



Clinical trial results:

An Interventional Open-Label Multicenter Phase IV Study to Evaluate the Impact of Emicizumab on Health-Related Quality of Life, Physical Activity, and Joint Health in Patients With Severe Hemophilia A Without FVIII Inhibitors in the Nordic Countries

Summary

EudraCT number	2020-003256-32
Trial protocol	SE NO FI DK
Global end of trial date	08 July 2024

Results information

Result version number	v1 (current)
This version publication date	01 January 2025
First version publication date	01 January 2025

Trial information

Trial identification

Sponsor protocol code	MO42245
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2024
Global end of trial reached?	Yes
Global end of trial date	08 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study aims to evaluate the impact of emicizumab on aspects of health-related quality of life (HRQoL) in subjects with severe hemophilia A without factor VIII (FVIII) inhibitors.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2022
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Sweden: 11
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	12
Adults (18-64 years)	16

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who completed at least 24 weeks of observation period in the non-interventional study (NIS) MO42590 took part in this study in Denmark, Finland, Norway, and Sweden from 04 April 2022 to 08 July 2024.

Pre-assignment

Screening details:

A total of 28 male adolescent and adult subjects with severe hemophilia A enrolled in this study to receive emicizumab.

Period 1

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

Arms

Arm title	Emicizumab
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Arm description:

Subjects received emicizumab, as subcutaneous (SC) injection, at a loading dose of 3 milligrams/kilograms (mg/kg), every week (QW) for 4 weeks followed by a maintenance dose of 1.5 mg/kg, QW or 3 mg/kg, every 2 weeks (Q2W) or 6 mg/kg, every 4 weeks (Q4W) for 44 weeks or until discontinuation from the study for any reason.

Arm type	Experimental
Investigational medicinal product name	Emicizumab
Investigational medicinal product code	RO5534262
Other name	Hemlibra, RG6013, ACE910
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Emicizumab, 3mg/kg, QW, as SC injection for 4 weeks followed by a maintenance dose of 1.5 mg/kg, QW or 3 mg/kg, Q2W, or 6 mg/kg (Q4W) for 44 weeks or until discontinuation from the study for any reason.

Number of subjects in period 1	Emicizumab
Started	28
Completed	26
Not completed	2
Physician decision	2

Baseline characteristics

Reporting groups

Reporting group title	Emicizumab
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Reporting group description:

Subjects received emicizumab, as subcutaneous (SC) injection, at a loading dose of 3 milligrams/kilograms (mg/kg), every week (QW) for 4 weeks followed by a maintenance dose of 1.5 mg/kg, QW or 3 mg/kg , every 2 weeks (Q2W) or 6 mg/kg, every 4 weeks (Q4W) for 44 weeks or until discontinuation from the study for any reason.

Reporting group values	Emicizumab	Total	
Number of subjects	28	28	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	28.4 ± 14.7	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	28	28	

End points

End points reporting groups

Reporting group title	Emicizumab
Reporting group description: Subjects received emicizumab, as subcutaneous (SC) injection, at a loading dose of 3 milligrams/kilograms (mg/kg), every week (QW) for 4 weeks followed by a maintenance dose of 1.5 mg/kg, QW or 3 mg/kg, every 2 weeks (Q2W) or 6 mg/kg, every 4 weeks (Q4W) for 44 weeks or until discontinuation from the study for any reason.	
Subject analysis set title	Emicizumab: Adults
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects aged ≥ 18 years received emicizumab, SC injection, at a loading dose of 3 mg/kg, QW for 4 weeks followed by a maintenance dose of 1.5 mg/kg, QW or 3 mg/kg, Q2W or 6 mg/kg, Q4W for 44 weeks or until discontinuation from the study for any reason.	
Subject analysis set title	Emicizumab: Adolescents
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects aged 12- <18 years received emicizumab, SC injection, at a loading dose of 3 mg/kg, QW for 4 weeks followed by a maintenance dose of 1.5 mg/kg, QW or 3 mg/kg, Q2W or 6 mg/kg, Q4W for 44 weeks or until discontinuation from the study for any reason.	
Subject analysis set title	FVIII Prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received FVIII prophylaxis and participated in the NIS MO42590 for up to 24 weeks.	

Primary: Change from Baseline in Risk Perception & Restrictions Experienced in Recreational Activities, Preoccupation With Disease, Impact of Treatment Burden on HRQoL & Pain Severity Assessed by Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Scores

End point title	Change from Baseline in Risk Perception & Restrictions Experienced in Recreational Activities, Preoccupation With Disease, Impact of Treatment Burden on HRQoL & Pain Severity Assessed by Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Scores ^[1]
End point description: CATCH assesses impact of hemophilia & its treatment on pediatric (8–17 years) & adult (≥ 18 years) subjects. Each version has 7 domains: daily activity risk perception (RP) & impact, social activity RP & impact, recreational activity (RA) RP & impact, work impact/school impact, preoccupation, treatment burden, & pain. Each domain has multiple items based on version used & is scored on ordinal scales with 11-point numeric rating scale for pain. Raw scores are linearly transformed on a scale of 0-100. Higher scores=higher perceived risk, higher impact & greater perceived burden of hemophilia. For adolescents higher score in treatment burden domain=lower perceived burden of hemophilia. Baseline (BL) = Week 24 assessment from NIS MO42590. Safety population. Number analysed=subjects with data available for analyses. n=subjects with data available for analyses at specified timepoints. 9999=No subjects were analysed at this timepoint.	
End point type	Primary
End point timeframe: Baseline, Week 25 and Week 49	

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: All analysis was descriptive only and no formal hypothesis testing was done.

End point values	Emicizumab: Adults	Emicizumab: Adolescents		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: score on a scale				
arithmetic mean (standard deviation)				
Rec. Activity (RA): RP - Value at BL (n=12,12)	30.65 (± 22.54)	21.46 (± 16.22)		
RA: RP - Change from BL, Week 25(n=11,11)	-2.18 (± 16.02)	0.76 (± 13.97)		
RA: RP - Change from BL, Week 49(n=11,9)	2.16 (± 14.97)	-1.36 (± 21.34)		
RA: Impact - Value at BL (n=12,12)	38.28 (± 30.15)	13.80 (± 10.98)		
RA: Impact - Change from BL, Week 25(n=11,11)	-2.92 (± 15.63)	1.55 (± 13.42)		
RA: Impact - Change from BL, Week 49(n=10,8)	-3.62 (± 15.57)	-1.15 (± 14.73)		
Preoccupation - Value at BL (n=15,12)	39.26 (± 27.21)	24.75 (± 22.80)		
Preoccupation - Change from BL, Week 25(n=15,11)	0.93 (± 20.05)	-1.45 (± 21.54)		
Preoccupation - Change from BL, Week 49(n=15,9)	-3.33 (± 14.44)	-3.67 (± 13.75)		
Treatment Burden - BL (n=15,12)	31.88 (± 24.36)	50.15 (± 22.83)		
Treatment Burden -Change from BL, Week 25(n=15,11)	-16.46 (± 22.14)	13.70 (± 19.73)		
Treatment Burden -Change from BL, Week 49(n=15,9)	-17.77 (± 21.10)	16.74 (± 15.53)		
Pain: Worst Pain - BL (n=15,0)	3.07 (± 3.45)	9999 (± 9999)		
Pain: Worst Pain - Change from BL, Week 25(n=15,0)	0.0 (± 1.73)	9999 (± 9999)		
Pain: Worst Pain - Change from BL, Week 49(n=15,0)	-0.27 (± 3.15)	9999 (± 9999)		
Pain: Least Pain - BL (n=15,0)	1.40 (± 1.76)	9999 (± 9999)		
Pain: Least Pain - Change from BL, Week 25(n=15,0)	0.67 (± 2.29)	9999 (± 9999)		
Pain: Least Pain - Change from BL, Week 49(n=15,0)	-0.53 (± 1.92)	9999 (± 9999)		
Pain: Average (Avg.) Pain - BL (n=15,0)	2.33 (± 2.66)	9999 (± 9999)		
Pain: Avg. Pain - Change from BL, Week 25(n=15,0)	-0.13 (± 0.99)	9999 (± 9999)		
Pain: Avg. Pain - Change from BL, Week 49(n=15,0)	-0.53 (± 2.13)	9999 (± 9999)		
Pain: Worst Body Hurt (WBH) - BL (n=0,12)	9999 (± 9999)	2.75 (± 1.71)		
Pain: WBH - Change from BL, Week 25(n=0,11)	9999 (± 9999)	0.18 (± 2.09)		
Pain: WBH - Change from BL, Week 49(n=0,9)	9999 (± 9999)	-0.11 (± 2.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Level of Physical Activity (PA) Assessed by Daily Step Count (DSC)

End point title	Level of Physical Activity (PA) Assessed by Daily Step Count (DSC)
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End point description:

Level of PA was measured using a Fitbit model Charge 4 and their standard algorithms for subjects aged 13 years and older (at Week 9 of this study). Subjects wore the activity tracker while they were awake every day on the same wrist. Baseline was defined as Week 9-16 assessment period of this study. Safety population included all subjects who received at least one dose of emicizumab. Number analysed included subjects who wore the device for at least 7 hours per day and with at least 100 steps recorded, on at least 21 days. n=subjects with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Weeks 9-16, Weeks 25-32 and Weeks 41-48

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: daily steps				
arithmetic mean (standard deviation)				
Week 9-16 (n=20)	8375.42 (± 3228.52)			
Week 25-32 (n=16)	8921.38 (± 2821.84)			
Week 41-48 (n=18)	8065.09 (± 3266.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of PA Assessed by Daily Active Minutes, Moderate to Vigorous Physical Activity (MVPA), and Sedentary Time

End point title	Level of PA Assessed by Daily Active Minutes, Moderate to Vigorous Physical Activity (MVPA), and Sedentary Time
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End point description:

Level of PA was measured using a Fitbit model Charge 4 and their standard algorithms for subjects aged 13 years and older (at Week 9 of this study). Subjects wore the activity tracker while they were awake every day on the same wrist. Active minutes identify the possibility of increased activity intensity. The subject must be active for at least ten minutes to earn active minutes. Intensity refers to the rate at which the activity was being performed/ the magnitude of the effort required to perform an activity/ exercise. MVPA was defined as per Fitbit default categorization. Sedentary time was calculated as time when there was no movement. Baseline was defined as Week 9-16 assessment period of this study. Safety population included all subjects who received at least one dose of emicizumab. Number analysed included subjects who wore the device for at least 7 hours per day and with at least 100 steps recorded, on at least 21 days.

End point type	Secondary
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End point timeframe:

Week 9-16, Week 25-32 and Week 41-48

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: minutes				
arithmetic mean (standard deviation)				
Daily Light PA: Week 9-16 (n=20)	189.81 (± 54.36)			
Daily Moderate PA: Week 9-16 (n=20)	29.98 (± 16.10)			
Daily Vigorous PA: Week 9-16 (n=20)	34.78 (± 19.90)			
Daily Total PA: Week 9-16 (n=20)	240.87 (± 68.26)			
Daily MVPA: Week 9-16 (n=20)	63.80 (± 26.77)			
Daily Sedentary PA: Week 9-16 (n=20)	583.33 (± 104.03)			
Daily Light PA: Week 25-32 (n=16)	213.47 (± 57.00)			
Daily Moderate PA: Week 25-32 (n=16)	32.99 (± 16.65)			
Daily Vigorous PA: Week 25-32 (n=16)	33.77 (± 17.73)			
Daily Total PA: Week 25-32 (n=16)	267.75 (± 76.92)			
Daily MVPA: Week 25-32 (n=16)	65.54 (± 30.31)			
Daily Sedentary PA: Week 25-32 (n=16)	549.19 (± 89.40)			
Daily Light PA: Week 41-48 (n=18)	199.50 (± 56.48)			
Daily Moderate PA: Week 41-48 (n=18)	32.05 (± 19.38)			
Daily Vigorous PA: Week 41-48 (n=18)	25.70 (± 14.37)			
Daily Total PA: Week 41-48 (n=18)	247.44 (± 80.33)			
Daily MVPA: Week 41-48 (n=18)	56.67 (± 31.51)			
Daily Sedentary PA: Week 41-48 (n=18)	581.37 (± 97.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of PA Assessed Using Metabolic Equivalent Tasks (METs)

End point title	Level of PA Assessed Using Metabolic Equivalent Tasks (METs)
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End point description:

Level of PA was measured using a Fitbit model Charge 4 and their standard algorithms for subjects aged 13 years and older (at Week 9 of this study). Subjects wore the activity tracker while they were awake every day on the same wrist. The METs measures energy expenditure during PA and were used to

express the intensity of PAs. Light=<3 METs; Moderate=3 to 6 METs; Vigorours=>6 METs. Baseline was defined as Week 9-16 assessment period of this study. Safety population included all subjects who received at least one dose of emicizumab. Number analysed included subjects who wore the device for at least 7 hours per day and with at least 100 steps recorded, on at least 21 days. n=subjects with data available for analysis at the specified timepoint.

End point type	Secondary
End point timeframe:	
Week 9-16, Week 25-32 and Week 41-48	

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: METs				
arithmetic mean (standard deviation)				
Week 9-16 (n=20)	1671.65 (± 284.93)			
Week 25-32 (n=16)	1744.58 (± 376.62)			
Week 41-48 (n=18)	1691.60 (± 385.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time and Intensity Level of PA Assessed Using International Physical Activity Questionnaire-Short Form (IPAQ-SF) Score Every Three Months

End point title	Time and Intensity Level of PA Assessed Using International Physical Activity Questionnaire-Short Form (IPAQ-SF) Score Every Three Months
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End point description:

The IPAQ-SF measured overall PA in last 7 days of adolescent subjects aged ≥ 15 years. It was completed via electronic patient-reported outcome (ePRO) in a smartphone application (app). The IPAQ comprises a set of 4 questionnaires to assess 3 specific types of activity undertaken in 4 domains (leisure time physical activity, domestic and gardening (yard) activities, work-related physical activity, transport-related physical activity). Specific types of activity assessed were walking, moderate-intensity & vigorous-intensity activities. The items in IPAQ-SF questionnaire were structured to provide separate scores on walking, moderate-intensity & vigorous-intensity activity, expressed in MET-minutes/week. Higher scores=better PA. Week1=Baseline assessment in MO42245. Safety population=subjects who received at least 1 dose of emicizumab. Number analysed=subjects aged 15 years & older with data available for analysis. n=subjects available with data for analysis at that specified timepoint.

End point type	Secondary
End point timeframe:	
Weeks 1, 13, 25, 37, and 49	

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: thousands MET-minutes/week				
median (full range (min-max))				
Vigorous Activity: Week 1 (n=17)	0.480 (0.00 to 3.60)			
Vigorous Activity: Week 13 (n=22)	1.320 (0.00 to 5.28)			
Vigorous Activity: Week 25 (n=19)	0.720 (0.00 to 19.20)			
Vigorous Activity: Week 37 (n=18)	1.520 (0.00 to 8.64)			
Vigorous Activity: Week 49 (n=19)	0.800 (0.00 to 9.60)			
Moderate Activity: Week 1 (n=20)	0.600 (0.00 to 3.60)			
Moderate Activity: Week 13 (n=22)	0.240 (0.00 to 4.80)			
Moderate Activity: Week 25 (n=18)	0.600 (0.00 to 9.60)			
Moderate Activity: Week 37 (n=16)	0.240 (0.00 to 5.76)			
Moderate Activity: Week 49 (n=18)	0.330 (0.00 to 3.84)			
Walking Activity: Week 1 (n=19)	0.495 (0.00 to 2.97)			
Walking Activity: Week 13 (n=19)	0.594 (0.00 to 8.43)			
Walking Activity: Week 25 (n=18)	0.297 (0.00 to 4.16)			
Walking Activity: Week 37 (n=16)	0.693 (0.13 to 6.93)			
Walking Activity: Week 49 (n=17)	0.990 (0.00 to 6.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intra-Patient Analysis of Change from Baseline in Level of PA Assessed From METs Using Activity Tracker as Compared with Study MO42590

End point title	Intra-Patient Analysis of Change from Baseline in Level of PA Assessed From METs Using Activity Tracker as Compared with Study MO42590
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End point description:

Level of PA was measured using a Fitbit model Charge 4 and their standard algorithms for subjects aged 13 years and older. Subjects wore the activity tracker while they were awake every day on the same wrist. The METs measures energy expenditure during PA and were used to express the intensity of PAs. Light=<3 METs; Moderate=3 to 6 METs; Vigorours=>6 METs. Safety population included all subjects who received at least one dose of emicizumab. Number analysed included subjects who wore the device for at least 7 hours per day and with at least 100 steps recorded, on at least 21 days. Baseline was defined as the Week 17-24 assessment in NIS MO42590.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 41-48

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: METs				
arithmetic mean (standard deviation)	18.60 (\pm 271.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intra-Patient Analysis of Change from Baseline in Level of PA Assessed From Daily Active Minutes, MVPA and Sedentary Time Using Activity Tracker as Compared with Study MO42590

End point title	Intra-Patient Analysis of Change from Baseline in Level of PA Assessed From Daily Active Minutes, MVPA and Sedentary Time Using Activity Tracker as Compared with Study MO42590
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End point description:

Level of PA was measured using a Fitbit model Charge 4 and their standard algorithms for subjects aged 13 years and older. Subjects wore the activity tracker while they were awake every day on the same wrist. Active minutes identify the possibility of increased activity intensity. The subject must be active for at least ten minutes to earn active minutes. Intensity refers to the rate at which the activity was being performed/ the magnitude of the effort required to perform an activity/ exercise. MVPA was defined as per Fitbit default categorization. Sedentary time was calculated as time when there was no movement. Safety population included all subjects who received at least one dose of emicizumab. Number analysed included subjects who wore the device for at least 7 hours per day and with at least 100 steps recorded, on at least 21 days. Baseline was defined as the Week 17-24 assessment in NIS MO42590.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 41-48

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: minutes				
arithmetic mean (standard deviation)				
Daily Light PA	-12.45 (\pm 17.36)			
Daily Moderate PA	-0.41 (\pm 19.37)			
Daily Vigorous PA	2.04 (\pm 16.77)			
Daily Total PA	-4.08 (\pm 42.30)			
Daily MVPA	1.64 (\pm 34.60)			
Daily Sedentary PA	-5.15 (\pm 71.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intra-Patient Analysis of Change from Baseline in Level of PA, Assessed From DSC Using Activity Tracker as Compared with Study MO42590

End point title	Intra-Patient Analysis of Change from Baseline in Level of PA, Assessed From DSC Using Activity Tracker as Compared with Study MO42590
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End point description:

Level of PA was measured using a Fitbit model Charge 4 and their standard algorithms for subjects aged 13 years and older. Subjects wore the activity tracker while they were awake every day on the same wrist. Safety population included all subjects who received at least one dose of emicizumab. Number analysed included subjects who wore the device for at least 7 hours per day and with at least 100 steps recorded, on at least 21 days. Baseline was defined as the Weeks 17-24 assessment in NIS MO42590.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 41-48

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: daily steps				
arithmetic mean (standard deviation)	636.58 (\pm 2879.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intra-Patient Analysis of Change from Baseline in Level of PA Assessed Using IPAQ-SF as Compared with Study MO42590

End point title	Intra-Patient Analysis of Change from Baseline in Level of PA Assessed Using IPAQ-SF as Compared with Study MO42590
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End point description:

The IPAQ-SF measured overall PA in last 7 days of adolescent subjects aged ≥ 15 years. IPAQ-SF questionnaire was completed via ePRO in a smartphone application (app). The IPAQ comprises a set of 4 questionnaires to assess 3 specific types of activity undertaken in 4 domains (leisure time physical activity, domestic and gardening (yard) activities, work-related physical activity, transport-related physical activity). Specific types of activity assessed were walking, moderate-intensity & vigorous-intensity activities. The items in IPAQ-SF questionnaire were structured to provide separate scores on walking, moderate-intensity & vigorous-intensity activity, expressed in MET-minutes/week. Higher scores=better PA. Safety population=subjects who received at least 1 dose of emicizumab. Baseline was defined as the Week 1 assessment in NIS MO42590. Number analysed=subjects with assessments performed at all planned visits. n=subjects with data available for analysis at the specified timepoint.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 1, 13, 25, 37, and 49	

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: thousands MET-minutes/week				
median (full range (min-max))				
Vigorous Activity: Baseline(n=12)	0.600 (0.00 to 2.40)			
Vigorous Activity: Change at Week 1(n=12)	0.00 (-1.92 to 1.08)			
Vigorous Activity: Change at Week 13(n=12)	0.00 (-0.96 to 4.56)			
Vigorous Activity: Change at Week 25(n=12)	-0.240 (-1.92 to 2.40)			
Vigorous Activity: Change at Week 37(n=12)	0.440 (-0.48 to 2.88)			
Vigorous Activity: Change at Week 49(n=12)	0.00 (-0.96 to 7.20)			
Moderate Activity: Baseline(n=9)	0.480 (0.00 to 1.80)			
Moderate Activity: Change at Week 1(n=9)	-0.240 (-0.84 to 1.80)			
Moderate Activity: Change at Week 13(n=9)	-0.240 (-0.68 to 0.12)			
Moderate Activity: Change at Week 25(n=9)	-0.240 (-0.84 to 0.96)			
Moderate Activity: Change at Week 37(n=9)	-0.240 (-0.96 to 3.96)			
Moderate Activity: Change at Week 49(n=9)	-0.160 (-0.96 to 0.96)			
Walking Activity: Baseline(n=9)	0.462 (0.03 to 2.77)			
Walking Activity: Change at Week 1(n=9)	-0.033 (-0.69 to 1.09)			
Walking Activity: Change at Week 13(n=9)	-0.033 (-1.98 to 2.48)			
Walking Activity: Change at Week 25(n=9)	-0.066 (-0.40 to 0.07)			
Walking Activity: Change at Week 37(n=9)	0.00 (-1.58 to 1.49)			
Walking Activity: Change at Week 49(n=9)	0.00 (-1.29 to 1.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Joint Health Assessed Using Hemophilia Early Arthropathy Detection With Ultrasound (HEAD-US) Score

End point title	Joint Health Assessed Using Hemophilia Early Arthropathy Detection With Ultrasound (HEAD-US) Score
End point description:	
The HEAD-US was a method for early detection of hemophilic arthropathy with ultrasound. HEAD-US assesses the following 3 domains for 6 joints (knees, elbows, and ankles): hypertrophic synovium, disease damage on cartilage & disease damaged on bone, with a maximum score of 8 points/joints. Scores were categorized based on severity. Joint abnormalities can be quantified using an additive scoring scale. A total HEAD-US score per subject was calculated as sum of total scores per joints, for subjects with all joints assessed. Higher scores=worse joint health. Week 1=MO42245 baseline assessment. Safety population=subjects who received at least one dose of emicizumab. Number analysed=subjects with data available for analysis.	
End point type	Secondary
End point timeframe:	
Week 1, Week 49	

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1	9.12 (± 12.71)			
Week 49	10.00 (± 12.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Joint Health Assessed Using Hemophilia Joint Health Score (HJHS) 2.1

End point title	Joint Health Assessed Using Hemophilia Joint Health Score (HJHS) 2.1
End point description:	
HJHS measures joint health, in domains of body structure & function (impairment) of joints most affected by bleeding in hemophilia: knees, ankles & elbows. It consists of assessment of swelling (0=None3=Severe); duration of swelling (0=no swelling/<6 months1=≥6 months); muscle atrophy (0=None2=Severe); crepitus on motion (0=None2=Severe); flexion loss & extension loss (0=<5° 3=>20°); joint pain (0=No pain through active range of motion2=Pain); strength (0=Holds test position against gravity within maximum resistance4=Trace/no contraction); & Global Gait Score (GGS; 0=All skills in normal limits(NL)4=No skills in NL). HJHS Total Score=sum of all joint domain scores (6*20 points+4 points for GGS). Higher score=worse joint health. Clinically relevant improvements=≥4-point reduction in Total HJHS/≥2-point reduction in HJHS joints domain. Week 1=MO42245 baseline. Safety population; subjects with all joints assessed by HJHS & GGS. n=number of subjects analysed at that timepoint.	
End point type	Secondary
End point timeframe:	
Week 1, Week 49	

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=28)	13.50 (± 15.45)			
Week 49 (n=25)	13.48 (± 15.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Zero Treated Bleeds Over Time

End point title	Number of Subjects With Zero Treated Bleeds Over Time
End point description:	
An event was considered a treated bleed if coagulation factors were administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). Bleeds and treatment of bleeds were captured through the BMQ. Bleed rate was calculated over the 48 weeks of MO42245 compared to 24 weeks of MO42590. Safety population included all subjects who received at least one dose of emicizumab.	
End point type	Secondary
End point timeframe:	
Up to Week 49	

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: subjects	16	8		

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Treated Spontaneous or Traumatic Bleeds Over Time

End point title	ABR for Treated Spontaneous or Traumatic Bleeds Over Time
End point description:	
An event was considered a treated bleed if coagulation factors were administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). Bleeds were classified as spontaneous if a subject recorded a bleed when there was no known contributing factor such as definite trauma, antecedent "strenuous" activity or "overuse" or "procedure/surgery." Bleeds were classified as traumatic if a subject recorded a bleed when there was a known or believed reason for the bleed. Bleeds & treatment of bleeds were captured through the BMQ. Number of treated bleeds was estimated as an ABR using a negative binomial regression model, which accounts for different follow-up times. Bleed rate was calculated over the 48 weeks of MO42245 compared to 24 weeks of MO42590. ABR was derived as follows: number of bleeds/number of days during observational period (the time that each subject stays in the study) * 365.25. Safety population=all subjects who received at least 1 dose of emicizumab.	

End point type	Secondary
End point timeframe:	
Up to Week 49	

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: bleeds per year				
number (confidence interval 95%)				
Treated Spontaneous Bleed (n=28)	0.3 (0.15 to 0.73)	2.7 (1.16 to 6.06)		
Treated Traumatic Bleed (n=28)	1.3 (0.63 to 2.56)	3.3 (2.17 to 5.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate (ABR) for Treated Bleeds Over Time

End point title	Annualized Bleeding Rate (ABR) for Treated Bleeds Over Time
End point description:	
<p>An event was considered a treated bleed if coagulation factors were administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). Bleeds and treatment of bleeds were captured through the Bleed Medication Questionnaire (BMQ). The number of treated bleeds was estimated as an ABR using a negative binomial regression model, which accounts for different follow-up times. Bleed rate was calculated over the 48 weeks of MO42245 compared to 24 weeks of MO42590. ABR was derived as follows: number of bleeds/number of days during observational period (the time that each subject stays in the study) * 365.25. Safety population included all subjects who received at least one dose of emicizumab.</p>	
End point type	Secondary
End point timeframe:	
Up to Week 49	

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: bleeds per year				
number (confidence interval 95%)	1.6 (0.81 to 3.19)	5.9 (3.68 to 9.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for All Bleeds Over Time

End point title	ABR for All Bleeds Over Time
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End point description:

All bleeds included both treated and non-treated bleeds. An event was considered a treated bleed if coagulation factors were administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). Bleeds and treatment of bleeds were captured through the BMQ. The number of treated bleeds was estimated as ABR using a negative binomial regression model, which accounts for different follow-up times. Bleed rate was calculated over the 48 weeks of MO42245 compared to 24 weeks of MO42590. ABR was derived as follows: number of bleeds/number of days during observational period (the time that each subject stays in the study) * 365.25. Safety population included all subjects who received at least one dose of emicizumab.

End point type	Secondary
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End point timeframe:

Up to Week 49

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: bleeds per year				
number (confidence interval 95%)	2.5 (1.44 to 4.36)	9.2 (6.31 to 13.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Treated Target Joint Bleeds Over Time

End point title	ABR for Treated Target Joint Bleeds Over Time
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End point description:

A treated bleed occurred if coagulation factors were administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). Treated target joint bleeds: treated joint bleeds that occurred in a target joint, defined as a joint in which 3 or more treated joint bleeds occurred during the 24 weeks prior to study entry. Bleeds and treatment of bleeds were captured through the BMQ. The number of treated bleeds was estimated as an ABR using a negative binomial regression model, which accounts for different follow-up times. Bleed rate was calculated over the 48 weeks of MO42245 compared to 24 weeks of MO42590. ABR was derived as follows: number of bleeds/number of days during observational period (the time that each subject stays in the study) * 365.25. Safety population. 99999=number and 95% confidence interval (CI) were not estimable as no subjects had an event.

End point type	Secondary
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End point timeframe:

Up to Week 49

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: bleeds per year				
number (confidence interval 95%)	99999 (99999 to 99999)	0.3 (0.05 to 1.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: ABR for Treated Joint Bleeds Over Time

End point title	ABR for Treated Joint Bleeds Over Time
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End point description:

An event was considered a treated bleed if coagulation factors were administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). Treated joint bleeds were treated bleeds where joint bleed was accompanied by increased swelling or warmth of the skin over the joint, increasing pain or decreased range of motion or difficulty using the joint compared with Baseline. Bleeds and treatment of bleeds were captured through the BMQ. The number of treated bleeds was estimated as an ABR using a negative binomial regression model, which accounts for different follow-up times. Bleed rate was calculated over the 48 weeks of MO42245 compared to 24 weeks of MO42590. ABR was derived as follows: number of bleeds/number of days during observational period (the time that each subject stays in the study) * 365.25. Safety population included all subjects who received at least one dose of emicizumab.

End point type	Secondary
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End point timeframe:

Up to Week 49

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: bleeds per year				
number (confidence interval 95%)	0.8 (0.40 to 1.77)	3.7 (2.21 to 6.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of FVIII Infusions Required to Treat a Breakthrough Bleed

End point title	Number of FVIII Infusions Required to Treat a Breakthrough Bleed
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End point description:

The non-emicizumab Factor VIII (FVIII) infusions used to treat a bleed were categorized as standard half-life [SHL] and extended half-life [EHL]. The number of FVIII infusions was counted per bleed (all treatments that are linked to the same bleed per the 72h rule were considered to belong to the same bleed). If the same treatment(s) were associated with multiple bleeds, these were counted multiple

times, i.e. linked to both bleeds. Participants experienced a total of 82 and 39 bleeds that required treatment with coagulation factors, while on FVIII and emicizumab prophylaxis respectively. Safety population included all subjects who received at least one dose of emicizumab.

End point type	Secondary
End point timeframe:	
Up to Week 49	

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: infusions per bleed				
arithmetic mean (standard deviation)				
EHL	0.6 (± 0.8)	0.6 (± 1.0)		
SHL	1.4 (± 3.0)	0.8 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amount of Doses Required to Treat a Breakthrough Bleed

End point title	Amount of Doses Required to Treat a Breakthrough Bleed
End point description:	
The number and percentages of subjects with non-emicizumab hemophilia medications was summarized by category of hemophilia medication [(SHL) and EHL]. The number of FVIII doses and the cumulative doses were summarized by category of hemophilia medication. Safety population included all subjects who received at least one dose of emicizumab.	
End point type	Secondary
End point timeframe:	
Up to Week 49	

End point values	Emicizumab	FVIII Prophylaxis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: international unit/kilograms (IU/kg)				
arithmetic mean (standard deviation)				
EHL	18.18 (± 22.98)	21.93 (± 39.29)		
SHL	51.76 (± 113.44)	20.53 (± 25.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Status Assessed Using European Quality of Life Five-Dimension-Five Level Questionnaire (EQ-5D-5L)

End point title	Health Status Assessed Using European Quality of Life Five-Dimension-Five Level Questionnaire (EQ-5D-5L)
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End point description:

The EQ-5D-5L was a validated, self-report, health status questionnaire that was used to calculate a health status utility score. The EQ-5D-5L consists of two parts, the first : health state classification, contains five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Overall scores typically range from 0 to 1. Low scores represent a higher level of dysfunction. The second part: VAS assesses current health status. using a score range of 0 to 100-points. Higher scores indicate better health. VAS was to be analysed from the EQ-5D-5L Week 1= MO42245 baseline assessment. Safety population included all subjects who received at least one dose of emicizumab. Number analysed included subjects with data available for analysis. n=subjects with data available for analysis at that specified timepoint.

End point type	Secondary
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End point timeframe:

Week 1, Week 25 and Week 49

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=27)	78.56 (± 16.90)			
Week 25 (n=26)	75.23 (± 19.42)			
Week 49 (n=25)	78.96 (± 14.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Preferred for Emicizumab SC Treatment Assessed Using Emicizumab Preference (EmiPref) Questionnaire

End point title	Number of Subjects who Preferred for Emicizumab SC Treatment Assessed Using Emicizumab Preference (EmiPref) Questionnaire
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End point description:

EmiPref questionnaire was used to assess subjects' preference of SC emicizumab over their former IV hemophilia treatment. The questionnaire builds on the results from previous studies, which noted that subjects expressed preference for treatments that did not have negative effects (e.g., pain that results from infusions), were not time consuming, were not associated with high treatment burden, and had a goal of achieving a "normal life". Safety population included all subjects who received at least one dose of emicizumab.

End point type	Secondary
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End point timeframe:
Week 25 and Week 49

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: subjects				
Preferred Emicizumab SC, Week 25 (n=26)	26			
Preferred Emicizumab SC, Week 49 (n=25)	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with at Least One Adverse Event

End point title	Number of Subjects with at Least One Adverse Event
End point description: An adverse event (AE) is untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment. An AE can therefore be any unfavorable & unintended sign (including an abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether or not considered related to investigational product. Safety population included all subjects who received at least one dose of emicizumab.	
End point type	Secondary
End point timeframe: From study start until 24 weeks after the last dose of the study drug (up to 72 weeks)	

End point values	Emicizumab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: subjects	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Caregiver Burden Assessed Using Hemophilia Associated Caregiver Burden Scale (HEMOCAB) Total Score

End point title	Caregiver Burden Assessed Using Hemophilia Associated Caregiver Burden Scale (HEMOCAB) Total Score
End point description: HEMOCAB is a caregiver questionnaire comprising 54 questions pertaining to 13 domains (emotional	

stress, financial burden, personal sacrifice and limitations, job-related burden, interactions with others, interaction of child with others, school, perception of child, dealing with child's hemophilia, medical management, work situation related to hemophilia, interaction with the child's father, and impact of child's hemophilia). Responses to each domain were answered on a five-point Likert scale, with the scale assessing the nine frequency of burden domains ranging from "never" to "always," and assessing the intensity of the four perceived burden domains ranging from "not at all" to "very much." High values imply high burden. Week 1= MO42245 baseline assessment. HEMOCAB was completed by the parent/caregiver of adolescents 12-17 years old. Safety population included all subjects who received at least one dose of emicizumab. Number analysed includes subjects with available data.

End point type	Secondary
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End point timeframe:

Week 1 and Week 49

End point values	Emicizumab: Adolescents			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1	16.46 (± 14.06)			
Week 49	13.32 (± 15.14)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study start until 24 weeks after the last dose of the study drug (up to 72 weeks)

Adverse event reporting additional description:

Safety Population included all subjects who received at least one dose of emicizumab.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Emicizumab
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Reporting group description:

Subjects received emicizumab, as SC injection, at a loading dose of 3 mg/kg, QW for 4 weeks followed by a maintenance dose of 1.5 mg/kg, QW or 3 mg/kg, Q2W or 6 mg/kg, Q4W for 44 weeks until discontinuation from the study for any reason, whichever occurred first.

Serious adverse events	Emicizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Emicizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 28 (64.29%)		
Investigations			
Vitamin E decreased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Intentional product misuse			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Incorrect dose administered			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Injection site reaction			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			

COVID-19			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2021	Protocol Version 2: 1. Fitbit activity tracker data collection was limited to subjects aged 13 and older and the specific data collected by the Fitbit Charge 4 device were explicitly defined to refine the objective for the activity tracker. 2. Intensity of physical activity was included when evaluating bleeds related to exercise. 3. Clarifications were made to differentiate between non-electronic case report form (eCRF) and eCRF data. 4. The socio-demographic section was removed from HEMOCAB. 5. New guidance was included to manage potential cases of neutralizing anti-drug antibodies, especially in scenarios where a loss of efficacy is noted.
17 March 2022	Protocol Version 3: 1. The total number of subjects was reduced from approximately 50 subjects to approximately 30 subjects. The adjustment has been done based on the recruitment at the time and realistic estimation of potential subjects from each site. 2. The inclusion criteria age was changed from ≥ 12 -51 years old to ≥ 12 -61 years, to provide adequate numbers for age group analysis considering the reduced total number of subjects. 3. HEMOCAB has been updated to the latest shortened version. 4. Use of FVIII, given before an activity, has been changed to "allowed under certain circumstances," where FVIII can be given before intense physical activity and the Medical Monitor should be informed in advance. 5. The anticipated recruitment period has been prolonged from 44 to 55 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported