# 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 |

### 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<br>1400 Atwater Drive<br>Malvern, PA 19355<br>USA, 001 4842167721 , Urdaneta.Veronica@endo.com |
| Scientific contact | Veronica Urdaneta, MD, MPH, Auxilium Pharmaceuticals, Inc<br>1400 Atwater Drive<br>Malvern, PA 19355<br>USA, 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 | 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:

| 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) | 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 |

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.

| **Number of subjects in period 1** | 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 |
| **Arm title** | 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.

| | |
|---|---|
| **Arm title** | XIAFLEX/XIAPEX PIP Joint |

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.

| **Number of subjects in period 2** | 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

| | |
|---|---|
| **Arm title** | XIAFLEX/XIAPEX |

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.

| **Number of subjects in period 3** | 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 |

Reporting group description: -

| Reporting group values | Baseline | Total | |
|---|---|---|---|
| Number of subjects | 52 | 52 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 20 | 20 | |
| From 65-84 years | 31 | 31 | |
| 85 years and over | 1 | 1 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 66.5 | | |
| standard deviation | ± 9.53 | - | |
| Gender categorical<br>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.<br>All efficacy parameters were summarized using this population. | |

### Primary: Clinical Success

| | |
|---|---|
| End point title | Clinical Success[1] |
| 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.<br>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[2] |
|---|---|

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 |
|---|---|

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/XIAPEX MP Joint | XIAFLEX/XIAPEX 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[3] |
|---|---|

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 |
|---|---|

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/XIAPEX MP Joint | XIAFLEX/XIAPEX 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/XIAPEX MP Joint | XIAFLEX/XIAPEX 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 |
|---|---|

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 |
|---|---|

End point timeframe:

30 days after last injection

| 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: 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 |
|---|---|

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 |
|---|---|

End point timeframe:

Day 365

| End point values | XIAFLEX/XIAPEX | | | |
|---|---|---|---|---|
| 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

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 11.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | XIAFLEX/XIAPEX |

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 %

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 01 November 2011 | The following change was made throughout the protocol:<br>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.<br>Changed to: Injections of AA4500 are to be separated by approximately 28 days.<br>Section 9.4 was added.<br>9.4 Interim Analysis<br>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. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported