Clinical trial results:
A Multicenter, Open-Label, Phase III Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Subcutaneous Administration of Emicizumab in Hemophilia A Pediatric Patients with Inhibitors

Summary

EudraCT number	2016-000073-21
Trial protocol	ES DE GB FR IT
Global end of trial date	11 November 2020

Results information

Result version number	v2 (current)
This version publication date	23 May 2021
First version publication date	27 April 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BH29992

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02795767
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001839-PIP01-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

No formal hypothesis testing is planned in the study. All the analyses will be descriptive and be performed for each cohort separately.

The main objectives of the study are to investigate the efficacy, safety, and pharmacokinetics of subcutaneous (SC) emicizumab administered at 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W in pediatric subjects with hemophilia A and factor VIII inhibitors who are currently receiving treatment with bypassing agents.

Protection of trial subjects:

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

An Informed Consent Form and Assent Form must be signed and dated by the pediatric subject's legally authorized representative and the subject (when applicable) before his or her participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 July 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Costa Rica: 1
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	88
EEA total number of subjects	30

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)	8
Children (2-11 years)	77
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Following completion of accrual to Cohort A: 1.5 mg/kg Emicizumab QW, enrollment was opened to Cohort B: 3 mg/kg Emicizumab Q2W and Cohort C: 6 mg/kg Emicizumab Q4W. Of note, enrollment remained open to Cohort A only for subjects who were <2 years old, and enrollment to Cohorts B and C was limited to subjects who were 2-11 years old.

Pre-assignment

Screening details:

A total of 88 subjects with hemophilia A with FVIII inhibitors who were receiving treatment with bypassing agents were enrolled in the study: 68 in Cohort A: 1.5 mg/kg Emicizumab QW, 10 in Cohort B: 3 mg/kg Emicizumab Q2W, and 10 in Cohort C: 6 mg/kg Emicizumab Q4W.

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	Cohort A: 1.5 mg/kg Emicizumab QW

Arm description:

Subjects received emicizumab at a loading dose of 3 milligrams per kilogram (mg/kg) once every week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg QW SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) once every week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg QW SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first. During the 52-week treatment period, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to have their emicizumab maintenance dose up-titrated to 3 mg/kg QW starting on Week 17.

Arm title	Cohort B: 3 mg/kg Emicizumab Q2W

Arm description:

Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 3 mg/kg once every 2 weeks (Q2W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 3 mg/kg once every 2 weeks (Q2W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first. During the 52-week treatment period, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to have their emicizumab maintenance dose up-titrated to 3 mg/kg QW starting on Week 17.

Arm title	Cohort C: 6 mg/kg Emicizumab Q4W

Arm description:

Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 6 mg/kg once every 4 weeks (Q4W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 6 mg/kg once every 4 weeks (Q4W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first. During the 52-week treatment period, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to have their emicizumab maintenance dose up-titrated to 3 mg/kg QW starting on Week 17.

Number of subjects in period 1	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W
Started	68	10	10
Received at Least One Dose of Emicizumab	68	10	10
Dose Up-Titrated to 3 mg/kg QW	0 [1]	0 [2]	3 [3]
Completed 52 Weeks in Study	67	10	9 [4]
Completed	67	10	10
Not completed	1	0	0
Received Commercial Emicizumab	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: During the clinical trial, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to have their emicizumab maintenance dose up-titrated to 3 mg/kg QW starting on Week 17.
[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: During the clinical trial, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to have their emicizumab maintenance dose up-titrated to 3 mg/kg QW starting on Week 17.
[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: During the clinical trial, individual subjects who experienced suboptimal bleeding control on emicizumab (according to protocol-defined criteria) had the opportunity to have their emicizumab maintenance dose up-titrated to 3 mg/kg QW starting on Week 17.
[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: Subjects who withdrew from treatment were still considered to have completed the study if they subsequently completed the safety follow-up visit 24 weeks after discontinuation.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: 1.5 mg/kg Emicizumab QW
Reporting group description:	
Subjects received emicizumab at a loading dose of 3 milligrams per kilogram (mg/kg) once every week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg QW SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.	
Reporting group title	Cohort B: 3 mg/kg Emicizumab Q2W
Reporting group description:	
Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 3 mg/kg once every 2 weeks (Q2W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.	
Reporting group title	Cohort C: 6 mg/kg Emicizumab Q4W
Reporting group description:	
Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 6 mg/kg once every 4 weeks (Q4W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.	

Reporting group values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W
Number of subjects	68	10	10
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	8	0	0
Children (2-11 years)	57	10	10
Adolescents (12-17 years)	3	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	6.2	6.9	7.9
standard deviation	± 3.6	± 3.2	± 3.0
Sex: Female, Male			
Units: Subjects			
Female	0	0	0
Male	68	10	10
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	10	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	11	1	0

White	39	7	8
More than one race	2	0	0
Unknown or Not Reported	6	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	1	1
Not Hispanic or Latino	61	9	9
Unknown or Not Reported	2	0	0
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 joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry.			
Units: Subjects			
0 Target Joints	44	3	7
1 Target Joint	9	6	1
>1 Target Joints	15	1	2

Reporting group values	Total		
Number of subjects	88		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	8		
Children (2-11 years)	77		
Adolescents (12-17 years)	3		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	0		
Male	88		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	13		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	12		
White	54		
More than one race	2		
Unknown or Not Reported	7		
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	7		
Not Hispanic or Latino	79		
Unknown or Not Reported	2		
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 joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry.			
Units: Subjects			
0 Target Joints	54		
1 Target Joint	16		
>1 Target Joints	18		

End points

End points reporting groups

Reporting group title	Cohort A: 1.5 mg/kg Emicizumab QW

Reporting group description:

Subjects received emicizumab at a loading dose of 3 milligrams per kilogram (mg/kg) once every week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg QW SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

Reporting group title	Cohort B: 3 mg/kg Emicizumab Q2W

Reporting group description:

Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 3 mg/kg once every 2 weeks (Q2W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

Reporting group title	Cohort C: 6 mg/kg Emicizumab Q4W

Reporting group description:

Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 6 mg/kg once every 4 weeks (Q4W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

Subject analysis set title	Cohort A NIS Population (<12 Years): Bypassing Agents
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This group includes historical data from subjects <12 years old who had participated in the non-interventional study (NIS) BH29768 (NCT02476942) in which they had received prophylactic or episodic treatment with bypassing agents and had been followed for a minimum of 24 weeks on the NIS prior to enrollment in Cohort A of this study (BH29992).

Subject analysis set title	Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects <12 years old who had previously received prophylactic or episodic treatment with bypassing agents in NIS BH29768 (NCT02476942) and were enrolled in Cohort A of this study (BH29992) received emicizumab at a loading dose of 3 milligrams per kilogram (mg/kg) once every week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

Primary: Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age[1][2]

End point description:

The number of treated bleeds over the efficacy period is presented as a model-based 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) 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 statistical 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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[3]			
Units: treated bleed rate per year				
number (confidence interval 95%)	0.3 (0.17 to 0.50)			

Notes:

[3] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age[4][5]

End point description:

The number of all bleeds over the efficacy period is presented as a model-based 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 subject 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. All statistical analyses are descriptive.
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[6]			
Units: all bleed rate per year				
number (confidence interval 95%)	3.2 (1.94 to 5.22)			

Notes:

[6] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age[7][8]

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented as a model-based 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 subject 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) 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 statistical 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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[9]			
Units: treated spontaneous bleed rate per year				
number (confidence interval 95%)	0.0 (0.0 to 0.1)			

Notes:

[9] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age[10][11]

End point description:

The number of treated joint bleeds over the efficacy period is presented as a model-based 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 subject 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Primary

End point timeframe:

From Baseline to 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[10] - 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 statistical analyses are descriptive.
[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[12]			
Units: treated joint bleed rate per year				
number (confidence interval 95%)	0.2 (0.08 to 0.29)			

Notes:

[12] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Model-Based Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age[13][14]

End point description:

The number of treated target joint bleeds over the efficacy period is presented as a model-based 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 subject 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. The number '99999' signifies that the model-based ABR and 95% CI were not estimable because too few events had occurred over the efficacy period to calculate values using the negative binomial regression model; 95.4% of subjects in this cohort had 0 treated target joint bleeds.

End point type	Primary

End point timeframe:

From Baseline to 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[13] - 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 statistical analyses are descriptive.
[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[15]			
Units: treated target joint bleed rate per year				
number (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[15] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Participants <12 Years of Age

End point title	Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Participants <12 Years of Age[16][17]

End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[16] - 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 statistical analyses are descriptive.
[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[18]			
Units: treated bleed rate per year				
arithmetic mean (confidence interval 95%)	0.3 (0.00 to 4.31)			

Notes:

[18] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Participants <12 Years of Age

End point title	Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Participants <12 Years of Age[19][20]

End point description:

The number of all bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[19] - 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 statistical analyses are descriptive.
[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[21]			
Units: all bleed rate per year				
arithmetic mean (confidence interval 95%)	3.2 (0.70 to 9.04)			

Notes:

[21] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Participants <12 Years of Age

End point title	Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Participants <12 Years of Age[22][23]

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[22] - 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 statistical analyses are descriptive.
[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis

for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[24]			
Units: treated spontaneous bleed rate per year				
arithmetic mean (confidence interval 95%)	0.0 (0.00 to 3.74)			

Notes:

[24] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Participants <12 Years of Age

End point title	Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Participants <12 Years of Age[25][26]

End point description:

The number of treated joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Primary

End point timeframe:

From Baseline to 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[25] - 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 statistical analyses are descriptive.
[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[27]			
Units: treated joint bleed rate per year				
arithmetic mean (confidence interval 95%)	0.2 (0.00 to 4.01)			

Notes:

[27] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point title	Cohort A: Mean Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Participants <12 Years of Age[28][29]

End point description:

The number of treated target joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[28] - 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 statistical analyses are descriptive.

[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[30]			
Units: treated target joint bleed rate per year				
arithmetic mean (confidence interval 95%)	0.1 (0.00 to 3.84)			

Notes:

[30] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age[31][32]

End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[31] - 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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.
[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[33]			
Units: treated bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)			

Notes:

[33] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Median Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Median Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age[34][35]

End point description:

The number of all bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[34] - 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 statistical analyses are descriptive.
[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[36]			
Units: all bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.6 (0.00 to 2.92)			

Notes:

[36] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age[37][38]

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[37] - 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 statistical analyses are descriptive.
[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: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[39]			
Units: treated spontaneous bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)			

Notes:

[39] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age[40][41]

End point description:

The number of treated joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Primary

End point timeframe:

From Baseline to 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[40] - 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 statistical analyses are descriptive.
[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[42]			
Units: treated joint bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)			

Notes:

[42] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohort A: Median Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age[43][44]

End point description:

The number of treated target joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[43] - 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 statistical analyses are descriptive.

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[45]			
Units: treated target joint bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)			

Notes:

[45] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Percentage of Subjects by Categorized Number of Treated Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohort A: Percentage of Subjects by Categorized Number of Treated Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[46][47]

End point description:

The percentage of subjects by categorized number of treated bleeds over the efficacy period is presented here. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[46] - 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 statistical analyses are descriptive.
[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[48]			
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	76.9 (64.8 to 86.5)			
0-3 Bleeds	100.0 (94.5 to 100.0)			
0-10 Bleeds	100.0 (94.5 to 100.0)			
>10 Bleeds	0.0 (0.0 to 5.5)			

Notes:

[48] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Percentage of Subjects by Categorized Number of All Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohort A: Percentage of Subjects by Categorized Number of All Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[49][50]

End point description:

The percentage of subjects by categorized number of all bleeds over the efficacy period is presented here. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[49] - 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 statistical analyses are descriptive.
[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[51]			
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	49.2 (36.6 to 61.9)			
0-3 Bleeds	72.3 (59.8 to 82.7)			
0-10 Bleeds	92.3 (83.0 to 97.5)			
>10 Bleeds	7.7 (2.5 to 17.0)			

Notes:

[51] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Percentage of Subjects by Categorized Number of Treated Spontaneous Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohort A: Percentage of Subjects by Categorized Number of Treated Spontaneous Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[52][53]

End point description:

The percentage of subjects by categorized number of treated spontaneous bleeds over the efficacy period is presented here. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[52] - 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 statistical analyses are descriptive.
[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[54]			
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	96.9 (89.3 to 99.6)			
0-3 Bleeds	100.0 (94.5 to 100.0)			
0-10 Bleeds	100.0 (94.5 to 100.0)			
>10 Bleeds	0.0 (0.0 to 5.5)			

Notes:

[54] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Percentage of Subjects by Categorized Number of Treated Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohort A: Percentage of Subjects by Categorized Number of Treated Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[55][56]

End point description:

The percentage of subjects by categorized number of treated joint bleeds over the efficacy period is presented here. 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Primary

End point timeframe:

From Baseline to 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[55] - 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 statistical analyses are descriptive.
[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[57]			
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	84.6 (73.5 to 92.4)			
0-3 Bleeds	100.0 (94.5 to 100.0)			
0-10 Bleeds	100.0 (94.5 to 100.0)			
>10 Bleeds	0.0 (0.0 to 5.5)			

Notes:

[57] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort A: Percentage of Subjects by Categorized Number of Treated Target Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohort A: Percentage of Subjects by Categorized Number of Treated Target Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[58][59]

End point description:

The percentage of subjects by categorized number of treated target joint bleeds over the efficacy period is presented here. 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 52 weeks; At the primary completion date, the median (min-max) duration of the efficacy period in Cohort A was 57.57 (17.9-92.6) weeks.

Notes:

[58] - 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 statistical analyses are descriptive.
[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW			
Subject group type	Reporting group			
Number of subjects analysed	65[60]			
Units: percentage of subjects				

number (confidence interval 95%)				
0 Bleeds	95.4 (87.1 to 99.0)			
0-3 Bleeds	100.0 (94.5 to 100.0)			
0-10 Bleeds	100.0 (94.5 to 100.0)			
>10 Bleeds	0.0 (0.0 to 5.5)			

Notes:

[60] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age[61]

End point description:

The number of treated bleeds over the efficacy period is presented as a model-based 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[62]	10[63]		
Units: treated bleed rate per year				
number (confidence interval 95%)	0.2 (0.03 to 1.72)	2.2 (0.69 to 6.81)		

Notes:

[62] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[63] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12

weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age[64]

End point description:

The number of all bleeds over the efficacy period is presented as a model-based 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 subject 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[65]	10[66]		
Units: all bleed rate per year				
number (confidence interval 95%)	1.5 (0.62 to 3.40)	3.8 (1.42 to 10.11)		

Notes:

[65] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[66] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age[67]

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented as a model-based ABR that was analyzed using a negative binomial (NB) regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., time that each subject stays on-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. The number '99999' signifies that model-based ABR and 95% CI were not estimable because too few events had occurred over the efficacy period to calculate values using the NB regression model; 100% of subjects in Cohort B had 0 treated spontaneous bleeds.

End point type	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[68]	10[69]		
Units: treated spontaneous bleed rate per year				
number (confidence interval 95%)	99999 (99999 to 99999)	0.8 (0.05 to 12.00)		

Notes:

[68] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[69] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age[70]

End point description:

The number of treated joint bleeds over the efficacy period is presented as a model-based 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 subject 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[71]	10[72]		
Units: treated joint bleed rate per year				
number (confidence interval 95%)	0.2 (0.03 to 1.72)	1.7 (0.60 to 4.89)		

Notes:

[71] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[72] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Model-Based Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age[73]

End point description:

The number of treated target joint bleeds over the efficacy period is presented as a model-based 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 subject 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

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

Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[74]	10[75]		
Units: treated target joint bleed rate per year				
number (confidence interval 95%)	0.2 (0.03 to 1.72)	0.5 (0.05 to 5.88)		

Notes:

[74] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[75] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Participants <12 Years of Age

End point title	Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Participants <12 Years of Age[76]

End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[77]	10[78]		
Units: treated bleed rate per year				
arithmetic mean (confidence interval 95%)	0.2 (0.00 to 4.13)	2.5 (0.43 to 8.06)		

Notes:

[77] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[78] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Participants <12 Years of Age

End point title	Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Participants <12 Years of Age[79]

End point description:

The number of all bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[79] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[80]	10[81]		
Units: all bleed rate per year				
arithmetic mean (confidence interval 95%)	1.5 (0.10 to 6.36)	4.0 (1.09 to 10.25)		

Notes:

[80] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

[81] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Participants <12 Years of Age

End point title	Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Participants <12 Years of Age[82]

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[82] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: treated spontaneous bleed rate per year				
arithmetic mean (confidence interval 95%)	0.0 (0.00 to 3.69)	0.8 (0.01 to 5.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for

Treated Joint Bleeds in Treated Participants <12 Years of Age

End point title	Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Participants <12 Years of Age[83]

End point description:

The number of treated joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[83] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: treated joint bleed rate per year				
arithmetic mean (confidence interval 95%)	0.2 (0.00 to 4.13)	1.9 (0.23 to 7.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point title	Cohorts B and C: Mean Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Participants <12 Years of Age[84]

End point description:

The number of treated target joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[84] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: treated target joint bleed rate per year				
arithmetic mean (confidence interval 95%)	0.2 (0.00 to 4.13)	0.5 (0.00 to 4.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age[85]

End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B

and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[86]	10[87]		
Units: treated bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)	0.0 (0.00 to 3.26)		

Notes:

[86] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[87] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age[88]

End point description:

The number of all bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[88] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[89]	10[90]		
Units: all bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 2.81)	1.6 (0.00 to 4.84)		

Notes:

[89] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[90] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age[91]

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[91] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[92]	10[93]		
Units: treated spontaneous bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)		

Notes:

[92] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[93] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age[94]

End point description:

The number of treated joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[94] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[95]	10[96]		
Units: treated joint bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)	0.0 (0.00 to 3.26)		

Notes:

[95] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[96] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Median Calculated Annualized Bleed Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age[97]

End point description:

The number of treated target joint bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[97] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[98]	10[99]		
Units: treated target joint bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)		

Notes:

[98] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[99] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[100]

End point description:

The percentage of subjects by categorized number of treated bleeds over the efficacy period is presented here. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[100] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis

for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[101]	10[102]		
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	90.0 (55.5 to 99.7)	60.0 (26.2 to 87.8)		
0-3 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
0-10 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
>10 Bleeds	0.0 (0.0 to 30.8)	0.0 (0.0 to 30.8)		

Notes:

[101] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[102] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Percentage of Subjects by Categorized Number of All Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Percentage of Subjects by Categorized Number of All Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[103]

End point description:

The percentage of subjects by categorized number of all bleeds over the efficacy period is presented here. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[103] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[104]	10[105]		
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	60.0 (26.2 to 87.8)	50.0 (18.7 to 81.3)		
0-3 Bleeds	100.0 (69.2 to 100.0)	90.0 (55.5 to 99.7)		
0-10 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
>10 Bleeds	0.0 (0.0 to 30.8)	0.0 (0.0 to 30.8)		

Notes:

[104] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[105] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Spontaneous Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Spontaneous Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[106]

End point description:

The percentage of subjects by categorized number of treated spontaneous bleeds over the efficacy period is presented here. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[106] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[107]	10[108]		
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	100.0 (69.2 to 100.0)	90.0 (55.5 to 99.7)		
0-3 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
0-10 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
>10 Bleeds	0.0 (0.0 to 30.8)	0.0 (0.0 to 30.8)		

Notes:

[107] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[108] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[109]

End point description:

The percentage of subjects by categorized number of treated joint bleeds over the efficacy period is presented here. 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). Only treated bleeds that fulfilled the 72-hour rule were included in the analysis of treated joint bleeds, excluding bleeds due to surgery/procedure.

End point type	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[109] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[110]	10[111]		
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	90.0 (55.5 to 99.7)	60.0 (26.2 to 87.8)		
0-3 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
0-10 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
>10 Bleeds	0.0 (0.0 to 30.8)	0.0 (0.0 to 30.8)		

Notes:

[110] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.
[111] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Target Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age

End point title	Cohorts B and C: Percentage of Subjects by Categorized Number of Treated Target Joint Bleeds Over the Efficacy Period in Treated Subjects <12 Years of Age[112]

End point description:

The percentage of subjects by categorized number of treated target joint bleeds over the efficacy period is presented here. 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	Secondary

End point timeframe:

From Baseline to 24 weeks; At the primary completion date, the median (min-max) duration of the efficacy periods in Cohorts B and C were 21.29 (18.6-24.1) weeks and 19.86 (8.9-24.1) weeks, respectively.

Notes:

[112] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Emicizumab QW; Cohorts B and C were added later in protocol version 4. Per protocol, primary analysis for all cohorts was to be performed 52 weeks after last subject in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. All available data from Cohorts B and C (efficacy period of about 6 months) were also to be analyzed and are reported as secondary end points.

End point values	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[113]	10[114]		
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	90.0 (55.5 to 99.7)	90.0 (55.5 to 99.7)		
0-3 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
0-10 Bleeds	100.0 (69.2 to 100.0)	100.0 (69.2 to 100.0)		
>10 Bleeds	0.0 (0.0 to 30.8)	0.0 (0.0 to 30.8)		

Notes:

[113] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

[114] - Analysis includes all treated subjects <12 years of age who were on same dose for at least 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A: Intra-Subject Comparison of the Model-Based ABR for Treated Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the Non-Interventional Study (NIS) Population

End point title	Cohort A: Intra-Subject Comparison of the Model-Based ABR for Treated Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the Non-Interventional Study (NIS) Population

End point description:

This is an intra-subject comparison of the model-based annualized bleeding rate (ABR) for treated bleeds (i.e., number of treated bleeds over efficacy period using negative binomial regression model) on study versus pre-study in the NIS population who had previously participated in study BH29768 (NCT02476942). A "treated bleed" is a bleed directly followed by a hemophilia medication reported to be a "treatment for bleed", irrespective of time between treatment and the preceding bleed. A bleed and first treatment thereafter 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	Secondary

End point timeframe:

Up to 24 weeks in NIS BH29768 (NCT02476942) prior to study entry and from Baseline to 52 weeks on this study; At primary completion date, the median (min-max) duration of the efficacy period in the NIS population was 88.57 (55.9-92.6) weeks.

End point values	Cohort A NIS Population (<12 Years): Bypassing Agents	Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		

Units: treated bleed rate per year				
number (confidence interval 95%)	19.9 (15.33 to 25.85)	0.2 (0.11 to 0.49)		

Statistical analyses

Statistical analysis title	Cohort A Intra-Subject ABR Ratio of Treated Bleeds

Statistical analysis description:

This is an intra-subject analysis of a total of 18 subjects (not 36) from Cohort A of the ABR ratio of treated bleeds over two different periods: on study while receiving emicizumab QW prophylaxis versus before study entry while participating in NIS BH29768 (NCT02476942) and receiving prophylactic/episodic bypassing agents.

Comparison groups	Cohort A NIS Population (<12 Years): Bypassing Agents v Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	ABR Ratio
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.023

Secondary: Cohort A: Intra-Subject Comparison of the Model-Based ABR for All Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point title	Cohort A: Intra-Subject Comparison of the Model-Based ABR for All Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point description:

This is an intra-subject comparison of the model-based annualized bleeding rate (ABR) for all bleeds (i.e., number of all bleeds over efficacy period using negative binomial regression model) on study versus pre-study in the NIS population who had previously participated in study BH29768 (NCT02476942). 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	Secondary

End point timeframe:

Up to 24 weeks in NIS BH29768 (NCT02476942) prior to study entry and from Baseline to 52 weeks on this study; At primary completion date, the median (min-max) duration of the efficacy period in the NIS population was 88.57 (55.9-92.6) weeks.

End point values	Cohort A NIS Population (<12 Years): Bypassing Agents	Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: all bleed rate per year				
number (confidence interval 95%)	31.9 (22.68 to 44.81)	3.3 (1.45 to 7.53)		

Statistical analyses

Statistical analysis title	Cohort A Intra-Subject ABR Ratio of All Bleeds

Statistical analysis description:

This is an intra-subject analysis of a total of 18 subjects (not 36) from Cohort A of the ABR ratio of all bleeds over two different periods: on study while receiving emicizumab QW prophylaxis versus before study entry while participating in NIS BH29768 (NCT02476942) and receiving prophylactic/episodic bypassing agents.

Comparison groups	Cohort A NIS Population (<12 Years): Bypassing Agents v Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	ABR Ratio
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.21

Secondary: Cohort A: Intra-Subject Comparison of the Median Calculated ABR for Treated Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point title	Cohort A: Intra-Subject Comparison of the Median Calculated ABR for Treated Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point description:

This is an intra-subject comparison of the calculated ABR for treated bleeds (annualized per subject using the following formula: ABR = [number of bleeds/number of days during the efficacy period] x 365.25) on study versus pre-study in the NIS population who had previously participated in study BH29768 (NCT02476942). A "treated bleed" is a bleed directly followed by a hemophilia medication reported to be a "treatment for bleed", irrespective of time between treatment and the preceding bleed. A bleed and first treatment thereafter 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	Secondary

End point timeframe:

Up to 24 weeks in NIS BH29768 (NCT02476942) prior to study entry and from Baseline to 52 weeks on this study; At primary completion date, the median (min-max) duration of the efficacy period in the NIS population was 88.57 (55.9-92.6) weeks.

End point values	Cohort A NIS Population (<12 Years): Bypassing Agents	Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: treated bleed rate per year				
median (inter-quartile range (Q1-Q3))	16.2 (11.49 to 25.78)	0.0 (0.00 to 0.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A: Intra-Subject Comparison of the Median Calculated ABR for All Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point title	Cohort A: Intra-Subject Comparison of the Median Calculated ABR for All Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point description:

This is an intra-subject comparison of the calculated annualized bleeding rate (ABR) for all bleeds (annualized for each subject using the following formula: ABR = [number of bleeds/number of days during the efficacy period] x 365.25) on study versus pre-study in the NIS population who had previously participated in study BH29768 (NCT02476942). 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	Secondary

End point timeframe:

Up to 24 weeks in NIS BH29768 (NCT02476942) prior to study entry and from Baseline to 52 weeks on this study; At primary completion date, the median (min-max) duration of the efficacy period in the NIS population was 88.57 (55.9-92.6) weeks.

End point values	Cohort A NIS Population (<12 Years): Bypassing Agents	Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: all bleed rate per year				
median (inter-quartile range (Q1-Q3))	21.3 (14.18 to 44.47)	1.1 (0.00 to 2.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A: Intra-Subject Comparison of Percentage of Subjects by Categorized Number of Treated Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point title	Cohort A: Intra-Subject Comparison of Percentage of Subjects by Categorized Number of Treated Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point description:

This is an intra-subject comparison of the percentage of subjects by categorized number of treated bleeds over the efficacy period on study versus pre-study in the NIS population who had previously participated in study BH29768 (NCT02476942). A "treated bleed" is a bleed directly followed by a hemophilia medication reported to be a "treatment for bleed", irrespective of time between treatment and the preceding bleed. A bleed and first treatment thereafter 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	Secondary

End point timeframe:

Up to 24 weeks in NIS BH29768 (NCT02476942) prior to study entry and from Baseline to 52 weeks on this study; At primary completion date, the median (min-max) duration of the efficacy period in the NIS population was 88.57 (55.9-92.6) weeks.

End point values	Cohort A NIS Population (<12 Years): Bypassing Agents	Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	5.6 (0.1 to 27.3)	72.2 (46.5 to 90.3)		
0-3 Bleeds	16.7 (3.6 to 41.4)	100.0 (81.5 to 100.0)		

0-10 Bleeds	66.7 (41.0 to 86.7)	100.0 (81.5 to 100.0)		
>10 Bleeds	33.3 (13.3 to 59.0)	0.0 (0.0 to 18.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A: Intra-Subject Comparison of Percentage of Subjects by Categorized Number of All Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point title	Cohort A: Intra-Subject Comparison of Percentage of Subjects by Categorized Number of All Bleeds on Study Versus Pre-Study in Treated Subjects <12 Years of Age From the NIS Population

End point description:

This is an intra-subject comparison of the percentage of subjects by categorized number of all bleeds over the efficacy period on study versus pre-study in the NIS population who had previously participated in study BH29768 (NCT02476942). 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	Secondary

End point timeframe:

Up to 24 weeks in NIS BH29768 (NCT02476942) prior to study entry and from Baseline to 52 weeks on this study; At primary completion date, the median (min-max) duration of the efficacy period in the NIS population was 88.57 (55.9-92.6) weeks.

End point values	Cohort A NIS Population (<12 Years): Bypassing Agents	Cohort A NIS Population (<12 Years): 1.5 mg/kg Emicizumab QW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: percentage of subjects				
number (confidence interval 95%)				
0 Bleeds	0.0 (0.0 to 18.5)	33.3 (13.3 to 59.0)		
0-3 Bleeds	11.1 (1.4 to 34.7)	72.2 (46.5 to 90.3)		
0-10 Bleeds	44.4 (21.5 to 69.2)	83.3 (58.6 to 96.4)		
>10 Bleeds	55.6 (30.8 to 78.5)	16.7 (3.6 to 41.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point title	Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point description:

The number of treated bleeds over the efficacy period is presented as a model-based 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	Secondary

End point timeframe:

From Baseline to 52 weeks

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	0[115]	0[116]	
Units: treated bleed rate per year				
number (confidence interval 95%)	0.8 (0.25 to 2.40)	(to)	(to)	

Notes:

[115] - None of the subjects enrolled in this cohort were ≥12 years of age.

[116] - None of the subjects enrolled in this cohort were ≥12 years of age.

Statistical analyses

No statistical analyses for this end point

Secondary: Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point title	Model-Based Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point description:

The number of all bleeds over the efficacy period is presented as a model-based ABR that was analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in followup times (i.e., the time that each subject 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	Secondary

End point timeframe:
From Baseline to 52 weeks

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	0[117]	0[118]	
Units: all bleed rate per year				
number (confidence interval 95%)	1.4 (0.49 to 4.16)	(to)	(to)	

Notes:

[117] - None of the subjects enrolled in this cohort were ≥12 years of age.

[118] - None of the subjects enrolled in this cohort were ≥12 years of age.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point title	Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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	Secondary

End point timeframe:
From Baseline to 52 weeks

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	0[119]	0[120]	
Units: treated bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.9 (0.00 to 1.14)	(to)	(to)	

Notes:

[119] - None of the subjects enrolled in this cohort were ≥12 years of age.

[120] - None of the subjects enrolled in this cohort were ≥12 years of age.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point title	Median Calculated Annualized Bleed Rate (ABR) for All Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

End point description:

The number of all bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each subject using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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	Secondary

End point timeframe:

From Baseline to 52 weeks

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	0[121]	0[122]	
Units: all bleed rate per year				
median (inter-quartile range (Q1-Q3))	0.9 (0.00 to 2.84)	(to)	(to)	

Notes:

[121] - None of the subjects enrolled in this cohort were ≥12 years of age.

[122] - None of the subjects enrolled in this cohort were ≥12 years of age.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treated Bleeds Over Time in Subjects with Dose Up-Titration

End point title	Number of Treated Bleeds Over Time in Subjects with Dose Up-Titration

End point description:

The number of treated bleeds over time was to be analyzed in subjects whose emicizumab maintenance dose was up-titrated to 3 mg/kg QW if they had experienced suboptimal bleeding control on emicizumab at steady-state, per protocol criteria. 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	Secondary

End point timeframe:

From Baseline to 52 weeks

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[123]	0[124]	0[125]	
Units: treated bleeds				

Notes:

[123] - None of the subjects in this cohort had dose up-titration.

[124] - None of the subjects in this cohort had dose up-titration.

[125] - There was no plan to aggregate these data; individual subject level data not shown (privacy reasons)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of All Bleeds Over Time in Subjects with Dose Up-Titration

End point title	Number of All Bleeds Over Time in Subjects with Dose Up-Titration

End point description:

The number of all bleeds over time was to be analyzed in subjects whose emicizumab maintenance dose was up-titrated to 3 mg/kg QW if they had experienced suboptimal bleeding control on emicizumab at steady-state, per protocol criteria. 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	Secondary

End point timeframe:

From Baseline to 52 weeks

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[126]	0[127]	0[128]	
Units: all bleeds				

Notes:

[126] - None of the subjects in this cohort had dose up-titration.

[127] - None of the subjects in this cohort had dose up-titration.

[128] - There was no plan to aggregate these data; individual subject level data not shown (privacy reasons)

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab in All Cohorts: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point title	Long-Term Efficacy of Emicizumab in All Cohorts: Model-Based Annualized Bleed Rate (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point description:

The number of bleeds over the efficacy period was shown as a model-based ABR that used 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. "All bleeds" included bleeds irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. Bleeds are classified as "spontaneous" if there is no other known contributing factor such as trauma or procedure/surgery. A "joint bleed" is defined as a bleed occurring in a joint. A "target joint bleed" is defined as a joint bleed in a target joint (≥3 bleeds have occurred over the last 24 weeks prior to study entry). '999999' means value could not be estimated because too few events had occurred.

End point type	Secondary

End point timeframe:

From Baseline to study completion (median [min-max] duration of the efficacy periods in Cohorts A, B, and C were 92.29 [36.1-187.7] weeks, 68.21 [56.7-129.4] weeks, and 69.43 [8.9-144.3] weeks, respectively)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65	10	10	
Units: bleed rate per year				
number (confidence interval 95%)				
Treated Bleeds	0.3 (0.19 to 0.43)	0.2 (0.06 to 0.54)	1.8 (0.32 to 10.59)	
All Bleeds	3.0 (1.93 to 4.55)	0.8 (0.42 to 1.54)	2.4 (0.78 to 7.51)	
Treated Spontaneous Bleeds	0.01 (0.01 to 0.07)	999999 (999999 to 999999)	0.9 (0.08 to 9.93)	
Treated Joint Bleeds	0.2 (0.09 to 0.25)	0.2 (0.06 to 0.54)	1.3 (0.25 to 7.11)	
Treated Target Joint Bleeds	0.1 (0.01 to 0.30)	0.1 (0.03 to 0.47)	0.5 (0.02 to 13.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab in All Cohorts: Mean Calculated Annualized Bleed Rate (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point title	Long-Term Efficacy of Emicizumab in All Cohorts: Mean Calculated Annualized Bleed Rate (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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. "All bleeds" included bleeds irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. Bleeds are classified as "spontaneous" if there is no other known contributing factor such as trauma or procedure/surgery. A "joint bleed" is defined as a bleed with type reported as "joint". 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.

End point type	Secondary

End point timeframe:

From Baseline to study completion (median [min-max] duration of the efficacy periods in Cohorts A, B, and C were 92.29 [36.1-187.7] weeks, 68.21 [56.7-129.4] weeks, and 69.43 [8.9-144.3] weeks, respectively)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65	10	10	
Units: bleed rate per year				
arithmetic mean (confidence interval 95%)				
Treated Bleeds	0.3 (0.00 to 4.25)	0.2 (0.00 to 4.02)	2.2 (0.32 to 7.59)	
All Bleeds	3.0 (0.61 to 8.74)	0.8 (0.01 to 5.17)	3.0 (0.63 to 8.82)	
Treated Spontaneous Bleeds	0.0 (0.00 to 3.72)	0.0 (0.00 to 3.69)	1.0 (0.02 to 5.53)	
Treated Joint Bleeds	0.1 (0.00 to 3.99)	0.2 (0.00 to 4.02)	1.6 (0.14 to 6.65)	
Treated Target Joint Bleeds	0.1 (0.00 to 3.82)	0.1 (0.00 to 3.86)	0.5 (0.00 to 4.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Long-Term Efficacy of Emicizumab in All Cohorts: Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point title	Long-Term Efficacy of Emicizumab in All Cohorts: Median Calculated Annualized Bleed Rate (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds in Treated Participants <12 Years of Age

End point description:

The number of treated bleeds over the efficacy period is presented here as a calculated ABR that was annualized for each participant using the following formula: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. 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. "All bleeds" included bleeds irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. Bleeds are classified as "spontaneous" if there is no other known contributing factor such as trauma or procedure/surgery. A "joint bleed" is defined as a bleed with type reported as "joint". 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.

End point type	Secondary

End point timeframe:

From Baseline to study completion (median [min-max] duration of the efficacy periods in Cohorts A, B, and C were 92.29 [36.1-187.7] weeks, 68.21 [56.7-129.4] weeks, and 69.43 [8.9-144.3] weeks, respectively)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65	10	10	
Units: bleed rate per year				
median (inter-quartile range (Q1-Q3))				
Treated Bleeds	0.0 (0.00 to 0.51)	0.0 (0.00 to 0.40)	0.0 (0.00 to 3.26)	
All Bleeds	0.7 (0.00 to 3.11)	0.8 (0.00 to 0.85)	0.6 (0.00 to 3.26)	
Treated Spontaneous Bleeds	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)	
Treated Joint Bleeds	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.40)	0.0 (0.00 to 3.26)	
Treated Target Joint Bleeds	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)	0.0 (0.00 to 0.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in the Hemophilia-Specific Quality of Life Short Form (Haemo-QoL-SF) Questionnaire Total Score, as Completed by Treated Subjects ≥8 to <12 Years of Age

End point title	Change from Baseline Over Time in the Hemophilia-Specific Quality of Life Short Form (Haemo-QoL-SF) Questionnaire Total Score, as Completed by Treated Subjects ≥8 to <12 Years of Age

End point description:

The Haemo-QoL-SF is a self-reported questionnaire for children ≥8 years of age. It contains 35 items, which cover nine domains considered relevant for the children's health-related quality of life: Physical Health, Feelings, View of Yourself, Family, Friends, Other People, Sports and School, Dealing with Hemophilia, and Treatment. Items are rated with five respective response options: never, seldom, sometimes, often, and always. The Total Score is derived from the scores for all domains and ranges from 0 to 100, with a lower score reflective of better health-related quality of life. The number '999999' signifies that no data was available at a given timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 13, 25, 37, 49, 57, 81, 105, 129, 153, and 177, and at study completion [SC] or early discontinuation [ED] (up to 188 weeks)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[129]	6[130]	6[131]	
Units: score on a scale				
arithmetic mean (confidence interval 95%)				
Baseline: value at visit (n=18,6,6)	33.37 (25.15 to 41.60)	25.60 (18.29 to 32.90)	25.12 (9.85 to 40.39)	
Change from Baseline at Week 13 (n=18,6,5)	-7.02 (-12.08 to -1.96)	-9.17 (-15.59 to -2.75)	0.29 (-23.12 to 23.69)	
Change from Baseline at Week 25 (n=18,6,4)	-9.17 (-15.97 to -2.37)	-13.21 (-23.43 to -2.99)	-14.64 (-42.98 to 13.70)	
Change from Baseline at Week 37 (n=17,6,3)	-11.64 (-16.11 to -7.17)	-15.48 (-24.58 to -6.37)	-17.86 (-71.56 to 35.85)	
Change from Baseline at Week 49 (n=17,5,3)	-9.62 (-13.59 to -5.65)	-15.14 (-25.05 to -5.24)	-16.43 (-67.33 to 34.47)	
Change from Baseline at Week 57 (n=12,4,2)	-11.13 (-17.92 to -4.34)	-16.43 (-25.85 to -7.01)	-25.00 (-215.59 to 165.59)	
Change from Baseline at Week 81 (n=12,3,0)	-11.79 (-20.23 to -3.34)	-14.52 (-31.76 to 2.71)	999999 (999999 to 999999)	

Change from Baseline at Week 105 (n=9,3,0)	-18.57 (-35.25 to -1.90)	-14.76 (-30.76 to 1.24)	999999 (999999 to 999999)	
Change from Baseline at Week 129 (n=7,0,0)	-14.90 (-29.47 to -0.32)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 153 (n=4,0,0)	-14.46 (-32.37 to 3.44)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 177 (n=2,0,0)	-5.36 (-118.81 to 108.09)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at SC or ED (n=11,3,2)	-13.05 (-22.31 to -3.79)	-21.43 (-37.40 to -5.46)	-28.21 (-241.50 to 185.07)	

Notes:

[129] - Analysis includes all treated subjects ≥8 to <12 years who completed a sufficient number of items.

[130] - Analysis includes all treated subjects ≥8 to <12 years who completed a sufficient number of items.

[131] - Analysis includes all treated subjects ≥8 to <12 years who completed a sufficient number of items.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in the Haemo-QoL-SF Questionnaire Physical Health Domain Score, as Completed by Treated Subjects ≥8 to <12 Years of Age

End point title	Change from Baseline Over Time in the Haemo-QoL-SF Questionnaire Physical Health Domain Score, as Completed by Treated Subjects ≥8 to <12 Years of Age

End point description:

The Haemo-QoL-SF is a self-reported questionnaire for children ≥8 years of age. It contains 35 items, which cover nine domains considered relevant for the children's health-related quality of life: Physical Health, Feelings, View of Yourself, Family, Friends, Other People, Sports and School, Dealing with Hemophilia, and Treatment. The Physical Health domain assesses hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement). Items are rated with five respective response options: never, seldom, sometimes, often, and always. The Physical Health domain score ranges from 0 to 100, with a lower score reflective of better physical health. The number '999999' signifies that no data was available at a given timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 13, 25, 37, 49, 57, 81, 105, 129, 153, and 177, and at study completion [SC] or early discontinuation [ED] (up to 188 weeks)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[132]	6[133]	6[134]	
Units: score on a scale				
arithmetic mean (confidence interval 95%)				
Baseline: value at visit (n=18,6,6)	29.51 (16.38 to 42.65)	30.21 (21.49 to 38.93)	19.79 (-7.23 to 46.81)	

Change from Baseline at Week 13 (n=18,6,5)	-18.40 (-31.08 to -5.72)	-23.96 (-28.90 to -19.02)	3.75 (-46.12 to 53.62)	
Change from Baseline at Week 25 (n=18,6,4)	-18.40 (-33.76 to -3.05)	-17.71 (-26.43 to -8.99)	-17.19 (-61.94 to 27.57)	
Change from Baseline at Week 37 (n=17,6,3)	-21.32 (-36.61 to -6.04)	-25.00 (-33.30 to -16.70)	-22.92 (-85.66 to 39.83)	
Change from Baseline at Week 49 (n=17,5,3)	-15.44 (-25.74 to -5.15)	-23.75 (-40.57 to -6.93)	-25.00 (-96.15 to 46.15)	
Change from Baseline at Week 57 (n=12,4,2)	-17.19 (-29.99 to -4.39)	-23.44 (-32.96 to -13.92)	-25.00 (-342.66 to 292.66)	
Change from Baseline at Week 81 (n=12,3,0)	-14.06 (-26.97 to -1.15)	-16.67 (-25.63 to -7.70)	999999 (999999 to 999999)	
Change from Baseline at Week 105 (n=9,3,0)	-16.67 (-45.29 to 11.96)	-20.83 (-29.80 to -11.87)	999999 (999999 to 999999)	
Change from Baseline at Week 129 (n=7,0,0)	-12.50 (-45.71 to 20.71)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 153 (n=4,0,0)	-21.88 (-66.72 to 22.97)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 177 (n=2,0,0)	6.25 (-152.58 to 165.08)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at SC or ED (n=11,3,2)	-23.30 (-43.35 to -3.24)	-29.17 (-52.88 to -5.45)	-40.63 (-318.57 to 237.32)	

Notes:

[132] - Analysis includes all treated subjects ≥8 to <12 years who completed a sufficient number of items.

[133] - Analysis includes all treated subjects ≥8 to <12 years who completed a sufficient number of items.

[134] - Analysis includes all treated subjects ≥8 to <12 years who completed a sufficient number of items.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in the Caregiver-Reported Adapted Health-Related Quality of Life for Hemophilia Patients with Inhibitors Including Aspects of Caregiver Burden (Adapted Inhib-QoL) Questionnaire Total Score, Treated Subjects <12 Years of Age

End point title	Change from Baseline Over Time in the Caregiver-Reported Adapted Health-Related Quality of Life for Hemophilia Patients with Inhibitors Including Aspects of Caregiver Burden (Adapted Inhib-QoL) Questionnaire Total Score, Treated Subjects <12 Years of Age

End point description:

Proxy assessment of health-related quality of life (HRQoL) and aspects of caregiver burden were assessed using the Adapted Inhib-QoL questionnaire, which comprises two parts with a total of 30 questions. The first part asks the caregiver for his/her opinion on the child's HRQoL and consists of two scales: Physical Health and Treatment. The second part asks the caregiver to rate the impact of the child's disease and treatment on them and consists of 6 scales (5 if the child does not have siblings): General Condition, Dealing with the Inhibitor, Perceive Treatment, Family life, Siblings, Contact with Others. Items are rated with five respective response options: never, seldom, sometimes, often, and all the time. The Total Score is derived from the individual scores of all of the domains and it ranges from 0 to 100, with lower scores reflective of better HRQoL. '999999' means that no data was available at that timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 13, 25, 37, 49, 57, 81, 105, 129, 153, and 177, and at study completion [SC] or early discontinuation [ED] (up to 188 weeks)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65[135]	10[136]	10[137]	
Units: score on a scale				
arithmetic mean (confidence interval 95%)				
Baseline: value at visit (n=58,10,10)	43.10 (39.63 to 46.56)	40.56 (32.46 to 48.65)	31.45 (19.93 to 42.97)	
Change from Baseline at Week 13 (n=58,10,9)	-19.76 (-23.55 to -15.96)	-21.46 (-27.21 to -15.72)	-9.24 (-21.69 to 3.21)	
Change from Baseline at Week 25 (n=58,10,8)	-21.67 (-25.39 to -17.94)	-26.11 (-32.64 to -19.58)	-13.93 (-24.21 to -3.64)	
Change from Baseline at Week 37 (n=57,10,7)	-21.79 (-25.30 to -18.28)	-24.62 (-32.28 to -16.97)	-12.55 (-25.73 to 0.64)	
Change from Baseline at Week 49 (n=56,9,7)	-22.12 (-25.50 to -18.74)	-24.57 (-32.66 to -16.49)	-18.18 (-31.98 to -4.38)	
Change from Baseline at Week 57 (n=41,7,6)	-20.86 (-24.87 to -16.85)	-24.37 (-34.52 to -14.22)	-20.28 (-39.65 to -0.92)	
Change from Baseline at Week 81 (n=32,4,4)	-22.29 (-27.58 to -17.00)	-24.95 (-35.71 to -14.18)	-14.84 (-33.45 to 3.76)	
Change from Baseline at Week 105 (n=20,4,4)	-18.04 (-26.73 to -9.34)	-21.82 (-43.00 to -0.64)	-15.82 (-31.09 to -0.55)	
Change from Baseline at Week 129 (n=16,0,0)	-15.43 (-24.41 to -6.46)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 153 (n=7,0,0)	-11.68 (-29.51 to 6.14)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 177 (n=6,0,0)	-22.41 (-42.41 to -2.40)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at SC or ED (n=52,6,4)	-23.59 (-27.38 to -19.80)	-25.83 (-36.77 to -14.89)	-13.73 (-52.15 to 24.69)	

Notes:

[135] - Includes all treated subjects <12 years with caregivers who completed a sufficient number of items

[136] - Includes all treated subjects <12 years with caregivers who completed a sufficient number of items

[137] - Includes all treated subjects <12 years with caregivers who completed a sufficient number of items

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in the Caregiver-Reported Adapted Inhib-QoL Questionnaire Physical Health Domain Score, Treated Subjects <12 Years of Age

End point title	Change from Baseline Over Time in the Caregiver-Reported Adapted Inhib-QoL Questionnaire Physical Health Domain Score, Treated Subjects <12 Years of Age

End point description:

Proxy assessment of health-related quality of life (HRQoL) and aspects of caregiver burden were assessed using the Adapted Inhib-QoL questionnaire, which comprises two parts with a total of 30 questions. The first part asks the caregiver for his/her opinion on the child's HRQoL and consists of two scales: Physical Health and Treatment. The second part asks the caregiver to rate the impact the child's disease and treatment has on them and consists of 6 scales (5 if child does not have siblings): General Condition, Dealing with the Inhibitor, Perceive Treatment, Family life, Siblings, Contact with Others. Items are rated with 5 respective response options: never, seldom, sometimes, often, and all the time. A total score is the sum of all of the items in the scale. The Physical Health domain score ranges from 0 to 100, with lower scores reflective of better physical health. '999999' means that no data was available at that timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 13, 25, 37, 49, 57, 81, 105, 129, 153, and 177, and at study completion [SC] or early discontinuation [ED] (up to 188 weeks)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65[138]	10[139]	10[140]	
Units: score on a scale				
arithmetic mean (confidence interval 95%)				
Baseline: value at visit (n=58,10,10)	37.13 (31.69 to 42.57)	34.64 (18.13 to 51.16)	20.00 (2.41 to 37.59)	
Change from Baseline at Week 13 (n=58,10,9)	-31.10 (-36.78 to -25.42)	-30.00 (-46.83 to -13.17)	-6.35 (-33.24 to 20.54)	
Change from Baseline at Week 25 (n=58,10,8)	-30.73 (-35.88 to -25.58)	-29.64 (-46.03 to -13.26)	-17.86 (-37.85 to 2.14)	
Change from Baseline at Week 37 (n=57,10,7)	-31.20 (-36.66 to -25.75)	-31.07 (-46.45 to -15.69)	-21.94 (-43.97 to 0.09)	
Change from Baseline at Week 49 (n=56,9,7)	-28.76 (-34.33 to -23.20)	-29.37 (-45.94 to -12.79)	-22.96 (-45.75 to -0.17)	
Change from Baseline at Week 57 (n=41,7,6)	-27.79 (-33.94 to -21.63)	-32.65 (-50.38 to -14.92)	-26.19 (-54.20 to 1.82)	
Change from Baseline at Week 81 (n=32,4,4)	-31.36 (-39.13 to -23.59)	-23.21 (-51.25 to 4.82)	-13.39 (-49.74 to 22.96)	
Change from Baseline at Week 105 (n=20,4,4)	-27.86 (-40.08 to -15.64)	-18.75 (-59.83 to 22.33)	-16.96 (-44.17 to 10.24)	
Change from Baseline at Week 129 (n=16,0,0)	-27.01 (-41.30 to -12.72)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 153 (n=7,0,0)	-30.10 (-45.58 to -14.63)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at Week 177 (n=6,0,0)	-32.14 (-61.17 to -3.11)	999999 (999999 to 999999)	999999 (999999 to 999999)	
Change from Baseline at SC or ED (n=52,6,4)	-30.29 (-36.26 to -24.32)	-35.12 (-58.99 to -11.25)	-21.43 (-79.38 to 36.53)	

Notes:

[138] - Includes all treated subjects <12 years with caregivers who completed a sufficient number of items

[139] - Includes all treated subjects <12 years with caregivers who completed a sufficient number of items

[140] - Includes all treated subjects <12 years with caregivers who completed a sufficient number of

items

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with at Least One Adverse Event

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

End point description:

The number of subjects experiencing at least one adverse event, including all non-serious and serious adverse events, are reported.

End point type	Secondary

End point timeframe:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects	64	9	10	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number 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 severity. For adverse events that are not specifically listed in the WHO toxicity grading scale, a grade 3 adverse event is defined as: severe, marked limitation in activity, some assistance usually required, medical intervention or therapy required, hospitalization possible; and a grade 4 adverse event is defined as: life-threatening, extreme limitation in activity, significant assistance required, significant medical intervention or therapy required, hospitalization or hospice care probable.

End point type	Secondary

End point timeframe:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects	15	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with at Least One Adverse Event Leading to Withdrawal From Treatment

End point title	Number of Subjects with at Least One Adverse Event Leading to Withdrawal From Treatment

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with at Least One Adverse Event of Local Injection Site Reaction

End point title	Number of Subjects with at Least One Adverse Event of 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.”

End point type	Secondary

End point timeframe:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects	23	2	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with at Least One Adverse Event of Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction

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

End point description:

Systemic hypersensitivity, anaphylaxis, or anaphylactoid reactions were identified by the investigator using Sampson's criteria, as defined in the protocol. At the primary completion date, one subject had reported two non-serious adverse events (cough and abdominal pain) that were identified as a potential case based on a Standardised MedDRA Queries (SMQ) search for Sampson's criteria. However, after medical review of the case, it was confirmed that this case was not indicative of systemic hypersensitivity, anaphylaxis, or anaphylactoid reaction.

End point type	Secondary

End point timeframe:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with at Least One Adverse Event of Thromboembolic Event

End point title	Number of Subjects with at Least One Adverse Event of Thromboembolic Event

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with at Least One Adverse Event of Thrombotic Microangiopathy

End point title	Number of Subjects with at Least One Adverse Event of Thrombotic Microangiopathy

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects Testing Negative or Positive for the Presence of Anti-Drug Antibodies (ADAs), Including Neutralizing ADAs, During the Study

End point description:

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

End point type	Secondary

End point timeframe:

Predose (0 hour) at Weeks 1, 5, 17, 33, 49, 57; then every 12 weeks until study completion (up to 188 weeks)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: subjects				
Total ADA Negative (Neg + Neg Unaffected)	63	10	9	
ADA Negative	59	10	9	
ADA Negative (Treatment Unaffected)	4	0	0	
Total ADA Positive (Boosted + Induced)	5	0	1	
ADA Positive (Treatment Boosted)	0	0	0	
ADA Positive (Treatment Induced)	5	0	1	
ADA Positive with Neutralizing ADAs	2	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects by Hematology Parameter Laboratory Test Results as a Shift from Baseline to Highest WHO Grade Post-Baseline

End point title	Number of Subjects by Hematology Parameter Laboratory Test Results as a Shift from Baseline to Highest WHO Grade Post-Baseline

End point description:

The World Health Organization (WHO) toxicity grading scale was used for determining the severity of laboratory abnormalities (i.e., test results outside of the reference range) for hematology parameters; Grade 0 is normal and Grades 1 to 4 represent worsening levels of the parameter outside of the normal range in the specified direction of the abnormality (high and low are above and below the range, respectively). Not every laboratory abnormality qualified as an adverse event (AE). A laboratory test result was reported as an AE if it met any of the following criteria: was accompanied by clinical symptoms; resulted in a change in study treatment; resulted in a medical intervention or a change in concomitant therapy; or was clinically significant in the investigator's judgment. Baseline was defined as the last available assessment prior to first receipt of study drug. Abs = absolute count

End point type	Secondary

End point timeframe:

From Baseline until study completion (up to 188 weeks)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: Subjects				
Hemoglobin, Low - Grade 0 to 0	53	10	9	
Hemoglobin, Low - Grade 0 to 1	3	0	1	
Hemoglobin, Low - Grade 0 to 2	4	0	0	
Hemoglobin, Low - Grade 1 to 0	3	0	0	
Hemoglobin, Low - Grade 1 to 1	4	0	0	
Hemoglobin, Low - Grade 2 to 2	1	0	0	
Neutrophils (Total, Abs), Low - Grade 0 to 0	39	7	9	
Neutrophils (Total, Abs), Low - Grade 0 to 1	14	1	1	
Neutrophils (Total, Abs), Low - Grade 0 to 2	5	2	0	
Neutrophils (Total, Abs), Low - Grade 0 to 3	3	0	0	
Neutrophils (Total, Abs), Low - Grade 0 to 4	1	0	0	
Neutrophils (Total, Abs), Low - Grade 1 to 1	4	0	0	
Neutrophils (Total, Abs), Low - Grade 1 to 2	1	0	0	
Neutrophils (Total, Abs), Low - Grade 1 to 3	1	0	0	
Platelets, Low - Grade 0 to 0	68	8	10	
Platelets, Low - Grade 0 to 1	0	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects by Chemistry Parameter Laboratory Test Results as a Shift from Baseline to Highest WHO Grade Post-Baseline

End point title	Number of Subjects by Chemistry Parameter Laboratory Test Results as a Shift from Baseline to Highest WHO Grade Post-Baseline

End point description:

The World Health Organization (WHO) toxicity grading scale was used for determining the severity of laboratory abnormalities (i.e., test results outside of the reference range) for chemistry parameters; Grade 0 is normal and Grades 1 to 4 represent worsening levels of the parameter outside of the normal range in the specified direction of the abnormality (high and low are above and below the range, respectively). Not every laboratory abnormality qualified as an adverse event (AE). A laboratory test result was reported as an AE if it met any of the following criteria: was accompanied by clinical symptoms; resulted in a change in study treatment; resulted in a medical intervention or a change in concomitant therapy; or was clinically significant in the investigator's judgment. Baseline was defined as the last available assessment prior to first receipt of study drug. SGOT/AST = aspartate aminotransferase; SGPT/ALT = alanine aminotransferase

End point type	Secondary

End point timeframe:

From Baseline until study completion (up 188 weeks)

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: Subjects				
Alkaline Phosphatase, High - Grade 0 to 0	49	8	6	
Alkaline Phosphatase, High - Grade 0 to 1	4	1	0	
Alkaline Phosphatase, High - Grade 0 to 2	2	0	0	
Alkaline Phosphatase, High - Grade 1 to 1	6	1	2	
Alkaline Phosphatase, High - Grade 1 to 2	3	0	1	
Alkaline Phosphatase, High - Grade 2 to 1	1	0	0	
Alkaline Phosphatase, High - Grade 2 to 2	1	0	0	
Alkaline Phosphatase, High - Missing to Grade 0	0	0	1	
Alkaline Phosphatase, High - Missing to Grade 3	2	0	0	
Bilirubin, High - Grade 0 to 0	62	10	10	
Bilirubin, High - Grade 0 to 1	1	0	0	
Bilirubin, High - Grade 0 to 2	2	0	0	
Bilirubin, High - Missing to Grade 0	3	0	0	
Blood Urea Nitrogen, High - Grade 0 to 0	58	10	9	
Blood Urea Nitrogen, High - Grade 0 to 1	3	0	1	

Blood Urea Nitrogen, High - Grade 1 to 1	3	0	0	
Blood Urea Nitrogen, High - Missing to Grade 0	1	0	0	
Blood Urea Nitrogen, High - Missing to Grade 1	1	0	0	
Blood Urea Nitrogen, High - Missing to Grade 2	2	0	0	
Calcium (Corrected), Low - Grade 0 to 0	54	7	9	
Calcium (Corrected), Low - Grade 0 to 1	5	3	0	
Calcium (Corrected), Low - Grade 0 to 2	2	0	0	
Calcium (Corrected), Low - Grade 0 to 4	1	0	0	
Calcium (Corrected), Low - Missing to Grade 0	5	0	1	
Calcium (Corrected), Low - Missing to Grade 2	1	0	0	
Calcium (Corrected), High - Grade 0 to 0	61	10	9	
Calcium (Corrected), High - Grade 2 to 0	1	0	0	
Calcium (Corrected), High - Missing to Grade 0	6	0	1	
Creatinine, High - Grade 0 to 0	62	9	9	
Creatinine, High - Grade 0 to 1	5	1	0	
Creatinine, High - Grade 1 to 1	1	0	1	
Glucose, Low - Grade 0 to 0	57	8	8	
Glucose, Low - Grade 0 to 1	6	2	1	
Glucose, Low - Grade 0 to 2	1	0	0	
Glucose, Low - Grade 0 to 3	1	0	0	
Glucose, Low - Grade 1 to 0	0	0	1	
Glucose, Low - Grade 2 to 0	1	0	0	
Glucose, Low - Missing to Grade 0	1	0	0	
Glucose, Low - Missing to Grade 1	1	0	0	
Glucose, High - Grade 0 to 0	31	5	4	
Glucose, High - Grade 0 to 1	28	3	6	
Glucose, High - Grade 0 to 2	4	0	0	
Glucose, High - Grade 1 to 0	1	1	0	
Glucose, High - Grade 1 to 1	1	0	0	
Glucose, High - Grade 2 to 1	1	0	0	
Glucose, High - Grade 2 to 3	0	1	0	
Glucose, High - Missing to Grade 0	1	0	0	
Glucose, High - Missing to Grade 1	1	0	0	
Magnesium, Low - Grade 0 to 0	57	9	9	
Magnesium, Low - Grade 0 to 1	6	1	1	
Magnesium, Low - Grade 4 to 1	1	0	0	
Magnesium, Low - Missing to Grade 0	3	0	0	
Magnesium, Low - Missing to Grade 2	1	0	0	
Phosphorus, Low - Grade 0 to 0	64	10	10	
Phosphorus, Low - Missing to Grade 0	4	0	0	
Potassium, Low - Grade 0 to 0	61	9	10	
Potassium, Low - Grade 0 to 1	5	1	0	
Potassium, Low - Grade 0 to 2	1	0	0	
Potassium, Low - Grade 1 to 0	1	0	0	
Potassium, High - Grade 0 to 0	66	10	10	
Potassium, High - Grade 0 to 1	1	0	0	

Potassium, High - Grade 0 to 4	1	0	0	
SGOT/AST, High - Grade 0 to 0	54	8	9	
SGOT/AST, High - Grade 0 to 1	9	1	1	
SGOT/AST, High - Grade 0 to 2	1	0	0	
SGOT/AST, High - Grade 1 to 1	3	0	0	
SGOT/AST, High - Missing to Grade 1	1	1	0	
SGPT/ALT, High - Grade 0 to 0	52	10	9	
SGPT/ALT, High - Grade 0 to 1	8	0	0	
SGPT/ALT, High - Grade 0 to 2	4	0	0	
SGPT/ALT, High - Grade 0 to 3	1	0	0	
SGPT/ALT, High - Grade 1 to 1	2	0	1	
SGPT/ALT, High - Missing to Grade 0	1	0	0	
Sodium, Low - Grade 0 to 0	45	8	8	
Sodium, Low - Grade 0 to 1	18	1	0	
Sodium, Low - Grade 0 to 2	2	0	0	
Sodium, Low - Grade 1 to 0	0	0	2	
Sodium, Low - Grade 1 to 1	2	1	0	
Sodium, Low - Grade 1 to 2	1	0	0	
Sodium, High - Grade 0 to 0	58	9	10	
Sodium, High - Grade 0 to 1	8	1	0	
Sodium, High - Grade 0 to 2	1	0	0	
Sodium, High - Grade 0 to 4	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Trough Concentration (Ctrough) of Emicizumab

End point title	Plasma Trough Concentration (Ctrough) of Emicizumab

End point description:

Pre-dose (trough) plasma concentrations of emicizumab were analyzed using a validated enzyme-linked immunosorbent assay (ELISA). The lower limit of quantitation was 0.1 micrograms per milliliter (µg/mL). '99999' signifies that the mean and standard deviation were not reportable because the measurements were below the lower limit of quantitation. '999999' means that no data was available at that timepoint.

End point type	Secondary

End point timeframe:

Predose (0 hour) at Weeks 1, 2, 3, 4, 5, 7, 9, 13, 17, 21, 25, 29, 33, 37, 41, 49, 57, 69, 81, 93, 105, 117, 129, 141, 153, 165, and 177

End point values	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	10	10	
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				

Week 1 (n=67,10,10)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Week 2 (n=66,10,10)	18.2 (± 5.5)	17.0 (± 3.9)	17.2 (± 4.1)	
Week 3 (n=67,10,9)	31.6 (± 5.6)	31.7 (± 6.8)	33.9 (± 5.8)	
Week 4 (n=67,10,10)	42.9 (± 8.0)	42.4 (± 9.5)	44.7 (± 7.0)	
Week 5 (n=66,10,9)	53.3 (± 10.6)	51.8 (± 10.5)	56.4 (± 12.3)	
Week 7 (n=68,10,8)	51.2 (± 10.5)	51.5 (± 9.6)	59.9 (± 24.6)	
Week 9 (n=67,10,9)	49.9 (± 9.7)	51.9 (± 11.2)	39.3 (± 16.7)	
Week 13 (n=67,10,9)	48.3 (± 13.3)	45.3 (± 10.8)	37.1 (± 10.6)	
Week 17 (n=68,10,8)	46.1 (± 11.2)	48.7 (± 10.4)	36.3 (± 6.1)	
Week 21 (n=67,10,8)	45.2 (± 11.1)	43.9 (± 11.0)	36.2 (± 12.4)	
Week 25 (n=68,10,8)	46.9 (± 11.7)	41.9 (± 8.5)	33.7 (± 8.9)	
Week 29 (n=68,9,8)	47.9 (± 13.0)	46.7 (± 5.1)	34.4 (± 9.0)	
Week 33 (n=67,10,7)	51.3 (± 13.8)	51.0 (± 6.8)	34.7 (± 11.2)	
Week 37 (n=66,9,7)	51.0 (± 15.3)	50.4 (± 6.4)	35.9 (± 9.1)	
Week 41 (n=66,10,7)	48.5 (± 14.2)	55.3 (± 10.7)	38.1 (± 9.9)	
Week 49 (n=66,10,7)	49.4 (± 12.6)	48.6 (± 9.2)	32.4 (± 7.5)	
Week 57 (n=60,9,6)	46.2 (± 15.9)	46.4 (± 9.8)	28.5 (± 10.7)	
Week 69 (n=52,4,4)	46.4 (± 16.0)	54.7 (± 11.5)	41.1 (± 5.2)	
Week 81 (n=36,4,4)	45.6 (± 14.2)	38.0 (± 5.3)	35.7 (± 21.2)	
Week 93 (n=34,4,4)	44.3 (± 13.8)	41.2 (± 6.6)	41.6 (± 26.8)	
Week 105 (n=22,4,4)	46.9 (± 15.9)	43.4 (± 5.7)	34.2 (± 14.4)	
Week 117 (n=19,4,4)	37.8 (± 12.3)	46.6 (± 10.2)	37.1 (± 12.9)	
Week 129 (n=18,0,0)	39.7 (± 13.8)	999999 (± 999999)	999999 (± 999999)	
Week 141 (n=17,0,0)	46.5 (± 17.2)	999999 (± 999999)	999999 (± 999999)	
Week 153 (n=12,0,0)	39.5 (± 15.6)	999999 (± 999999)	999999 (± 999999)	
Week 165 (n=11,0,0)	39.9 (± 17.8)	999999 (± 999999)	999999 (± 999999)	
Week 177 (n=12,0,0)	38.9 (± 19.0)	999999 (± 999999)	999999 (± 999999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 24 weeks after study drug discontinuation; the median (min-max) observation periods in Cohorts A, B, and C were 96.93 (36.1-188.1) weeks, 68.21 (56.7-129.4) weeks, and 69.43 (38.9-144.3) weeks, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Cohort A: 1.5 mg/kg Emicizumab QW

Reporting group description:

Subjects received emicizumab at a loading dose of 3 milligrams per kilogram (mg/kg) once every week (QW) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg QW SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

Reporting group title	Cohort B: 3 mg/kg Emicizumab Q2W

Reporting group description:

Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 3 mg/kg once every 2 weeks (Q2W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

Reporting group title	Cohort C: 6 mg/kg Emicizumab Q4W

Reporting group description:

Subjects received emicizumab at a loading dose of 3 mg/kg QW subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 6 mg/kg once every 4 weeks (Q4W) SC for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurred first.

Serious adverse events	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 68 (33.82%)	1 / 10 (10.00%)	3 / 10 (30.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Neutralising antibodies positive			
subjects affected / exposed	0 / 68 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			

subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth injury			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haemorrhage			
subjects affected / exposed	2 / 68 (2.94%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	2 / 68 (2.94%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	2 / 68 (2.94%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	3 / 68 (4.41%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			

subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	3 / 68 (4.41%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Ketoacidosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort A: 1.5 mg/kg Emicizumab QW	Cohort B: 3 mg/kg Emicizumab Q2W	Cohort C: 6 mg/kg Emicizumab Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 68 (94.12%)	9 / 10 (90.00%)	10 / 10 (100.00%)
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	22 / 68 (32.35%)	2 / 10 (20.00%)	6 / 10 (60.00%)
occurrences (all)	44	6	19
Pain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	21 / 68 (30.88%)	6 / 10 (60.00%)	4 / 10 (40.00%)
occurrences (all)	44	8	5
Peripheral swelling			
subjects affected / exposed	2 / 68 (2.94%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Swelling face			
subjects affected / exposed	1 / 68 (1.47%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Vaccination site erythema			
subjects affected / exposed	3 / 68 (4.41%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 68 (5.88%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 68 (30.88%)	4 / 10 (40.00%)	0 / 10 (0.00%)
occurrences (all)	28	4	0
Oropharyngeal pain			
subjects affected / exposed	5 / 68 (7.35%)	2 / 10 (20.00%)	0 / 10 (0.00%)
occurrences (all)	8	4	0

Rhinorrhoea			
subjects affected / exposed	5 / 68 (7.35%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	5	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 68 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Product issues			
Device breakage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Device malfunction			
subjects affected / exposed	0 / 68 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			
Indeterminable ABO blood type			
subjects affected / exposed	1 / 68 (1.47%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	11 / 68 (16.18%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	70	0	2
Fall			
subjects affected / exposed	10 / 68 (14.71%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	21	1	1
Head injury			
subjects affected / exposed	3 / 68 (4.41%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Joint injury			
subjects affected / exposed	3 / 68 (4.41%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
Ligament sprain			
subjects affected / exposed	8 / 68 (11.76%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	11	0	1
Limb injury			

subjects affected / exposed	6 / 68 (8.82%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	6	0	0
Skin abrasion			
subjects affected / exposed	8 / 68 (11.76%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	15	0	0
Skin laceration			
subjects affected / exposed	5 / 68 (7.35%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	6	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 68 (17.65%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	17	10	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 68 (2.94%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 68 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 68 (5.88%)	2 / 10 (20.00%)	0 / 10 (0.00%)
occurrences (all)	4	2	0
Abdominal pain upper			
subjects affected / exposed	4 / 68 (5.88%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	6	0	1
Constipation			
subjects affected / exposed	4 / 68 (5.88%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
Diarrhoea			
subjects affected / exposed	12 / 68 (17.65%)	3 / 10 (30.00%)	0 / 10 (0.00%)
occurrences (all)	16	5	0
Nausea			
subjects affected / exposed	3 / 68 (4.41%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	3	2	1
Vomiting			

subjects affected / exposed	13 / 68 (19.12%)	2 / 10 (20.00%)	0 / 10 (0.00%)
occurrences (all)	15	2	0
Dental caries			
subjects affected / exposed	5 / 68 (7.35%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	7	1	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 68 (2.94%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	3
Rash			
subjects affected / exposed	5 / 68 (7.35%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	6	0	0
Rash pruritic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	4 / 68 (5.88%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	5	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 68 (11.76%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	19	2	13
Groin pain			
subjects affected / exposed	0 / 68 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Limb discomfort			
subjects affected / exposed	0 / 68 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 68 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pain in extremity			

subjects affected / exposed	6 / 68 (8.82%)	0 / 10 (0.00%)	3 / 10 (30.00%)
occurrences (all)	6	0	5
Arthropathy			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Synovitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 68 (10.29%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	10	0	0
Conjunctivitis			
subjects affected / exposed	3 / 68 (4.41%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	7	0	2
Ear infection			
subjects affected / exposed	4 / 68 (5.88%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Gastroenteritis			
subjects affected / exposed	8 / 68 (11.76%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	9	0	0
Influenza			
subjects affected / exposed	8 / 68 (11.76%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	13	2	0
Nasopharyngitis			
subjects affected / exposed	29 / 68 (42.65%)	3 / 10 (30.00%)	4 / 10 (40.00%)
occurrences (all)	53	11	10
Otitis media			
subjects affected / exposed	7 / 68 (10.29%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	8	0	0
Rhinitis			
subjects affected / exposed	3 / 68 (4.41%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
Sinusitis			
subjects affected / exposed	2 / 68 (2.94%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	2

Tinea versicolour			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tracheitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	23 / 68 (33.82%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	44	0	2
Varicella			
subjects affected / exposed	4 / 68 (5.88%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Tonsillitis			
subjects affected / exposed	7 / 68 (10.29%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	13	0	0
Paronychia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Pharyngitis			
subjects affected / exposed	4 / 68 (5.88%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	7	0	0
Gastrointestinal infection			
subjects affected / exposed	4 / 68 (5.88%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 68 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	3 / 68 (4.41%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2016	The key changes in Protocol Amendment 1 (Version 2) that modified the study design or analyses, along with a rationale for each change, are summarized as follows: - Due to the anticipated rapid enrollment of the study, recruitment was placed on a temporary halt after the first 20 subjects had enrolled until the Joint Monitoring Committee (JMC) released recommendations on the appropriateness of the maintenance dose; -Modified dose up-titration criteria to more precisely define the subpopulation who may stand to benefit from an increased dose of emicizumab; -Added additional efficacy objectives and endpoints to evaluate all bleeds (i.e., both treated and not treated with coagulation factors) given that some subjects may report bleeds that they did not treat, as well as spontaneous bleeds as additional assessments of efficacy; -Based on feasibility and desire to expand the safety database, the Sponsor increased the maximum number of pediatric subjects with hemophilia A with inhibitors who were previously treated with episodic or prophylactic bypassing agents from 40 to approximately 60. Additionally, if no subjects <2 years are included in the primary cohort (QW Arm), the primary analysis would still occur at the specified time. However, enrollment in the study may be left open exclusively for subjects <2 years in order to enroll up to 5 such subjects.; Removed activated partial thromboplastin time (aPTT) point-of-care testing using the CoaguChek Pro II in order to reduce burden on subjects and sites given the sizeable schedule of assessments; Provided the option for subjects to potentially combine emicizumab volumes (if necessary) from more than 1 vial into 1 syringe to reduce the number of subcutaneous injections they may require.
08 December 2016	The key changes in Protocol Amendment 2 (Version 3) that modified the study design or analyses, along with a rationale for each change, are summarized as follows: -Most recent information on safety findings of thromboembolic events and thrombotic microangiopathy (TMA) events observed in Study BH29884 was added, including requirements for laboratory monitoring of coagulation status following bypassing agent use; -TMA was newly classified as an adverse event of special interest, and an exclusion criterion to exclude patients at high risk to experience TMA (e.g., have a previous medical or family history of TMA) was added; -The permitted and prohibited treatment for control and prevention of bleeds was specified with guidance for use of bypassing agents in combination with emicizumab; -Additional efficacy objectives and endpoints to evaluate treated joint bleeds and treated target joint bleeds were added to the analyses.
01 September 2017	The key changes in Protocol Amendment 3 (Version 4) that modified the study design or analyses, along with a rationale for each change, are summarized as follows: -Two arms (designated as the Q2W Arm and Q4W Arm; subjects 2 to 11 years of age) were added to the study to investigate additional, less frequent emicizumab dosing schedules (Q2W and Q4W).; -Approximately 80 subjects were planned to be included in the study, with 60 subjects in the QW Arm and 20 subjects in the additional Q2W and Q4W arms (10 subjects each).; -The up-titration schema was modified with removal of the 2.25 mg/kg QW dosing level. This was based on an interim data review, and JMC recommendation characterizing exposure at 1.5 mg/kg QW in subjects 2 to 12 years of age to be similar to adolescent/adult patients. As such, the up-titration dose was the same used in adolescent/adult subjects (3 mg/kg QW). The efficacy endpoint was revised to characterize the efficacy of up-titration on an intra-subject level based on the basis of the number of bleeds over time. This was due to the small number of subjects that were up-titrated.; -A new safety risk associated with emicizumab was added as follows: Life-threatening bleeding due to unreliable standard coagulation tests and inhibitors assays in the setting of emicizumab. Coagulation laboratory tests (including, but not limited to, aPTT, one-stage factor VIII (FVIII) activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and are impacted by the presence of emicizumab and, therefore, did not reflect patients' underlying hemostatic status accurately.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 October 2016	The initial emicizumab maintenance dose of 1.5 mg/kg QW was evaluated by the Study BH29992 Joint Monitoring Committee (JMC) during an interim data review. At that time, further enrollment in the study was on the prespecified, protocol-defined hold, pending JMC interim data review and recommendations. All available data (including safety, efficacy, and pharmacokinetics) from the first 20 subjects enrolled in Cohort A was assessed by the JMC to determine the appropriateness of the starting maintenance dose, as well as to decide whether the study could begin enrolling subjects <2 years of age. On 7 December 2016, the JMC recommended continuing enrollment of subjects in Cohort A at the maintenance dose of 1.5 mg/kg QW, as well as to open enrollment to subjects <2 years of age at that same maintenance dose.	07 December 2016

Notes:

Limitations and caveats

None reported