Clinical trial results:
A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL TO EVALUATE THE EFFECT OF 300 MG OF INCLISIRAN SODIUM GIVEN AS SUBCUTANEOUS INJECTIONS IN SUBJECTS WITH ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR ASCVD-RISK EQUIVALENTS AND ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C)

Summary

EudraCT number	2017-001846-90
Trial protocol	DE HU GB CZ NL
Global end of trial date	31 July 2019

Results information

Result version number	v1 (current)
This version publication date	16 August 2020
First version publication date	16 August 2020

Trial information

Trial identification

Sponsor protocol code	MDCO-PCS-17-08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03400800
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Medicines Company
Sponsor organisation address	8 Sylvan Way, Parsippany, United States, NJ 07054
Public contact	Global Health Science Center , The Medicines Company, +1 9732906000, medical.information@themedco.com
Scientific contact	Global Health Science Center , The Medicines Company, +1 9732906000, medical.information@themedco.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	05 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2019
Global end of trial reached?	Yes
Global end of trial date	31 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of inclisiran treatment on:
•LDL-C levels at Day 510
•Time adjusted percent change in LDL-C levels from baseline between Day 90 and Day 540 levels

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

All subjects participating must be on and maintain maximally tolerated statin therapy and/or other LDLC lowering therapies such as ezetimibe in addition to receiving inclisiran or placebo.

Evidence for comparator:

Use of placebo is consistent with other investigational lipid lowering therapy Phase III designs, including the statins and the monoclonal antibody PCSK9 inhibitors. All subjects participating must be on and maintain maximally tolerated statin therapy and/or other LDL-C lowering therapies such as ezetimibe in addition to receiving inclisiran or placebo. The use of placebo in this type of study is consistent with EU guidance on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013, Rev. 3).

Actual start date of recruitment	01 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 717
Country: Number of subjects enrolled	United Kingdom: 462
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Germany: 83
Country: Number of subjects enrolled	Hungary: 104
Country: Number of subjects enrolled	South Africa: 121
Country: Number of subjects enrolled	Ukraine: 109
Worldwide total number of subjects	1617
EEA total number of subjects	1387

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)	733
From 65 to 84 years	884
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Not applicable

Pre-assignment

Screening details:

Screening occurred prior to randomization and consisted of confirming eligibility and collecting baseline assessments. Subjects enrolled must have fasting triglyceride <4.52 mmol/L (<400 mg/dL) and serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) at screening.

Pre-assignment period milestones

Number of subjects started	1617
Number of subjects completed	1617

Period 1

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

Blinding implementation details:

As inclisiran may by visually distinguishable from placebo, blinded syrunges were provided to all study sites and used to maintain the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Inclisiran

Arm description:

Inclisiran sodium 300 mg

Arm type	Experimental
Investigational medicinal product name	Inclisiran
Investigational medicinal product code	ALN-60212
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Inclisiran sodium 300 milligrams (mg) was administered as a subcutaneous injection on Day 1, Day 90 then every 6 months.

Arm title	Placebo

Arm description:

Placebo arm

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:

Placebo was administered as a subcutaneous injection on Day 1, Day 90 then every 6 months.

Number of subjects in period 1	Inclisiran	Placebo
Started	810	807
Completed	772	770
Not completed	38	37
Consent withdrawn by subject	13	17
Physician decision	1	1
Adverse Event	4	-
Death	14	15
Not specified	-	1
Lost to follow-up	6	3

Baseline characteristics

Reporting groups	
Reporting group title	Inclisiran
Reporting group description: Inclisiran sodium 300 mg	
Reporting group title	Placebo
Reporting group description: Placebo arm	

Reporting group values	Inclisiran	Placebo	Total
Number of subjects	810	807	1617
Age categorical Units: Subjects			
Adults (18-64 years)	367	366	733
Adults (65 - 74 years)	354	327	681
Adults (from 75 years)	89	114	203
Gender categorical Units: Subjects			
Female	231	226	457
Male	579	581	1160

Subject analysis sets	
Subject analysis set title	Inclisiran
Subject analysis set type	Intention-to-treat
Subject analysis set description: Inclisiran Intention-to-treat population	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo Intention-to-treat population	

Reporting group values	Inclisiran	Placebo	
Number of subjects	810	807	
Age categorical Units: Subjects			
Adults (18-64 years)	367	366	
Adults (65 - 74 years)	354	327	
Adults (from 75 years)	89	114	
Gender categorical Units: Subjects			
Female	231	226	
Male	579	581	

End points

End points reporting groups

Reporting group title	Inclisiran
Reporting group description: Inclisiran sodium 300 mg	
Reporting group title	Placebo
Reporting group description: Placebo arm	
Subject analysis set title	Inclisiran
Subject analysis set type	Intention-to-treat
Subject analysis set description: Inclisiran Intention-to-treat population	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo Intention-to-treat population	

Primary: Percentage Change in LDL-C From Baseline to Day 510

End point title	Percentage Change in LDL-C From Baseline to Day 510
End point description:	
End point type	Primary
End point timeframe: Baseline to Day 510	

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: % change				
least squares mean (confidence interval 95%)	-49.3 (-51.22 to -47.48)	4.2 (1.62 to 6.69)	-49.3 (-51.22 to -47.48)	4.2 (1.62 to 6.69)

Statistical analyses

Statistical analysis title	Percentage Change in LDL-C from Baseline - Day 510
Statistical analysis description: Difference in the percentage change in LDL-C from baseline to Day 510 between inclisiran and placebo arms	
Comparison groups	Inclisiran v Placebo

Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-53.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.7
upper limit	-50.3

Primary: Time-adjusted Percent Change in LDL-C Levels from Baseline After Day 90 to up Day 540

End point title	Time-adjusted Percent Change in LDL-C Levels from Baseline After Day 90 to up Day 540

End point description:

End point type	Primary

End point timeframe:

Baseline, Day 90, Day 540

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: % change				
least squares mean (confidence interval 95%)	-45.82 (-47.52 to -44.13)	3.35 (1.65 to 5.05)	-45.82 (-47.52 to -44.13)	3.35 (1.65 to 5.05)

Statistical analyses

Statistical analysis title	Percentage Change in LDL-C from Day 90 to Day 540

Statistical analysis description:

Difference in time-adjusted percentage change in LDL-C Levels From Baseline After Day 90 and up to Day 540 between inclisiran and placebo arms

Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-49.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.57
upper limit	-46.77

Secondary: Absolute Change in LDL-C from Baseline to Day 510

End point title	Absolute Change in LDL-C from Baseline to Day 510
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Day 510	

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: % change				
least squares mean (confidence interval 95%)	-50.91 (-53.14 to -48.67)	0.96 (-1.26 to 3.18)	-50.91 (-53.14 to -48.67)	0.96 (0.96 to 3.18)

Statistical analyses

Statistical analysis title	Absolute Change in LDL-C From Baseline To Day 510
Statistical analysis description:	
Difference in Absolute Change in LDL-C From Baseline To Day 510 between inclisiran and placebo arms	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-51.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.01
upper limit	-48.72

Secondary: Time-adjusted Absolute Change in LDL-C From Baseline After Day 90

and up to Day 540

End point title	Time-adjusted Absolute Change in LDL-C From Baseline After Day 90 and up to Day 540

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 90, Day 540

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: % change				
least squares mean (confidence interval 95%)	-48.63 (-50.37 to -46.89)	0.31 (-1.42 to 2.04)	-48.63 (-50.37 to -46.89)	0.31 (-1.42 to 2.04)

Statistical analyses

Statistical analysis title	Absolute Change in Time-adjusted Change in LDL-C

Statistical analysis description:

Difference in the change in time-adjusted LDL-C after Day 90 and up to Day 540, between inclisiran and placebo groups

Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-48.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.39
upper limit	-46.48

Secondary: Percentage Change in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) From Baseline to Day 510

End point title	Percentage Change in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) From Baseline to Day 510

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 510

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: & change				
least squares mean (confidence interval 95%)	-63.64 (-65.55 to -61.74)	15.62 (13.72 to 17.53)	-63.64 (-65.55 to -61.74)	15.62 (13.72 to 17.53)

Statistical analyses

Statistical analysis title	Percentage change in PCSK9 from Baseline - Day 510

Statistical analysis description:

Difference in percentage change in PCSK9 from baseline to Day 510, between inclisiran and placebo arms

Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-79.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.97
upper limit	-76.57

Secondary: Percentange Change in Total Cholesterol From Baseline to Day 510

End point title	Percentange Change in Total Cholesterol From Baseline to Day 510

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 510

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: % change				
least squares mean (confidence interval 95%)	-28.00 (-29.40 to -26.60)	1.79 (0.38 to 3.21)	-28.00 (-29.40 to -26.60)	1.79 (0.38 to 3.21)

Statistical analyses

Statistical analysis title	Percentage change in Total Cholesterol

Statistical analysis description:

Difference in the percentage change in total cholesterol from baseline to Day 510, between inclisiran and placebo arms

Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-29.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.78
upper limit	-27.81

Secondary: Percentage change in Apolipoprotein B From Baseline to Day 510

End point title	Percentage change in Apolipoprotein B From Baseline to Day 510

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 510

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: % Change				
least squares mean (confidence interval 95%)	-38.15 (-39.76 to -36.54)	0.79 (-0.82 to 2.41)	-38.15 (-39.76 to -36.54)	0.79 (-0.82 to 2.41)

Statistical analyses

Statistical analysis title	Percentage change in Apo B form Baseline - Day 510
Statistical analysis description: Difference in the percentage change in Apolipoprotein B (ApoB) from baseline to Day 510	
Comparison groups	Placebo v Inclisiran
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-38.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.21
upper limit	-36.67

Secondary: Percentage Change in Non-HDL-C From Baseline to Day 510	
End point title	Percentage Change in Non-HDL-C From Baseline to Day 510
End point description:	
End point type	Secondary
End point timeframe: Baseline, Day 510	

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	810	807	810	807
Units: % change				
least squares mean (confidence interval 95%)	-41.16 (-43.09 to -39.24)	2.15 (0.22 to 4.09)	-41.16 (-43.09 to -39.24)	2.15 (0.22 to 4.09)

Statistical analyses

Statistical analysis title	Percentage Change in Non-HDL-C: baseline - Day 510

Statistical analysis description:

Difference in the percentage change in Non-HDL-C from baseline to Day 510, between inclisiran and placebo arms

Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-43.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46
upper limit	-40.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

17 months

Adverse event reporting additional description:

The Efficacy population was comprised of 807 (Placebo) and 810 (Inclisiran) for a total of 1617 subjects. The Safety population consisted of 804 (Placebo) and 811 (Inclisiran). Two randomized subjects (Placebo) were not dosed. One placebo subject received inclisiran at Day 450 so was reallocated to the inclisiran group for safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Inclisiran
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Inclisiran	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	181 / 811 (22.32%)	181 / 804 (22.51%)	
number of deaths (all causes)	14	15	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder neoplasm			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma recurrent			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour of the stomach			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer stage IV			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Linitis plastica			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified recurrent			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	2 / 811 (0.25%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastases to liver			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic carcinoma of the bladder			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oral neoplasm			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral nerve sheath tumour malignant			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 811 (0.12%)	6 / 804 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland cancer			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal neoplasm			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure inadequately controlled			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatosis with polyangiitis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 811 (0.25%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery embolism			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	7 / 811 (0.86%)	8 / 804 (1.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboangiitis obliterans			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Leg amputation			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Exercise tolerance decreased			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	4 / 811 (0.49%)	8 / 804 (1.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden cardiac death			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vascular stent occlusion			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent restenosis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic prolapse			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 811 (0.37%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 811 (0.37%)	3 / 804 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	2 / 811 (0.25%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test increased			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial bypass occlusion			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary vascular graft occlusion			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 811 (0.25%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site pain			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial reocclusion			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprocedural myocardial infarction			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 811 (0.00%)	3 / 804 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	14 / 811 (1.73%)	13 / 804 (1.62%)	
occurrences causally related to treatment / all	0 / 14	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	5 / 811 (0.62%)	18 / 804 (2.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	11 / 811 (1.36%)	11 / 804 (1.37%)	
occurrences causally related to treatment / all	0 / 12	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	10 / 811 (1.23%)	6 / 804 (0.75%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 811 (0.37%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 811 (0.37%)	6 / 804 (0.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	5 / 811 (0.62%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			

subjects affected / exposed	8 / 811 (0.99%)	11 / 804 (1.37%)	
occurrences causally related to treatment / all	0 / 8	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular dysfunction			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	2 / 811 (0.25%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	5 / 811 (0.62%)	4 / 804 (0.50%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	4 / 811 (0.49%)	5 / 804 (0.62%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Palpitations			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paroxysmal arrhythmia			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial venous sinus thrombosis			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 811 (0.12%)	3 / 804 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lacunar stroke			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 811 (0.37%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic gastritis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	2 / 811 (0.25%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	3 / 811 (0.37%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	3 / 811 (0.37%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 811 (0.62%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis membranous			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Facet joint syndrome			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inclusion body myositis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc space narrowing			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	3 / 811 (0.37%)	3 / 804 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	2 / 811 (0.25%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Undifferentiated connective tissue disease			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	2 / 811 (0.25%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			

subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 811 (0.25%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 811 (0.25%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Erysipelas			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder abscess			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder empyema			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 811 (0.12%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 811 (0.37%)	3 / 804 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuroborreliosis			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathogen resistance			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	9 / 811 (1.11%)	7 / 804 (0.87%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 811 (0.00%)	2 / 804 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sialoadenitis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 811 (0.37%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 811 (0.25%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 811 (0.12%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 811 (0.25%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 811 (0.12%)	0 / 804 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 811 (0.00%)	1 / 804 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Inclisiran	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 811 (40.81%)	319 / 804 (39.68%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	53 / 811 (6.54%)	54 / 804 (6.72%)	
occurrences (all)	60	59	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	47 / 811 (5.80%)	32 / 804 (3.98%)	
occurrences (all)	56	37	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	91 / 811 (11.22%)	90 / 804 (11.19%)	
occurrences (all)	105	110	
Upper respiratory tract infection			
subjects affected / exposed	52 / 811 (6.41%)	49 / 804 (6.09%)	
occurrences (all)	59	57	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	88 / 811 (10.85%)	94 / 804 (11.69%)	
occurrences (all)	101	100	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2017	Clarifications to the protocol synopsis and main body were included in order to address comments received from the FDA. The exclusion criterion #3, site training requirements and statistics sections were revised. Changes were made to the following sections: Synopsis-Exclusion Criteria, Synopsis-Statistical Methods, Section 4.3-Exclusion Criteria, Section 10.3.2.1-Intent-to-Treat (ITT) Population, Section 10.3.2.2-Modified Intent-to-Treat (mITT) Population, Section 10.3.4-Missing Data Handling, Section 10.4.3-Efficacy Analysis, 10.4.3.1.1-Sensitivity Analysis for Primary Efficacy Endpoints and 10.4.3.2-Secondary Efficacy Endpoint. Administrative amendments were made to the protocol.
31 January 2019	Synopsis, Section 2.1, Section 3.3, Section 3.4, Section 7.2.1, Section 10.4.3.1 to account for refinement in the description of time adjusted analyses of LDL-C. Section 6.1. Table 2. Section 6.4, Section 6.6, Section 6.8, Section 7.1.8.8 to clarify the plan to test for ADA. Section 6.1. Table 2. Schedule of Assessments to align with Health Authority feedback for wider visit windows. Section 10.3.2.2., Section 10.4.1., Section 10.4.3 to add to account for the addition of a new analysis set (Full Analysis Set). Section 10.3.3. Analysis Windows and Baseline to clarify that analysis windows will be defined to maximize the amount of data that are included in the analysis models and that full details will be provided in the Statistical Analysis Plan. Synopsis, Section 10.3.4, Section 10.4.3.1, Section 10.4.3.1.1. Missing Data Handling to align approach to missing data handling with Health Authority feedback and that details are provided in the Statistical Analysis Plan. Section 10.4.4.2. Laboratory Tests to add analyses for clinically significant laboratory parameters.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32187462