



## Clinical trial results:

**Retreatment of recurrent contractures in joints effectively treated with AA4500 (collagenase clostridium histolyticum [XIAFLEX®/XIAPEX®]) in an Auxilium-sponsored Phase 3 Study in the United States, Australia, and Europe.**

### Summary

EudraCT number	2011-005065-21
Trial protocol	SE GB
Global end of trial date	07 October 2013

### Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	09 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	AUX-CC-862
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01498640
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 USA, 001 4842167721 , Urdaneta.Veronica@endo.com
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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	07 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2013
Global end of trial reached?	Yes
Global end of trial date	07 October 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objectives of this study were to assess the safety and efficacy of AA4500 in the retreatment of recurrent contractures in joints that were effectively treated with AA4500 in a previous Auxilium-sponsored Phase 3 study.

Protection of trial subjects:

Care After Injection

To evaluate the subject for possible immediate immunological AEs, the subject was to remain 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 could have been discharged from the study unit after a 60-minute observation period, provided:

- The subject exhibited no sign of an immunological or other significant systemic or local AE and
- The subject's vital signs remained stable throughout the 60-minute observation period

Before discharge, subjects were instructed not to flex or extend the fingers on the treated hand for 12 hours after the 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 themselves.

Local Anesthesia

Before each finger extension procedure, the investigator could have administered local anesthesia according to the practice of his/her institution and the subject's willingness to receive anesthesia. Local anesthesia was to be recorded as a concomitant medication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 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	Australia: 21
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	52
EEA total number of subjects	10

Notes:

<b>Subjects enrolled per age group</b>	
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)	20
From 65 to 84 years	31
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

The recruitment period was March 2012 to October 2013.

Recruitment took place in the Australia, Sweden, the United Kingdom and the United States,

### Pre-assignment

Screening details:

Subjects who had recurrence of contracture in a joint that was effectively treated with AA4500 in a Phase 3 Auxilium-sponsored study, were determined by the investigator as eligible and who provided informed consent were enrolled.

### 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
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Arm description:

XIAFLEX/XIAPEX: up to three 0.58 mg injections

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:

AA4500 was administered after reconstitution with diluent (0.9% NaCl containing 0.03% calcium chloride). The volume of injection was 0.25 mL for metacarpophalangeal (MP) joints and 0.20 mL for proximal interphalangeal (PIP) joints.

The investigator treated the recurrent cord affecting the joint with up to three injections of AA4500 until the outcome was deemed satisfactory by the investigator and/or the subject, or until the cord was no longer palpable. Injections of AA4500 were to be separated by approximately 28 days. Each subject in this study had only one recurrent contracture treated.

<b>Number of subjects in period 1</b>	XIAFLEX/XIAPEX
Started	52
Completed	52

**Period 2**

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

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	XIAFLEX/XIAPEX MP Joint

Arm description:

Up to 3 injections of collagenase clostridium histolyticum 0.58 mg 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	Intracartilaginous use

Dosage and administration details:

AA4500 was administered after reconstitution with diluent (0.9% NaCl containing 0.03% calcium chloride). The volume of injection was 0.25 mL for metacarpophalangeal (MP) joints and 0.20 mL for proximal interphalangeal (PIP) joints.

The investigator treated the recurrent cord affecting the joint with up to three injections of AA4500 until the outcome was deemed satisfactory by the investigator and/or the subject, or until the cord was no longer palpable. Injections of AA4500 were to be separated by approximately 28 days. Each subject in this study had only one recurrent contracture treated.

<b>Arm title</b>	XIAFLEX/XIAPEX PIP Joint
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Arm description:

Up to 3 injections of collagenase clostridium histolyticum 0.58 mg 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	Intracartilaginous use

Dosage and administration details:

AA4500 was administered after reconstitution with diluent (0.9% NaCl containing 0.03% calcium chloride). The volume of injection was 0.25 mL for metacarpophalangeal (MP) joints and 0.20 mL for proximal interphalangeal (PIP) joints.

The investigator treated the recurrent cord affecting the joint with up to three injections of AA4500 until the outcome was deemed satisfactory by the investigator and/or the subject, or until the cord was no longer palpable. Injections of AA4500 were to be separated by approximately 28 days. Each subject in this study had only one recurrent contracture treated.

<b>Number of subjects in period 2</b>	XIAFLEX/XIAPEX MP Joint	XIAFLEX/XIAPEX PIP Joint
Started	31	21
Completed	31	21

**Period 3**

Period 3 title	Post-treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	XIAFLEX/XIAPEX
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Arm description:

XIAFLEX/XIAPEX: up to three 0.58 mg injections

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:

AA4500 was administered after reconstitution with diluent (0.9% NaCl containing 0.03% calcium chloride). The volume of injection was 0.25 mL for metacarpophalangeal (MP) joints and 0.20 mL for proximal interphalangeal (PIP) joints.

The investigator treated the recurrent cord affecting the joint with up to three injections of AA4500 until the outcome was deemed satisfactory by the investigator and/or the subject, or until the cord was no longer palpable. Injections of AA4500 were to be separated by approximately 28 days. Each subject in this study had only one recurrent contracture treated.

<b>Number of subjects in period 3</b>	XIAFLEX/XIAPEX
Started	52
Completed	47
Not completed	5
Adverse event, serious fatal	1
Discontinued to join Study AUX-CC-867	3
Lost to follow-up	1

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	52	52	
Age categorical			
Units: Subjects			
Adults (18-64 years)	20	20	
From 65-84 years	31	31	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	66.5		
standard deviation	± 9.53	-	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	50	50	

## End points

### End points reporting groups

Reporting group title	XIAFLEX/XIAPEX
Reporting group description: XIAFLEX/XIAPEX: up to three 0.58 mg injections	
Reporting group title	XIAFLEX/XIAPEX MP Joint
Reporting group description: Up to 3 injections of collagenase clostridium histolyticum 0.58 mg in the metacarpophalangeal (MP) joint cord	
Reporting group title	XIAFLEX/XIAPEX PIP Joint
Reporting group description: Up to 3 injections of collagenase clostridium histolyticum 0.58 mg in the proximal interphalangeal (PIP) joint cord	
Reporting group title	XIAFLEX/XIAPEX
Reporting group description: XIAFLEX/XIAPEX: up to three 0.58 mg injections	
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 ITT subjects who had a recurrent joint contracture retreated in the current study. If the joint treated in the current study did not meet the definition of a recurrent joint then the subject was not included in the mITT population. All efficacy parameters were summarized using this population.	

### Primary: Clinical Success

End point title	Clinical Success <sup>[1]</sup>
End point description: Clinical success defined as reduction in fixed-flexion contracture to less than or equal to 5 degrees 30 days after the last injection of AA4500. Efficacy assessment based on modified intent-to-treat (mITT) population which includes all enrolled subjects who received at least 1 AA4500 injection to the treated joint and had at least 1 post-injection efficacy measure.	
End point type	Primary
End point timeframe: 30 days after last injection	
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 MP Joint	XIAFLEX/XIAPEX PIP Joint		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	20		
Units: Percentage of Participants				
number (confidence interval 95%)	64.5 (45.37 to 80.77)	45 (23.06 to 68.47)		



## Statistical analyses

No statistical analyses for this end point

### Primary: Percent Change from Baseline in Degree of Contracture

End point title	Percent Change from Baseline in Degree of Contracture <sup>[2]</sup>
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End point description:

Change in fixed-flexion contracture measured in degrees where a decrease of 100% would correspond to a reduction in contracture to 0 degrees.

Efficacy assessment based on modified intent-to-treat (mITT) population which includes all enrolled subjects who received at least 1 AA4500 injection to the treated joint and had at least 1 post-injection efficacy measure.

End point type	Primary
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End point timeframe:

Baseline and 30 days after last injection

Notes:

[2] - 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/XIAPE X MP Joint	XIAFLEX/XIAPE X PIP Joint		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	20		
Units: Percentage of contracture change				
arithmetic mean (standard deviation)	83.24 (± 24.275)	69.1 (± 26.776)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in Range of Motion

End point title	Change in Range of Motion <sup>[3]</sup>
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End point description:

Range of motion defined as difference between full flexion angle and full extension angle expressed in degrees.

Efficacy assessment based on modified intent-to-treat (mITT) population which includes all enrolled subjects who received at least 1 AA4500 injection to the treated joint and had at least 1 post-injection efficacy measure.

End point type	Primary
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End point timeframe:

Baseline and 30 days after last injection

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/XIAPE X MP Joint	XIAFLEX/XIAPE X PIP Joint		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	20		
Units: Degrees				
arithmetic mean (standard deviation)	31.4 (± 17.52)	26.8 (± 17.39)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Physician Global Assessment of Improvement

End point title	Physician Global Assessment of Improvement
End point description:	
Physician global assessment of change (improvement) in subject's Dupuytren's contracture. Efficacy assessment based on modified intent-to-treat (mITT) population which includes all enrolled subjects who received at least 1 AA4500 injection to the treated joint and had at least 1 post-injection efficacy measure.	
End point type	Secondary
End point timeframe:	
30 days after last injection	

End point values	XIAFLEX/XIAPE X MP Joint	XIAFLEX/XIAPE X PIP Joint		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	20		
Units: Participants				
number (not applicable)				
Very much improved	18	12		
Much improved	11	5		
Minimally improved	0	2		
No change	1	1		
Minimally worse	0	0		
Much worse	0	0		
Very much worst	0	0		
Not done	1	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Subject Global Assessment of Satisfaction

End point title	Subject Global Assessment of Satisfaction
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End point description:

Subject global assessment of overall treatment satisfaction.

Efficacy assessment based on modified intent-to-treat (mITT) population which includes all enrolled subjects who received at least 1 AA4500 injection to the treated joint and had at least 1 post-injection efficacy measure.

End point type	Secondary
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End point timeframe:

30 days after last injection

End point values	XIAFLEX/XIAPE X MP Joint	XIAFLEX/XIAPE X PIP Joint		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	20		
Units: Participants				
number (not applicable)				
Very satisfied	20	10		
Quite satisfied	9	5		
Neither satisfied nor dissatisfied	1	2		
Quite dissatisfied	0	1		
Very dissatisfied	0	0		
Not done	1	2		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Recurrence of Contracture

End point title	Recurrence of Contracture
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End point description:

Recurrence of contracture in the joint at day 365 that was successfully treated 30 days after last injection assessed. Recurrence was defined as 20 degree or greater increase of contracture of the treated joint at day 365 or medication intervention of the treated joint between the 2 time points.

Efficacy assessment based on mITT population which includes all enrolled subjects who received at least 1 AA4500 injection to the treated joint and had at least 1 post-injection efficacy measure; only joints that were successfully treated (reduction in contracture to 5 degrees or less) 30 days after last injection were assessed

End point type	Secondary
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End point timeframe:

Day 365

<b>End point values</b>	XIAFLEX/XIAPE X			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Joints				
number (not applicable)				
Number of joints analysed	29			
Number of joints with recurrence of contracture	6			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

1 year

Adverse event reporting additional description:

XIAFLEX/XIAPEX: up to three 0.58 mg injections

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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### Reporting groups

Reporting group title	XIAFLEX/XIAPEX
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Reporting group description: -

Serious adverse events	XIAFLEX/XIAPEX		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 52 (7.69%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebellar infarction	Additional description: Resulted in death		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Dupuytren's contracture			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 52 (1.92%)		
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 %

<b>Non-serious adverse events</b>	XIAFLEX/XIAPEX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 52 (84.62%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	23 / 52 (44.23%)		
occurrences (all)	28		
Skin laceration			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
General disorders and administration site conditions			

Injection site haematoma subjects affected / exposed occurrences (all)	8 / 52 (15.38%) 12		
Injection site pain subjects affected / exposed occurrences (all)	10 / 52 (19.23%) 14		
Injection site pruritus subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 5		
Injection site swelling subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 9		
Oedema peripheral subjects affected / exposed occurrences (all)	32 / 52 (61.54%) 41		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	10 / 52 (19.23%) 13		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	16 / 52 (30.77%) 22		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2011	<p>The following change was made throughout the protocol:</p> <p>WAS: Injections of AA4500 should be separated by a minimum of 28 days. The maximum interval between the first and last injection should be less than or equal to 6 months.</p> <p>Changed to: Injections of AA4500 are to be separated by approximately 28 days.</p> <p>Section 9.4 was added.</p> <p>9.4 Interim Analysis</p> <p>An interim analysis of data will be performed after the last subject completes the Day 30 follow-up visit after the last injection. The final analysis of data will be performed after the last subject completes the Day 365 follow-up visit.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported