



## Clinical trial results:

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

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2016-000072-17       |
| Trial protocol           | GB IE ES DE PL FR IT |
| Global end of trial date | 12 May 2022          |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v2 (current)      |
| This version publication date  | 05 November 2022  |
| First version publication date | 30 September 2018 |
| Version creation reason        |                   |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BH30071 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |                        |
|------------------------------------|------------------------|
| ISRCTN number                      | -                      |
| ClinicalTrials.gov id (NCT number) | NCT02847637            |
| WHO universal trial number (UTN)   | -                      |
| Other trial identifiers            | Study Acronym: HAVEN 3 |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |             |
|--|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 12 May 2022 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 12 May 2022 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 27 September 2016 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Efficacy, Safety  |
| Long term follow-up duration                              | 5 Years           |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 12         |
| Country: Number of subjects enrolled | Costa Rica: 9         |
| Country: Number of subjects enrolled | France: 9             |
| Country: Number of subjects enrolled | Germany: 8            |
| Country: Number of subjects enrolled | Ireland: 4            |
| Country: Number of subjects enrolled | Italy: 12             |
| Country: Number of subjects enrolled | Japan: 19             |
| Country: Number of subjects enrolled | Poland: 13            |
| Country: Number of subjects enrolled | South Africa: 10      |
| Country: Number of subjects enrolled | Korea, Republic of: 4 |
| Country: Number of subjects enrolled | Spain: 14             |
| Country: Number of subjects enrolled | Taiwan: 5             |
| Country: Number of subjects enrolled | United Kingdom: 7     |
| Country: Number of subjects enrolled | United States: 26     |
| Worldwide total number of subjects   | 152                   |
| EEA total number of subjects         | 60                    |

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)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 8   |
| Adults (18-64 years)                      | 139 |
| From 65 to 84 years                       | 5   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|                              |                                 |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes                             |
| <b>Arm title</b>             | Arm C (Control): No Prophylaxis |

Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial. After completing 24 weeks of no prophylaxis (i.e., episodic FVIII treatment) on study, then they were given the opportunity to switch to emicizumab prophylaxis of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

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

Dosage and administration details:

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

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Arm A: Emicizumab 1.5 mg/kg QW |
|------------------|--------------------------------|

Arm description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

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

**Dosage and administration details:**

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

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Arm B: Emicizumab 3 mg/kg Q2W |
|------------------|-------------------------------|

**Arm description:**

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

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

**Dosage and administration details:**

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

|                  |  |
|------------------|--|
| <b>Arm title</b> | Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis) |
|------------------|--|

**Arm description:**

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

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

**Dosage and administration details:**

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

| <b>Number of subjects in period 1</b> | Arm C (Control): No Prophylaxis | Arm A: Emicizumab 1.5 mg/kg QW | Arm B: Emicizumab 3 mg/kg Q2W |
|---------------------------------------|---------------------------------|--------------------------------|-------------------------------|
| Started                               | 18                              | 36                             | 35                            |
| Completed First 24 Weeks of Treatment | 16 <sup>[1]</sup>               | 35                             | 34                            |
| Emicizumab Dose Was Up-Titrated       | 0 <sup>[2]</sup>                | 1 <sup>[3]</sup>               | 1 <sup>[4]</sup>              |
| Changed Emicizumab Dosing Regimen     | 1 <sup>[5]</sup>                | 3 <sup>[6]</sup>               | 1 <sup>[7]</sup>              |
| Completed                             | 17                              | 34                             | 34                            |
| Not completed                         | 1                               | 2                              | 1                             |

|                              |   |   |   |
|------------------------------|---|---|---|
| Consent withdrawn by subject | - | 1 | 1 |
| Lost to follow-up            | 1 | 1 | - |

| Number of subjects in period 1        | Arm D: Emicizumab<br>1.5 mg/kg QW (Pre-<br>study FVIII<br>Prophylaxis) |
|---------------------------------------|--|
| Started                               | 63   |
| Completed First 24 Weeks of Treatment | 63   |
| Emicizumab Dose Was Up-Titrated       | 7 <sup>[8]</sup>   |
| Changed Emicizumab Dosing Regimen     | 1 <sup>[9]</sup>   |
| Completed                             | 63   |
| Not completed                         | 0  |
| Consent withdrawn by subject          | -  |
| Lost to follow-up                     | -  |

Notes:

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

Justification: A total of 17 participants switched from No Prophylaxis to emicizumab prophylaxis after 24 weeks and completed the study, but 1 of those participants did so after having completed just 23.5 weeks on No Prophylaxis.

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

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

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

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

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

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

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

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

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

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

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

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

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

Justification: Emicizumab dose up-titration was not a study milestone that applied to all participants, but rather only to those who met the criteria for such a change to their dosing.

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

Justification: Change to a preferred emicizumab dosing regimen was not a study milestone that applied to all participants, but rather only to those who opted for such a change to their dosing after the implementation of protocol version 4.

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Arm C (Control): No Prophylaxis                              |
| Reporting group description:  |  |
| Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial. After completing 24 weeks of no prophylaxis (i.e., episodic FVIII treatment) on study, then they were given the opportunity to switch to emicizumab prophylaxis of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study. |  |
| Reporting group title   | Arm A: Emicizumab 1.5 mg/kg QW                               |
| Reporting group description:  |  |
| Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.   |  |
| Reporting group title   | Arm B: Emicizumab 3 mg/kg Q2W                                |
| Reporting group description:  |  |
| Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.   |  |
| Reporting group title   | Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis) |
| Reporting group description:  |  |
| Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.   |  |

| Reporting group values                             | Arm C (Control): No Prophylaxis | Arm A: Emicizumab 1.5 mg/kg QW | Arm B: Emicizumab 3 mg/kg Q2W |
|--|---------------------------------|--------------------------------|-------------------------------|
| Number of subjects                                 | 18                              | 36                             | 35                            |
| Age categorical                                    |                                 |                                |                               |
| Units: Subjects                                    |                                 |                                |                               |
| In utero   | 0                               | 0                              | 0                             |
| Preterm newborn infants (gestational age < 37 wks) | 0                               | 0                              | 0                             |
| Newborns (0-27 days)                               | 0                               | 0                              | 0                             |
| Infants and toddlers (28 days-23 months)           | 0                               | 0                              | 0                             |
| Children (2-11 years)                              | 0                               | 0                              | 0                             |
| Adolescents (12-17 years)                          | 1                               | 0                              | 0                             |
| Adults (18-64 years)                               | 17                              | 34                             | 34                            |
| From 65-84 years                                   | 0                               | 2                              | 1                             |

|                   |   |   |   |
|-------------------|---|---|---|
| 85 years and over | 0 | 0 | 0 |
|-------------------|---|---|---|

|  |                |                |                |
|--|----------------|----------------|----------------|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | 37.8<br>± 12.9 | 39.8<br>± 14.0 | 40.4<br>± 11.4 |
| Sex: Female, Male<br>Units: participants   |                |                |                |
| Female   | 0              | 0              | 0              |
| Male   | 18             | 36             | 35             |
| Number of Participants with <9 or ≥9<br>Bleeds in the Last 24 Weeks Prior to<br>Study Entry<br>Units: Subjects   |                |                |                |
| Less Than (<) 9 Bleeds   | 4              | 9              | 5              |
| Greater Than or Equal To (≥) 9<br>Bleeds   | 14             | 27             | 30             |
| Race (NIH/OMB)<br>Units: Subjects  |                |                |                |
| American Indian or Alaska Native   | 0              | 0              | 0              |
| Asian  | 4              | 6              | 10             |
| Native Hawaiian or Other Pacific<br>Islander   | 0              | 1              | 0              |
| Black or African American  | 3              | 3              | 1              |
| White  | 11             | 24             | 20             |
| More than one race   | 0              | 0              | 0              |
| Unknown or Not Reported  | 0              | 2              | 4              |
| Ethnicity (NIH/OMB)<br>Units: Subjects   |                |                |                |
| Hispanic or Latino   | 0              | 4              | 5              |
| Not Hispanic or Latino   | 17             | 32             | 30             |
| Unknown or Not Reported  | 1              | 0              | 0              |
| Number of Target Joints in the Last 24<br>Weeks Prior to Study Entry   |                |                |                |
| A target joint was defined as at least 3 bleeds into the same joint over the last 24 weeks prior to study entry. |                |                |                |
| Units: target joints<br>arithmetic mean<br>standard deviation  | 2.2<br>± 1.4   | 2.1<br>± 1.4   | 2.2<br>± 1.7   |

|   |  |       |  |
|---|--|-------|--|
| <b>Reporting group values</b>                         | Arm D: Emicizumab<br>1.5 mg/kg QW (Pre-<br>study FVIII<br>Prophylaxis) | Total |  |
| Number of subjects                                    | 63   | 152   |  |
| Age categorical<br>Units: Subjects                    |  |       |  |
| In utero  | 0  | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0  | 0     |  |
| Newborns (0-27 days)                                  | 0  | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0  | 0     |  |
| Children (2-11 years)                                 | 0  | 0     |  |

|  |        |     |  |
|--|--------|-----|--|
| Adolescents (12-17 years)  | 7      | 8   |  |
| Adults (18-64 years)   | 54     | 139 |  |
| From 65-84 years   | 2      | 5   |  |
| 85 years and over  | 0      | 0   |  |
| Age Continuous   |        |     |  |
| Units: years   |        |     |  |
| arithmetic mean  | 36.4   |     |  |
| standard deviation   | ± 14.4 | -   |  |
| Sex: Female, Male  |        |     |  |
| Units: participants  |        |     |  |
| Female   | 0      | 0   |  |
| Male   | 63     | 152 |  |
| Number of Participants with <9 or ≥9 Bleeds in the Last 24 Weeks Prior to Study Entry                            |        |     |  |
| Units: Subjects  |        |     |  |
| Less Than (<) 9 Bleeds   | 53     | 71  |  |
| Greater Than or Equal To (≥) 9 Bleeds  | 10     | 81  |  |
| Race (NIH/OMB)   |        |     |  |
| Units: Subjects  |        |     |  |
| American Indian or Alaska Native   | 0      | 0   |  |
| Asian  | 12     | 32  |  |
| Native Hawaiian or Other Pacific Islander  | 0      | 1   |  |
| Black or African American  | 1      | 8   |  |
| White  | 47     | 102 |  |
| More than one race   | 0      | 0   |  |
| Unknown or Not Reported  | 3      | 9   |  |
| Ethnicity (NIH/OMB)  |        |     |  |
| Units: Subjects  |        |     |  |
| Hispanic or Latino   | 7      | 16  |  |
| Not Hispanic or Latino   | 53     | 132 |  |
| Unknown or Not Reported  | 3      | 4   |  |
| Number of Target Joints in the Last 24 Weeks Prior to Study Entry  |        |     |  |
| A target joint was defined as at least 3 bleeds into the same joint over the last 24 weeks prior to study entry. |        |     |  |
| Units: target joints   |        |     |  |
| arithmetic mean  | 1.0    |     |  |
| standard deviation   | ± 1.6  | -   |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Arm C (Control): No Prophylaxis                              |
| Reporting group description:<br>Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial. After completing 24 weeks of no prophylaxis (i.e., episodic FVIII treatment) on study, then they were given the opportunity to switch to emicizumab prophylaxis of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study. |  |
| Reporting group title   | Arm A: Emicizumab 1.5 mg/kg QW                               |
| Reporting group description:<br>Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.   |  |
| Reporting group title   | Arm B: Emicizumab 3 mg/kg Q2W                                |
| Reporting group description:<br>Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.   |  |
| Reporting group title   | Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis) |
| Reporting group description:<br>Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.   |  |
| Subject analysis set title  | Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768            |
| Subject analysis set type   | Sub-group analysis   |
| Subject analysis set description:<br>This arm includes historical data from participants in the non-interventional study (NIS) BH29768 who had received FVIII prophylaxis and were followed for a minimum of 24 weeks on the NIS prior to enrollment in Arm D of this study.  |  |
| Subject analysis set title  | Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis)  |
| Subject analysis set type   | Sub-group analysis   |
| Subject analysis set description:<br>This arm includes data from the same participants who had received FVIII prophylaxis in NIS BH29768 prior to study entry and then enrolled in Arm D of this study to receive emicizumab prophylaxis at a dose of 3 mg/kg once per week (QW) subcutaneously (SC) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW until the end of study. The data reported was collected only during emicizumab prophylaxis treatment.  |  |
| Subject analysis set title  | A+Bnise: Pre-Study Episodic FVIII in NIS BH29768             |
| Subject analysis set type   | Sub-group analysis   |
| Subject analysis set description:<br>This arm includes historical data from participants in the non-interventional study (NIS) BH29768 who  |  |

had received episodic FVIII treatment and were followed for a minimum of 24 weeks on the NIS prior to randomization to Arms A or B of this study. A pooled analysis, as opposed to two separate analyses, was performed due to the small number of NIS episodic patients (NISE) randomized to either Arm A or B.

|                            |  |
|----------------------------|--|
| Subject analysis set title | A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII) |
| Subject analysis set type  | Sub-group analysis   |

Subject analysis set description:

This arm includes data from the same participants who had received episodic FVIII treatment in NIS BH29768 prior to study entry and then were randomized to Arms A or B of this study to receive emicizumab prophylaxis at a dose of 3 mg/kg subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of either 1.5 mg/kg emicizumab SC QW (Arm A) or 3 mg/kg emicizumab SC Q2W (Arm B). A pooled analysis, as opposed to two separate analyses, was performed due to the small number of NIS episodic patients (NISE) randomized to either Arm A or B. The data reported was collected only during emicizumab prophylaxis treatment.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD) |
| Subject analysis set type  | Safety analysis                                       |

Subject analysis set description:

This arm includes all participants from Arm C who had switched to emicizumab prophylaxis up to the primary completion date (PCD; i.e., analysis cutoff) after having completed 24 weeks on No Prophylaxis. The data reported was collected only during emicizumab prophylaxis treatment up to the PCD. Emicizumab was administered at a loading dose of 3 mg/kg SC once per week (QW) for the first 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC Q2W.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis) |
| Subject analysis set type  | Safety analysis  |

Subject analysis set description:

This arm includes all participants from Arm C who switched to emicizumab prophylaxis during the entire study after completing 24 weeks on No Prophylaxis. The data reported was collected only during emicizumab prophylaxis treatment. Emicizumab was administered at a loading dose of 3 mg/kg SC once per week (QW) for the first 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC Q2W. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | All Emicizumab Participants |
| Subject analysis set type  | Safety analysis             |

Subject analysis set description:

This analysis set included all participants who received emicizumab on the study. For Arm C, it only includes participants starting after Week 24 on study when they crossed over to first receive prophylactic treatment with emicizumab.

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | Arms A and D: Emicizumab 1.5 mg/kg QW |
| Subject analysis set type  | Sub-group analysis                    |

Subject analysis set description:

This analysis set is a combination of all emicizumab-treated participants from Arms A and D who received the same emicizumab prophylaxis dosing regimen at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Arms B and C (Emi): Emicizumab 3 mg/kg Q2W |
| Subject analysis set type  | Sub-group analysis                         |

Subject analysis set description:

This analysis set is a combination of all emicizumab-treated participants from Arms B and C (Emi) who received the same emicizumab prophylaxis dosing regimen at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC once every 2 weeks (Q2W).

## Primary: Annualized Bleeding Rate (ABR) for Treated Bleeds

|                 |   |
|-----------------|---|
| End point title | Annualized Bleeding Rate (ABR) for Treated Bleeds |
|-----------------|---|

End point description:

The number of treated bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was assessed using a negative binomial (NB) regression model, which accounts for different follow-up times, with the number of bleeds as a function of randomization and the time that each participant

stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry as a stratification factor. A bleed is considered a “treated bleed” if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a “treatment for bleed”, irrespective of the time between treatment and the preceding bleed. Bleeds due to surgery/procedure are excluded.

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks) |         |

| End point values                   | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                 | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed        | 18                                    | 36                                   | 35                                  | 63  |
| Units: treated bleed rate per year |                                       |                                      |                                     |   |
| number (confidence interval 95%)   | 38.2 (22.86 to 63.76)                 | 1.5 (0.89 to 2.47)                   | 1.3 (0.75 to 2.25)                  | 1.6 (1.07 to 2.44)  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | ABR Ratio for Arm A versus Arm C                                 |
| Statistical analysis description:  |  |
| H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C ≠ 1. |  |
| Comparison groups  | Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW |
| Number of subjects included in analysis  | 54   |
| Analysis specification   | Pre-specified  |
| Analysis type  | superiority  |
| P-value  | < 0.0001 <sup>[1]</sup>  |
| Method   | Stratified Wald test   |
| Parameter estimate   | ABR Ratio  |
| Point estimate   | 0.04   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.02   |
| upper limit  | 0.075  |

Notes:

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

|                            |                                  |
|----------------------------|----------------------------------|
| Statistical analysis title | ABR Ratio for Arm B versus Arm C |
|----------------------------|----------------------------------|

Statistical analysis description:

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

|   |   |
|---|---|
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis | 53  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001 [2]  |
| Method                                  | Stratified Wald test  |
| Parameter estimate                      | ABR Ratio   |
| Point estimate                          | 0.03  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.017   |
| upper limit                             | 0.066   |

Notes:

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

### Secondary: Annualized Bleeding Rate (ABR) for All Bleeds

|                 |   |
|-----------------|---|
| End point title | Annualized Bleeding Rate (ABR) for All Bleeds |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

| End point values                 | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type               | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed      | 18                                    | 36                                   | 35                                  | 63  |
| Units: all bleed rate per year   |                                       |                                      |                                     |   |
| number (confidence interval 95%) | 47.6 (28.45 to 79.59)                 | 2.5 (1.63 to 3.90)                   | 2.6 (1.63 to 4.29)                  | 3.3 (2.22 to 4.83)  |

### Statistical analyses

|                            |                                  |
|----------------------------|----------------------------------|
| Statistical analysis title | ABR Ratio for Arm B versus Arm C |
|----------------------------|----------------------------------|

**Statistical analysis description:**

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

|   |   |
|---|---|
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis | 53  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001 <sup>[3]</sup>   |
| Method                                  | Stratified Wald test  |
| Parameter estimate                      | ABR Ratio   |
| Point estimate                          | 0.06  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.03  |
| upper limit                             | 0.103   |

**Notes:**

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

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | ABR Ratio for Arm A versus Arm C |
|-----------------------------------|----------------------------------|

**Statistical analysis description:**

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

|   |  |
|---|--|
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW |
| Number of subjects included in analysis | 54   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001 <sup>[4]</sup>  |
| Method                                  | Stratified Wald test   |
| Parameter estimate                      | ABR Ratio  |
| Point estimate                          | 0.05   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.028  |
| upper limit                             | 0.099  |

**Notes:**

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

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

|                 |   |
|-----------------|---|
| End point title | Annualized Bleeding Rate (ABR) for Treated Joint Bleeds |
|-----------------|---|

**End point description:**

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

surgery/procedure are excluded.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks) |           |

| End point values                         | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|--|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                       | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed              | 18                                    | 36                                   | 35                                  | 63  |
| Units: treated joint bleed rate per year |                                       |                                      |                                     |   |
| number (confidence interval 95%)         | 26.5 (14.67 to<br>47.79)              | 1.1 (0.59 to<br>1.89)                | 0.9 (0.44 to<br>1.67)               | 1.2 (0.70 to<br>2.01)   |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | ABR Ratio for Arm B versus Arm C                                |
| Statistical analysis description:   |   |
| H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C $\neq$ 1. |   |
| Comparison groups   | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis   | 53  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | < 0.0001 [5]  |
| Method  | Stratified Wald test  |
| Parameter estimate  | ABR Ratio   |
| Point estimate  | 0.03  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.015   |
| upper limit   | 0.07  |

Notes:

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

|   |  |
|---|--|
| Statistical analysis title  | ABR Ratio for Arm A versus Arm C                                 |
| Statistical analysis description:   |  |
| H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C $\neq$ 1. |  |
| Comparison groups   | Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 54                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[6]</sup> |
| Method                                  | Stratified Wald test    |
| Parameter estimate                      | ABR Ratio               |
| Point estimate                          | 0.04                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.019                   |
| upper limit                             | 0.085                   |

Notes:

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

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

|                 |   |
|-----------------|---|
| End point title | Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks)

| End point values                               | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|--|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                             | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed                    | 18                                    | 36                                   | 35                                  | 63  |
| Units: treated spontaneous bleed rate per year |                                       |                                      |                                     |   |
| number (confidence interval 95%)               | 15.6 (7.60 to 31.91)                  | 1.0 (0.48 to 1.91)                   | 0.3 (0.11 to 0.75)                  | 0.5 (0.23 to 0.94)  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | ABR Ratio for Arm B versus Arm C                                |
| Statistical analysis description:   |   |
| H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C $\neq$ 1. |   |
| Comparison groups   | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis   | 53  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | < 0.0001 <sup>[7]</sup>   |
| Method  | Stratified Wald test  |
| Parameter estimate  | ABR Ratio   |
| Point estimate  | 0.02  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.006   |
| upper limit   | 0.056   |

Notes:

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

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | ABR Ratio for Arm A versus Arm C                                 |
| Statistical analysis description:   |  |
| H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C $\neq$ 1. |  |
| Comparison groups   | Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW |
| Number of subjects included in analysis   | 54   |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | < 0.0001 <sup>[8]</sup>  |
| Method  | Stratified Wald test   |
| Parameter estimate  | ABR Ratio  |
| Point estimate  | 0.06   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.025  |
| upper limit   | 0.151  |

Notes:

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

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

|  |  |
|--|--|
| <b>End point title</b>   | Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds |
| End point description:   |  |
| The number of treated target joint bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was assessed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or $\geq$ 9) in the last 24 weeks prior to study entry as a stratification factor. A "target joint bleed" is defined as a bleed reported as a joint bleed into a target joint, defined as at least 3 bleeds into the same joint during the last 24 weeks prior to study entry. It is |  |

considered a “treated target joint bleed” if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a “treatment for bleed”. Bleeds due to surgery/procedure are excluded.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From Baseline to at least 24 weeks (median [min-max] efficacy periods for Arm C: 24.00 [14.4-25.0] weeks; Arm A: 29.57 [17.3-49.6] weeks; Arm B: 31.29 [3.3-50.6] weeks; Arm D: 33.14 [18.4-48.6] weeks) |           |

| End point values                                | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|---|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                              | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed                     | 18                                    | 36                                   | 35                                  | 63  |
| Units: treated target joint bleed rate per year |                                       |                                      |                                     |   |
| number (confidence interval 95%)                | 13.0 (5.22 to 32.33)                  | 0.6 (0.28 to 1.42)                   | 0.7 (0.27 to 1.64)                  | 0.6 (0.26 to 1.53)  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | ABR Ratio for Arm A versus Arm C                                 |
| Statistical analysis description:  |  |
| H0 (null hypothesis): ABR Ratio for Arm A versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm A versus Arm C ≠ 1. |  |
| Comparison groups  | Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 mg/kg QW |
| Number of subjects included in analysis  | 54   |
| Analysis specification   | Pre-specified  |
| Analysis type  | superiority  |
| P-value  | < 0.0001 [9]   |
| Method   | Stratified Wald test   |
| Parameter estimate   | ABR Ratio  |
| Point estimate   | 0.05   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.016  |
| upper limit  | 0.143  |

Notes:

[9] - Not controlled for type I error

|  |   |
|--|---|
| Statistical analysis title   | ABR Ratio for Arm B versus Arm C                            |
| Statistical analysis description:  |   |
| H0 (null hypothesis): ABR Ratio for Arm B versus Arm C = 1. H1 (alternative hypothesis): ABR Ratio for Arm B versus Arm C ≠ 1. |   |
| Comparison groups  | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg |

|   |                          |
|---|--------------------------|
|   | Q2W                      |
| Number of subjects included in analysis | 53                       |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.0001 <sup>[10]</sup> |
| Method                                  | Stratified Wald test     |
| Parameter estimate                      | ABR Ratio                |
| Point estimate                          | 0.05                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.018                    |
| upper limit                             | 0.147                    |

Notes:

[10] - Not controlled for type I error

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

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

End point description:

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

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

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for Dnisp-FVIII Prophylaxis: 30.07 [5.0-45.1] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for Dnisp-Emicizumab Prophylaxis: 33.71 [20.1-48.6] weeks)

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

## Statistical analyses

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

Notes:

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

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

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

End point description:

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

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

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for Dnisp-FVIII Prophylaxis: 30.07 [5.0-45.1] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for Dnisp-Emicizumab Prophylaxis: 33.71 [20.1-48.6] weeks)

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

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | ABR Ratio - Dnisp: Emicizumab vs FVIII Prophylaxis  |
| Statistical analysis description:   |   |
| H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio $\neq$ 1. This is an intra-participant analysis of the ABR Ratio for a total of 48 participants (not 96) over two different periods: on study while receiving emicizumab prophylaxis (Dnisp: Emicizumab Prophylaxis) versus before study entry while receiving FVIII prophylaxis in NIS BH29768 (Dnisp: Pre-Study FVIII Prophylaxis). |   |
| Comparison groups   | Dnisp: Pre-Study FVIII Prophylaxis in NIS BH29768 v Dnisp: Emicizumab Prophylaxis (Pre-Study FVIII Prophylaxis) |
| Number of subjects included in analysis   | 96  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0002 <sup>[12]</sup>  |
| Method  | Non-stratified Wald test  |
| Parameter estimate  | ABR Ratio   |
| Point estimate  | 0.37  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.22  |
| upper limit   | 0.626   |

Notes:

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

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

|   |  |
|---|--|
| End point title   | Intra-Participant Comparison of ABR for Treated Bleeds on Study Versus Pre-Study in Participants from the NIS Population Previously Treated with Episodic FVIII (NISE) |
| End point description:  |  |
| This is an intra-participant comparison of the annualized bleeding rate (ABR) for treated bleeds on study versus pre-study in the NIS population previously treated with episodic FVIII in NIS BH29768. The number of treated bleeds over the efficacy period is presented as an ABR that was assessed using a NB regression model, which accounts for different follow-up times, with the number of bleeds as a function of treatment and the time that each participant stays in the study (i.e., length of the efficacy period) included as an offset in the model. The model also includes a repeated statement to account for intra-participant comparison. A bleed is considered a "treated bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed", irrespective of the time between treatment and the preceding bleed. Bleeds due to surgery/procedure are excluded. |  |
| End point type  | Secondary  |

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for A+Bnise-FVIII Episodic: 25.71 [15.4-40.9] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for A+Bnise-Emicizumab: 34.71 [24.1-50.6] weeks)

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

## Statistical analyses

| Statistical analysis title  | ABR Ratio Emicizumab Prophylaxis vs Episodic FVIII  |
|---|---|
| Statistical analysis description:   |   |
| H0 (null hypothesis): ABR Ratio = 1. H1 (alternative hypothesis): ABR Ratio $\neq$ 1. This is an intra-participant analysis of the ABR Ratio for a total of 20 participants (not 40) over two different periods: on study while receiving emicizumab prophylaxis (A+Bnise: Emicizumab Prophylaxis) versus before study entry while receiving episodic FVIII in NIS BH29768 (A+Bnise: Pre-Study Episodic FVIII). |   |
| Comparison groups   | A+Bnise: Pre-Study Episodic FVIII in NIS BH29768 v A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII) |
| Number of subjects included in analysis   | 40  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | < 0.0001 <sup>[13]</sup>  |
| Method  | Non-stratified Wald test  |
| Parameter estimate  | ABR Ratio   |
| Point estimate  | 0.03  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.014   |
| upper limit   | 0.067   |

Notes:

[13] - Not controlled for type I error

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

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

End point description:

This is an intra-participant comparison of the annualized bleeding rate (ABR) for all bleeds on study versus pre-study in the NIS population previously treated with episodic FVIII in NIS BH29768. The number of all bleeds over the efficacy period is presented as an ABR that was assessed using a NB

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

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

End point timeframe:

Efficacy periods: At least 24 weeks prior to study entry (median [min-max] for A+Bnise-FVIII Episodic: 25.71 [15.4-40.9] weeks); and From Baseline to at least 24 weeks on study (median [min-max] for A+Bnise-Emicizumab: 34.71 [24.1-50.6] weeks)

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

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | ABR Ratio Emicizumab Prophylaxis vs Episodic FVIII |
|----------------------------|--|

Statistical analysis description:

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

|   |   |
|---|---|
| Comparison groups                       | A+Bnise: Pre-Study Episodic FVIII in NIS BH29768 v A+Bnise: Emicizumab Prophylaxis (Pre-study Episodic FVIII) |
| Number of subjects included in analysis | 40  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001 <sup>[14]</sup>  |
| Method                                  | Non-stratified Wald test  |
| Parameter estimate                      | ABR Ratio   |
| Point estimate                          | 0.04  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.023   |
| upper limit                             | 0.068   |

Notes:

[14] - Not controlled for type I error

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

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

End point description:

The Haem-A-QoL questionnaire has been developed and used in hemophilia A participants, assessing very specific aspects of dealing with hemophilia. The questionnaire consists of items pertaining to 10 domains: physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain ranges from 0 to 100 with lower scores reflective of better quality of life. Physical Health domain score is reported (range 0 to 100, with lower scores reflective of better physical health). The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variables: baseline score, treatment group, and treatment by baseline interaction term.

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

End point timeframe:

Baseline, Week 25

Notes:

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

Justification: This endpoint applies to adults in the randomized population, and only participants in Arms A, B, and C were randomized in this study.

| End point values                     | Arm C (Control): No Prophylaxis | Arm A: Emicizumab 1.5 mg/kg QW | Arm B: Emicizumab 3 mg/kg Q2W |  |
|--------------------------------------|---------------------------------|--------------------------------|-------------------------------|--|
| Subject group type                   | Reporting group                 | Reporting group                | Reporting group               |  |
| Number of subjects analysed          | 13                              | 34                             | 29                            |  |
| Units: units on a scale              |                                 |                                |                               |  |
| arithmetic mean (standard deviation) | 44.32 (± 17.15)                 | 31.81 (± 27.86)                | 28.35 (± 25.57)               |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Difference in Adjusted Means (Arm C vs. Arm B)                  |
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis | 42  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0349 <sup>[16]</sup>  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                                  |
| Point estimate                          | 15.97   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.16  |
| upper limit                             | 30.78   |

Notes:

[16] - Not controlled for type I error

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference in Adjusted Means (Arm C vs. Arm A)          |
| Comparison groups                 | Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 |

|   |                                |
|---|--------------------------------|
|   | mg/kg QW                       |
| Number of subjects included in analysis | 47                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.0891 <sup>[17]</sup>       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 12.51                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.96                          |
| upper limit                             | 26.98                          |

Notes:

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

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

|                 |  |
|-----------------|--|
| End point title | Haem-A-QoL Questionnaire Total Score for Adult Participants (≥18 Years of Age) in the Randomized Population at Week 25 <sup>[18]</sup> |
|-----------------|--|

End point description:

The Haem-A-QoL questionnaire has been developed and used in hemophilia A participants, assessing very specific aspects of dealing with hemophilia. The questionnaire consists of items pertaining to 10 domains: physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain ranges from 0 to 100 with lower scores reflective of better quality of life. Haem-A-QoL Total Score is the average of all domain scores and it ranges from 0 to 100, with lower scores reflective of better quality of life. The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variates: baseline score, treatment group, and treatment by baseline interaction term.

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

End point timeframe:

Baseline, Week 25

Notes:

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

Justification: This endpoint applies to adults in the randomized population, and only participants in Arms A, B, and C were randomized in this study.

| End point values                     | Arm C (Control): No Prophylaxis | Arm A: Emicizumab 1.5 mg/kg QW | Arm B: Emicizumab 3 mg/kg Q2W |  |
|--------------------------------------|---------------------------------|--------------------------------|-------------------------------|--|
| Subject group type                   | Reporting group                 | Reporting group                | Reporting group               |  |
| Number of subjects analysed          | 13                              | 34                             | 29                            |  |
| Units: units on a scale              |                                 |                                |                               |  |
| arithmetic mean (standard deviation) | 29.95 (± 13.56)                 | 24.04 (± 15.26)                | 21.39 (± 12.64)               |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Difference in Adjusted Means (Arm C vs. Arm A)          |
| Comparison groups          | Arm C (Control): No Prophylaxis v Arm A: Emicizumab 1.5 |

|   |                                |
|---|--------------------------------|
|   | mg/kg QW                       |
| Number of subjects included in analysis | 47                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.1269 <sup>[19]</sup>       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 5.91                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.72                          |
| upper limit                             | 13.55                          |

Notes:

[19] - Not controlled for type I error

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Difference in Adjusted Means (Arm C vs. Arm B)                  |
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis | 42  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0317 <sup>[20]</sup>  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                                  |
| Point estimate                          | 8.56  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.77  |
| upper limit                             | 16.35   |

Notes:

[20] - Not controlled for type I error

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

|                 |   |
|-----------------|---|
| End point title | European Quality of Life 5-Dimensions-5 Levels (EQ-5D-5L) Questionnaire Visual Analogue Scale (VAS) Score in the Randomized Population at Week 25 <sup>[21]</sup> |
|-----------------|---|

End point description:

EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L VAS. The VAS is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variables: baseline score, treatment group, and treatment by baseline interaction term.

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

Notes:

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

Justification: This endpoint applies to the randomized population, and only participants in Arms A, B, and C were randomized in this study.

| End point values                     | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W |  |
|--------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|--|
| Subject group type                   | Reporting group                       | Reporting group                      | Reporting group                     |  |
| Number of subjects analysed          | 14                                    | 34                                   | 29                                  |  |
| Units: units on a scale              |                                       |                                      |                                     |  |
| arithmetic mean (standard deviation) | 72.57 ( $\pm$ 8.20)                   | 76.61 ( $\pm$ 20.99)                 | 81.72 ( $\pm$ 15.55)                |  |

### Statistical analyses

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

Notes:

[22] - Not controlled for type I error

| Statistical analysis title              | Difference in Adjusted Means (Arm C vs. Arm B)                  |
|---|---|
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis | 43  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0373 <sup>[23]</sup>  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                                  |
| Point estimate                          | -9.15   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -17.74  |
| upper limit                             | -0.55   |

Notes:

[23] - Not controlled for type I error

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

|                 |  |
|-----------------|--|
| End point title | EQ-5D-5L Questionnaire Index Utility Score in the Randomized Population at Week 25 <sup>[24]</sup> |
|-----------------|--|

End point description:

EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L VAS. The EQ-5D-5L health state profile is designed to record the participant's current health state in 5 domains: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Responses from the five domains are used to calculate a single index utility score on a scale of 0 to 1, with higher scores reflective of better quality of life. The means were derived via an analysis of covariance (ANCOVA) model and have been adjusted for the following co-variables: baseline score, treatment group, and treatment by baseline interaction term.

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

End point timeframe:

Baseline, Week 25

Notes:

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

Justification: This endpoint applies to the randomized population, and only participants in Arms A, B, and C were randomized in this study.

| End point values                     | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Eticizumab<br>1.5 mg/kg QW | Arm B:<br>Eticizumab 3<br>mg/kg Q2W |  |
|--------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|--|
| Subject group type                   | Reporting group                       | Reporting group                      | Reporting group                     |  |
| Number of subjects analysed          | 14                                    | 34                                   | 29                                  |  |
| Units: units on a scale              |                                       |                                      |                                     |  |
| arithmetic mean (standard deviation) | 0.63 (± 0.20)                         | 0.76 (± 0.24)                        | 0.76 (± 0.18)                       |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Difference in Adjusted Means (Arm C vs. Arm A)                   |
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm A: Eticizumab 1.5 mg/kg QW |
| Number of subjects included in analysis | 48   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.006 <sup>[25]</sup>  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (final values)                                   |
| Point estimate                          | -0.13  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.22  |
| upper limit                             | -0.04  |

Notes:

[25] - Not controlled for type I error

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Difference in Adjusted Means (Arm C vs. Arm B)                  |
| Comparison groups                       | Arm C (Control): No Prophylaxis v Arm B: Emicizumab 3 mg/kg Q2W |
| Number of subjects included in analysis | 43  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0059 <sup>[26]</sup>  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                                  |
| Point estimate                          | -0.13   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.23   |
| upper limit                             | -0.04   |

Notes:

[26] - Not controlled for type I error

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

|                 |  |
|-----------------|--|
| End point title | Hemophilia-Specific Quality of Life - Short Form (Haemo-QoL-SF) Questionnaire Score in Adolescent Participants (12 to 17 Years of Age) in the Randomized Population at Week 25 <sup>[27]</sup> |
|-----------------|--|

End point description:

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

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

End point timeframe:

Week 25

Notes:

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

Justification: This endpoint applies to adolescents in the randomized population, and only participants in Arms A, B, and C were randomized in this study.

| <b>End point values</b>              | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W |  |
|--------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|--|
| Subject group type                   | Reporting group                       | Reporting group                      | Reporting group                     |  |
| Number of subjects analysed          | 0 <sup>[28]</sup>                     | 0 <sup>[29]</sup>                    | 0 <sup>[30]</sup>                   |  |
| Units: units on a scale              |                                       |                                      |                                     |  |
| arithmetic mean (standard deviation) | ()                                    | ()                                   | ()                                  |  |

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With at Least One Adverse Event During the First 24 Weeks of the Study, Primary Analysis

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With at Least One Adverse Event During the First 24 Weeks of the Study, Primary Analysis |
|-----------------|---|

End point description:

The percentage of participants experiencing at least one adverse event, including all non-serious and serious adverse events, is reported here. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values                  | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 33.3                                  | 94.4                                 | 85.7                                | 87.3  |

| End point values                  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 50.0  |  |  |  |

## Statistical analyses

**Secondary: Percentage of Participants With at Least One Grade  $\geq 3$  Adverse Event During the First 24 Weeks of the Study, Primary Analysis**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With at Least One Grade $\geq 3$ Adverse Event During the First 24 Weeks of the Study, Primary Analysis |
|-----------------|--|

## End point description:

The World Health Organization (WHO) toxicity grading scale will be used for assessing adverse event severity. For adverse events that are not specifically listed in the WHO toxicity grading scale, a grade 3 adverse event is defined as: severe, marked limitation in activity, some assistance usually required, medical intervention or therapy required, hospitalization possible; and a grade 4 adverse event is defined as: life-threatening, extreme limitation in activity, significant assistance required, significant medical intervention or therapy required, hospitalization or hospice care probable. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

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

## End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values                  | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 5.6                                   | 8.3                                  | 11.4                                | 9.3   |

| End point values                  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 0   |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Participants With at Least One Adverse Event Leading to Withdrawal From Treatment During the First 24 Weeks of the Study, Primary Analysis**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With at Least One Adverse Event |
|-----------------|--|

End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

End point type Secondary

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values                  | Arm C (Control): No Prophylaxis | Arm A: Emicizumab 1.5 mg/kg QW | Arm B: Emicizumab 3 mg/kg Q2W | Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis) |
|-----------------------------------|---------------------------------|--------------------------------|-------------------------------|--|
| Subject group type                | Reporting group                 | Reporting group                | Reporting group               | Reporting group  |
| Number of subjects analysed       | 18                              | 36                             | 35                            | 63   |
| Units: percentage of participants |                                 |                                |                               |  |
| number (not applicable)           | 0                               | 0                              | 2.9                           | 0  |

| End point values                  | Arm C(Emi): Emicizumab 3 mg/kg Q2W (Switch up to PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set                                  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 0   |  |  |  |

Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Vital Signs During the First 24 Weeks of the Study, Primary Analysis**

End point title Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Vital Signs During the First 24 Weeks of the Study, Primary Analysis

End point description:

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

analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks) |           |

| End point values                  | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 0                                     | 0                                    | 0                                   | 0   |

| End point values                  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 0   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with at Least One Adverse Event of Abnormal Laboratory Values During the First 24 Weeks of the Study, Primary Analysis

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with at Least One Adverse Event of Abnormal Laboratory Values During the First 24 Weeks of the Study, Primary Analysis |
|-----------------|---|

End point description:

The percentage of participants with adverse events of abnormal laboratory values is reported here. An abnormal laboratory value is defined as a laboratory test result outside of the normal range for hematology or serum chemistries. It is reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); results in a medical intervention or a change in concomitant therapy; or is clinically significant in the investigator's judgment. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values                  | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 0                                     | 5.6                                  | 17.1                                | 4.8   |

| End point values                  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 6.3   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Physical Examination Findings During the First 24 Weeks of the Study, Primary Analysis

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With at Least One Adverse Event of Changes from Baseline in Physical Examination Findings During the First 24 Weeks of the Study, Primary Analysis |
|-----------------|---|

End point description:

Post-baseline physical examination abnormalities that were not present at baseline or worsened were reported as adverse events. At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values                  | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 0                                     | 0                                    | 0                                   | 0   |

| End point values                  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 0   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With at Least One Local Injection-Site Reaction During the First 24 Weeks of the Study, Primary Analysis

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With at Least One Local Injection-Site Reaction During the First 24 Weeks of the Study, Primary Analysis |
|-----------------|---|

End point description:

Local adverse events that occurred within 24 hours after study drug administration and, in the investigator's opinion, were judged to be related to study drug injection, were captured as an "injection-site reaction" on the Adverse Event electronic Case Report Form (eCRF). An injection-related reaction that was localized was marked as a "local injection-site reaction." At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values            | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type          | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed | 18                                    | 36                                   | 35                                  | 63  |

|                                   |   |      |      |      |
|-----------------------------------|---|------|------|------|
| Units: percentage of participants |   |      |      |      |
| number (not applicable)           | 0 | 25.0 | 20.0 | 33.3 |

|                                   |   |  |  |  |
|-----------------------------------|---|--|--|--|
| <b>End point values</b>           | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 12.5  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With at Least One Thrombotic Microangiopathy During the First 24 Weeks of the Study, Primary Analysis

|   |  |
|---|--|
| End point title   | Percentage of Participants With at Least One Thrombotic Microangiopathy During the First 24 Weeks of the Study, Primary Analysis |
| End point description:  |  |
| At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.   |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks) |  |

|                                   |                                       |                                      |                                     |   |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| <b>End point values</b>           | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 0                                     | 0                                    | 0                                   | 0   |

|                         |   |  |  |  |
|-------------------------|---|--|--|--|
| <b>End point values</b> | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to |  |  |  |
|-------------------------|---|--|--|--|

|                                   |                      |  |  |  |
|-----------------------------------|----------------------|--|--|--|
|                                   | PCD)                 |  |  |  |
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 16                   |  |  |  |
| Units: percentage of participants |                      |  |  |  |
| number (not applicable)           | 0                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With at Least One Thromboembolic Event During the First 24 Weeks of the Study, Primary Analysis

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With at Least One Thromboembolic Event During the First 24 Weeks of the Study, Primary Analysis |
|-----------------|--|

End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values                  | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 0                                     | 0                                    | 0                                   | 0   |

| End point values                  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 0   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction During the First 24 Weeks of the Study, Primary Analysis

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With at Least One Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reaction During the First 24 Weeks of the Study, Primary Analysis |
|-----------------|---|

End point description:

At the clinical cut-off date for primary analysis (15 Sep 2017), data was collected over a period of at least 24 weeks.

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

End point timeframe:

From Baseline to at least 24 weeks (median [min-max] safety periods for Arm C (Control): 24.00 [14.4-25.0] weeks; Arm A: 30.00 [21.4-49.6] weeks; Arm B: 31.29 [24.4-50.6] weeks; Arm C (Emi): 7.57 [0.3-26.3] weeks; Arm D: 33.71 [18.4-49.6] weeks)

| End point values                  | Arm C<br>(Control): No<br>Prophylaxis | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) |
|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                      | Reporting group                     | Reporting group   |
| Number of subjects analysed       | 18                                    | 36                                   | 35                                  | 63  |
| Units: percentage of participants |                                       |                                      |                                     |   |
| number (not applicable)           | 0                                     | 0                                    | 0                                   | 0   |

| End point values                  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W<br>(Switch up to<br>PCD) |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  |  |  |  |
| Number of subjects analysed       | 16  |  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 0   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Safety Summary of the Percentage of Emicizumab-Treated Participants With at Least One Adverse Event During the Study

|                 |  |
|-----------------|--|
| End point title | Safety Summary of the Percentage of Emicizumab-Treated Participants With at Least One Adverse Event During the Study <sup>[31]</sup> |
|-----------------|--|

**End point description:**

Investigators sought information on adverse events (AEs) at each contact with participants. The WHO toxicity grading scale was used for assessing AE severity (i.e., intensity of an AE); any AEs not specifically listed in the WHO toxicity grading scale were assessed for severity according to the following grades: Grade 1 is mild; Grade 2 is moderate, Grade 3 is severe; Grade 4 is life-threatening; and Grade 5 is death. Regardless of severity, some AEs may have also met seriousness criteria. The terms "severe" and "serious" are not synonymous; severity and seriousness were independently assessed for each AE. For participants whose emicizumab dose was up-titrated and those who opted for a change in dosing regimen (after implementation of protocol v4), only AEs that occurred before either one of those events are included. Hypersens.= hypersensitivity; Mod. = modification

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

**End point timeframe:**

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

**Notes:**

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

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

| <b>End point values</b>                             | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) | Arm C(Emi):<br>Emicizumab 3<br>mg/kg<br>Q2W(Switch<br>From No<br>Prophylaxis) |
|---|--------------------------------------|-------------------------------------|---|---|
| Subject group type                                  | Reporting group                      | Reporting group                     | Reporting group   | Subject analysis set  |
| Number of subjects analysed                         | 36                                   | 35                                  | 63  | 17  |
| Units: percentage of participants                   |                                      |                                     |   |   |
| number (not applicable)                             |                                      |                                     |   |   |
| Any Adverse Event (AE)                              | 100.0                                | 97.1                                | 100.0   | 88.2  |
| AE with Fatal Outcome                               | 0.0                                  | 0.0                                 | 0.0   | 0.0   |
| Serious AE  | 27.8                                 | 22.9                                | 25.4  | 5.9   |
| AE Leading to Withdrawal from<br>Treatment          | 0.0                                  | 2.9                                 | 0.0   | 0.0   |
| AE Leading to Dose Mod./Interruption                | 2.8                                  | 0.0                                 | 1.6   | 0.0   |
| Grade ≥3 AE   | 36.1                                 | 28.6                                | 20.6  | 5.9   |
| Related AE  | 30.6                                 | 34.3                                | 47.6  | 23.5  |
| Local Injection Site Reaction                       | 27.8                                 | 22.9                                | 39.7  | 23.5  |
| Systemic<br>Hypersens./Anaphylac(tic/toid) Reaction | 0.0                                  | 0.0                                 | 0.0   | 0.0   |
| Thromboembolic Event (TE)                           | 0.0                                  | 2.9                                 | 1.6   | 0.0   |
| Thrombotic Microangiopathy (TMA)                    | 0.0                                  | 0.0                                 | 0.0   | 0.0   |

| <b>End point values</b>           | All Emicizumab<br>Participants |  |  |  |
|-----------------------------------|--------------------------------|--|--|--|
| Subject group type                | Subject analysis set           |  |  |  |
| Number of subjects analysed       | 151                            |  |  |  |
| Units: percentage of participants |                                |  |  |  |
| number (not applicable)           |                                |  |  |  |
| Any Adverse Event (AE)            | 98.0                           |  |  |  |
| AE with Fatal Outcome             | 0.0                            |  |  |  |
| Serious AE                        | 23.2                           |  |  |  |

|   |      |  |  |  |
|---|------|--|--|--|
| AE Leading to Withdrawal from Treatment | 0.7  |  |  |  |
| AE Leading to Dose Mod./Interruption    | 1.3  |  |  |  |
| Grade $\geq 3$ AE                       | 24.5 |  |  |  |
| Related AE                              | 37.7 |  |  |  |
| Local Injection Site Reaction           | 31.1 |  |  |  |
| Systemic                                | 0.0  |  |  |  |
| Hypersens./Anaphylac(tic/toid) Reaction |      |  |  |  |
| Thromboembolic Event (TE)               | 1.3  |  |  |  |
| Thrombotic Microangiopathy (TMA)        | 0.0  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Long-Term Efficacy of Emicizumab: Model-Based Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants <sup>[32]</sup> |
|-----------------|--|

End point description:

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

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

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

Notes:

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

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

| End point values                 | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) | Arm C(Emi):<br>Emicizumab 3<br>mg/kg<br>Q2W(Switch<br>From No<br>Prophylaxis) |
|----------------------------------|--------------------------------------|-------------------------------------|---|---|
| Subject group type               | Reporting group                      | Reporting group                     | Reporting group   | Subject analysis set  |
| Number of subjects analysed      | 36                                   | 35                                  | 63  | 17  |
| Units: bleeds per year           |                                      |                                     |   |   |
| number (confidence interval 95%) |                                      |                                     |   |   |
| Treated Bleeds                   | 0.8 (0.48 to 1.29)                   | 0.7 (0.40 to 1.08)                  | 1.5 (1.02 to 2.34)  | 1.2 (0.47 to 3.19)  |

|                             |                    |                    |                    |                    |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| All Bleeds                  | 1.1 (0.72 to 1.66) | 1.1 (0.73 to 1.73) | 2.4 (1.68 to 3.43) | 2.2 (1.16 to 4.15) |
| Treated Spontaneous Bleeds  | 0.5 (0.23 to 1.03) | 0.2 (0.10 to 0.45) | 0.5 (0.30 to 0.78) | 0.4 (0.12 to 1.35) |
| Treated Joint Bleeds        | 0.4 (0.24 to 0.73) | 0.4 (0.21 to 0.68) | 1.0 (0.60 to 1.76) | 0.7 (0.25 to 1.66) |
| Treated Target Joint Bleeds | 0.2 (0.11 to 0.43) | 0.2 (0.08 to 0.39) | 0.6 (0.26 to 1.42) | 0.4 (0.13 to 1.31) |

|                                  |                              |  |  |  |
|----------------------------------|------------------------------|--|--|--|
| <b>End point values</b>          | All Efficizumab Participants |  |  |  |
| Subject group type               | Subject analysis set         |  |  |  |
| Number of subjects analysed      | 151                          |  |  |  |
| Units: bleeds per year           |                              |  |  |  |
| number (confidence interval 95%) |                              |  |  |  |
| Treated Bleeds                   | 1.2 (0.92 to 1.56)           |  |  |  |
| All Bleeds                       | 1.8 (1.46 to 2.29)           |  |  |  |
| Treated Spontaneous Bleeds       | 0.4 (0.29 to 0.58)           |  |  |  |
| Treated Joint Bleeds             | 0.7 (0.53 to 1.00)           |  |  |  |
| Treated Target Joint Bleeds      | 0.4 (0.29 to 0.66)           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Long-Term Efficacy of Efficizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Efficizumab Participants <sup>[33]</sup> |
|-----------------|--|

### End point description:

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

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

### End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

Notes:

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

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

| <b>End point values</b>                      | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) | Arm C(Emi):<br>Emicizumab 3<br>mg/kg<br>Q2W(Switch<br>From No<br>Prophylaxis) |
|--|--------------------------------------|-------------------------------------|---|---|
| Subject group type                           | Reporting group                      | Reporting group                     | Reporting group   | Subject analysis set  |
| Number of subjects analysed                  | 36                                   | 35                                  | 63  | 17  |
| Units: bleeds per year                       |                                      |                                     |   |   |
| arithmetic mean (confidence interval<br>95%) |                                      |                                     |   |   |
| Treated Bleeds                               | 1.2 (0.04 to<br>5.83)                | 0.8 (0.01 to<br>5.23)               | 1.7 (0.15 to<br>6.69)   | 1.2 (0.05 to<br>5.95)   |
| All Bleeds                                   | 1.4 (0.09 to<br>6.29)                | 1.3 (0.07 to<br>6.10)               | 2.6 (0.45 to<br>8.15)   | 2.2 (0.32 to<br>7.58)   |
| Treated Spontaneous Bleeds                   | 0.7 (0.00 to<br>4.97)                | 0.3 (0.00 to<br>4.22)               | 0.6 (0.00 to<br>4.81)   | 0.4 (0.00 to<br>4.48)   |
| Treated Joint Bleeds                         | 0.6 (0.00 to<br>4.94)                | 0.5 (0.00 to<br>4.64)               | 1.1 (0.04 to<br>5.78)   | 0.6 (0.00 to<br>4.95)   |
| Treated Target Joint Bleeds                  | 0.4 (0.00 to<br>4.54)                | 0.3 (0.00 to<br>4.28)               | 0.6 (0.00 to<br>4.92)   | 0.4 (0.00 to<br>4.50)   |

| <b>End point values</b>                      | All Emicizumab<br>Participants |  |  |  |
|--|--------------------------------|--|--|--|
| Subject group type                           | Subject analysis set           |  |  |  |
| Number of subjects analysed                  | 151                            |  |  |  |
| Units: bleeds per year                       |                                |  |  |  |
| arithmetic mean (confidence interval<br>95%) |                                |  |  |  |
| Treated Bleeds                               | 1.3 (0.07 to<br>6.07)          |  |  |  |
| All Bleeds                                   | 2.0 (0.23 to<br>7.19)          |  |  |  |
| Treated Spontaneous Bleeds                   | 0.5 (0.00 to<br>4.68)          |  |  |  |
| Treated Joint Bleeds                         | 0.8 (0.01 to<br>5.23)          |  |  |  |
| Treated Target Joint Bleeds                  | 0.5 (0.00 to<br>4.64)          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds, All Bleeds, Treated Spontaneous Bleeds, Treated Joint Bleeds, and Treated Target Joint Bleeds, All Emicizumab Participants <sup>[34]</sup> |
|-----------------|--|

End point description:

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

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

End point timeframe:

From start of emicizumab treatment to study completion, dose up-titration, or change of dosing regimen (median [min-max] efficacy period for all emicizumab participants: 228.14 [7.3-288.3] weeks)

Notes:

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

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

| End point values                      | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) | Arm C(Emi):<br>Emicizumab 3<br>mg/kg<br>Q2W(Switch<br>From No<br>Prophylaxis) |
|---------------------------------------|--------------------------------------|-------------------------------------|---|---|
| Subject group type                    | Reporting group                      | Reporting group                     | Reporting group   | Subject analysis set  |
| Number of subjects analysed           | 36                                   | 35                                  | 63  | 17  |
| Units: bleeds per year                |                                      |                                     |   |   |
| median (inter-quartile range (Q1-Q3)) |                                      |                                     |   |   |
| Treated Bleeds                        | 0.4 (0.00 to 1.28)                   | 0.4 (0.00 to 1.06)                  | 0.5 (0.00 to 1.07)  | 0.0 (0.00 to 2.48)  |
| All Bleeds                            | 0.5 (0.09 to 1.77)                   | 0.8 (0.23 to 1.92)                  | 1.0 (0.38 to 2.70)  | 1.6 (0.20 to 3.8)   |
| Treated Spontaneous Bleeds            | 0.0 (0.00 to 0.51)                   | 0.0 (0.00 to 0.23)                  | 0.0 (0.00 to 0.48)  | 0.0 (0.00 to 0.65)  |
| Treated Joint Bleeds                  | 0.2 (0.00 to 0.89)                   | 0.2 (0.00 to 0.49)                  | 0.0 (0.00 to 0.59)  | 0.0 (0.00 to 1.09)  |
| Treated Target Joint Bleeds           | 0.1 (0.00 to 0.55)                   | 0.0 (0.00 to 0.37)                  | 0.0 (0.00 to 0.00)  | 0.0 (0.00 to 0.81)  |

| End point values                      | All Emicizumab<br>Participants |  |  |  |
|---------------------------------------|--------------------------------|--|--|--|
| Subject group type                    | Subject analysis set           |  |  |  |
| Number of subjects analysed           | 151                            |  |  |  |
| Units: bleeds per year                |                                |  |  |  |
| median (inter-quartile range (Q1-Q3)) |                                |  |  |  |
| Treated Bleeds                        | 0.4 (0.00 to 1.15)             |  |  |  |
| All Bleeds                            | 1.0 (0.19 to 2.37)             |  |  |  |

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Treated Spontaneous Bleeds  | 0.0 (0.00 to 0.40) |  |  |  |
| Treated Joint Bleeds        | 0.2 (0.00 to 0.72) |  |  |  |
| Treated Target Joint Bleeds | 0.0 (0.00 to 0.38) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Long-Term Efficacy of Efficizumab: Mean Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Efficizumab Participants |
|-----------------|---|

End point description:

The number of treated bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated bleeds: a bleed for which coagulation factors were administered. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

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

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

| End point values                          | All Efficizumab Participants |  |  |  |
|---|------------------------------|--|--|--|
| Subject group type                        | Subject analysis set         |  |  |  |
| Number of subjects analysed               | 151                          |  |  |  |
| Units: Treated bleeds per year            |                              |  |  |  |
| arithmetic mean (confidence interval 95%) |                              |  |  |  |
| 1 to 12 Weeks (n = 150)                   | 1.9 (0.21 to 7.04)           |  |  |  |
| 13 to 24 Weeks (n = 148)                  | 1.9 (0.20 to 6.99)           |  |  |  |
| 25 to 36 Weeks (n = 144)                  | 1.0 (0.02 to 5.57)           |  |  |  |
| 37 to 48 Weeks (n = 144)                  | 0.9 (0.01 to 5.35)           |  |  |  |
| 49 to 60 Weeks (n = 142)                  | 1.0 (0.02 to 5.54)           |  |  |  |
| 61 to 72 Weeks (n = 140)                  | 1.1 (0.04 to 5.72)           |  |  |  |
| 73 to 84 Weeks (n = 140)                  | 0.7 (0.01 to 5.12)           |  |  |  |

|                            |                    |  |  |  |
|----------------------------|--------------------|--|--|--|
| 85 to 96 Weeks (n = 131)   | 1.1 (0.03 to 5.68) |  |  |  |
| 97 to 108 Weeks (n = 117)  | 0.9 (0.01 to 5.32) |  |  |  |
| 109 to 120 Weeks (n = 104) | 0.6 (0.00 to 4.83) |  |  |  |
| 121 to 132 Weeks (n = 99)  | 0.5 (0.00 to 4.72) |  |  |  |
| 133 to 144 Weeks (n = 94)  | 1.1 (0.03 to 5.68) |  |  |  |
| 145 to 156 Weeks (n = 93)  | 1.1 (0.03 to 5.70) |  |  |  |
| 157 to 168 Weeks (n = 89)  | 1.1 (0.04 to 5.78) |  |  |  |
| 169 to 180 Weeks (n = 85)  | 1.3 (0.06 to 6.05) |  |  |  |
| 181 to 192 Weeks (n = 83)  | 1.0 (0.02 to 5.56) |  |  |  |
| 193 to 204 Weeks (n = 82)  | 1.6 (0.13 to 6.57) |  |  |  |
| 205 to 216 Weeks (n = 80)  | 0.8 (0.01 to 5.15) |  |  |  |
| 217 to 228 Weeks (n = 76)  | 0.5 (0.00 to 4.59) |  |  |  |
| 229 to 240 Weeks (n = 72)  | 0.8 (0.01 to 5.30) |  |  |  |
| 241 to 252 Weeks (n = 67)  | 0.3 (0.00 to 4.21) |  |  |  |
| 253 to 264 Weeks (n = 58)  | 0.5 (0.00 to 4.72) |  |  |  |
| 265 to 276 Weeks (n = 22)  | 0.2 (0.00 to 4.09) |  |  |  |
| 277 to 288 Weeks (n = 5)   | 0.0 (0.0 to 3.69)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Long-Term Efficacy of Emicizumab: Median Calculated Annualized Bleeding Rates (ABR) for Treated Bleeds per 12-Week Intervals Over Time, All Emicizumab Participants |
|-----------------|---|

End point description:

The number of treated bleeds over the efficacy period was calculated as:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . Treated bleeds: a bleed for which coagulation factors were administered. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

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

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and

| End point values                      | All Efficizumab Participants |  |  |  |
|---------------------------------------|------------------------------|--|--|--|
| Subject group type                    | Subject analysis set         |  |  |  |
| Number of subjects analysed           | 151                          |  |  |  |
| Units: Treated bleeds per year        |                              |  |  |  |
| median (inter-quartile range (Q1-Q3)) |                              |  |  |  |
| 1 to 12 Weeks (n = 150)               | 0.0 (0.00 to 4.35)           |  |  |  |
| 13 to 24 Weeks (n = 148)              | 0.0 (0.00 to 2.17)           |  |  |  |
| 25 to 36 Weeks (n = 144)              | 0.0 (0.00 to 0.00)           |  |  |  |
| 37 to 48 Weeks (n = 144)              | 0.0 (0.00 to 0.00)           |  |  |  |
| 49 to 60 Weeks (n = 142)              | 0.0 (0.00 to 0.00)           |  |  |  |
| 61 to 72 Weeks (n = 140)              | 0.0 (0.00 to 0.00)           |  |  |  |
| 73 to 84 Weeks (n = 140)              | 0.0 (0.00 to 0.00)           |  |  |  |
| 85 to 96 Weeks (n = 131)              | 0.0 (0.00 to 0.00)           |  |  |  |
| 97 to 108 Weeks (n = 117)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 109 to 120 Weeks (n = 104)            | 0.0 (0.00 to 0.00)           |  |  |  |
| 121 to 132 Weeks (n = 99)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 133 to 144 Weeks (n = 94)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 145 to 156 Weeks (n = 93)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 157 to 168 Weeks (n = 89)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 169 to 180 Weeks (n = 85)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 181 to 192 Weeks (n = 83)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 193 to 204 Weeks (n = 82)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 205 to 216 Weeks (n = 80)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 217 to 228 Weeks (n = 76)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 229 to 240 Weeks (n = 72)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 241 to 252 Weeks (n = 67)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 253 to 264 Weeks (n = 58)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 265 to 276 Weeks (n = 22)             | 0.0 (0.00 to 0.00)           |  |  |  |
| 277 to 288 Weeks (n = 5)              | 0.0 (0.00 to 0.00)           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The number of all bleeds over the efficacy period was calculated as:  $ABR = (\text{number of bleeds/number of days during the efficacy period}) \times 365.25$ . All bleeds included both treated bleeds (with coagulation factors) and non-treated bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

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

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

| End point values                          | All Emicizumab Participants |  |  |  |
|---|-----------------------------|--|--|--|
| Subject group type                        | Subject analysis set        |  |  |  |
| Number of subjects analysed               | 151                         |  |  |  |
| Units: All bleeds per year                |                             |  |  |  |
| arithmetic mean (confidence interval 95%) |                             |  |  |  |
| 1 to 12 Weeks (n = 150)                   | 3.8 (0.97 to 9.91)          |  |  |  |
| 13 to 24 Weeks (n = 148)                  | 2.8 (0.53 to 8.45)          |  |  |  |
| 25 to 36 Weeks (n = 144)                  | 1.8 (0.17 to 6.83)          |  |  |  |
| 37 to 48 Weeks (n = 144)                  | 1.4 (0.10 to 6.33)          |  |  |  |
| 49 to 60 Weeks (n = 142)                  | 1.5 (0.10 to 6.37)          |  |  |  |
| 61 to 72 Weeks (n = 140)                  | 1.6 (0.14 to 6.66)          |  |  |  |
| 73 to 84 Weeks (n = 140)                  | 1.2 (0.05 to 5.88)          |  |  |  |
| 85 to 96 Weeks (n = 131)                  | 1.4 (0.09 to 6.30)          |  |  |  |

|                            |                    |  |  |  |
|----------------------------|--------------------|--|--|--|
| 97 to 108 Weeks (n = 117)  | 1.3 (0.06 to 6.02) |  |  |  |
| 109 to 120 Weeks (n = 104) | 0.8 (0.01 to 5.21) |  |  |  |
| 121 to 132 Weeks (n = 99)  | 0.8 (0.01 to 5.20) |  |  |  |
| 133 to 144 Weeks (n = 94)  | 1.2 (0.04 to 5.84) |  |  |  |
| 145 to 156 Weeks (n = 93)  | 1.3 (0.06 to 6.02) |  |  |  |
| 157 to 168 Weeks (n = 89)  | 1.4 (0.09 to 6.28) |  |  |  |
| 169 to 180 Weeks (n = 85)  | 1.7 (0.15 to 6.72) |  |  |  |
| 181 to 192 Weeks (n = 83)  | 1.4 (0.08 to 6.19) |  |  |  |
| 193 to 204 Weeks (n = 82)  | 1.7 (0.16 to 6.74) |  |  |  |
| 205 to 216 Weeks (n = 80)  | 1.1 (0.04 to 5.72) |  |  |  |
| 217 to 228 Weeks (n = 76)  | 0.6 (0.00 to 4.91) |  |  |  |
| 229 to 240 Weeks (n = 72)  | 0.9 (0.02 to 5.41) |  |  |  |
| 241 to 252 Weeks (n = 67)  | 0.4 (0.00 to 4.47) |  |  |  |
| 253 to 264 Weeks (n = 58)  | 0.6 (0.00 to 4.86) |  |  |  |
| 265 to 276 Weeks (n = 22)  | 0.2 (0.00 to 4.09) |  |  |  |
| 277 to 288 Weeks (n = 5)   | 0.0 (0.0 to 3.69)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The number of all bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. All bleeds included both treated bleeds (with coagulation factors) and non-treated bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

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

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

| End point values                      | All Emicizumab Participants |  |  |  |
|---------------------------------------|-----------------------------|--|--|--|
| Subject group type                    | Subject analysis set        |  |  |  |
| Number of subjects analysed           | 151                         |  |  |  |
| Units: All bleeds per year            |                             |  |  |  |
| median (inter-quartile range (Q1-Q3)) |                             |  |  |  |
| 1 to 12 Weeks (n = 150)               | 0.0 (0.00 to 4.35)          |  |  |  |
| 13 to 24 Weeks (n = 148)              | 0.0 (0.00 to 4.35)          |  |  |  |
| 25 to 36 Weeks (n = 144)              | 0.0 (0.00 to 4.35)          |  |  |  |
| 37 to 48 Weeks (n = 144)              | 0.0 (0.00 to 0.00)          |  |  |  |
| 49 to 60 Weeks (n = 142)              | 0.0 (0.00 to 0.00)          |  |  |  |
| 61 to 72 Weeks (n = 140)              | 0.0 (0.00 to 0.00)          |  |  |  |
| 73 to 84 Weeks (n = 140)              | 0.0 (0.00 to 0.00)          |  |  |  |
| 85 to 96 Weeks (n = 131)              | 0.0 (0.00 to 0.00)          |  |  |  |
| 97 to 108 Weeks (n = 117)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 109 to 120 Weeks (n = 104)            | 0.0 (0.00 to 0.00)          |  |  |  |
| 121 to 132 Weeks (n = 99)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 133 to 144 Weeks (n = 94)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 145 to 156 Weeks (n = 93)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 157 to 168 Weeks (n = 89)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 169 to 180 Weeks (n = 85)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 181 to 192 Weeks (n = 83)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 193 to 204 Weeks (n = 82)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 205 to 216 Weeks (n = 80)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 217 to 228 Weeks (n = 76)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 229 to 240 Weeks (n = 72)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 241 to 252 Weeks (n = 67)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 253 to 264 Weeks (n = 58)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 265 to 276 Weeks (n = 22)             | 0.0 (0.00 to 0.00)          |  |  |  |
| 277 to 288 Weeks (n = 5)              | 0.0 (0.00 to 0.00)          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

#### End point description:

The number of treated spontaneous bleeds over the efficacy period was calculated as:  $ABR = (\text{number of bleeds} / \text{number of days during the efficacy period}) \times 365.25$ . Treated spontaneous bleeds were defined as treated (with coagulation factors) bleeds with no known contributing factor (e.g., trauma, surgery). The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

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

#### End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

| End point values                           | All Emicizumab Participants |  |  |  |
|--|-----------------------------|--|--|--|
| Subject group type                         | Subject analysis set        |  |  |  |
| Number of subjects analysed                | 151                         |  |  |  |
| Units: Treated spontaneous bleeds per year |                             |  |  |  |
| arithmetic mean (confidence interval 95%)  |                             |  |  |  |
| 1 to 12 Weeks (n = 150)                    | 0.7 (0.00 to 4.98)          |  |  |  |
| 13 to 24 Weeks (n = 148)                   | 0.7 (0.00 to 5.00)          |  |  |  |
| 25 to 36 Weeks (n = 144)                   | 0.3 (0.00 to 4.30)          |  |  |  |
| 37 to 48 Weeks (n = 144)                   | 0.4 (0.00 to 4.53)          |  |  |  |
| 49 to 60 Weeks (n = 142)                   | 0.5 (0.00 to 4.60)          |  |  |  |
| 61 to 72 Weeks (n = 140)                   | 0.3 (0.00 to 4.25)          |  |  |  |
| 73 to 84 Weeks (n = 140)                   | 0.1 (0.00 to 3.95)          |  |  |  |
| 85 to 96 Weeks (n = 131)                   | 0.4 (0.00 to 4.48)          |  |  |  |

|                            |                    |  |  |  |
|----------------------------|--------------------|--|--|--|
| 97 to 108 Weeks (n = 117)  | 0.2 (0.00 to 4.14) |  |  |  |
| 109 to 120 Weeks (n = 104) | 0.2 (0.00 to 4.03) |  |  |  |
| 121 to 132 Weeks (n = 99)  | 0.1 (0.00 to 3.96) |  |  |  |
| 133 to 144 Weeks (n = 94)  | 0.6 (0.00 to 4.78) |  |  |  |
| 145 to 156 Weeks (n = 93)  | 0.6 (0.00 to 4.87) |  |  |  |
| 157 to 168 Weeks (n = 89)  | 0.2 (0.00 to 4.09) |  |  |  |
| 169 to 180 Weeks (n = 85)  | 0.4 (0.00 to 4.50) |  |  |  |
| 181 to 192 Weeks (n = 83)  | 0.2 (0.00 to 4.01) |  |  |  |
| 193 to 204 Weeks (n = 82)  | 0.1 (0.00 to 3.80) |  |  |  |
| 205 to 216 Weeks (n = 80)  | 0.3 (0.00 to 4.24) |  |  |  |
| 217 to 228 Weeks (n = 76)  | 0.1 (0.00 to 3.81) |  |  |  |
| 229 to 240 Weeks (n = 72)  | 0.1 (0.00 to 3.94) |  |  |  |
| 241 to 252 Weeks (n = 67)  | 0.1 (0.00 to 3.82) |  |  |  |
| 253 to 264 Weeks (n = 58)  | 0.3 (0.00 to 4.29) |  |  |  |
| 265 to 276 Weeks (n = 22)  | 0.2 (0.00 to 4.09) |  |  |  |
| 277 to 288 Weeks (n = 5)   | 0.0 (0.0 to 3.69)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The number of treated spontaneous bleeds over the efficacy period was calculated as: ABR = (number of bleeds/number of days during the efficacy period) x 365.25. Treated spontaneous bleeds were defined as treated (with coagulation factors) bleeds with no known contributing factor (e.g., trauma, surgery). The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location were counted as one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure were excluded. For participants with dose up-titration or a change in emicizumab dosing regimen (after implementation of protocol v4), the efficacy period ended the day before the first day on the up-titrated dose or changed dosing regimen.

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

End point timeframe:

1-12, 13-24, 25-36, 37-48, 49-60, 61-72, 73-84, 85-96, 97-108, 109-120, 121-132, 133-144, 145-156, 157-168, 169-180, 181-192, 193-204, 205-216, 217-228, 229-240, 241-252, 253-264, 265-276, and 277-288 weeks

| End point values                           | All Efficizumab Participants |  |  |  |
|--|------------------------------|--|--|--|
| Subject group type                         | Subject analysis set         |  |  |  |
| Number of subjects analysed                | 151                          |  |  |  |
| Units: Treated spontaneous bleeds per year |                              |  |  |  |
| median (inter-quartile range (Q1-Q3))      |                              |  |  |  |
| 1 to 12 Weeks (n = 150)                    | 0.0 (0.00 to 0.00)           |  |  |  |
| 13 to 24 Weeks (n = 148)                   | 0.0 (0.00 to 0.00)           |  |  |  |
| 25 to 36 Weeks (n = 144)                   | 0.0 (0.00 to 0.00)           |  |  |  |
| 37 to 48 Weeks (n = 144)                   | 0.0 (0.00 to 0.00)           |  |  |  |
| 49 to 60 Weeks (n = 142)                   | 0.0 (0.00 to 0.00)           |  |  |  |
| 61 to 72 Weeks (n = 140)                   | 0.0 (0.00 to 0.00)           |  |  |  |
| 73 to 84 Weeks (n = 140)                   | 0.0 (0.00 to 0.00)           |  |  |  |
| 85 to 96 Weeks (n = 131)                   | 0.0 (0.00 to 0.00)           |  |  |  |
| 97 to 108 Weeks (n = 117)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 109 to 120 Weeks (n = 104)                 | 0.0 (0.00 to 0.00)           |  |  |  |
| 121 to 132 Weeks (n = 99)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 133 to 144 Weeks (n = 94)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 145 to 156 Weeks (n = 93)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 157 to 168 Weeks (n = 89)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 169 to 180 Weeks (n = 85)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 181 to 192 Weeks (n = 83)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 193 to 204 Weeks (n = 82)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 205 to 216 Weeks (n = 80)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 217 to 228 Weeks (n = 76)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 229 to 240 Weeks (n = 72)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 241 to 252 Weeks (n = 67)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 253 to 264 Weeks (n = 58)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 265 to 276 Weeks (n = 22)                  | 0.0 (0.00 to 0.00)           |  |  |  |
| 277 to 288 Weeks (n = 5)                   | 0.0 (0.00 to 0.00)           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Anti-Emicizumab Antibodies at Any Time Post-Baseline During the Study

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With Anti-Emicizumab Antibodies at Any Time Post-Baseline During the Study <sup>[35]</sup> |
|-----------------|---|

End point description:

A validated enzyme-linked immunosorbent assay (ELISA) method was used to analyze the levels of anti-drug antibodies (ADAs) against emicizumab in plasma. A sample was considered positive for anti-emicizumab antibodies if the test result reached or exceeded a pre-determined threshold. '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.

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

End point timeframe:

From Baseline to discontinuation from study (median [min-max] observation period for all emicizumab participants: 262.3 [14.4-288.3] weeks)

Notes:

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

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

| End point values                     | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) | Arm C(Emi):<br>Emicizumab 3<br>mg/kg<br>Q2W(Switch<br>From No<br>Prophylaxis) |
|--------------------------------------|--------------------------------------|-------------------------------------|---|---|
| Subject group type                   | Reporting group                      | Reporting group                     | Reporting group   | Subject analysis set  |
| Number of subjects analysed          | 36                                   | 35                                  | 63  | 17  |
| Units: percentage of participants    |                                      |                                     |   |   |
| number (not applicable)              |                                      |                                     |   |   |
| Total ADA Positive (Boosted+Induced) | 8.3                                  | 5.7                                 | 1.6   | 0.0   |
| ADA Positive (Treatment Boosted)     | 0.0                                  | 2.9                                 | 0.0   | 0.0   |
| ADA Positive (Treatment Induced)     | 8.3                                  | 2.9                                 | 1.6   | 0.0   |

| End point values                  | All Emicizumab<br>Participants |  |  |  |
|-----------------------------------|--------------------------------|--|--|--|
| Subject group type                | Subject analysis set           |  |  |  |
| Number of subjects analysed       | 151                            |  |  |  |
| Units: percentage of participants |                                |  |  |  |
| number (not applicable)           |                                |  |  |  |

|                                      |     |  |  |  |
|--------------------------------------|-----|--|--|--|
| Total ADA Positive (Boosted+Induced) | 4.0 |  |  |  |
| ADA Positive (Treatment Boosted)     | 0.7 |  |  |  |
| ADA Positive (Treatment Induced)     | 3.3 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With De Novo Development of Factor VIII (FVIII) Inhibitors <sup>[36]</sup> |
|-----------------|---|

End point description:

Levels of anti-FVIII antibodies (inhibitors) were analyzed using a validated FVIII activity assay. A participant was considered to have developed de novo FVIII inhibitors if the inhibitor levels detected in a post-baseline sample reached or exceeded a pre-determined threshold.

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

End point timeframe:

From Baseline to discontinuation from study (median [min-max] observation period for all emicizumab participants: 262.3 [14.4-288.3] weeks)

Notes:

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

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

| End point values                  | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) | Arm C(Emi):<br>Emicizumab 3<br>mg/kg<br>Q2W(Switch<br>From No<br>Prophylaxis) |
|-----------------------------------|--------------------------------------|-------------------------------------|---|---|
| Subject group type                | Reporting group                      | Reporting group                     | Reporting group   | Subject analysis set  |
| Number of subjects analysed       | 36                                   | 35                                  | 63  | 17  |
| Units: percentage of participants |                                      |                                     |   |   |
| number (not applicable)           | 0.0                                  | 0.0                                 | 0.0   | 0.0   |

| End point values                  | All Emicizumab<br>Participants |  |  |  |
|-----------------------------------|--------------------------------|--|--|--|
| Subject group type                | Subject analysis set           |  |  |  |
| Number of subjects analysed       | 151                            |  |  |  |
| Units: percentage of participants |                                |  |  |  |
| number (not applicable)           | 0.0                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Trough Plasma Concentration (Ctrough) of Emicizumab

|  |   |
|--|---|
| End point title  | Trough Plasma Concentration (Ctrough) of Emicizumab <sup>[37]</sup> |
| End point description:   |   |
| Trough plasma concentrations of emicizumab were analyzed using a validated Enzyme Linked Immunosorbent Assay (ELISA). The lower limit of quantification (LLOQ) was 100 nanograms per milliliter (ng/mL). Because participants in Arm C (Control) switched from no prophylaxis to start receiving emicizumab prophylaxis after Week 24, the timepoints for Arm C (Emi) are expressed relative to first emicizumab dose. The pharmacokinetic (PK) evaluable population included all participants who received at least one dose of emicizumab and had at least one post-dose emicizumab concentration result. Here, n=participants with available data for this endpoint at specified timepoints in each arm (A, B, D, Cemi), respectively. Here, '999999' represents no data available because no patient samples were taken at that timepoint. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Predose at Weeks 1, 2, 3, 4, 5, 7, 9, 13, 17, 21, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, 229, 241, 253, 265, and 277  |   |

### Notes:

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

Justification: This endpoint only applies to participants in Arms A, B, C (Emi), and D who were treated with emicizumab.

| End point values                         | Arm A:<br>Emicizumab<br>1.5 mg/kg QW | Arm B:<br>Emicizumab 3<br>mg/kg Q2W | Arm D:<br>Emicizumab<br>1.5 mg/kg QW<br>(Pre-study<br>FVIII<br>Prophylaxis) | Arm C(Emi):<br>Emicizumab 3<br>mg/kg<br>Q2W(Switch<br>From No<br>Prophylaxis) |
|--|--------------------------------------|-------------------------------------|---|---|
| Subject group type                       | Reporting group                      | Reporting group                     | Reporting group   | Subject analysis set  |
| Number of subjects analysed              | 36                                   | 35                                  | 63  | 17  |
| Units: micrograms per milliliter (µg/mL) |                                      |                                     |   |   |
| arithmetic mean (standard deviation)     |                                      |                                     |   |   |
| Week 1 (n=35,35,61,17,96,52)             | 0 (± 0)                              | 0 (± 0)                             | 0 (± 0)   | 0 (± 0)   |
| Week 2 (n=36,35,62,17,98,52)             | 16.3 (± 6.1)                         | 16.8 (± 5.9)                        | 17.3 (± 5.4)  | 19.6 (± 8.2)  |
| Week 3 (n=36,35,62,17,98,52)             | 29.1 (± 9.3)                         | 29.2 (± 6.5)                        | 30.5 (± 8.7)  | 33.0 (± 12.6)   |
| Week 4 (n=36,35,62,17,98,52)             | 41.9 (± 11.8)                        | 41.4 (± 9.7)                        | 42.4 (± 9.4)  | 47.9 (± 15.0)   |
| Week 5 (n=34,35,62,17,96,52)             | 48.0 (± 13.7)                        | 48.8 (± 12.3)                       | 54.5 (± 12.5)   | 59.6 (± 20.7)   |
| Week 7 (n=32,33,61,17,93,50)             | 47.9 (± 16.1)                        | 48.4 (± 11.4)                       | 52.4 (± 13.3)   | 55.2 (± 16.2)   |
| Week 9 (n=33,34,63,17,96,51)             | 49.0 (± 16.4)                        | 46.4 (± 14.1)                       | 55.1 (± 16.1)   | 53.1 (± 15.7)   |
| Week 13 (n=33,34,63,17,96,51)            | 48.7 (± 18.3)                        | 47.6 (± 16.0)                       | 55.0 (± 15.9)   | 47.9 (± 18.1)   |
| Week 17 (n=33,34,62,17,95,51)            | 54.3 (± 24.0)                        | 48.9 (± 17.7)                       | 55.0 (± 16.5)   | 43.4 (± 16.2)   |
| Week 21 (n=32,34,61,16,93,50)            | 50.7 (± 20.2)                        | 47.3 (± 15.5)                       | 55.1 (± 16.2)   | 45.6 (± 18.8)   |
| Week 25 (n=31,34,58,17,89,51)            | 50.5 (± 21.7)                        | 47.6 (± 18.9)                       | 54.8 (± 16.8)   | 51.8 (± 23.4)   |
| Week 33 (n=30,34,58,16,88,50)            | 56.3 (± 25.3)                        | 52.9 (± 22.4)                       | 59.1 (± 18.5)   | 52.0 (± 21.3)   |
| Week 41 (n=31,34,58,17,89,51)            | 54.8 (± 24.2)                        | 48.4 (± 18.8)                       | 59.6 (± 21.4)   | 50.7 (± 24.4)   |
| Week 49 (n=31,32,58,17,89,49)            | 55.4 (± 22.9)                        | 52.2 (± 20.2)                       | 60.2 (± 19.9)   | 54.3 (± 21.3)   |
| Week 61 (n=31,33,57,17,88,50)            | 55.3 (± 21.4)                        | 52.0 (± 21.1)                       | 61.1 (± 22.5)   | 52.5 (± 19.8)   |
| Week 73 (n=31,32,57,15,88,47)            | 54.4 (± 21.5)                        | 51.6 (± 21.3)                       | 58.5 (± 19.2)   | 47.8 (± 18.4)   |
| Week 85 (n=31,32,55,13,86,45)            | 48.8 (± 17.4)                        | 46.4 (± 20.4)                       | 56.7 (± 18.5)   | 47.7 (± 17.9)   |
| Week 97 (n=28,29,48,11,76,40)            | 52.6 (± 20.0)                        | 50.9 (± 21.0)                       | 58.5 (± 18.7)   | 51.7 (± 28.3)   |
| Week 109 (n=26,26,39,11,65,37)           | 53.9 (± 19.2)                        | 52.3 (± 19.5)                       | 59.0 (± 19.1)   | 46.4 (± 27.0)   |
| Week 121 (n=23,24,37,10,60,34)           | 58.8 (± 21.1)                        | 55.0 (± 22.0)                       | 57.1 (± 18.2)   | 50.0 (± 25.2)   |
| Week 133 (n=23,23,34,10,57,33)           | 55.3 (± 26.0)                        | 54.7 (± 18.5)                       | 59.3 (± 19.2)   | 54.6 (± 26.9)   |
| Week 145 (n=23,22,33,6,56,28)            | 54.1 (± 23.7)                        | 51.3 (± 17.7)                       | 55.7 (± 20.4)   | 44.8 (± 11.6)   |
| Week 157 (n=19,21,30,9,49,30)            | 57.6 (± 27.8)                        | 52.2 (± 21.4)                       | 55.9 (± 23.7)   | 46.8 (± 24.0)   |

|                               |               |               |               |                   |
|-------------------------------|---------------|---------------|---------------|-------------------|
| Week 169 (n=16,16,22,8,38,24) | 53.9 (± 21.8) | 50.3 (± 19.6) | 56.4 (± 18.0) | 45.8 (± 20.6)     |
| Week 181 (n=15,11,17,8,32,19) | 59.8 (± 24.8) | 48.8 (± 22.1) | 57.5 (± 21.3) | 43.5 (± 26.2)     |
| Week 193 (n=17,18,21,7,38,25) | 53.9 (± 21.0) | 52.4 (± 24.6) | 60.5 (± 19.6) | 42.1 (± 19.1)     |
| Week 205 (n=18,20,23,8,41,28) | 53.5 (± 20.8) | 51.9 (± 22.4) | 58.6 (± 24.1) | 54.2 (± 31.1)     |
| Week 217 (n=16,19,26,9,42,28) | 54.4 (± 20.8) | 55.0 (± 20.6) | 60.8 (± 23.2) | 50.8 (± 26.1)     |
| Week 229 (n=17,17,26,9,43,26) | 54.9 (± 20.9) | 47.9 (± 18.9) | 54.4 (± 19.3) | 53.5 (± 30.4)     |
| Week 241 (n=16,18,24,6,40,24) | 51.9 (± 19.3) | 50.2 (± 16.8) | 60.1 (± 23.3) | 52.0 (± 36.1)     |
| Week 253 (n=15,15,22,4,37,19) | 58.6 (± 28.7) | 46.5 (± 17.8) | 58.4 (± 24.7) | 40.3 (± 43.9)     |
| Week 265 (n=10,13,17,0,27,13) | 58.7 (± 25.8) | 47.3 (± 14.5) | 60.0 (± 23.9) | 999999 (± 999999) |
| Week 277 (n=6,5,2,0,8,5)      | 71.9 (± 34.2) | 49.0 (± 16.2) | 61.3 (± 17.2) | 999999 (± 999999) |

| End point values                         | Arms A and D:<br>Emicizumab<br>1.5 mg/kg QW | Arms B and C<br>(Emi):<br>Emicizumab 3<br>mg/kg Q2W |  |  |
|--|---|---|--|--|
| Subject group type                       | Subject analysis set                        | Subject analysis set                                |  |  |
| Number of subjects analysed              | 99  | 52  |  |  |
| Units: micrograms per milliliter (µg/mL) |   |   |  |  |
| arithmetic mean (standard deviation)     |   |   |  |  |
| Week 1 (n=35,35,61,17,96,52)             | 0 (± 0)                                     | 0 (± 0)   |  |  |
| Week 2 (n=36,35,62,17,98,52)             | 16.9 (± 5.7)                                | 17.7 (± 6.8)  |  |  |
| Week 3 (n=36,35,62,17,98,52)             | 30.0 (± 8.9)                                | 30.5 (± 9.0)  |  |  |
| Week 4 (n=36,35,62,17,98,52)             | 42.2 (± 10.3)                               | 43.6 (± 11.9)                                       |  |  |
| Week 5 (n=34,35,62,17,96,52)             | 52.2 (± 13.2)                               | 52.4 (± 16.2)                                       |  |  |
| Week 7 (n=32,33,61,17,93,50)             | 50.9 (± 14.4)                               | 50.7 (± 13.5)                                       |  |  |
| Week 9 (n=33,34,63,17,96,51)             | 53.0 (± 16.4)                               | 48.7 (± 14.9)                                       |  |  |
| Week 13 (n=33,34,63,17,96,51)            | 52.8 (± 16.9)                               | 47.7 (± 16.5)                                       |  |  |
| Week 17 (n=33,34,62,17,95,51)            | 54.7 (± 19.3)                               | 47.0 (± 17.2)                                       |  |  |
| Week 21 (n=32,34,61,16,93,50)            | 53.6 (± 17.7)                               | 46.7 (± 16.4)                                       |  |  |
| Week 25 (n=31,34,58,17,89,51)            | 53.3 (± 18.7)                               | 49.0 (± 20.4)                                       |  |  |
| Week 33 (n=30,34,58,16,88,50)            | 58.1 (± 20.9)                               | 52.6 (± 21.9)                                       |  |  |
| Week 41 (n=31,34,58,17,89,51)            | 57.9 (± 22.4)                               | 49.2 (± 20.6)                                       |  |  |
| Week 49 (n=31,32,58,17,89,49)            | 58.5 (± 21.0)                               | 52.9 (± 20.4)                                       |  |  |
| Week 61 (n=31,33,57,17,88,50)            | 59.1 (± 22.1)                               | 52.2 (± 20.5)                                       |  |  |
| Week 73 (n=31,32,57,15,88,47)            | 57.1 (± 20.0)                               | 50.4 (± 20.3)                                       |  |  |
| Week 85 (n=31,32,55,13,86,45)            | 53.8 (± 18.5)                               | 46.8 (± 19.5)                                       |  |  |
| Week 97 (n=28,29,48,11,76,40)            | 56.3 (± 19.3)                               | 51.1 (± 22.9)                                       |  |  |
| Week 109 (n=26,26,39,11,65,37)           | 57.0 (± 19.1)                               | 50.5 (± 21.7)                                       |  |  |
| Week 121 (n=23,24,37,10,60,34)           | 57.7 (± 19.2)                               | 53.5 (± 22.7)                                       |  |  |
| Week 133 (n=23,23,34,10,57,33)           | 57.7 (± 22.1)                               | 54.7 (± 20.9)                                       |  |  |
| Week 145 (n=23,22,33,6,56,28)            | 55.0 (± 21.6)                               | 49.9 (± 16.6)                                       |  |  |
| Week 157 (n=19,21,30,9,49,30)            | 56.6 (± 25.1)                               | 50.6 (± 21.9)                                       |  |  |
| Week 169 (n=16,16,22,8,38,24)            | 55.3 (± 19.4)                               | 48.8 (± 19.6)                                       |  |  |
| Week 181 (n=15,11,17,8,32,19)            | 58.6 (± 22.7)                               | 46.5 (± 23.4)                                       |  |  |
| Week 193 (n=17,18,21,7,38,25)            | 57.5 (± 20.2)                               | 49.5 (± 23.3)                                       |  |  |
| Week 205 (n=18,20,23,8,41,28)            | 56.4 (± 22.6)                               | 52.6 (± 24.6)                                       |  |  |
| Week 217 (n=16,19,26,9,42,28)            | 58.3 (± 22.2)                               | 53.6 (± 22.1)                                       |  |  |
| Week 229 (n=17,17,26,9,43,26)            | 54.6 (± 19.7)                               | 49.8 (± 23.1)                                       |  |  |
| Week 241 (n=16,18,24,6,40,24)            | 56.8 (± 21.9)                               | 50.6 (± 22.2)                                       |  |  |

|                               |               |               |  |  |
|-------------------------------|---------------|---------------|--|--|
| Week 253 (n=15,15,22,4,37,19) | 58.5 (± 26.0) | 45.2 (± 23.9) |  |  |
| Week 265 (n=10,13,17,0,27,13) | 59.5 (± 24.2) | 47.3 (± 14.5) |  |  |
| Week 277 (n=6,5,2,0,8,5)      | 69.2 (± 30.1) | 49.0 (± 16.2) |  |  |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Total observation time for all participants: From enrollment until study completion (median [min-max] 262.3 [14.4-288.3] weeks); Arm C (Control): From enrollment to 24 weeks on no prophylaxis (median [min-max]: 24.00 [14.4-25.0] weeks)

Adverse event reporting additional description:

Adverse events (AEs) in emicizumab-treated subjects are reported from first dose until study completion, including after dose up-titration or change of dosing regimen. AEs in Arm C are reported in 2 groups: Arm C (Control) for the first 24 weeks on no prophylaxis; Arm C (Emi) for those who switched after 24 weeks to receive emicizumab prophylaxis.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 25.0   |

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Arm C (Control): No Prophylaxis |
|-----------------------|---------------------------------|

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to continue episodic FVIII treatment when they started the trial; they were given the opportunity to switch to emicizumab prophylaxis after completing 24 weeks of no prophylaxis. The results for this control arm represent data collected during the first 24 weeks on study while receiving their usual care of episodic treatment with FVIII.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Arm A: Emicizumab 1.5 mg/kg QW |
|-----------------------|--------------------------------|

Reporting group description:

Participants who had received episodic treatment with FVIII prior to study entry were randomized to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

|                       |  |
|-----------------------|--|
| Reporting group title | Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis) |
|-----------------------|--|

Reporting group description:

Participants who had received FVIII prophylaxis prior to study entry were enrolled to receive emicizumab prophylaxis at a dose of 3 milligrams per kilogram (mg/kg) subcutaneously (SC) once per week (QW) for 4 weeks, followed by maintenance dosing of 1.5 mg/kg emicizumab SC QW. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

|                       |  |
|-----------------------|--|
| Reporting group title | Arm C(Emi): Emicizumab 3 mg/kg Q2W(Switch From No Prophylaxis) |
|-----------------------|--|

Reporting group description:

This arm includes all participants from Arm C who switched to emicizumab prophylaxis after completing 24 weeks on No Prophylaxis. The data reported was collected only during emicizumab prophylaxis treatment. Emicizumab was administered at a loading dose of 3 milligrams per kilogram (mg/kg) SC QW for the first 4 weeks, followed by maintenance dosing of 3 mg/kg emicizumab SC Q2W. Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Arm B: Emicizumab 3 mg/kg Q2W |
|-----------------------|-------------------------------|

Reporting group description:

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

every 2 weeks (Q2W). Upon implementation of protocol version 4 (20-Dec-2019), treatment duration was extended. During this study prolongation, each participant was given the option to choose a preferred emicizumab dosing regimen among those permitted and continue on that dosing regimen until discontinuation from the study.

| <b>Serious adverse events</b>                                       | Arm C (Control): No Prophylaxis | Arm A: Emicizumab 1.5 mg/kg QW | Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis) |
|---|---------------------------------|--------------------------------|--|
| Total subjects affected by serious adverse events                   |                                 |                                |  |
| subjects affected / exposed   | 1 / 18 (5.56%)                  | 10 / 36 (27.78%)               | 16 / 63 (25.40%)   |
| number of deaths (all causes)                                       | 0                               | 0                              | 0  |
| number of deaths resulting from adverse events                      | 0                               | 0                              | 0  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |                                |  |
| PARATHYROID TUMOUR BENIGN   |                                 |                                |  |
| subjects affected / exposed   | 0 / 18 (0.00%)                  | 0 / 36 (0.00%)                 | 0 / 63 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0                           | 0 / 0                          | 0 / 0  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                          | 0 / 0  |
| BONE GIANT CELL TUMOUR BENIGN                                       |                                 |                                |  |
| subjects affected / exposed   | 0 / 18 (0.00%)                  | 0 / 36 (0.00%)                 | 1 / 63 (1.59%)   |
| occurrences causally related to treatment / all                     | 0 / 0                           | 0 / 0                          | 0 / 1  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                          | 0 / 0  |
| PAPILLARY THYROID CANCER  |                                 |                                |  |
| subjects affected / exposed   | 0 / 18 (0.00%)                  | 0 / 36 (0.00%)                 | 1 / 63 (1.59%)   |
| occurrences causally related to treatment / all                     | 0 / 0                           | 0 / 0                          | 0 / 1  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                          | 0 / 0  |
| SALIVARY GLAND NEOPLASM   |                                 |                                |  |
| subjects affected / exposed   | 0 / 18 (0.00%)                  | 1 / 36 (2.78%)                 | 0 / 63 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0                           | 0 / 1                          | 0 / 0  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                          | 0 / 0  |
| Vascular disorders  |                                 |                                |  |
| HAEMATOMA   |                                 |                                |  |
| subjects affected / exposed   | 1 / 18 (5.56%)                  | 1 / 36 (2.78%)                 | 1 / 63 (1.59%)   |
| occurrences causally related to treatment / all                     | 0 / 1                           | 0 / 1                          | 0 / 1  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                          | 0 / 0  |
| HAEMORRHAGE   |                                 |                                |  |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| ASTHENIA   |                |                |                |
| subjects affected / exposed                          | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| EPISTAXIS  |                |                |                |
| subjects affected / exposed                          | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                                |                |                |                |
| SUICIDAL IDEATION                                    |                |                |                |
| subjects affected / exposed                          | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Product issues                                       |                |                |                |
| DEVICE LOOSENING                                     |                |                |                |
| subjects affected / exposed                          | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications       |                |                |                |
| POST PROCEDURAL HAEMATOMA                            |                |                |                |
| subjects affected / exposed                          | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| MUSCLE STRAIN  |                |                |                |
| subjects affected / exposed                          | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| MUSCLE RUPTURE                                       |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| FEMORAL NECK FRACTURE                           |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DURAL TEAR                                      |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| FEMUR FRACTURE                                  |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| POISONING                                       |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ROAD TRAFFIC ACCIDENT                           |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| TENDON RUPTURE                                  |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| ATRIAL FLUTTER                                  |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ACUTE MYOCARDIAL INFARCTION                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ACUTE CORONARY SYNDROME                         |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ARRHYTHMIA                                      |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| CEREBROSPINAL FLUID LEAKAGE                     |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HEADACHE  |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PUTAMEN HAEMORRHAGE                             |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SEIZURE   |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CEREBRAL HAEMORRHAGE                            |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| FISTULA OF SMALL INTESTINE                      |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| MELAENA   |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| GASTRIC HAEMORRHAGE                             |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SPLENIC ARTERY ANEURYSM                         |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HAEMATEMESIS                                    |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HAEMATOCHEZIA                                   |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RECTAL HAEMORRHAGE                              |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ANAL HAEMORRHAGE                                |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PANCREATITIS                                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RETROPERITONEAL HAEMORRHAGE                     |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| MALLORY-WEISS SYNDROME                          |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| UPPER GASTROINTESTINAL HAEMORRHAGE              |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| NEPHROLITHIASIS                                 |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HAEMATURIA                                      |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| URETEROLITHIASIS                                |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RENAL HAEMATOMA                                 |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| HYPERPARATHYROIDISM                             |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| GROIN PAIN                                      |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| BACK PAIN                                       |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| OSTEOARTHRITIS                                  |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| RHABDOMYOLYSIS                                  |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SYNOVITIS                                       |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| PYELONEPHRITIS ACUTE                            |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ABSCESS LIMB                                    |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| APPENDICITIS                                    |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ARTHRITIS BACTERIAL                             |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| GINGIVAL ABSCESS                                |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SUBPERIOSTEAL ABSCESS                           |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| TONSILLITIS                                     |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| WOUND INFECTION                                 |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| INFECTION                                       |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 1 / 63 (1.59%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| DIABETES MELLITUS                               |                |                |                |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>  | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W(Switch<br>From No<br>Prophylaxis) | Arm B: Emicizumab<br>3 mg/kg Q2W |  |
|--|--|----------------------------------|--|
| Total subjects affected by serious<br>adverse events                   |  |                                  |  |
| subjects affected / exposed  | 1 / 17 (5.88%)   | 8 / 35 (22.86%)                  |  |
| number of deaths (all causes)  | 0  | 0                                |  |
| number of deaths resulting from<br>adverse events                      | 0  | 0                                |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |  |                                  |  |
| PARATHYROID TUMOUR BENIGN  |  |                                  |  |
| subjects affected / exposed  | 0 / 17 (0.00%)   | 1 / 35 (2.86%)                   |  |
| occurrences causally related to<br>treatment / all                     | 0 / 0  | 0 / 1                            |  |
| deaths causally related to<br>treatment / all                          | 0 / 0  | 0 / 0                            |  |
| BONE GIANT CELL TUMOUR BENIGN  |  |                                  |  |
| subjects affected / exposed  | 0 / 17 (0.00%)   | 0 / 35 (0.00%)                   |  |
| occurrences causally related to<br>treatment / all                     | 0 / 0  | 0 / 0                            |  |
| deaths causally related to<br>treatment / all                          | 0 / 0  | 0 / 0                            |  |
| PAPILLARY THYROID CANCER   |  |                                  |  |
| subjects affected / exposed  | 0 / 17 (0.00%)   | 0 / 35 (0.00%)                   |  |
| occurrences causally related to<br>treatment / all                     | 0 / 0  | 0 / 0                            |  |
| deaths causally related to<br>treatment / all                          | 0 / 0  | 0 / 0                            |  |
| SALIVARY GLAND NEOPLASM  |  |                                  |  |
| subjects affected / exposed  | 0 / 17 (0.00%)   | 0 / 35 (0.00%)                   |  |
| occurrences causally related to<br>treatment / all                     | 0 / 0  | 0 / 0                            |  |
| deaths causally related to<br>treatment / all                          | 0 / 0  | 0 / 0                            |  |
| Vascular disorders   |  |                                  |  |
| HAEMATOMA  |  |                                  |  |
| subjects affected / exposed  | 0 / 17 (0.00%)   | 0 / 35 (0.00%)                   |  |
| occurrences causally related to<br>treatment / all                     | 0 / 0  | 0 / 0                            |  |
| deaths causally related to<br>treatment / all                          | 0 / 0  | 0 / 0                            |  |
| HAEMORRHAGE  |  |                                  |  |
| subjects affected / exposed  | 0 / 17 (0.00%)   | 1 / 35 (2.86%)                   |  |
| occurrences causally related to<br>treatment / all                     | 0 / 0  | 0 / 1                            |  |
| deaths causally related to<br>treatment / all                          | 0 / 0  | 0 / 0                            |  |
| General disorders and administration<br>site conditions                |  |                                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| ASTHENIA  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| EPISTAXIS                                       |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| SUICIDAL IDEATION                               |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Product issues                                  |                |                |  |
| DEVICE LOOSENING                                |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| POST PROCEDURAL HAEMATOMA                       |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| MUSCLE STRAIN                                   |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| MUSCLE RUPTURE                                  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| FEMORAL NECK FRACTURE                           |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DURAL TEAR                                      |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| FEMUR FRACTURE                                  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| POISONING                                       |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ROAD TRAFFIC ACCIDENT                           |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| TENDON RUPTURE                                  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| ATRIAL FLUTTER                                  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ACUTE MYOCARDIAL INFARCTION                     |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ACUTE CORONARY SYNDROME                         |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ARRHYTHMIA                                      |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| CEREBROSPINAL FLUID LEAKAGE                     |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HEADACHE  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PUTAMEN HAEMORRHAGE                             |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SEIZURE   |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| CEREBRAL HAEMORRHAGE                            |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| FISTULA OF SMALL INTESTINE                      |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| MELAENA   |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>GASTRIC HAEMORRHAGE</b>                      |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>SPLENIC ARTERY ANEURYSM</b>                  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>HAEMATEMESIS</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>HAEMATOCHEZIA</b>                            |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>RECTAL HAEMORRHAGE</b>                       |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>ANAL HAEMORRHAGE</b>                         |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>PANCREATITIS</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>RETROPERITONEAL HAEMORRHAGE</b>              |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| MALLORY-WEISS SYNDROME                          |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| UPPER GASTROINTESTINAL HAEMORRHAGE              |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| NEPHROLITHIASIS                                 |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HAEMATURIA                                      |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| URETEROLITHIASIS                                |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| RENAL HAEMATOMA                                 |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Endocrine disorders                             |                |                |  |
| HYPERPARATHYROIDISM                             |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Musculoskeletal and connective tissue disorders |                |                |  |
| GROIN PAIN                                      |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| BACK PAIN                                       |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| OSTEOARTHRITIS                                  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| RHABDOMYOLYSIS                                  |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SYNOVITIS                                       |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| PYELONEPHRITIS ACUTE                            |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ABSCESS LIMB                                    |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| APPENDICITIS                                    |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| ARTHRITIS BACTERIAL                             |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| GINGIVAL ABSCESS                                |                |                |  |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SUBPERIOSTEAL ABSCESS                           |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| TONSILLITIS                                     |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| WOUND INFECTION                                 |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| INFECTION                                       |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| DIABETES MELLITUS                               |                |                |  |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>  | Arm C (Control): No Prophylaxis   | Arm A: Emicizumab 1.5 mg/kg QW  | Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)   |
|--|---|---|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed   | 5 / 18 (27.78%)   | 35 / 36 (97.22%)  | 61 / 63 (96.83%)   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>PAPILLOMA<br>subjects affected / exposed<br>occurrences (all)   | 0 / 18 (0.00%)<br>0   | 0 / 36 (0.00%)<br>0   | 0 / 63 (0.00%)<br>0  |
| Vascular disorders<br>HAEMATOMA<br>subjects affected / exposed<br>occurrences (all)<br><br>HYPERTENSION<br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0<br><br>0 / 18 (0.00%)<br>0  | 2 / 36 (5.56%)<br>2<br><br>1 / 36 (2.78%)<br>1  | 1 / 63 (1.59%)<br>1<br><br>4 / 63 (6.35%)<br>4   |
| General disorders and administration site conditions<br>INFLUENZA LIKE ILLNESS<br>subjects affected / exposed<br>occurrences (all)<br><br>PAIN<br>subjects affected / exposed<br>occurrences (all)<br><br>PYREXIA<br>subjects affected / exposed<br>occurrences (all)<br><br>ASTHENIA<br>subjects affected / exposed<br>occurrences (all)<br><br>INJECTION SITE REACTION<br>subjects affected / exposed<br>occurrences (all) | 0 / 18 (0.00%)<br>0<br><br>0 / 18 (0.00%)<br>0<br><br>0 / 18 (0.00%)<br>0<br><br>0 / 18 (0.00%)<br>0<br><br>0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0<br><br>1 / 36 (2.78%)<br>1<br><br>4 / 36 (11.11%)<br>4<br><br>0 / 36 (0.00%)<br>0<br><br>10 / 36 (27.78%)<br>37 | 2 / 63 (3.17%)<br>2<br><br>2 / 63 (3.17%)<br>2<br><br>6 / 63 (9.52%)<br>7<br><br>0 / 63 (0.00%)<br>0<br><br>24 / 63 (38.10%)<br>42 |
| Immune system disorders<br>SEASONAL ALLERGY<br>subjects affected / exposed<br>occurrences (all)<br><br>DRUG HYPERSENSITIVITY   | 0 / 18 (0.00%)<br>0   | 1 / 36 (2.78%)<br>1   | 2 / 63 (3.17%)<br>2  |

|  |                     |                      |                      |
|--|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 0 / 63 (0.00%)<br>0  |
| <b>HYPERSENSITIVITY</b><br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 0 / 63 (0.00%)<br>0  |
| Reproductive system and breast disorders<br><b>ERECTILE DYSFUNCTION</b><br>subjects affected / exposed<br>occurrences (all)    | 0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 1 / 63 (1.59%)<br>1  |
| Respiratory, thoracic and mediastinal disorders<br><b>NASAL CONGESTION</b><br>subjects affected / exposed<br>occurrences (all) | 0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 2 / 63 (3.17%)<br>2  |
| <b>OROPHARYNGEAL PAIN</b><br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 1 / 36 (2.78%)<br>1  | 6 / 63 (9.52%)<br>12 |
| <b>COUGH</b><br>subjects affected / exposed<br>occurrences (all)   | 0 / 18 (0.00%)<br>0 | 4 / 36 (11.11%)<br>7 | 7 / 63 (11.11%)<br>9 |
| Psychiatric disorders<br><b>DEPRESSION</b><br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 4 / 63 (6.35%)<br>4  |
| <b>SLEEP DISORDER</b><br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 0 / 63 (0.00%)<br>0  |
| <b>INSOMNIA</b><br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 1 / 36 (2.78%)<br>1  | 2 / 63 (3.17%)<br>2  |
| <b>ANXIETY</b><br>subjects affected / exposed<br>occurrences (all)   | 0 / 18 (0.00%)<br>0 | 4 / 36 (11.11%)<br>4 | 4 / 63 (6.35%)<br>7  |
| Investigations<br><b>BLOOD CREATININE INCREASED</b><br>subjects affected / exposed<br>occurrences (all)                        | 0 / 18 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 0 / 63 (0.00%)<br>0  |

|  |                             |                |                |                  |
|--|-----------------------------|----------------|----------------|------------------|
| BLOOD CREATINE PHOSPHOKINASE INCREASED         | subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%) | 5 / 63 (7.94%)   |
|  | occurrences (all)           | 0              | 2              | 5                |
| ASPARTATE AMINOTRANSFERASE INCREASED           | subjects affected / exposed | 0 / 18 (0.00%) | 1 / 36 (2.78%) | 3 / 63 (4.76%)   |
|  | occurrences (all)           | 0              | 1              | 3                |
| BLOOD PRESSURE DIASTOLIC INCREASED             | subjects affected / exposed | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%)   |
|  | occurrences (all)           | 0              | 0              | 0                |
| ALANINE AMINOTRANSFERASE INCREASED             | subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%) | 4 / 63 (6.35%)   |
|  | occurrences (all)           | 0              | 2              | 4                |
| Injury, poisoning and procedural complications |                             |                |                |                  |
| BITE   | subjects affected / exposed | 1 / 18 (5.56%) | 0 / 36 (0.00%) | 1 / 63 (1.59%)   |
|  | occurrences (all)           | 1              | 0              | 2                |
| LIMB INJURY                                    | subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%) | 3 / 63 (4.76%)   |
|  | occurrences (all)           | 0              | 2              | 5                |
| TOOTH FRACTURE                                 | subjects affected / exposed | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 2 / 63 (3.17%)   |
|  | occurrences (all)           | 0              | 0              | 2                |
| LIGAMENT SPRAIN                                | subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%) | 10 / 63 (15.87%) |
|  | occurrences (all)           | 0              | 2              | 17               |
| ARTHROPOD BITE                                 | subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%) | 1 / 63 (1.59%)   |
|  | occurrences (all)           | 0              | 2              | 5                |
| LIGAMENT INJURY                                | subjects affected / exposed | 0 / 18 (0.00%) | 0 / 36 (0.00%) | 0 / 63 (0.00%)   |
|  | occurrences (all)           | 0              | 0              | 0                |
| CONTUSION                                      | subjects affected / exposed | 0 / 18 (0.00%) | 3 / 36 (8.33%) | 6 / 63 (9.52%)   |
|  | occurrences (all)           | 0              | 15             | 13               |

|  |                |                 |                  |
|--|----------------|-----------------|------------------|
| JOINT INJURY                               |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 5 / 63 (7.94%)   |
| occurrences (all)                          | 0              | 0               | 9                |
| MUSCLE STRAIN                              |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 3 / 36 (8.33%)  | 2 / 63 (3.17%)   |
| occurrences (all)                          | 0              | 3               | 2                |
| SKIN ABRASION                              |                |                 |                  |
| subjects affected / exposed                | 1 / 18 (5.56%) | 0 / 36 (0.00%)  | 3 / 63 (4.76%)   |
| occurrences (all)                          | 1              | 0               | 3                |
| BACK INJURY                                |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 0 / 63 (0.00%)   |
| occurrences (all)                          | 0              | 1               | 0                |
| FALL                                       |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 8 / 63 (12.70%)  |
| occurrences (all)                          | 0              | 2               | 9                |
| SKIN LACERATION                            |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 3 / 63 (4.76%)   |
| occurrences (all)                          | 0              | 1               | 3                |
| TONGUE INJURY                              |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)   |
| occurrences (all)                          | 0              | 0               | 0                |
| ROAD TRAFFIC ACCIDENT                      |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 0 / 63 (0.00%)   |
| occurrences (all)                          | 0              | 1               | 0                |
| Congenital, familial and genetic disorders |                |                 |                  |
| HYDROCELE                                  |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)   |
| occurrences (all)                          | 0              | 0               | 0                |
| Nervous system disorders                   |                |                 |                  |
| HEADACHE                                   |                |                 |                  |
| subjects affected / exposed                | 1 / 18 (5.56%) | 7 / 36 (19.44%) | 14 / 63 (22.22%) |
| occurrences (all)                          | 1              | 13              | 33               |
| PARAESTHESIA                               |                |                 |                  |
| subjects affected / exposed                | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 3 / 63 (4.76%)   |
| occurrences (all)                          | 0              | 1               | 3                |
| DIZZINESS                                  |                |                 |                  |

|   |                     |                      |                     |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 1 / 63 (1.59%)<br>1 |
| SCIATICA<br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 0 / 63 (0.00%)<br>0 |
| Ear and labyrinth disorders<br>TINNITUS<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 18 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 1 / 63 (1.59%)<br>1 |
| Eye disorders<br>CATARACT<br>subjects affected / exposed<br>occurrences (all)   | 0 / 18 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 0 / 63 (0.00%)<br>0 |
| Gastrointestinal disorders<br>GASTROOESOPHAGEAL REFLUX<br>DISEASE<br>subjects affected / exposed<br>occurrences (all) | 0 / 18 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 1 / 63 (1.59%)<br>2 |
| CONSTIPATION<br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 5 / 63 (7.94%)<br>6 |
| GASTRITIS<br>subjects affected / exposed<br>occurrences (all)   | 0 / 18 (0.00%)<br>0 | 1 / 36 (2.78%)<br>1  | 1 / 63 (1.59%)<br>1 |
| DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)   | 1 / 18 (5.56%)<br>2 | 4 / 36 (11.11%)<br>4 | 6 / 63 (9.52%)<br>6 |
| VOMITING<br>subjects affected / exposed<br>occurrences (all)  | 1 / 18 (5.56%)<br>2 | 1 / 36 (2.78%)<br>1  | 3 / 63 (4.76%)<br>5 |
| DENTAL CARIES<br>subjects affected / exposed<br>occurrences (all)   | 0 / 18 (0.00%)<br>0 | 2 / 36 (5.56%)<br>7  | 3 / 63 (4.76%)<br>3 |
| ABDOMINAL PAIN<br>subjects affected / exposed<br>occurrences (all)  | 0 / 18 (0.00%)<br>0 | 3 / 36 (8.33%)<br>5  | 2 / 63 (3.17%)<br>3 |
| NAUSEA  |                     |                      |                     |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 7 / 63 (11.11%) |
| occurrences (all)                               | 0              | 1               | 9               |
| ABDOMINAL PAIN UPPER                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 4 / 63 (6.35%)  |
| occurrences (all)                               | 0              | 0               | 4               |
| DYSPEPSIA                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 1 / 63 (1.59%)  |
| occurrences (all)                               | 0              | 0               | 1               |
| LARGE INTESTINE POLYP                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 1 / 63 (1.59%)  |
| occurrences (all)                               | 0              | 1               | 1               |
| Skin and subcutaneous tissue disorders          |                |                 |                 |
| RASH  |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 5 / 36 (13.89%) | 9 / 63 (14.29%) |
| occurrences (all)                               | 0              | 7               | 9               |
| ECZEMA  |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 3 / 63 (4.76%)  |
| occurrences (all)                               | 0              | 2               | 3               |
| PRURITUS  |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 4 / 63 (6.35%)  |
| occurrences (all)                               | 0              | 1               | 5               |
| RASH MACULO-PAPULAR                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| ALOPECIA  |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Renal and urinary disorders                     |                |                 |                 |
| NEPHROLITHIASIS                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 0 / 63 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0               |
| Endocrine disorders                             |                |                 |                 |
| HYPOTHYROIDISM                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0               |
| Musculoskeletal and connective tissue disorders |                |                 |                 |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| GROIN PAIN                  |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 4 / 63 (6.35%)  |
| occurrences (all)           | 0              | 1               | 5               |
| ARTHRITIS                   |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 0 / 63 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| JOINT SWELLING              |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 8 / 63 (12.70%) |
| occurrences (all)           | 0              | 0               | 10              |
| PAIN IN EXTREMITY           |                |                 |                 |
| subjects affected / exposed | 1 / 18 (5.56%) | 5 / 36 (13.89%) | 6 / 63 (9.52%)  |
| occurrences (all)           | 1              | 6               | 7               |
| SYNOVITIS                   |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 7 / 63 (11.11%) |
| occurrences (all)           | 0              | 3               | 9               |
| MUSCLE SPASMS               |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 2 / 63 (3.17%)  |
| occurrences (all)           | 0              | 3               | 2               |
| MUSCLE CONTRACTURE          |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 2 / 63 (3.17%)  |
| occurrences (all)           | 0              | 1               | 2               |
| MUSCULOSKELETAL STIFFNESS   |                |                 |                 |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 36 (0.00%)  | 1 / 63 (1.59%)  |
| occurrences (all)           | 1              | 0               | 1               |
| TENOSYNOVITIS               |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 0 / 63 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0               |
| TENDONITIS                  |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 2 / 63 (3.17%)  |
| occurrences (all)           | 0              | 2               | 3               |
| BACK PAIN                   |                |                 |                 |
| subjects affected / exposed | 1 / 18 (5.56%) | 6 / 36 (16.67%) | 8 / 63 (12.70%) |
| occurrences (all)           | 1              | 11              | 10              |
| HAEMOPHILIC ARTHROPATHY     |                |                 |                 |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 1 / 63 (1.59%)  |
| occurrences (all)           | 0              | 1               | 1               |

|                                   |                |                  |                  |
|-----------------------------------|----------------|------------------|------------------|
| MYALGIA                           |                |                  |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 4 / 36 (11.11%)  | 6 / 63 (9.52%)   |
| occurrences (all)                 | 0              | 4                | 7                |
| ARTHRALGIA                        |                |                  |                  |
| subjects affected / exposed       | 1 / 18 (5.56%) | 16 / 36 (44.44%) | 25 / 63 (39.68%) |
| occurrences (all)                 | 1              | 41               | 78               |
| Infections and infestations       |                |                  |                  |
| SINUSITIS                         |                |                  |                  |
| subjects affected / exposed       | 1 / 18 (5.56%) | 0 / 36 (0.00%)   | 4 / 63 (6.35%)   |
| occurrences (all)                 | 3              | 0                | 4                |
| BRONCHITIS                        |                |                  |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 2 / 36 (5.56%)   | 3 / 63 (4.76%)   |
| occurrences (all)                 | 0              | 4                | 4                |
| LOWER RESPIRATORY TRACT INFECTION |                |                  |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 2 / 36 (5.56%)   | 1 / 63 (1.59%)   |
| occurrences (all)                 | 0              | 2                | 1                |
| BACTERIAL INFECTION               |                |                  |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 0 / 36 (0.00%)   | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 0                | 0                |
| GASTRIC INFECTION                 |                |                  |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 0 / 36 (0.00%)   | 1 / 63 (1.59%)   |
| occurrences (all)                 | 0              | 0                | 1                |
| INFLUENZA                         |                |                  |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 7 / 36 (19.44%)  | 9 / 63 (14.29%)  |
| occurrences (all)                 | 0              | 8                | 10               |
| NASOPHARYNGITIS                   |                |                  |                  |
| subjects affected / exposed       | 1 / 18 (5.56%) | 9 / 36 (25.00%)  | 20 / 63 (31.75%) |
| occurrences (all)                 | 1              | 16               | 35               |
| EAR INFECTION                     |                |                  |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 2 / 36 (5.56%)   | 1 / 63 (1.59%)   |
| occurrences (all)                 | 0              | 2                | 1                |
| CONJUNCTIVITIS                    |                |                  |                  |
| subjects affected / exposed       | 1 / 18 (5.56%) | 1 / 36 (2.78%)   | 0 / 63 (0.00%)   |
| occurrences (all)                 | 1              | 1                | 0                |
| LOCALISED INFECTION               |                |                  |                  |

|                                   |                |                 |                  |
|-----------------------------------|----------------|-----------------|------------------|
| subjects affected / exposed       | 1 / 18 (5.56%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 1              | 0               | 0                |
| UPPER RESPIRATORY TRACT INFECTION |                |                 |                  |
| subjects affected / exposed       | 1 / 18 (5.56%) | 8 / 36 (22.22%) | 14 / 63 (22.22%) |
| occurrences (all)                 | 2              | 11              | 19               |
| GASTROENTERITIS                   |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 3 / 36 (8.33%)  | 1 / 63 (1.59%)   |
| occurrences (all)                 | 0              | 3               | 1                |
| PHARYNGITIS                       |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 4 / 36 (11.11%) | 3 / 63 (4.76%)   |
| occurrences (all)                 | 0              | 4               | 10               |
| RHINITIS                          |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 2               | 0                |
| DIARRHOEA INFECTIOUS              |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 0               | 0                |
| COVID-19                          |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 3 / 36 (8.33%)  | 7 / 63 (11.11%)  |
| occurrences (all)                 | 0              | 3               | 7                |
| BODY TINEA                        |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 0               | 0                |
| RESPIRATORY TRACT INFECTION       |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 2               | 0                |
| PERIODONTITIS                     |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 1 / 36 (2.78%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 1               | 0                |
| ABSCESS LIMB                      |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 2 / 36 (5.56%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 2               | 0                |
| CORONAVIRUS INFECTION             |                |                 |                  |
| subjects affected / exposed       | 0 / 18 (0.00%) | 0 / 36 (0.00%)  | 0 / 63 (0.00%)   |
| occurrences (all)                 | 0              | 0               | 0                |

|                                    |                |                |                |
|------------------------------------|----------------|----------------|----------------|
| Metabolism and nutrition disorders |                |                |                |
| HYPERURICAEMIA                     |                |                |                |
| subjects affected / exposed        | 0 / 18 (0.00%) | 2 / 36 (5.56%) | 0 / 63 (0.00%) |
| occurrences (all)                  | 0              | 2              | 0              |
| HYPERCHOLESTEROLAEMIA              |                |                |                |
| subjects affected / exposed        | 0 / 18 (0.00%) | 2 / 36 (5.56%) | 1 / 63 (1.59%) |
| occurrences (all)                  | 0              | 2              | 1              |

| <b>Non-serious adverse events</b>                                   | Arm C(Emi):<br>Emicizumab 3<br>mg/kg Q2W(Switch<br>From No<br>Prophylaxis) | Arm B: Emicizumab<br>3 mg/kg Q2W |  |
|---|--|----------------------------------|--|
| Total subjects affected by non-serious adverse events               |  |                                  |  |
| subjects affected / exposed   | 15 / 17 (88.24%)   | 33 / 35 (94.29%)                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                                  |  |
| PAPILLOMA   |  |                                  |  |
| subjects affected / exposed   | 1 / 17 (5.88%)   | 0 / 35 (0.00%)                   |  |
| occurrences (all)   | 1  | 0                                |  |
| Vascular disorders  |  |                                  |  |
| HAEMATOMA   |  |                                  |  |
| subjects affected / exposed   | 0 / 17 (0.00%)   | 1 / 35 (2.86%)                   |  |
| occurrences (all)   | 0  | 1                                |  |
| HYPERTENSION  |  |                                  |  |
| subjects affected / exposed   | 0 / 17 (0.00%)   | 0 / 35 (0.00%)                   |  |
| occurrences (all)   | 0  | 0                                |  |
| General disorders and administration site conditions                |  |                                  |  |
| INFLUENZA LIKE ILLNESS  |  |                                  |  |
| subjects affected / exposed   | 1 / 17 (5.88%)   | 0 / 35 (0.00%)                   |  |
| occurrences (all)   | 1  | 0                                |  |
| PAIN  |  |                                  |  |
| subjects affected / exposed   | 1 / 17 (5.88%)   | 1 / 35 (2.86%)                   |  |
| occurrences (all)   | 1  | 1                                |  |
| PYREXIA   |  |                                  |  |
| subjects affected / exposed   | 1 / 17 (5.88%)   | 2 / 35 (5.71%)                   |  |
| occurrences (all)   | 1  | 2                                |  |
| ASTHENIA  |  |                                  |  |
| subjects affected / exposed   | 1 / 17 (5.88%)   | 1 / 35 (2.86%)                   |  |
| occurrences (all)   | 1  | 2                                |  |

|   |                      |                       |  |
|---|----------------------|-----------------------|--|
| INJECTION SITE REACTION<br>subjects affected / exposed<br>occurrences (all)   | 4 / 17 (23.53%)<br>4 | 8 / 35 (22.86%)<br>25 |  |
| Immune system disorders<br>SEASONAL ALLERGY<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 17 (5.88%)<br>1  | 0 / 35 (0.00%)<br>0   |  |
| DRUG HYPERSENSITIVITY<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0  | 2 / 35 (5.71%)<br>2   |  |
| HYPERSENSITIVITY<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0  | 2 / 35 (5.71%)<br>2   |  |
| Reproductive system and breast disorders<br>ERECTILE DYSFUNCTION<br>subjects affected / exposed<br>occurrences (all)    | 1 / 17 (5.88%)<br>1  | 0 / 35 (0.00%)<br>0   |  |
| Respiratory, thoracic and mediastinal disorders<br>NASAL CONGESTION<br>subjects affected / exposed<br>occurrences (all) | 1 / 17 (5.88%)<br>1  | 0 / 35 (0.00%)<br>0   |  |
| OROPHARYNGEAL PAIN<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1   |  |
| COUGH<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0  | 0 / 35 (0.00%)<br>0   |  |
| Psychiatric disorders<br>DEPRESSION<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 17 (0.00%)<br>0  | 1 / 35 (2.86%)<br>2   |  |
| SLEEP DISORDER<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0  | 0 / 35 (0.00%)<br>0   |  |
| INSOMNIA  |                      |                       |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                    | 0 / 17 (0.00%) | 2 / 35 (5.71%) |  |
| occurrences (all)                              | 0              | 2              |  |
| ANXIETY  |                |                |  |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 2 / 35 (5.71%) |  |
| occurrences (all)                              | 0              | 2              |  |
| Investigations                                 |                |                |  |
| BLOOD CREATININE INCREASED                     |                |                |  |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences (all)                              | 0              | 0              |  |
| BLOOD CREATINE PHOSPHOKINASE INCREASED         |                |                |  |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 2 / 35 (5.71%) |  |
| occurrences (all)                              | 1              | 4              |  |
| ASPARTATE AMINOTRANSFERASE INCREASED           |                |                |  |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 2 / 35 (5.71%) |  |
| occurrences (all)                              | 0              | 3              |  |
| BLOOD PRESSURE DIASTOLIC INCREASED             |                |                |  |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 0 / 35 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| ALANINE AMINOTRANSFERASE INCREASED             |                |                |  |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 2 / 35 (5.71%) |  |
| occurrences (all)                              | 1              | 3              |  |
| Injury, poisoning and procedural complications |                |                |  |
| BITE   |                |                |  |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 0 / 35 (0.00%) |  |
| occurrences (all)                              | 0              | 0              |  |
| LIMB INJURY                                    |                |                |  |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 3 / 35 (8.57%) |  |
| occurrences (all)                              | 1              | 5              |  |
| TOOTH FRACTURE                                 |                |                |  |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 0 / 35 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| LIGAMENT SPRAIN                                |                |                |  |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 1              | 1              |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| ARTHROPOD BITE                             |                 |                |  |
| subjects affected / exposed                | 0 / 17 (0.00%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                          | 0               | 0              |  |
| LIGAMENT INJURY                            |                 |                |  |
| subjects affected / exposed                | 1 / 17 (5.88%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| CONTUSION                                  |                 |                |  |
| subjects affected / exposed                | 2 / 17 (11.76%) | 2 / 35 (5.71%) |  |
| occurrences (all)                          | 3               | 3              |  |
| JOINT INJURY                               |                 |                |  |
| subjects affected / exposed                | 0 / 17 (0.00%)  | 2 / 35 (5.71%) |  |
| occurrences (all)                          | 0               | 5              |  |
| MUSCLE STRAIN                              |                 |                |  |
| subjects affected / exposed                | 0 / 17 (0.00%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                          | 0               | 0              |  |
| SKIN ABRASION                              |                 |                |  |
| subjects affected / exposed                | 0 / 17 (0.00%)  | 1 / 35 (2.86%) |  |
| occurrences (all)                          | 0               | 1              |  |
| BACK INJURY                                |                 |                |  |
| subjects affected / exposed                | 1 / 17 (5.88%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| FALL                                       |                 |                |  |
| subjects affected / exposed                | 1 / 17 (5.88%)  | 1 / 35 (2.86%) |  |
| occurrences (all)                          | 1               | 1              |  |
| SKIN LACERATION                            |                 |                |  |
| subjects affected / exposed                | 2 / 17 (11.76%) | 1 / 35 (2.86%) |  |
| occurrences (all)                          | 2               | 1              |  |
| TONGUE INJURY                              |                 |                |  |
| subjects affected / exposed                | 1 / 17 (5.88%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| ROAD TRAFFIC ACCIDENT                      |                 |                |  |
| subjects affected / exposed                | 1 / 17 (5.88%)  | 1 / 35 (2.86%) |  |
| occurrences (all)                          | 1               | 1              |  |
| Congenital, familial and genetic disorders |                 |                |  |

|  |                      |                       |  |
|--|----------------------|-----------------------|--|
| HYDROCELE<br>subjects affected / exposed<br>occurrences (all)  | 1 / 17 (5.88%)<br>1  | 0 / 35 (0.00%)<br>0   |  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 17 (11.76%)<br>2 | 7 / 35 (20.00%)<br>30 |  |
| PARAESTHESIA<br>subjects affected / exposed<br>occurrences (all)   | 1 / 17 (5.88%)<br>1  | 1 / 35 (2.86%)<br>1   |  |
| DIZZINESS<br>subjects affected / exposed<br>occurrences (all)  | 1 / 17 (5.88%)<br>1  | 1 / 35 (2.86%)<br>2   |  |
| SCIATICA<br>subjects affected / exposed<br>occurrences (all)   | 1 / 17 (5.88%)<br>3  | 1 / 35 (2.86%)<br>1   |  |
| Ear and labyrinth disorders<br>TINNITUS<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 17 (0.00%)<br>0  | 0 / 35 (0.00%)<br>0   |  |
| Eye disorders<br>CATARACT<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0  | 0 / 35 (0.00%)<br>0   |  |
| Gastrointestinal disorders<br>GASTROESOPHAGEAL REFLUX<br>DISEASE<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1   |  |
| CONSTIPATION<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1   |  |
| GASTRITIS<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0  | 2 / 35 (5.71%)<br>3   |  |
| DIARRHOEA  |                      |                       |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed            | 2 / 17 (11.76%) | 5 / 35 (14.29%) |  |
| occurrences (all)                      | 3               | 6               |  |
| VOMITING                               |                 |                 |  |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                      | 1               | 1               |  |
| DENTAL CARIES                          |                 |                 |  |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| ABDOMINAL PAIN                         |                 |                 |  |
| subjects affected / exposed            | 3 / 17 (17.65%) | 0 / 35 (0.00%)  |  |
| occurrences (all)                      | 4               | 0               |  |
| NAUSEA                                 |                 |                 |  |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 4 / 35 (11.43%) |  |
| occurrences (all)                      | 0               | 4               |  |
| ABDOMINAL PAIN UPPER                   |                 |                 |  |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 3 / 35 (8.57%)  |  |
| occurrences (all)                      | 0               | 3               |  |
| DYSPEPSIA                              |                 |                 |  |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 2 / 35 (5.71%)  |  |
| occurrences (all)                      | 0               | 2               |  |
| LARGE INTESTINE POLYP                  |                 |                 |  |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                      | 1               | 1               |  |
| Skin and subcutaneous tissue disorders |                 |                 |  |
| RASH                                   |                 |                 |  |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| ECZEMA                                 |                 |                 |  |
| subjects affected / exposed            | 0 / 17 (0.00%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)                      | 0               | 0               |  |
| PRURITUS                               |                 |                 |  |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 2 / 35 (5.71%)  |  |
| occurrences (all)                      | 1               | 2               |  |
| RASH MACULO-PAPULAR                    |                 |                 |  |
| subjects affected / exposed            | 1 / 17 (5.88%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |

|   |                     |                      |  |
|---|---------------------|----------------------|--|
| ALOPECIA<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0 | 2 / 35 (5.71%)<br>2  |  |
| Renal and urinary disorders<br>NEPHROLITHIASIS<br>subjects affected / exposed<br>occurrences (all)                | 0 / 17 (0.00%)<br>0 | 2 / 35 (5.71%)<br>3  |  |
| Endocrine disorders<br>HYPOTHYROIDISM<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 17 (0.00%)<br>0 | 2 / 35 (5.71%)<br>2  |  |
| Musculoskeletal and connective tissue disorders<br>GROIN PAIN<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0 | 0 / 35 (0.00%)<br>0  |  |
| ARTHRITIS<br>subjects affected / exposed<br>occurrences (all)   | 1 / 17 (5.88%)<br>1 | 0 / 35 (0.00%)<br>0  |  |
| JOINT SWELLING<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0 | 4 / 35 (11.43%)<br>4 |  |
| SYNOVITIS<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0 | 0 / 35 (0.00%)<br>0  |  |
| MUSCLE SPASMS<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0 | 0 / 35 (0.00%)<br>0  |  |
| MUSCLE CONTRACTURE<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0 | 2 / 35 (5.71%)<br>2  |  |
| MUSCULOSKELETAL STIFFNESS<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 17 (0.00%)<br>0 | 0 / 35 (0.00%)<br>0  |  |

|                                   |                 |                  |  |
|-----------------------------------|-----------------|------------------|--|
| TENOSYNOVITIS                     |                 |                  |  |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 0 / 35 (0.00%)   |  |
| occurrences (all)                 | 0               | 0                |  |
| TENDONITIS                        |                 |                  |  |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 0 / 35 (0.00%)   |  |
| occurrences (all)                 | 0               | 0                |  |
| BACK PAIN                         |                 |                  |  |
| subjects affected / exposed       | 2 / 17 (11.76%) | 3 / 35 (8.57%)   |  |
| occurrences (all)                 | 3               | 4                |  |
| HAEMOPHILIC ARTHROPATHY           |                 |                  |  |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 2 / 35 (5.71%)   |  |
| occurrences (all)                 | 0               | 2                |  |
| MYALGIA                           |                 |                  |  |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 1 / 35 (2.86%)   |  |
| occurrences (all)                 | 0               | 1                |  |
| ARTHRALGIA                        |                 |                  |  |
| subjects affected / exposed       | 3 / 17 (17.65%) | 11 / 35 (31.43%) |  |
| occurrences (all)                 | 5               | 26               |  |
| Infections and infestations       |                 |                  |  |
| SINUSITIS                         |                 |                  |  |
| subjects affected / exposed       | 2 / 17 (11.76%) | 0 / 35 (0.00%)   |  |
| occurrences (all)                 | 2               | 0                |  |
| BRONCHITIS                        |                 |                  |  |
| subjects affected / exposed       | 2 / 17 (11.76%) | 1 / 35 (2.86%)   |  |
| occurrences (all)                 | 2               | 1                |  |
| LOWER RESPIRATORY TRACT INFECTION |                 |                  |  |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 0 / 35 (0.00%)   |  |
| occurrences (all)                 | 0               | 0                |  |
| BACTERIAL INFECTION               |                 |                  |  |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 35 (0.00%)   |  |
| occurrences (all)                 | 1               | 0                |  |
| GASTRIC INFECTION                 |                 |                  |  |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 35 (0.00%)   |  |
| occurrences (all)                 | 1               | 0                |  |
| INFLUENZA                         |                 |                  |  |

|                                   |                 |                 |
|-----------------------------------|-----------------|-----------------|
| subjects affected / exposed       | 2 / 17 (11.76%) | 4 / 35 (11.43%) |
| occurrences (all)                 | 2               | 4               |
| NASOPHARYNGITIS                   |                 |                 |
| subjects affected / exposed       | 3 / 17 (17.65%) | 8 / 35 (22.86%) |
| occurrences (all)                 | 4               | 19              |
| EAR INFECTION                     |                 |                 |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 0 / 35 (0.00%)  |
| occurrences (all)                 | 0               | 0               |
| CONJUNCTIVITIS                    |                 |                 |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 2 / 35 (5.71%)  |
| occurrences (all)                 | 1               | 2               |
| LOCALISED INFECTION               |                 |                 |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)                 | 0               | 2               |
| UPPER RESPIRATORY TRACT INFECTION |                 |                 |
| subjects affected / exposed       | 3 / 17 (17.65%) | 6 / 35 (17.14%) |
| occurrences (all)                 | 4               | 9               |
| GASTROENTERITIS                   |                 |                 |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)                 | 0               | 2               |
| PHARYNGITIS                       |                 |                 |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 1 / 35 (2.86%)  |
| occurrences (all)                 | 0               | 1               |
| RHINITIS                          |                 |                 |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 2 / 35 (5.71%)  |
| occurrences (all)                 | 0               | 2               |
| DIARRHOEA INFECTIOUS              |                 |                 |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 35 (0.00%)  |
| occurrences (all)                 | 1               | 0               |
| COVID-19                          |                 |                 |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 35 (0.00%)  |
| occurrences (all)                 | 1               | 0               |
| BODY TINEA                        |                 |                 |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 35 (0.00%)  |
| occurrences (all)                 | 1               | 0               |

|                                    |                 |                |  |
|------------------------------------|-----------------|----------------|--|
| RESPIRATORY TRACT INFECTION        |                 |                |  |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                  | 0               | 0              |  |
| PERIODONTITIS                      |                 |                |  |
| subjects affected / exposed        | 2 / 17 (11.76%) | 1 / 35 (2.86%) |  |
| occurrences (all)                  | 2               | 1              |  |
| ABSCESS LIMB                       |                 |                |  |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                  | 0               | 0              |  |
| CORONAVIRUS INFECTION              |                 |                |  |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                  | 1               | 0              |  |
| Metabolism and nutrition disorders |                 |                |  |
| HYPERURICAEMIA                     |                 |                |  |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 2 / 35 (5.71%) |  |
| occurrences (all)                  | 0               | 2              |  |
| HYPERCHOLESTEROLAEMIA              |                 |                |  |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 0 / 35 (0.00%) |  |
| occurrences (all)                  | 0               | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 12 September 2016 | The main changes to the protocol are as follows: - The specific factor VIII (FVIII) prophylactic dose and frequency was removed from the definition for FVIII prophylaxis regimen for the inclusion criterion for patients previously treated with FVIII prophylaxis to be enrolled in Arm D.; - Modified dose escalation criteria to more precisely define the subpopulation who may benefit from an increased dose of emicizumab; - Added clarification regarding the efficacy analyses that will be performed for treated bleeds (i.e., treated with coagulation factors) and all bleeds (i.e., both treated and not treated with coagulation factors) given that some patients may report bleeds that they did not treat. In addition, rate of spontaneous bleeds was added as a secondary endpoint.; - Added safety updates regarding a case of atypical hemolytic uremic syndrome (aHUS) and a patient who developed cavernous sinus thrombosis. Both occurred in patients with hemophilia A with FVIII inhibitors receiving bypassing agents.; - The optional interim analysis section was removed based on the anticipated study timelines, as no interim analyses are expected for this study.; - Provided the option for patients to potentially combine emicizumab volumes (if necessary) from up to two vials into 1 syringe to reduce the number of subcutaneous injections they may require. |
| 30 November 2016  | The main changes to the protocol are as follows: - The safety sections were updated with the most recent safety information regarding 2 cases of thrombotic microangiopathy (TMA) and 2 patients who developed thromboembolic events in Study BH29884. Both occurred in patients with hemophilia A with FVIII inhibitors receiving bypassing agents. The section for risks associated with emicizumab was updated accordingly, and microangiopathic hemolytic anemia/TMA is newly classified as an adverse event of special interest.; - Although factor VIII (FVIII) and activated prothrombin complex concentrate (aPCC) are fundamentally different in their potential interaction with emicizumab, the amended protocol points investigators to the fact that circulating emicizumab increases patients' coagulation potential and provides suggestions about the use of FVIII in conjunction with emicizumab.; - The van Elteren test will be used as back-up statistical method for the primary analysis instead of the Wilcoxon rank sum test to allow a stratified analysis to be performed.; - Although the use of bypassing agents is unlikely in patients without inhibitors, for completeness and clarity, the amended protocol includes guidelines for their use in patients receiving emicizumab, including dosage and requirements for laboratory monitoring.                               |
| 20 December 2019  | Protocol v4 (dated 20 December 2019): Upon implementation of this amendment, treatment duration was extended until 5 years after the last patient was enrolled to enable the collection of additional long-term safety and efficacy data. During this study prolongation, each patient chose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg every 4 weeks [Q4W]) and continued on that dosing regimen until discontinuation from the study.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported