



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study followed by an Open-Label continuation Period to Assess the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients with Familial Hypercholesterolemia and Inadequately Controlled Low-Density-Lipoprotein Cholesterol

Summary

EudraCT number	2011-001480-42
Trial protocol	ES SE BE GB FR HU DE CZ GR IT PL SK NL DK
Global end of trial date	16 February 2016

Results information

Result version number	v1 (current)
This version publication date	18 July 2019
First version publication date	18 July 2019

Trial information

Trial identification

Sponsor protocol code	MIPO3801011
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01475825
WHO universal trial number (UTN)	-
Other trial identifiers	Sanofi: EFC12875

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, MA, United States, 02142
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.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	21 April 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether mipomersen (ISIS 301012) significantly reduces atherogenic lipid levels in subjects with severe heterozygous familial hypercholesterolemia (severe HeFH), defined as low-density lipoprotein cholesterol (LDL-C) levels ≥ 200 mg/dL plus the presence of coronary heart disease (CHD)/risk equivalents or LDL-C levels ≥ 300 mg/dL regardless of the presence of CHD/risk equivalents (referred to as Cohort 1) compared to placebo. Two different mipomersen dosing regimens will be studied: subcutaneous (SC) mipomersen 200 mg once weekly versus placebo, and SC mipomersen 70 mg thrice weekly versus placebo.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Brazil: 8

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Russian Federation: 62
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	310
EEA total number of subjects	117

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)	260
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted from 15 Dec 2011 to 16 Feb 2016. Out of 310 randomized subjects, 201 were in Cohort 1 and 109 in Cohort 2. One subject in the Cohort 1/Regimen B/Placebo group was randomized but not treated, hence not considered in safety population.

Pre-assignment

Screening details:

During the 4-week Screening period, subjects were evaluated for inclusion in the study, and assigned to 1 of 2 cohorts. One subject in Cohort 1/Regimen B/ placebo group was randomized and completed some of the screening procedures (laboratory tests and imaging evaluations) into the study but withdrew prior to receiving treatment.

Period 1

Period 1 title	BTP/BTP Follow up & OLC, except OLC FU (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Regimen A: Mipomersen, 200 mg, Once Weekly

Arm description:

Subjects received once weekly subcutaneous (SC) injections of mipomersen sodium 200 milligrams (mg) during the 60-week Blinded Treatment Period (BTP). Subjects who chose to participate in the open label continuation (OLC) received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety Follow-up (FU) Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.

Arm type	Experimental
Investigational medicinal product name	Mipomersen Sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mipomersen Sodium 200 mg injection once weekly during the double-blind treatment period followed by same treatment in open label period in Regimen A.

Arm title	Regimen A: Placebo, Once Weekly
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Arm description:

Subjects received once weekly SC injections of Placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo injection once weekly during the double blind treatment period in Regimen A.

Investigational medicinal product name	Mipomersen Sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mipomersen Sodium 200 mg injection once weekly during the open label period in Regimen A.

Arm title	Regimen B: Mipomersen, 70 mg, Thrice Weekly
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Arm description:

Subjects received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.

Arm type	Experimental
Investigational medicinal product name	Mipomersen Sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mipomersen Sodium 70 mg injections thrice weekly during the double blind treatment period followed by same treatment in open label period in Regimen B.

Arm title	Regimen B: Placebo, Thrice Weekly
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Arm description:

Subjects received thrice weekly SC injections of placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo injection thrice weekly during the double blind treatment period in Regimen B.

Investigational medicinal product name	Mipomersen Sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mipomersen Sodium 70 mg injections thrice weekly during the open label period in Regimen B.

Number of subjects in period 1 ^[1]	Regimen A: Mipomersen, 200 mg, Once Weekly	Regimen A: Placebo, Once Weekly	Regimen B: Mipomersen, 70 mg, Thrice Weekly
Started	104	51	102
Randomized and Treated	104	51	102
Completed Blinded Treatment Period (BTP)	60	42	59
Entered Open-Label Continuation (OLC)	45	31	44
Completed BTP, BTP Follow up, OLC	37	19	38
Completed	37	19	38
Not completed	67	32	64
Consent withdrawn by subject	9	3	11
Non-compliance with Study Drug	1	2	4
Physician decision	-	1	-
Not Available	-	-	2
Did not enter OLC	13	11	15
Adverse Event	41	15	27
Death	1	-	1
Lost to follow-up	1	-	3
Protocol deviation	1	-	-
Lack of efficacy	-	-	1

Number of subjects in period 1 ^[1]	Regimen B: Placebo, Thrice Weekly
Started	52
Randomized and Treated	52
Completed Blinded Treatment Period (BTP)	40
Entered Open-Label Continuation (OLC)	29
Completed BTP, BTP Follow up, OLC	22
Completed	22
Not completed	30
Consent withdrawn by subject	8
Non-compliance with Study Drug	-
Physician decision	-
Not Available	-
Did not enter OLC	10
Adverse Event	11
Death	-
Lost to follow-up	1

Protocol deviation	-
Lack of efficacy	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Subject disposition has been reported for the treated subjects.

Baseline characteristics

Reporting groups

Reporting group title	Regimen A: Mipomersen, 200 mg, Once Weekly
Reporting group description:	
Subjects received once weekly subcutaneous (SC) injections of mipomersen sodium 200 milligrams (mg) during the 60-week Blinded Treatment Period (BTP). Subjects who chose to participate in the open label continuation (OLC) received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety Follow-up (FU) Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	
Reporting group title	Regimen A: Placebo, Once Weekly
Reporting group description:	
Subjects received once weekly SC injections of Placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	
Reporting group title	Regimen B: Mipomersen, 70 mg, Thrice Weekly
Reporting group description:	
Subjects received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	
Reporting group title	Regimen B: Placebo, Thrice Weekly
Reporting group description:	
Subjects received thrice weekly SC injections of placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	

Reporting group values	Regimen A: Mipomersen, 200 mg, Once Weekly	Regimen A: Placebo, Once Weekly	Regimen B: Mipomersen, 70 mg, Thrice Weekly
Number of subjects	104	51	102
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	56.36 ± 9.766	55.49 ± 10.481	53.15 ± 11.918
Gender categorical Units: Subjects			
Female	58	29	54
Male	46	22	48
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	4	4

Not Hispanic or Latino	99	45	95
Unknown or Not Reported	1	2	3

LDL-C Baseline Values			
Units: mg/dL			
arithmetic mean	232	229	240
standard deviation	± 93.1	± 72.3	± 76.7

Reporting group values	Regimen B: Placebo, Thrice Weekly	Total	
Number of subjects	52	309	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	54.38		
standard deviation	± 9.939	-	
Gender categorical			
Units: Subjects			
Female	27	168	
Male	25	141	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	6	18	
Not Hispanic or Latino	46	285	
Unknown or Not Reported	0	6	
LDL-C Baseline Values			
Units: mg/dL			
arithmetic mean	229		
standard deviation	± 81.4	-	

Subject analysis sets

Subject analysis set title	Cohort 1: Regimen A: Mipomersen, 200 mg, Once Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 1, who received once weekly SC injections of mipomersen sodium 200 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Subject analysis set title	Cohort 1: Regimen A: Placebo, Once Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 1, who received once weekly SC injections of Placebo during the 60-week Blinded Treatment Period, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Subject analysis set title	Cohort 1: Regimen B: Mipomersen, 70 mg, Thrice Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 1, who received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Subject analysis set title	Cohort 1: Regimen B: Placebo, Thrice Weekly
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Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in Cohort 1, who received thrice weekly SC injections of placebo during the 60-week BTP, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	
Subject analysis set title	Cohort 2: Regimen A: Mipomersen, 200 mg, Once Weekly
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in Cohort 2, who received once weekly SC injections of mipomersen sodium 200 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	
Subject analysis set title	Cohort 2: Regimen A: Placebo, Once Weekly
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in Cohort 2, who received once weekly SC injections of Placebo during the 60-week Blinded Treatment Period, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	
Subject analysis set title	Cohort 2: Regimen B: Mipomersen, 70 mg, Thrice Weekly
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in Cohort 2, who received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	
Subject analysis set title	Cohort 2: Regimen B: Placebo, Thrice Weekly
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in Cohort 2, who received thrice weekly SC injections of placebo during the 60-week Blinded Treatment Period, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	

Reporting group values	Cohort 1: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 1: Regimen A: Placebo, Once Weekly	Cohort 1: Regimen B: Mipomersen, 70 mg, Thrice Weekly
Number of subjects	67	34	66
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	55.2	56.2	51.7
standard deviation	± 10.05	± 10.77	± 12.75
Gender categorical			
Units: Subjects			
Female	42	21	39
Male	25	13	27
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	2	3
Not Hispanic or Latino	64	31	60
Unknown or Not Reported	1	1	3
LDL-C Baseline Values			
Units: mg/dL			
arithmetic mean	262	255	274

standard deviation	± 103.1	± 75.0	± 75.1
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Reporting group values	Cohort 1: Regimen B: Placebo, Thrice Weekly	Cohort 2: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 2: Regimen A: Placebo, Once Weekly
Number of subjects	33	37	17
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	56.1 ± 8.93	58.5 ± 8.97	54.1 ± 10.04
Gender categorical Units: Subjects			
Female	19	16	8
Male	14	21	9
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	2
Not Hispanic or Latino	31	35	14
Unknown or Not Reported	0	0	1
LDL-C Baseline Values Units: mg/dL arithmetic mean standard deviation	263 ± 82.9	177 ± 20.8	179 ± 25.6

Reporting group values	Cohort 2: Regimen B: Mipomersen, 70 mg, Thrice Weekly	Cohort 2: Regimen B: Placebo, Thrice Weekly	
Number of subjects	36	19	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	55.8 ± 9.83	51.5 ± 11.14	
Gender categorical Units: Subjects			
Female	15	8	
Male	21	11	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	4	
Not Hispanic or Latino	35	15	
Unknown or Not Reported	0	0	
LDL-C Baseline Values Units: mg/dL arithmetic mean	178	169	

standard deviation	± 17.6	± 26.6	
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End points

End points reporting groups

Reporting group title	Regimen A: Mipomersen, 200 mg, Once Weekly
Reporting group description: Subjects received once weekly subcutaneous (SC) injections of mipomersen sodium 200 milligrams (mg) during the 60-week Blinded Treatment Period (BTP). Subjects who chose to participate in the open label continuation (OLC) received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety Follow-up (FU) Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	
Reporting group title	Regimen A: Placebo, Once Weekly
Reporting group description: Subjects received once weekly SC injections of Placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	
Reporting group title	Regimen B: Mipomersen, 70 mg, Thrice Weekly
Reporting group description: Subjects received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	
Reporting group title	Regimen B: Placebo, Thrice Weekly
Reporting group description: Subjects received thrice weekly SC injections of placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.	
Subject analysis set title	Cohort 1: Regimen A: Mipomersen, 200 mg, Once Weekly
Subject analysis set type	Full analysis
Subject analysis set description: Subjects in Cohort 1, who received once weekly SC injections of mipomersen sodium 200 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	
Subject analysis set title	Cohort 1: Regimen A: Placebo, Once Weekly
Subject analysis set type	Full analysis
Subject analysis set description: Subjects in Cohort 1, who received once weekly SC injections of Placebo during the 60-week Blinded Treatment Period, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	
Subject analysis set title	Cohort 1: Regimen B: Mipomersen, 70 mg, Thrice Weekly
Subject analysis set type	Full analysis
Subject analysis set description: Subjects in Cohort 1, who received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.	
Subject analysis set title	Cohort 1: Regimen B: Placebo, Thrice Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 1, who received thrice weekly SC injections of placebo during the 60-week BTP, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Subject analysis set title	Cohort 2: Regimen A: Mipomersen, 200 mg, Once Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 2, who received once weekly SC injections of mipomersen sodium 200 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Subject analysis set title	Cohort 2: Regimen A: Placebo, Once Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 2, who received once weekly SC injections of Placebo during the 60-week Blinded Treatment Period, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Subject analysis set title	Cohort 2: Regimen B: Mipomersen, 70 mg, Thrice Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 2, who received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week Blinded Treatment Period, continued the dosing regimen during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Subject analysis set title	Cohort 2: Regimen B: Placebo, Thrice Weekly
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in Cohort 2, who received thrice weekly SC injections of placebo during the 60-week Blinded Treatment Period, received the same full dose regimen of mipomersen (per their assigned regimen during the BTP) during the 26-week Open-Label Continuation Period, and then entered the 24-week post-treatment safety FU period.

Primary: Percent Change From Baseline To Primary Efficacy Time Point (PET) In LDL-C In Cohort 1

End point title	Percent Change From Baseline To Primary Efficacy Time Point (PET) In LDL-C In Cohort 1
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End point description:

The percent change from baseline to PET in LDL-C was measured in Cohort 1, which included subjects with severe heterozygous familial hypercholesterolemia (HeFH). Severe HeFH was defined as LDL-C levels ≥ 200 mg/deciliter (dL) plus the presence of coronary heart disease (CHD)/risk equivalents or LDL-C levels ≥ 300 mg/dL regardless of the presence of CHD/risk equivalents. The full analysis set for Cohort 1 included all randomized subjects who took at least 1 dose of study drug in Cohort 1 (mipomersen or placebo), had a valid baseline LDL-C measurement, and had at least 1 post-baseline LDL-C measurement.

End point type	Primary
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End point timeframe:

Baseline and Week 61

End point values	Cohort 1: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 1: Regimen A: Placebo, Once Weekly	Cohort 1: Regimen B: Mipomersen, 70 mg, Thrice Weekly	Cohort 1: Regimen B: Placebo, Thrice Weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	67	34	66	33
Units: percent change				
least squares mean (standard error)	-27.17 (\pm 5.653)	-6.77 (\pm 6.749)	-22.96 (\pm 5.362)	-10.62 (\pm 5.765)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The comparison of percent changes between active treatment and placebo is performed using a mixed model for repeated measured (MMRM) with terms for baseline LDL-C, geographic region, gender, and statin use, treatment group, study visit, and study visit by treatment group interaction. The visits used in the model include Weeks 5, 17, 30, 42, 55 and 61. An unstructured variance-covariance structure was used to model within-subject errors.	
Comparison groups	Cohort 1: Regimen A: Mipomersen, 200 mg, Once Weekly v Cohort 1: Regimen A: Placebo, Once Weekly
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-20.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.8
upper limit	-7
Variability estimate	Standard error of the mean
Dispersion value	6.697

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
The comparison of percent changes between active treatment and placebo is performed using a MMRM with terms for baseline LDL-C, geographic region, gender, and statin use, treatment group, study visit, and study visit by treatment group interaction. The visits used in the model include Weeks 5, 17, 30, 42, 55 and 61. An unstructured variance-covariance structure was used to model within-subject errors.	
Comparison groups	Cohort 1: Regimen B: Placebo, Thrice Weekly v Cohort 1: Regimen B: Mipomersen, 70 mg, Thrice Weekly

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	MMRM
Parameter estimate	Least squares mean difference
Point estimate	-12.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.09
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	6.406

Secondary: Percent Change From Baseline To Primary Efficacy Time Point (PET) In LDL-C In Cohort 2

End point title	Percent Change From Baseline To Primary Efficacy Time Point (PET) In LDL-C In Cohort 2
End point description:	The percent change from baseline to PET in LDL-C was measured in Cohort 2, which included participants with HeFH with LDL-C levels ≥ 160 mg/dL and < 200 mg/dL, plus the presence of CHD/risk equivalents. The full analysis set included all randomized subjects who took at least 1 dose of study drug (mipomersen or placebo), had a valid baseline LDL-C measurement, and had at least 1 post-baseline LDL-C measurement.
End point type	Secondary
End point timeframe:	Baseline, PET (up to 60 weeks)

End point values	Cohort 2: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 2: Regimen A: Placebo, Once Weekly	Cohort 2: Regimen B: Mipomersen, 70 mg, Thrice Weekly	Cohort 2: Regimen B: Placebo, Thrice Weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	17	36	19
Units: percent change				
least squares mean (standard error)	-31.20 (\pm 8.927)	-9.25 (\pm 10.621)	-43.60 (\pm 8.342)	-13.57 (\pm 9.066)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline To Primary Efficacy Time Point (PET) In Apolipoprotein B (Apo B) In Cohort 1

End point title	Percent Change From Baseline To Primary Efficacy Time Point
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End point description:

The percent change from baseline to PET in Apo B was measured in subjects in Cohort 1 with HeFH during the Blinded Treatment Period. The full analysis set included all randomized subjects who took at least 1 dose of study drug (mipomersen or placebo), had a valid baseline LDL-C measurement, and had at least 1 post-baseline LDL-C measurement.

End point type	Secondary
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End point timeframe:

Baseline and Week 61

End point values	Cohort 1: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 1: Regimen A: Placebo, Once Weekly	Cohort 1: Regimen B: Mipomersen, 70 mg, Thrice Weekly	Cohort 1: Regimen B: Placebo, Thrice Weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	67	34	66	33
Units: percent change				
least squares mean (standard deviation)	-24.14 (\pm 5.058)	-2.83 (\pm 6.115)	-21.43 (\pm 4.861)	-7.28 (\pm 5.309)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline To Primary Efficacy Time Point (PET) In Apolipoprotein B (Apo B) In Cohort 2

End point title	Percent Change From Baseline To Primary Efficacy Time Point (PET) In Apolipoprotein B (Apo B) In Cohort 2
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End point description:

The percent change from baseline to PET in Apo B was measured in subjects in Cohort 2 with HeFH during the Blinded Treatment Period. The full analysis set included all randomized subjects who took at least 1 dose of study drug (mipomersen or placebo), had a valid baseline LDL-C measurement, and had at least 1 post-baseline LDL-C measurement.

End point type	Secondary
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End point timeframe:

Baseline and Week 61

End point values	Cohort 2: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 2: Regimen A: Placebo, Once Weekly	Cohort 2: Regimen B: Mipomersen, 70 mg, Thrice Weekly	Cohort 2: Regimen B: Placebo, Thrice Weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	17	36	19
Units: percent change				
least squares mean (standard error)	-30.76 (\pm 7.309)	-6.67 (\pm 8.758)	-36.34 (\pm 7.039)	-3.77 (\pm 8.109)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline To Primary Efficacy Time Point (PET) in Lipoprotein (a) In Cohort 1

End point title	Percent Change From Baseline To Primary Efficacy Time Point (PET) in Lipoprotein (a) In Cohort 1
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End point description:

The percent change from baseline to PET in Lipoprotein A1 was measured in subjects in Cohort 1 with HeFH during the Blinded Treatment Period. The full analysis set included all randomized subjects who took at least 1 dose of study drug (mipomersen or placebo), had a valid baseline LDL-C measurement, and had at least 1 post-baseline LDL-C measurement.

End point type	Secondary
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End point timeframe:

Baseline and Week 61

End point values	Cohort 1: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 1: Regimen A: Placebo, Once Weekly	Cohort 1: Regimen B: Mipomersen, 70 mg, Thrice Weekly	Cohort 1: Regimen B: Placebo, Thrice Weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	67	34	66	33
Units: Percent change				
least squares mean (standard error)	-18.84 (\pm 7.870)	-16.85 (\pm 9.959)	-27.18 (\pm 5.497)	-10.08 (\pm 5.992)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline To Primary Efficacy Time Point (PET) in Lipoprotein (a) In Cohort 2

End point title	Percent Change From Baseline To Primary Efficacy Time Point (PET) in Lipoprotein (a) In Cohort 2
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End point description:

The percent change from baseline to PET in Lipoprotein A1 was measured in subjects in Cohort 2 with HeFH during the Blinded Treatment Period. The full analysis set included all randomized subjects who took at least 1 dose of study drug (mipomersen or placebo), had a valid baseline LDL-C measurement, and had at least 1 post-baseline LDL-C measurement.

End point type	Secondary
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End point timeframe:
Baseline and Week 61

End point values	Cohort 2: Regimen A: Mipomersen, 200 mg, Once Weekly	Cohort 2: Regimen A: Placebo, Once Weekly	Cohort 2: Regimen B: Mipomersen, 70 mg, Thrice Weekly	Cohort 2: Regimen B: Placebo, Thrice Weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	17	36	19
Units: percent change				
least squares mean (standard error)	-23.41 (± 10.002)	-11.86 (± 11.871)	-35.56 (± 11.846)	18.79 (± 15.271)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from the time of the administration of the subject's first dose of study drug (mipomersen or placebo) through the subject's last visit of the Post-Treatment Period, up to Week 110.

Adverse event reporting additional description:

Adverse events were collected for all randomized subjects who received at least 1 dose of study drug (mipomersen or placebo). There were 4 deaths occurred during the study of which one death occurred during OLC follow up.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Regimen A: Placebo, Once Weekly
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Reporting group description:

Subjects received once weekly SC injections of Placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period. One death occurred during BTP follow up.

Reporting group title	Regimen A: Mipomersen, 200 mg, Once Weekly
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Reporting group description:

Subjects received once weekly SC injections of mipomersen sodium 200 mg during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period. One death occurred during BTP and the other one occurred during OLC follow up period.

Reporting group title	Regimen B: Placebo, Thrice Weekly
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Reporting group description:

Subjects received thrice weekly SC injections of placebo during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period.

Reporting group title	Regimen B: Mipomersen, 70 mg, Thrice Weekly
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Reporting group description:

Subjects received thrice weekly SC injections of mipomersen sodium 70 mg during the 60-week BTP. Subjects who chose to participate in the OLC received during 26 weeks the same full dose regimen of mipomersen per their assigned regimen during the BTP. A 24-week post-treatment safety FU Period was conducted during which subjects, including those who discontinued prematurely and received ≥ 1 dose of investigational product, were asked to complete 2 post-treatment visits. Subjects who chose not to participate in the OLC continued directly into the post-treatment safety FU Period. One death occurred during BTP follow up.

Serious adverse events	Regimen A: Placebo, Once Weekly	Regimen A: Mipomersen, 200 mg, Once Weekly	Regimen B: Placebo, Thrice Weekly
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 51 (25.49%)	17 / 104 (16.35%)	11 / 52 (21.15%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Embolism Venous			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Hypertension			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Hypertensive Crisis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
Peripheral Artery Stenosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			

subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Chest Pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Death			
subjects affected / exposed	0 / 51 (0.00%)	2 / 104 (1.92%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Drug Intolerance			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza Like Illness			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 51 (3.92%)	1 / 104 (0.96%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
Reproductive system and breast disorders			

Benign Prostatic Hyperplasia subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Cervical Polyp subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrocystic Breast Disease subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Ovarian Cyst Torsion subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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			
Asthma subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Dyspnoea Exertional subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Pleuritic Pain subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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

Pulmonary Oedema			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major Depression			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Helicobacter Test Negative			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Low Density Lipoprotein Increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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			
Coronary Artery Restenosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			

subjects affected / exposed	2 / 51 (3.92%)	0 / 104 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	4 / 51 (7.84%)	7 / 104 (6.73%)	4 / 52 (7.69%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	3 / 51 (5.88%)	1 / 104 (0.96%)	3 / 52 (5.77%)
occurrences causally related to treatment / all	0 / 8	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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 Flutter			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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 Arrest			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac Failure Congestive			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Coronary Artery Disease			

subjects affected / exposed	0 / 51 (0.00%)	3 / 104 (2.88%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Stenosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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 Ischaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Tachycardia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Carotid Artery Stenosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Cerebral Infarction			

subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Hemiparesis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 104 (0.96%)	0 / 52 (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
Eye disorders			
Eye Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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			
Abdominal Hernia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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

Constipation			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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
Gastric Ulcer			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Erosive			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
Large Intestine Perforation			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction Gastric			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
Pancreatic Cyst			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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			
Cholelithiasis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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

Haematuria			
subjects affected / exposed	1 / 51 (1.96%)	1 / 104 (0.96%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cyst			
subjects affected / exposed	0 / 51 (0.00%)	1 / 104 (0.96%)	0 / 52 (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			
Arthralgia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
Back Pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
Joint Contracture			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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 Pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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
Osteoarthritis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 104 (0.00%)	0 / 52 (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 Osteoarthritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 104 (0.00%)	0 / 52 (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

Infections and infestations Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 51 (0.00%) 0 / 0 0 / 0	0 / 104 (0.00%) 0 / 0 0 / 0	0 / 52 (0.00%) 0 / 0 0 / 0
Device Related Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 51 (0.00%) 0 / 0 0 / 0	0 / 104 (0.00%) 0 / 0 0 / 0	1 / 52 (1.92%) 0 / 1 0 / 0
Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 51 (1.96%) 0 / 1 0 / 0	0 / 104 (0.00%) 0 / 0 0 / 0	0 / 52 (0.00%) 0 / 0 0 / 0
Escherichia Pyelonephritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 51 (0.00%) 0 / 0 0 / 0	1 / 104 (0.96%) 0 / 1 0 / 0	0 / 52 (0.00%) 0 / 0 0 / 0
Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 51 (0.00%) 0 / 0 0 / 0	0 / 104 (0.00%) 0 / 0 0 / 0	0 / 52 (0.00%) 0 / 0 0 / 0
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 51 (0.00%) 0 / 0 0 / 0	0 / 104 (0.00%) 0 / 0 0 / 0	0 / 52 (0.00%) 0 / 0 0 / 0

Serious adverse events	Regimen B: Mipomersen, 70 mg, Thrice Weekly		
Total subjects affected by serious adverse events			
subjects affected / exposed number of deaths (all causes) number of deaths resulting from adverse events	23 / 102 (22.55%) 1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Lymphoma			

subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism Venous			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive Crisis			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral Artery Stenosis			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest Pain			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug Intolerance			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza Like Illness			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical Polyp			

subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fibrocystic Breast Disease			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian Cyst Torsion			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea Exertional			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic Pain			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Oedema			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Major Depression			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Helicobacter Test Negative			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Low Density Lipoprotein Increased			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Coronary Artery Restenosis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute Myocardial Infarction			

subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Angina Pectoris			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina Unstable			
subjects affected / exposed	4 / 102 (3.92%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Atrial Fibrillation			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial Flutter			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Congestive			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary Artery Disease			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary Artery Stenosis			

subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial Infarction			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Myocardial Ischaemia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular Tachycardia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid Artery Stenosis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral Infarction			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hemiparesis			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic Stroke			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye Haemorrhage			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastric Ulcer			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis Erosive			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large Intestine Perforation			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Obstruction Gastric			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic Cyst			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal Cyst			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back Pain			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint Contracture			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Pain			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Osteoarthritis			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Device Related Infection				
subjects affected / exposed	0 / 102 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia Pyelonephritis				
subjects affected / exposed	0 / 102 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Regimen A: Placebo, Once Weekly	Regimen A: Mipomersen, 200 mg, Once Weekly	Regimen B: Placebo, Thrice Weekly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 51 (70.59%)	87 / 104 (83.65%)	37 / 52 (71.15%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 51 (11.76%)	7 / 104 (6.73%)	6 / 52 (11.54%)
occurrences (all)	6	14	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 51 (1.96%)	7 / 104 (6.73%)	3 / 52 (5.77%)
occurrences (all)	1	9	3

Influenza Like Illness subjects affected / exposed occurrences (all)	15 / 51 (29.41%) 55	46 / 104 (44.23%) 160	14 / 52 (26.92%) 32
Injection Site Discolouration subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	6 / 104 (5.77%) 7	3 / 52 (5.77%) 3
Injection Site Erythema subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5	8 / 104 (7.69%) 13	5 / 52 (9.62%) 6
Injection Site Induration subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	1 / 104 (0.96%) 1	4 / 52 (7.69%) 5
Injection Site Pain subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	14 / 104 (13.46%) 27	3 / 52 (5.77%) 4
Injection Site Pruritus subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5	3 / 104 (2.88%) 4	3 / 52 (5.77%) 4
Injection Site Swelling subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	4 / 104 (3.85%) 8	2 / 52 (3.85%) 9
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	5 / 104 (4.81%) 6	3 / 52 (5.77%) 3
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	8 / 51 (15.69%) 10	22 / 104 (21.15%) 29	1 / 52 (1.92%) 1
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	7 / 51 (13.73%) 10	18 / 104 (17.31%) 24	2 / 52 (3.85%) 2
Bacterial Test Positive subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4	1 / 104 (0.96%) 1	1 / 52 (1.92%) 1
Blood Creatine Phosphokinase			

Increased subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	1 / 104 (0.96%) 1	3 / 52 (5.77%) 3
C-Reactive Protein Increased subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4	4 / 104 (3.85%) 4	3 / 52 (5.77%) 3
Hepatic Enzyme Increased subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	9 / 104 (8.65%) 9	0 / 52 (0.00%) 0
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4	0 / 104 (0.00%) 0	0 / 52 (0.00%) 0
Cardiac disorders Angina Pectoris subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6	10 / 104 (9.62%) 15	7 / 52 (13.46%) 8
Palpitations subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	2 / 104 (1.92%) 2	3 / 52 (5.77%) 5
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 2	9 / 104 (8.65%) 14	1 / 52 (1.92%) 1
Headache subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 6	8 / 104 (7.69%) 17	5 / 52 (9.62%) 9
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 2	2 / 104 (1.92%) 2	3 / 52 (5.77%) 3
Gastrointestinal disorders Abdominal Pain Lower subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 104 (0.00%) 0	1 / 52 (1.92%) 1
Diarrhoea			

subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	7 / 104 (6.73%) 7	1 / 52 (1.92%) 1
Nausea subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	9 / 104 (8.65%) 13	2 / 52 (3.85%) 4
Hepatobiliary disorders Hepatic Steatosis subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	11 / 104 (10.58%) 11	1 / 52 (1.92%) 1
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 104 (0.00%) 0	3 / 52 (5.77%) 3
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 6	3 / 104 (2.88%) 5	3 / 52 (5.77%) 3
Back Pain subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	6 / 104 (5.77%) 6	4 / 52 (7.69%) 4
Musculoskeletal Pain subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	5 / 104 (4.81%) 5	3 / 52 (5.77%) 3
Myalgia subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	9 / 104 (8.65%) 9	4 / 52 (7.69%) 4
Pain In Extremity subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	5 / 104 (4.81%) 6	0 / 52 (0.00%) 0
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 8	7 / 104 (6.73%) 10	4 / 52 (7.69%) 4
Influenza subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 6	5 / 104 (4.81%) 7	6 / 52 (11.54%) 8

Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6	7 / 104 (6.73%) 10	7 / 52 (13.46%) 9
Respiratory Tract Infection Viral subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	6 / 104 (5.77%) 15	0 / 52 (0.00%) 0
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5	5 / 104 (4.81%) 5	3 / 52 (5.77%) 3
Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	4 / 104 (3.85%) 4	1 / 52 (1.92%) 1

Non-serious adverse events	Regimen B: Mipomersen, 70 mg, Thrice Weekly		
Total subjects affected by non-serious adverse events subjects affected / exposed	82 / 102 (80.39%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	6 / 102 (5.88%) 6		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 102 (1.96%) 2		
Influenza Like Illness subjects affected / exposed occurrences (all)	29 / 102 (28.43%) 109		
Injection Site Discolouration subjects affected / exposed occurrences (all)	5 / 102 (4.90%) 5		
Injection Site Erythema subjects affected / exposed occurrences (all)	14 / 102 (13.73%) 17		
Injection Site Induration subjects affected / exposed occurrences (all)	4 / 102 (3.92%) 4		

Injection Site Pain subjects affected / exposed occurrences (all)	8 / 102 (7.84%) 10		
Injection Site Pruritus subjects affected / exposed occurrences (all)	7 / 102 (6.86%) 7		
Injection Site Swelling subjects affected / exposed occurrences (all)	8 / 102 (7.84%) 9		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	6 / 102 (5.88%) 6		
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	20 / 102 (19.61%) 30		
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	13 / 102 (12.75%) 16		
Bacterial Test Positive subjects affected / exposed occurrences (all)	3 / 102 (2.94%) 3		
Blood Creatine Phosphokinase Increased subjects affected / exposed occurrences (all)	6 / 102 (5.88%) 6		
C-Reactive Protein Increased subjects affected / exposed occurrences (all)	7 / 102 (6.86%) 7		
Hepatic Enzyme Increased subjects affected / exposed occurrences (all)	4 / 102 (3.92%) 4		
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Cardiac disorders Angina Pectoris subjects affected / exposed occurrences (all)	5 / 102 (4.90%) 5		
Palpitations subjects affected / exposed occurrences (all)	3 / 102 (2.94%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	5 / 102 (4.90%) 5		
Headache subjects affected / exposed occurrences (all)	10 / 102 (9.80%) 11		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 102 (1.96%) 2		
Gastrointestinal disorders Abdominal Pain Lower subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	8 / 102 (7.84%) 11		
Nausea subjects affected / exposed occurrences (all)	8 / 102 (7.84%) 10		
Hepatobiliary disorders Hepatic Steatosis subjects affected / exposed occurrences (all)	11 / 102 (10.78%) 11		
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	4		
Back Pain			
subjects affected / exposed	4 / 102 (3.92%)		
occurrences (all)	4		
Musculoskeletal Pain			
subjects affected / exposed	4 / 102 (3.92%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	7 / 102 (6.86%)		
occurrences (all)	9		
Pain In Extremity			
subjects affected / exposed	5 / 102 (4.90%)		
occurrences (all)	6		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	10 / 102 (9.80%)		
occurrences (all)	11		
Nasopharyngitis			
subjects affected / exposed	12 / 102 (11.76%)		
occurrences (all)	13		
Respiratory Tract Infection Viral			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	6		
Upper Respiratory Tract Infection			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	12		
Urinary Tract Infection			

subjects affected / exposed	10 / 102 (9.80%)		
occurrences (all)	13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 January 2016	Following amendments were made: 1) OLC period was introduced. Subjects who completed BTP prior to implementation of amendment 2 and had been followed ≤ 8 weeks during the safety follow-up period were allowed to restart dosing immediately. Subjects who had completed the BTP and had been followed for ≥ 8 weeks during the safety follow up period were allowed to restart dosing after a 1-week evaluation period if the results were acceptable. 2) An Independent Cardiovascular Adjudication Committee was established to apply uniform criteria for the evaluation of prospectively defined major adverse cardiac events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported