



Clinical trial results:

A placebo-controlled, double-blind, randomized trial to compare the effect of different doses of inclisiran given as single or multiple subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C.

Summary

EudraCT number	2015-003772-74
Trial protocol	GB DE NL
Global end of trial date	07 June 2017

Results information

Result version number	v1 (current)
This version publication date	20 February 2019
First version publication date	20 February 2019

Trial information

Trial identification

Sponsor protocol code	MDCO-PCS-15-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02597127
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Name: ORION-1

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	07 June 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of inclisiran treatment on low-density lipoprotein cholesterol (LDL-C) levels at Day 180.

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: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 71
Country: Number of subjects enrolled	United States: 84
Country: Number of subjects enrolled	Netherlands: 169
Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	Germany: 91
Worldwide total number of subjects	501
EEA total number of subjects	346

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)	253
From 65 to 84 years	245
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included male or female participants ≥ 18 years of age with a history of atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents or a $>20\%$ ten-year risk of a cardiovascular (CV) event assessed by Framingham Risk Score or equivalent and receiving maximum-tolerated lipid-lowering therapy.

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, Subject

Blinding implementation details:

The study drug was blinded within each injection regimen: either 1 or 2 injections on Day 1 or a single injection on Day 1 and on Day 90. Study drug was prepared by the unblinded hospital pharmacist and was dispensed in a blinded syringe as randomized by the interactive web response system. Blinding was achieved by placing an over label on each unique syringe dispensed by the pharmacist, masking the color of the solution within because inclisiran could be visually distinguishable from placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Single Dose

Arm description:

Participants received 1 of 3 different doses (200 milligrams [mg], 300 mg, or 500 mg) of inclisiran or matching placebo on Day 1. These 4 groups received no further study drug or placebo.

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

Dosage and administration details:

All eligible participants were randomized and received their first subcutaneous (SC) injection of inclisiran (200 mg, 300 mg, or 500 mg) on Day 1. The 500-mg dose was administered as 2 injections, 1 of 300 mg (1.5 milliliters [mL]) and 1 of 200 mg (1.0 mL) in 2 different injection sites. A volume of 1.5 mL was the maximum injection volume for a single injection site.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline (sterile, normal, 0.9%)
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered as an SC injection in an amount matched to the doses within the Single Dose Arm.

Arm title	Double Dose
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Arm description:

Participants received 1 of 3 different doses (100 mg, 200 mg, or 300 mg) of inclisiran or matching placebo on Day 1. These 4 groups then received a second dose on Day 90.

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

Dosage and administration details:

All eligible participants were randomized and received their SC injections of inclisiran (100 mg, 200 mg, or 300 mg) on Days 1 and 90. A volume of 1.5 mL was the maximum injection volume for a single injection.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline (sterile, normal, 0.9%)
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered as an SC injection in an amount matched to the doses within the Double Dose Arm.

Number of subjects in period 1	Single Dose	Double Dose
Started	253	248
Completed	236	233
Not completed	17	15
Physician decision	1	1
Consent withdrawn by subject	6	7
Adverse event, non-fatal	3	4
Death	1	1
Other	4	2
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Single Dose
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Reporting group description:

Participants received 1 of 3 different doses (200 milligrams [mg], 300 mg, or 500 mg) of inclisiran or matching placebo on Day 1. These 4 groups received no further study drug or placebo.

Reporting group title	Double Dose
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Reporting group description:

Participants received 1 of 3 different doses (100 mg, 200 mg, or 300 mg) of inclisiran or matching placebo on Day 1. These 4 groups then received a second dose on Day 90.

Reporting group values	Single Dose	Double Dose	Total
Number of subjects	253	248	501
Age categorical			
Units: Subjects			
Adults (18-64 years)	129	124	253
From 65-84 years	123	122	245
85 years and over	1	2	3
Age continuous			
Units: years			
arithmetic mean	63	63.6	
standard deviation	± 11.9	± 10	-
Gender categorical			
Units: Subjects			
Female	83	92	175
Male	170	156	326
Race			
Units: Subjects			
American Indian or Alaska Native	3	3	6
Asian	6	3	9
Black or African	10	8	18
Native Hawaiian or Other Pacific Islander	1	0	1
White	231	234	465
Undisclosed	2	0	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	15	14	29
Not Hispanic or Latino	238	234	472

Subject analysis sets

Subject analysis set title	Intent-to-Treat (ITT) Population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All participants randomized into the trial. Treatment classification was based on the randomized treatment. This population was used to assess the randomness of treatment allocation.

Subject analysis set title	Modified Intent-to-Treat (mITT) Population
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

All randomized participants who received at least 1 dose of study drug and had both the baseline and the 180-day follow-up LDL-C assessment. Treatment classification was based on the randomized treatment. This was the primary population for analysis of the primary and secondary endpoints.

Subject analysis set title	Single Dose Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received an SC injection of placebo (0.9% saline) in amounts matched to the doses administered in the Single Dose Arm.

Subject analysis set title	Single Dose 200 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in this group received a 200-mg SC injection of inclisiran on Day 1 of the study.

Subject analysis set title	Single Dose 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in this group received a 300-mg SC injection of inclisiran on Day 1 of the study.

Subject analysis set title	Single Dose 500 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

On Day 1 of the study, participants in this group received a 500-mg dose of inclisiran as 2 injections, 1 of 300 mg and 1 of 200 mg.

Subject analysis set title	Double Dose Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received SC injections of placebo (0.9% saline) in amounts matched to the doses administered in the Double Dose Arm.

Subject analysis set title	Double Dose 100 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in this group received their first 100-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Subject analysis set title	Double Dose 200 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in this group received their first 200-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Subject analysis set title	Double Dose 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in this group received their first 300-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Subject analysis set title	Single and Double Dose Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose placebo groups.

Subject analysis set title	Single and Double Dose 200 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 200 mg groups.

Subject analysis set title	Single and Double Dose 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 300 mg groups.

Reporting group values	Intent-to-Treat (ITT) Population	Modified Intent-to-Treat (mITT) Population	Single Dose Placebo
Number of subjects	501	483	65
Age categorical Units: Subjects			
Adults (18-64 years)	253	243	40
From 65-84 years	245	237	24
85 years and over	3	3	1
Age continuous Units: years			
arithmetic mean	63.3	63.4	62
standard deviation	± 10.97	± 11.01	± 11.4
Gender categorical Units: Subjects			
Female	175	170	23
Male	326	313	42
Race Units: Subjects			
American Indian or Alaska Native	6	5	1
Asian	9	8	0
Black or African	18	16	4
Native Hawaiian or Other Pacific Islander	1	1	0
White	465	451	59
Undisclosed	2	2	1
Ethnicity Units: Subjects			
Hispanic or Latino	29	29	7
Not Hispanic or Latino	472	454	58

Reporting group values	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Number of subjects	60	62	66
Age categorical Units: Subjects			
Adults (18-64 years)	30	27	32
From 65-84 years	30	35	34
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.9	64.1	62.1
standard deviation	± 10.8	± 12.8	± 12.4
Gender categorical Units: Subjects			
Female	21	20	19
Male	39	42	47
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	2	2	2
Black or African	4	2	0

Native Hawaiian or Other Pacific Islander	0	1	0
White	53	56	63
Undisclosed	1	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	4	3	1
Not Hispanic or Latino	56	59	65

Reporting group values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg
Number of subjects	62	62	63
Age categorical Units: Subjects			
Adults (18-64 years)	32	24	37
From 65-84 years	29	38	26
85 years and over	1	0	0
Age continuous Units: years			
arithmetic mean	62.8	65.2	62.3
standard deviation	± 10.3	± 9.4	± 10.8
Gender categorical Units: Subjects			
Female	29	23	24
Male	33	39	39
Race Units: Subjects			
American Indian or Alaska Native	0	2	0
Asian	1	1	0
Black or African	3	2	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	58	57	61
Undisclosed	0		0
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	6
Not Hispanic or Latino	60	60	57

Reporting group values	Double Dose 300 mg	Single and Double Dose Placebo	Single and Double Dose 200 mg
Number of subjects	61	127	123
Age categorical Units: Subjects			
Adults (18-64 years)	31	72	67
From 65-84 years	29	53	56
85 years and over	1	2	0
Age continuous Units: years			
arithmetic mean	64.1	62.4	63.1
standard deviation	± 9.4	± 10.8	± 10.8

Gender categorical Units: Subjects			
Female	16	52	45
Male	45	75	78
Race Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	1	1	2
Black or African	1	7	6
Native Hawaiian or Other Pacific Islander	0	0	0
White	58	117	114
Undisclosed	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	4	9	10
Not Hispanic or Latino	57	118	113

Reporting group values	Single and Double Dose 300 mg		
Number of subjects	123		
Age categorical Units: Subjects			
Adults (18-64 years)	58		
From 65-84 years	64		
85 years and over	1		
Age continuous Units: years			
arithmetic mean	64.1		
standard deviation	± 11.2		
Gender categorical Units: Subjects			
Female	36		
Male	87		
Race Units: Subjects			
American Indian or Alaska Native	2		
Asian	3		
Black or African	3		
Native Hawaiian or Other Pacific Islander	1		
White	114		
Undisclosed	0		
Ethnicity Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	116		

End points

End points reporting groups

Reporting group title	Single Dose
Reporting group description: Participants received 1 of 3 different doses (200 milligrams [mg], 300 mg, or 500 mg) of inclisiran or matching placebo on Day 1. These 4 groups received no further study drug or placebo.	
Reporting group title	Double Dose
Reporting group description: Participants received 1 of 3 different doses (100 mg, 200 mg, or 300 mg) of inclisiran or matching placebo on Day 1. These 4 groups then received a second dose on Day 90.	
Subject analysis set title	Intent-to-Treat (ITT) Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants randomized into the trial. Treatment classification was based on the randomized treatment. This population was used to assess the randomness of treatment allocation.	
Subject analysis set title	Modified Intent-to-Treat (mITT) Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All randomized participants who received at least 1 dose of study drug and had both the baseline and the 180-day follow-up LDL-C assessment. Treatment classification was based on the randomized treatment. This was the primary population for analysis of the primary and secondary endpoints.	
Subject analysis set title	Single Dose Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received an SC injection of placebo (0.9% saline) in amounts matched to the doses administered in the Single Dose Arm.	
Subject analysis set title	Single Dose 200 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants in this group received a 200-mg SC injection of inclisiran on Day 1 of the study.	
Subject analysis set title	Single Dose 300 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants in this group received a 300-mg SC injection of inclisiran on Day 1 of the study.	
Subject analysis set title	Single Dose 500 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: On Day 1 of the study, participants in this group received a 500-mg dose of inclisiran as 2 injections, 1 of 300 mg and 1 of 200 mg.	
Subject analysis set title	Double Dose Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received SC injections of placebo (0.9% saline) in amounts matched to the doses administered in the Double Dose Arm.	
Subject analysis set title	Double Dose 100 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants in this group received their first 100-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.	
Subject analysis set title	Double Dose 200 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in this group received their first 200-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Subject analysis set title	Double Dose 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in this group received their first 300-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Subject analysis set title	Single and Double Dose Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose placebo groups.

Subject analysis set title	Single and Double Dose 200 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 200 mg groups.

Subject analysis set title	Single and Double Dose 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 300 mg groups.

Primary: Change From Baseline In LDL-C Levels For Single-Dose Inclisiran At Day 180

End point title	Change From Baseline In LDL-C Levels For Single-Dose Inclisiran At Day 180
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End point description:

This outcome measure evaluated the effect of single-dose (200 mg, 300 mg, 500 mg) inclisiran treatments on LDL-C levels in the mITT population at Day 180. The least square (LS) mean was calculated using a repeated measurement linear effect model. The model included treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit. The p value was adjusted for multiple comparisons using Dunnett's Test.

End point type	Primary
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End point timeframe:

Baseline, Day 180

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	60	60
Units: percent change				
least squares mean (confidence interval 95%)	2.1 (-2.9 to 7.2)	-27.9 (-33.1 to -22.7)	-38.4 (-43.6 to -33.2)	-41.9 (-47.2 to -36.7)

Statistical analyses

Statistical analysis title	Placebo versus 200 mg
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Statistical analysis description:

Two-sample t-tests were performed to test the superiority of any dosing group over placebo.

Comparison groups	Single Dose Placebo v Single Dose 200 mg
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Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	Dunnett's Test
Parameter estimate	Treatment Difference

Notes:

[1] - The p value was adjusted for multiple comparisons using Dunnett's Test.

Statistical analysis title	Placebo versus 300 mg
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Statistical analysis description:

Two-sample t-tests were performed to test the superiority of any dosing group over placebo.

Comparison groups	Single Dose Placebo v Single Dose 300 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Dunnett's Test
Parameter estimate	Treatment Difference

Notes:

[2] - The p value was adjusted for multiple comparisons using Dunnett's Test.

Statistical analysis title	Placebo versus 500 mg
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Statistical analysis description:

Two-sample t-tests were performed to test the superiority of any dosing group over placebo.

Comparison groups	Single Dose Placebo v Single Dose 500 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[3]
Method	Dunnett's Test
Parameter estimate	Treatment Difference

Notes:

[3] - The p value was adjusted for multiple comparisons using Dunnett's Test.

Primary: Change From Baseline In LDL-C Levels For Double-Dose Inclisiran At Day 180

End point title	Change From Baseline In LDL-C Levels For Double-Dose Inclisiran At Day 180
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End point description:

This outcome measure evaluated the effect of double-dose (100 mg, 200 mg, 300 mg) inclisiran treatments on LDL-C levels in the mITT population at Day 180. The LS mean was calculated using a repeated measurement linear effect model. The model included treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit. The p value was adjusted for multiple comparisons using Dunnett's Test.

End point type	Primary
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End point timeframe:

Baseline, Day 180

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	59	60	59
Units: percent change				
least squares mean (confidence interval 95%)	1.8 (-2.6 to 6.3)	-35.5 (-40 to -31)	-44.9 (-49.3 to -40.4)	-52.6 (-57.1 to -48.1)

Statistical analyses

Statistical analysis title	Placebo versus 100 mg
Statistical analysis description: Two-sample t-tests were performed to test the superiority of any dosing group over placebo.	
Comparison groups	Double Dose Placebo v Double Dose 100 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	Dunnett's Test
Parameter estimate	Treatment Difference

Notes:

[4] - The p value was adjusted for multiple comparisons using Dunnett's Test.

Statistical analysis title	Placebo versus 200 mg
Statistical analysis description: Two-sample t-tests were performed to test the superiority of any dosing group over placebo.	
Comparison groups	Double Dose Placebo v Double Dose 200 mg
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001
Method	Dunnett's Test
Parameter estimate	Treatment Difference

Notes:

[5] - The p value was adjusted for multiple comparisons using Dunnett's Test.

Statistical analysis title	Placebo versus 300 mg
Statistical analysis description: Two-sample t-tests were performed to test the superiority of any dosing group over placebo.	
Comparison groups	Double Dose Placebo v Double Dose 300 mg

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	Dunnett's Test
Parameter estimate	Treatment Difference

Notes:

[6] - The p value was adjusted for multiple comparisons using Dunnett's Test.

Secondary: Change From Baseline In LDL-C Levels at Day 90

End point title	Change From Baseline In LDL-C Levels at Day 90
End point description:	
This outcome measure evaluated the effects of single- and double-dose inclisiran on LDL-C levels in the mITT population at Day 90. The LS mean was calculated using a repeated measurement linear effect model. The model included treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit.	
End point type	Secondary
End point timeframe:	
Baseline, Day 90	

End point values	Single Dose 500 mg	Double Dose 100 mg	Single and Double Dose Placebo	Single and Double Dose 200 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	59	125	120
Units: participants				
least squares mean (confidence interval 95%)	-49 (-53.8 to -44.2)	-34.2 (-39.1 to -29.3)	-0.8 (-4.2 to 2.5)	-41.8 (-45.3 to -38.4)

End point values	Single and Double Dose 300 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	118			
Units: participants				
least squares mean (confidence interval 95%)	-45.7 (-49.2 to -42.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In LDL-C Levels At Day 60, Day 120, and Day 210

End point title	Change From Baseline In LDL-C Levels At Day 60, Day 120, and Day 210
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End point description:

This outcome measure evaluated the effects of both single- and double-dose inclisiran on LDL-C levels in the mITT population from baseline to Day 60, Day 120, and Day 210.

End point type	Secondary
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End point timeframe:

Baseline, Day 60, Day 120, and Day 210

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64 ^[7]	60 ^[8]	60	60 ^[9]
Units: percentage change				
arithmetic mean (confidence interval 95%)				
Day 60	-4.27 (-7.84 to -0.7)	-44.32 (-50.55 to -38.09)	-50.87 (-55.62 to -46.12)	-49.58 (-54.12 to -45.04)
Day 120	-0.91 (-5.17 to 3.34)	-36.94 (-42.8 to -31.08)	-43.32 (-48.95 to -37.68)	-46.42 (-50.63 to -42.22)
Day 210	1.45 (-3.61 to 6.06)	-28.98 (-36.83 to -21.12)	-35.39 (-41.47 to -29.31)	-39.2 (-43.71 to -34.68)

Notes:

[7] - Day 60 (62); Day 210 (62)

[8] - Day 120 (58)

[9] - Day 60 (58); Day 120 (57)

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61 ^[10]	59 ^[11]	60 ^[12]	59 ^[13]
Units: percentage change				
arithmetic mean (confidence interval 95%)				
Day 60	-1.92 (-6.7 to 2.85)	-35.73 (-40.23 to -31.23)	-44.28 (-49.1 to -39.47)	-50.59 (-55.51 to -45.67)
Day 120	0.17 (-3.61 to 3.95)	-41.37 (-45.94 to -36.8)	-49.54 (-54.6 to -44.49)	-54.73 (-59.88 to -49.58)
Day 210	0.58 (-4.58 to 5.74)	-31.67 (-36.08 to -27.27)	-42.59 (-47.11 to -38.08)	-50.54 (-54.83 to -46.25)

Notes:

[10] - Day 210 (60)

[11] - Day 90 (58); Day 120 (58)

[12] - Day 120 (59)

[13] - Day 120 (58); Day 210 (58)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants With An LDL-C Greater Than 80% Of The Baseline Value At Day 180 and Day 210

End point title	Proportion Of Participants With An LDL-C Greater Than 80% Of The Baseline Value At Day 180 and Day 210
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End point description:

This outcome measure evaluated the number of participants (single and double dose) in the mITT population with an LDL-C greater than 80% of the baseline value at Day 180 and Day 210.

End point type	Secondary
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End point timeframe:

Baseline, Day 180, Day 210

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64 ^[14]	60	60	60
Units: participants				
Day 180	35	6	5	0
Day 210	34	8	5	2

Notes:

[14] - Day 180 (64); Day 210 (62)

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61 ^[15]	59	60	59
Units: participants				
Day 180	29	2	1	0
Day 210	34	1	1	1

Notes:

[15] - Day 180 (61); Day 210 (60)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants With Individual Responsiveness as Measured By LDL-C Levels At Day 90 and Day 180

End point title	Proportion Of Participants With Individual Responsiveness as Measured By LDL-C Levels At Day 90 and Day 180
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End point description:

This outcome measure evaluated the individual responsiveness of participants to inclisiran (single and double dose) in the mITT population as defined by an LDL-C level of <25 mg/deciliter [dL] at Day 90 and Day 180.

End point type	Secondary
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End point timeframe:

Day 90, Day 180

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64 ^[16]	60	60 ^[17]	60
Units: participants				
Day 90	0	0	5	3
Day 180	0	0	1	2

Notes:

[16] - Day 90 (63)

[17] - Day 90 (59)

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61 ^[18]	59	60	59
Units: participants				
Day 90	0	0	1	0
Day 180	0	1	2	3

Notes:

[18] - Day 90 (60)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants With Greater Or Equal To 50% LDL-C Reduction From Baseline At Day 180

End point title	Proportion Of Participants With Greater Or Equal To 50% LDL-C Reduction From Baseline At Day 180
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End point description:

This outcome measure evaluated the number of participants (single and double dose) in the mITT population with an LDL-C reduction greater than 50% of the baseline value at Day 180.

End point type	Secondary
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End point timeframe:

Baseline, Day 180

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	60	60
Units: participant	0	9	19	16

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	59	60	59
Units: participant	0	14	27	32

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change In PCSK9 Levels From Baseline At Day 180

End point title	Percentage Change In PCSK9 Levels From Baseline At Day 180
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End point description:

This outcome measure evaluated the percent change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to Day 180 in participants (single and double dose) in the mITT population.

End point type	Secondary
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End point timeframe:

Baseline, Day 180

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	60	60
Units: percent change				
arithmetic mean (standard deviation)	2.2 (± 23.4)	-47.9 (± 21)	-56 (± 19.2)	-59.3 (± 18)

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	59	60	59
Units: percent change				
arithmetic mean (standard deviation)	-1.2 (± 20.7)	-53.2 (± 20.9)	-66.2 (± 15.6)	-69.1 (± 12.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change In Other Lipids and Apolipoproteins From Baseline To Day 180

End point title	Percentage Change In Other Lipids and Apolipoproteins From Baseline To Day 180
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End point description:

This outcome measure evaluated the percent change from baseline to Day 180 in cholesterol (total, high-density lipoprotein [HDL], non-HDL) and apolipoproteins (B, A1) in participants (single and double dose) in the mITT population.

End point type	Secondary
End point timeframe:	
Baseline, Day 180	

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	60	60
Units: percent change				
arithmetic mean (standard deviation)				
Total Cholesterol	1.8 (± 12.1)	-17.6 (± 19)	-23.7 (± 15.7)	-26.6 (± 10.7)
Non-HDL Cholesterol	1.5 (± 16.7)	-25.1 (± 26.2)	-35.2 (± 20.2)	-36.9 (± 14)
HDL Cholesterol	3.8 (± 15.6)	4.4 (± 14.8)	8.8 (± 11.1)	6.9 (± 14)
Apolipoprotein B	1.7 (± 14.7)	-22.9 (± 21)	-30.8 (± 18)	-33.1 (± 12.7)
Apolipoprotein A1	3.6 (± 10.6)	2.9 (± 9.3)	3.8 (± 8.9)	4.1 (± 10.9)

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	59	60	59
Units: percent change				
arithmetic mean (standard deviation)				
Total Cholesterol	0.7 (± 12.3)	-22.4 (± 12.4)	-26.8 (± 13)	-33.2 (± 11.3)
Non-HDL Cholesterol	1.3 (± 16.9)	-31.7 (± 15.1)	-38.9 (± 16.8)	-46 (± 14.6)
HDL Cholesterol	0.5 (± 12.5)	7.6 (± 12.2)	10.3 (± 15.3)	8.6 (± 14.9)
Apolipoprotein B	0.9 (± 13)	-27.8 (± 13.4)	-35 (± 15.8)	-40.9 (± 14.8)
Apolipoprotein A1	0.8 (± 8.3)	5.5 (± 10.6)	8.6 (± 11.5)	6.2 (± 11.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants Who Attained Global Lipid Modification Targets For Level Of Atherosclerotic Cardiovascular Disease Risk

End point title	Proportion Of Participants Who Attained Global Lipid Modification Targets For Level Of Atherosclerotic Cardiovascular Disease Risk
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End point description:

This outcome measure evaluated the proportion of participants (single and double dose) in the mITT population who attained a global lipid modification target by baseline cardiovascular risk group, looking specifically at LDL-C levels (mg/dL) in the category of cardiovascular disease (CVD).

CVD was defined as a participant who had at least 1 of the following: prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke, prior transient ischemic attack, peripheral artery disease.

End point type	Secondary
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End point timeframe:

Baseline, Day 180

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	60	60
Units: participant				
CVD	45	43	46	33
<70 mg/dL	0	16	27	18

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	59	60	59
Units: participant				
CVD	45	41	39	42
<70 mg/dL	1	24	27	33

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change In Other Lipids And Inflammatory Markers From Baseline To Day 180

End point title	Percentage Change In Other Lipids And Inflammatory Markers From Baseline To Day 180
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End point description:

This outcome measure evaluated the percent change from baseline to Day 180 in triglycerides, very-low-density lipoprotein (VLDL) cholesterol, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) in participants (single and double dose) in the mITT population.

End point type	Secondary
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End point timeframe:

Baseline, Day 180

End point values	Single Dose Placebo	Single Dose 200 mg	Single Dose 300 mg	Single Dose 500 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	60	60
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Triglycerides	6.4 (-15.9 to 21.9)	1.1 (-18.5 to 17.8)	-12.8 (-27.8 to 7.8)	-12.2 (-25.6 to 7.7)

VLDL Cholesterol	2.4 (-30.7 to 30.5)	-11.6 (-35.8 to 23.3)	-23.8 (-43 to -6.4)	-14.6 (-34.8 to 3.5)
Lipoprotein(a)	0.5 (-13.9 to 14.8)	-14.3 (-29.5 to -3.5)	-14.3 (-25.4 to -5.6)	-18.2 (-35 to -1.6)
hsCRP	-5.3 (-40.8 to 28.4)	7.1 (-30.7 to 70.9)	-16.2 (-45.8 to 50)	-19.8 (-50 to 32.7)

End point values	Double Dose Placebo	Double Dose 100 mg	Double Dose 200 mg	Double Dose 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	59	60	59
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Triglycerides	-3 (-17.2 to 22.6)	-6.3 (-17.6 to 10.9)	0.7 (-22.4 to 11.3)	-14.2 (-26.4 to 5.4)
VLDL Cholesterol	2.7 (-20 to 26.7)	-16.4 (-31.3 to 0)	-21.2 (-38.5 to 13.2)	-16 (-38.2 to 9.1)
Lipoprotein(a)	0 (-10 to 12.4)	-14.9 (-26.2 to -1.9)	-17.3 (-31.9 to -7.7)	-25.6 (-38.5 to -15.2)
hsCRP	-20 (-50 to 30)	-12.5 (-42.9 to 29.4)	-16.3 (-34.6 to 24.3)	-16.7 (-50.9 to 33.3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 360 days (\pm 3 days) post randomization and treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo - Single Dose
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Reporting group description:

Participants received an SC injection of placebo (0.9% saline) that matched the doses administered in the Single Dose Arm.

Reporting group title	200 mg - Single Dose
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Reporting group description:

Participants in this group only received a 200-mg SC injection of inclisiran on Day 1 of the study.

Reporting group title	300 mg - Single Dose
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Reporting group description:

Participants in this group only received a 300-mg SC injection of inclisiran on Day 1 of the study.

Reporting group title	500 mg - Single Dose
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Reporting group description:

On Day 1 only of the study, participants in this group received a 500-mg dose of inclisiran as 2 injections, 1 of 300 mg and 1 of 200 mg.

Reporting group title	Placebo - Double Dose
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Reporting group description:

Participants received SC injections of placebo (0.9% saline) in amounts that matched doses administered in the Double Dose Arm.

Reporting group title	100 mg - Double Dose
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Reporting group description:

Participants in this group received their first 100-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Reporting group title	200 mg - Double Dose
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Reporting group description:

Participants in this group received their first 200-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Reporting group title	300 mg - Double Dose
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Reporting group description:

Participants in this group received their first 300-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

Serious adverse events	Placebo - Single Dose	200 mg - Single Dose	300 mg - Single Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 65 (4.62%)	11 / 60 (18.33%)	11 / 61 (18.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 65 (0.00%)	2 / 60 (3.33%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Tongue neoplasm malignant stage			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Bladder cancer			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Glioblastoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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

Bladder transitional cell carcinoma stage 0			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Pituitary tumour benign			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Hypotension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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

Orthostatic hypotension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Intermittent claudication			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Vascular stent restenosis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Platelet count decreased			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	0 / 61 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Traumatic haemothorax			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Upper limb fracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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

Facial bones fracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Humerus fracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Intentional overdose			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Ligament sprain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Post procedural complication			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Weaning failure			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Limb crushing injury			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Multiple injuries			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	0 / 61 (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
Myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Atrial flutter			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Atrial tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Atrioventricular block complete			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Coronary artery disease			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Atrial fibrillation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Cardiac arrest			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Pericarditis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Ventricular extrasystoles			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	0 / 61 (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
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Ischaemic stroke			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Spinal cord ischaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Syncope			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Proctitis ulcerative			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aorto-oesophageal fistula			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Gastritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Large intestine polyp			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Volvulus			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Vomiting			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Stress urinary incontinence			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Musculoskeletal and connective tissue disorders			
Muscle necrosis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 61 (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
Osteoarthritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Device related infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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

Erysipelas			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Gastroenteritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Implant site infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Listeria sepsis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Osteomyelitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Urosepsis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Wound abscess			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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
Hypoglycaemia			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 61 (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

Serious adverse events	500 mg - Single Dose	Placebo - Double Dose	100 mg - Double Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 65 (12.31%)	7 / 62 (11.29%)	13 / 61 (21.31%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Prostate cancer			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Tongue neoplasm malignant stage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Bladder cancer			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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

Glioblastoma	subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Intestinal adenocarcinoma	subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Bladder transitional cell carcinoma stage 0	subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Gastrointestinal tract adenoma	subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Non-small cell lung cancer stage I	subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Oesophageal adenocarcinoma	subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Pituitary tumour benign	subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Squamous cell carcinoma of skin	subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Vascular disorders				

Aortic dissection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Hypotension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Intermittent claudication			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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

Vascular stent restenosis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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
Platelet count decreased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Thoracic vertebral fracture			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Traumatic haemothorax			

subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Upper limb fracture			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Facial bones fracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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
Ligament sprain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Post procedural complication			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	1 / 62 (1.61%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weaning failure			

subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Limb crushing injury			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Multiple injuries			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Pneumothorax traumatic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Angina unstable			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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	2 / 65 (3.08%)	0 / 62 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Atrial tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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
Coronary artery disease			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Atrial fibrillation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Cardiac arrest			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Pericarditis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Nervous system disorders			
Carpal tunnel syndrome			

subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Ischaemic stroke			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Lacunar stroke			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord ischaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Syncope			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Inguinal hernia			

subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Proctitis ulcerative			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Aorto-oesophageal fistula			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Gastritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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
Large intestine polyp			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Vomiting			
subjects affected / exposed	1 / 65 (1.54%)	0 / 62 (0.00%)	0 / 61 (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
Hepatobiliary disorders			
Hepatic haemorrhage			

subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Acute kidney injury			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Stress urinary incontinence			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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
Musculoskeletal and connective tissue disorders			
Muscle necrosis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Osteitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Osteoarthritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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

Appendicitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Erysipelas			
subjects affected / exposed	0 / 65 (0.00%)	1 / 62 (1.61%)	0 / 61 (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
Gastroenteritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeria sepsis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Osteomyelitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Wound abscess			

subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	0 / 61 (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
Hypoglycaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 62 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	200 mg - Double Dose	300 mg - Double Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 62 (12.90%)	9 / 61 (14.75%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage			

subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma stage 0			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			

subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (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			
Device dislocation			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent-graft endoleak			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (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 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			

subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (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	2 / 62 (3.23%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weaning failure			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb crushing injury			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 62 (3.23%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 62 (0.00%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord ischaemia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 62 (1.61%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis ulcerative			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aorto-oesophageal fistula			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress urinary incontinence			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle necrosis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			

subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 62 (1.61%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo - Single Dose	200 mg - Single Dose	300 mg - Single Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 65 (76.92%)	49 / 60 (81.67%)	49 / 61 (80.33%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 65 (4.62%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences (all)	3	1	1

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Contusion			
subjects affected / exposed	1 / 65 (1.54%)	1 / 60 (1.67%)	2 / 61 (3.28%)
occurrences (all)	1	1	2
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 65 (0.00%)	2 / 60 (3.33%)	3 / 61 (4.92%)
occurrences (all)	0	2	3
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 65 (1.54%)	2 / 60 (3.33%)	4 / 61 (6.56%)
occurrences (all)	1	2	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 65 (4.62%)	1 / 60 (1.67%)	2 / 61 (3.28%)
occurrences (all)	4	1	2
Headache			
subjects affected / exposed	6 / 65 (9.23%)	2 / 60 (3.33%)	2 / 61 (3.28%)
occurrences (all)	6	2	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 65 (7.69%)	2 / 60 (3.33%)	4 / 61 (6.56%)
occurrences (all)	7	2	4
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 65 (1.54%)	4 / 60 (6.67%)	2 / 61 (3.28%)
occurrences (all)	1	5	2
Diarrhoea			
subjects affected / exposed	1 / 65 (1.54%)	1 / 60 (1.67%)	4 / 61 (6.56%)
occurrences (all)	1	1	4
Abdominal pain			
subjects affected / exposed	2 / 65 (3.08%)	3 / 60 (5.00%)	2 / 61 (3.28%)
occurrences (all)	2	4	2
Nausea			

subjects affected / exposed	2 / 65 (3.08%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences (all)	2	1	1
Vomiting			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	2 / 61 (3.28%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 65 (3.08%)	4 / 60 (6.67%)	7 / 61 (11.48%)
occurrences (all)	2	4	7
Epistaxis			
subjects affected / exposed	4 / 65 (6.15%)	0 / 60 (0.00%)	0 / 61 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 65 (3.08%)	4 / 60 (6.67%)	4 / 61 (6.56%)
occurrences (all)	2	6	4
Back pain			
subjects affected / exposed	5 / 65 (7.69%)	4 / 60 (6.67%)	4 / 61 (6.56%)
occurrences (all)	5	4	4
Myalgia			
subjects affected / exposed	3 / 65 (4.62%)	2 / 60 (3.33%)	6 / 61 (9.84%)
occurrences (all)	4	2	7
Musculoskeletal pain			
subjects affected / exposed	1 / 65 (1.54%)	2 / 60 (3.33%)	0 / 61 (0.00%)
occurrences (all)	1	2	0
Pain in extremity			
subjects affected / exposed	2 / 65 (3.08%)	2 / 60 (3.33%)	1 / 61 (1.64%)
occurrences (all)	2	2	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 65 (0.00%)	3 / 60 (5.00%)	2 / 61 (3.28%)
occurrences (all)	0	4	2
Nasopharyngitis			
subjects affected / exposed	4 / 65 (6.15%)	8 / 60 (13.33%)	9 / 61 (14.75%)
occurrences (all)	4	13	12
Urinary tract infection			

subjects affected / exposed	1 / 65 (1.54%)	1 / 60 (1.67%)	5 / 61 (8.20%)
occurrences (all)	1	1	10
Influenza			
subjects affected / exposed	3 / 65 (4.62%)	3 / 60 (5.00%)	4 / 61 (6.56%)
occurrences (all)	3	3	4
Upper respiratory tract infection			
subjects affected / exposed	2 / 65 (3.08%)	2 / 60 (3.33%)	4 / 61 (6.56%)
occurrences (all)	2	2	5

Non-serious adverse events	500 mg - Single Dose	Placebo - Double Dose	100 mg - Double Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 65 (83.08%)	51 / 62 (82.26%)	47 / 61 (77.05%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 65 (0.00%)	5 / 62 (8.06%)	0 / 61 (0.00%)
occurrences (all)	0	6	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 65 (1.54%)	1 / 62 (1.61%)	4 / 61 (6.56%)
occurrences (all)	1	1	4
Contusion			
subjects affected / exposed	2 / 65 (3.08%)	5 / 62 (8.06%)	3 / 61 (4.92%)
occurrences (all)	3	5	4
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 65 (1.54%)	3 / 62 (4.84%)	4 / 61 (6.56%)
occurrences (all)	1	5	4
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 65 (1.54%)	2 / 62 (3.23%)	0 / 61 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 65 (3.08%)	6 / 62 (9.68%)	3 / 61 (4.92%)
occurrences (all)	2	8	3
Headache			

subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	5 / 62 (8.06%) 7	5 / 61 (8.20%) 6
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	6 / 62 (9.68%) 7	2 / 61 (3.28%) 2
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1 4 / 65 (6.15%) 5 0 / 65 (0.00%) 0 4 / 65 (6.15%) 4 1 / 65 (1.54%) 1	2 / 62 (3.23%) 2 2 / 62 (3.23%) 2 3 / 62 (4.84%) 3 3 / 62 (4.84%) 3 0 / 62 (0.00%) 0	0 / 61 (0.00%) 0 3 / 61 (4.92%) 3 2 / 61 (3.28%) 2 2 / 61 (3.28%) 2 0 / 61 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3 1 / 65 (1.54%) 1	3 / 62 (4.84%) 3 1 / 62 (1.61%) 1	1 / 61 (1.64%) 1 0 / 61 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain	4 / 65 (6.15%) 4	1 / 62 (1.61%) 1	2 / 61 (3.28%) 2

subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4	2 / 62 (3.23%) 2	6 / 61 (9.84%) 6
Myalgia subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	3 / 62 (4.84%) 3	7 / 61 (11.48%) 7
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	4 / 62 (6.45%) 5	0 / 61 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	4 / 62 (6.45%) 4	1 / 61 (1.64%) 2
Infections and infestations			
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	2 / 62 (3.23%) 2	3 / 61 (4.92%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 65 (13.85%) 10	8 / 62 (12.90%) 9	8 / 61 (13.11%) 13
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	4 / 62 (6.45%) 4	1 / 61 (1.64%) 1
Influenza subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5	2 / 62 (3.23%) 2	3 / 61 (4.92%) 4
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 6	2 / 62 (3.23%) 2	2 / 61 (3.28%) 3

Non-serious adverse events	200 mg - Double Dose	300 mg - Double Dose	
Total subjects affected by non-serious adverse events subjects affected / exposed	49 / 62 (79.03%)	51 / 61 (83.61%)	
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3	0 / 61 (0.00%) 0	
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 61 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	2 / 61 (3.28%) 2	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 3	1 / 61 (1.64%) 1	
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2	0 / 61 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3 1 / 62 (1.61%) 1	3 / 61 (4.92%) 3 5 / 61 (8.20%) 6	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	1 / 61 (1.64%) 1	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea	2 / 62 (3.23%) 2 7 / 62 (11.29%) 7 1 / 62 (1.61%) 1	1 / 61 (1.64%) 1 5 / 61 (8.20%) 6 4 / 61 (6.56%) 5	

subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4	3 / 61 (4.92%) 3	
Vomiting subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4	0 / 61 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	6 / 62 (9.68%) 6	3 / 61 (4.92%) 3	
Epistaxis subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	0 / 61 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5	3 / 61 (4.92%) 3	
Back pain subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	4 / 61 (6.56%) 5	
Myalgia subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5	5 / 61 (8.20%) 8	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	6 / 61 (9.84%) 6	
Pain in extremity subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 5	1 / 61 (1.64%) 1	
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	1 / 61 (1.64%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5	11 / 61 (18.03%) 12	
Urinary tract infection			

subjects affected / exposed	1 / 62 (1.61%)	2 / 61 (3.28%)	
occurrences (all)	2	2	
Influenza			
subjects affected / exposed	4 / 62 (6.45%)	5 / 61 (8.20%)	
occurrences (all)	4	5	
Upper respiratory tract infection			
subjects affected / exposed	1 / 62 (1.61%)	3 / 61 (4.92%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2016	<ul style="list-style-type: none">• Addition of an interim analysis of lipids and PCSK9 at Day 90. Addition of a secondary endpoint for LDL-C levels at Day 90• The exploratory objective has been re-worded to provide a more specific description of the event terms that will be reported• Any participants in whom LDL-C levels have not returned to >80% of baseline values will continue to be followed-up monthly as part of this study until either this level has been reached or until Day 360. Additional follow-up visits added to schedule• Anti-drug antibodies will be assessed when LDL-C returns to >80% baseline or at Day 360• Amended exclusion criterion 11 to state that contraception must be used during the entire study period• Additional exclusion criterion 17 to exclude participants that have received monoclonal antibodies directed towards PCSK9• Additional description of sample size calculation and statistical methods• Removal of description of the open-label extension study• Neurological examination added as part of the physical examination• Addition of monthly pregnancy test for women of childbearing potential• Addition of Sampson Criteria for diagnosing anaphylaxis
18 March 2016	<ul style="list-style-type: none">• Additional anti-drug antibody assessments at Day 60 and Day 90 (and at Day 150 and Day 180 in participants that received a second dose).• Addition of reference to the open-label extension study• Additional information on completed in vitro and in vivo non-clinical studies• Specify that height and weight to be recorded as part of the physical examination
12 April 2016	<ul style="list-style-type: none">• Amended exclusion criterion 13 to exclude participants with a history of alcohol / drug abuse within the last five years• Amended exclusion criteria 17 to clarify that participants should not have received monoclonal antibodies directed towards PCSK9 within 90 days of screening• Specified that abnormal neurological examination or anaphylactic reaction must be recorded on the source documentation and the electronic case report form

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported