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
Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	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	-

Number of subjects in period 1	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:	
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.	

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 Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	54	50	56
standard deviation	± 10	± 9	± 6
Gender categorical 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			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	62	45	61
standard deviation	± 8	± 11	± 8
Gender categorical			
Units: Subjects			
Female	3	2	6
Male	0	0	2

Reporting group values	Total		
Number of subjects	64		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	31		
Male	33		

End points

End points 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.	
Subject analysis set title	Cohort A: Placebo (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
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:	
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:	
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:	
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)[1]

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

Statistical analysis title	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

Serious adverse events	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 %

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

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

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

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

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

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

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

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported