



## Clinical trial results:

### A Randomized, Double Blind, Placebo-Controlled, Dose Titration, Phase 2 Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ISIS 494372 Administered Subcutaneously to Patients with High Lipoprotein(a)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-000701-13   |
| Trial protocol           | DE GB DK NL      |
| Global end of trial date | 18 November 2015 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 18 December 2019 |
| First version publication date | 18 December 2019 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | ISIS494372-CS3 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02160899 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Ionis Pharmaceuticals, Inc.   |
| Sponsor organisation address | 2855 Gazelle Court, Carlsbad, United States, CA 92010   |
| Public contact               | Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com |
| Scientific contact           | Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.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                       | 18 November 2015 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 18 November 2015 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective this study is to characterize the safety and tolerability of ISIS-APO(a)Rx in individual subjects at escalating doses of 100, 200, and 300 mg/week; and to characterize the efficacy of ISIS-APO(a)Rx in lowering Lp(a) using a dose titration study design.

Protection of trial subjects:

Each subject, or legally acceptable representative, signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 25 June 2014     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 3 Months         |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 10        |
| Country: Number of subjects enrolled | Netherlands: 30   |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Denmark: 7        |
| Country: Number of subjects enrolled | Germany: 11       |
| Worldwide total number of subjects   | 64                |
| EEA total number of subjects         | 54                |

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)      | 55 |
| From 65 to 84 years       | 9  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 51 subjects were enrolled in Cohort A and 13 subjects were enrolled in Cohort B.

### Pre-assignment

Screening details:

A total of 86 subjects were screened for the study and 64 subjects were randomized into Cohort A and Cohort B and received study treatment. Two subjects in Cohort B did not complete the study treatment but completed the post-treatment follow-up.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | Cohort A: Placebo |

Arm description:

Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Cohort A: ISIS-APO(a)Rx < 2000 mg |
|------------------|-----------------------------------|

Arm description:

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | ISIS-APO(a)Rx          |
| Investigational medicinal product code |                        |
| Other name                             | ISIS 494372            |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Cohort A: ISIS-APO(a)Rx ≥ 2000 mg |
|------------------|-----------------------------------|

Arm description:

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                        |
|--|------------------------|
| Investigational medicinal product name | ISIS-APO(a)Rx          |
| Investigational medicinal product code |                        |
| Other name                             | ISIS 494372            |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Cohort B: Placebo |
|------------------|-------------------|

**Arm description:**

Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Cohort B: ISIS-APO(a)Rx < 2000 mg |
|------------------|-----------------------------------|

**Arm description:**

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | ISIS-APO(a)Rx          |
| Investigational medicinal product code |                        |
| Other name                             | ISIS 494372            |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Cohort B: ISIS-APO(a)Rx >= 2000 mg |
|------------------|------------------------------------|

**Arm description:**

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | ISIS-APO(a)Rx          |
| Investigational medicinal product code |                        |
| Other name                             | ISIS 494372            |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

| <b>Number of subjects in period 1</b>  | Cohort A: Placebo | Cohort A: ISIS-APO(a)Rx < 2000 | Cohort A: ISIS-APO(a)Rx >= 2000 |
|--|-------------------|--------------------------------|---------------------------------|
| Started                                | 26                | 4                              | 21                              |
| Completed                              | 26                | 3                              | 21                              |
| Not completed                          | 0                 | 1                              | 0                               |
| Adverse Event or Serious Adverse Event | -                 | 1                              | -                               |

| <b>Number of subjects in period 1</b>  | Cohort B: Placebo | Cohort B: ISIS-APO(a)Rx < 2000 | Cohort B: ISIS-APO(a)Rx >= 2000 |
|--|-------------------|--------------------------------|---------------------------------|
| Started                                | 3                 | 2                              | 8                               |
| Completed                              | 2                 | 0                              | 8                               |
| Not completed                          | 1                 | 2                              | 0                               |
| Adverse Event or Serious Adverse Event | 1                 | 2                              | -                               |

## Baseline characteristics

### Reporting groups

|  |                                   |
|--|-----------------------------------|
| Reporting group title  | Cohort A: Placebo                 |
| Reporting group description:<br>Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.   |                                   |
| Reporting group title  | Cohort A: ISIS-APO(a)Rx < 2000 mg |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated. |                                   |
| Reporting group title  | Cohort A: ISIS-APO(a)Rx ≥ 2000 mg |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated. |                                   |
| Reporting group title  | Cohort B: Placebo                 |
| Reporting group description:<br>Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.   |                                   |
| Reporting group title  | Cohort B: ISIS-APO(a)Rx < 2000 mg |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated. |                                   |
| Reporting group title  | Cohort B: ISIS-APO(a)Rx ≥ 2000 mg |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated. |                                   |

| Reporting group values  | Cohort A: Placebo | Cohort A: ISIS-APO(a)Rx < 2000 | Cohort A: ISIS-APO(a)Rx ≥ 2000 |
|---|-------------------|--------------------------------|--------------------------------|
| Number of subjects  | 26                | 4                              | 21                             |
| Age categorical<br>Units: Subjects  |                   |                                |                                |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                   |                                |                                |
| Age continuous<br>Units: years  |                   |                                |                                |
| arithmetic mean   | 54                | 50                             | 56                             |
| standard deviation  | ± 10              | ± 9                            | ± 6                            |
| Gender categorical<br>Units: Subjects   |                   |                                |                                |
| Female  | 6                 | 2                              | 12                             |
| Male  | 20                | 2                              | 9                              |

| Reporting group values  | Cohort B: Placebo | Cohort B: ISIS-APO(a)Rx < 2000 | Cohort B: ISIS-APO(a)Rx ≥ 2000 |
|---|-------------------|--------------------------------|--------------------------------|
| Number of subjects  | 3                 | 2                              | 8                              |
| Age categorical<br>Units: Subjects  |                   |                                |                                |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                   |                                |                                |
| Age continuous<br>Units: years  |                   |                                |                                |
| arithmetic mean<br>standard deviation   | 62<br>± 8         | 45<br>± 11                     | 61<br>± 8                      |
| Gender categorical<br>Units: Subjects   |                   |                                |                                |
| Female  | 3                 | 2                              | 6                              |
| Male  | 0                 | 0                              | 2                              |

| Reporting group values  | Total                                     |  |  |
|---|---|--|--|
| Number of subjects  | 64  |  |  |
| Age categorical<br>Units: Subjects  |   |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | 0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0 |  |  |
| Age continuous<br>Units: years  |   |  |  |
| arithmetic mean<br>standard deviation   | -   |  |  |
| Gender categorical<br>Units: Subjects   |   |  |  |
| Female  | 31  |  |  |
| Male  | 33  |  |  |



## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Cohort A: Placebo                       |
| Reporting group description:<br>Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.   |   |
| Reporting group title  | Cohort A: ISIS-APO(a)Rx < 2000 mg       |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.   |   |
| Reporting group title  | Cohort A: ISIS-APO(a)Rx ≥ 2000 mg       |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.   |   |
| Reporting group title  | Cohort B: Placebo                       |
| Reporting group description:<br>Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.   |   |
| Reporting group title  | Cohort B: ISIS-APO(a)Rx < 2000 mg       |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.   |   |
| Reporting group title  | Cohort B: ISIS-APO(a)Rx ≥ 2000 mg       |
| Reporting group description:<br>Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.   |   |
| Subject analysis set title   | Cohort A: Placebo (PPS)                 |
| Subject analysis set type  | Per protocol                            |
| Subject analysis set description:<br>The Per-Protocol Set (PPS) included the subset of the Full Analysis Set who received at least 9 doses of Study Drug within the 12-week treatment period and who had no significant protocol deviations that would have been expected to affect efficacy assessments. The Full Analysis Set included the subset of the Safety Set with at least 1 post-baseline Lp(a) measurement. |   |
| Subject analysis set title   | Cohort A: ISIS-APO(a)Rx < 2000 mg (PPS) |
| Subject analysis set type  | Per protocol                            |
| Subject analysis set description:<br>The PPS included the subset of the Full Analysis Set who received at least 9 doses of Study Drug within the 12-week treatment period and who had no significant protocol deviations that would have been expected to affect efficacy assessments. The Full Analysis Set included the subset of the Safety Set with at least 1 post-baseline Lp(a) measurement.                    |   |
| Subject analysis set title   | Cohort A: ISIS-APO(a)Rx ≥ 2000 mg (PPS) |
| Subject analysis set type  | Per protocol                            |
| Subject analysis set description:<br>The PPS included the subset of the Full Analysis Set who received at least 9 doses of Study Drug within the 12-week treatment period and who had no significant protocol deviations that would have been expected to affect efficacy assessments. The Full Analysis Set included the subset of the Safety Set with at least 1 post-baseline Lp(a) measurement.                    |   |
| Subject analysis set title   | Cohort B: Placebo (PPS)                 |
| Subject analysis set type  | Per protocol                            |
| Subject analysis set description:<br>The PPS included the subset of the Full Analysis Set who received at least 9 doses of Study Drug within the 12-week treatment period and who had no significant protocol deviations that would have been expected to affect efficacy assessments. The Full Analysis Set included the subset of the Safety Set with at least 1 post-baseline Lp(a) measurement.                    |   |
| Subject analysis set title   | Cohort B: ISIS-APO(a)Rx ≥ 2000 mg (PPS) |

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The PPS included the subset of the Full Analysis Set who received at least 9 doses of Study Drug within the 12-week treatment period and who had no significant protocol deviations that would have been expected to affect efficacy assessments. The Full Analysis Set included the subset of the Safety Set with at least 1 post-baseline Lp(a) measurement.

### Primary: Number of Subjects With at Least One Treatment-emergent Adverse Event (TEAE)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With at Least One Treatment-emergent Adverse Event (TEAE) <sup>[1]</sup> |
|-----------------|---|

End point description:

An adverse event is any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product. The Safety Set included all randomised subjects who received at least one dose of study drug.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 32 weeks

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 primary endpoint.

| End point values              | Cohort A: Placebo | Cohort A: ISIS-APO(a)Rx < 2000 mg | Cohort A: ISIS-APO(a)Rx ≥ 2000 mg | Cohort B: Placebo |
|-------------------------------|-------------------|-----------------------------------|-----------------------------------|-------------------|
| Subject group type            | Reporting group   | Reporting group                   | Reporting group                   | Reporting group   |
| Number of subjects analysed   | 26                | 4                                 | 21                                | 3                 |
| Units: percentage of subjects |                   |                                   |                                   |                   |
| number (not applicable)       | 23                | 4                                 | 21                                | 2                 |

| End point values              | Cohort B: ISIS-APO(a)Rx < 2000 mg | Cohort B: ISIS-APO(a)Rx ≥ 2000 mg |  |  |
|-------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type            | Reporting group                   | Reporting group                   |  |  |
| Number of subjects analysed   | 2                                 | 8                                 |  |  |
| Units: percentage of subjects |                                   |                                   |  |  |
| number (not applicable)       | 2                                 | 8                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Percent Change From Baseline in Lipoprotein Lp(a) Plasma Concentration at Day 85/Day 99

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Lipoprotein Lp(a) Plasma Concentration at Day 85/Day 99 |
|-----------------|---|

End point description:

The Per-Protocol Set included the subset of the Full Analysis Set who received at least 9 doses of Study Drug within the 12-week treatment period and who had no significant protocol deviations that would

have been expected to affect efficacy assessments. The Full Analysis Set included the subset of the Safety Set with at least 1 post-baseline Lp(a) measurement. Day 85/Day 99 result is defined as the result at Day 85 or Day 99.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Day 85/Day 99        |         |

| End point values                     | Cohort A: Placebo (PPS) | Cohort A: ISIS-APO(a)Rx < 2000 mg (PPS) | Cohort A: ISIS-APO(a)Rx ≥ 2000 mg (PPS) | Cohort B: Placebo (PPS) |
|--------------------------------------|-------------------------|---|---|-------------------------|
| Subject group type                   | Subject analysis set    | Subject analysis set                    | Subject analysis set                    | Subject analysis set    |
| Number of subjects analysed          | 26                      | 3                                       | 21                                      | 2                       |
| Units: percent change                |                         |   |   |                         |
| arithmetic mean (standard deviation) | -3.7 (± 13.7)           | -44.5 (± 13.1)                          | -70.0 (± 19.6)                          | -5.6 (± 3.9)            |

| End point values                     | Cohort B: ISIS-APO(a)Rx ≥ 2000 mg (PPS) |  |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Subject analysis set                    |  |  |  |
| Number of subjects analysed          | 8                                       |  |  |  |
| Units: percent change                |   |  |  |  |
| arithmetic mean (standard deviation) | -71.6 (± 13.0)                          |  |  |  |

## Statistical analyses

| Statistical analysis title              | Cohort A:Placebo v Cohort A: ISIS-APO(a)Rx < 2000                 |
|---|---|
| Comparison groups                       | Cohort A: Placebo (PPS) v Cohort A: ISIS-APO(a)Rx < 2000 mg (PPS) |
| Number of subjects included in analysis | 29  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.001   |
| Method                                  | ANOVA   |

| Statistical analysis title              | Cohort A:Placebo v Cohort A: ISIS-APO(a)Rx ≥ 200                  |
|---|---|
| Comparison groups                       | Cohort A: Placebo (PPS) v Cohort A: ISIS-APO(a)Rx ≥ 2000 mg (PPS) |
| Number of subjects included in analysis | 47  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.001   |
| Method                                  | ANOVA   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Cohort B:Placebo v Cohort B: ISIS-APO(a)Rx >= 200                  |
| Comparison groups                       | Cohort B: Placebo (PPS) v Cohort B: ISIS-APO(a)Rx >= 2000 mg (PPS) |
| Number of subjects included in analysis | 10   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.044  |
| Method                                  | Exact Wilcoxon Rank Sum Test                                       |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 32 weeks

Adverse event reporting additional description:

The Safety Set included all randomised subjects who received at least one dose of study drug.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Cohort A: Placebo |
|-----------------------|-------------------|

Reporting group description:

Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Cohort A: ISIS-APO(a)Rx < 2000 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Cohort A: ISIS-APO(a)Rx ≥ 2000 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Cohort B: Placebo |
|-----------------------|-------------------|

Reporting group description:

Subjects received placebo (normal saline) subcutaneously on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Cohort B: ISIS-APO(a)Rx < 2000 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Cohort B: ISIS-APO(a)Rx ≥ 2000 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects received ISIS-APO(a)Rx subcutaneously: 100 mg on Days 1, 8, 15, and 22; 200 mg on Days 29, 36, 43, and 50 unless down-titrated; and 300 mg on Days 57, 64, 71, and 78 unless down-titrated.

| Serious adverse events                            | Cohort A: Placebo | Cohort A: ISIS-APO(a)Rx < 2000 | Cohort A: ISIS-APO(a)Rx ≥ 2000 |
|---|-------------------|--------------------------------|--------------------------------|
| Total subjects affected by serious adverse events |                   |                                |                                |
| subjects affected / exposed                       | 0 / 26 (0.00%)    | 2 / 4 (50.00%)                 | 0 / 21 (0.00%)                 |
| number of deaths (all causes)                     | 0                 | 0                              | 0                              |
| number of deaths resulting from adverse events    | 0                 | 0                              | 0                              |
| Cardiac disorders                                 |                   |                                |                                |
| Angina pectoris                                   |                   |                                |                                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 26 (0.00%) | 1 / 4 (25.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 26 (0.00%) | 1 / 4 (25.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | Cohort B: Placebo | Cohort B: ISIS-APO(a)Rx < 2000 | Cohort B: ISIS-APO(a)Rx >= 2000 |
|---|-------------------|--------------------------------|---------------------------------|
| Total subjects affected by serious adverse events |                   |                                |                                 |
| subjects affected / exposed                       | 1 / 3 (33.33%)    | 0 / 2 (0.00%)                  | 0 / 8 (0.00%)                   |
| number of deaths (all causes)                     | 0                 | 0                              | 0                               |
| number of deaths resulting from adverse events    | 0                 | 0                              | 0                               |
| Cardiac disorders                                 |                   |                                |                                 |
| Angina pectoris                                   |                   |                                |                                 |
| subjects affected / exposed                       | 0 / 3 (0.00%)     | 0 / 2 (0.00%)                  | 0 / 8 (0.00%)                   |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 0                          | 0 / 0                           |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0                          | 0 / 0                           |
| Myocardial infarction                             |                   |                                |                                 |
| subjects affected / exposed                       | 1 / 3 (33.33%)    | 0 / 2 (0.00%)                  | 0 / 8 (0.00%)                   |
| occurrences causally related to treatment / all   | 0 / 1             | 0 / 0                          | 0 / 0                           |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0                          | 0 / 0                           |

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

| <b>Non-serious adverse events</b>                     | Cohort A: Placebo | Cohort A: ISIS-APO(a)Rx < 2000 | Cohort A: ISIS-APO(a)Rx >= 2000 |
|---|-------------------|--------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events |                   |                                |                                 |
| subjects affected / exposed                           | 23 / 26 (88.46%)  | 3 / 4 (75.00%)                 | 21 / 21 (100.00%)               |
| Vascular disorders                                    |                   |                                |                                 |
| Hot flush   |                   |                                |                                 |
| subjects affected / exposed                           | 0 / 26 (0.00%)    | 0 / 4 (0.00%)                  | 1 / 21 (4.76%)                  |
| occurrences (all)                                     | 0                 | 0                              | 1                               |
| Pallor  |                   |                                |                                 |
| subjects affected / exposed                           | 0 / 26 (0.00%)    | 0 / 4 (0.00%)                  | 0 / 21 (0.00%)                  |
| occurrences (all)                                     | 0                 | 0                              | 0                               |

|  |                 |                |                  |
|--|-----------------|----------------|------------------|
| General disorders and administration site conditions |                 |                |                  |
| Injection site erythema                              |                 |                |                  |
| subjects affected / exposed                          | 0 / 26 (0.00%)  | 3 / 4 (75.00%) | 16 / 21 (76.19%) |
| occurrences (all)                                    | 0               | 23             | 103              |
| Injection site pain                                  |                 |                |                  |
| subjects affected / exposed                          | 2 / 26 (7.69%)  | 1 / 4 (25.00%) | 12 / 21 (57.14%) |
| occurrences (all)                                    | 7               | 7              | 71               |
| Injection site induration                            |                 |                |                  |
| subjects affected / exposed                          | 0 / 26 (0.00%)  | 3 / 4 (75.00%) | 8 / 21 (38.10%)  |
| occurrences (all)                                    | 0               | 13             | 20               |
| Injection site swelling                              |                 |                |                  |
| subjects affected / exposed                          | 0 / 26 (0.00%)  | 1 / 4 (25.00%) | 10 / 21 (47.62%) |
| occurrences (all)                                    | 0               | 2              | 45               |
| Injection site warmth                                |                 |                |                  |
| subjects affected / exposed                          | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 2 / 21 (9.52%)   |
| occurrences (all)                                    | 0               | 0              | 9                |
| Injection site pruritus                              |                 |                |                  |
| subjects affected / exposed                          | 0 / 26 (0.00%)  | 2 / 4 (50.00%) | 8 / 21 (38.10%)  |
| occurrences (all)                                    | 0               | 5              | 23               |
| Injection site reaction                              |                 |                |                  |
| subjects affected / exposed                          | 1 / 26 (3.85%)  | 0 / 4 (0.00%)  | 7 / 21 (33.33%)  |
| occurrences (all)                                    | 1               | 0              | 11               |
| Chills   |                 |                |                  |
| subjects affected / exposed                          | 1 / 26 (3.85%)  | 2 / 4 (50.00%) | 3 / 21 (14.29%)  |
| occurrences (all)                                    | 1               | 2              | 4                |
| Fatigue  |                 |                |                  |
| subjects affected / exposed                          | 3 / 26 (11.54%) | 2 / 4 (50.00%) | 3 / 21 (14.29%)  |
| occurrences (all)                                    | 11              | 9              | 7                |
| Injection site discolouration                        |                 |                |                  |
| subjects affected / exposed                          | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 5 / 21 (23.81%)  |
| occurrences (all)                                    | 0               | 0              | 14               |
| Malaise  |                 |                |                  |
| subjects affected / exposed                          | 3 / 26 (11.54%) | 0 / 4 (0.00%)  | 4 / 21 (19.05%)  |
| occurrences (all)                                    | 3               | 0              | 12               |
| Injection site haematoma                             |                 |                |                  |

|                               |                 |                |                 |
|-------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed   | 2 / 26 (7.69%)  | 0 / 4 (0.00%)  | 3 / 21 (14.29%) |
| occurrences (all)             | 2               | 0              | 8               |
| Injection site urticaria      |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 3 / 21 (14.29%) |
| occurrences (all)             | 0               | 0              | 12              |
| Asthenia                      |                 |                |                 |
| subjects affected / exposed   | 2 / 26 (7.69%)  | 1 / 4 (25.00%) | 1 / 21 (4.76%)  |
| occurrences (all)             | 2               | 1              | 1               |
| Hyperthermia                  |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)             | 0               | 0              | 2               |
| Injection site hyperaesthesia |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)             | 0               | 0              | 8               |
| Injection site oedema         |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)             | 0               | 0              | 12              |
| Oedema peripheral             |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)             | 0               | 0              | 3               |
| Pyrexia                       |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 1 / 4 (25.00%) | 1 / 21 (4.76%)  |
| occurrences (all)             | 0               | 1              | 1               |
| Pain                          |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 1 / 4 (25.00%) | 0 / 21 (0.00%)  |
| occurrences (all)             | 0               | 1              | 0               |
| Chest pain                    |                 |                |                 |
| subjects affected / exposed   | 3 / 26 (11.54%) | 0 / 4 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)             | 3               | 0              | 0               |
| Injection site bruising       |                 |                |                 |
| subjects affected / exposed   | 1 / 26 (3.85%)  | 0 / 4 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)             | 1               | 0              | 0               |
| Injection site haemorrhage    |                 |                |                 |
| subjects affected / exposed   | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)             | 0               | 0              | 0               |
| Injection site pallor         |                 |                |                 |



|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Injection site paraesthesia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 26 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)              | 0 / 26 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 3 / 26 (11.54%)<br>3 | 0 / 4 (0.00%)<br>0  | 3 / 21 (14.29%)<br>3 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 26 (3.85%)<br>1  | 0 / 4 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1  |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 26 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 26 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Psychiatric disorders<br>Agitation<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Restlessness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>2 | 0 / 21 (0.00%)<br>0  |
| Mood swings  |                      |                     |                      |

|   |                       |                     |                        |
|---|-----------------------|---------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 26 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0    |
| Nightmare<br>subjects affected / exposed<br>occurrences (all)   | 1 / 26 (3.85%)<br>1   | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0    |
| Investigations<br>General physical condition abnormal<br>subjects affected / exposed<br>occurrences (all)       | 0 / 26 (0.00%)<br>0   | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0    |
| Urine analysis abnormal<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 26 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0    |
| Injury, poisoning and procedural complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all) | 1 / 26 (3.85%)<br>1   | 0 / 4 (0.00%)<br>0  | 2 / 21 (9.52%)<br>3    |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0  | 2 / 21 (9.52%)<br>3    |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0   | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0    |
| Cardiac disorders<br>Angina pectoris<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 26 (0.00%)<br>0   | 1 / 4 (25.00%)<br>2 | 1 / 21 (4.76%)<br>4    |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)  | 0 / 26 (0.00%)<br>0   | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0    |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                        | 6 / 26 (23.08%)<br>10 | 1 / 4 (25.00%)<br>1 | 10 / 21 (47.62%)<br>12 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 3 / 26 (11.54%)<br>4  | 0 / 4 (0.00%)<br>0  | 4 / 21 (19.05%)<br>5   |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| Disturbance in attention<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 26 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Dysaesthesia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 26 (0.00%)<br>0 | 1 / 4 (25.00%)<br>2 | 0 / 21 (0.00%)<br>0  |
| Burning sensation<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Tension headache<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 26 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)         | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Eye disorders<br>Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Vitreous detachment<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)            | 2 / 26 (7.69%)<br>2 | 1 / 4 (25.00%)<br>1 | 3 / 21 (14.29%)<br>4 |

|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 2 / 26 (7.69%)<br>2 | 0 / 4 (0.00%)<br>0  | 3 / 21 (14.29%)<br>3 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 2 / 26 (7.69%)<br>2 | 0 / 4 (0.00%)<br>0  | 2 / 21 (9.52%)<br>5  |
| Cheilitis<br>subjects affected / exposed<br>occurrences (all)            | 0 / 26 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)            | 0 / 26 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)         | 2 / 26 (7.69%)<br>2 | 0 / 4 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 2 / 26 (7.69%)<br>2 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 26 (7.69%)<br>2 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 2 / 26 (7.69%)<br>2 | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders                                   |                     |                     |                      |
| Erythema<br>subjects affected / exposed<br>occurrences (all)             | 0 / 26 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  | 2 / 21 (9.52%)<br>2  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 26 (0.00%)<br>0 | 1 / 4 (25.00%)<br>2 | 1 / 21 (4.76%)<br>1  |
| Erythema annulare<br>subjects affected / exposed<br>occurrences (all)    | 0 / 26 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Dry skin   |                     |                     |                      |

|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1  |
| Pruritus generalised<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0  |
| Renal and urinary disorders<br>Leukocyturia<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Nocturia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 26 (3.85%)<br>1  | 1 / 4 (25.00%)<br>1 | 4 / 21 (19.05%)<br>5 |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)  | 6 / 26 (23.08%)<br>7 | 2 / 4 (50.00%)<br>4 | 2 / 21 (9.52%)<br>11 |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 4 / 26 (15.38%)<br>7 | 2 / 4 (50.00%)<br>3 | 1 / 21 (4.76%)<br>2  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 26 (7.69%)<br>2  | 0 / 4 (0.00%)<br>0  | 2 / 21 (9.52%)<br>3  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>2 | 1 / 21 (4.76%)<br>1  |
| Joint stiffness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)   | 0 / 26 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 21 (0.00%)<br>0  |
| Muscle spasms  |                      |                     |                      |

|                                    |                 |                |                 |
|------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed        | 1 / 26 (3.85%)  | 0 / 4 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences (all)                  | 1               | 0              | 3               |
| Neck pain                          |                 |                |                 |
| subjects affected / exposed        | 0 / 26 (0.00%)  | 0 / 4 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)                  | 0               | 0              | 0               |
| Infections and infestations        |                 |                |                 |
| Nasopharyngitis                    |                 |                |                 |
| subjects affected / exposed        | 9 / 26 (34.62%) | 0 / 4 (0.00%)  | 8 / 21 (38.10%) |
| occurrences (all)                  | 11              | 0              | 10              |
| Urinary tract infection            |                 |                |                 |
| subjects affected / exposed        | 1 / 26 (3.85%)  | 0 / 4 (0.00%)  | 3 / 21 (14.29%) |
| occurrences (all)                  | 1               | 0              | 4               |
| Bronchitis                         |                 |                |                 |
| subjects affected / exposed        | 1 / 26 (3.85%)  | 0 / 4 (0.00%)  | 2 / 21 (9.52%)  |
| occurrences (all)                  | 2               | 0              | 2               |
| Bacteriuria                        |                 |                |                 |
| subjects affected / exposed        | 2 / 26 (7.69%)  | 0 / 4 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences (all)                  | 2               | 0              | 1               |
| Gastrointestinal infection         |                 |                |                 |
| subjects affected / exposed        | 0 / 26 (0.00%)  | 1 / 4 (25.00%) | 0 / 21 (0.00%)  |
| occurrences (all)                  | 0               | 1              | 0               |
| Oral herpes                        |                 |                |                 |
| subjects affected / exposed        | 1 / 26 (3.85%)  | 1 / 4 (25.00%) | 0 / 21 (0.00%)  |
| occurrences (all)                  | 1               | 1              | 0               |
| Tonsillitis                        |                 |                |                 |
| subjects affected / exposed        | 0 / 26 (0.00%)  | 1 / 4 (25.00%) | 0 / 21 (0.00%)  |
| occurrences (all)                  | 0               | 1              | 0               |
| Upper respiratory tract infection  |                 |                |                 |
| subjects affected / exposed        | 2 / 26 (7.69%)  | 0 / 4 (0.00%)  | 1 / 21 (4.76%)  |
| occurrences (all)                  | 2               | 0              | 1               |
| Influenza                          |                 |                |                 |
| subjects affected / exposed        | 2 / 26 (7.69%)  | 0 / 4 (0.00%)  | 0 / 21 (0.00%)  |
| occurrences (all)                  | 2               | 0              | 0               |
| Metabolism and nutrition disorders |                 |                |                 |
| Vitamin D deficiency               |                 |                |                 |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 4 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |

| <b>Non-serious adverse events</b>                     | Cohort B: Placebo | Cohort B: ISIS-APO(a)Rx < 2000 | Cohort B: ISIS-APO(a)Rx ≥ 2000 |
|---|-------------------|--------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events |                   |                                |                                |
| subjects affected / exposed                           | 2 / 3 (66.67%)    | 2 / 2 (100.00%)                | 8 / 8 (100.00%)                |
| Vascular disorders                                    |                   |                                |                                |
| Hot flush   |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 0 / 2 (0.00%)                  | 1 / 8 (12.50%)                 |
| occurrences (all)                                     | 0                 | 0                              | 1                              |
| Pallor  |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 1 / 2 (50.00%)                 | 0 / 8 (0.00%)                  |
| occurrences (all)                                     | 0                 | 2                              | 0                              |
| General disorders and administration site conditions  |                   |                                |                                |
| Injection site erythema                               |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 2 / 2 (100.00%)                | 6 / 8 (75.00%)                 |
| occurrences (all)                                     | 0                 | 8                              | 48                             |
| Injection site pain                                   |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 2 / 2 (100.00%)                | 2 / 8 (25.00%)                 |
| occurrences (all)                                     | 0                 | 7                              | 14                             |
| Injection site induration                             |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 0 / 2 (0.00%)                  | 4 / 8 (50.00%)                 |
| occurrences (all)                                     | 0                 | 0                              | 26                             |
| Injection site swelling                               |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 1 / 2 (50.00%)                 | 3 / 8 (37.50%)                 |
| occurrences (all)                                     | 0                 | 2                              | 19                             |
| Injection site warmth                                 |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 1 / 2 (50.00%)                 | 3 / 8 (37.50%)                 |
| occurrences (all)                                     | 0                 | 1                              | 10                             |
| Injection site pruritus                               |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 0 / 2 (0.00%)                  | 3 / 8 (37.50%)                 |
| occurrences (all)                                     | 0                 | 0                              | 16                             |
| Injection site reaction                               |                   |                                |                                |
| subjects affected / exposed                           | 0 / 3 (0.00%)     | 1 / 2 (50.00%)                 | 1 / 8 (12.50%)                 |
| occurrences (all)                                     | 0                 | 1                              | 2                              |
| Chills  |                   |                                |                                |

|                               |                |               |                |
|-------------------------------|----------------|---------------|----------------|
| subjects affected / exposed   | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)             | 2              | 0             | 1              |
| Fatigue                       |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 3 / 8 (37.50%) |
| occurrences (all)             | 0              | 0             | 4              |
| Injection site discolouration |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all)             | 0              | 0             | 5              |
| Malaise                       |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all)             | 0              | 0             | 10             |
| Injection site haematoma      |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)             | 0              | 0             | 2              |
| Injection site urticaria      |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all)             | 0              | 0             | 2              |
| Asthenia                      |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)             | 0              | 0             | 1              |
| Hyperthermia                  |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)             | 0              | 0             | 0              |
| Injection site hyperaesthesia |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 3 / 8 (37.50%) |
| occurrences (all)             | 0              | 0             | 11             |
| Injection site oedema         |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)             | 0              | 0             | 12             |
| Oedema peripheral             |                |               |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all)             | 0              | 0             | 4              |
| Pyrexia                       |                |               |                |
| subjects affected / exposed   | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all)             | 1              | 0             | 3              |
| Pain                          |                |               |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                               | 1              | 0              | 0              |
| Chest pain                                      |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0              |
| Injection site bruising                         |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 2 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)                               | 0              | 0              | 2              |
| Injection site haemorrhage                      |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 2 (50.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Injection site pallor                           |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 2 (50.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Injection site paraesthesia                     |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 2 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Immune system disorders                         |                |                |                |
| Hypersensitivity                                |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 2 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Cough   |                |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                               | 1              | 0              | 0              |
| Oropharyngeal pain                              |                |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 1 / 2 (50.00%) | 1 / 8 (12.50%) |
| occurrences (all)                               | 1              | 1              | 1              |
| Dyspnoea exertional                             |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 2 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Rhinorrhoea                                     |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 2 (50.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0              |
| Psychiatric disorders                           |                |                |                |

|  |               |                |               |
|--|---------------|----------------|---------------|
| Agitation                                      |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Insomnia                                       |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Restlessness                                   |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Sleep disorder                                 |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Mood swings                                    |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 1 / 2 (50.00%) | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 1              | 0             |
| Nightmare                                      |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 1 / 2 (50.00%) | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 1              | 0             |
| Investigations                                 |               |                |               |
| General physical condition abnormal            |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Urine analysis abnormal                        |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 1 / 2 (50.00%) | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 1              | 0             |
| Injury, poisoning and procedural complications |               |                |               |
| Contusion                                      |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Ligament sprain                                |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Procedural pain                                |               |                |               |
| subjects affected / exposed                    | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)                              | 0             | 0              | 0             |
| Cardiac disorders                              |               |                |               |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Angina pectoris<br>subjects affected / exposed<br>occurrences (all)          | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)             | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Nervous system disorders   |                     |                     |                     |
| Headache<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0  | 1 / 2 (50.00%)<br>2 | 1 / 8 (12.50%)<br>1 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 2 / 8 (25.00%)<br>4 |
| Disturbance in attention<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Dysaesthesia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Burning sensation<br>subjects affected / exposed<br>occurrences (all)        | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)               | 0 / 3 (0.00%)<br>0  | 1 / 2 (50.00%)<br>2 | 0 / 8 (0.00%)<br>0  |
| Tension headache<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0  | 1 / 2 (50.00%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Blood and lymphatic system disorders   |                     |                     |                     |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |
| Ear and labyrinth disorders  |                     |                     |                     |

|  |                    |                     |                     |
|--|--------------------|---------------------|---------------------|
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |
| Eye disorders<br>Lacrimation increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 1 / 2 (50.00%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Vitreous detachment<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 1 / 8 (12.50%)<br>2 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0 | 1 / 2 (50.00%)<br>2 | 2 / 8 (25.00%)<br>2 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0 | 1 / 2 (50.00%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |
| Cheilitis<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 3 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Vomiting   |                    |                     |                     |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 1 / 2 (50.00%)<br>1 | 0 / 8 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders           |                    |                     |                    |
| Erythema   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 1 / 8 (12.50%)     |
| occurrences (all)                                | 0                  | 0                   | 4                  |
| Hyperhidrosis                                    |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Erythema annulare                                |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Dry skin   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 1 / 2 (50.00%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                  | 2                   | 0                  |
| Pruritus generalised                             |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 1 / 2 (50.00%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                  | 1                   | 0                  |
| Renal and urinary disorders                      |                    |                     |                    |
| Leukocyturia                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Nocturia   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Musculoskeletal and connective tissue disorders  |                    |                     |                    |
| Back pain  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 2 / 8 (25.00%)     |
| occurrences (all)                                | 0                  | 0                   | 2                  |
| Myalgia  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 1 / 8 (12.50%)     |
| occurrences (all)                                | 0                  | 0                   | 1                  |
| Arthralgia                                       |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 2 (0.00%)       | 2 / 8 (25.00%)     |
| occurrences (all)                                | 0                  | 0                   | 3                  |
| Musculoskeletal pain                             |                    |                     |                    |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Pain in extremity           |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Joint stiffness             |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Joint swelling              |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Muscle spasms               |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 2 (50.00%) | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 1              | 1              |
| Neck pain                   |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 0              | 2              |
| Infections and infestations |               |                |                |
| Nasopharyngitis             |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Urinary tract infection     |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)           | 0             | 0              | 1              |
| Bronchitis                  |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Bacteriuria                 |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Gastrointestinal infection  |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Oral herpes                 |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |

|                                    |                |               |                |
|------------------------------------|----------------|---------------|----------------|
| Tonsillitis                        |                |               |                |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Upper respiratory tract infection  |                |               |                |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Influenza                          |                |               |                |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 0 / 2 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                  | 0              | 0             | 1              |
| Metabolism and nutrition disorders |                |               |                |
| Vitamin D deficiency               |                |               |                |
| subjects affected / exposed        | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                  | 1              | 0             | 0              |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported