Clinical trial results:
A Phase 3b open-label, historically-controlled study to assess the safety and efficacy of two concurrent injections of AA4500 in adult subjects with multiple Dupuytren's contractures with palpable cords

Summary

EudraCT number	2012-004091-19
Trial protocol	SE GB DK
Global end of trial date	12 July 2013

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	12 July 2015

Trial information

Trial identification

Sponsor protocol code	AUX-CC-867

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01674634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Auxilium Pharmaceuticals, Inc.
Sponsor organisation address	1400 Atwater Drive, Malvern, United States, PA 19355
Public contact	Veronica Urdaneta, MD, MPH, Auxilium Pharmaceuticals, Inc 1400 Atwater Drive Malvern, PA 19355, 001 4842167721, Urdaneta.Veronica@endo.com
Scientific contact	Veronica Urdaneta, MD, MPH, Auxilium Pharmaceuticals, Inc 1400 Atwater Drive Malvern, PA 19355, 001 4842167721, Urdaneta.Veronica@endo.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 July 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2013
Global end of trial reached?	Yes
Global end of trial date	12 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the safety of two concurrent injections of AA4500 0.58 mg (one injection per joint) into the same hand in subjects with multiple Dupuytren's contractures with palpable cords followed 24 to 72 hours later by a finger extension procedure, and compare the rate of occurrence of targeted SAEs (tendon rupture/ligament injury and anaphylaxis) to historical rates of the same in clinical studies and post-marketing commercial use (ie, historical controls).
The secondary objective was to evaluate the efficacy of two concurrent injections of AA4500 0.58 mg (one injection per joint) into the same hand.
An additional objective was to evaluate the efficacy and safety of two concurrent injections of AA4500 0.58 mg (one injection per joint) in the same hand based upon the time between injection and finger extension procedure (ie, 24 hours, 48 hours or 72 hours).

Protection of trial subjects:

Care After Injection
In order to evaluate the subject for possible immediate immunological AEs, the subject remained in direct observation of medical personnel who were skilled in the management of acute allergic reactions for the first 20 minutes after receiving an injection of study drug. A subject may have been discharged from the study unit after a 60-minute observation provided:
• The subject exhibited no sign of an immunological or other significant systemic or local AE.
• The subject's vital signs remained stable throughout the 60-minute observation period.
Subjects were instructed not to flex or extend the fingers on the treated hand for 12 hours after injection to prevent extravasation of AA4500 out of the cord. A soft bulky gauze dressing was applied to the treated hand. The dressing served as a reminder to the subject not to move the treated hand. Subjects were instructed when to remove the dressing and to inspect the treated hand for edema, sensation, and movement. The subject was instructed to contact the investigator immediately if any problems were noticed. Subjects were instructed not to manipulate the injected finger(s) themselves.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 50
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Denmark: 87
Country: Number of subjects enrolled	Australia: 196
Country: Number of subjects enrolled	New Zealand: 70
Country: Number of subjects enrolled	United States: 278

Worldwide total number of subjects	715
EEA total number of subjects	171

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)	0
Adults (18-64 years)	348
From 65 to 84 years	360
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

The recruitment period was September 2012 to April 2013.
Patients were recruited in Europe (Sweden, Denmark and United Kingdom) , Australia, New Zealand and the United States.

Pre-assignment

Screening details:

Provide a signed and dated informed consent. Male or female ≥18 years of age. Diagnosis of Dupuytren's disease with at least two fixed flexion contractures on the same hand that were ≥20º in PIP and/or MP joints in fingers, other than the thumbs, which were caused by palpable cord(s) suitable for treatment. Have a positive "table top test".

Period 1

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

Arms

Arm title	XIAFLEX/XIAPEX

Arm description:

XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride])

Arm type	Experimental
Investigational medicinal product name	XIAFLEX/XIAPEX
Investigational medicinal product code	AA4500
Other name	Collagenase Clostridium histolyticum
Pharmaceutical forms	Injection
Routes of administration	Intracartilaginous use

Dosage and administration details:

XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride]).
Study drug was administered in a volume of 0.25 mL for MP joints and 0.20 mL for PIP joints. Study drug was injected directly into the cord using a 26 or 27 gauge ½ inch (13 mm) needle.
On Day 1 of this study, each subject received two concurrent injections of AA4500 0.58 mg (one injection per joint) into the same hand (selected hand). After completing the Day 61 follow-up visit, 10 subjects with bilateral disease were granted special permission to re-enroll into the study and receive a second series of two injections in their contralateral hand.

Number of subjects in period 1	XIAFLEX/XIAPEX
Started	715
Completed	715

Period 2

Period 2 title	Treatment/Assessment/Follow up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	XIAFLEX/XIAPEX

Arm description:

XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride])

Arm type	Experimental
Investigational medicinal product name	XIAFLEX/XIAPEX
Investigational medicinal product code	AA4500
Other name	Collagenase Clostridium histolyticum
Pharmaceutical forms	Injection
Routes of administration	Intracartilaginous use

Dosage and administration details:

XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride]).
Study drug was administered in a volume of 0.25 mL for MP joints and 0.20 mL for PIP joints. Study drug was injected directly into the cord using a 26 or 27 gauge ½ inch (13 mm) needle.
On Day 1 of this study, each subject received two concurrent injections of AA4500 0.58 mg (one injection per joint) into the same hand (selected hand). After completing the Day 61 follow-up visit, 10 subjects with bilateral disease were granted special permission to re-enroll into the study and receive a second series of two injections in their contralateral hand.

Arm title	XIAFLEX/XIAPEX MP Joint

Arm description:

AA4500 (collagenase clostridium histolyticum); 0.58 mg injection in the metacarpophalangeal (MP) joint cord.

Arm type	Experimental
Investigational medicinal product name	XIAFLEX/XIAPEX
Investigational medicinal product code	AA4500
Other name	Collagenase Clostridium histolyticum
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride]).
Study drug was administered in a volume of 0.25 mL for MP joints and 0.20 mL for PIP joints. Study drug was injected directly into the cord using a 26 or 27 gauge ½ inch (13 mm) needle.
On Day 1 of this study, each subject received two concurrent injections of AA4500 0.58 mg (one injection per joint) into the same hand (selected hand). After completing the Day 61 follow-up visit, 10 subjects with bilateral disease were granted special permission to re-enroll into the study and receive a second series of two injections in their contralateral hand.

Arm title	XIAFLEX/XIAPEX PIP Joint

Arm description:

AA4500 (collagenase clostridium histolyticum); 0.58 mg injection in the proximal interphalangeal (PIP) joint cord.

Arm type	Experimental

Investigational medicinal product name	XIAFLEX/XIAPEX
Investigational medicinal product code	AA4500
Other name	Collagenase Clostridium histolyticum
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride]).
Study drug was administered in a volume of 0.25 mL for MP joints and 0.20 mL for PIP joints. Study drug was injected directly into the cord using a 26 or 27 gauge ½ inch (13 mm) needle.
On Day 1 of this study, each subject received two concurrent injections of AA4500 0.58 mg (one injection per joint) into the same hand (selected hand). After completing the Day 61 follow-up visit, 10 subjects with bilateral disease were granted special permission to re-enroll into the study and receive a second series of two injections in their contralateral hand.

Number of subjects in period 2	XIAFLEX/XIAPEX	XIAFLEX/XIAPEX MP Joint	XIAFLEX/XIAPEX PIP Joint
Started	715	715	715
Completed	709	709	709
Not completed	6	6	6
Consent withdrawn by subject	3	3	3
Lost to follow-up	3	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	715	715	
Age categorical Units: Subjects			
Adults < 45 years	14	14	
Adults 45 to 54 years	97	97	
Adults 55 to 64 years	237	237	
Adults 65 to 74 years	284	284	
Adults 75 years and over	83	83	
Age continuous Units: years			
arithmetic mean	64		
standard deviation	± 9.26	-	
Gender categorical Units: Subjects			
Female	99	99	
Male	616	616	

End points

End points reporting groups

Reporting group title	XIAFLEX/XIAPEX
Reporting group description:	
XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride])	
Reporting group title	XIAFLEX/XIAPEX
Reporting group description:	
XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride])	
Reporting group title	XIAFLEX/XIAPEX MP Joint
Reporting group description:	
AA4500 (collagenase clostridium histolyticum); 0.58 mg injection in the metacarpophalangeal (MP) joint cord.	
Reporting group title	XIAFLEX/XIAPEX PIP Joint
Reporting group description:	
AA4500 (collagenase clostridium histolyticum); 0.58 mg injection in the proximal interphalangeal (PIP) joint cord.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population was defined as all enrolled subjects who had at least one AA4500 injection. All safety parameters were summarized based on this population.	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The mITT population was defined as all enrolled subjects who had both AA4500 injections and had at least one post-injection efficacy measurement of either fixed flexion contracture or a global assessment. All efficacy parameters were summarized based on this population.	
Subject analysis set title	Per-Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population was defined as all safety subjects who did not have any major protocol deviation.	

Primary: Percent Change From Baseline in Total Fixed Flexion

End point title	Percent Change From Baseline in Total Fixed Flexion[1]
End point description:	
Percent change from baseline in total fixed flexion = 100 * (baseline total FFC - day 31 total FFC)/baseline total FFC, where total fixed flexion is defined as the sum of the fixed flexion contracture (FCC) of the 2 joints receiving treatment. Positive percent change from baseline indicates improvement.	
End point type	Primary
End point timeframe:	
Baseline, Day 31	

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: The statistical methods were composed entirely of summary tables with descriptive statistics. There were no explicit hypotheses being tested in this study.

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[2]			
Units: Percentage of contracture change				
arithmetic mean (standard deviation)	74.41 (± 24.83)			

Notes:

[2] - Number of Treated Joint Pairs Analysed =724

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Total Range of Motion

End point title	Change From Baseline in Total Range of Motion[3]

End point description:

The total range of motion (ROM) is the sum of the range of motion measurements of the 2 treated joints. ROM is defined as difference between full flexion angle and full extension expressed in degrees. A positive change from baseline indicates increased (improved) ROM.

End point type	Primary

End point timeframe:

Baseline, Day 31

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical methods were composed entirely of summary tables with descriptive statistics. There were no explicit hypotheses being tested in this study.

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[4]			
Units: Degrees				
arithmetic mean (confidence interval 95%)	66.6 (64.3 to 68.9)			

Notes:

[4] - Number of Treated Joint Pairs Analysed = 724

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Success

End point title	Clinical Success

End point description:

Clinical success is defined as reduction of FFC of a treated joint to within 0-5 degrees of normal within 30 days of injection

End point type	Secondary

End point timeframe:

Within 30 days.

End point values	XIAFLEX/XIAPEX MP Joint	XIAFLEX/XIAPEX PIP Joint		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	714[5]	714[6]		
Units: Joints				
No	317	394		
Yes	579	158		

Notes:

[5] - Number of treated joints analysed=896

[6] - Number of treated joints analysed = 552

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Improvement

End point title	Clinical Improvement

End point description:

Clinical improvement is defined as a reduction of FFC by 50% or greater of the baseline value within 30 days of injection.

End point type	Secondary

End point timeframe:

Within 30 days.

End point values	XIAFLEX/XIAPEX MP Joint	XIAFLEX/XIAPEX PIP Joint		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	714[7]	714[8]		
Units: Joints				
No	96	157		
Yes	800	395		

Notes:

[7] - Number of treated joints analysed = 896

[8] - Number of treated joints analysed = 552

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Assessment of Satisfaction With Treatment at Day 31

End point title	Subject Assessment of Satisfaction With Treatment at Day 31

End point description:

Subject's were asked to rate satisfaction with treatment at the day 31 follow-up visit

End point type	Secondary

End point timeframe:

Day 31

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[9]			
Units: Joint pairs				
Very satisfied	461			
Quite satisfied	198			
Neither satisfied nor dissatisfied	38			
Quite dissatisfied	9			
Very dissatisfied	6			
Not done	12			

Notes:

[9] - Number of Treated Joint Pairs Analysed =724

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Assessment of Satisfaction With Treatment at Day 61

End point title	Subject Assessment of Satisfaction With Treatment at Day 61

End point description:

Subject's were asked to rate satisfaction with treatment at the day 61 follow-up visit

End point type	Secondary

End point timeframe:

Day 61

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[10]			
Units: Joint pairs				
Very satisfied	496			
Quite satisfied	167			
Neither satisfied nor dissatisfied	38			
Quite dissatisfied	11			
Very dissatisfied	8			
Not done	4			

Notes:

[10] - Number of Treated Joint Pairs Analysed =724

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator Assessment of Improvement With Treatment at Day 31

End point title	Investigator Assessment of Improvement With Treatment at Day 31

End point description:

Investigator's determined the degree of improvement in the severity of the subject's treated finger(s) compared with screening at the day 31 follow-up visit.

End point type	Secondary

End point timeframe:

Day 31

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[11]			
Units: Joint pairs				
Very much improved	375			
Much improved	271			
Minimally improved	51			
No change	4			
Minimally worse	3			
Much worse	0			
Very much worse	0			
Not done	12			

Notes:

[11] - Number of Treated Joint Pairs Analysed=724

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator Assessment of Improvement With Treatment at Day 61

End point title	Investigator Assessment of Improvement With Treatment at Day 61

End point description:

Investigator's determined the degree of improvement in the severity of the subject's treated finger(s) compared with screening at the day 61 follow-up visit.

End point type	Secondary

End point timeframe:

Day 61

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[12]			
Units: Joint pairs				
Very much improved	382			
Much improved	263			
Minimally improved	62			

No change	7			
Minimally worse	2			
Much worse	0			
Very much worse	0			
Not done	8			

Notes:

[12] - Number of Treated Joint Pairs Analysed= 724

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline for Unité Rhumatologique Des Affections de la Main Scale at Day 31

End point title	Change From Baseline for Unité Rhumatologique Des Affections de la Main Scale at Day 31

End point description:

The Unité Rhumatologique des Affections de la Main (URAM) scale is a patient-reported functional 9-item scale (total score 0-45) developed and validated to assess functional outcome of patients suffering from Dupuytren's disease with higher scores indicating greater difficulty using the hand.The estimated clinically important change of the URAM scale is 2.9 points. A decrease in total URAM score indicates improvement in hand function.

End point type	Secondary

End point timeframe:

Baseline, Day 31

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[13]			
Units: joint pairs analysed				
arithmetic mean (standard deviation)	-11.3 (± 9.19)			

Notes:

[13] - Number of Treated Joint Pairs Analysed=724

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline for Unité Rhumatologique Des Affections de la Main Scale at Day 61

End point title	Change From Baseline for Unité Rhumatologique Des Affections de la Main Scale at Day 61

End point description:

The URAM scale is a patient-reported functional 9-item scale (total score 0-45) developed and validated to assess functional outcome of patients suffering from Dupuytren's disease with higher scores indicating greater difficulty using the hand.The estimated clinically important change of the URAM scale is 2.9 points. A decrease in total URAM score indicates improvement in hand function.

End point type	Secondary

End point timeframe:

Baseline, Day 61

End point values	XIAFLEX/XIAPEX			
Subject group type	Reporting group			
Number of subjects analysed	714[14]			
Units: Joint pairs analysed				
arithmetic mean (standard deviation)	-12.3 (± 9.75)			

Notes:

[14] - Number of Treated Joint Pairs Analysed =724

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening visit to end of study.

Adverse event reporting additional description:

AA4500 (collagenase clostridium histolyticum): 2 concurrent 0.58 mg injections (1 injection per joint) in the same hand

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	XIAFLEX/XIAPEX

Reporting group description:

XIAFLEX / XIAPEX injection (0.58 mg after reconstitution with sterile diluent [0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride])

Serious adverse events	XIAFLEX/XIAPEX		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 715 (2.24%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Feeding tube complication	Additional description: PEG feeding tube obstruction		
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage	Additional description: Bleeding left hand post procedure.		
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture	Additional description: Upgraded to an SAE by the sponsor		

subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Deep vein thrombosis			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Myelopathy			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 715 (0.28%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal column stenosis			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis	Additional description: Left lower leg.		
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphangitis			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 715 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	XIAFLEX/XIAPEX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	680 / 715 (95.10%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	420 / 715 (58.74%)		
occurrences (all)	513		
Laceration			
subjects affected / exposed	184 / 715 (25.73%)		
occurrences (all)	192		
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	92 / 715 (12.87%)		
occurrences (all)	102		
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	51 / 715 (7.13%)		
occurrences (all)	53		
Injection site haematoma			
subjects affected / exposed	60 / 715 (8.39%)		
occurrences (all)	61		
Injection site pain			
subjects affected / exposed	102 / 715 (14.27%)		
occurrences (all)	109		
Injection site swelling			
subjects affected / exposed	42 / 715 (5.87%)		
occurrences (all)	42		
Oedema peripheral			
subjects affected / exposed	552 / 715 (77.20%)		
occurrences (all)	626		
Injection site haemorrhage	Additional description: Injection site ecchymosis		
subjects affected / exposed	45 / 715 (6.29%)		
occurrences (all)	45		
Skin and subcutaneous tissue disorders			
Blood blister			
subjects affected / exposed	89 / 715 (12.45%)		
occurrences (all)	98		
Ecchymosis			
subjects affected / exposed	37 / 715 (5.17%)		
occurrences (all)	39		
Pruritus			
subjects affected / exposed	107 / 715 (14.97%)		
occurrences (all)	121		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	361 / 715 (50.49%)		
occurrences (all)	431		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	Clarified that the study period of 60 days for the core study was followed by an optional 90-day additional treatment period. Added that subjects who required additional treatment in the treated hand may have received up to three additional injections of AA4500 according to the XIAFLEX package insert. Updated that the end of the core study occurred when the last subject completed the Day 61 follow-up visit. The end of the completed study occurred when the last subject completed the Day 30 visit after the last additional injection. Added that AEs, including targeted AEs, were to be captured on the eCRF. In addition, the date of each additional injection and the finger and joint treated were to be recorded on the eCRF.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported