Clinical trial results:
An Open-Label Study to Evaluate Prophylaxis Treatment, and to Characterize the Efficacy, Safety, and Pharmacokinetics of B-Domain Deleted Recombinant Factor VIII Albumin Free (Moroctocog Alfa [AF-CC]) in Children With Hemophilia A

Summary

EudraCT number	2006-005575-17
Trial protocol	ES DE AT IT
Global end of trial date	18 April 2018

Results information

Result version number	v1
This version publication date	10 October 2018
First version publication date	10 October 2018

Trial information

Trial identification

Sponsor protocol code	3082B2-313

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00543439
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that moroctocog alfa prophylaxis reduces annualized bleeding rates relative to on-demand (OD) therapy. Enrollment into the OD cohort has been closed.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Oman: 10
Country: Number of subjects enrolled	Jordan: 6
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Croatia: 1
Worldwide total number of subjects	65
EEA total number of subjects	23

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)	5
Children (2-11 years)	59
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects for 1 of the sites, were excluded from efficacy and safety analysis due to data integrity issues, however were reported in subject disposition and baseline. Out of 66 enrolled subjects, 65 were treated (started Period 1). Period 1 and Period 2 both were post-baseline.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy

Arm description:

In Period 1 subjects for, on-demand (OD) therapy were treated with intravenous (IV) infusion of moroctocog alfa (AF-CC) for 6 months (Day 1 up to Month 6) as prescribed by investigator based on current recommendations for on demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of AF-CC, 20-40 international units per kilogram [IU/kg], every 12-24 hours until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of AF-CC, 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of AF-CC, 60-100 IU/kg, every 8-24 hours until bleeding was resolved). Period 1 was followed by Period 2 where subjects received IV infusion of AF-CC at 25 IU/kg once in 2 days up to 12 months (Month 7 to Month 18) as routine prophylaxis (RP) therapy.

Arm type	Experimental
Investigational medicinal product name	Moroctocog alfa (AF-CC)
Investigational medicinal product code	
Other name	Xyntha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

First period: Subjects were treated with moroctocog alfa (AF-CC) IV infusion for 6 months as prescribed by investigator based on current recommendations for on demand treatment with licensed product Xyntha.

Arm title	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg

Arm description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg once in 2 days up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Arm type	Experimental
Investigational medicinal product name	Moroctocog alfa (AF-CC)
Investigational medicinal product code	
Other name	Xyntha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

First period: Subjects received moroctocog alfa (AF-CC) infusion intravenously at 25 IU/kg, once in 2 days up to 12 months.

Arm title	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg

Arm description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg twice per week up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Arm type	Experimental
Investigational medicinal product name	Moroctocog alfa (AF-CC)
Investigational medicinal product code	
Other name	Xyntha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

First period: Subjects received 45 IU/kg moroctocog alfa (AF-CC) infusion intravenously twice per week up to 12 months.

Number of subjects in period 1	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg
Started	9	29	27
Completed	9	26	25
Not completed	0	3	2
Consent withdrawn by subject	-	1	-
Physician decision	-	-	1
Adverse Event	-	2	1

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy

Arm description:

In Period 1 subjects for, on-demand (OD) therapy were treated with intravenous (IV) infusion of moroctocog alfa (AF-CC) for 6 months (Day 1 up to Month 6) as prescribed by investigator based on current recommendations for on demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of AF-CC, 20-40 international units per kilogram [IU/kg], every 12-24 hours until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of AF-CC, 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of AF-CC, 60-100 IU/kg, every 8-24 hours until bleeding was resolved). Period 1 was followed by Period 2 where subjects received IV infusion of AF-CC at 25 IU/kg once in 2 days up to 12 months (Month 7 to Month 18) as routine prophylaxis (RP) therapy.

Arm type	Experimental
Investigational medicinal product name	Moroctocog alfa (AF-CC)
Investigational medicinal product code	
Other name	Xyntha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Second period: Subjects received 25 IU/kg moroctocog alfa (AF-CC) infusion intravenously once in 2 days up to 12 months.

Arm title	Moroctocog alfa, RP Cohort: RP 25 IU/kg Then RP 45 IU/kg

Arm description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg once in 2 days up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Arm type	Experimental
Investigational medicinal product name	Moroctocog alfa (AF-CC)
Investigational medicinal product code	
Other name	Xyntha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Second period: Subjects received 45 IU/kg moroctocog alfa (AF-CC) infusion intravenously twice per week up to 12 months.

Arm title	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg

Arm description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg twice per week up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Arm type	Experimental
Investigational medicinal product name	Moroctocog alfa (AF-CC)
Investigational medicinal product code	
Other name	Xyntha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Second period: Subjects received 25 IU/kg moroctocog alfa (AF-CC) infusion intravenously once in 2 days up to 12 months.

Number of subjects in period 2	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy	Moroctocog alfa, RP Cohort: RP 25 IU/kg Then RP 45 IU/kg	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg
Started	9	26	25
Completed	8	25	23
Not completed	1	1	2
Adverse Event	-	1	1
Protocol deviation	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy

Reporting group description:

In Period 1 subjects for, on-demand (OD) therapy were treated with intravenous (IV) infusion of moroctocog alfa (AF-CC) for 6 months (Day 1 up to Month 6) as prescribed by investigator based on current recommendations for on demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of AF-CC, 20-40 international units per kilogram [IU/kg], every 12-24 hours until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of AF-CC, 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of AF-CC, 60-100 IU/kg, every 8-24 hours until bleeding was resolved). Period 1 was followed by Period 2 where subjects received IV infusion of AF-CC at 25 IU/kg once in 2 days up to 12 months (Month 7 to Month 18) as routine prophylaxis (RP) therapy.

Reporting group title	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg once in 2 days up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Reporting group title	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg twice per week up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Reporting group values	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg
Number of subjects	9	29	27
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	2	3
Children (2-11 years)	9	27	23
Adolescents (12-17 years)	0	0	1
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	4.7	4.4	4.1
standard deviation	± 1.05	± 1.84	± 2.28
Sex: Female, Male Units: Subjects			
Female	0	0	0

Male	9	29	27

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	8	24	22
More than one race	0	0	0
Unknown or Not Reported	1	5	5

Reporting group values	Total		
Number of subjects	65		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	5		
Children (2-11 years)	59		
Adolescents (12-17 years)	1		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	0		
Male	65		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	54		
More than one race	0		
Unknown or Not Reported	11		

End points

End points reporting groups

Reporting group title	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy

Reporting group description:

In Period 1 subjects for, on-demand (OD) therapy were treated with intravenous (IV) infusion of moroctocog alfa (AF-CC) for 6 months (Day 1 up to Month 6) as prescribed by investigator based on current recommendations for on demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of AF-CC, 20-40 international units per kilogram [IU/kg], every 12-24 hours until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of AF-CC, 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of AF-CC, 60-100 IU/kg, every 8-24 hours until bleeding was resolved). Period 1 was followed by Period 2 where subjects received IV infusion of AF-CC at 25 IU/kg once in 2 days up to 12 months (Month 7 to Month 18) as routine prophylaxis (RP) therapy.

Reporting group title	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg once in 2 days up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Reporting group title	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg twice per week up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Reporting group title	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy

Reporting group description:

In Period 1 subjects for, on-demand (OD) therapy were treated with intravenous (IV) infusion of moroctocog alfa (AF-CC) for 6 months (Day 1 up to Month 6) as prescribed by investigator based on current recommendations for on demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of AF-CC, 20-40 international units per kilogram [IU/kg], every 12-24 hours until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of AF-CC, 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of AF-CC, 60-100 IU/kg, every 8-24 hours until bleeding was resolved). Period 1 was followed by Period 2 where subjects received IV infusion of AF-CC at 25 IU/kg once in 2 days up to 12 months (Month 7 to Month 18) as routine prophylaxis (RP) therapy.

Reporting group title	Moroctocog alfa, RP Cohort: RP 25 IU/kg Then RP 45 IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg once in 2 days up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Reporting group title	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg twice per week up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Subject analysis set title	Moroctocog alfa (AF-CC), On Demand Cohort: On Demand Therapy
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

In Period 1, subjects for on-demand therapy were treated with IV infusion of moroctocog alfa (AF-CC)

for 6 months (Day 1 up to Month 6) as prescribed by the investigator based on current recommendations for on-demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of moroctocog alfa (AF-CC), 20-40 IU/kg, every 12-24 hours as necessary until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of Moroctocog alfa, 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of moroctocog alfa (AF-CC), 60-100 IU/kg, every 8-24 hours until bleeding was resolved).

Subject analysis set title	Moroctocog alfa (AF-CC), On Demand Cohort: RP Therapy 25 IU/kg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

In Period 2, subjects for on-demand cohort received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg once in 2 days up to 12 months (Month 7 up to Month 18) as routine prophylaxis therapy.

Subject analysis set title	Moroctocog alfa (AF-CC): On Demand Therapy
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects of either on demand cohort or routine prophylaxis cohort were treated for bleeds, as needed on demand, with IV infusion of moroctocog alfa (AF-CC) up to 24 months as prescribed by the investigator based on current recommendations for on-demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of moroctocog alfa (AF-CC), 20-40 IU/kg, every 12-24 hours as necessary until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of moroctocog alfa (AF-CC), 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of moroctocog alfa (AF-CC), 60-100 IU/kg, every 8-24 hours until bleeding was resolved).

Subject analysis set title	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 25 IU/kg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects of routine prophylaxis cohort, as routine prophylaxis therapy received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months as routine prophylaxis therapy for either Period 1 (Day 1 up to Month 12) or Period 2 (Month 13 up to Month 24) of the study.

Subject analysis set title	Moroctocog alfa (AF-CC): 50 IU/kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single 50 IU/kg infusion of moroctocog alfa (AF-CC) on Day 1 before initiation of moroctocog alfa (AF-CC) study treatment either in on demand cohort or routine prophylaxis cohort.

Subject analysis set title	Moroctocog alfa (AF-CC): All Subjects
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects enrolled to receive moroctocog alfa (AF-CC) in on demand cohort as on demand therapy in Period 1 and routine prophylaxis 25 IU/kg therapy in Period 2 or in routine prophylaxis cohort as routine prophylaxis 45 IU/kg therapy each for either in Period 1 or Period 2 and routine prophylaxis 25 IU/kg therapy either in Period 1 or Period 2.

Subject analysis set title	Moroctocog alfa (AF-CC) RP Cohort: RP therapy
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received moroctocog alfa (AF-CC) in routine prophylaxis cohort as RP 45 IU/kg, twice per week up to 12 months either in Period 1 (Day 1 up to Month 12) or Period 2 (Month 13 up to Month 24); and as RP 25 IU/kg, once in 2 days up to 12 months either in Period 1 (Day 1 up to Month 12) or Period 2 (Month 13 up to Month 24).

Subject analysis set title	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to the routine prophylaxis cohort, in which IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months as routine prophylaxis therapy would be assigned for either Period 1 (Day 1 up to Month 12) or Period 2 (Month 13 up to Month 24) of the study.

Subject analysis set title	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects of routine prophylaxis cohort received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once

in 2 days up to 12 months as routine prophylaxis therapy each for either Period 1 (Day 1 up to Month 12) or Period 2 (Month 13 up to Month 24) of the study. And subjects of on demand cohort for Period 2 of the study, received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days as routine prophylaxis therapy up to 12 months (Month 7 up to Month 18).

Subject analysis set title	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects of routine prophylaxis cohort, received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months as routine prophylaxis therapy each for either Period 1 (Day 1 up to Month 12) or Period 2 (Month 13 up to Month 24) of the study.

Subject analysis set title	Moroctocog alfa (AF-CC): All Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects of either on demand cohort or routine prophylaxis cohort who were at risk for developing inhibitor to FVIII, and who received moroctocog alfa (AF-CC) in on demand cohort as on demand therapy in Period 1 and routine prophylaxis 25 IU/kg therapy in Period 2 or in routine prophylaxis cohort as routine prophylaxis 45 IU/kg therapy each for either in Period 1 or Period 2 and routine prophylaxis 25 IU/kg therapy either in Period 1 or Period 2.

Subject analysis set title	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to routine prophylaxis cohort to receive IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months as routine prophylaxis therapy for either Period 1 (Day 1 up to Month 12) or Period 2 (Month 13 up to Month 24) of the study. And subjects randomized to on demand cohort for Period 2 of the study, to receive IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days as routine prophylaxis therapy up to 12 months (Month 7 up to Month 18).

Primary: Mean Annualized Bleed Rate (ABR) by Treatment: On Demand Cohort

End point title	Mean Annualized Bleed Rate (ABR) by Treatment: On Demand Cohort

End point description:

ABR for each subject was calculated as the number of bleeds requiring administration of moroctocog alfa (AF-CC) divided by the total therapy duration (in days), then multiplied by 365.25 (days in a year). Intent-to-treat (ITT) analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form. Here, "Overall Number of Subjects Analysed" signifies subjects who were evaluable for this end point.

End point type	Primary

End point timeframe:

Day 1 up to Month 6 (OD Cohort, OD Therapy, Period 1); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), On Demand Cohort: On Demand Therapy	Moroctocog alfa (AF-CC), On Demand Cohort: RP Therapy 25 IU/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	8		
Units: Bleeds per year				
arithmetic mean (standard deviation)	47.0 (± 32.2)	1.5 (± 2.2)		

Statistical analyses

Statistical analysis title	OD Cohort: OD therapy versus RP therapy 25 IU/kg

Statistical analysis description:

Ratio of the arithmetic means of the ABR for on demand cohort, on demand therapy to routine prophylaxis therapy 25 IU/kg was calculated. One-sided 95% CI for this ratio was reported. Number of subjects contributing to ratio of means and CI =9.

Comparison groups	Moroctocog alfa (AF-CC), On Demand Cohort: On Demand Therapy v Moroctocog alfa (AF-CC), On Demand Cohort: RP Therapy 25 IU/kg
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.002 [2]
Method	Paired t-test
Parameter estimate	Ratio of arithmetic means
Point estimate	0.03
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.08

Notes:

[1] - Field appearing in later section: "Number of subjects included in analysis", is an auto populated field from database (sum of number of subjects analysed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis.
[2] - Number of subjects contributing to P-value = 8.

Secondary: Mean Annualized Bleed Rate (ABR) by Treatment: Routine Prophylaxis Cohort

End point title	Mean Annualized Bleed Rate (ABR) by Treatment: Routine Prophylaxis Cohort

End point description:

ABR for each subject was calculated as the number of bleeds requiring administration of moroctocog alfa (AF-CC) divided by the total therapy duration (in days), then multiplied by 365.25 (days in a year). ITT analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form. Here, "Overall Number of Subjects Analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, Period 1 and Period 2)

End point values	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: Bleeds per year				
arithmetic mean (standard deviation)	2.2 (± 4.1)	3.3 (± 5.3)		

Statistical analyses

Statistical analysis title	RP Cohort: RP 45 IU/kg versus RP 25 IU/kg

Statistical analysis description:

Field appearing in later section: "Number of subjects included in analysis", is auto populated from database (sum of number of subjects analysed for reporting arms selected to report statistical data): which may not be actual number of subjects contributing to statistical analysis. Here, number of subjects contributing to statistical analysis =35.

Comparison groups	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 25 IU/kg v Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.03
upper limit	2.22

Notes:

[3] - 90% 2-sided CI for the mean difference in ABRs for the 2 prophylaxis regimens for ITT subjects was constructed using the t distribution with n-1 degrees of freedom (n equals the number of subjects) to assess the equivalence of the 2 regimens. Equivalence was demonstrated and the null hypothesis rejected if the limits of the 90% CI fell wholly within the interval of (–4, 4) bleeds per year.

Secondary: Mean of Moroctocog alfa (AF-CC) Infusions Administered To Treat Bleeding Episode

End point title	Mean of Moroctocog alfa (AF-CC) Infusions Administered To Treat Bleeding Episode

End point description:

In this end point mean of total number of moroctocog alfa (AF-CC) infusions administered to treat each bleeding episode was reported. ITT analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form. Here, "Overall Number of Subjects Analysed" signifies subjects who were evaluable for this endpoint. Number of bleeds analysed: Moroctocog alfa: All Subjects (562)

End point type	Secondary

End point timeframe:

Day 1 up to Month 24

End point values	Moroctocog alfa (AF-CC): All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Infusions				
arithmetic mean (standard deviation)	1.5 (± 1.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treated Bleeds Classified on Basis of Response to First Infusion of Moroctocog alfa (AF-CC) as On-Demand Treatment

End point title	Number of Treated Bleeds Classified on Basis of Response to First Infusion of Moroctocog alfa (AF-CC) as On-Demand Treatment

End point description:

Number (no.) of bleeds treated reported on basis of response to first (1st) infusion of study drug, at 4-point scale: excellent, good, moderate, no response. Excellent: definite pain relief and improvement (DPRI) in bleeding signs within 8 hours (hr) after infusion, no additional infusion given; Good: DPRI in bleeding signs within 8 hr after infusion, at least 1 additional infusion given for complete resolution or with no additional infusion given; Moderate: probable or slight improvement starting after 8 hr following infusion, at least 1 additional infusion given for complete resolution; No Response: no improvement at all between infusions or during 24 hr interval following infusion or condition worsen. Bleeds in which response not recorded, reported as: Data Not Recorded. No. of 1st infusions not=total no. of bleeds if bleed was: missing start date/dose information or treated initially with non study FVIII. ITT analysis. Subjects Analysed=subjects evaluable. Bleeds analysed=559.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24

End point values	Moroctocog alfa (AF-CC): On Demand Therapy			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Bleeds				
Excellent	376			
Good	150			
Moderate	27			
No Response	2			
Data Not Recorded	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treated Spontaneous Bleeds by Time Interval between Bleed Onset and Prior Moroctocog alfa (AF-CC) Prophylaxis Dose: Routine Prophylaxis Therapy

End point title	Number of Treated Spontaneous Bleeds by Time Interval between Bleed Onset and Prior Moroctocog alfa (AF-CC) Prophylaxis Dose: Routine Prophylaxis Therapy

End point description:

In this end point number of treated spontaneous bleeding episodes for following time intervals between bleed onset and prior moroctocog alfa (AF-CC) prophylaxis dose are reported: lesser than or equal to (<=) 24 hours, greater than (>) 24 hours to <=48 hours, >48 hours to <=72 hours, >72 hours. For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for routine prophylaxis cohort (Day 1 up to Month 24, Period 1 and Period 2) and on demand cohort (Month 7 up to Month 18, Period 2) is reported. Analysis population included all subjects for whom a legal acceptable representative had

signed the informed consent/assent form and only subjects who reported a spontaneous bleeding episode following a routine prophylaxis dose. Number of bleeds analysed: Moroctocog alfa, RP Therapy 45 IU/kg (28) and Moroctocog alfa: RP Therapy 25 IU/kg (18).

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, RP 25 IU/kg and 45 IU/kg, Period 1 and 2); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	9		
Units: Bleeds				
<=24 hours	3	1		
>24 hours to <=48 hours	6	4		
>48 hours to <=72 hours	2	10		
>72 hours	7	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Requiring Prophylaxis Regimen Escalation: Routine Prophylaxis Therapy

End point title	Number of Subjects Requiring Prophylaxis Regimen Escalation: Routine Prophylaxis Therapy

End point description:

During prophylaxis, criteria for prophylaxis regimen escalation are occurrence, over 4-week duration of (a) 2 or more spontaneous bleeds into a major joint and target joint, or (b) 3 or more spontaneous bleeds (consisting of joint bleeds and significant soft tissue/muscle or other site bleeds). If either criterion was met, subject was escalated to more intense prophylaxis regimen of 45 IU/kg, administered every other day. Subject who met dose escalation criteria while on prophylaxis regimen of 45 IU/kg, were escalated to higher intensity regimen designated by investigator. Significant spontaneous bleeds were those that led to transient or persistent loss of function. For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for RP cohort (Day 1 up to Month 24, Period 1 and Period 2) and OD cohort (Month 7 up to Month 18, Period 2) is reported. ITT analysis set. Overall Number of Subjects Analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, RP 25 IU/kg and 45 IU/kg, Period 1 and 2); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	39		
Units: Subjects	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Routine Prophylaxis Dose (IU/kg) of Moroctocog alfa (AF-CC) Received: Routine Prophylaxis Therapy

End point title	Mean Routine Prophylaxis Dose (IU/kg) of Moroctocog alfa (AF-CC) Received: Routine Prophylaxis Therapy

End point description:

Mean RP dose (by weight) for each subject was calculated as his total moroctocog alfa (AF-CC) consumption (in IU) divided by weight (in kg). For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for routine prophylaxis cohort (Day 1 up to Month 24, Period 1 and Period 2) and on demand cohort (Month 7 up to Month 18, Period 2) is reported. ITT analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form. Here, "Overall Number of Subjects Analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, Period 1 and Period 2); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), On Demand Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	40	48	39
Units: IU/kg				
arithmetic mean (standard deviation)	25 (± 4.6)	26 (± 5.4)	26 (± 5.2)	46 (± 5.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean of Total Number Moroctocog alfa (AF-CC) Infusions Received: Routine Prophylaxis Therapy

End point title	Mean of Total Number Moroctocog alfa (AF-CC) Infusions Received: Routine Prophylaxis Therapy

End point description:

In this end point mean of total number of infusions of moroctocog alfa (AF-CC) received by subject is reported. For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for routine prophylaxis cohort (Day 1 up to Month 24, Period 1 and Period 2) and on demand cohort (Month 7 up to Month 18, Period 2) is reported. ITT analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form. Here, "Overall Number of Subjects Analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, Period 1 and Period 2); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), On Demand Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	40	48	39
Units: Infusions				
arithmetic mean (standard deviation)	170 (± 31.3)	150 (± 37.0)	154 (± 36.6)	91 (± 22.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean of Total Number of Days Subjects Exposed to Moroctocog alfa (AF-CC): Routine Prophylaxis Therapy

End point title	Mean of Total Number of Days Subjects Exposed to Moroctocog alfa (AF-CC): Routine Prophylaxis Therapy

End point description:

For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for routine prophylaxis cohort (Day 1 up to Month 24, Period 1 and Period 2) and on demand cohort (Month 7 up to Month 18, Period 2) is reported. ITT analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form. Here, "Overall Number of Subjects Analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, Period 1 and Period 2); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), On Demand Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	40	48	39

Units: Days				
arithmetic mean (standard deviation)	170 (± 31.3)	150 (± 37.0)	153 (± 36.5)	91 (± 22.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean of Total Number of Infusions of Moroctocog alfa (AF-CC) Received per Week to Assess Compliance: Routine Prophylaxis Therapy

End point title	Mean of Total Number of Infusions of Moroctocog alfa (AF-CC) Received per Week to Assess Compliance: Routine Prophylaxis Therapy

End point description:

Subjects' compliance to their assigned prophylaxis regimen was measured by following: a) number of infusions received per week and b) dose received. In this end point mean of total number of infusions of moroctocog alfa (AF-CC) received by subjects per week is reported. For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for routine prophylaxis cohort (Day 1 up to Month 24, Period 1 and Period 2) and on demand cohort (Month 7 up to Month 18, Period 2) is reported. ITT analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form. Here, "Overall Number of Subjects Analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, RP 25 IU/kg and 45 IU/kg, Period 1 and 2); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	39		
Units: Infusions per week				
arithmetic mean (standard deviation)	3.3 (± 0.18)	2.1 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Phase Half Life (t1/2) of Factor VIII (FVIII) Activity

End point title	Terminal Phase Half Life (t1/2) of Factor VIII (FVIII) Activity

End point description:

Plasma decay half-life is the time measured for the FVIII activity to decrease by one half. Analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form, were in a non bleeding state, participated in a single pharmacokinetic (PK) assessment at the start of the study and for whom an adequate PK profile had been obtained.

End point type	Secondary

End point timeframe:

0.5, 8, 24, 28 and 32 hours post dose on Day 1

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Hour				
arithmetic mean (standard deviation)	8.86 (± 2.3513)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of Factor VIII Activity

End point title	Clearance (CL) of Factor VIII Activity

End point description:

Clearance is a measure of the volume of plasma from which FVIII activity is removed per unit time. It was reported in units milliliter per hour per kilogram (mL/hr/kg). Analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form, were in a non bleeding state, participated in a single PK assessment at the start of the study and for whom an adequate PK profile had been obtained.

End point type	Secondary

End point timeframe:

0.5, 8, 24, 28 and 32 hours post dose on Day 1

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: mL/hr/kg				
geometric mean (geometric coefficient of variation)	5.822 (± 59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery of Factor VIII Activity

End point title	Incremental Recovery of Factor VIII Activity

End point description:

Incremental recovery was the increase in circulating factor VIII (FVIII) activity for every international unit (IU) of moroctocog alfa (AF-CC) administered per kilogram of body weight of subject. It was measured in international units per deciliter per international units per kilogram (IU/dL)/(IU/kg). Analysis population included all subjects for whom legal acceptable representative had signed informed consent/assent form, were in a non-bleeding state, participated in single PK assessment at start of the study and for whom an adequate PK profile had been obtained. Here, "n" signifies number of subjects evaluable at specified time point.

End point type	Secondary

End point timeframe:

Day 1, Month 6

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
Day 1(n=6) Month 6 (n=2)	1.4438 (± 0.6145) 1.4148 (± 0.4046)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration of Factor VIII Activity

End point title	Maximum Concentration of Factor VIII Activity

End point description:

Maximum concentration of FVIII activity was measured in international units per milliliter (IU/mL). Analysis population included all subjects for whom legal acceptable representative had signed informed consent/assent form, were in a non-bleeding state, participated in single PK assessment at start of the study and for whom an adequate PK profile had been obtained.

End point type	Secondary

End point timeframe:

0.5, 8, 24, 28 and 32 hours post dose on Day 1

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: IU/mL				
geometric mean (geometric coefficient of variation)	0.7005 (± 60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to Extrapolated Infinite Time (AUCinf) of Factor VIII Activity

End point title	Area Under the Curve From Time Zero to Extrapolated Infinite Time (AUCinf) of Factor VIII Activity

End point description:

Area under FVIII activity-time profile from time zero extrapolated to infinite time. AUCinf is reported in units: international units*hour per milliliter (IU*hour/mL). Analysis population included all subjects for whom legal acceptable representative had signed informed consent/assent form, were in a non-bleeding state, participated in single PK assessment at start of the study and for whom an adequate PK profile had been obtained.

End point type	Secondary

End point timeframe:

0.5, 8, 24, 28 and 32 hours post dose on Day 1

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: IU*hr/mL				
geometric mean (geometric coefficient of variation)	9.02 (± 50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to Last Measurable Concentration (AUClast) of Factor VIII Activity

End point title	Area Under the Curve From Time Zero to Last Measurable Concentration (AUClast) of Factor VIII Activity

End point description:

Area under the FVIII activity-versus-time curve from time zero to the time of the last quantifiable concentration. Analysis population included all subjects for whom legal acceptable representative had signed informed consent/assent form, were in a non-bleeding state, participated in single PK assessment at start of the study and for whom an adequate PK profile had been obtained.

End point type	Secondary

End point timeframe:

0.5, 8, 24, 28 and 32 hours post dose on Day 1

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: IU*hr/mL				
geometric mean (geometric coefficient of variation)	8.04 (± 46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Volume of Distribution (Vss) of Factor VIII Activity

End point title	Steady-State Volume of Distribution (Vss) of Factor VIII Activity

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of FVIII would need to be uniformly distributed to produce the observed plasma concentration of FVIII. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state. Analysis population included all subjects for whom legal acceptable representative had signed informed consent/assent form, were in a non-bleeding state, participated in single PK assessment at start of the study and for whom an adequate PK profile had been obtained.

End point type	Secondary

End point timeframe:

0.5, 8, 24, 28 and 32 hours post dose on Day 1

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Milliliter per kilogram				
geometric mean (geometric coefficient of variation)	78.38 (± 50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) of Factor VIII Activity

End point title	Mean Residence Time (MRT) of Factor VIII Activity

End point description:

MRT was calculated as AUMCinf /AUCinf-TI/2, where AUMCinf is the area under the moment curve from time zero to infinity and TI is the duration of infusion. Analysis population included all subjects for whom legal acceptable representative had signed informed consent/assent form, were in a non-bleeding state, participated in single PK assessment at start of the study and for whom an adequate PK profile had been obtained.

End point type	Secondary

End point timeframe:

0.5, 8, 24, 28 and 32 hours post dose on Day 1

End point values	Moroctocog alfa (AF-CC): 50 IU/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Hour				
geometric mean (geometric coefficient of variation)	13.46 (± 33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (AEs) According to Severity

End point title	Number of Subjects with Treatment Emergent Adverse Events (AEs) According to Severity

End point description:

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily had a causal relationship with the treatment or usage. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose of study drug (up to 25 months) that were absent before treatment or that worsened relative to pretreatment state. AEs were classified into following on basis of severity: 1) mild = did not interfere with subject's usual function; 2) moderate = interfered to some extent with subject's usual function; 3) severe = interfered significantly with subject's usual function; 4) life threatening = AE required discontinuation of the study drug, subject was at immediate risk of death. Analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form and were analysed for safety. N = number of subjects were evaluable for this end point.

End point type	Secondary

End point timeframe:

Day 1 up to Month 25

End point values	Moroctocog alfa (AF-CC): All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: Subjects				
Mild	12			

Moderate	29			
Severe	8			
Life threatening	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Related Adverse Events

End point title	Number of Subjects With Treatment-Related Adverse Events

End point description:

A treatment related AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event had a causal relationship with the treatment or usage. Analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form and were analysed for safety.

End point type	Secondary

End point timeframe:

Day 1 up to Month 25

End point values	Moroctocog alfa (AF-CC): All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Subjects	49			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Confirmed FVIII Inhibitor Development

End point title	Number of Subjects With Confirmed FVIII Inhibitor Development

End point description:

Confirmed FVIII inhibitors were defined as a neutralizing antibody to FVIII with a titer value of greater than or equal to (>=) 0.6 Bethesda units (BU) per millimeter in a sample assayed using the Nijmegen assay at the central laboratory. Modified intent-to-treat (mITT) analysis population included all subjects for whom a legal acceptable representative had signed the informed consent/assent form and who received at least 1 dose of moroctocog alfa (AF-CC). Here, "Overall Number of Subjects Analysed" signifies those subjects who were evaluable for this end point and "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24

End point values	Moroctocog alfa (AF-CC): All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: Subjects				
OD Cohort (n =8)	0			
RP Cohort (n = 41)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Incidence of Less than Expected Therapeutic Effect (LETE): On Demand Therapy

End point title	Number of Subjects With Incidence of Less than Expected Therapeutic Effect (LETE): On Demand Therapy

End point description:

LETE occurs in on-demand setting if subject recorded 2 successive "No Response" ratings after 2 successive infusions of study drug. Infusions must have been administered within 24 hours of each other for treatment of same bleeding event in the absence of confounding factors (known presence or subsequent identification of a FVIII inhibitor, known inadequate dose for type and severity of bleed in opinion of investigator, delay of >4 hours between onset of bleed to infusion, delay of >24 hours before administration of a follow-up infusion, known compromised study drug, faulty administration of study drug, subject had an underlying, predisposing condition responsible for bleed in opinion of investigator. For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for RP cohort (Day 1 up to Month 24, Period 1 and Period 2) and OD cohort (Month 7 up to Month 18, Period 2) is reported. ITT analysis population. Number of Subjects Analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, RP 25 IU/kg and 45 IU/kg, Period 1 and 2); Day 1 up to Month 6 (OD Cohort, OD Therapy, Period 1); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), On Demand Cohort: On Demand Therapy	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	42	51	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Incidence of Less than Expected Therapeutic Effect (LETE): Routine Prophylaxis Therapy

End point title	Number of Subjects With Incidence of Less than Expected Therapeutic Effect (LETE): Routine Prophylaxis Therapy

End point description:

LETE in prophylaxis setting if there was spontaneous bleed within 48 hours after regularly scheduled prophylactic dose of study drug in absence of confounding factors (known presence or subsequent identification of a FVIII inhibitor, known inadequate prophylactic dose [a dose less than that prescribed in subject's regimen], known lack of adherence to the prescribed prophylaxis regimen, bleed occurs in a target joint identified at the start of the study, known compromised study drug, faulty administration of study drug, subject had an underlying, predisposing condition responsible for bleed in opinion of investigator. Therefore, LETE in prophylaxis setting was occurrence of a bleed. For reporting arm: routine prophylaxis 25 IU/kg therapy, cumulative data for RP cohort (Day 1 up to Month 24, Period 1 and Period 2) and OD cohort (Month 7 up to Month 18, Period 2) is reported. ITT analysis population. Number of Subjects Analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Day 1 up to Month 24 (RP Cohort, RP 25 IU/kg and 45 IU/kg, Period 1 and 2); Month 7 up to Month 18 (OD Cohort, RP 25 IU/kg, Period 2)

End point values	Moroctocog alfa (AF-CC), RP Cohort: RP Therapy 45 IU/kg	Moroctocog alfa (AF-CC), OD and RP Cohort: RP Therapy 25 IU/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	51		
Units: Subjects	3	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Month 25

Adverse event reporting additional description:

Same event may be as both AE and serious SAE, but distinct events. An event might be as serious in 1 subject and as non-serious in other, or subject may experienced both serious and non-serious event. Analysis population = all subjects for whom legal acceptable representative had signed informed consent/assent form and were analysed for safety.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy

Reporting group description:

In Period 1 subjects for, OD therapy were treated with IV infusion of moroctocog alfa (AF-CC) for 6 months (Day 1 up to Month 6) as prescribed by investigator based on current recommendations for on demand treatment with licensed product Xyntha (Minor bleeding: repetition of IV infusion of AF-CC, 20-40 IU/kg, every 12-24 hours until resolved for at least 1 day, depending upon severity of bleeding episode; Moderate bleeding: repetition of IV infusion of AF-CC, 30-60 IU/kg, every 12-24 hours for 3-4 days or until adequate local hemostasis was achieved; Major bleeding: repetition of IV infusion of AF-CC, 60-100 IU/kg, every 8-24 hours until bleeding was resolved). Period 1 was followed by Period 2 where subjects received IV infusion of AF-CC at 25 IU/kg once in 2 days up to 12 months (Month 7 to Month 18) as RP therapy.

Reporting group title	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg twice per week up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg, once in 2 days up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Reporting group title	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg

Reporting group description:

In Period 1 subjects for routine prophylaxis therapy, received IV infusion of moroctocog alfa (AF-CC) at 25 IU/kg once in 2 days up to 12 months (Day 1 up to Month 12). Period 1 was followed by Period 2 where subjects received IV infusion of moroctocog alfa (AF-CC) at 45 IU/kg, twice per week up to 12 months (Month 13 up to Month 24) as routine prophylaxis therapy.

Serious adverse events	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	5 / 18 (27.78%)	7 / 24 (29.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			

Limb injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Monoplegia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	2 / 24 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Torticollis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Moroctocog alfa (AF-CC), OD Cohort: OD Therapy Then RP Therapy	Moroctocog alfa(AF-CC), RP Cohort: RP 45 IU/kg Then RP 25IU/kg	Moroctocog alfa (AF-CC), RP Cohort: RP 25IU/kg Then RP 45IU/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	18 / 18 (100.00%)	24 / 24 (100.00%)
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 9 (0.00%)	3 / 18 (16.67%)	0 / 24 (0.00%)
occurrences (all)	0	4	0
Central venous catheterisation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 9 (44.44%)	13 / 18 (72.22%)	7 / 24 (29.17%)
occurrences (all)	12	32	12
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	4 / 24 (16.67%)
occurrences (all)	0	0	4
Catheter site discharge			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Catheter site haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Catheter site swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 9 (55.56%)	5 / 18 (27.78%)	5 / 24 (20.83%)
occurrences (all)	8	7	6
Rhinorrhoea			
subjects affected / exposed	1 / 9 (11.11%)	2 / 18 (11.11%)	4 / 24 (16.67%)
occurrences (all)	3	2	6
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	2 / 24 (8.33%)
occurrences (all)	0	4	2
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	4	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 18 (5.56%)	3 / 24 (12.50%)
occurrences (all)	1	1	3
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 9 (11.11%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Body temperature increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Platelet count decreased			

subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 9 (0.00%)	5 / 18 (27.78%)	5 / 24 (20.83%)
occurrences (all)	0	14	5
Limb injury			
subjects affected / exposed	0 / 9 (0.00%)	5 / 18 (27.78%)	5 / 24 (20.83%)
occurrences (all)	0	6	5
Head injury			
subjects affected / exposed	0 / 9 (0.00%)	2 / 18 (11.11%)	5 / 24 (20.83%)
occurrences (all)	0	11	7
Contusion			
subjects affected / exposed	1 / 9 (11.11%)	1 / 18 (5.56%)	3 / 24 (12.50%)
occurrences (all)	7	1	3
Fall			
subjects affected / exposed	0 / 9 (0.00%)	3 / 18 (16.67%)	2 / 24 (8.33%)
occurrences (all)	0	5	3
Face injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	3
Laceration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Traumatic haematoma			
subjects affected / exposed	0 / 9 (0.00%)	3 / 18 (16.67%)	0 / 24 (0.00%)
occurrences (all)	0	4	0
Eye injury			
subjects affected / exposed	0 / 9 (0.00%)	2 / 18 (11.11%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Skin abrasion			

subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Arthropod bite			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Arthropod sting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Traumatic haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)	4 / 18 (22.22%)	3 / 24 (12.50%)
occurrences (all)	0	6	7
Restless legs syndrome			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	5
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Vitreous floaters			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	5 / 18 (27.78%)	4 / 24 (16.67%)
occurrences (all)	1	9	8
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 18 (5.56%)	5 / 24 (20.83%)
occurrences (all)	1	1	5
Abdominal pain			
subjects affected / exposed	2 / 9 (22.22%)	1 / 18 (5.56%)	3 / 24 (12.50%)
occurrences (all)	2	1	3
Toothache			
subjects affected / exposed	1 / 9 (11.11%)	4 / 18 (22.22%)	1 / 24 (4.17%)
occurrences (all)	1	4	1
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	4 / 24 (16.67%)
occurrences (all)	0	2	6
Tooth loss			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	3 / 24 (12.50%)
occurrences (all)	0	1	3
Constipation			

subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Dental caries			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Gingival swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lip haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Oral disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Swelling face			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Intertrigo			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Ecchymosis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 18 (11.11%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 18 (11.11%)	8 / 24 (33.33%)
occurrences (all)	0	2	12
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)	2 / 18 (11.11%)	7 / 24 (29.17%)
occurrences (all)	1	2	14
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	4 / 24 (16.67%)
occurrences (all)	0	0	6
Haemarthrosis			
subjects affected / exposed	1 / 9 (11.11%)	2 / 18 (11.11%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
Joint swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	1 / 24 (4.17%)
occurrences (all)	0	1	2
Osteochondrosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	7 / 18 (38.89%)	8 / 24 (33.33%)
occurrences (all)	1	12	22
Nasopharyngitis			
subjects affected / exposed	2 / 9 (22.22%)	5 / 18 (27.78%)	7 / 24 (29.17%)
occurrences (all)	5	14	14
Influenza			
subjects affected / exposed	3 / 9 (33.33%)	1 / 18 (5.56%)	4 / 24 (16.67%)
occurrences (all)	6	2	4
Tonsillitis			
subjects affected / exposed	3 / 9 (33.33%)	1 / 18 (5.56%)	3 / 24 (12.50%)
occurrences (all)	5	1	3
Pharyngitis			

subjects affected / exposed	2 / 9 (22.22%)	1 / 18 (5.56%)	2 / 24 (8.33%)
occurrences (all)	7	1	3
Varicella			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	3 / 24 (12.50%)
occurrences (all)	1	0	3
Viral infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	3
Device related infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	1 / 24 (4.17%)
occurrences (all)	6	0	1
Eye infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 18 (11.11%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	1 / 24 (4.17%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	4
Laryngitis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	4	0	0
Otitis media			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Pharyngitis streptococcal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Body tinea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			

subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Enterobiasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 18 (5.56%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Pharyngotonsillitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 18 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 18 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2007	Duration of each treatment period (Period 1 and 2) was lengthened from 9 months per treatment period to 12 months per treatment period.
31 August 2011	Segment 1 for the OD cohort was shortened to 6 months duration from 12 months. Segment 2 for the OD cohort and Segments 1 and 2 for the RP cohort remained at 12 months duration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported