

**Clinical trial results:**

A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL TO EVALUATE THE EFFECT OF 300 MG OF INCLISIRAN SODIUM GIVEN AS SUBCUTANEOUS INJECTIONS IN SUBJECTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HeFH) AND ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C)

Summary

EudraCT number	2017-002472-30
Trial protocol	GB ES CZ SE DK
Global end of trial date	27 August 2019

Results information

Result version number	v1 (current)
This version publication date	11 September 2020
First version publication date	11 September 2020

Trial information**Trial identification**

Sponsor protocol code	MDCO-PCS-17-03
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03397121
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Medicines Company
Sponsor organisation address	8 Sylvan Way, Parsippany, United States, NJ 07054
Public contact	Global Health Science Center, The Medicines Company, +1 9732906000, medical.information@themedco.com
Scientific contact	Global Health Science Center, The Medicines Company, +1 9732906000, medical.information@themedco.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2019
Global end of trial reached?	Yes
Global end of trial date	27 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of inclisiran treatment on:

- LDL-C levels at Day 510
- Time adjusted percent change in LDL-C levels from baseline between Day 90 and Day 540 levels

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator:

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

Actual start date of recruitment	01 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 38
Country: Number of subjects enrolled	Spain: 84
Country: Number of subjects enrolled	Sweden: 34
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Denmark: 49
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	South Africa: 177
Country: Number of subjects enrolled	United States: 65
Worldwide total number of subjects	482
EEA total number of subjects	217

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)	374
From 65 to 84 years	108
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Not applicable

Pre-assignment

Screening details:

Screening occurred prior to randomization and consisted of confirming eligibility and collecting Baseline assessments. Subjects enrolled must have fasting triglyceride <4.52 mmol/L (<400 mg/dL) and serum LDL-C \geq 2.6 mmol/L (\geq 100 mg/dL) at screening.

Pre-assignment period milestones

Number of subjects started	482
Number of subjects completed	482

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	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Inclisiran

Arm description:

Inclisiran sodium 300 milligrams

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

Dosage and administration details:

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

Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis.

Arm title	Placebo
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Arm description:

Placebo

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

Dosage and administration details:

Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.

Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection).

Number of subjects in period 1	Inclisiran	Placebo
Started	242	240
Completed	235	231
Not completed	7	9
Initiation of protocol-prohibited PCSK9 inhibitor	-	1
Consent withdrawn by subject	-	4
death	1	1
Not specified	5	1
Lost to follow-up	1	2

Baseline characteristics

Reporting groups

Reporting group title	Inclisiran
Reporting group description: Inclisiran sodium 300 milligrams	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Inclisiran	Placebo	Total
Number of subjects	242	240	482
Age categorical			
Age categorical			
Units: Subjects			
Adults (18-64 years)	189	185	374
Adults (65 - 74 years)	45	48	93
Adults (75+ years)	8	7	15
Age continuous			
Age			
Units: years			
arithmetic mean	54.4	55.0	
standard deviation	± 12.48	± 12.48	-
Gender categorical			
Gender			
Units: Subjects			
Female	130	125	255
Male	112	115	227

Subject analysis sets

Subject analysis set title	Inclisiran
Subject analysis set type	Intention-to-treat
Subject analysis set description: Inclisiran sodium 300 milligrams (mg) will be administered as a SC injection on Day 1, Day 90 then every 6 months. Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:
Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.
Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection).

Reporting group values	Inclisiran	Placebo	
Number of subjects	242	240	
Age categorical			
Age categorical			
Units: Subjects			
Adults (18-64 years)	189	185	

Adults (65 - 74 years)	45	48	
Adults (75+ years)	8	7	
Age continuous			
Age			
Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical			
Gender			
Units: Subjects			
Female	130	125	
Male	112	115	

End points

End points reporting groups

Reporting group title	Inclisiran
Reporting group description:	
Inclisiran sodium 300 milligrams	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Subject analysis set title	Inclisiran
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Inclisiran sodium 300 milligrams (mg) will be administered as a SC injection on Day 1, Day 90 then every 6 months.	
Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.	
Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection).	

Primary: Percentage Change In LDL-C From Baseline To Day 510

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

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: Percentage change				
least squares mean (confidence interval 95%)	-41.15 (-44.52 to -37.77)	8.37 (3.96 to 12.77)	-41.15 (-44.52 to -37.77)	8.37 (3.96 to 12.77)

Statistical analyses

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

Number of subjects included in analysis	964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-49.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.04
upper limit	-43.99

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

End point title	Time-adjusted Percent Change in LDL-C From Baseline After Day 90 and up to Day 540
End point description:	
Time adjusted change in LDL-C	
End point type	Primary
End point timeframe:	
Baseline, Day 90 to Day 540	

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: Percentage change				
least squares mean (confidence interval 95%)	-38.08 (-41.03 to -35.14)	6.22 (3.26 to 9.17)	-38.08 (-41.03 to -35.14)	6.22 (3.26 to 9.17)

Statistical analyses

Statistical analysis title	Percentage Change In LDL-C From Day 90 to Day 540
Statistical analysis description:	
Difference in time-adjusted percentage change in LDL-C Levels From Baseline After Day 90 and up to Day 540 between inclisiran and placebo arms	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-44.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.48
upper limit	-40.12

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

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

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: mg/dL				
least squares mean (confidence interval 95%)	-58.95 (-64.75 to -53.15)	9.94 (4.10 to 15.78)	-58.95 (-64.75 to -53.15)	9.94 (4.10 to 15.78)

Statistical analyses

Statistical analysis title	Absolute Change in LDL-C From Baseline To Day 510
Statistical analysis description: Difference in Absolute Change in LDL-C From Baseline To Day 510 between inclisiran and placebo arms	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-68.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.11
upper limit	-60.67

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

and up to Day 540

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

Time-adjusted absolute change in LDL-C

End point type	Secondary
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End point timeframe:

From Baseline After Day 90 and up to Day 540

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: mg/dL				
least squares mean (confidence interval 95%)	-56.58 (-60.98 to -52.17)	6.17 (1.72 to 10.62)	-56.58 (-60.98 to -52.17)	6.17 (1.72 to 10.62)

Statistical analyses

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

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

Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-62.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69.01
upper limit	-56.48

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

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

Change in PCSK9

End point type	Secondary
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End point timeframe:

Baseline to Day 510

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: percentage change				
least squares mean (confidence interval 95%)	-60.68 (-64.40 to -56.96)	17.66 (13.91 to 21.42)	-60.68 (-64.40 to -56.96)	17.66 (13.91 to 21.42)

Statistical analyses

Statistical analysis title	Percentage change in PCSK9 from Baseline - Day 510
Statistical analysis description: Difference in percentage change in PCSK9 from baseline to Day 510, between inclisiran and placebo arms	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-78.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.65
upper limit	-73.04

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

End point title	Percentage Change in Total Cholesterol From Baseline to Day 510
End point description: Change in total cholesterol	
End point type	Secondary
End point timeframe: Baseline to Day 510	

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: Percentage change				
least squares mean (confidence interval 95%)	-25.11 (-27.83 to -22.39)	6.66 (3.96 to 9.36)	-25.11 (-27.83 to -22.39)	6.66 (3.96 to 9.36)

Statistical analyses

Statistical analysis title	Percentage change in Total Cholesterol
Statistical analysis description:	
Difference in the percentage change in total cholesterol from baseline to Day 510, between inclisiran and placebo arms	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-31.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.59
upper limit	-27.94

Secondary: Percentage Change in Apolipoprotein B (ApoB) From Baseline To Day 510

End point title	Percentage Change in Apolipoprotein B (ApoB) From Baseline To Day 510
End point description:	
Change in ApoB	
End point type	Secondary
End point timeframe:	
Baseline To Day 510	

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: Percentage change				
least squares mean (confidence interval 95%)	-33.14 (-35.91 to -30.36)	2.93 (0.14 to 5.71)	-33.14 (-35.91 to -30.36)	2.93 (0.14 to 5.71)

Statistical analyses

Statistical analysis title	Percentage change in Apo B form Baseline - Day 510
Statistical analysis description:	
Difference in the percentage change in Apolipoprotein B (ApoB) from baseline to Day 510	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-36.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.99
upper limit	-32.14

Secondary: Percentage Change in Non-high-density Lipoprotein (HDL)-C From Baseline To Day 510

End point title	Percentage Change in Non-high-density Lipoprotein (HDL)-C From Baseline To Day 510
End point description:	
Change in non-HDL-C	
End point type	Secondary
End point timeframe:	
Baseline To Day 510	

End point values	Inclisiran	Placebo	Inclisiran	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	240	242	240
Units: Percentage change				
least squares mean (confidence interval 95%)	-34.93 (-38.46 to -31.40)	7.43 (3.93 to 10.92)	-34.93 (-38.46 to -31.40)	7.43 (3.93 to 10.92)

Statistical analyses

Statistical analysis title	Percentage Change in Non-HDL-C: baseline - Day 510
Statistical analysis description:	
Difference in the percentage change in Non-HDL-C from baseline to Day 510, between inclisiran and placebo arms	
Comparison groups	Placebo v Inclisiran
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-42.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.32
upper limit	-37.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 0 to Day 510

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Inclisiran
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Reporting group description:

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

Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis.

Reporting group title	Placebo
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Reporting group description:

Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.

Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection).

Serious adverse events	Inclisiran	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 241 (7.47%)	33 / 240 (13.75%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 241 (0.41%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Soft tissue injury			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 241 (0.83%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 241 (0.41%)	4 / 240 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	2 / 241 (0.83%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
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	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery disease			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 241 (0.41%)	3 / 240 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sensory disturbance			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis erosive			

subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 241 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective tenosynovitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 241 (0.41%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelitis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tick-borne fever			

subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Inclisiran	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 241 (39.83%)	67 / 240 (27.92%)	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	22 / 241 (9.13%)	0 / 240 (0.00%)	
occurrences (all)	37	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	17 / 241 (7.05%)	10 / 240 (4.17%)	
occurrences (all)	19	11	
Infections and infestations			
Influenza			
subjects affected / exposed	13 / 241 (5.39%)	21 / 240 (8.75%)	
occurrences (all)	15	24	
Nasopharyngitis			
subjects affected / exposed	28 / 241 (11.62%)	20 / 240 (8.33%)	
occurrences (all)	36	21	
Upper respiratory tract infection			

subjects affected / exposed	16 / 241 (6.64%)	16 / 240 (6.67%)	
occurrences (all)	19	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2017	<p>Global Amendment #1</p> <p>Clarifications have been made to the various sections of the protocol synopsis and main body in order to address comments received from an FDA review of the study. These clarification are related to exclusion criterion #3, site training requirements and statistics.</p> <p>Changes made to the Synopsis section to include an update to exclusion criterion #3 and the Statistical Methods – Key Secondary Endpoints Analysis.</p> <p>Changes made to the Protocol Main Body include:</p> <p>Section 4.3-Exclusion Criteria,</p> <p>Section 10.3.2.1-Intent-to-Treat (ITT) Population,</p> <p>Section 10.3.2.2-Modified Intent-to-Treat (mITT) Population,</p> <p>Section 10.3.4-Missing Data Handling,</p> <p>Section 10.4.3-Efficacy Analysis, 10.4.3.1.1-Sensitivity Analysis for Primary Efficacy Endpoints and 10.4.3.2-Secondary Efficacy Endpoint.</p> <p>Changes made to the Appendices included the addition of a new Appendix C, Genetic Informed Consent, which shifted the numbering of subsequent appendices.</p>
08 January 2018	<p>Global Amendment #2</p> <p>Clarifications made to the protocol main body were included in order to address comments received from the FDA.</p> <p>Changes were made to the following sections:</p> <p>Section 4.4-Withdrawal criteria,</p> <p>Section 6.1-Table 2 Schedule of Assessments (including footnote 7) and</p> <p>Section 7.1.3-Vital Signs.</p>
30 August 2018	<p>Global Amendment #3</p> <p>Changes were made to the Procedures in Case of Emergency section of the protocol to replace Pharmaceutical Product Development, LLC with The Medicines Company.</p> <p>Changes were made to the following sections to remove the month, year and/or edition associated with the Investigator's Brochure as investigative sites should always refer to the latest edition:</p> <p>Section 1.3 Known and Potential Risks and Benefits</p> <p>Section 16 References</p>
31 January 2019	<p>Global Amendment # 4</p> <p>Changes have been made to the following sections:</p> <ul style="list-style-type: none">- Synopsis, Section 3.1, Section 4.1, Section 6.4, Section 10 to account for actual number of randomized subjects.- Synopsis, Section 2.1, Section 3.3, Section 3.4, Section 7.2.1, Section 10.4.3.1 to account for refinement in the description of time adjusted analyses of LDL-C.- Section 6.1. Table 2. Section 6.4, Section 6.6, Section 6.8, Section 7.1.8.8 to clarify the plan to test for ADA.- Section 6.1. Table 2, Schedule of Assessments to align with Health Authority feedback for wider visit windows.- Section 10.3.2.2., Section 10.4.1., Section 10.4.3 to add to account for the addition of a new analysis set (Full Analysis Set).- Section 10.3.3. Analysis Windows and Baseline to clarify that analysis windows will be defined to maximize the amount of data that are included in the analysis models and that full details will be provided in the Statistical Analysis Plan.- Synopsis, Section 10.3.4, Section 10.4.3.1, Section 10.4.3.1.1. Missing Data Handling to align approach to missing data handling with Health Authority feedback and that details are provided in the Statistical Analysis Plan.- Section 10.4.4.2. Laboratory Tests to add analyses for clinically significant laboratory parameters.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Not applicable.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32197277>