Clinical trial results:
A Phase II/III Open-label, Multicenter, Safety and Efficacy Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B

Summary

EudraCT number	2011-002415-28
Trial protocol	DE AT ES IT BG
Global end of trial date	21 July 2014

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	04 February 2015
Version creation reason	• Correction of full data set Minor correction made

Trial information

Trial identification

Sponsor protocol code	CSL654_3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01496274
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Str. 76, Marburg, Germany, 35041
Public contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001107-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are to evaluate the efficacy of rIX-FP in preventing bleeding episodes (prophylaxis) and safety of rIX-FP with respect to the development of inhibitors to FIX in patients with severe hemophilia B.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB).
The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers.
Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2012
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	Spain: 5
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Japan: 10
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	63
EEA total number of subjects	35

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)	7
Adults (18-64 years)	56
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 30 sites in 10 countries.

Pre-assignment

Screening details:

A total of 69 subjects provided informed consent and were screened for study participation. Of these, 63 subjects were enrolled and treated with rIX-FP.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Prophylaxis

Arm description:

Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Arm type	Experimental
Investigational medicinal product name	rIX-FP
Investigational medicinal product code	CSL654 or rIX-FP
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Recombinant IX-FP (rIX-FP) is a fusion protein linking coagulation factor IX with albumin, and will be administered by intravenous administration.

Arm title	On-demand

Arm description:

Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Arm type	Experimental
Investigational medicinal product name	rIX-FP
Investigational medicinal product code	CSL654 or rIX-FP
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Recombinant IX-FP (rIX-FP) is a fusion protein linking coagulation factor IX with albumin, and will be administered by intravenous administration.

Number of subjects in period 1	Prophylaxis	On-demand
Started	40	23
Completed	37	18
Not completed	3	5
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	1
Protocol violation	-	1
Lost to follow-up	-	3

Baseline characteristics

Reporting groups

Reporting group title	Prophylaxis

Reporting group description:

Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Reporting group title	On-demand

Reporting group description:

Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Reporting group values	Prophylaxis	On-demand	Total
Number of subjects	40	23	63
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	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	7	0	7
Adults (18-64 years)	33	23	56
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	40	23	63

End points

End points reporting groups

Reporting group title	Prophylaxis

Reporting group description:

Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Reporting group title	On-demand

Reporting group description:

Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Subject analysis set title	Safety Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Safety population consisted of subjects who received at least 1 dose of rIX-FP during the study.

Subject analysis set title	On-demand Arm, on-demand regimen
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the On-demand Arm, when receiving episodic treatment for bleeding episodes (on-demand regimen).

Subject analysis set title	On-demand Arm, prophylaxis regimen
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the On-demand Arm, when receiving routine weekly prophylaxis (prophylaxis regimen).

Subject analysis set title	Prophylaxis Arm, 7-day regimen
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received prophylactic rIX-FP on a weekly basis.

Subject analysis set title	Prophylaxis Arm, 10-day regimen
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received prophylactic rIX-FP every 10 days.

Subject analysis set title	Prophylaxis Arm, 14-day regimen
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received prophylactic rIX-FP every 14 days.

Subject analysis set title	PK - Prophylaxis Arm
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects included in the Pharmacokinetic (PK) population from the prophylaxis arm who received at least 1 dose of rIX-FP at 50 IU/kg. Data are presented for subjects from the PK population who had a sufficient number of analyzable PK samples for evaluation of the PK profile of rIX-FP.

Subject analysis set title	PK - On-demand Arm
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects included in the PK population from the on-demand arm who received at least 1 dose of rIX-FP at 50 IU/kg. Data are presented for subjects from the PK population who had a sufficient number of analyzable PK samples for evaluation of the PK profile of rIX-FP.

Subject analysis set title	Surgical population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Surgical population consisted of 3 subjects in the prophylaxis arm and 1 subject in the on demand arm who received at least 1 dose of rIX FP for a major or minor surgical procedure.

Primary: Number of subjects developing inhibitors against factor IX (FIX)

End point title	Number of subjects developing inhibitors against factor IX (FIX)[1]

End point description:

The number of participants developing inhibitors against factor IX (FIX) along with the 95% Clopper-Pearson confidence interval, are summarized for subjects with 50 or more exposure days (EDs) to rIX-FP, and for all participants in the study.

End point type	Primary

End point timeframe:

Up to 27.7 months (maximum)

Notes:

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

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: Participants				
number (confidence interval 95%)				
Participants with >=50 EDs to rIX-FP (n = 49)	0 (0 to 7.3)			
All participants (n = 63)	0 (0 to 5.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in frequency of spontaneous bleeding events between on-demand and prophylaxis treatments (annualized)

End point title	Change in frequency of spontaneous bleeding events between on-demand and prophylaxis treatments (annualized)

End point description:

Subjects in the on-demand arm received on-demand dosing with rIX-FP for up to 26 weeks (on-demand regimen), and then received weekly prophylaxis with rIX-FP for the remainder of the study (prophylaxis regimen). The effectiveness of prophylaxis in comparison to on-demand therapy was investigated by comparing the same subject's annualized spontaneous bleeding rate (AsBR) during the on-demand regimen and during the prophylaxis regimen.

End point type	Primary

End point timeframe:

Up to 26 weeks for on-demand regimen, and between 1 and 17 months for prophylaxis regimen.

End point values	On-demand Arm, on-demand regimen	On-demand Arm, prophylaxis regimen		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: bleeds/year/subject				
median (inter-quartile range (Q1-Q3))	15.43 (7.98 to 17.96)	0 (0 to 0.96)		

Statistical analyses

Statistical analysis title	Percent reduction in AsBR

Statistical analysis description:

Matched pairs design with 19 subjects and 2 observations per subject.

Comparison groups	On-demand Arm, prophylaxis regimen v On-demand Arm, on-demand regimen
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	Wilcoxon signed-rank test

Notes:

[2] - A test of null hypothesis that the ratio of AsBR (prophylaxis regimen/on-demand regimen) was ≥ 0.50 was conducted at the 1-sided 0.025 level.
[3] - P value is based on a Wilcoxon signed-rank test of H0: AsBR ratio (prophylaxis regimen/on-demand regimen) ≥ 0.50. The ratio was based on the original scale.

Secondary: Number of subjects developing antibodies against rIX-FP

End point title	Number of subjects developing antibodies against rIX-FP

End point description:

End point type	Secondary

End point timeframe:

For the duration of the study; median 20.27 months.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: rIX-FP consumed per month while maintaining assigned prophylactic

treatment interval during routine prophylaxis.

End point title	rIX-FP consumed per month while maintaining assigned prophylactic treatment interval during routine prophylaxis.

End point description:

End point type	Secondary

End point timeframe:

For Prophylaxis Arm 7-, 10- and 14-day regimens, median 269, 240 and 386 days respectively. For On-demand Arm, prophylaxis regimen, median 316 days.

End point values	On-demand Arm, prophylaxis regimen	Prophylaxis Arm, 7-day regimen	Prophylaxis Arm, 10-day regimen	Prophylaxis Arm, 14-day regimen
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	40	7	21
Units: IU/kg/month				
arithmetic mean (standard deviation)	191.69 (± 36.33)	202.68 (± 47.92)	201.5 (± 42.56)	157.44 (± 16.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery of rIX-FP

End point title	Incremental recovery of rIX-FP

End point description:

Pharmacokinetic (PK) data are presented for a single 50 IU/kg dose of rIX-FP.

End point type	Secondary

End point timeframe:

336 hours

End point values	PK - Prophylaxis Arm	PK - On-demand Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	18		
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)	1.29 (± 0.33)	1.24 (± 0.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency of related adverse events

End point title	The frequency of related adverse events

End point description:

The percentage of participants experiencing treatment-related adverse-events (TEAEs).

End point type	Secondary

End point timeframe:

For the duration of the study; median 20.27 months.

End point values	Prophylaxis	On-demand	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	23	63	
Units: percentage of participants				
number (not applicable)				
Related TEAE	10	4.3	7.9	
Not related TEAE	87.5	78.3	84.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of bleeding episodes requiring one or ≤ two injections of rIX-FP

End point title	Proportion of bleeding episodes requiring one or ≤ two injections of rIX-FP[4]

End point description:

Number of injections required to achieve hemostasis expressed as a percentage of the bleeding episodes requiring treatment. The number of bleeding episodes requiring treatment were 101, 220 and 37 in the Prophylaxis Arm, On-demand Arm (On-demand Regimen) and On-demand Arm (Prophylaxis Regimen), respectively.

End point type	Secondary

End point timeframe:

For the duration of the study; median 20.27 months.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for the On-demand Arm are provided for the two On-demand sub-group regimens (On-demand regimen and prophylaxis regimen), rather than for the overall On-demand Arm.

End point values	Prophylaxis	On-demand Arm, on-demand regimen	On-demand Arm, prophylaxis regimen	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	23	19	
Units: percentage of bleeding episodes				
number (not applicable)				

1 injection	92.1	94.5	91.9	
1 or 2 injections	100	98.6	94.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes, based on a four point ordinal scales (excellent, good, moderate, poor/no response)

End point title	Investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes, based on a four point ordinal scales (excellent, good, moderate, poor/no response)

End point description:

Number of bleeding episodes requiring treatment that resulted in hemostatic efficacy of excellent, good, moderate, poor/no response, according to the Investigator's clinical assessment of hemostatic efficacy, expressed as a percentage of the bleeding episodes requiring treatment. The number of bleeding episodes requiring treatment were 101 and 257 in the Prophylaxis Arm and On-demand Arm, respectively.

End point type	Secondary

End point timeframe:

For the duration of the study; median 20.27 months.

End point values	Prophylaxis	On-demand		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	23		
Units: percentage of bleeding episodes				
number (not applicable)				
Excellent	71.3	87.5		
Good	20.8	7.4		
Moderate	3	2.3		
Poor/No response	0	0.4		
Missing	5	2.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t1/2) of a single dose of rIX-FP

End point title	Half-life (t1/2) of a single dose of rIX-FP

End point description:

PK data are presented for a single 50 IU/kg dose of rIX-FP.

End point type	Secondary

End point timeframe:

336 hours

End point values	PK - Prophylaxis Arm	PK - On-demand Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	17		
Units: hour				
arithmetic mean (standard deviation)	104.77 (± 22.73)	96.88 (± 20.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve (AUC)

End point title	Area under the curve (AUC)

End point description:

AUC to the last sample with quantifiable drug concentration (AUClast) of a single dose of rIX-FP. PK data are presented for a single 50 IU/kg dose of rIX-FP.

End point type	Secondary

End point timeframe:

336 hours

End point values	PK - Prophylaxis Arm	PK - On-demand Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	18		
Units: IU*hr/dL				
arithmetic mean (standard deviation)	6534.15 (± 1856.96)	5963.3 (± 1893)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance of a single dose of rIX-FP

End point title	Clearance of a single dose of rIX-FP

End point description:

PK data are presented for a single 50 IU/kg dose of rIX-FP.

End point type	Secondary

End point timeframe:

336 hours

End point values	PK - Prophylaxis Arm	PK - On-demand Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	17		
Units: mL/hr				
arithmetic mean (standard deviation)	50.19 (± 12.92)	59 (± 19.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's (or surgeon's) overall clinical assessment of hemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor/no response

End point title	Investigator's (or surgeon's) overall clinical assessment of hemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor/no response

End point description:

Number of surgical events treated prophylactically with rIX-FP that resulted in hemostatic efficacy of excellent, good, moderate, poor/no response, according to the Investigator’s (surgeon’s) overall assessment of hemostatic efficacy for surgical prophylaxis. There were six surgical events overall.

End point type	Secondary

End point timeframe:

Up to 14 days after surgery

End point values	Surgical population			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: events				
Excellent	6			
Good	0			
Moderate	0			
Poor / No response	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized spontaneous bleeding events compared between 7 day prophylactic and extended regimens

End point title	Annualized spontaneous bleeding events compared between 7 day prophylactic and extended regimens

End point description:

Median number of spontaneous bleeds per year per subject comparing 7-, 10- and 14- day prophylactic regimens.

End point type	Secondary

End point timeframe:

During treatment, between median 240 and 386 days per subject.

End point values	Prophylaxis Arm, 7-day regimen	Prophylaxis Arm, 10-day regimen	Prophylaxis Arm, 14-day regimen	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38	7	21	
Units: bleeds/year/subject				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)	0 (0 to 1)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the duration of the study, up to 27.7 months.

Adverse event reporting additional description:

The Safety analysis population consisted of subjects who received at least 1 dose of rIX-FP during the study. Adverse Event data are treatment-emergent data unless otherwise noted.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Prophylaxis

Reporting group description:

Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Reporting group title	On-demand

Reporting group description:

Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.
Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

Serious adverse events	Prophylaxis	On-demand	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	2 / 23 (8.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
ACQUIRED EPILEPTIC APHASIA			
subjects affected / exposed	0 / 40 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
SYNOVITIS			
subjects affected / exposed	0 / 40 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY	Additional description: This SAE was not treatment-emergent.		

subjects affected / exposed	1 / 40 (2.50%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE HAEMORRHAGE	Additional description: This SAE was not treatment-emergent.		
subjects affected / exposed	1 / 40 (2.50%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prophylaxis	On-demand	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 40 (75.00%)	14 / 23 (60.87%)	
Injury, poisoning and procedural complications			
LIMB INJURY			
subjects affected / exposed	5 / 40 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	5	1	
CONTUSION			
subjects affected / exposed	3 / 40 (7.50%)	1 / 23 (4.35%)	
occurrences (all)	5	3	
LACERATION			
subjects affected / exposed	1 / 40 (2.50%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	11 / 40 (27.50%)	4 / 23 (17.39%)	
occurrences (all)	26	8	
DIZZINESS			
subjects affected / exposed	4 / 40 (10.00%)	0 / 23 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	2 / 40 (5.00%)	3 / 23 (13.04%)	
occurrences (all)	2	4	
TOOTHACHE			

subjects affected / exposed	4 / 40 (10.00%)	1 / 23 (4.35%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	3 / 40 (7.50%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	3 / 40 (7.50%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	9 / 40 (22.50%)	0 / 23 (0.00%)	
occurrences (all)	19	0	
BACK PAIN			
subjects affected / exposed	4 / 40 (10.00%)	2 / 23 (8.70%)	
occurrences (all)	5	3	
SYNOVITIS			
subjects affected / exposed	3 / 40 (7.50%)	0 / 23 (0.00%)	
occurrences (all)	6	0	
PAIN IN EXTREMITY			
subjects affected / exposed	3 / 40 (7.50%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
JOINT SWELLING			
subjects affected / exposed	3 / 40 (7.50%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
TENDONITIS			
subjects affected / exposed	3 / 40 (7.50%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	10 / 40 (25.00%)	6 / 23 (26.09%)	
occurrences (all)	27	11	
INFLUENZA			
subjects affected / exposed	4 / 40 (10.00%)	3 / 23 (13.04%)	
occurrences (all)	7	3	

UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 40 (12.50%)	0 / 23 (0.00%)	
occurrences (all)	7	0	
BRONCHITIS			
subjects affected / exposed	4 / 40 (10.00%)	1 / 23 (4.35%)	
occurrences (all)	4	1	
PHARYNGITIS			
subjects affected / exposed	3 / 40 (7.50%)	2 / 23 (8.70%)	
occurrences (all)	3	2	
GASTROENTERITIS			
subjects affected / exposed	3 / 40 (7.50%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
ACUTE TONSILLITIS			
subjects affected / exposed	0 / 40 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2011	Protocol Amendment 1 was issued before the enrollment of the first subject. Key changes to the protocol included: - Re-assigning a secondary endpoint to be a primary endpoint - Adding an efficacy evaluation algorithm for the Investigator rating of bleeding episodes for clarification - Updating treatment groups and assigned doses - Adding the criteria for dose adjustment and treatment regimen switching, as well as an algorithm for the new dose interval - Updating the statistical methodology section
18 October 2012	Protocol amendment 2 included the following key changes: - Added that, for on-demand treatment (Arm 2), a subject's prophylaxis dose could only be adjusted during the first 4 weeks, and that the dose prescribed after 4 weeks of prophylaxis treatment was to be maintained for the rest of the study. - Updated the statistical methodology section with analysis population definitions, additional secondary and exploratory endpoints, and additional details on statistical methods - Added the comparison of mean annualized bleeding rates between different prophylaxis regimens as one of the secondary endpoints
27 February 2014	Protocol Amendment 3 included the following key changes: - The bleeding episodes that occurred during the 4-week run-in period of prophylaxis therapy for subjects in Arm 2 (on-demand) were no longer to be excluded from analyses of the 26-week treatment period, and the total duration of treatment for Arm 2 was reduced from 30 weeks to 26 weeks, but a minimum of 12 weeks - Added additional statistical methods to clarify how missing data were handled during the primary efficacy analysis - Clarified that the test proposed for the comparison between the 7-day and the 10-day or 14-day prophylaxis regimens was referred to as a non-inferiority test

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported