Clinical trial results:
An Open-Label, Single-Arm, Post-Authorization Pragmatic Clinical Trial on the Safety and Efficacy of Xyntha (Moroctocog-Alfa (AF CC), Recombinant FVIII) in Subjects With Hemophilia A in Usual Care Settings in China

Summary

EudraCT number	2015-005040-33
Trial protocol	Outside EU/EEA
Global end of trial date	22 August 2016

Results information

Result version number	v1 (current)
This version publication date	04 January 2017
First version publication date	04 January 2017

Trial information

Trial identification

Sponsor protocol code	B1831083

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, 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	14 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2016
Global end of trial reached?	Yes
Global end of trial date	22 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the product medically important event (MIE) (FVIII inhibitor development during the study) of Xyntha in subjects with hemophilia A in usual care settings in China.

Protection of trial subjects:

This study used an External Data Monitoring Committee (E-DMC). The E-DMC periodically reviewed data from the study to ensure patient safety according to the Charter. The recommendations made by the E DMC to continue or alter the conduct of the study were forwarded to Pfizer for final decision.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 85
Worldwide total number of subjects	85
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	64
Adolescents (12-17 years)	7
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

As there were 2 subjects who rolled over from the surgical prophylaxis group to the on-demand group should be counted once in total column, the total number of baseline subjects was 85.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	On-Demand Group

Arm description:

Subjects were treated with intravenous infusions of Xyntha 500 International Unit (IU)/vial at a dose and frequency prescribed by the subject's treating physician in accordance with the China Xyntha Package Insert for approximately 6 months or approximately 50 exposure days (EDs).

Arm type	Experimental
Investigational medicinal product name	Xyntha
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were treated with intravenous infusions of Xyntha 500 IU/vial at a dose and frequency prescribed by the subject’s treating physician in accordance with the China Xyntha Package Insert.

Arm title	Surgical Prophylaxis Group

Arm description:

Subjects were treated with intravenous infusions of Xyntha 500 IU/vial. The treatment duration for surgical prophylaxis was decided by the investigator depending on surgery nature and subject conditions.

Arm type	Experimental
Investigational medicinal product name	Xyntha
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were treated with intravenous infusions of Xyntha 500 IU/vial. The treatment duration for surgical prophylaxis was decided by the investigator depending on surgery nature and subject conditions.

Number of subjects in period 1	On-Demand Group	Surgical Prophylaxis Group
Started	73	14
Completed	70	14
Not completed	3	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	On-Demand Group
Reporting group description:	
Subjects were treated with intravenous infusions of Xyntha 500 International Unit (IU)/vial at a dose and frequency prescribed by the subject's treating physician in accordance with the China Xyntha Package Insert for approximately 6 months or approximately 50 exposure days (EDs).	
Reporting group title	Surgical Prophylaxis Group
Reporting group description:	
Subjects were treated with intravenous infusions of Xyntha 500 IU/vial. The treatment duration for surgical prophylaxis was decided by the investigator depending on surgery nature and subject conditions.	

Reporting group values	On-Demand Group	Surgical Prophylaxis Group	Total
Number of subjects	73	14	85
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)	4	0	4
Children (2-11 years)	60	6	64
Adolescents (12-17 years)	7	0	7
Adults (18-64 years)	2	8	10
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	7.2	21	
standard deviation	± 4.8	± 15	-
Gender, Male/Female Units: Subjects			
FEMALE	1	0	1
MALE	72	14	84

End points

End points reporting groups

Reporting group title	On-Demand Group
Reporting group description:	
Subjects were treated with intravenous infusions of Xyntha 500 International Unit (IU)/vial at a dose and frequency prescribed by the subject's treating physician in accordance with the China Xyntha Package Insert for approximately 6 months or approximately 50 exposure days (EDs).	
Reporting group title	Surgical Prophylaxis Group
Reporting group description:	
Subjects were treated with intravenous infusions of Xyntha 500 IU/vial. The treatment duration for surgical prophylaxis was decided by the investigator depending on surgery nature and subject conditions.	

Primary: Percentage of Subjects With Factor VIII (FVIII) Inhibitors

End point title	Percentage of Subjects With Factor VIII (FVIII) Inhibitors[1]
End point description:	
Percentage of subjects with the product medically important event (MIE) (FVIII inhibitor development during the study).	
End point type	Primary
End point timeframe:	
From Day 1 up to 28 calendar days after End of Treatment (subjects had received treatment for 6 months or when subjects had achieved 50 exposure days [EDs] whichever occurred first).	

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 analysis was planned for this endpoint.

End point values	On-Demand Group	Surgical Prophylaxis Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	14		
Units: percentage of subjects				
number (confidence interval 95%)	8.22 (3.08 to 17.04)	7.14 (0.18 to 33.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with All Causality Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Subjects with All Causality Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)
End point description:	
An AE was any untoward medical occurrence without regard to causality in a subject who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. An AE was considered	

treatment emergent if it started for the first time in a subject on or after the first day of active treatment, or the event started before the first day of active treatment but increased in severity during active treatment. AEs included both SAEs and non-serious AEs.

End point type	Secondary

End point timeframe:

From Day 1 up to 28 calendar after End of Treatment (subjects had received treatment for 6 months or when subjects had achieved 50 EDs whichever occurred first).

End point values	On-Demand Group	Surgical Prophylaxis Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	14		
Units: subjects				
Subjects with AEs	65	10		
Subjects with SAEs	7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Assessment of On-Demand Treatment of Bleeds

End point title	Response Assessment of On-Demand Treatment of Bleeds[2]

End point description:

The proportion of infusions (initial and subsequent for a bleed) in each response category (excellent, good, moderate, no response) was reported. Excellent: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered. Good: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with at least 1 additional infusion administered for complete resolution of the bleeding episode or definite pain relief and/or improvement in signs of bleeding starting after 8 hours following the infusion, with no additional infusion administered. Moderate: Probable or slight improvement starting after 8 hours following the infusion, with at least 1 additional infusion administered for complete resolution of the bleeding episode. No Response: No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens.

End point type	Secondary

End point timeframe:

From Day 1 up to subjects had received treatment for 6 months or when subjects had achieved 50 EDs whichever occurred first.

Notes:

[2] - 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: No statistical analysis was planned for this endpoint.

End point values	On-Demand Group			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of infusions				
number (not applicable)				
Excellent	46.9			
Good	40			

Moderate	12.7			
No Response	0.3			
Data Not Recorded	0.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infusions Needed to Treat Each New Bleed for On-Demand Treatment

End point title	Number of Infusions Needed to Treat Each New Bleed for On-Demand Treatment[3]

End point description:

The number of Xyntha infusions administered to treat a bleed was determined. This was calculated by adding the on-demand initial treatment and any on-demand follow-up infusions for the same bleed (same bleed start date/time).

End point type	Secondary

End point timeframe:

From Day 1 up to subjects had received treatment for 6 months or when subjects had achieved 50 EDs whichever occurred first.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint.

End point values	On-Demand Group			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: infusions				
arithmetic mean (standard deviation)	1.6 (± 0.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Xyntha Infusions to Treat Each New Bleed for On-Demand Group

End point title	Frequency of Xyntha Infusions to Treat Each New Bleed for On-Demand Group[4]

End point description:

The number of bleeds resolved with 1, 2, 3, 4, or >4 infusions was reported for each of the categories (1, 2, 3, 4, or >4 infusions needed to treat the bleed), in which the numerator was the number of bleeds falling into each category, and the denominator was the total number of new bleeds across all subjects.

End point type	Secondary

End point timeframe:

From Day 1 up to subjects had received treatment for 6 months or when subjects had achieved 50 EDs whichever occurred first.

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: No statistical analysis was planned for this endpoint.

End point values	On-Demand Group			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of bleeds				
number (not applicable)				
1 Infusion	63			
2 Infusions	21.9			
3 Infusions	8.6			
4 Infusions	6			
>4 Infusions	0.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Hemostatic Efficacy for Surgical Prophylaxis Treatment

End point title	Hemostatic Efficacy for Surgical Prophylaxis Treatment[5]

End point description:

Assessment of hemostatic efficacy was determined by the investigator and/or surgeon using the 4 point Surgical Hemostasis Efficacy Rating Scale. Excellent: Achieved hemostasis comparable to that expected after similar surgery in a non hemophilic subject. Good: Prolonged time to hemostasis, with somewhat increased bleeding compared to that expected after similar surgery in a non hemophilic subject. Moderate: Obviously delayed hemostasis, but manageable with additional infusions. No Response: No hemostatic response. The percentage of observations in each hemostatic efficacy response category (excellent, good, moderate, none) was reported.

End point type	Secondary

End point timeframe:

From day of surgery to postoperative period

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint.

End point values	Surgical Prophylaxis Group			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percentage of observations				
number (not applicable)				
Day of Surgery: Excellent	71.4			
Day of Surgery: Good	28.6			
Day of Surgery: Moderate	0			
Day of Surgery: None	0			
Post-Operative: Excellent	75.5			
Post-Operative: Good	24.5			

Post-Operative: Moderate	0			
Post-Operative: None	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Estimated Blood Loss for Surgical Prophylaxis Treatment

End point title	Actual Estimated Blood Loss for Surgical Prophylaxis

End point description:

Number of subjects with blood loss in each category (Abnormal, Normal, and Absence). Blood loss during the intraoperative and the postoperative period were assessed by investigator or surgeon, which were rated as Abnormal, Normal, and Absence. Abnormal blood loss meant the blood loss was higher over the expectation for the non hemophilic subject.

End point type	Secondary

End point timeframe:

From day of surgery to postoperative period

Notes:

[6] - 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: No statistical analysis was planned for this endpoint.

End point values	Surgical Prophylaxis Group			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: partcipants				
Abnormal	0			
Normal	13			
Absence	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Units Transfused and Transfusion Type for Surgical Prophylaxis Treatment

End point title	Number of Units Transfused and Transfusion Type for Surgical Prophylaxis Treatment[7]

End point description:

The number of units and types of blood products transfused during the intraoperative and the postoperative period were recorded.

End point type	Secondary

End point timeframe:

From day of surgery to postoperative period.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint.

End point values	Surgical Prophylaxis Group			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: blood products				
Plasma	4			
Packed red blood cell	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Infusion Dose and Total Factor VIII Consumption for On-Demand Treatment and Surgical Prophylaxis Treatment

End point title	Average Infusion Dose and Total Factor VIII Consumption for On-Demand Treatment and Surgical Prophylaxis Treatment

End point description:

The total amount (IU) infused for each Xyntha infusion recorded in the study drug infusion log case report form (CRF) was summed to calculate the total factor VIII consumption for each subject. The average infusion dose for each subject was calculated as his total factor VIII consumption (in IU) divided by the number of infusions administered. The total factor VIII consumption, divided by number of infusions, was summarized similarly to average infusion dose (IU).

End point type	Secondary

End point timeframe:

Day 1 up to 6 months or 50 EDs whichever occurred first for On-Demand Group and Day of surgery to postoperative period for Surgical Prophylaxis Group

End point values	On-Demand Group	Surgical Prophylaxis Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	14		
Units: International Unit (IU)				
arithmetic mean (standard deviation)				
Average Infusion Dose	674.68 (± 357.613)	1245.07 (± 494.268)		
Total FVIII Consumption per Subject	25211 (± 22035.35)	39860.7 (± 27546.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Less Than Expected Therapeutic Effect (LETE) in the On-Demand Setting

End point title	Percentage of Less Than Expected Therapeutic Effect (LETE) in the On-Demand Setting[8]

End point description:

LETE occurred in the on demand setting if 2 successive "No Response" ratings were recorded after 2 successive Xyntha drug infusions, respectively.The infusions must have been administered within 24 hours (less than or equal to 24 hours) of each other for treatment of the same bleeding event in the absence of confounding factors (prespecified). Therefore, LETE in the on demand setting was based on the response to treatment of a bleeding episode (including those occurring during the surgical prophylaxis period). Note that on-demand treatments administered during the surgical prophylaxis period were also to be included.

End point type	Secondary

End point timeframe:

From Day 1 up to subjects had received treatment for 6 months or subjects had achieved 50 EDs whichever occurred first.

Notes:

[8] - 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: No statistical analysis was planned for this endpoint.

End point values	On-Demand Group			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of bleeding episodes				
number (confidence interval 95%)	0.06 (0 to 0.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Confirmed LETE in the Low Recovery Setting

End point title	Number of Confirmed LETE in the Low Recovery Setting

End point description:

LETE could also be lower than expected recovery of FVIII in the opinion of the investigator following infusion of Xyntha in the absence of confounding factors. The only confounding factors for low recovery were: known presence or subsequent identification of a FVIII inhibitor; known compromised Xyntha; faulty administration of Xyntha, including inadequate dosing.

End point type	Secondary

End point timeframe:

From Day 1 up to subjects had received treatment for approximately 6 months or when subjects had achieved approximately 50 EDs whichever occurred first.

End point values	On-Demand Group	Surgical Prophylaxis Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	14		
Units: LETE bleeds	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 28 calendar days after End of Treatment (subjects had received treatment for 6 months or when subjects had achieved 50 EDs whichever occurred first).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	On-Demand Group

Reporting group description:

Subjects were treated with intravenous infusions of Xyntha 500 International Unit (IU)/vial at a dose and frequency prescribed by the subject's treating physician in accordance with the China Xyntha Package Insert for approximately 6 months or approximately 50 exposure days (EDs).

Reporting group title	Surgical Prophylaxis Group

Reporting group description:

Subjects were treated with intravenous infusions of Xyntha 500 IU/vial. The treatment duration for surgical prophylaxis was decided by the investigator depending on surgery nature and subject conditions.

Serious adverse events	On-Demand Group	Surgical Prophylaxis Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 73 (9.59%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Gingival injury			
subjects affected / exposed	1 / 73 (1.37%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	6 / 73 (8.22%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	On-Demand Group	Surgical Prophylaxis Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 73 (84.93%)	9 / 14 (64.29%)	
General disorders and administration site conditions			
Local swelling			
subjects affected / exposed	4 / 73 (5.48%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Peripheral swelling			
subjects affected / exposed	15 / 73 (20.55%)	0 / 14 (0.00%)	
occurrences (all)	36	0	
Pyrexia			
subjects affected / exposed	15 / 73 (20.55%)	2 / 14 (14.29%)	
occurrences (all)	22	4	
Reproductive system and breast disorders			
Penile oedema			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	4	
Penile pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 73 (13.70%)	0 / 14 (0.00%)	
occurrences (all)	13	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 73 (8.22%)	0 / 14 (0.00%)	
occurrences (all)	10	0	
Joint injury			
subjects affected / exposed	5 / 73 (6.85%)	0 / 14 (0.00%)	
occurrences (all)	8	0	
Incision site pain			

subjects affected / exposed	0 / 73 (0.00%)	4 / 14 (28.57%)	
occurrences (all)	0	5	
Incision site oedema			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	9 / 73 (12.33%)	0 / 14 (0.00%)	
occurrences (all)	18	0	
Ligament sprain			
subjects affected / exposed	4 / 73 (5.48%)	0 / 14 (0.00%)	
occurrences (all)	5	0	
Procedural complication			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 73 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 73 (1.37%)	1 / 14 (7.14%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hepatobiliary disorders			

Hepatic function abnormal			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 73 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Ecchymosis			
subjects affected / exposed	9 / 73 (12.33%)	0 / 14 (0.00%)	
occurrences (all)	12	0	
Swelling face			
subjects affected / exposed	6 / 73 (8.22%)	0 / 14 (0.00%)	
occurrences (all)	7	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 73 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 73 (32.88%)	2 / 14 (14.29%)	
occurrences (all)	147	3	
Arthropathy			
subjects affected / exposed	4 / 73 (5.48%)	0 / 14 (0.00%)	
occurrences (all)	7	0	
Haemarthrosis			
subjects affected / exposed	3 / 73 (4.11%)	1 / 14 (7.14%)	
occurrences (all)	3	1	
Joint range of motion decreased			
subjects affected / exposed	4 / 73 (5.48%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Joint swelling			
subjects affected / exposed	34 / 73 (46.58%)	3 / 14 (21.43%)	
occurrences (all)	121	4	

Pain in extremity			
subjects affected / exposed	18 / 73 (24.66%)	0 / 14 (0.00%)	
occurrences (all)	31	0	
Muscle swelling			
subjects affected / exposed	11 / 73 (15.07%)	0 / 14 (0.00%)	
occurrences (all)	13	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 73 (24.66%)	0 / 14 (0.00%)	
occurrences (all)	21	0	
Tonsillitis			
subjects affected / exposed	6 / 73 (8.22%)	1 / 14 (7.14%)	
occurrences (all)	9	1	
Upper respiratory tract infection			
subjects affected / exposed	7 / 73 (9.59%)	0 / 14 (0.00%)	
occurrences (all)	16	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported