



## 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 |                |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 27 April 2019 |
| First version publication date | 27 April 2019 |

#### 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)                          | EMA-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                                       | Interim       |
| Date of interim/final analysis                       | 30 April 2018 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 30 April 2018 |
| Global end of trial reached?                         | 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 | Germany: 7         |
| Country: Number of subjects enrolled | Costa Rica: 1      |
| 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         | 40                 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 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: Emicizumab QW, enrollment was opened to Cohort B: Emicizumab Q2W and Cohort C: 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: Emicizumab QW, 10 in Cohort B: Emicizumab Q2W, and 10 in Cohort C: 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                     |
| <b>Arm title</b>             | Cohort A: 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 occurs 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.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Cohort B: 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 occurs 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.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Cohort C: 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 occurs 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.

| <b>Number of subjects in period 1</b> | <b>Cohort A:<br/>Emicizumab QW</b> | <b>Cohort B:<br/>Emicizumab Q2W</b> | <b>Cohort C:<br/>Emicizumab Q4W</b> |
|---------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|
| Started                               | 68                                 | 10                                  | 10                                  |
| Dose Up-Titrated to 3 mg/kg QW        | 0                                  | 0                                   | 2                                   |
| Completed 52 Weeks in Study           | 59                                 | 0                                   | 0                                   |
| Discontinued from Study Treatment     | 2                                  | 0                                   | 1                                   |
| Completed                             | 0                                  | 0                                   | 0                                   |
| Not completed                         | 68                                 | 10                                  | 10                                  |
| Received Commercial Emicizumab        | 2                                  | -                                   | -                                   |
| Ongoing Study Treatment               | 66                                 | 10                                  | 9                                   |
| Lack of efficacy                      | -                                  | -                                   | 1                                   |

## Baseline characteristics

### Reporting groups

|   |                          |
|---|--------------------------|
| Reporting group title   | Cohort A: 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 occurs first. |                          |
| Reporting group title   | Cohort B: 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 occurs first.                         |                          |
| Reporting group title   | Cohort C: 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 occurs first.                         |                          |

| Reporting group values                                | Cohort A:<br>Emicizumab QW | Cohort B:<br>Emicizumab Q2W | Cohort C:<br>Emicizumab Q4W |
|---|----------------------------|-----------------------------|-----------------------------|
| Number of subjects                                    | 68                         | 10                          | 10                          |
| Age categorical                                       |                            |                             |                             |
| Units: Subjects                                       |                            |                             |                             |
| In utero  | 0                          | 0                           | 0                           |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                          | 0                           | 0                           |
| Newborns (0-27 days)                                  | 0                          | 0                           | 0                           |
| Infants and toddlers (28 days-23<br>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<br>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 |

|  |       |  |  |
|--|-------|--|--|
| <b>Reporting group values</b>                      | 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: Emicizumab QW  |
| Reporting group description:<br>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 occurs first.  |  |
| Reporting group title  | Cohort B: Emicizumab Q2W                                       |
| Reporting group description:<br>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 occurs first.  |  |
| Reporting group title  | Cohort C: Emicizumab Q4W                                       |
| Reporting group description:<br>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 occurs first.  |  |
| Subject analysis set title   | Cohort A NIS Population: Prophylactic/Episodic Bypassing Agent |
| Subject analysis set type  | Sub-group analysis   |
| Subject analysis set description:<br>This group includes historical data from subjects in the non-interventional study (NIS) BH29768 (NCT02476942) who had received prophylactic or episodic treatment with bypassing agents and were followed for a minimum of 24 weeks on the NIS prior to enrollment in Cohort A of this study.   |  |
| Subject analysis set title   | Cohort A NIS Population: Emicizumab QW                         |
| Subject analysis set type  | Sub-group analysis   |
| Subject analysis set description:<br>Subjects who had previously received episodic or prophylactic treatment with bypassing agents in NIS BH29768 (NCT02476942) and were enrolled in Cohort A of this study 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 occurs first. |  |

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

|  |  |
|--|--|
| End point title  | Cohort A: Model-Based Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age <sup>[1][2]</sup> |
| End point description:<br>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:<br>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 all subjects 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.

|                                    |                               |  |  |  |
|------------------------------------|-------------------------------|--|--|--|
| <b>End point values</b>            | Cohort A:<br>Emicizumab<br>QW |  |  |  |
| Subject group type                 | Reporting group               |  |  |  |
| Number of subjects analysed        | 65 <sup>[3]</sup>             |  |  |  |
| Units: treated bleed rate per year |                               |  |  |  |
| number (confidence interval 95%)   | 0.3 (0.17 to<br>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 Bleeding Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age

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

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 all subjects 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.

|                                  |                               |  |  |  |
|----------------------------------|-------------------------------|--|--|--|
| <b>End point values</b>          | Cohort A:<br>Emicizumab<br>QW |  |  |  |
| Subject group type               | Reporting group               |  |  |  |
| Number of subjects analysed      | 65 <sup>[6]</sup>             |  |  |  |
| 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 Bleeding Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

|                 |   |
|-----------------|---|
| End point title | Cohort A: Model-Based Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age <sup>[7]</sup> [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 all subjects 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.

|  |                               |  |  |  |
|--|-------------------------------|--|--|--|
| <b>End point values</b>                        | Cohort A:<br>Emicizumab<br>QW |  |  |  |
| Subject group type                             | Reporting group               |  |  |  |
| Number of subjects analysed                    | 65 <sup>[9]</sup>             |  |  |  |
| 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 Bleeding Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age

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

#### 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: Efficizumab 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 all subjects 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.

|  |                                |  |  |  |
|--|--------------------------------|--|--|--|
| <b>End point values</b>                  | Cohort A:<br>Efficizumab<br>QW |  |  |  |
| Subject group type                       | Reporting group                |  |  |  |
| Number of subjects analysed              | 65 <sup>[12]</sup>             |  |  |  |
| 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 Bleeding Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age

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

#### 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: Efficizumab 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 all subjects 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.

|   |                                |  |  |  |
|---|--------------------------------|--|--|--|
| <b>End point values</b>                         | Cohort A:<br>Efficizumab<br>QW |  |  |  |
| Subject group type                              | Reporting group                |  |  |  |
| Number of subjects analysed                     | 65 <sup>[15]</sup>             |  |  |  |
| 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: Calculated Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age

|                 |   |
|-----------------|---|
| End point title | Cohort A: Calculated Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age <sup>[16][17]</sup> |
|-----------------|---|

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:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . 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 all subjects 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.

|                                       |                               |  |  |  |
|---------------------------------------|-------------------------------|--|--|--|
| <b>End point values</b>               | Cohort A:<br>Emicizumab<br>QW |  |  |  |
| Subject group type                    | Reporting group               |  |  |  |
| Number of subjects analysed           | 65 <sup>[18]</sup>            |  |  |  |
| Units: treated bleed rate per year    |                               |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 0.0 (0.00 to<br>0.00)         |  |  |  |

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: Calculated Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age

|                 |   |
|-----------------|---|
| End point title | Cohort A: Calculated Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age <sup>[19][20]</sup> |
|-----------------|---|

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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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 all subjects 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:<br>Emicizumab<br>QW |  |  |  |
|---------------------------------------|-------------------------------|--|--|--|
| Subject group type                    | Reporting group               |  |  |  |
| Number of subjects analysed           | 65 <sup>[21]</sup>            |  |  |  |
| Units: all bleed rate per year        |                               |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 0.6 (0.00 to 2.92)            |  |  |  |

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: Calculated Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

|                 |   |
|-----------------|---|
| End point title | Cohort A: Calculated Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age <sup>[22]</sup> <sup>[23]</sup> |
|-----------------|---|

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:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . 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 all subjects 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:<br>Emicizumab<br>QW |  |  |  |
|--|-------------------------------|--|--|--|
| Subject group type                             | Reporting group               |  |  |  |
| Number of subjects analysed                    | 65 <sup>[24]</sup>            |  |  |  |
| Units: treated spontaneous bleed rate per year |                               |  |  |  |
| median (inter-quartile range (Q1-Q3))          | 0.0 (0.00 to                  |  |  |  |

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: Calculated Annualized Bleeding Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age

|                 |   |
|-----------------|---|
| End point title | Cohort A: Calculated Annualized Bleeding Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age <sup>[25][26]</sup> |
|-----------------|---|

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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . 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 all subjects 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:<br>Emicizumab<br>QW |  |  |  |
|--|-------------------------------|--|--|--|
| Subject group type                       | Reporting group               |  |  |  |
| Number of subjects analysed              | 65 <sup>[27]</sup>            |  |  |  |
| Units: treated joint bleed rate per year |                               |  |  |  |
| median (inter-quartile range (Q1-Q3))    | 0.0 (0.00 to 0.00)            |  |  |  |

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: Calculated Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age

|                 |  |
|-----------------|--|
| End point title | Cohort A: Calculated Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age <sup>[28]</sup> <sup>[29]</sup> |
|-----------------|--|

### 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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . 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: Efficizumab 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 all subjects 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:<br>Efficizumab<br>QW |  |  |  |
| Subject group type                              | Reporting group                |  |  |  |
| Number of subjects analysed                     | 65 <sup>[30]</sup>             |  |  |  |
| Units: treated target joint bleed rate per year |                                |  |  |  |
| median (inter-quartile range (Q1-Q3))           | 0.0 (0.00 to 0.00)             |  |  |  |

### 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: 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 <sup>[31]</sup> <sup>[32]</sup> |
|-----------------|--|

### 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:

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

[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 all subjects 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:<br>Emicizumab<br>QW |  |  |  |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type               | Reporting group               |  |  |  |
| Number of subjects analysed      | 65 <sup>[33]</sup>            |  |  |  |
| 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:

[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: 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 <sup>[34]</sup> <sup>[35]</sup> |
|-----------------|--|

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:

[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 all subjects 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:<br>Emicizumab<br>QW |  |  |  |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type               | Reporting group               |  |  |  |
| Number of subjects analysed      | 65 <sup>[36]</sup>            |  |  |  |
| 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:

[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: 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 <sup>[37]</sup> <sup>[38]</sup> |
|-----------------|--|

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:

[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 all subjects 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:<br>Emicizumab<br>QW |  |  |  |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type               | Reporting group               |  |  |  |
| Number of subjects analysed      | 65 <sup>[39]</sup>            |  |  |  |
| 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:

[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: 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 <sup>[40]</sup> <sup>[41]</sup> |
|-----------------|--|

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:

[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 all subjects 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:<br>Emicizumab<br>QW |  |  |  |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type               | Reporting group               |  |  |  |
| Number of subjects analysed      | 65 <sup>[42]</sup>            |  |  |  |
| 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:

[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: 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 <sup>[43]</sup> <sup>[44]</sup> |
|-----------------|---|

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:

[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 all subjects 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.

|                                  |                               |  |  |  |
|----------------------------------|-------------------------------|--|--|--|
| <b>End point values</b>          | Cohort A:<br>Emicizumab<br>QW |  |  |  |
| Subject group type               | Reporting group               |  |  |  |
| Number of subjects analysed      | 65 <sup>[45]</sup>            |  |  |  |
| 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:

[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

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

|                 |   |
|-----------------|---|
| End point title | Cohorts B and C: Model-Based Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age <sup>[46]</sup> |
|-----------------|---|

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; 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:

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

Justification: This is a 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

|                                    |                                |                                |  |  |
|------------------------------------|--------------------------------|--------------------------------|--|--|
| <b>End point values</b>            | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
| Subject group type                 | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed        | 10 <sup>[47]</sup>             | 10 <sup>[48]</sup>             |  |  |
| Units: treated bleed rate per year |                                |                                |  |  |
| number (confidence interval 95%)   | 0.2 (0.03 to                   | 2.2 (0.69 to                   |  |  |

**Notes:**

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

[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

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

|                 |   |
|-----------------|---|
| End point title | Cohorts B and C: Model-Based Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age <sup>[49]</sup> |
|-----------------|---|

**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 52 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:**

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

Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Efficizumab 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                 | Cohort B:<br>Efficizumab<br>Q2W | Cohort C:<br>Efficizumab<br>Q4W |  |  |
|----------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type               | Reporting group                 | Reporting group                 |  |  |
| Number of subjects analysed      | 10 <sup>[50]</sup>              | 10 <sup>[51]</sup>              |  |  |
| 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:**

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

[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

**Secondary: Cohorts B and C: Model-Based Annualized Bleeding Rate (ABR) for**

## Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

|                 |   |
|-----------------|---|
| End point title | Cohorts B and C: Model-Based Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age <sup>[52]</sup> |
|-----------------|---|

### 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 52 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:

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

Justification: This is a non-randomized study that began by recruiting subjects only to Cohort A: Efficizumab 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                               | Cohort B:<br>Efficizumab<br>Q2W | Cohort C:<br>Efficizumab<br>Q4W |  |  |
|--|---------------------------------|---------------------------------|--|--|
| Subject group type                             | Reporting group                 | Reporting group                 |  |  |
| Number of subjects analysed                    | 10 <sup>[53]</sup>              | 10 <sup>[54]</sup>              |  |  |
| Units: treated spontaneous bleed rate per year |                                 |                                 |  |  |
| number (confidence interval 95%)               | 99999 (99999 to 99999)          | 0.8 (0.05 to 12.00)             |  |  |

### Notes:

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

[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

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

|                 |   |
|-----------------|---|
| End point title | Cohorts B and C: Model-Based Annualized Bleeding Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age <sup>[55]</sup> |
|-----------------|---|

### 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 52 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:

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

Justification: 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                         | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|--|--------------------------------|--------------------------------|--|--|
| Subject group type                       | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed              | 10 <sup>[56]</sup>             | 10 <sup>[57]</sup>             |  |  |
| 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:

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

[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

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

|                 |  |
|-----------------|--|
| End point title | Cohorts B and C: Model-Based Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age <sup>[58]</sup> |
|-----------------|--|

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 52 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:

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

Justification: 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                                | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                              | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                     | 10 <sup>[59]</sup>             | 10 <sup>[60]</sup>             |  |  |
| 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:

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

[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: Calculated Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age

|                 |  |
|-----------------|--|
| End point title | Cohorts B and C: Calculated Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects <12 Years of Age <sup>[61]</sup> |
|-----------------|--|

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:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . 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; 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                      | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|---------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type                    | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed           | 10 <sup>[62]</sup>             | 10 <sup>[63]</sup>             |  |  |
| 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:

[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: Calculated Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age

|                 |  |
|-----------------|--|
| End point title | Cohorts B and C: Calculated Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects <12 Years of Age <sup>[64]</sup> |
|-----------------|--|

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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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; 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                      | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|---------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type                    | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed           | 10 <sup>[65]</sup>             | 10 <sup>[66]</sup>             |  |  |
| 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:

[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: Calculated Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age

|                 |  |
|-----------------|--|
| End point title | Cohorts B and C: Calculated Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds in Treated Subjects <12 Years of Age <sup>[67]</sup> |
|-----------------|--|

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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . 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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                               | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|--|--------------------------------|--------------------------------|--|--|
| Subject group type                             | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                    | 10 <sup>[68]</sup>             | 10 <sup>[69]</sup>             |  |  |
| 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:

[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: Calculated Annualized Bleeding Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age

|                 |  |
|-----------------|--|
| End point title | Cohorts B and C: Calculated Annualized Bleeding Rate (ABR) for Treated Joint Bleeds in Treated Subjects <12 Years of Age <sup>[70]</sup> |
|-----------------|--|

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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . 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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                         | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|--|--------------------------------|--------------------------------|--|--|
| Subject group type                       | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed              | 10 <sup>[71]</sup>             | 10 <sup>[72]</sup>             |  |  |
| 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:

[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: Calculated Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age

|                 |   |
|-----------------|---|
| End point title | Cohorts B and C: Calculated Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds in Treated Subjects <12 Years of Age <sup>[73]</sup> |
|-----------------|---|

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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . 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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                                | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                              | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                     | 10 <sup>[74]</sup>             | 10 <sup>[75]</sup>             |  |  |
| 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:

[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: 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 <sup>[76]</sup> |
|-----------------|---|

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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                 | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|----------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed      | 10 <sup>[77]</sup>             | 10 <sup>[78]</sup>             |  |  |
| 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:

[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: 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 <sup>[79]</sup> |
|-----------------|---|

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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                 | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|----------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed      | 10 <sup>[80]</sup>             | 10 <sup>[81]</sup>             |  |  |
| 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:

[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: 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 <sup>[82]</sup> |
|-----------------|---|

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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.



| End point values                 | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|----------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed      | 10 <sup>[83]</sup>             | 10 <sup>[84]</sup>             |  |  |
| 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:

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

[84] - 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 <sup>[85]</sup> |
|-----------------|---|

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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                 | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|----------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed      | 10 <sup>[86]</sup>             | 10 <sup>[87]</sup>             |  |  |
| 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:

[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: 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 <sup>[88]</sup> |
|-----------------|--|

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 52 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 all subjects in the primary population of Cohort A had been enrolled or withdrawn prematurely, whichever occurred first. Results for Cohort A are reported as primary end points, while corresponding results for Cohorts B and C are reported as secondary end points.

| End point values                 | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |  |
|----------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed      | 10 <sup>[89]</sup>             | 10 <sup>[90]</sup>             |  |  |
| 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:

[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: 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: Prophylactic/Episodic Bypassing Agent | Cohort A NIS Population: Efficacy 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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: Prophylactic/Episodic Bypassing Agent v Cohort A NIS Population: 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: Prophylactic/Episodic Bypassing Agent | Cohort A NIS Population: 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   | 3.3 (1.45 to                           |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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: Prophylactic/Episodic Bypassing Agent v Cohort A NIS Population: 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 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 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: $ABR = [\text{number of bleeds}/\text{number of days during the efficacy period}] \times 365.25$ ) 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<br>Population:<br>Prophylactic/Ep<br>isodic<br>Bypassing<br>Agent | Cohort A NIS<br>Population:<br>Emicizumab<br>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 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 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:  $ABR = [\text{number of bleeds/number of days during the efficacy period}] \times 365.25$ ) 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<br>Population:<br>Prophylactic/Ep<br>isodic<br>Bypassing<br>Agent | Cohort A NIS<br>Population:<br>Emicizumab<br>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: Prophylactic/Episodic Bypassing Agent | Cohort A NIS Population: Efficizumab 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: Prophylactic/Episodic Bypassing Agent | Cohort A NIS Population: 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 Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects ≥12 Years of Age and <40 kg Body Weight

|   |   |
|---|---|
| End point title   | Model-Based Annualized Bleeding 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:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|------------------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                 | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed        | 3                             | 0 <sup>[91]</sup>              | 0 <sup>[92]</sup>              |  |
| Units: treated bleed rate per year |                               |                                |                                |  |
| number (confidence interval 95%)   | 0.8 (0.25 to 2.40)            | ( to )                         | ( to )                         |  |

Notes:

[91] - None of the subjects enrolled in this cohort were  $\geq 12$  years of age.

[92] - None of the subjects enrolled in this cohort were  $\geq 12$  years of age.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Model-Based Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects $\geq 12$ Years of Age and $< 40$ kg Body Weight

|                 |  |
|-----------------|--|
| End point title | Model-Based Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects $\geq 12$ 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:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|----------------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type               | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed      | 3                             | 0 <sup>[93]</sup>              | 0 <sup>[94]</sup>              |  |
| Units: all bleed rate per year   |                               |                                |                                |  |
| number (confidence interval 95%) | 1.4 (0.49 to 4.16)            | ( to )                         | ( to )                         |  |

Notes:

[93] - None of the subjects enrolled in this cohort were  $\geq 12$  years of age.

[94] - None of the subjects enrolled in this cohort were  $\geq 12$  years of age.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Calculated Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects $\geq 12$ Years of Age and $< 40$ kg Body Weight

|                 |   |
|-----------------|---|
| End point title | Calculated Annualized Bleeding Rate (ABR) for Treated Bleeds in Treated Subjects $\geq 12$ 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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . 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:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|---------------------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                    | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed           | 3                             | 0 <sup>[95]</sup>              | 0 <sup>[96]</sup>              |  |
| Units: treated bleed rate per year    |                               |                                |                                |  |
| median (inter-quartile range (Q1-Q3)) | 0.9 (0.00 to 1.14)            | ( to )                         | ( to )                         |  |

Notes:

[95] - None of the subjects enrolled in this cohort were  $\geq 12$  years of age.

[96] - None of the subjects enrolled in this cohort were  $\geq 12$  years of age.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Calculated Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects $\geq 12$ Years of Age and $< 40$ kg Body Weight

|                 |   |
|-----------------|---|
| End point title | Calculated Annualized Bleeding Rate (ABR) for All Bleeds in Treated Subjects $\geq 12$ 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:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . In this outcome measure, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are

excluded. As "all bleeds" comprises both treated and non-treated bleeds, the 72-hour rule was implemented separately for treated and non-treated bleeds. For treated bleeds, the 72-hour rule 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:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|---------------------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                    | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed           | 3                             | 0 <sup>[97]</sup>              | 0 <sup>[98]</sup>              |  |
| Units: all bleed rate per year        |                               |                                |                                |  |
| median (inter-quartile range (Q1-Q3)) | 0.9 (0.00 to 2.84)            | ( to )                         | ( to )                         |  |

Notes:

[97] - None of the subjects enrolled in this cohort were  $\geq 12$  years of age.

[98] - None of the subjects enrolled in this cohort were  $\geq 12$  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:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|-----------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type          | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed | 0 <sup>[99]</sup>             | 0 <sup>[100]</sup>             | 0 <sup>[101]</sup>             |  |
| Units: treated bleeds       |                               |                                |                                |  |

Notes:

[99] - At the primary completion date, none of the subjects in this cohort had their dose up-titrated.

- [100] - At the primary completion date, none of the subjects in this cohort had their dose up-titrated.  
 [101] - Because only 2 subjects had dose up-titrated, data could not be analyzed on a population level.

## 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. Due to the small sample size at the primary completion date, data could not be analyzed on a population level. Data collection is ongoing, and results will be reported upon study completion. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From Baseline to 52 weeks  |   |

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|-----------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type          | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed | 0 <sup>[102]</sup>            | 0 <sup>[103]</sup>             | 0 <sup>[104]</sup>             |  |
| Units: all bleeds           |                               |                                |                                |  |

Notes:

- [102] - At the primary completion date, none of the subjects in this cohort had dose up-titration.  
 [103] - At the primary completion date, none of the subjects in this cohort had their dose up-titration.  
 [104] - Because only 2 subjects had dose up-titration, data could not be analyzed on a population level.

## 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 '99999' signifies that a 95% confidence interval could not be calculated for data from a single subject. 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, and 57, and then every 24 weeks until end of study (up to approximately 152 weeks)

| End point values                           | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|--|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                         | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed                | 22 <sup>[105]</sup>           | 6 <sup>[106]</sup>             | 6 <sup>[107]</sup>             |  |
| Units: units 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=18,1,1) | -9.17 (-15.97 to -2.37)       | -21.43 (-99999 to 99999)       | -39.29 (-99999 to 99999)       |  |
| Change from Baseline at Week 37 (n=17,0,0) | -11.64 (-16.11 to -7.17)      | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 49 (n=17,0,0) | -9.62 (-13.59 to -5.65)       | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 57 (n=6,0,0)  | -8.57 (-20.64 to 3.50)        | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 81 (n=7,0,0)  | -10.31 (-23.04 to 2.43)       | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |

Notes:

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

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

[107] - 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 '99999' signifies that a 95% confidence interval could not be calculated for data from a single subject. 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, and 57, and then every 24 weeks until end of study (up to approximately 152 weeks)

| End point values                           | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|--|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                         | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed                | 22 <sup>[108]</sup>           | 6 <sup>[109]</sup>             | 6 <sup>[110]</sup>             |  |
| Units: units 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=18,1,1) | -18.40 (-33.76 to -3.05)      | -18.75 (-99999 to 99999)       | -56.25 (-99999 to 99999)       |  |
| Change from Baseline at Week 37 (n=17,0,0) | -21.32 (-36.61 to -6.04)      | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 49 (n=17,0,0) | -15.44 (-25.74 to -5.15)      | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 57 (n=6,0,0)  | -16.67 (-35.98 to 2.64)       | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 81 (n=7,0,0)  | -13.39 (-36.38 to 9.59)       | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |

Notes:

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

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

[110] - 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. '99999' means 95% CI not calculated for data from 1 subject; '999999' means no data available at that timepoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

Baseline (Week 1), Weeks 13, 25, 37, 49, and 57, and then every 24 weeks until end of study (up to approximately 152 weeks)

| End point values                            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|---|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                          | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed                 | 65 <sup>[111]</sup>           | 10 <sup>[112]</sup>            | 10 <sup>[113]</sup>            |  |
| Units: units 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=56,1,1)  | -21.72 (-25.59 to -17.86)     | -26.52 (-99999 to 99999)       | -33.33 (-99999 to 99999)       |  |
| Change from Baseline at Week 37 (n=53,0,0)  | -21.60 (-25.29 to -17.91)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 49 (n=51,0,0)  | -21.30 (-24.82 to -17.78)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 57 (n=22,0,0)  | -22.93 (-26.89 to -18.97)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 81 (n=16,0,0)  | -24.25 (-30.70 to -17.81)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |

**Notes:**

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

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

[113] - 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 |
|-----------------|--|

## 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. '99999' means 95% CI not calculated for data from 1 subject; '999999' means no data available at that timepoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Baseline (Week 1), Weeks 13, 25, 37, 49, and 57, and then every 24 weeks until end of study (up to approximately 152 weeks)

| End point values                            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|---|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                          | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed                 | 65 <sup>[114]</sup>           | 10 <sup>[115]</sup>            | 10 <sup>[116]</sup>            |  |
| Units: units 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=56,1,1)  | -31.06 (-36.37 to -25.74)     | -28.57 (-99999 to 99999)       | -64.29 (-99999 to 99999)       |  |
| Change from Baseline at Week 37 (n=53,0,0)  | -31.20 (-36.86 to -25.53)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 49 (n=51,0,0)  | -28.29 (-34.23 to -22.36)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 57 (n=22,0,0)  | -29.22 (-37.29 to -21.15)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |
| Change from Baseline at Week 81 (n=16,0,0)  | -30.36 (-42.85 to -17.87)     | 999999 (999999 to 999999)      | 999999 (999999 to 999999)      |  |

## Notes:

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

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

[116] - 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; At the primary completion date, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6), 21.29 (18.6-24.1), and 20.71 (18.0-24.1) weeks, respectively.

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|-----------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type          | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed | 68                            | 10                             | 10                             |  |
| Units: subjects             | 63                            | 9                              | 10                             |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with at Least One Grade $\geq 3$ Adverse Event

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with at Least One Grade $\geq 3$ 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; At the primary completion date, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6), 21.29 (18.6-24.1), and 20.71 (18.0-24.1) weeks, respectively.

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|-----------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type          | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed | 68                            | 10                             | 10                             |  |
| Units: subjects             | 11                            | 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; At the primary completion date, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6), 21.29 (18.6-24.1), and 20.71 (18.0-24.1) weeks, respectively.

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>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; At the primary completion date, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6), 21.29 (18.6-24.1), and 20.71 (18.0-24.1) weeks, respectively.

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|-----------------------------|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type          | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed | 68                            | 10                             | 10                             |  |
| Units: subjects             | 19                            | 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; At the primary completion date, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6), 21.29 (18.6-24.1), and 20.71 (18.0-24.1) weeks, respectively.

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>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; At the primary completion date, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6), 21.29 (18.6-24.1), and 20.71 (18.0-24.1) weeks, respectively.

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>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; At the primary completion date, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6), 21.29 (18.6-24.1), and 20.71 (18.0-24.1) weeks, respectively.

| End point values            | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>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 (ADA), Including Non-Neutralizing ADA and ADA with Neutralizing Potential

|                 |  |
|-----------------|--|
| End point title | Number of Subjects Testing Negative or Positive for the Presence of Anti-Drug Antibodies (ADA), Including Non-Neutralizing ADA and ADA with Neutralizing Potential |
|-----------------|--|

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  $\geq 4$ -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  $\geq 4$ -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. ADAs associated with consistent decline of emicizumab exposure (corroborated by associated loss of effect) were considered as having a neutralizing potential.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose (0 hour) at Weeks 1, 5, 17, 33, 49, 57; then every 12 weeks until end of study or 24 weeks after treatment discontinuation (up to approximately 152 weeks)

| End point values                         | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>Q4W |  |
|--|-------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                       | Reporting group               | Reporting group                | Reporting group                |  |
| Number of subjects analysed              | 68                            | 10                             | 10                             |  |
| Units: subjects                          |                               |                                |                                |  |
| Total ADA Negative                       | 65                            | 10                             | 9                              |  |
| ADA Negative                             | 61                            | 10                             | 9                              |  |
| ADA Negative (Treatment Unaffected)      | 4                             | 0                              | 0                              |  |
| Total ADA Positive                       | 3                             | 0                              | 1                              |  |
| ADA Positive (Treatment Boosted)         | 0                             | 0                              | 0                              |  |
| ADA Positive (Treatment Induced)         | 3                             | 0                              | 1                              |  |
| ADA Positive with Neutralizing Potential | 1                             | 0                              | 1                              |  |
| ADA Positive with Non-Neutralizing ADA   | 2                             | 0                              | 0                              |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Trough Concentration (C<sub>trough</sub>) of Emicizumab

|                 |  |
|-----------------|--|
| End point title | Plasma Trough Concentration (C <sub>trough</sub> ) 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 ( $\mu\text{g/mL}$ ).

|                |           |
|----------------|-----------|
| 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, and 57; then every 12 weeks until end of study or 24 weeks after treatment discontinuation (up to approximately 152 weeks)

| End point values                         | Cohort A:<br>Emicizumab<br>QW | Cohort B:<br>Emicizumab<br>Q2W | Cohort C:<br>Emicizumab<br>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=67,10,8)                      | 46.1 (± 11.3)                 | 48.7 (± 10.4)                  | 36.3 (± 6.1)                   |  |
| Week 21 (n=65,5,4)                       | 44.9 (± 11.0)                 | 49.8 (± 9.0)                   | 37.4 (± 16.9)                  |  |
| Week 25 (n=65,1,0)                       | 46.4 (± 11.4)                 | 33.3 (± 99999)                 | 99999 (± 99999)                |  |
| Week 29 (n=63,0,0)                       | 47.4 (± 12.9)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 33 (n=62,0,0)                       | 50.9 (± 13.9)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 37 (n=62,0,0)                       | 50.4 (± 15.2)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 41 (n=60,0,0)                       | 47.3 (± 13.5)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 49 (n=59,0,0)                       | 48.8 (± 12.5)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 57 (n=36,0,0)                       | 49.3 (± 14.2)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 69 (n=19,0,0)                       | 49.6 (± 10.7)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 81 (n=19,0,0)                       | 51.2 (± 10.3)                 | 999999 (± 999999)              | 999999 (± 999999)              |  |
| Week 93 (n=1,0,0)                        | 49.9 (± 99999)                | 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 until the primary completion date (30-Apr-2018); at that time, the median (min-max) duration of observation in Cohorts A, B, and C were 57.36 (17.9-92.6) weeks, 21.29 (18.6-24.1) weeks, and 20.71 (18.0-24.1) weeks, respectively.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Cohort A: 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 occurs first.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cohort C: 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 occurs first.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cohort B: 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 occurs first.

| Serious adverse events                            | Cohort A:<br>Emicizumab QW | Cohort C:<br>Emicizumab Q4W | Cohort B:<br>Emicizumab Q2W |
|---|----------------------------|-----------------------------|-----------------------------|
| Total subjects affected by serious adverse events |                            |                             |                             |
| subjects affected / exposed                       | 14 / 68 (20.59%)           | 2 / 10 (20.00%)             | 1 / 10 (10.00%)             |
| 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%)             | 1 / 10 (10.00%)             | 0 / 10 (0.00%)              |
| occurrences causally related to treatment / all   | 0 / 0                      | 1 / 1                       | 0 / 0                       |
| deaths causally related to treatment / all        | 0 / 0                      | 0 / 0                       | 0 / 0                       |
| 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          |
| Vascular disorders                              |                |                 |                |
| Haemorrhage                                     |                |                 |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 10 (10.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 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          |
| 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 |                |                |                |
| Muscle haemorrhage                              |                |                |                |
| 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          |
| Infections and infestations                     |                |                |                |
| Appendicitis                                    |                |                |                |
| 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          |
| 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          |
| Catheter site infection                         |                |                |                |
| 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          |
| Device related infection                        |                |                |                |
| 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          |
| 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          |
| Metabolism and nutrition disorders              |                |                |                |
| Ketoacidosis                                    |                |                |                |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| 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          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Cohort A:<br>Emicizumab QW | Cohort C:<br>Emicizumab Q4W | Cohort B:<br>Emicizumab Q2W |
|---|----------------------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events |                            |                             |                             |
| subjects affected / exposed                           | 62 / 68 (91.18%)           | 10 / 10 (100.00%)           | 9 / 10 (90.00%)             |
| General disorders and administration site conditions  |                            |                             |                             |
| Injection site reaction                               |                            |                             |                             |
| subjects affected / exposed                           | 19 / 68 (27.94%)           | 6 / 10 (60.00%)             | 2 / 10 (20.00%)             |
| occurrences (all)                                     | 42                         | 15                          | 7                           |
| Pain  |                            |                             |                             |
| subjects affected / exposed                           | 0 / 68 (0.00%)             | 0 / 10 (0.00%)              | 1 / 10 (10.00%)             |
| occurrences (all)                                     | 0                          | 0                           | 1                           |
| Pyrexia   |                            |                             |                             |
| subjects affected / exposed                           | 16 / 68 (23.53%)           | 3 / 10 (30.00%)             | 2 / 10 (20.00%)             |
| occurrences (all)                                     | 26                         | 4                           | 3                           |
| Swelling  |                            |                             |                             |
| subjects affected / exposed                           | 1 / 68 (1.47%)             | 0 / 10 (0.00%)              | 1 / 10 (10.00%)             |
| occurrences (all)                                     | 1                          | 0                           | 1                           |
| Respiratory, thoracic and mediastinal disorders       |                            |                             |                             |
| Cough   |                            |                             |                             |
| subjects affected / exposed                           | 17 / 68 (25.00%)           | 0 / 10 (0.00%)              | 4 / 10 (40.00%)             |
| occurrences (all)                                     | 24                         | 0                           | 4                           |
| Oropharyngeal pain                                    |                            |                             |                             |
| subjects affected / exposed                           | 4 / 68 (5.88%)             | 0 / 10 (0.00%)              | 1 / 10 (10.00%)             |
| occurrences (all)                                     | 6                          | 0                           | 1                           |
| Rhinorrhoea   |                            |                             |                             |
| subjects affected / exposed                           | 4 / 68 (5.88%)             | 0 / 10 (0.00%)              | 0 / 10 (0.00%)              |
| occurrences (all)                                     | 4                          | 0                           | 0                           |
| Psychiatric disorders                                 |                            |                             |                             |
| Anxiety   |                            |                             |                             |

|   |                        |                      |                      |
|---|------------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                  | 0 / 68 (0.00%)<br>0    | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Product issues  |                        |                      |                      |
| Device breakage<br>subjects affected / exposed<br>occurrences (all)               | 0 / 68 (0.00%)<br>0    | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Device malfunction<br>subjects affected / exposed<br>occurrences (all)            | 0 / 68 (0.00%)<br>0    | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Investigations  |                        |                      |                      |
| Indeterminable ABO blood type<br>subjects affected / exposed<br>occurrences (all) | 1 / 68 (1.47%)<br>1    | 1 / 10 (10.00%)<br>1 | 1 / 10 (10.00%)<br>1 |
| Injury, poisoning and procedural complications                                    |                        |                      |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                     | 11 / 68 (16.18%)<br>63 | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                          | 9 / 68 (13.24%)<br>16  | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Head injury<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 68 (2.94%)<br>2    | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Joint injury<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 68 (2.94%)<br>3    | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 68 (5.88%)<br>4    | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)               | 6 / 68 (8.82%)<br>9    | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                   | 5 / 68 (7.35%)<br>5    | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Skin abrasion   |                        |                      |                      |

|  |                        |                      |                      |
|--|------------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 8 / 68 (11.76%)<br>15  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)               | 9 / 68 (13.24%)<br>12  | 2 / 10 (20.00%)<br>2 | 1 / 10 (10.00%)<br>2 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)    | 2 / 68 (2.94%)<br>2    | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 3 / 68 (4.41%)<br>3    | 0 / 10 (0.00%)<br>0  | 2 / 10 (20.00%)<br>2 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                               | 4 / 68 (5.88%)<br>5    | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 68 (1.47%)<br>1    | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 12 / 68 (17.65%)<br>14 | 0 / 10 (0.00%)<br>0  | 2 / 10 (20.00%)<br>2 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 3 / 68 (4.41%)<br>3    | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 13 / 68 (19.12%)<br>14 | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Skin and subcutaneous tissue disorders<br>Erythema<br>subjects affected / exposed<br>occurrences (all) | 2 / 68 (2.94%)<br>3    | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 4 / 68 (5.88%)<br>5    | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Rash pruritic  |                        |                      |                      |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                           | 0 / 68 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Seborrhoeic dermatitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 68 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)              | 4 / 68 (5.88%)<br>4  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders                            |                      |                      |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)             | 6 / 68 (8.82%)<br>12 | 1 / 10 (10.00%)<br>7 | 1 / 10 (10.00%)<br>1 |
| Groin pain<br>subjects affected / exposed<br>occurrences (all)             | 0 / 68 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Limb discomfort<br>subjects affected / exposed<br>occurrences (all)        | 0 / 68 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)              | 0 / 68 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)      | 5 / 68 (7.35%)<br>5  | 3 / 10 (30.00%)<br>4 | 0 / 10 (0.00%)<br>0  |
| Infections and infestations  |                      |                      |                      |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)             | 5 / 68 (7.35%)<br>5  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)         | 2 / 68 (2.94%)<br>5  | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Ear infection<br>subjects affected / exposed<br>occurrences (all)          | 5 / 68 (7.35%)<br>5  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Gastroenteritis  |                      |                      |                      |

|                                    |                  |                 |                 |
|------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed        | 6 / 68 (8.82%)   | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 6                | 0               | 0               |
| Influenza                          |                  |                 |                 |
| subjects affected / exposed        | 8 / 68 (11.76%)  | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 12               | 0               | 1               |
| Nasopharyngitis                    |                  |                 |                 |
| subjects affected / exposed        | 27 / 68 (39.71%) | 4 / 10 (40.00%) | 2 / 10 (20.00%) |
| occurrences (all)                  | 43               | 5               | 6               |
| Otitis media                       |                  |                 |                 |
| subjects affected / exposed        | 6 / 68 (8.82%)   | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 7                | 0               | 0               |
| Rhinitis                           |                  |                 |                 |
| subjects affected / exposed        | 2 / 68 (2.94%)   | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                  | 3                | 1               | 0               |
| Sinusitis                          |                  |                 |                 |
| subjects affected / exposed        | 1 / 68 (1.47%)   | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                  | 1                | 1               | 0               |
| Tinea versicolour                  |                  |                 |                 |
| subjects affected / exposed        | 0 / 68 (0.00%)   | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 0                | 0               | 1               |
| Tonsillitis                        |                  |                 |                 |
| subjects affected / exposed        | 4 / 68 (5.88%)   | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                  | 5                | 0               | 0               |
| Tracheitis                         |                  |                 |                 |
| subjects affected / exposed        | 0 / 68 (0.00%)   | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 0                | 0               | 1               |
| Upper respiratory tract infection  |                  |                 |                 |
| subjects affected / exposed        | 19 / 68 (27.94%) | 2 / 10 (20.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                  | 33               | 2               | 0               |
| Varicella                          |                  |                 |                 |
| 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%)   | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                  | 0                | 0               | 1               |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 12 July 2016      | <p>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 &lt;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 &lt;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.</p> |
| 08 December 2016  | <p>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.</p>   |
| 01 September 2017 | <p>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.</p>  |



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Notes:

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## 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