



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BO39182 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03020160 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 15 December 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 December 2017 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

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

PK Run-In Part Objectives:

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

Expansion Part Objectives:

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

Protection of trial subjects:

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. Each study subject or their legally authorized representative was required to read and sign an Informed Consent Form or an Informed Assent Form (ages 12-17), as applicable.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 4 |
| Adults (18-64 years) | 41 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|----------------------------|
| Arm title | Emicizumab: Expansion Part |
|------------------|----------------------------|

Arm description:

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

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

Dosage and administration details:

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

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

| | | |
|----------------------------------|---|----|
| Continuing to receive emicizumab | 7 | 41 |
|----------------------------------|---|----|

Baseline characteristics

Reporting groups

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

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

End points

End points reporting groups

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

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

| | |
|--|---|
| End point title | Expansion Part: Annualized Bleeding Rate (ABR) for Treated Bleeds ^{[1][2]} |
| End point description: | |
| The number of treated bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times. A bleed is considered a "treated bleed" if it is directly followed (i.e., no intervening bleed) by a hemophilia medication reported to be a "treatment for bleed", irrespective of time between treatment and the preceding bleed. A bleed and the first treatment thereafter and before a new bleed starts, are considered to be pairs, with the following exception: if multiple bleeds occur on the same calendar day, the subsequent treatment is considered to apply for each of these multiple bleeds. The 72-hour rule was implemented: two bleeds of the same type and at the same anatomical location are counted as one bleed if the second bleed occurs within 72 hours from the last treatment for the first bleed. Bleeds due to surgery/procedure are excluded. | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline to at least 24 weeks | |

Notes:

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Expansion Part: Annualized Bleeding Rate (ABR) for All |
|-----------------|--|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Expansion Part: Annualized Bleeding Rate (ABR) for Treated Spontaneous Bleeds ^{[5][6]} |
|-----------------|---|

End point description:

The number of treated spontaneous bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., the time that each participant stays in the study). A bleed is classified as "spontaneous" if there is no other known contributing factor such as trauma or procedure/surgery. A "treated spontaneous bleed" is a spontaneous bleed that also fulfills the conditions of a treated bleed (see ABR for Treated Bleeds for the definition). Treated bleeds that fulfilled the 72-hour rule were included in the analysis of spontaneous bleeds. Bleeds due to surgery/procedure are excluded.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Expansion Part: Annualized Bleeding Rate (ABR) for Treated Joint Bleeds ^[7] ^[8] |
|-----------------|---|

End point description:

The number of treated joint bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., the time that each participant stays in the study). A "joint bleed" is defined as a bleed with type reported as "joint" and with at least one of the following symptoms: increasing swelling or warmth of the skin over the joint and/or increasing pain, decreased range of motion, or difficulty using the joint compared with baseline. A "treated joint bleed" is a joint bleed that also fulfills the conditions of a treated bleed (see ABR for Treated Bleeds for the definition). Treated bleeds that fulfilled the 72-hour rule were included in the analysis of joint bleeds, excluding bleeds due to surgery/procedure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Expansion Part: Annualized Bleeding Rate (ABR) for Treated Target Joint Bleeds ^{[9][10]} |
|-----------------|---|

End point description:

The number of treated target joint bleeds over the efficacy period is presented as an annualized bleeding rate (ABR) that was analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times (i.e., the time that each participant stays in the study). A "target joint bleed" is defined as a joint bleed in a target joint, which is a joint location where at least 3 bleeds have occurred over the last 24 weeks prior to study entry. A "treated target joint bleed" is a target joint bleed that also fulfills the conditions of a treated bleed (see ABR for Treated Bleeds for the definition). Bleeds due to surgery/procedure are excluded.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline to at least 24 weeks

Notes:

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 25

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

and Week 25.

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 25

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 25

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score, as well as a visual analogue scale (VAS) that measures health state. The VAS is designed to rate the subject's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. An increase in the VAS score of 7 points or greater was defined as the threshold for a meaningful improvement. The analysis included all subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline

and Week 25.

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score, as well as a visual analogue scale (VAS) that measures health state. The VAS is designed to rate the subject's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. An increase in the VAS score of 7 points or greater was defined as the threshold for a meaningful improvement. The analysis included all subjects enrolled in the expansion part of the study. The number of subjects analyzed indicates those who completed the questionnaire at Baseline and Week 25.

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 25

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 25

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Part: Number of Days Hospitalized

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

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Predose at Week 17

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

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

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with At Least One Adverse Event

| | |
|-----------------|--|
| End point title | Number of Subjects with At Least One Adverse Event |
|-----------------|--|

End point description:

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Grade ≥3 Adverse Events

| | |
|-----------------|---|
| End point title | Number of Subjects with Grade ≥3 Adverse Events |
|-----------------|---|

End point description:

The World Health Organization (WHO) toxicity grading scale will be used for assessing adverse event severity. For adverse events that are not specifically listed in the WHO toxicity grading scale, a grade 3 adverse event is defined as: severe, marked limitation in activity, some assistance usually required, medical intervention or therapy required, hospitalization possible; and a grade 4 adverse event is defined as: life-threatening, extreme limitation in activity, significant assistance required, significant medical intervention or therapy required, hospitalization or hospice care probable. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|--|
| End point title | Number of Subjects with Adverse Events of Changes from Baseline in Vital Signs |
| End point description: The number of subjects with adverse events of changes from baseline in vital signs is reported here. Vital signs measurements consisted of heart and respiratory rate, temperature, and systolic and diastolic blood pressures, with an abnormal vital sign value being outside of the normal range. An abnormal vital sign result is reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); results in a medical intervention or a change in concomitant therapy; or is clinically significant in the investigator's judgment. The analysis included all subjects who received at | |

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Number of Subjects with Adverse Events of Changes from Baseline in Physical Examination Findings |
|-----------------|--|

End point description:

Post-baseline physical examination abnormalities that were not present at baseline or worsened were reported as adverse events. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Number of Subjects with Adverse Events of Abnormal Laboratory Values |
|-----------------|--|

End point description:

The number of subjects with adverse events of abnormal laboratory values is reported here. An

abnormal laboratory value is defined as a laboratory test result outside of the normal range for hematology or serum chemistries. It is reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment (e.g., dosage modification, treatment interruption or discontinuation); results in a medical intervention or a change in concomitant therapy; or is clinically significant in the investigator's judgment. The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks).

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Local Injection-Site Reactions

| | |
|--|--|
| End point title | Number of Subjects with Local Injection-Site Reactions |
| End point description: | |
| Local adverse events that occurred within 24 hours after study drug administration and, in the investigator's opinion, were judged to be related to study drug injection, were captured as an "injection-site reaction" on the Adverse Event electronic Case Report Form (eCRF). An injection-related reaction that was localized was marked as a "local injection-site reaction." The analysis included all subjects who received at least one dose of emicizumab. At the clinical cut-off date for primary analysis (15 Dec 2017), the median observation time was 43.71 weeks (range: 41.7-45.7 weeks). | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to study completion (up to approximately 4 years) | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Thromboembolic Events

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Thrombotic Microangiopathy

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Number of Subjects with Systemic Hypersensitivity, Anaphylaxis, or Anaphylactoid Reactions |
|-----------------|--|

End point description:

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Emicizumab: PK Run-In Part |
|-----------------------|----------------------------|

Reporting group description:

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

| | |
|-----------------------|----------------------------|
| Reporting group title | Emicizumab: Expansion Part |
|-----------------------|----------------------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: