Clinical trial results:
A Phase IV, Multicenter, Single-Arm, Open-Label Study of Emicizumab Prophylaxis in Patients with Hemophilia A With or Without Inhibitors Undergoing Minor Surgical Procedures

Summary

EudraCT number	2020-005916-23
Trial protocol	Outside EU/EEA
Global end of trial date	13 March 2020

Results information

Result version number	v1 (current)
This version publication date	22 February 2021
First version publication date	22 February 2021

Trial information

Trial identification

Sponsor protocol code	ML39791

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03361137
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2020
Global end of trial reached?	Yes
Global end of trial date	13 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of emicizumab in preventing surgery-related bleeding in patients with hemophilia A (PwHA) with and without inhibitors undergoing minor surgical procedures.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2018
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	United States: 14
Worldwide total number of subjects	14
EEA total number of subjects	0

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 14 participants were enrolled in the study.

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	PwHA With Inhibitors, Emicizumab: Surgery Not Performed

Arm description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled but did not have surgery. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

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

Dosage and administration details:

Participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery. Dosing was to be adjusted if the participant had a significant change in body weight.

Arm title	PwHA With Inhibitors, Emicizumab: CVAD Removal

Arm description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

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

Dosage and administration details:

Participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5

mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery. Dosing was to be adjusted if the participant had a significant change in body weight.

Arm title	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction

Arm description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

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

Dosage and administration details:

Participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery. Dosing was to be adjusted if the participant had a significant change in body weight.

Arm title	PwHA Without Inhibitors, Emicizumab: CVAD Removal

Arm description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

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

Dosage and administration details:

Participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery. Dosing was to be adjusted if the participant had a significant change in body weight.

Arm title	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction

Arm description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

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

Dosage and administration details:

Participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery. Dosing was to be adjusted if the participant had a significant change in body weight.

Number of subjects in period 1	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction
Started	1	9	1
Completed	0	9	1
Not completed	1	0	0
Reason not specified	1	-	-

Number of subjects in period 1	PwHA Without Inhibitors, Emicizumab: CVAD Removal	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction
Started	2	1
Completed	2	1
Not completed	0	0
Reason not specified	-	-

Baseline characteristics

Reporting groups

Reporting group title	PwHA With Inhibitors, Emicizumab: Surgery Not Performed

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled but did not have surgery. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA With Inhibitors, Emicizumab: CVAD Removal

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA Without Inhibitors, Emicizumab: CVAD Removal

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group values	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction
Number of subjects	1	9	1
Age Categorical Units: Participants			
<18 Years Old	1	7	1
≥18 to <65 Years Old	0	2	0

Sex: Female, Male Units: Participants			
Female	0	0	0
Male	1	9	1
Race/Ethnicity, Customized Units: Subjects			
Asian	0	1	0
Black or African American	1	0	0
White	0	5	1
Multiple	0	2	0
Unknown	0	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	3	1
Not Hispanic or Latino	1	6	0
Unknown or Not Reported	0	0	0

Reporting group values	PwHA Without Inhibitors, Emicizumab: CVAD Removal	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction	Total
Number of subjects	2	1	14
Age Categorical Units: Participants			
<18 Years Old	2	0	11
≥18 to <65 Years Old	0	1	3
Sex: Female, Male Units: Participants			
Female	0	0	0
Male	2	1	14
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	1
Black or African American	0	1	2
White	1	0	7
Multiple	0	0	2
Unknown	1	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	5
Not Hispanic or Latino	1	1	9
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	PwHA With Inhibitors, Emicizumab: Surgery Not Performed

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled but did not have surgery. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA With Inhibitors, Emicizumab: CVAD Removal

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA Without Inhibitors, Emicizumab: CVAD Removal

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Subject analysis set title	PwHA With Inhibitors, Emicizumab: All Surgery Cohorts
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set included all participants with Hemophilia A (PwHA) with inhibitors who had undergone surgery. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Subject analysis set title	PwHA Without Inhibitors, Emicizumab: All Surgery Cohorts
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set included all participants with Hemophilia A (PwHA) without inhibitors who had undergone surgery. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Primary: Percentage of Participants Without Excessive Bleeding at Surgical Sites and Did Not Require BPA/FVIII Use for Bleeding Related to the Surgery, From the Start of Surgery Until Discharge, as Measured by the ISTH Hemostatic Efficacy Scale

End point title	Percentage of Participants Without Excessive Bleeding at Surgical Sites and Did Not Require BPA/FVIII Use for Bleeding Related to the Surgery, From the Start of Surgery Until Discharge, as Measured by the ISTH Hemostatic Efficacy Scale[1]

End point description:

The International Society on Thrombosis and Haemostasis (ISTH) Assessment of Hemostatic Response for Surgical Procedures scale (see reference PubMed ID:25059285) has four categories, listed here in order of best to worst response: Excellent, Good, Fair, and Poor. The participant's bleeding related to surgery was evaluated by the healthcare professional who performed the procedure using the hemostatic efficacy scale, with an absence of excessive bleeding at the surgical site indicated by a good to excellent rating. The endpoint was met when the response to "Intraoperative and/or postoperative blood loss increased over expectation for the non-hemophilic patient determined at the time of discharge" was "0 to <10%" or "10% to < 25%" AND the response to the question "Did the patient use any bypassing agent (BPA)/factor VIII (FVIII) for the surgery before the discharge?" was "No".

End point type	Primary

End point timeframe:

Determined at the time of discharge (within approximately 48 hours after surgery)

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 statistical hypothesis was to be tested, and only descriptive summaries were to be presented for the data collected in this study.

End point values	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction	PwHA Without Inhibitors, Emicizumab: CVAD Removal
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	9	1	2
Units: Percentage of participants				
number (not applicable)		66.7	100.0	100.0

Notes:

[2] - Subject was excluded from analysis because they did not have surgery.

End point values	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of participants				
number (not applicable)	100.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Excessive Bleeding at Surgical Sites and Required BPA/FVIII Use for Treating Bleeding Related to the Surgery, From the Start of Surgery Until Discharge, as Measured by the ISTH Hemostatic Efficacy Scale

End point title	Percentage of Participants With Excessive Bleeding at Surgical Sites and Required BPA/FVIII Use for Treating Bleeding Related to the Surgery, From the Start of Surgery Until Discharge, as Measured by the ISTH Hemostatic Efficacy Scale[3]

End point description:

The ISTH Assessment of Hemostatic Response for Surgical Procedures scale (see reference PubMed ID:25059285) has four categories, listed here in order of best to worst response: Excellent, Good, Fair, and Poor. The participant's bleeding related to surgery was evaluated by the healthcare professional who performed the procedure using the hemostatic efficacy scale, with excessive bleeding at the surgical site indicated by a fair to poor rating. The endpoint was met when the response to "Intraoperative and/or postoperative blood loss increased over expectation for the non-hemophilic patient determined at the time of discharge" was "25% to <50%" or "≥50%" AND the response to the question "Did the patient use any bypassing agent (BPA)/factor VIII (FVIII) for the surgery before the discharge?" was "Yes". The percentage of participants by type and dose of BPA/FVIII used to treat the bleeding is also reported. rFVIIa = recombinant activated human factor VII (eptacog alfa [activated])

End point type	Primary

End point timeframe:

Determined at the time of discharge (within approximately 48 hours after surgery)

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 statistical hypothesis was to be tested, and only descriptive summaries were to be presented for the data collected in this study.

End point values	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction	PwHA Without Inhibitors, Emicizumab: CVAD Removal
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[4]	9	1	2
Units: Percentage of participants				
number (not applicable)				
Total with Excessive Bleeding and BPA/FVIII Use		11.1	0.0	0.0
Treated with 2 mg rFVIIa		11.1	0.0	0.0

Notes:

[4] - Subject was excluded from analysis because they did not have surgery.

End point values	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of participants				
number (not applicable)				
Total with Excessive Bleeding and BPA/FVIII Use	0.0			
Treated with 2 mg rFVIIa	0.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who, After Being Discharged from Surgery, Experienced Bleeds That Were Either Related or Unrelated to Surgery and Also Required BPA/FVIII Use

End point title	Percentage of Participants Who, After Being Discharged from Surgery, Experienced Bleeds That Were Either Related or Unrelated to Surgery and Also Required BPA/FVIII Use[5]

End point description:

Post-surgical bleeding information was self-reported by participants (or the participant's legally authorized representative) on the "Bleed and Medication Diary". Bypassing agents (BPAs)/factor VIII (FVIII) used to treat excessive bleeding were also self-reported by participants if it was self-administered. BPAs/FVIII administered by the investigators to treat the bleeding were reported on the "Concomitant Medications" case report form page. The percentage of participants by type and dose of BPA/FVIII used to treat the bleeding is also reported. rFVIIa = recombinant activated human factor VII (eptacog alfa [activated])

End point type	Primary

End point timeframe:

Within 48 hours (if discharged home), and 8 and 28 days after surgery

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 statistical hypothesis was to be tested, and only descriptive summaries were to be presented for the data collected in this study.

End point values	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction	PwHA Without Inhibitors, Emicizumab: CVAD Removal
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	9	1	2
Units: Percentage of participants				
number (not applicable)				
Total with Post-surgical Bleeding & BPA/FVIII Use		22.2	100.0	0.0
Treated with 2 mg rFVIIa		11.1	100.0	0.0
Treated with 5 mg rFVIIa		11.1	0.0	0.0

Notes:

[6] - Subject was excluded from analysis because they did not have surgery.

End point values	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of participants				

number (not applicable)				
Total with Post-surgical Bleeding & BPA/FVIII Use	0.0			
Treated with 2 mg rFVIIa	0.0			
Treated with 5 mg rFVIIa	0.0			

Statistical analyses

No statistical analyses for this end point

Primary: Emicizumab Plasma Concentration on the Day of Surgery

End point title	Emicizumab Plasma Concentration on the Day of Surgery[7]

End point description:

Enrolled participants received a minimum of four loading doses of emicizumab prior to their surgical procedure. Pharmacokinetic blood samples were obtained at study sites 24 hours before the procedures in order to describe emicizumab plasma concentration on the day of surgery for each of the inhibitor and non-inhibitor cohorts.

End point type	Primary

End point timeframe:

Approximately 24 hours prior to surgery

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 statistical hypothesis was to be tested, and only descriptive summaries were to be presented for the data collected in this study.

End point values	PwHA With Inhibitors, Emicizumab: All Surgery Cohorts	PwHA Without Inhibitors, Emicizumab: All Surgery Cohorts		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	3		
Units: micrograms per millilitre (µg/mL)				
arithmetic mean (standard deviation)	53.74 (± 28.67)	38.40 (± 8.95)		

Statistical analyses

No statistical analyses for this end point

Primary: Safety Summary of the Number of Participants with at Least One Adverse Event

End point title	Safety Summary of the Number of Participants with at Least One Adverse Event[8]

End point description:

All adverse events (AEs) that occurred after informed consent was obtained were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.0, summarized by severity according to the World Health Organization (WHO) toxicity grading scale (Grade 1 is mild; Grade 2 is moderate; Grade 3 is severe; Grade 4 is life-threatening; and Grade 5 is death related to AE), and tabulated by body system and preferred term (PT) for individual events within each system organ class (SOC). For each AE, the investigator independently assessed its severity and seriousness, and whether it was considered

to be related to the study drug. Mod. = modification

End point type	Primary

End point timeframe:

From Baseline up to 30 days after surgery

Notes:

[8] - 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 statistical hypothesis was to be tested, and only descriptive summaries were to be presented for the data collected in this study.

End point values	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction	PwHA Without Inhibitors, Emicizumab: CVAD Removal
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	9	1	2
Units: Participants				
Any Adverse Event (AE)	1	4	0	0
AE with Fatal Outcome	0	0	0	0
Serious Adverse Event (SAE)	0	0	0	0
SAE Leading to Withdrawal from Treatment	0	0	0	0
SAE Leading to Dose Modification/Interruption	0	0	0	0
Related SAE	0	0	0	0
AE Leading to Withdrawal from Treatment	0	0	0	0
AE Leading to Dose Modification/Interruption	0	0	0	0
Related AE	0	0	0	0
Related AE Leading to Withdrawal from Treatment	0	0	0	0
Related AE Leading to Dose Mod./Interruption	0	0	0	0
Grade 3–5 AE	0	0	0	0

End point values	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants				
Any Adverse Event (AE)	0			
AE with Fatal Outcome	0			
Serious Adverse Event (SAE)	0			
SAE Leading to Withdrawal from Treatment	0			
SAE Leading to Dose Modification/Interruption	0			
Related SAE	0			
AE Leading to Withdrawal from Treatment	0			

AE Leading to Dose Modification/Interruption	0			
Related AE	0			
Related AE Leading to Withdrawal from Treatment	0			
Related AE Leading to Dose Mod./Interruption	0			
Grade 3–5 AE	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Surgical Complications Requiring Hospitalization or Return to Surgery

End point title	Percentage of Participants with Surgical Complications Requiring Hospitalization or Return to Surgery[9]

End point description:

This safety endpoint was a composite endpoint. Surgical complications were entered as adverse events on the case report form page with “Other suspected causes” marked as “Study Surgery or Procedure”. This endpoint was met when response to "It required or prolonged inpatient hospitalization” was checked OR response to “Was procedure/surgery performed?” was “Yes”.

End point type	Primary

End point timeframe:

Within 48 hours after surgery, and 8 and 28 days after initial surgery

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 statistical hypothesis was to be tested, and only descriptive summaries were to be presented for the data collected in this study.

End point values	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction	PwHA Without Inhibitors, Emicizumab: CVAD Removal
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[10]	9	1	2
Units: Percentage of participants				
number (not applicable)		0.0	0.0	0.0

Notes:

[10] - Subject was excluded from analysis because they did not have surgery.

End point values	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants who Needed Blood/Blood Product Transfusions During Surgery

End point title	Percentage of Participants who Needed Blood/Blood Product Transfusions During Surgery[11]

End point description:

The percentage of participants who needed blood or blood product transfusions (e.g., platelets, plasma, etc.) during surgery was evaluated.

End point type	Primary

End point timeframe:

Within 48 hours after surgery, and 8 and 28 days after initial surgery

Notes:

[11] - 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 statistical hypothesis was to be tested, and only descriptive summaries were to be presented for the data collected in this study.

End point values	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction	PwHA Without Inhibitors, Emicizumab: CVAD Removal
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[12]	9	1	2
Units: Percentage of participants				
number (not applicable)		0.0	0.0	0.0

Notes:

[12] - Subject was excluded from analysis because they did not have surgery.

End point values	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 30 days after surgery

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	PwHA With Inhibitors, Emicizumab: Surgery Not Performed

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled but did not have surgery. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA With Inhibitors, Emicizumab: CVAD Removal

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) with inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA Without Inhibitors, Emicizumab: CVAD Removal

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for central venous access device (CVAD) removal. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Reporting group title	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction

Reporting group description:

This cohort included participants with Hemophilia A (PwHA) without inhibitors that were enrolled and had surgery for simple dental extraction. All participants received emicizumab via subcutaneous (SC) injection at a loading dose of 3 milligrams of medication per kilogram of body weight (mg/kg) once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continued to derive sufficient benefit. Participants must have received all loading doses prior to surgery and planned to continue emicizumab for a minimum of 1 month after surgery.

Serious adverse events	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 9 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	PwHA Without Inhibitors, Emicizumab: CVAD Removal	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	PwHA With Inhibitors, Emicizumab: Surgery Not Performed	PwHA With Inhibitors, Emicizumab: CVAD Removal	PwHA With Inhibitors, Emicizumab: Simple Dental Extraction
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	4 / 9 (44.44%)	0 / 1 (0.00%)
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 1 (100.00%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			

Adhesiolysis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 1 (100.00%)	2 / 9 (22.22%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 1 (100.00%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	PwHA Without Inhibitors, Emicizumab: CVAD Removal	PwHA Without Inhibitors, Emicizumab: Simple Dental Extraction	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 1 (0.00%)	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Surgical and medical procedures			

Adhesiolysis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 1 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 1 (0.00%) 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 1 (0.00%) 0	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 1 (0.00%) 0	
Product issues Device occlusion subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 1 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2017	Protocol Version 2: - Exclusion criteria were revised to remove the use of pre-operative anti-fibrinolytics and to expressly state allowance for use of anti-fibrinolytics in the Permitted Therapy section. This was based on exploratory data analysis of surgical procedures in HAVEN 1 and an interim analysis of HAVEN 2, which showed minimal risk in allowing pre-operative use of anti-fibrinolytics, as well as the potential to help with intra- and post-operative bleeding and avoid the use of bypassing agents for bleeding. -Throughout the protocol, references to "days" was revised to "Study Days." - Objectives and Endpoints language was revised to indicate that applicable endpoints would be determined at the time of patient discharge, rather than a specific number of days after surgery. - Language describing thrombotic microangiopathy (TMA) and thromboembolic events (TE) was revised to reflect number of patients as opposed to number of cases/events. - Protocol references to a bleed/medication questionnaire were replaced with the Bleeds and Medications Diary, to match the Case Report Form. - Language was added regarding the total number of patients in Study BH29884 who received emicizumab prior to the clinical cutoff for the primary analysis. - Language was added to clarify that all bleeds would be recorded in the Bleeds and Medications Diary. - Text was revised to clarify that after surgery, serious adverse events (SAEs) and adverse events of special interest (AESIs) would be reported until 28 days after surgery, not 28 days after the last dose of study drug. - Protocol references to "binary outcome" were revised to "binary efficacy endpoint."
15 June 2018	Protocol Version 3: -The protocol was amended primarily to clarify and differentiate between primary efficacy and safety analysis reporting. -Efficacy and safety endpoints were modified for clarity and consistency. -The background on emicizumab was updated to reflect approval by the United States Food and Drug Administration and to align with the US Package Insert (USPI). -The term "study treatment" was clarified to indicate that the Sponsor is not providing the study drug; rather, treatment with emicizumab is required for all patients during the study. -The Internal Monitoring Committee is no longer a part of the study and its description was removed from the protocol. -The maximum number of patients per procedure category was increased from 7 to 9 patients. -Inclusion criteria were clarified to indicate that patients must plan to receive at least 4 loading doses of emicizumab and have been adherent to emicizumab prophylaxis by the time of the surgery. -Language was updated to indicate that the study treatment regimen may include other approved maintenance regimens, if and when available. -Prohibited therapy was modified to clarify that use of FVIII or BPA to treat a breakthrough bleed within 24 hours prior to surgery is prohibited. -It was clarified that if the screening period extends beyond 60 days, a patient must be re-consented prior to expiration of the original 60-day screening window. Only one extension of a patient's screening period will be allowed. -Risks associated with emicizumab were updated to align with the USPI. -Language was updated to indicate that all AEs should be reported beginning from the time a patient provides informed consent until the end of the study. -Instructions regarding the reporting of overdoses, medication errors, drug abuse, or drug misuse were added. -A footnote was added to the Schedule of Activities to clarify that a patient's PK sample must be obtained at the study site 24 hours prior to surgery.

15 March 2019	Protocol Version 4: The primary reason for this amendment was to add an additional cohort of study patients: PwHA without inhibitors. -Emicizumab was approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric PwHA (congenital factor VIII deficiency) with or without factor VIII inhibitors. Because of this label change, the following updates were made: -An additional cohort of PwHA without inhibitors was added to provide prospectively collected data surrounding minor surgical procedures in this population. The Phase III trials were not designed to determine surgical outcomes from procedures that may have occurred. The study design, including the total length of the study, was updated to reflect the addition of PwHA without inhibitors. -Inclusion and exclusion criteria were updated to reflect the additional cohort and label change. -Background and other general language was updated to reflect the label change. -The length of study was corrected to begin at the time the first patient was enrolled. -Contraception requirements were updated to align with the Phase III HAVEN studies. -The timing for HIV testing was updated to within 24 weeks of enrollment. -The time window for concomitant therapy was updated to 28 days before enrollment until Study Day 28. -Height was removed as a necessary assessment. -It was clarified that biological samples will be destroyed no later than 5 years after final study results have been reported. -The Background and Safety sections of the protocol were updated with recent clinical data to align with the USPI. -A section on immunogenicity was added to align with the USPI. -The date of patient consent was clarified as the date of study enrollment. Timing for standard-of-care tests or examinations performed prior to obtaining informed consent was clarified. -The list of minor surgical procedures acceptable for entry into the study was updated to include lysis of penile adhesions.

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.

No definitive efficacy conclusions were drawn due to study limitations that included early enrollment termination, limited number of participants enrolled, and evaluation in only 2 minor surgical procedure types.

Notes: