bleeds per year				
median (inter-quartile range (Q1-Q3))				
Treated Bleeds	0.6 (0.20 to 2.20)			
All Bleeds	1.2 (0.60 to 3.78)			
Treated Spontaneous Bleeds	0.0 (0.00 to 0.59)			
Treated Joint Bleeds	0.3 (0.00 to 1.22)			
Treated Target Joint Bleeds	0.0 (0.00 to 0.20)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time[37]

End point description:

The number of treated bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated bleeds: a bleed for which coagulation factors were administered. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v5), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

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

Notes:

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

Justification: 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Treated bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 41)	2.3 (0.35 to 7.75)			
13 to 24 Weeks (n = 41)	2.5 (0.43 to 8.08)			
25 to 36 Weeks (n = 38)	1.5 (0.11 to 6.40)			
37 to 48 Weeks (n = 38)	1.9 (0.23 to 7.14)			
49 to 60 Weeks (n = 38)	1.3 (0.06 to 6.01)			
61 to 72 Weeks (n = 36)	2.7 (0.48 to 8.25)			

73 to 84 Weeks (n = 32)	1.1 (0.04 to 5.72)				
85 to 96 Weeks (n = 24)	1.4 (0.10 to 6.33)				
97 to 108 Weeks (n = 22)	2.0 (0.23 to 7.19)				
109 to 120 Weeks (n = 22)	1.4 (0.08 to 6.22)				
121 to 132 Weeks (n = 22)	1.8 (0.18 to 6.87)				
133 to 144 Weeks (n = 22)	1.0 (0.02 to 5.55)				
145 to 156 Weeks (n = 22)	1.6 (0.13 to 6.55)				
157 to 168 Weeks (n = 22)	2.0 (0.23 to 7.19)				
169 to 180 Weeks (n = 21)	2.1 (0.26 to 7.34)				
181 to 192 Weeks (n = 20)	1.3 (0.07 to 6.09)				
193 to 204 Weeks (n = 18)	1.7 (0.15 to 6.73)				
205 to 216 Weeks (n = 18)	1.4 (0.10 to 6.33)				
217 to 228 Weeks (n = 18)	1.2 (0.05 to 5.93)				
229 to 240 Weeks (n = 18)	1.0 (0.02 to 5.51)				
241 to 252 Weeks (n = 16)	2.4 (0.40 to 7.92)				
253 to 264 Weeks (n = 5)	2.6 (0.46 to 8.17)				

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time[38]

End point description:

The number of treated bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated bleeds: a bleed for which coagulation factors were administered. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v5), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

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

Notes:

[38] - 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Treated bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 41)	0.0 (0.00 to 4.35)			
13 to 24 Weeks (n = 41)	0.0 (0.00 to 4.35)			
25 to 36 Weeks (n = 38)	0.0 (0.00 to 0.00)			
37 to 48 Weeks (n = 38)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 38)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 36)	0.0 (0.00 to 2.17)			
73 to 84 Weeks (n = 32)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 24)	0.0 (0.00 to 0.00)			
97 to 108 Weeks (n = 22)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 22)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 22)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 22)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 22)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 22)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 21)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 20)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 18)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 18)	0.0 (0.00 to 4.35)			
217 to 228 Weeks (n = 18)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 18)	0.0 (0.00 to 0.00)			
241 to 252 Weeks (n = 16)	0.0 (0.00 to 4.35)			
253 to 264 Weeks (n = 5)	4.3 (0.00 to 4.35)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for All Bleeds per 12-Week Intervals Over Time[39]

End point description:

The number of all bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. All bleeds included both treated bleeds (with coagulation factors) and non-treated bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v5), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

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

Notes:

[39] - 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: All bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 41)	5.1 (1.67 to 11.80)			
13 to 24 Weeks (n = 41)	4.0 (1.11 to 10.29)			
25 to 36 Weeks (n = 38)	3.1 (0.66 to 8.90)			
37 to 48 Weeks (n = 38)	2.5 (0.42 to 8.03)			
49 to 60 Weeks (n = 38)	2.2 (0.30 to 7.50)			
61 to 72 Weeks (n = 36)	3.5 (0.85 to 9.52)			

73 to 84 Weeks (n = 32)	1.8 (0.17 to 6.85)			
85 to 96 Weeks (n = 24)	2.0 (0.24 to 7.21)			
97 to 108 Weeks (n = 22)	2.4 (0.37 to 7.81)			
109 to 120 Weeks (n = 22)	1.6 (0.13 to 6.55)			
121 to 132 Weeks (n = 22)	2.2 (0.30 to 7.50)			
133 to 144 Weeks (n = 22)	1.2 (0.05 to 5.89)			
145 to 156 Weeks (n = 22)	2.0 (0.23 to 7.19)			
157 to 168 Weeks (n = 22)	2.0 (0.23 to 7.19)			
169 to 180 Weeks (n = 21)	2.3 (0.33 to 7.66)			
181 to 192 Weeks (n = 20)	1.7 (0.17 to 6.81)			
193 to 204 Weeks (n = 18)	1.9 (0.22 to 7.12)			
205 to 216 Weeks (n = 18)	1.4 (0.10 to 6.33)			
217 to 228 Weeks (n = 18)	1.7 (0.15 to 6.73)			
229 to 240 Weeks (n = 18)	1.0 (0.02 to 5.51)			
241 to 252 Weeks (n = 16)	2.4 (0.40 to 7.92)			
253 to 264 Weeks (n = 5)	2.6 (0.46 to 8.17)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for All Bleeds per 12-Week Intervals Over Time[40]

End point description:

The number of all bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. All bleeds included both treated bleeds (with coagulation factors) and non-treated bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v5), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

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

Notes:

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

Justification: 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: All bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 41)	0.0 (0.00 to 8.70)			
13 to 24 Weeks (n = 41)	4.3 (0.00 to 4.35)			
25 to 36 Weeks (n = 38)	0.0 (0.00 to 4.35)			
37 to 48 Weeks (n = 38)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 38)	0.0 (0.00 to 4.35)			
61 to 72 Weeks (n = 36)	0.0 (0.00 to 4.35)			
73 to 84 Weeks (n = 32)	0.0 (0.00 to 4.35)			
85 to 96 Weeks (n = 24)	0.0 (0.00 to 2.17)			
97 to 108 Weeks (n = 22)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 22)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 22)	0.0 (0.00 to 4.35)			
133 to 144 Weeks (n = 22)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 22)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 22)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 21)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 20)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 18)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 18)	0.0 (0.00 to 4.35)			
217 to 228 Weeks (n = 18)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 18)	0.0 (0.00 to 0.00)			
241 to 252 Weeks (n = 16)	0.0 (0.00 to 4.35)			
253 to 264 Weeks (n = 5)	4.3 (0.00 to 4.35)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time[41]

End point description:

The number of treated spontaneous bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated spontaneous bleeds were defined as treated (with coagulation factors) bleeds with no known contributing factor (e.g., trauma, surgery). The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v5), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

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

Notes:

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

Justification: 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Treated spontaneous bleeds per year				
arithmetic mean (confidence interval 95%)				
1 to 12 Weeks (n = 41)	0.4 (0.00 to 4.35)			
13 to 24 Weeks (n = 41)	1.0 (0.02 to 5.49)			
25 to 36 Weeks (n = 38)	0.1 (0.00 to 3.93)			
37 to 48 Weeks (n = 38)	0.0 (0 to 3.69)			
49 to 60 Weeks (n = 38)	0.3 (0.00 to 4.38)			
61 to 72 Weeks (n = 36)	0.2 (0.00 to 4.18)			

73 to 84 Weeks (n = 32)	0.1 (0.00 to 3.97)				
85 to 96 Weeks (n = 24)	0.0 (0 to 3.69)				
97 to 108 Weeks (n = 22)	0.2 (0.00 to 4.09)				
109 to 120 Weeks (n = 22)	0.4 (0.00 to 4.48)				
121 to 132 Weeks (n = 22)	0.4 (0.00 to 4.48)				
133 to 144 Weeks (n = 22)	0.4 (0.00 to 4.48)				
145 to 156 Weeks (n = 22)	1.0 (0.02 to 5.55)				
157 to 168 Weeks (n = 22)	1.8 (0.18 to 6.87)				
169 to 180 Weeks (n = 21)	0.0 (0 to 3.69)				
181 to 192 Weeks (n = 20)	0.0 (0 to 3.69)				
193 to 204 Weeks (n = 18)	0.7 (0.01 to 5.09)				
205 to 216 Weeks (n = 18)	0.5 (0.00 to 4.64)				
217 to 228 Weeks (n = 18)	0.0 (0 to 3.69)				
229 to 240 Weeks (n = 18)	0.2 (0.00 to 4.18)				
241 to 252 Weeks (n = 16)	0.8 (0.01 to 5.25)				
253 to 264 Weeks (n = 5)	0.0 (0 to 3.69)				

Statistical analyses

No statistical analyses for this end point

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

End point title	Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Spontaneous Bleeds per 12-Week Intervals Over Time[42]

End point description:

The number of treated spontaneous bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated spontaneous bleeds were defined as treated (with coagulation factors) bleeds with no known contributing factor (e.g., trauma, surgery). The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v5), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

End point type	Secondary

End point timeframe:

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

Notes:

[42] - 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 Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Treated spontaneous bleeds per year				
median (inter-quartile range (Q1-Q3))				
1 to 12 Weeks (n = 41)	0.0 (0.00 to 0.00)			
13 to 24 Weeks (n = 41)	0.0 (0.00 to 0.00)			
25 to 36 Weeks (n = 38)	0.0 (0.00 to 0.00)			
37 to 48 Weeks (n = 38)	0.0 (0.00 to 0.00)			
49 to 60 Weeks (n = 38)	0.0 (0.00 to 0.00)			
61 to 72 Weeks (n = 36)	0.0 (0.00 to 0.00)			
73 to 84 Weeks (n = 32)	0.0 (0.00 to 0.00)			
85 to 96 Weeks (n = 24)	0.0 (0.00 to 0.00)			
97 to 108 Weeks (n = 22)	0.0 (0.00 to 0.00)			
109 to 120 Weeks (n = 22)	0.0 (0.00 to 0.00)			
121 to 132 Weeks (n = 22)	0.0 (0.00 to 0.00)			
133 to 144 Weeks (n = 22)	0.0 (0.00 to 0.00)			
145 to 156 Weeks (n = 22)	0.0 (0.00 to 0.00)			
157 to 168 Weeks (n = 22)	0.0 (0.00 to 0.00)			
169 to 180 Weeks (n = 21)	0.0 (0.00 to 0.00)			
181 to 192 Weeks (n = 20)	0.0 (0.00 to 0.00)			
193 to 204 Weeks (n = 18)	0.0 (0.00 to 0.00)			
205 to 216 Weeks (n = 18)	0.0 (0.00 to 0.00)			
217 to 228 Weeks (n = 18)	0.0 (0.00 to 0.00)			
229 to 240 Weeks (n = 18)	0.0 (0.00 to 0.00)			
241 to 252 Weeks (n = 16)	0.0 (0.00 to 0.00)			
253 to 264 Weeks (n = 5)	0.0 (0.00 to 0.00)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to study completion, dose up-titration, or change of dosing regimen, whichever occurred first (up to 5 years, 5 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Emicizumab: PK Run-In Cohort

Reporting group description:

Participants received emicizumab subcutaneously (SC) at a dose of 6 mg/kg once every 4 weeks (Q4W), with no loading dose, for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W) and continue on that dosing regimen until discontinuation from the study.

Reporting group title	Emicizumab: Expansion Cohort

Reporting group description:

Participants received emicizumab subcutaneously (SC) at a loading dose of 3 mg/kg once every week for the first 4 weeks followed by a maintenance dose of 6 mg/kg emicizumab SC once every 4 weeks (Q4W) for at least 24 weeks. Upon implementation of protocol version 5 (20-Dec-2019), each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg once every week [QW], 3 mg/kg once every 2 weeks [Q2W], or 6 mg/kg Q4W) and continue on that dosing regimen until discontinuation from the study.

Serious adverse events	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	8 / 41 (19.51%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BLADDER NEOPLASM			
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	
DIFFUSE LARGE B-CELL LYMPHOMA			
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	
TUMOUR COMPRESSION			

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	

Injury, poisoning and procedural complications

HEAD INJURY

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	

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	

HAEMORRHAGE

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	

Cardiac disorders

ATRIAL FIBRILLATION

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	

Gastrointestinal disorders

TOOTHACHE

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	

Hepatobiliary disorders

CHOLELITHIASIS OBSTRUCTIVE

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	

Renal and urinary disorders

NEPHROLITHIASIS

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	
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	
Product issues			
DEVICE LOOSENING			
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	
Infections and infestations			
CELLULITIS			
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: 5 %

Non-serious adverse events	Emicizumab: PK Run-In Cohort	Emicizumab: Expansion Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	37 / 41 (90.24%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	2 / 7 (28.57%)	4 / 41 (9.76%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
COMPLICATION ASSOCIATED WITH DEVICE			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
PYREXIA			

subjects affected / exposed	1 / 7 (14.29%)	4 / 41 (9.76%)
occurrences (all)	1	5
PAIN		
subjects affected / exposed	0 / 7 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	4
CHEST PAIN		
subjects affected / exposed	1 / 7 (14.29%)	1 / 41 (2.44%)
occurrences (all)	2	1
MEDICAL DEVICE DISCOMFORT		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0
INJECTION SITE REACTION		
subjects affected / exposed	1 / 7 (14.29%)	9 / 41 (21.95%)
occurrences (all)	1	40
INFLAMMATION		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0
Immune system disorders		
SEASONAL ALLERGY		
subjects affected / exposed	1 / 7 (14.29%)	1 / 41 (2.44%)
occurrences (all)	1	1
Psychiatric disorders		
ANXIETY		
subjects affected / exposed	1 / 7 (14.29%)	2 / 41 (4.88%)
occurrences (all)	1	2
Product issues		
DEVICE BREAKAGE		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0
Injury, poisoning and procedural complications		
GINGIVAL INJURY		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0
FALL		
subjects affected / exposed	1 / 7 (14.29%)	3 / 41 (7.32%)
occurrences (all)	1	3

HEAD INJURY		
subjects affected / exposed	1 / 7 (14.29%)	2 / 41 (4.88%)
occurrences (all)	1	2
POST PROCEDURAL INFLAMMATION		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0
LIMB INJURY		
subjects affected / exposed	0 / 7 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	5
LIGAMENT SPRAIN		
subjects affected / exposed	0 / 7 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	3
TONGUE INJURY		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	2	0
CONTUSION		
subjects affected / exposed	2 / 7 (28.57%)	0 / 41 (0.00%)
occurrences (all)	3	0
JOINT INJURY		
subjects affected / exposed	0 / 7 (0.00%)	6 / 41 (14.63%)
occurrences (all)	0	6
Nervous system disorders		
MOTOR DYSFUNCTION		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0
PARAESTHESIA		
subjects affected / exposed	1 / 7 (14.29%)	1 / 41 (2.44%)
occurrences (all)	1	1
HEADACHE		
subjects affected / exposed	4 / 7 (57.14%)	12 / 41 (29.27%)
occurrences (all)	7	17
Blood and lymphatic system disorders		
IRON DEFICIENCY ANAEMIA		
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0
Eye disorders		

ECZEMA EYELIDS			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 7 (14.29%)	2 / 41 (4.88%)	
occurrences (all)	1	3	
TOOTHACHE			
subjects affected / exposed	1 / 7 (14.29%)	5 / 41 (12.20%)	
occurrences (all)	1	5	
DYSPEPSIA			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
ODYNOPHAGIA			
subjects affected / exposed	2 / 7 (28.57%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
ABDOMINAL PAIN			
subjects affected / exposed	2 / 7 (28.57%)	2 / 41 (4.88%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	1 / 7 (14.29%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
TENDON DISORDER			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
TEMPOROMANDIBULAR JOINT SYNDROME			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
EXOSTOSIS			
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
NECK PAIN			
subjects affected / exposed	0 / 7 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	

ARTHRITIS				
subjects affected / exposed	1 / 7 (14.29%)	1 / 41 (2.44%)		
occurrences (all)	1	1		
PAIN IN EXTREMITY				
subjects affected / exposed	0 / 7 (0.00%)	6 / 41 (14.63%)		
occurrences (all)	0	8		
SYNOVITIS				
subjects affected / exposed	3 / 7 (42.86%)	2 / 41 (4.88%)		
occurrences (all)	6	5		
GREATER TROCHANTERIC PAIN SYNDROME				
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)		
occurrences (all)	1	0		
JOINT LOCK				
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)		
occurrences (all)	1	0		
JOINT CONTRACTURE				
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)		
occurrences (all)	1	0		
SPINAL OSTEOARTHRITIS				
subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)		
occurrences (all)	1	0		
BACK PAIN				
subjects affected / exposed	2 / 7 (28.57%)	6 / 41 (14.63%)		
occurrences (all)	7	8		
MUSCULOSKELETAL CHEST PAIN				
subjects affected / exposed	1 / 7 (14.29%)	1 / 41 (2.44%)		
occurrences (all)	1	1		
OSTEOARTHRITIS				
subjects affected / exposed	3 / 7 (42.86%)	1 / 41 (2.44%)		
occurrences (all)	4	1		
ARTHRALGIA				
subjects affected / exposed	4 / 7 (57.14%)	17 / 41 (41.46%)		
occurrences (all)	18	43		
MYALGIA				

subjects affected / exposed	1 / 7 (14.29%)	2 / 41 (4.88%)
occurrences (all)	1	2

Infections and infestations

COVID-19

subjects affected / exposed	1 / 7 (14.29%)	6 / 41 (14.63%)
occurrences (all)	1	6

NASOPHARYNGITIS

subjects affected / exposed	0 / 7 (0.00%)	14 / 41 (34.15%)
occurrences (all)	0	17

INFLUENZA

subjects affected / exposed	0 / 7 (0.00%)	4 / 41 (9.76%)
occurrences (all)	0	4

SUBCUTANEOUS ABSCESS

subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	1	0

PHARYNGITIS

subjects affected / exposed	2 / 7 (28.57%)	0 / 41 (0.00%)
occurrences (all)	2	0

TINEA CAPITIS

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	5

EAR INFECTION

subjects affected / exposed	2 / 7 (28.57%)	0 / 41 (0.00%)
occurrences (all)	2	0

URINARY TRACT INFECTION

subjects affected / exposed	2 / 7 (28.57%)	1 / 41 (2.44%)
occurrences (all)	2	1

DEVICE RELATED INFECTION

subjects affected / exposed	1 / 7 (14.29%)	0 / 41 (0.00%)
occurrences (all)	3	0

Metabolism and nutrition disorders

VITAMIN D DEFICIENCY		
subjects affected / exposed	1 / 7 (14.29%)	1 / 41 (2.44%)
occurrences (all)	1	1
HYPERCHOLESTEROLAEMIA		
subjects affected / exposed	1 / 7 (14.29%)	2 / 41 (4.88%)
occurrences (all)	1	2

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.
25 May 2018	Protocol amendment 3 (version 4) has been amended to clarify the requirements for emicizumab up-titration, to revise the length of the study, and update the exploratory biomarker testing beyond Week 24. Changes to the protocol, along with a rationale for each change, are summarized: -To align with other studies in the emicizumab program, additional options for dose up-titration (if medically indicated) per investigator's judgment and in agreement with the Medical Monitor were added.; -The total length of the study has been extended from 20 months to 4 years to ensure patients continued access to emicizumab until its marketing authorization and commercial availability of emicizumab dosing regimen of every 4 weeks in individual countries.; -To further strengthen safety monitoring for special situations that may or may not result in an adverse event, instructions regarding the reporting of overdose (accidental or intentional), medication error, drug abuse, or drug misuse have been added.; -In order to assess coagulation status in patients on prophylactic emicizumab who received FVIII or bypassing agents and to assess the performance of different FVIII assays in measuring FVIII activity when emicizumab is present in blood with other coagulation factors, additional biomarker blood samples will be obtained from patients during hospitalization, e.g., because of surgery, severe bleedings, and at the time of hospital visits.; -To align with other studies in the emicizumab program, additional clarification has been added on adverse event reporting for patients who experience a worsening of hemophilia.; -Testing of the FIX antigen and FX antigen after Week 24 will no longer be conducted as no changes induced by emicizumab in these biomarkers have been observed across the emicizumab program.

20 December 2019	Protocol amendment 4 (version 5) has been amended primarily to extend study duration to enable collection of long-term safety and efficacy data; patients will be able to continue in the study until 5 years after the last patient is enrolled. Changes to the protocol, along with a rationale for each change, are summarized: -The duration of the study has been extended to enable the collection of additional safety and efficacy data, including data on adverse events and anti-drug antibody development. Thromboembolic events and thrombotic microangiopathy, both protocol-defined adverse events of special interest, have been reported when an average cumulative dose of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was co-administered with emicizumab. Continued collection of data related to concomitant hemophilia medications, emicizumab administration, and bleeds will contribute to a better understanding of these adverse events of special interest should they occur. The total length of the study has been extended, from screening of the first patient to the end of study, from 4 years to 6 years accordingly.; -The opportunity to switch to a preferred dosing regimen (1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/ kg every 4 weeks) during study prolongation has been added to provide the same flexibility in choosing preferred dosing regimen as with commercial product.; -The definition for end of study for an individual patient has been modified to include a switch to commercially available product.; -Text has been modified and relocated to account for the fact that special situations (i.e., overdoses, medication errors, drug abuse, and drug misuse) are not required to be reported within 24 hours. Note that serious adverse events associated with special situations are still required to be reported within 24 hours.

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: