

**Clinical trial results:****A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)
Summary**

EudraCT number	2016-003373-18
Trial protocol	DE NL DK
Global end of trial date	13 November 2018

Results information

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

Trial information**Trial identification**

Sponsor protocol code	ISIS681257-CS6
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03070782
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Akcea Therapeutics
Sponsor organisation address	22 Boston Wharf Rd, 9th Floor, Boston, Massachusetts, United States, 02210
Public contact	Study Director, Akcea Therapeutics- An Affiliate of Ionis Pharmaceuticals, Inc., +1 6172070289, clinicalstudies@akceatx.com
Scientific contact	Study Director, Akcea Therapeutics- An Affiliate of Ionis Pharmaceuticals, Inc., +1 6172070289, clinicalstudies@akceatx.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	13 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lipoprotein(a) [Lp(a)] levels in participants with hyperlipoproteinemia(a) and established CVD.

Protection of trial subjects:

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines to ensure the safety of participants. Before commencement of the trial, the Investigator was responsible for obtaining written informed consent from the participant or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drug (ISIS 681257 or placebo) were administered. The protocol provided prespecified safety monitoring rules. An independent Data and Safety Monitoring (DSMB) was also assembled to review safety, tolerability and efficacy (as needed) data collected during the study and provided recommendations to the sponsor for modifying, stopping or continuing the study as planned.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Canada: 57
Country: Number of subjects enrolled	United States: 140
Worldwide total number of subjects	286
EEA total number of subjects	89

Notes:

Subjects enrolled per age group

In utero	0
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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)	178
From 65 to 84 years	108
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with a clinical diagnosis of hyperlipoproteinemia(a) and established CVD were enrolled in 31 study centers in United States, Canada, Denmark, Germany and Netherlands between 7th March 2017 to 13th November 2018.

Pre-assignment

Screening details:

286 participants were randomized in a 1:1:1:1:1 ratio to Cohorts A, B, C, D or E. In each cohort, participants were randomized in a 5:1 ratio to receive ISIS 681257 or placebo. 250 participants completed the treatment period. 263 of 286 participants completed the follow-up period. Here, Completed refers to participants who completed study treatment

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: ISIS 681257: 20 mg Q4W

Arm description:

Cohort A participants received 20 milligrams (mg) ISIS 681257, subcutaneous (SC) injection, once every 4 weeks (Q4W), for up to 49 weeks and a maximum of 13 doses.

Arm type	Experimental
Investigational medicinal product name	ISIS 681257
Investigational medicinal product code	ISIS 681257
Other name	AKCEA-APO(a)-LRx, IONIS-APO(a)-LRx, TQJ230 and Pelacarsen
Pharmaceutical forms	Injection, Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 681257 at dose 20 milligrams (mg), administered via subcutaneous (SC) injection, once every 4 weeks (Q4W).

Arm title	Cohort B: ISIS 681257: 40 mg Q4W
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Arm description:

Cohort B participants received 40 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a maximum of 13 doses.

Arm type	Experimental
Investigational medicinal product name	ISIS 681257
Investigational medicinal product code	ISIS 681257
Other name	AKCEA-APO(a)-LRx, IONIS-APO(a)-LRx, TQJ230 and Pelacarsen
Pharmaceutical forms	Solution for injection, Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 681257 at dose 20 milligrams (mg), administered via subcutaneous (SC) injection, once every 4 weeks (Q4W).

Arm title	Cohort C: ISIS 681257: 60 mg Q4W
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Arm description:

Cohort C participants received 60 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a

maximum of 13 doses.

Arm type	Experimental
Investigational medicinal product name	ISIS 681257
Investigational medicinal product code	ISIS 681257
Other name	AKCEA-APO(a)-LRx, IONIS-APO(a)-LRx, TQJ230 and Pelacarsen
Pharmaceutical forms	Solution for injection, Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 681257 at dose 20 milligrams (mg), administered via subcutaneous (SC) injection, once every 4 weeks (Q4W).

Arm title	Cohort D: ISIS 681257: 20 mg Q2W
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Arm description:

Cohort D participants received 20 mg of ISIS 681257, SC injection, once every 2 weeks (Q2W), for up to 51 weeks and a maximum of 26 doses.

Arm type	Experimental
Investigational medicinal product name	ISIS 681257
Investigational medicinal product code	ISIS 681257
Other name	AKCEA-APO(a)-LRx, IONIS-APO(a)-LRx, TQJ230 and Pelacarsen
Pharmaceutical forms	Injection, Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 681257 at dose 20 milligrams (mg), administered via subcutaneous (SC) injection, once every 4 weeks (Q4W).

Arm title	Cohort E: ISIS 681257: 20 mg QW
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Arm description:

Cohort E participants received 20 mg of ISIS 681257, SC injection, once weekly (QW), for up to 52 weeks and a maximum of 52 doses.

Arm type	Experimental
Investigational medicinal product name	ISIS 681257
Investigational medicinal product code	ISIS 681257
Other name	AKCEA-APO(a)-LRx, IONIS-APO(a)-LRx, TQJ230 and Pelacarsen
Pharmaceutical forms	Injection, Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 681257 at dose 20 milligrams (mg), administered via subcutaneous (SC) injection, once every 4 weeks (Q4W).

Arm title	Placebo
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Arm description:

Participants in each cohort were randomized to receive placebo at a dose-matched volume of study drug (ISIS 681257).

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

Dosage and administration details:

Sterile normal saline (0.9% NaCl)

Number of subjects in period 1	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W
Started	48	48	47
Completed	41	47	43
Not completed	7	1	4
Adverse event, serious fatal	3	-	3
Consent withdrawn by subject	2	1	1
Investigator judgement	-	-	-
Pregnancy	-	-	-
Reason not specified	2	-	-
Ineligibility	-	-	-

Number of subjects in period 1	Cohort D: ISIS 681257: 20 mg Q2W	Cohort E: ISIS 681257: 20 mg QW	Placebo
Started	48	48	47
Completed	43	36	40
Not completed	5	12	7
Adverse event, serious fatal	1	6	2
Consent withdrawn by subject	-	4	3
Investigator judgement	1	-	-
Pregnancy	1	-	-
Reason not specified	1	2	1
Ineligibility	1	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort A: ISIS 681257: 20 mg Q4W
Reporting group description: Cohort A participants received 20 milligrams (mg) ISIS 681257, subcutaneous (SC) injection, once every 4 weeks (Q4W), for up to 49 weeks and a maximum of 13 doses.	
Reporting group title	Cohort B: ISIS 681257: 40 mg Q4W
Reporting group description: Cohort B participants received 40 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a maximum of 13 doses.	
Reporting group title	Cohort C: ISIS 681257: 60 mg Q4W
Reporting group description: Cohort C participants received 60 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a maximum of 13 doses.	
Reporting group title	Cohort D: ISIS 681257: 20 mg Q2W
Reporting group description: Cohort D participants received 20 mg of ISIS 681257, SC injection, once every 2 weeks (Q2W), for up to 51 weeks and a maximum of 26 doses.	
Reporting group title	Cohort E: ISIS 681257: 20 mg QW
Reporting group description: Cohort E participants received 20 mg of ISIS 681257, SC injection, once weekly (QW), for up to 52 weeks and a maximum of 52 doses.	
Reporting group title	Placebo
Reporting group description: Participants in each cohort were randomized to receive placebo at a dose-matched volume of study drug (ISIS 681257).	

Reporting group values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W
Number of subjects	48	48	47
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	32	28	25
From 65-84 years	16	20	22
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.0	61.3	62.2
standard deviation	± 9.62	± 10.55	± 9.69
Gender categorical Units: Subjects			
Female	19	12	14

Male	29	36	33
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Race			
Units: Subjects			
White	44	45	47
Black or African American	2	3	0
Asian	1	0	0
American Indian or Alaskan Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Unknown or Not Reported	1	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	1	0
Not Hispanic or Latino	46	47	47

Reporting group values	Cohort D: ISIS 681257: 20 mg Q2W	Cohort E: ISIS 681257: 20 mg QW	Placebo
Number of subjects	48	48	47
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	35	28
From 65-84 years	18	13	19
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	57.9	58.9	59.9
standard deviation	± 11.48	± 7.98	± 10.49
Gender categorical			
Units: Subjects			
Female	17	20	15
Male	31	28	32
Race			
Units: Subjects			
White	47	47	46
Black or African American	0	1	0
Asian	0	0	1
American Indian or Alaskan Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Unknown or Not Reported	1	0	0
Ethnicity			
Units: Subjects			

Hispanic or Latino	0	1	1
Not Hispanic or Latino	48	47	46

Reporting group values	Total		
Number of subjects	286		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	178		
From 65-84 years	108		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	97		
Male	189		
Race			
Units: Subjects			
White	276		
Black or African American	6		
Asian	2		
American Indian or Alaskan Native	0		
Native Hawaiian or Other Pacific Islander	0		
Unknown or Not Reported	2		
Ethnicity			
Units: Subjects			
Hispanic or Latino	5		
Not Hispanic or Latino	281		

End points

End points reporting groups

Reporting group title	Cohort A: ISIS 681257: 20 mg Q4W
Reporting group description: Cohort A participants received 20 milligrams (mg) ISIS 681257, subcutaneous (SC) injection, once every 4 weeks (Q4W), for up to 49 weeks and a maximum of 13 doses.	
Reporting group title	Cohort B: ISIS 681257: 40 mg Q4W
Reporting group description: Cohort B participants received 40 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a maximum of 13 doses.	
Reporting group title	Cohort C: ISIS 681257: 60 mg Q4W
Reporting group description: Cohort C participants received 60 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a maximum of 13 doses.	
Reporting group title	Cohort D: ISIS 681257: 20 mg Q2W
Reporting group description: Cohort D participants received 20 mg of ISIS 681257, SC injection, once every 2 weeks (Q2W), for up to 51 weeks and a maximum of 26 doses.	
Reporting group title	Cohort E: ISIS 681257: 20 mg QW
Reporting group description: Cohort E participants received 20 mg of ISIS 681257, SC injection, once weekly (QW), for up to 52 weeks and a maximum of 52 doses.	
Reporting group title	Placebo
Reporting group description: Participants in each cohort were randomized to receive placebo at a dose-matched volume of study drug (ISIS 681257).	

Primary: Percent Change From Baseline in Fasting Lipoprotein A [Lp(a)] at the Primary Analysis Time Point

End point title	Percent Change From Baseline in Fasting Lipoprotein A [Lp(a)] at the Primary Analysis Time Point
End point description: An ANCOVA model was performed on the log ratio of Lp(a) value at the Primary Analysis Time Point to Lp(a) value at Baseline. The estimate of the log ratio was converted back to the original scale and percent change was calculated using formula: $\text{Percent Change} = (\text{ratio of Lp(a) value at the Primary Analysis Time Point to Lp(a) value at Baseline} - 1) \times 100$. Full Analysis Set (FAS) included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo). FAS represented the practically feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.	
End point type	Primary
End point timeframe: Baseline and Month 6 (Week 25 for Cohorts A, B and C and Week 27 for Cohorts D and E)	

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: percent change				
geometric mean (confidence interval)	-35 (-45 to	-56 (-63 to	-72 (-76 to	-58 (-65 to

95%)	-22)	-48)	-67)	-50)
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End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: percent change				
geometric mean (confidence interval 95%)	-80 (-83 to -76)	-6 (-21 to 12)		

Statistical analyses

Statistical analysis title	Cohort A: ISIS 681257: 20 mg Q4W versus Placebo
Comparison groups	Cohort A: ISIS 681257: 20 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0032
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46
upper limit	-12

Notes:

[1] - Mean difference in percent (%) change from baseline (CFB) based on difference in least square mean (LSM) of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort B: ISIS 681257: 40 mg Q4W versus Placebo
Comparison groups	Placebo v Cohort B: ISIS 681257: 40 mg Q4W
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64
upper limit	-41

Notes:

[2] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort C: ISIS 681257: 60 mg Q4W versus Placebo
Comparison groups	Cohort C: ISIS 681257: 60 mg Q4W v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-70
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77
upper limit	-62

Notes:

[3] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort D: ISIS 681257: 20 mg Q2W versus Placebo
Comparison groups	Cohort D: ISIS 681257: 20 mg Q2W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65
upper limit	-43

Notes:

[4] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort E: ISIS 681257: 20 mg QW versus Placebo
Comparison groups	Cohort E: ISIS 681257: 20 mg QW v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-78

Confidence interval	
level	95 %
sides	2-sided
lower limit	-83
upper limit	-72

Notes:

[5] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Primary: Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) ^[6]
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End point description:

An adverse event (AE) was defined as any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE was considered related to the investigational drug product. TEAEs was defined as any AE with onset after the first administration of study medication through the end of the study, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. Safety Set included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo).

End point type	Primary
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End point timeframe:

Up to 16 weeks post treatment period (up to approximately 1.3 years)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses was performed for this end point.

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: participants	46	43	43	41

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: participants	44	41		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With TEAEs by Maximum Severity

End point title	Number of Participants With TEAEs by Maximum Severity ^[7]
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End point description:

An AE was defined as any unfavorable and unintended sign (including a clinically significant abnormal

laboratory finding), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE was considered related to the investigational drug product. TEAEs was defined as any AE with onset after the first administration of study medication through the end of the study, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. The severity of TEAEs was assessed based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. TEAEs were graded on a 5-point scale where 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Potentially life-threatening and 5 = Death. Safety Set included all participants who were randomized and received at least 1 dose of study drug- ISIS 681257 or placebo.

End point type	Primary
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End point timeframe:

Up to 16 weeks post treatment period (up to approximately 1.3 years)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses was performed for this end point.

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46 ^[8]	43 ^[9]	43 ^[10]	41 ^[11]
Units: participants				
Mild	20	21	16	24
Moderate	20	19	21	15
Severe	6	3	6	2

Notes:

[8] - Only participants with at least one TEAE were analyzed for this outcome measure.

[9] - Only participants with at least one TEAE were analyzed for this outcome measure.

[10] - Only participants with at least one TEAE were analyzed for this outcome measure.

[11] - Only participants with at least one TEAE were analyzed for this outcome measure.

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44 ^[12]	41 ^[13]		
Units: participants				
Mild	21	22		
Moderate	20	16		
Severe	3	3		

Notes:

[12] - Only participants with at least one TEAE were analyzed for this outcome measure.

[13] - Only participants with at least one TEAE were analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With TEAEs Leading to Study Discontinuation

End point title	Number of Participants With TEAEs Leading to Study Discontinuation ^[14]
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End point description:

An AE was defined as any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE was considered related to the investigational drug product. TEAE was defined as any AE with onset after the first administration of study medication through the end of

the study, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. Safety Set included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo).

End point type	Primary
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End point timeframe:

Up to 16 weeks post treatment period (up to approximately 1.3 years)

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses was performed for this end point.

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: participants	3	0	3	1

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: participants	6	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Fasting Low-Density Lipoprotein Cholesterol (LDL-C)

End point title	Percent Change From Baseline in Fasting Low-Density Lipoprotein Cholesterol (LDL-C)
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End point description:

An ANCOVA model was performed on the log ratio of LDL-C value at the Primary Analysis Time Point to LDL-C value at Baseline. The estimate of the log ratio was converted back to the original scale and percent change was calculated using formula: $\text{Percent Change} = (\text{ratio of LDL-C value at the Primary Analysis Time Point to LDL-C value at Baseline} - 1) \times 100$. FAS included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo). FAS represented the practically feasible ITT population as delineated in ICH Guideline E9.

End point type	Secondary
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End point timeframe:

Baseline and Month 6 (Week 25 for Cohorts A, B and C and Week 27 for Cohorts D and E)

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: percent change				
geometric mean (confidence interval 95%)	-7 (-16 to 3)	-26 (-33 to -18)	-16 (-24 to -7)	-17 (-25 to -8)

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: percent change				
geometric mean (confidence interval 95%)	-23 (-31 to -14)	-1 (-11 to 9)		

Statistical analyses

Statistical analysis title	Cohort A: ISIS 681257: 20 mg Q4W versus Placebo
Comparison groups	Cohort A: ISIS 681257: 20 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.4407
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	9

Notes:

[15] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort B: ISIS 681257: 40 mg Q4W versus Placebo
Comparison groups	Cohort B: ISIS 681257: 40 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-35
upper limit	-13

Notes:

[16] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort C: ISIS 681257: 60 mg Q4W versus Placebo
Comparison groups	Cohort C: ISIS 681257: 60 mg Q4W v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.0368
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	-1

Notes:

[17] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort D: ISIS 681257: 20 mg Q2W versus Placebo
Comparison groups	Cohort D: ISIS 681257: 20 mg Q2W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	= 0.0216
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28
upper limit	-3

Notes:

[18] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort E: ISIS 681257: 20 mg QW versus Placebo
Comparison groups	Cohort E: ISIS 681257: 20 mg QW v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.0012
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33
upper limit	-9

Notes:

[19] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Secondary: Percentage of Participants Who Achieved Plasma Lp(a) ≤ 125 Nanomoles Per Liter (nmol/L) or ≤ 50 Milligrams Per Deciliter (mg/dL)

End point title	Percentage of Participants Who Achieved Plasma Lp(a) ≤ 125 Nanomoles Per Liter (nmol/L) or ≤ 50 Milligrams Per Deciliter (mg/dL)
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End point description:

The percentage of participants who achieved ≤ 125 nmol/L or ≤ 50 mg/dL in fasting Lp(a) at the primary analysis time point were compared between each ISIS 681257 treatment group and pooled placebo group using a logistic regression model with log-transformed baseline Lp(a) as a covariate. FAS included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo). FAS represented the practically feasible ITT population as delineated in ICH Guideline E9.

End point type	Secondary
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End point timeframe:

Baseline and Month 6 (Week 25 for Cohorts A, B and C and Week 27 for Cohorts D and E)

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: percentage of participants				
number (not applicable)	22.9	62.5	80.9	64.6

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: percentage of participants				
number (not applicable)	97.9	6.4		

Statistical analyses

Statistical analysis title	Cohort A: ISIS 681257: 20 mg Q4W versus Placebo
Comparison groups	Cohort A: ISIS 681257: 20 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0286
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	21

Statistical analysis title	Cohort B: ISIS 681257: 40 mg Q4W versus Placebo
Comparison groups	Cohort B: ISIS 681257: 40 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	31.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.3
upper limit	131.4

Statistical analysis title	Cohort C: ISIS 681257: 60 mg Q4W versus Placebo
Comparison groups	Cohort C: ISIS 681257: 60 mg Q4W v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	122.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	24
upper limit	627.4

Statistical analysis title	Cohort D: ISIS 681257: 20 mg Q2W versus Placebo
Comparison groups	Cohort D: ISIS 681257: 20 mg Q2W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	43.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.8
upper limit	195

Statistical analysis title	Cohort E: ISIS 681257: 20 mg QW versus Placebo
Comparison groups	Cohort E: ISIS 681257: 20 mg QW v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1124.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	109.3
upper limit	11571

Secondary: Percentage of Participants Who Achieved Plasma Lp(a) \leq 75 nmol/L or \leq 30 mg/dL

End point title	Percentage of Participants Who Achieved Plasma Lp(a) \leq 75 nmol/L or \leq 30 mg/dL
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End point description:

The percentage of participants who achieved \leq 75 nmol/L or \leq 30 mg/dL in fasting Lp(a) at the primary analysis time point were compared between each ISIS 681257 treatment group and pooled placebo group using a logistic regression model with log-transformed baseline Lp(a) as a covariate. FAS included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo). FAS represented the practically feasible ITT population as delineated in ICH Guideline E9.

End point type	Secondary
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End point timeframe:

Baseline and Month 6 (Week 25 for Cohorts A, B and C and Week 27 for Cohorts D and E)

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: percentage of participants				
number (not applicable)	6.3	25.0	53.2	33.3

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: percentage of participants				
number (not applicable)	70.8	0		

Statistical analyses

Statistical analysis title	Cohort A: ISIS 681257: 20 mg Q4W versus Placebo
Comparison groups	Cohort A: ISIS 681257: 20 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2007
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	155.3

Statistical analysis title	Cohort B: ISIS 681257: 40 mg Q4W versus Placebo
Comparison groups	Cohort B: ISIS 681257: 40 mg Q4W v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0258
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	27.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	521.5

Statistical analysis title	Cohort C: ISIS 681257: 60 mg Q4W versus Placebo
Comparison groups	Cohort C: ISIS 681257: 60 mg Q4W v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	113.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	2098.5

Statistical analysis title	Cohort D: ISIS 681257: 20 mg Q2W versus Placebo
Comparison groups	Cohort D: ISIS 681257: 20 mg Q2W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0063
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	59.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	1128

Statistical analysis title	Cohort E: ISIS 681257: 20 mg QW versus Placebo
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Comparison groups	Cohort E: ISIS 681257: 20 mg QW v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	347.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.3
upper limit	6597.9

Secondary: Percent Change From Baseline in the Plasma Levels of Apolipoprotein B (apoB)

End point title	Percent Change From Baseline in the Plasma Levels of Apolipoprotein B (apoB)
End point description:	An ANCOVA model was performed on the log ratio of apoB value at the Primary Analysis Time Point to apoB value at Baseline. The estimate of the log ratio was converted back to the original scale and percent change was calculated using formula: $= (\text{ratio of apoB value at the Primary Analysis Time Point to apoB value at Baseline} - 1) \times 100$. FAS included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo). FAS represented the practically feasible ITT population as delineated in ICH Guideline E9.
End point type	Secondary
End point timeframe:	Baseline and Month 6 (Week 25 for Cohorts A, B and C and Week 27 for Cohorts D and E)

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: percent change				
geometric mean (confidence interval 95%)	-3 (-9 to 4)	-15 (-20 to -10)	-8 (-14 to -2)	-9 (-15 to -3)

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: percent change				
geometric mean (confidence interval 95%)	-16 (-21 to -10)	1 (-5 to 8)		

Statistical analyses

Statistical analysis title	Cohort A: ISIS 681257: 20 mg Q4W versus Placebo
Comparison groups	Placebo v Cohort A: ISIS 681257: 20 mg Q4W
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.4022
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	5

Notes:

[20] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort B: ISIS 681257: 40 mg Q4W versus Placebo
Comparison groups	Cohort B: ISIS 681257: 40 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23
upper limit	-9

Notes:

[21] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort C: ISIS 681257: 60 mg Q4W versus Placebo
Comparison groups	Cohort C: ISIS 681257: 60 mg Q4W v Placebo

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[22]
P-value	= 0.0323
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	-1

Notes:

[22] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort D: ISIS 681257: 20 mg Q2W versus Placebo
Comparison groups	Cohort D: ISIS 681257: 20 mg Q2W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.0157
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	-2

Notes:

[23] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort E: ISIS 681257: 20 mg QW versus Placebo
Comparison groups	Cohort E: ISIS 681257: 20 mg QW v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	-9

Notes:

[24] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Secondary: Percent Change From Baseline in the Plasma Levels of Oxidized

Phospholipids (OxPL) on Apolipoprotein(a) [OxPL-apo(a)]

End point title	Percent Change From Baseline in the Plasma Levels of Oxidized Phospholipids (OxPL) on Apolipoprotein(a) [OxPL-apo(a)]
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End point description:

An ANCOVA model was performed on the log ratio of OxPL-apo(a) value at the Primary Analysis Time Point to OxPL-apo(a) value at Baseline. The estimate of the log ratio was converted back to the original scale and percent change was calculated using formula: $\text{Percent Change} = (\text{ratio of percent change in OxPL-apo(a) value at the Primary Analysis Time Point to corresponding time/percent change in OxPL-apo(a) value at Baseline} - 1) \times 100$. FAS included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo). FAS represented the practically feasible ITT population as delineated in ICH Guideline E9.

End point type	Secondary
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End point timeframe:

Baseline and Month 6 (Week 25 for Cohorts A, B and C and Week 27 for Cohorts D and E)

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: percent change				
geometric mean (confidence interval 95%)	-28 (-41 to -12)	-49 (-58 to -38)	-63 (-70 to -55)	-45 (-55 to -33)

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: percent change				
geometric mean (confidence interval 95%)	-70 (-75 to -62)	-20 (-35 to -2)		

Statistical analyses

Statistical analysis title	Cohort A: ISIS 681257: 20 mg Q4W versus Placebo
Comparison groups	Cohort A: ISIS 681257: 20 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.4956
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-32
upper limit	21

Notes:

[25] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort B: ISIS 681257: 40 mg Q4W versus Placebo
Comparison groups	Cohort B: ISIS 681257: 40 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.0027
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52
upper limit	-14

Notes:

[26] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort C: ISIS 681257: 60 mg Q4W versus Placebo
Comparison groups	Cohort C: ISIS 681257: 60 mg Q4W v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65
upper limit	-38

Notes:

[27] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort D: ISIS 681257: 20 mg Q2W versus Placebo
Comparison groups	Cohort D: ISIS 681257: 20 mg Q2W v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.0114
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48
upper limit	-8

Notes:

[28] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort E: ISIS 681257: 20 mg QW versus Placebo
Comparison groups	Cohort E: ISIS 681257: 20 mg QW v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-72
upper limit	-49

Notes:

[29] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Secondary: Percent Change From Baseline in the Plasma Levels of Oxidized Phospholipids (OxPL) on Apolipoprotein B (OxPL-apoB)

End point title	Percent Change From Baseline in the Plasma Levels of Oxidized Phospholipids (OxPL) on Apolipoprotein B (OxPL-apoB)
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End point description:

An ANCOVA model was performed on the log ratio of OxPL-apoB value at the Primary Analysis Time Point to OxPL-apoB value at Baseline. The estimate of the log ratio was converted back to the original scale and percent change was calculated using formula: $\text{Percent Change} = (\text{ratio of OxPL-apoB value at the Primary Analysis Time Point to OxPL-apoB value at Baseline} - 1) \times 100$. FAS included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo). FAS represented the practically feasible ITT population as delineated in ICH Guideline E9.

End point type	Secondary
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End point timeframe:

Baseline and Month 6 (Week 25 for Cohorts A, B and C and Week 27 for Cohorts D and E)

End point values	Cohort A: ISIS 681257: 20 mg Q4W	Cohort B: ISIS 681257: 40 mg Q4W	Cohort C: ISIS 681257: 60 mg Q4W	Cohort D: ISIS 681257: 20 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	48	47	48
Units: percent change				
geometric mean (confidence interval 95%)	-37 (-52 to -17)	-57 (-67 to -45)	-79 (-84 to -73)	-64 (-72 to -53)

End point values	Cohort E: ISIS 681257: 20 mg QW	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: percent change				
geometric mean (confidence interval 95%)	-88 (-91 to -84)	14 (-12 to 49)		

Statistical analyses

Statistical analysis title	Cohort A: ISIS 681257: 20 mg Q4W versus Placebo
Comparison groups	Cohort A: ISIS 681257: 20 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62
upper limit	-19

Notes:

[30] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort B: ISIS 681257: 40 mg Q4W versus Placebo
Comparison groups	Cohort B: ISIS 681257: 40 mg Q4W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-74
upper limit	-46

Notes:

[31] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort C: ISIS 681257: 60 mg Q4W versus Placebo
Comparison groups	Cohort C: ISIS 681257: 60 mg Q4W v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87
upper limit	-73

Notes:

[32] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort D: ISIS 681257: 20 mg Q2W versus Placebo
Comparison groups	Cohort D: ISIS 681257: 20 mg Q2W v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78
upper limit	-54

Notes:

[33] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Statistical analysis title	Cohort E: ISIS 681257: 20 mg QW versus Placebo
Comparison groups	Cohort E: ISIS 681257: 20 mg QW v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Difference in % CFB
Point estimate	-89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-93
upper limit	-84

Notes:

[34] - Mean difference in percent (%) change from baseline (CFB) based on difference in LSM of log (Primary Analysis Time Point/Baseline) was estimated.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 16 weeks post-treatment period (up to approximately 1.3 years)

Adverse event reporting additional description:

Safety Set included all participants who were randomized and received at least 1 dose of study drug (ISIS 681257 or placebo).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Cohort A: ISIS 681257: 20mg Q4W
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Reporting group description:

Cohort A participants received 20 milligrams (mg) ISIS 681257, subcutaneous (SC) injection, once every 4 weeks (Q4W), for up to 49 weeks and a maximum of 13 doses.

Reporting group title	Cohort B: ISIS 681257: 40mg Q4W
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Reporting group description:

Cohort B participants received 40 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a maximum of 13 doses.

Reporting group title	Cohort C: ISIS 681257: 60mg Q4W
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Reporting group description:

Cohort C participants received 60 mg of ISIS 681257, SC injection, once Q4W, for up to 49 weeks and a maximum of 13 doses.

Reporting group title	Cohort D: ISIS 681257: 20mg Q2W
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Reporting group description:

Cohort D participants received 20 mg of ISIS 681257, SC injection, once every 2 weeks (Q2W), for up to 51 weeks and a maximum of 26 doses.

Reporting group title	Cohort E: ISIS 681257: 20mg QW
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Reporting group description:

Cohort E participants received 20 mg of ISIS 681257, SC injection, once weekly (QW), for up to 52 weeks and a maximum of 52 doses.

Reporting group title	Placebo
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Reporting group description:

Participants in each cohort were randomized to receive placebo at a dose-matched volume of study drug (ISIS 681257).

Serious adverse events	Cohort A: ISIS 681257: 20mg Q4W	Cohort B: ISIS 681257: 40mg Q4W	Cohort C: ISIS 681257: 60mg Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 48 (14.58%)	7 / 48 (14.58%)	7 / 47 (14.89%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			

subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Open reduction of fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Cyst			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Reproductive system and breast disorders			
Vaginal haemorrhage			

subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Depression			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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			
Ankle fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Joint dislocation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Lower limb fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Radius fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Gastrointestinal anastomotic stenosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 48 (4.17%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 48 (2.08%)	1 / 48 (2.08%)	0 / 47 (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
Coronary artery disease			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (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
Ischaemic stroke			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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			
Oesophagitis haemorrhagic			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (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
Pancreatitis acute			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort D: ISIS 681257: 20mg Q2W	Cohort E: ISIS 681257: 20mg QW	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 48 (6.25%)	4 / 48 (8.33%)	3 / 47 (6.38%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Surgical and medical procedures			
Open reduction of fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Cyst			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Vaginal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Depression			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Joint dislocation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Lower limb fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Radius fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Road traffic accident			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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 anastomotic stenosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
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 myocardial infarction			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Oesophagitis haemorrhagic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (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
Pancreatitis acute			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (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
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort A: ISIS 681257: 20mg Q4W	Cohort B: ISIS 681257: 40mg Q4W	Cohort C: ISIS 681257: 60mg Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 48 (79.17%)	42 / 48 (87.50%)	40 / 47 (85.11%)

Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 48 (10.42%)	1 / 48 (2.08%)	1 / 47 (2.13%)
occurrences (all)	7	2	2
Blood bilirubin increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	2 / 47 (4.26%)
occurrences (all)	2	0	2
Laboratory test abnormal			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	1 / 47 (2.13%)
occurrences (all)	4	1	1
Alanine aminotransferase increased			
subjects affected / exposed	2 / 48 (4.17%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 48 (4.17%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences (all)	4	0	1
Fall			
subjects affected / exposed	2 / 48 (4.17%)	3 / 48 (6.25%)	0 / 47 (0.00%)
occurrences (all)	2	4	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	3 / 47 (6.38%)
occurrences (all)	3	1	4
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	8 / 48 (16.67%)	3 / 48 (6.25%)	2 / 47 (4.26%)
occurrences (all)	8	5	10
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 48 (12.50%)	7 / 48 (14.58%)	4 / 47 (8.51%)
occurrences (all)	9	11	8
Dizziness			
subjects affected / exposed	4 / 48 (8.33%)	3 / 48 (6.25%)	4 / 47 (8.51%)
occurrences (all)	5	3	4
General disorders and administration site conditions			

Injection site erythema subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 4	13 / 48 (27.08%) 31	13 / 47 (27.66%) 31
Fatigue subjects affected / exposed occurrences (all)	8 / 48 (16.67%) 8	7 / 48 (14.58%) 9	2 / 47 (4.26%) 2
Injection site pain subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	2 / 48 (4.17%) 2	3 / 47 (6.38%) 3
Influenza like illness subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	2 / 48 (4.17%) 2	4 / 47 (8.51%) 4
Injection site pruritus subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	4 / 48 (8.33%) 8	1 / 47 (2.13%) 1
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	2 / 48 (4.17%) 3	2 / 47 (4.26%) 2
Pyrexia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	3 / 48 (6.25%) 7	1 / 47 (2.13%) 1
Injection site bruising subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 48 (0.00%) 0	0 / 47 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 48 (2.08%) 1	2 / 47 (4.26%) 3
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 7	3 / 48 (6.25%) 3	2 / 47 (4.26%) 2
Nausea subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	3 / 48 (6.25%) 3	3 / 47 (6.38%) 3
Vomiting			

subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	3 / 48 (6.25%) 3	2 / 47 (4.26%) 2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 48 (4.17%)	3 / 48 (6.25%)	3 / 47 (6.38%)
occurrences (all)	3	3	3
Oropharyngeal pain			
subjects affected / exposed	3 / 48 (6.25%)	3 / 48 (6.25%)	4 / 47 (8.51%)
occurrences (all)	3	3	4
Dyspnoea			
subjects affected / exposed	2 / 48 (4.17%)	5 / 48 (10.42%)	0 / 47 (0.00%)
occurrences (all)	2	5	0
Rhinorrhoea			
subjects affected / exposed	3 / 48 (6.25%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences (all)	3	0	1
Nasal congestion			
subjects affected / exposed	1 / 48 (2.08%)	3 / 48 (6.25%)	0 / 47 (0.00%)
occurrences (all)	2	3	0
Epistaxis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	4 / 48 (8.33%)	5 / 48 (10.42%)	10 / 47 (21.28%)
occurrences (all)	5	6	16
Arthralgia			
subjects affected / exposed	1 / 48 (2.08%)	5 / 48 (10.42%)	4 / 47 (8.51%)
occurrences (all)	1	6	6
Back pain			
subjects affected / exposed	2 / 48 (4.17%)	7 / 48 (14.58%)	2 / 47 (4.26%)
occurrences (all)	2	9	2
Pain in extremity			

subjects affected / exposed	4 / 48 (8.33%)	2 / 48 (4.17%)	3 / 47 (6.38%)
occurrences (all)	5	2	4
Neck pain			
subjects affected / exposed	1 / 48 (2.08%)	1 / 48 (2.08%)	4 / 47 (8.51%)
occurrences (all)	1	1	4
Muscle spasms			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 48 (2.08%)	3 / 48 (6.25%)	0 / 47 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 48 (16.67%)	10 / 48 (20.83%)	8 / 47 (17.02%)
occurrences (all)	8	12	10
Urinary tract infection			
subjects affected / exposed	7 / 48 (14.58%)	7 / 48 (14.58%)	10 / 47 (21.28%)
occurrences (all)	10	12	18
Sinusitis			
subjects affected / exposed	2 / 48 (4.17%)	2 / 48 (4.17%)	4 / 47 (8.51%)
occurrences (all)	2	2	4
Upper respiratory tract infection			
subjects affected / exposed	4 / 48 (8.33%)	3 / 48 (6.25%)	0 / 47 (0.00%)
occurrences (all)	5	3	0
Influenza			
subjects affected / exposed	5 / 48 (10.42%)	0 / 48 (0.00%)	2 / 47 (4.26%)
occurrences (all)	6	0	2
Gastroenteritis			
subjects affected / exposed	2 / 48 (4.17%)	1 / 48 (2.08%)	1 / 47 (2.13%)
occurrences (all)	2	1	1

Bronchitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	2 / 47 (4.26%)
occurrences (all)	1	0	2
Conjunctivitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort D: ISIS 681257: 20mg Q2W	Cohort E: ISIS 681257: 20mg QW	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 48 (75.00%)	42 / 48 (87.50%)	36 / 47 (76.60%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 48 (6.25%)	3 / 48 (6.25%)	2 / 47 (4.26%)
occurrences (all)	4	3	2
Blood bilirubin increased			
subjects affected / exposed	2 / 48 (4.17%)	5 / 48 (10.42%)	3 / 47 (6.38%)
occurrences (all)	3	6	5
Laboratory test abnormal			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	1 / 47 (2.13%)
occurrences (all)	3	1	1
Alanine aminotransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	3 / 48 (6.25%)	0 / 47 (0.00%)
occurrences (all)	1	3	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 48 (6.25%)	3 / 48 (6.25%)	0 / 47 (0.00%)
occurrences (all)	3	3	0
Fall			
subjects affected / exposed	1 / 48 (2.08%)	2 / 48 (4.17%)	0 / 47 (0.00%)
occurrences (all)	1	2	0
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 48 (8.33%)	4 / 48 (8.33%)	2 / 47 (4.26%)
occurrences (all)	4	4	2
Cardiac disorders			

Angina pectoris subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	2 / 48 (4.17%) 2	1 / 47 (2.13%) 1
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 7	6 / 48 (12.50%) 8	5 / 47 (10.64%) 5
Dizziness subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 3	4 / 48 (8.33%) 4	2 / 47 (4.26%) 4
General disorders and administration site conditions			
Injection site erythema subjects affected / exposed occurrences (all)	11 / 48 (22.92%) 58	22 / 48 (45.83%) 113	0 / 47 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	3 / 48 (6.25%) 3	1 / 47 (2.13%) 1
Injection site pain subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	3 / 48 (6.25%) 4	0 / 47 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 48 (0.00%) 0	2 / 47 (4.26%) 2
Injection site pruritus subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	2 / 48 (4.17%) 3	0 / 47 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 3	0 / 48 (0.00%) 0	4 / 47 (8.51%) 5
Pyrexia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	2 / 48 (4.17%) 2	3 / 47 (6.38%) 3
Injection site bruising subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	4 / 48 (8.33%) 6	0 / 47 (0.00%) 0
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	2 / 48 (4.17%) 2	3 / 47 (6.38%) 3
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 4	5 / 48 (10.42%) 7	1 / 47 (2.13%) 4
Nausea subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	2 / 48 (4.17%) 2	1 / 47 (2.13%) 1
Vomiting subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	1 / 48 (2.08%) 1	0 / 47 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	6 / 48 (12.50%) 9	5 / 47 (10.64%) 5
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 2	5 / 48 (10.42%) 6	1 / 47 (2.13%) 1
Dyspnoea subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	3 / 48 (6.25%) 3	2 / 47 (4.26%) 2
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	2 / 48 (4.17%) 2	1 / 47 (2.13%) 1
Nasal congestion subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 48 (2.08%) 3	2 / 47 (4.26%) 2
Epistaxis subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	1 / 48 (2.08%) 1	4 / 47 (8.51%) 7
Skin and subcutaneous tissue disorders			
Dermatitis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	3 / 48 (6.25%) 3	1 / 47 (2.13%) 1

Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	6 / 48 (12.50%)	3 / 48 (6.25%)	5 / 47 (10.64%)
occurrences (all)	23	4	6
Arthralgia			
subjects affected / exposed	2 / 48 (4.17%)	4 / 48 (8.33%)	2 / 47 (4.26%)
occurrences (all)	2	5	3
Back pain			
subjects affected / exposed	1 / 48 (2.08%)	4 / 48 (8.33%)	3 / 47 (6.38%)
occurrences (all)	1	4	3
Pain in extremity			
subjects affected / exposed	1 / 48 (2.08%)	3 / 48 (6.25%)	1 / 47 (2.13%)
occurrences (all)	1	4	1
Neck pain			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	1 / 47 (2.13%)
occurrences (all)	3	1	1
Muscle spasms			
subjects affected / exposed	2 / 48 (4.17%)	3 / 48 (6.25%)	2 / 47 (4.26%)
occurrences (all)	2	3	2
Musculoskeletal pain			
subjects affected / exposed	1 / 48 (2.08%)	1 / 48 (2.08%)	2 / 47 (4.26%)
occurrences (all)	1	1	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 48 (0.00%)	3 / 48 (6.25%)	0 / 47 (0.00%)
occurrences (all)	0	3	0
Flank pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 48 (16.67%)	15 / 48 (31.25%)	11 / 47 (23.40%)
occurrences (all)	11	21	17
Urinary tract infection			
subjects affected / exposed	6 / 48 (12.50%)	9 / 48 (18.75%)	3 / 47 (6.38%)
occurrences (all)	6	13	4
Sinusitis			

subjects affected / exposed	4 / 48 (8.33%)	3 / 48 (6.25%)	3 / 47 (6.38%)
occurrences (all)	4	4	3
Upper respiratory tract infection			
subjects affected / exposed	3 / 48 (6.25%)	4 / 48 (8.33%)	5 / 47 (10.64%)
occurrences (all)	3	5	5
Influenza			
subjects affected / exposed	2 / 48 (4.17%)	5 / 48 (10.42%)	1 / 47 (2.13%)
occurrences (all)	2	7	1
Gastroenteritis			
subjects affected / exposed	2 / 48 (4.17%)	4 / 48 (8.33%)	3 / 47 (6.38%)
occurrences (all)	2	4	3
Bronchitis			
subjects affected / exposed	2 / 48 (4.17%)	0 / 48 (0.00%)	3 / 47 (6.38%)
occurrences (all)	2	0	3
Conjunctivitis			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences (all)	3	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2016	Regulatory advice on inclusion of more detailed description of processes for platelet monitoring, and more frequent monitoring of liver function.
29 November 2016	Regulatory advice on inclusion of biomarkers of renal damage and increased frequency of renal monitoring. Addition of a Data Safety Monitoring Board.
30 December 2016	Adjustment of the frequency, and alert and intervention limits, for renal safety and adjustment of the frequency of liver safety testing.
05 January 2017	The study population was increased to 270 participants (54 per cohort) to support a statistical assessment of risk of platelet reduction in this population. In addition, the 10 mg weekly treatment cohort was modified to 20 mg every 2 weeks (biweekly).
30 May 2017	Regulatory advice on addition of exclusion criteria, reduced permitted timeframe for identifying critical laboratory results by the investigator and replacement of the Adverse Event (AE) definition.
25 January 2018	Updated platelet monitoring to allow for potential to return to every 2-week monitoring, clarified definition and scheduling of the follow-up period and End of Treatment visit for last participant to complete primary endpoint visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported