



Clinical trial results:

A Randomized, Multicenter, Open-Label, Phase III Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Patients With Inhibitors

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2015-002866-21 |
| Trial protocol | DE ES GB PL FR IT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 04 November 2017 |
| First version publication date | 04 November 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BH29884 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02622321 |
| 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 | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 25 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 October 2016 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety, efficacy and pharmacokinetics of prophylactic emicizumab treatment in participants previously treated with episodic or prophylactic bypassing agents.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 18 November 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Costa Rica: 5 |
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Japan: 12 |
| Country: Number of subjects enrolled | New Zealand: 2 |
| Country: Number of subjects enrolled | Poland: 9 |
| Country: Number of subjects enrolled | South Africa: 6 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Taiwan: 4 |
| Country: Number of subjects enrolled | United States: 36 |
| Worldwide total number of subjects | 109 |
| EEA total number of subjects | 39 |

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) | 32 |
| Adults (18-64 years) | 73 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 114 participants were screened, of which 5 were screen failure and 109 were enrolled in this study. Participants in Arm A and Arm B were randomized in a 2:1 ratio; participants in Arm C and Arm D were enrolled without randomization.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A (Episodic Treatment): Emicizumab |

Arm description:

Participants, who received episodic treatment with bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 milligrams per kilogram per week (mg/kg/week) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive episodic bypassing agent therapy to treat breakthrough bleeds, with recombinant activated factor VII (rFVIIa) and/or activated prothrombin complex concentrate (aPCC).

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

Dosage and administration details:

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

| | |
|------------------|---|
| Arm title | Arm B (Episodic Treatment): No Emicizumab |
|------------------|---|

Arm description:

Participants, who received episodic treatment with bypassing agents prior to study entry, did not receive emicizumab prophylaxis. Participants in this arm could switch to emicizumab prophylaxis after completing at least 24 weeks on-study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 mg/kg/week for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week up to the end of study.

| | |
|------------------|--|
| Arm title | Arm C (Prophylactic Treatment): Emicizumab |
|------------------|--|

Arm description:

Participants, who received prophylactic bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks

followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 mg/kg/week for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week up to the end of study.

| | |
|------------------|--|
| Arm title | Arm D (Episodic or Prophylactic Treatment): Emicizumab |
|------------------|--|

Arm description:

Participants, who received episodic bypassing agents prior to study entry, who participated in Study BH29768 but were unable to enroll in Arms A or B, were enrolled in this arm to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

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

Dosage and administration details:

Emicizumab was administered at a loading dose of 3 mg/kg/week for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week up to the end of study.

| Number of subjects in period 1 | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | Arm C (Prophylactic Treatment): Emicizumab |
|---------------------------------------|--|---|--|
| Started | 35 | 18 | 49 |
| Treated | 34 | 18 | 49 |
| Completed | 0 | 0 | 0 |
| Not completed | 35 | 18 | 49 |
| Ongoing treatment with no emicizumab | - | 5 | - |
| Consent withdrawn by subject | 1 | - | - |
| Ongoing in safety follow-up | 3 | - | - |
| Ongoing treatment with emicizumab | 31 | 13 | 49 |

| Number of subjects in period 1 | Arm D (Episodic or Prophylactic Treatment): Emicizumab |
|---------------------------------------|--|
| Started | 7 |
| Treated | 7 |
| Completed | 0 |
| Not completed | 7 |
| Ongoing treatment with no emicizumab | - |

| | |
|-----------------------------------|---|
| Consent withdrawn by subject | - |
| Ongoing in safety follow-up | - |
| Ongoing treatment with emicizumab | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Arm A (Episodic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received episodic treatment with bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 milligrams per kilogram per week (mg/kg/week) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive episodic bypassing agent therapy to treat breakthrough bleeds, with recombinant activated factor VII (rFVIIa) and/or activated prothrombin complex concentrate (aPCC).

| | |
|-----------------------|---|
| Reporting group title | Arm B (Episodic Treatment): No Emicizumab |
|-----------------------|---|

Reporting group description:

Participants, who received episodic treatment with bypassing agents prior to study entry, did not receive emicizumab prophylaxis. Participants in this arm could switch to emicizumab prophylaxis after completing at least 24 weeks on-study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|-----------------------|--|
| Reporting group title | Arm C (Prophylactic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received prophylactic bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|-----------------------|--|
| Reporting group title | Arm D (Episodic or Prophylactic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received episodic bypassing agents prior to study entry, who participated in Study BH29768 but were unable to enroll in Arms A or B, were enrolled in this arm to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| Reporting group values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | Arm C (Prophylactic Treatment): Emicizumab |
|------------------------------------|--|---|--|
| Number of subjects | 35 | 18 | 49 |
| Age Categorical Units: Subjects | | | |

| | | | |
|---|----------------|----------------|----------------|
| Age Continuous Units: years arithmetic mean standard deviation | 35.8 ± 13.9 | 37.2 ± 13.7 | 25.6 ± 16.8 |
| Gender Categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 35 | 18 | 49 |

| Reporting group values | Arm D (Episodic or Prophylactic Treatment): Emicizumab | Total | |
|------------------------------------|--|-------|--|
| Number of subjects | 7 | 109 | |
| Age Categorical Units: Subjects | | | |

| | | | |
|--------------------|--------|-----|--|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 30.3 | | |
| standard deviation | ± 10.8 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 7 | 109 | |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Arm A (Episodic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received episodic treatment with bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 milligrams per kilogram per week (mg/kg/week) subcutaneously (SC) for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive episodic bypassing agent therapy to treat breakthrough bleeds, with recombinant activated factor VII (rFVIIa) and/or activated prothrombin complex concentrate (aPCC).

| | |
|-----------------------|---|
| Reporting group title | Arm B (Episodic Treatment): No Emicizumab |
|-----------------------|---|

Reporting group description:

Participants, who received episodic treatment with bypassing agents prior to study entry, did not receive emicizumab prophylaxis. Participants in this arm could switch to emicizumab prophylaxis after completing at least 24 weeks on-study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|-----------------------|--|
| Reporting group title | Arm C (Prophylactic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received prophylactic bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|-----------------------|--|
| Reporting group title | Arm D (Episodic or Prophylactic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received episodic bypassing agents prior to study entry, who participated in Study BH29768 but were unable to enroll in Arms A or B, were enrolled in this arm to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|----------------------------|--|
| Subject analysis set title | Arm Anis: Episodic Bypassing Agents in NIS BH29768 |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

This arm includes data up to 52 weeks before study entry (assessed retrospectively at baseline) from Arm A participants who participated in NIS BH29768 before study entry and received episodic bypassing agents (rFVIIa or/and aPCC) during NIS BH29768.

| | |
|----------------------------|--|
| Subject analysis set title | Arm Cnis: Prophylactic Bypassing Agents in NIS BH29768 |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

This arm includes data up to 52 weeks before study entry (assessed retrospectively at baseline) from Arm C participants who participated in NIS BH29768 before study entry and received prophylactic bypassing agents (rFVIIa or/and aPCC) during NIS BH29768.

| | |
|----------------------------|-------------------------------------|
| Subject analysis set title | Arm Bemis: Emicizumab after Week 24 |
|----------------------------|-------------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

This arm includes Arm B participants who switched to emicizumab prophylaxis after completing at least 24-week no prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks (after at least Week 24) followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study.

Primary: Arms A and B: Annualized Bleed Rate (ABR) for Treated Bleeds

| | |
|-----------------|---|
| End point title | Arms A and B: Annualized Bleed Rate (ABR) for Treated |
|-----------------|---|

End point description:

Number of treated bleeds over the efficacy period was assessed through ABR using a negative binomial (NB) regression model. Treated bleeds were defined as a bleed for which coagulation factors were administered. Bleeds due to surgery/procedure were excluded. Intent-to-treat (ITT) population defined as all participants who were randomized to Arm A or Arm B.

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

End point timeframe:

From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

Notes:

[1] - 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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 18 | | |
| Units: treated bleeds per year | | | | |
| number (confidence interval 95%) | 2.9 (1.69 to 5.02) | 23.3 (12.33 to 43.89) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (less than [$<$] 9 or greater than or equal to [\geq] 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization.

| | |
|---|--|
| Comparison groups | Arm B (Episodic Treatment): No Emicizumab v Arm A (Episodic Treatment): Emicizumab |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.057 |
| upper limit | 0.277 |

Notes:

[2] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms A and B: ABR for All Bleeds

| | |
|-----------------|---|
| End point title | Arms A and B: ABR for All Bleeds ^[3] |
|-----------------|---|

End point description:

Number of all bleeds over the efficacy period was assessed through ABR using an NB regression model. All bleeds included both treated (with coagulation factors) and not treated bleeds. Bleeds due to surgery/procedure were excluded. ITT population.

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

End point timeframe:

From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

Notes:

[3] - 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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 18 | | |
| Units: all bleeds per year | | | | |
| number (confidence interval 95%) | 5.5 (3.58 to 8.60) | 28.3 (16.79 to 47.76) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization.

| | |
|---|--|
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.102 |
| upper limit | 0.375 |

Notes:

[4] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms A and Anis: ABR for All Bleeds

| | |
|-----------------|--|
| End point title | Arms A and Anis: ABR for All Bleeds ^[5] |
|-----------------|--|

End point description:

Number of all bleeds over the efficacy period was assessed through ABR using an NB regression model. All bleeds included both treated (with coagulation factors) and not treated bleeds. Bleeds due to surgery/procedure were excluded. Intra-participant comparison of ABR of all bleeds prior to study entry, while receiving episodic bypassing agents during non-interventional study (NIS) BH29768 (NCT02476942) (Arm Anis), with ABR of all bleeds on emicizumab prophylaxis (in this study) (Arm A) was reported. Arm A NIS population included all Arm A participants who participated in NIS BH29768 before study entry and received episodic bypassing agents during NIS BH29768.

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

End point timeframe:

For Arm Anis: up to 52 weeks before study entry (assessed retrospectively at baseline); for Arm A: From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm Anis: Episodic Bypassing Agents in NIS BH29768 | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 24 | 24 | | |
| Units: all bleeds per year | | | | |
| number (confidence interval 95%) | 4.1 (2.10 to 8.02) | 37.7 (28.40 to 50.04) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|--|---|
| Statistical analysis description: | |
| This intra-participant comparison of ABR for all bleeds was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm Anis) and on study (Arm A). | |
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm Anis: Episodic Bypassing Agents in NIS BH29768 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [6] |
| Method | Non-Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.055 |
| upper limit | 0.218 |

Notes:

[6] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms A and Anis: ABR for Treated Bleeds

| | |
|-----------------|--|
| End point title | Arms A and Anis: ABR for Treated Bleeds ^[7] |
|-----------------|--|

End point description:

Number of treated bleeds over the efficacy period was assessed through ABR using an NB regression model. Treated bleeds were defined as a bleed for which coagulation factors were administered. Bleeds due to surgery/procedure were excluded. Intra-participant comparison of ABR of treated bleeds prior to study entry, while receiving episodic bypassing agents during NIS BH29768 (Arm Anis), with ABR of treated bleeds on emicizumab prophylaxis (in this study) (Arm A) was reported. Arm A NIS population included all Arm A participants who participated in NIS BH29768 before study entry and received episodic bypassing agents during NIS BH29768.

| | | | | |
|---|--|--|--|--|
| End point type | Secondary | | | |
| End point timeframe: | | | | |
| For Arm Anis: up to 52 weeks before study entry (assessed retrospectively at baseline); for Arm A: From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year) | | | | |
| Notes: | | | | |
| [7] - 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 endpoint is applicable only for the reported arms; hence, other arms are not included. | | | | |
| End point values | Arm A (Episodic Treatment): Emicizumab | Arm Anis: Episodic Bypassing Agents in NIS BH29768 | | |
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 24 | 24 | | |
| Units: treated bleeds per year | | | | |
| number (confidence interval 95%) | 1.7 (0.71 to 4.06) | 21.6 (15.40 to 30.22) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| This intra-participant comparison of ABR for treated bleeds was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm Anis) and on study (Arm A). | |
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm Anis: Episodic Bypassing Agents in NIS BH29768 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[8] |
| Method | Non-Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.031 |
| upper limit | 0.198 |

Notes:

[8] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms A and B: ABR for Treated Joint Bleeds

| | |
|---|---|
| End point title | Arms A and B: ABR for Treated Joint Bleeds ^[9] |
| End point description: | |
| Number of treated joint bleeds over the efficacy period was assessed through ABR using an NB regression model. Treated joint bleeds were defined as treated bleeds in a joint associated with unusual sensation (aura) in a joint, in combination with another symptom: unusual sensation, swelling/warmth, pain/decreased range of motion (RoM), difficulty moving the joint. Bleeds due to surgery/procedure were excluded. ITT population. | |
| End point type | Secondary |

End point timeframe:

From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

Notes:

[9] - 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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 18 | | |
| Units: treated joint bleeds per year | | | | |
| number (confidence interval 95%) | 0.8 (0.26 to 2.20) | 6.7 (1.99 to 22.42) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization.

| | |
|---|--|
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 ^[10] |
| Method | Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.025 |
| upper limit | 0.52 |

Notes:

[10] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms C and Cnis: ABR for All Bleeds

| | |
|-----------------|---|
| End point title | Arms C and Cnis: ABR for All Bleeds ^[11] |
|-----------------|---|

End point description:

Number of all bleeds over the efficacy period was assessed through ABR using an NB regression model. All bleeds included both treated (with coagulation factors) and not treated bleeds. Bleeds due to surgery/procedure were excluded. Intra-participant comparison of ABR of all bleeds prior to study entry, while receiving prophylactic bypassing agents during NIS BH29768 (Arm Cnis), with ABR of all bleeds on emicizumab prophylaxis (in this study) (Arm C) was reported. Arm C NIS population included all Arm C participants who participated in NIS BH29768 before study entry and received prophylactic bypassing agents during NIS BH29768.

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

End point timeframe:

For Arm Cnis: up to 52 weeks before study entry (assessed retrospectively at baseline); for Arm C: From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm C (Prophylactic Treatment): Emicizumab | Arm Cnis: Prophylactic Bypassing Agents in NIS BH29768 | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 24 | 24 | | |
| Units: all bleeds per year | | | | |
| number (confidence interval 95%) | 5.5 (2.98 to 10.26) | 24.3 (18.11 to 32.67) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

This intra-participant comparison of ABR for all bleeds was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm Cnis) and on study (Arm C).

| | |
|---|---|
| Comparison groups | Arm C (Prophylactic Treatment): Emicizumab v Arm Cnis: Prophylactic Bypassing Agents in NIS BH29768 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[12] |
| Method | Non-Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.119 |
| upper limit | 0.435 |

Notes:

[12] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms C and Cnis: ABR for Treated Bleeds

| | |
|-----------------|---|
| End point title | Arms C and Cnis: ABR for Treated Bleeds ^[13] |
|-----------------|---|

End point description:

Number of treated bleeds over the efficacy period was assessed through ABR using an NB regression model. Treated bleeds were defined as a bleed for which coagulation factors were administered. Bleeds due to surgery/procedure were excluded. Intra-participant comparison of ABR of treated bleeds prior to study entry, while receiving prophylactic bypassing agents during NIS BH29768 (Arm Cnis), with ABR of treated bleeds on emicizumab prophylaxis (in this study) (Arm C) was reported. Arm C NIS population included all Arm C participants who participated in NIS BH29768 before study entry and received prophylactic bypassing agents during NIS BH29768.

| | | | | |
|--|--|--|--|--|
| End point type | Secondary | | | |
| End point timeframe: | | | | |
| For Arm Cnis: up to 52 weeks before study entry (assessed retrospectively at baseline); for Arm C: From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year) | | | | |
| 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 endpoint is applicable only for the reported arms; hence, other arms are not included. | | | | |
| End point values | Arm C (Prophylactic Treatment): Emicizumab | Arm Cnis: Prophylactic Bypassing Agents in NIS BH29768 | | |
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 24 | 24 | | |
| Units: treated bleeds per year | | | | |
| number (confidence interval 95%) | 3.3 (1.33 to 8.08) | 15.7 (11.08 to 22.29) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| This intra-participant comparison of ABR for treated bleeds between arms was performed using an NB regression model. There was a total of 24 participants (not 48) analyzed over two different periods: before study entry (Arm Cnis) and on study (Arm C). | |
| Comparison groups | Arm C (Prophylactic Treatment): Emicizumab v Arm Cnis: Prophylactic Bypassing Agents in NIS BH29768 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 ^[14] |
| Method | Non-Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.089 |
| upper limit | 0.486 |

Notes:

[14] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms A and B: ABR for Treated Spontaneous Bleeds

| | |
|--|--|
| End point title | Arms A and B: ABR for Treated Spontaneous Bleeds ^[15] |
| End point description: | |
| Number of treated spontaneous bleeds over the efficacy period was assessed through ABR using an NB regression model. Treated spontaneous bleeds were defined as treated (with coagulation factors) bleeds with no known contributing factor (e.g., trauma, surgery). ITT population. | |
| End point type | Secondary |

End point timeframe:

From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 18 | | |
| Units: treated spontaneous bleeds per year | | | | |
| number (confidence interval 95%) | 1.3 (0.73 to 2.19) | 16.8 (9.94 to 28.30) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization

| | |
|---|--|
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[16] |
| Method | Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.037 |
| upper limit | 0.154 |

Notes:

[16] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arms A and B: ABR for Treated Target Joint Bleeds

| | |
|-----------------|---|
| End point title | Arms A and B: ABR for Treated Target Joint Bleeds ^[17] |
|-----------------|---|

End point description:

Number of treated target joint bleeds over the efficacy period was assessed through ABR using an NB regression model. Treated target joint bleeds included treated (with coagulation factors) joint bleeds in a target joint, defined as a joint in which greater than or equal to (>=) 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. Bleeds due to surgery/procedure are excluded. ITT population.

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

End point timeframe:

From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 18 | | |
| Units: treated target joint bleeds per year | | | | |
| number (confidence interval 95%) | 0.1 (0.03 to 0.58) | 3.0 (0.96 to 9.13) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|--|--|
| Statistical analysis description: | |
| Analysis was performed using an NB regression model, which accounted for different follow-up times, with the participant's number of bleeds as a function of randomization and the time that each participant stays in the study included as an offset in the model. The model also included the number of bleeds (<9 or >=9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. | |
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 ^[18] |
| Method | Stratified Wald Test |
| Parameter estimate | ABR Ratio |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.009 |
| upper limit | 0.227 |

Notes:

[18] - Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure.

Secondary: Arm A and B: Hemophilia-Specific Quality of Life (Haem-A-QoL) Questionnaire Physical Health Score in Adult Participants (>=18 Years Old)

| | |
|-----------------|--|
| End point title | Arm A and B: Hemophilia-Specific Quality of Life (Haem-A-QoL) Questionnaire Physical Health Score in Adult Participants (>=18 Years Old) ^[19] |
|-----------------|--|

End point description:

Haem-A-QoL questionnaire has been developed and used in hemophilia A participants. As a hemophilia-specific questionnaire, this measure assesses very specific aspects of dealing with hemophilia. This questionnaire consists of items pertaining to 10 domains specific to living with hemophilia. The 10 domains are: physical health, sports and leisure, school and work, dealing with hemophilia, family

planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain range from 0 to 100 with lower scores reflective of better quality of life. Physical Health domain score is reported. Physical Health domain score is reported (range 0 to 100, with lower scores reflective of better physical health). ITT population. Number of subjects analyzed=participants with available data for this endpoint.

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

End point timeframe:

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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 14 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 30.19 (± 26.59) | 57.14 (± 23.35) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Actual number of participants included for inferential statistics in Arm A is 25. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term. Analysis was performed using Analysis of Covariance (ANCOVA).

| | |
|---|--|
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0029 ^[20] |
| Method | ANCOVA |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | 21.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.89 |
| upper limit | 35.22 |

Notes:

[20] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Secondary: Arm A and B: Haem-A-QoL Questionnaire Total Score in Adult Participants (>/=18 Years Old)

| | |
|-----------------|---|
| End point title | Arm A and B: Haem-A-QoL Questionnaire Total Score in Adult Participants (>/=18 Years Old) ^[21] |
|-----------------|---|

End point description:

Haem-A-QoL questionnaire has been developed and used in hemophilia A participants. As a hemophilia-specific questionnaire, this measure assesses very specific aspects of dealing with hemophilia. This questionnaire consists of items pertaining to 10 domains specific to living with hemophilia. The 10 domains are: physical health, sports and leisure, school and work, dealing with hemophilia, family planning, feeling, relationships, treatment, view of yourself, and outlook for the future. The total score for each domain range from 0 to 100 with lower scores reflective of better quality of life. Haem-A-QoL Questionnaire Total Score is the average of the all domain scores and range from 0 to 100, with lower scores reflective of better quality of life. ITT population. Number of subjects analyzed=participants with available data for this endpoint.

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

End point timeframe:

Week 25

Notes:

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

Justification: The endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 14 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 26.465 (\pm 18.666) | 47.504 (\pm 17.435) | | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Actual number of participants included for inferential statistics in Arm A is 25. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term.

| | |
|---|--|
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0019 ^[22] |
| Method | ANCOVA |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | 14.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.56 |
| upper limit | 22.45 |

Notes:

[22] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Secondary: Arm A and B: European Quality of Life-5 Dimensions-5 Levels (EQ-5D-

5L) Visual Analog Scale Score

| | |
|-----------------|--|
| End point title | Arm A and B: European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analog Scale Score ^[23] |
|-----------------|--|

End point description:

EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L Visual Analog Scale. The Visual Analogue Scale is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. ITT population. Number of subjects analyzed=participants with available data for this endpoint.

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

End point timeframe:

Week 25

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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 16 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 83.8 (± 12.9) | 76.4 (± 15.7) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Actual number of participants included for inferential statistics in Arm A is 29. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term.

| | |
|---|--|
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0171 ^[24] |
| Method | ANCOVA |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | -9.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.62 |
| upper limit | -1.82 |

Notes:

[24] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Secondary: Arm A and B: EQ-5D-5L Index Utility Score

| | |
|---|---|
| End point title | Arm A and B: EQ-5D-5L Index Utility Score ^[25] |
| End point description: | |
| EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L Visual Analog Scale. The EQ-5D-5L health state profile is designed to record the participant's current health state in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses from the five domains are used to calculate a single utility index value ranging from 1 to 5, where 1 indicates better health state (no problems) and 5 indicates worst health state (confined to bed). ITT population. Number of subjects analyzed=participants with available data for this endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 25 | |

Notes:

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

Justification: The endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 16 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.83 (± 0.22) | 0.60 (± 0.35) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Actual number of participants included for inferential statistics in Arm A is 29. Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term. | |
| Comparison groups | Arm A (Episodic Treatment): Emicizumab v Arm B (Episodic Treatment): No Emicizumab |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0014 ^[26] |
| Method | ANCOVA |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.25 |
| upper limit | -0.07 |

Notes:

[26] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Secondary: Arm A and B: Hemophilia-Specific Quality of Life – Short Form (Haemo-QoL-SF) Questionnaire Total Score in Adolescents Participants (12-17 Years Old)

| | |
|-----------------|--|
| End point title | Arm A and B: Hemophilia-Specific Quality of Life – Short Form (Haemo-QoL-SF) Questionnaire Total Score in Adolescents Participants (12-17 Years Old) ^[27] |
|-----------------|--|

End point description:

The Haemo-QoL-SF contains 35 items, which cover nine domains considered relevant for the children's health-related quality of life (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated with five respective response options: never, seldom, sometimes, often, and always. Haemo-QoL-SF total score range from 0 to 100, where lower scores reflect better health-related quality of life. Data for this outcome was to be analyzed only if >3 participant (in each arm) have available data. ITT population. Number of subjects analyzed=participants with available data for this endpoint. Here, '99999' represents data not analysed as the criterion for data analysis not met. Data was to be analyzed only if >3 participants have available data.

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

End point timeframe:

Week 25

Notes:

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

Justification: The endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 2 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Emicizumab Antibodies

| | |
|-----------------|--|
| End point title | Percentage of Participants With Anti-Emicizumab Antibodies ^[28] |
|-----------------|--|

End point description:

All emicizumab participants, referred to as all participants 2, included Arms A, C, and D and Arm B participants who switched to receive emicizumab (Arm Bemis). Number of subjects analyzed=participants with at least one post-baseline antibody assessment.

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

End point timeframe:

Baseline up to approximately 1 year

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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm C (Prophylactic Treatment): Emicizumab | Arm D (Episodic or Prophylactic Treatment): Emicizumab | Arm Bemis: Emicizumab after Week 24 |
|-----------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 33 | 49 | 6 | 8 |
| Units: percentage of participants | | | | |
| number (not applicable) | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Trough Concentration of Emicizumab

| | |
|---|---|
| End point title | Plasma Trough Concentration of Emicizumab ^[29] |
| End point description: | |
| Plasma concentrations of emicizumab were analyzed using a validated Enzyme Linked Immunosorbent Assay (ELISA). The lower limit of quantification (LLOQ) was 100 nanograms per milliliter (ng/mL). Pharmacokinetic (PK) evaluable population included all participants who received at least one dose of emicizumab and had at least one post-dose emicizumab concentration result. Here, n=participants with available data for this endpoint at specified timepoints, each arm, respectively. Here, '99999' represents data not calculable due to single participant; '9999' represents data collection not planned for this arm at this time-point; and '999' represents no data available as the measurements were below LLOQ. | |
| End point type | Secondary |
| End point timeframe: | |
| Arm A: Pre-dose (0 hour [hr]) on Weeks 1-5, 7, 9, 13, 17, 21, 25, 33, 41, 49; Arm B: Pre-dose (0 hr) on Weeks 25-29, 31, 33, 37, 41; Arm C: Pre-dose (0 hr) on Weeks 1-5, 7, 9, 13, 17, 21, 25, 33, 41; Arm D: Pre-dose (0 hr) on Weeks 1-5, 7, 9, 13 | |

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 endpoint is applicable only for the reported arms; hence, other arms are not included.

| End point values | Arm A (Episodic Treatment): Emicizumab | Arm C (Prophylactic Treatment): Emicizumab | Arm D (Episodic or Prophylactic Treatment): Emicizumab | Arm Bemis: Emicizumab after Week 24 |
|---|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 34 | 48 | 7 | 13 |
| Units: micrograms per milliliter (mcg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=33, 0, 48, 7) | 999 (± 999) | 999 (± 999) | 999 (± 999) | 9999 (± 9999) |
| Week 2 (n=34, 0, 47, 6) | 16.2 (± 4.4) | 15.7 (± 5.6) | 19.8 (± 7.2) | 9999 (± 9999) |
| Week 3 (n=34, 0, 48, 7) | 31.6 (± 7.3) | 31.4 (± 8.5) | 34.7 (± 15.3) | 9999 (± 9999) |
| Week 4 (n=32, 0, 47, 7) | 43.8 (± 12.2) | 44.4 (± 11.7) | 53.0 (± 13.0) | 9999 (± 9999) |
| Week 5 (n=33, 0, 46, 6) | 53.5 (± 15.1) | 54.0 (± 13.2) | 65.8 (± 13.1) | 9999 (± 9999) |
| Week 7 (n=33, 0, 46, 4) | 52.8 (± 16.2) | 53.6 (± 14.3) | 58.2 (± 9.1) | 9999 (± 9999) |
| Week 9 (n=32, 0, 40, 3) | 50.4 (± 12.4) | 54.4 (± 15.6) | 67.0 (± 10.2) | 9999 (± 9999) |
| Week 13 (n=32, 0, 34, 1) | 49.3 (± 13.4) | 53.8 (± 14.9) | 63.6 (± 99999) | 9999 (± 9999) |
| Week 17 (n=32, 0, 27, 0) | 50.7 (± 15.0) | 51.9 (± 12.4) | 9999 (± 9999) | 9999 (± 9999) |
| Week 21 (n=32, 0, 22, 0) | 52.6 (± 17.4) | 53.2 (± 14.5) | 9999 (± 9999) | 9999 (± 9999) |

| | | | | |
|---------------------------|----------------|---------------|---------------|----------------|
| Week 25 (n=30, 13, 19, 0) | 54.9 (± 19.3) | 47.3 (± 10.2) | 9999 (± 9999) | 999 (± 999) |
| Week 26 (n=0, 12, 0, 0) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 22.6 (± 12.5) |
| Week 27 (n=0, 13, 0, 0) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 32.2 (± 12.3) |
| Week 28 (n=0, 13, 0, 0) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 46.1 (± 21.6) |
| Week 29 (n=0, 13, 0, 0) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 54.1 (± 15.8) |
| Week 31 (n=0, 10, 0, 0) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 55.2 (± 22.7) |
| Week 33 (n=13, 7, 10, 0) | 52.7 (± 19.3) | 54.0 (± 19.0) | 9999 (± 9999) | 54.6 (± 23.6) |
| Week 37 (n=0, 3, 0, 0) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | 53.6 (± 19.0) |
| Week 41 (n=3, 1, 4, 0) | 44.2 (± 16.8) | 51.9 (± 6.6) | 9999 (± 9999) | 46.0 (± 99999) |
| Week 49 (n=1, 0, 0, 0) | 32.5 (± 99999) | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to clinical cut-off date (25 Oct 2016) (up to approximately 1 year)

Adverse event reporting additional description:

Safety population 1 included for Arms A, C, and D, all participants who received at least one dose of emicizumab, and for Arm B, all participants who started the study period. Safety population 2 is exactly the same for Arms A, C, and D, but for Arm B it included only participants who received at least one dose of emicizumab (Arm Bemis).

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Arm A (Episodic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received episodic treatment with bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive episodic bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|-----------------------|---|
| Reporting group title | Arm B (Episodic Treatment): No Emicizumab |
|-----------------------|---|

Reporting group description:

Participants, who received episodic treatment with bypassing agents prior to study entry, did not receive emicizumab prophylaxis. Participants in this arm could switch to emicizumab prophylaxis after completing at least 24 weeks on study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC. Data reported for this arm represents data collected from all Arm B participants during 'no emicizumab' treatment; data from those participants who switched to emicizumab after at least 24 weeks is reported separately in Arm Bemis.

| | |
|-----------------------|--|
| Reporting group title | Arm C (Prophylactic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received prophylactic bypassing agents prior to study entry, received prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|-----------------------|--|
| Reporting group title | Arm D (Episodic or Prophylactic Treatment): Emicizumab |
|-----------------------|--|

Reporting group description:

Participants, who received episodic bypassing agents prior to study entry, who participated in Study BH29768 but were unable to enroll in Arms A or B, were enrolled in this arm to receive prophylactic emicizumab. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Participants continued to receive bypassing agent therapy to treat breakthrough bleeds, with rFVIIa and/or aPCC.

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Arm Bemis: Emicizumab after Week 24 |
|-----------------------|-------------------------------------|

Reporting group description:

This arm includes Arm B participants who switched to emicizumab prophylaxis after completing at least 24-week no prophylaxis. Emicizumab was administered at a loading dose of 3 mg/kg/week SC for the first 4 weeks (after at least 24 weeks) followed by a maintenance dose of 1.5 mg/kg/week SC up to the end of study. Data reported represents data collected during emicizumab treatment only.

| Serious adverse events | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | Arm C (Prophylactic Treatment): Emicizumab |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 4 / 18 (22.22%) | 4 / 49 (8.16%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 18 (5.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 18 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 18 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 18 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 18 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 18 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 18 (5.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 18 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 18 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 18 (11.11%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 18 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cavernous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 18 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 18 (5.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 18 (5.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 18 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 18 (5.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Arm D (Episodic or Prophylactic Treatment): Emicizumab | Arm Bemis: Emicizumab after Week 24 | |
|---|--|-------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 13 (7.69%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---------------|----------------|--|
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin necrosis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle haemorrhage | | | |

| | | | |
|---|---------------|----------------|--|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cavernous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm A (Episodic Treatment): Emicizumab | Arm B (Episodic Treatment): No Emicizumab | Arm C (Prophylactic Treatment): Emicizumab |
|---|---|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 34 (64.71%) | 8 / 18 (44.44%) | 15 / 49 (30.61%) |
| Investigations | | | |
| Blood glucose increased | | | |

| | | | |
|--|-----------------------|---------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Post procedural constipation subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Procedural hypotension subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Procedural nausea subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Procedural pain subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Vascular disorders | | | |
| Deep vein thrombosis subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 0 / 18 (0.00%) 0 | 5 / 49 (10.20%) 6 |
| General disorders and administration site conditions | | | |
| Chest pain subjects affected / exposed occurrences (all) | 1 / 34 (2.94%) 1 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 0 / 18 (0.00%) 0 | 2 / 49 (4.08%) 2 |
| Injection site reaction subjects affected / exposed occurrences (all) | 8 / 34 (23.53%) 15 | 0 / 18 (0.00%) 0 | 5 / 49 (10.20%) 11 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |

| | | | |
|---|--|--|--|
| Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Enteritis subjects affected / exposed occurrences (all) Large intestine polyp subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 2 / 34 (5.88%) 2 0 / 34 (0.00%) 0 2 / 34 (5.88%) 2 | 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 3 0 / 34 (0.00%) 0 | 0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Hair growth abnormal subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 0 / 34 (0.00%) 0 | 0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia | 2 / 34 (5.88%) 3 | 0 / 18 (0.00%) 0 | 3 / 49 (6.12%) 6 |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 0 / 18 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Infections and infestations | | | |
| Folliculitis | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 18 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 18 (11.11%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 34 (20.59%) | 3 / 18 (16.67%) | 2 / 49 (4.08%) |
| occurrences (all) | 9 | 3 | 2 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 18 (5.56%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 18 (5.56%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|--|-------------------------------------|--|
| Non-serious adverse events | Arm D (Episodic or Prophylactic Treatment): Emicizumab | Arm Bemis: Emicizumab after Week 24 | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 4 / 13 (30.77%) | |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Post procedural constipation | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Procedural hypotension | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Procedural nausea | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Procedural pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Vascular disorders Deep vein thrombosis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 1 / 13 (7.69%) 1 | |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Injection site reaction subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 13 (7.69%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Enteritis | | | |

| | | | |
|--|--------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Large intestine polyp subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Hair growth abnormal subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Infections and infestations Folliculitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |

| | | | |
|---|--------------------|---------------------|--|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |
| Electrolyte imbalance subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 13 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 21 April 2016 | <p>The main changes were as follows:</p> <ul style="list-style-type: none">- The planned number of participants to be enrolled in Arm C was increased from approximately 10-20 to 30-50, to enable the collection of additional safety and efficacy data from participants previously treated with prophylactic bypassing agents;- An additional emicizumab treatment arm (Arm D) was added, to enroll participants on episodic bypassing agents who had participated in NIS BH29768 but were unable to enroll in time to either Arm A or Arm B. This arm enabled the collection of additional efficacy, safety, pharmacokinetic, and pharmacodynamic data and plasma samples for the development and validation of in vitro diagnostic assay(s) suitable for participants receiving emicizumab treatment;- A secondary endpoint was added to compare all bleeds (i.e., treated with coagulation factors or not treated) as an additional assessment of efficacy given that some participants might have reported bleeds they did not treat;- A planned interim analysis by the independent Data Monitoring Committee (iDMC), scheduled to occur during the execution of the primary efficacy period, was removed. This was due to the anticipated rapid completion of enrollment (i.e., approximately 7 months) and the very short time interval between the interim and primary analyses;- An option was provided for participants who were approved to up-titrate their dose to potentially combine emicizumab volumes from more than 1 vial into 1 syringe to reduce the number of subcutaneous injections they required. |
| 30 November 2016 | <p>The main changes were as follows:</p> <ul style="list-style-type: none">- The permitted treatment for breakthrough bleeds was specified with guidance regarding the use of concomitant bypassing agents in participants being treated with emicizumab, as well as additional local and central laboratory assessments, in order to minimize the risk and monitor for thromboembolic and thrombotic microangiopathy events;- The use of short-term prophylaxis with aPCC concomitantly with emicizumab was prohibited, in order to minimize the risk of thromboembolic and thrombotic microangiopathy events;- Microangiopathic hemolytic anemia/ thrombotic microangiopathy was newly classified as an adverse event of special interest (AESI), and an exclusion criterion to exclude participants at high risk to experience thrombotic microangiopathy was added;- A new efficacy objective to evaluate the clinical effect of emicizumab prophylaxis on the number of spontaneous bleeds over time (spontaneous bleed rate) was added, because this is a bleed category that is impacted by an effective treatment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|---|------------------|
| 07 October 2016 | 4 participants experienced serious adverse events (2 participants experienced thromboembolic events and 2 participants experienced thrombotic microangiopathy) that resulted in temporary enrollment halt until further evaluation of these safety events, implementation of adequate mitigation measures and discussion with iDMC. | 28 November 2016 |

Notes:

Limitations and caveats

None reported