Clinical trial results:
A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo Controlled Study of MGL-3196 in Patients with Heterozygous Familial Hypercholesterolemia

Summary

EudraCT number	2016-002315-17
Trial protocol	NO DK NL
Global end of trial date	15 January 2018

Results information

Result version number	v1 (current)
This version publication date	19 August 2022
First version publication date	19 August 2022

Trial information

Trial identification

Sponsor protocol code	MGL-3196-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03038022
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Madrigal Pharmaceuticals
Sponsor organisation address	200 Barr Harbor Drive, Conshohocken, PA, United States,
Public contact	Information, Madrigal Pharmaceuticals, Inc., +1 267-520-0252, info@madrgalpharma.com
Scientific contact	Information, Madrigal Pharmaceuticals, Inc., +1 267-520-0252, info@madrgalpharma.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	15 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 January 2018
Global end of trial reached?	Yes
Global end of trial date	15 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the effect of once-daily oral dose of MGL-3196 and matching placebo after 12 weeks on the percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in participants with heterozygous familial hypercholesterolemia (HeFH).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator:

A placebo was used as a comparator to assess the safety and efficacy of the study drug.

Actual start date of recruitment	09 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Norway: 43
Country: Number of subjects enrolled	Denmark: 49
Worldwide total number of subjects	116
EEA total number of subjects	116

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)	81
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 137 participants diagnosed with HeFH were screened at 13 sites in Norway, Denmark and The Netherlands, of which 116 were randomized. Twenty-one participants failed screening, including 17 who failed to meet randomization criteria, 3 participants who withdrew, and 1 participant who was lost to follow-up.

Period 1

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

Blinding implementation details:

Blinding was accomplished by providing visually indistinguishable MGL-3196 and placebo capsules. Packaging for MGL-3196 and placebo product was identical with the exception of a unique bottle identification number on the label.

Arms

Are arms mutually exclusive?	Yes
Arm title	MGL-3196

Arm description:

Participants randomized to MGL-3196 received 100 mg daily during the first 2 weeks, 60 mg daily during Weeks 2 to 4, and then either 60 or 100 mg daily to Week 12 based on Week 2 measured pharmacokinetic (PK) assessments of MGL-3196 exposure.

Arm type	Experimental
Investigational medicinal product name	MGL-3196
Investigational medicinal product code	
Other name	Resmetirom
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received once-daily MGL-3196 hard gelatin capsule taken orally.

Arm title	Placebo

Arm description:

Participants administered matching oral placebo once daily for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received once-daily matching oral placebo.

Number of subjects in period 1	MGL-3196	Placebo
Started	78	38
Received At Least 1 Dose of Study Drug	78	38
Completed	72	36
Not completed	6	2
Adverse Event	4	2
Withdrawal by Subject	2	-

Baseline characteristics

Reporting groups	
Reporting group title	MGL-3196
Reporting group description:	
Participants randomized to MGL-3196 received 100 mg daily during the first 2 weeks, 60 mg daily during Weeks 2 to 4, and then either 60 or 100 mg daily to Week 12 based on Week 2 measured pharmacokinetic (PK) assessments of MGL-3196 exposure.	
Reporting group title	Placebo
Reporting group description:	
Participants administered matching oral placebo once daily for 12 weeks.	

Reporting group values	MGL-3196	Placebo	Total
Number of subjects	78	38	116
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)	56	25	81
From 65-84 years	22	13	35
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.4	59.1	
standard deviation	± 12.38	± 11.33	-
Gender categorical Units: Subjects			
Female	39	16	55
Male	39	22	61
Race Units: Subjects			
Asian	0	1	1
White	78	37	115
Smoking Units: Subjects			
History of smoking	4	3	7
No history of smoking	74	35	109
Diabetes Units: Subjects			
History of diabetes	3	4	7
No history of diabetes	75	34	109
Hypertension Units: Subjects			
History of hypertension	21	12	33

No history of hypertension	57	26	83
ASCVD Units: Subjects			
History of ASCVD	24	10	34
No history of ASCVD	54	28	82
Ezetimibe Units: Subjects			
Participants using ezetimibe	57	26	83
Participants not using ezetimibe	21	12	33
Bile Acid Sequestrants Units: Subjects			
Participants using bile acid sequestrants	6	4	10
Participants not using bile acid sequestrants	72	34	106
Fish Oil or Omega-3 Units: Subjects			
Participants using fish oil or Omega-3	3	5	8
Participants not using fish oil or Omega-3	75	33	108
PCSK9 Units: Subjects			
Undergoing PCSK9 inhibitor treatment	1	1	2
Not undergoing PCSK9 inhibitor treatment	77	37	114
LDL Cholesterol ≥100 mg/dL Units: Subjects			
LDL Cholesterol <100 mg/dL	15	12	27
LDL Cholesterol ≥100 mg/dL	63	26	89
Lp(a) >10 nmol/L Units: Subjects			
Lp-a <10 nmol/L	22	13	35
Lp-a >10 nmol/L	56	25	81
HeFH Units: Subjects			
HeFH	78	38	116
Statin Units: Subjects			
None	3	4	7
Atorvastatin	40	16	56
Rosuvastatin	34	17	51
Pravastatin	1	1	2
BMI Units: kg/m^2			
arithmetic mean	28.51	27.69	
standard deviation	± 4.490	± 3.607	-
Total Cholesterol Units: mg/dL			
arithmetic mean	206.1	209.1	
standard deviation	± 54.74	± 57.97	-
HDL Cholesterol			

Units: mg/dL			
arithmetic mean	51.8	51.5	
standard deviation	± 13.92	± 13.00	-
LDL-C (Screening)			
Units: mg/dL			
arithmetic mean	137.1	140.3	
standard deviation	± 42.87	± 55.18	-
LDL Cholesterol (Baseline - Direct)			
Units: mg/dL			
arithmetic mean	131.4	137.0	
standard deviation	± 47.24	± 57.53	-
LDL Cholesterol ≥100 mg/dL			
Units: mg/dL			
arithmetic mean	142.2	153.6	
standard deviation	± 47.46	± 50.16	-
Apolipoprotein B			
Units: mg/dL			
arithmetic mean	106.9	111.1	
standard deviation	± 27.97	± 36.08	-
Non-HDL Cholesterol			
Units: mg/dL			
arithmetic mean	154.3	162.7	
standard deviation	± 54.25	± 68.73	-
Apolipoprotein A1			
Units: mg/dL			
arithmetic mean	144.3	144.4	
standard deviation	± 23.41	± 20.66	-
Triglycerides			
Units: mg/dL			
arithmetic mean	106.4	127.9	
standard deviation	± 57.93	± 89.27	-
Lipoprotein-a			
Units: nmol/L			
arithmetic mean	84.3	67.6	
standard deviation	± 142.01	± 110.06	-
Lp-a >10 nmol/L			
Units: nmol/L			
arithmetic mean	114.8	98.8	
standard deviation	± 157.70	± 125.25	-
ApoB/ApoA1			
Units: mg/dL			
arithmetic mean	0.757	0.790	
standard deviation	± 0.2306	± 0.3277	-
Chol/HDL-C			
Units: mg/dL			
arithmetic mean	4.184	4.481	
standard deviation	± 1.3620	± 2.1862	-
Remnant Chol (Calc)			
Units: mg/dL			
arithmetic mean	22.8	25.0	
standard deviation	± 10.34	± 15.16	-
PCSK9			

Units: ng/mL			
arithmetic mean	571.37	595.05	
standard deviation	± 449.835	± 593.893	-
Thyrotropin			
Units: mIU/L			
arithmetic mean	1.926	2.226	
standard deviation	± 1.0106	± 0.9998	-
FT4			
Units: ng/dL			
arithmetic mean	1.134	1.122	
standard deviation	± 0.1506	± 0.1474	-
FT3			
Units: ng/L			
arithmetic mean	3.06	3.05	
standard deviation	± 0.392	± 0.342	-
Sex Hormone Binding Globulin			
Units: nmol/L			
arithmetic mean	56.017	50.743	
standard deviation	± 33.9798	± 26.7125	-
Thyroxine Binding Globulin			
Units: mg/L			
arithmetic mean	18.10	16.88	
standard deviation	± 3.921	± 3.315	-
Reverse T3			
Units: ng/dL			
arithmetic mean	14.76	14.98	
standard deviation	± 4.058	± 4.637	-

End points

End points reporting groups

Reporting group title	MGL-3196
Reporting group description:	
Participants randomized to MGL-3196 received 100 mg daily during the first 2 weeks, 60 mg daily during Weeks 2 to 4, and then either 60 or 100 mg daily to Week 12 based on Week 2 measured pharmacokinetic (PK) assessments of MGL-3196 exposure.	
Reporting group title	Placebo
Reporting group description:	
Participants administered matching oral placebo once daily for 12 weeks.	

Primary: Percent Change In LDL-C From Baseline To Week 12

End point title	Percent Change In LDL-C From Baseline To Week 12
End point description:	
LDL-C was determined by ultracentrifugation. Least-squares (LS) mean was provided for the comparison of MGL-3196 versus placebo and it used a linear model with percent change from baseline as the dependent variable and treatment as a factor.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	MGL-3196	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	37		
Units: Percentage				
least squares mean (standard error)	-10.6 (± 2.6)	8.2 (± 3.7)		

Statistical analyses

Statistical analysis title	Least Squares Mean Difference
Comparison groups	MGL-3196 v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-18.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.8
upper limit	-9.8

Variability estimate	Standard error of the mean

Secondary: Percent Change In Triglycerides From Baseline To Week 12

End point title	Percent Change In Triglycerides From Baseline To Week 12

End point description:

Triglycerides were determined by ultracentrifugation. LS mean was provided for the comparison of MGL-3196 versus placebo and it used a linear model with percent change from baseline as the dependent variable and treatment as a factor.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	MGL-3196	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	37		
Units: Percentage				
least squares mean (standard error)	-18.3 (± 3.2)	7.2 (± 4.6)		

Statistical analyses

Statistical analysis title	Least Squares Mean Difference
Comparison groups	Placebo v MGL-3196
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-25.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.7
upper limit	-14.2
Variability estimate	Standard error of the mean

Secondary: Percent Change In Lp(a) From Baseline To Week 12

End point title	Percent Change In Lp(a) From Baseline To Week 12

End point description:

Lp(a) was determined by ultracentrifugation. LS mean was provided for the comparison of MGL-3196 versus placebo and it used a linear model with percent change from baseline as the dependent variable and treatment as a factor.

End point type	Secondary
End point timeframe:	
Baseline up to Week 12	

End point values	MGL-3196	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	37		
Units: Percentage				
least squares mean (standard error)	-21.8 (± 2.9)	4.4 (± 4.1)		

Statistical analyses

Statistical analysis title	Least Squares Mean Difference
Comparison groups	MGL-3196 v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.2
upper limit	-16.4
Variability estimate	Standard error of the mean

Secondary: Percent Change In ApoB From Baseline To Week 12

End point title	Percent Change In ApoB From Baseline To Week 12
End point description:	
ApoB was determined by ultracentrifugation. LS mean was provided for the comparison of MGL-3196 versus placebo and it used a linear model with percent change from baseline as the dependent variable and treatment as a factor.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 12	

End point values	MGL-3196	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	37		
Units: Percentage				
least squares mean (standard error)	-14.2 (± 1.7)	3.8 (± 2.4)		

Statistical analyses

Statistical analysis title	Least Squares Mean Difference
Comparison groups	Placebo v MGL-3196
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.7
upper limit	-12.2
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 12

Adverse event reporting additional description:

Adverse event (AE) data are from the safety population. Although AEs for increased liver enzymes were reported in MGL-3196 participants, all elevations were asymptomatic and transient, related to absolute change in statin levels compared to baseline, and statistically significantly correlated with absolute change in statin, not MGL-3196.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	MGL-3196

Reporting group description:

Participants randomized to MGL-3196 received 100 mg daily during the first 2 weeks, 60 mg daily during Weeks 2 to 4 and then either 60 or 100 mg daily to Week 12 based on Week 2 measured PK assessments of MGL-3196 exposure.

Reporting group title	Placebo

Reporting group description:

Participants administered matching oral placebo once daily for 12 weeks.

Serious adverse events	MGL-3196	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 78 (0.00%)	1 / 38 (2.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MGL-3196	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 78 (83.33%)	28 / 38 (73.68%)	
Investigations			

Alanine aminotransferase (ALT) increased	Additional description: Standard grading of ALT using CTCAE was not used by investigators. 7/8 AEs were mild (Grade [G] 1 >1XULN, <3XULN), clinically insignificant, asymptomatic, transient while remaining on IP; 1/8 AE was transient, asymptomatic G2 >3XULN, <5XULN.		
subjects affected / exposed	8 / 78 (10.26%)	0 / 38 (0.00%)	
occurrences (all)	8	0	
Aspartate aminotransferase (AST) increased	Additional description: Standard grading of AST using CTCAE was not used by investigators. All AEs were G1 (>1XULN, <3XULN), clinically insignificant, asymptomatic, transient while remaining on IP, associated with baseline elevations, alcohol or statin levels.		
subjects affected / exposed	8 / 78 (10.26%)	0 / 38 (0.00%)	
occurrences (all)	9	0	
Hepatic enzyme increased	Additional description: Standard CTCAE grading of liver enzymes was not used by investigators. 6/7 AEs: G1 (>1XULN, <3XULN) clinically insignificant and/or unconfirmed, transient while staying on IP; 1/7 AEs: ALT elevation off IP in FU period, resolved when statin withdrawn		
subjects affected / exposed	7 / 78 (8.97%)	0 / 38 (0.00%)	
occurrences (all)	7	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 78 (2.56%)	2 / 38 (5.26%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 78 (12.82%)	6 / 38 (15.79%)	
occurrences (all)	13	7	
Dizziness			
subjects affected / exposed	4 / 78 (5.13%)	4 / 38 (10.53%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 78 (8.97%)	2 / 38 (5.26%)	
occurrences (all)	7	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 78 (19.23%)	4 / 38 (10.53%)	
occurrences (all)	22	5	
Nausea			
subjects affected / exposed	16 / 78 (20.51%)	2 / 38 (5.26%)	
occurrences (all)	25	3	
Abdominal Pain			

subjects affected / exposed	5 / 78 (6.41%)	2 / 38 (5.26%)	
occurrences (all)	5	2	
Flatulence			
subjects affected / exposed	5 / 78 (6.41%)	0 / 38 (0.00%)	
occurrences (all)	7	0	
Vomiting			
subjects affected / exposed	4 / 78 (5.13%)	1 / 38 (2.63%)	
occurrences (all)	6	1	
Abdominal Pain Upper			
subjects affected / exposed	4 / 78 (5.13%)	0 / 38 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Night Sweats			
subjects affected / exposed	0 / 78 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 78 (1.28%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	5 / 78 (6.41%)	5 / 38 (13.16%)	
occurrences (all)	7	6	
Arthralgia			
subjects affected / exposed	2 / 78 (2.56%)	3 / 38 (7.89%)	
occurrences (all)	3	4	
Muscle Spasms			
subjects affected / exposed	4 / 78 (5.13%)	0 / 38 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 78 (12.82%)	6 / 38 (15.79%)	
occurrences (all)	11	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2016	Amendment 1 (Denmark, The Netherlands, and Norway) - Added Exclusion Criteria #9 – Thyroid replacement therapy - Exclusion Criteria #10 – updated note regarding hypothyroidism - Exclusion Criteria #15 – changed eGFR rate from < 40 to < 60 mL/min - Treatment groups were changed from placebo, 80, and 120 mg to placebo and 100 mg and 60 mg groups. - The protocol employed an adaptive dose design. Participants, two-thirds of whom were randomized to MGL-3196 100 mg per day (one-third on placebo), received 100 mg for the first 2 weeks post-randomization, then received MGL-3196 60 mg between Weeks 2 and 4 visits. At Week 2 visit, a 4 hour post-dose PK sample was added and based on the results of that PK sample, at the Week 4 visit, participants randomized to MGL-3196 either continued on 60 mg or received 100 mg per day for the duration of the study. - Participants were instructed to take statins every evening starting 2 weeks before randomization and during the study, participants were to record the exact timing of statin intake the evening before the study visit. - Participants were to fast at least 10 hours before the study visits. - Language regarding a DSMB meeting was changed. - Drug Inducted Liver Injury Monitoring was added. - Additional secondary objectives were added. - Instructions on when participants should take their bile acid sequestrants were added.
30 December 2016	Amendment 2 (The Netherlands) -Removal of requirement for 30 min rest at Week 4 electrocardiogram (ECG) (Section 6.4.3) -Corrected the QTc assessment to QTcB assessment (Section 9.10)
05 January 2017	Amendment 2 (Norway) - Removal of requirement for 30 minutes rest at Week 4 ECG (Section 6.4.3) - Corrected QTc assessment to QTcB (Section 9.10)
18 May 2017	Amendment 3 (The Netherlands) - Update of inclusion criteria to allow for inclusion of participants with documented history of cardiovascular disease with a fasting LDL-C of >/= 1.8 mmol/L (70 mg/dL)
18 May 2017	Amendment 3 (Norway) - Update of inclusion criteria to allow for inclusion of participants with documented history of cardiovascular disease with a fasting LDL-C of >/= 1.8 mmol/L (70 mg/dL)
18 May 2017	Amendment 2 (Denmark) - Update of inclusion criteria to allow for inclusion of participants with documented history of cardiovascular disease with a fasting LDL-C of >/= 1.8 mmol/L (70 mg/dL)

04 July 2017	Amendment 3 (Denmark) -Change to allow rosuvastatin doses up to 40 mg. (Synopsis, Sections 1.2.1, 4.1, and 6.2). - Change to Inclusion Criteria #4 to allow up to 10% of study participants with probable HeFH based on a score of >=6, <=8 using World Health Organization (WHO)/Dutch criteria. (Synopsis and Section 4.1). - Update to Protocol Section 5.6.1 Excluded Medications and/or Procedures to allow up to 10% of study participants to be on stably dosed PCSK9 inhibitors (at least 3 months). - Added that for participants undergoing PCSK9 inhibitor treatment that the baseline and Week 12 visits occur within 5 days of the next scheduled PCSK9 inhibitor dose (Sections 6.4.1 and 6.4.5).
04 July 2017	Amendment 4 (The Netherlands) - Change to allow rosuvastatin doses up to 40 mg. (Synopsis, Sections 1.2.1, 4.1, and 6.2). - Change to Inclusion Criteria #4 to allow up to 10% of study participants with probable HeFH based on a score of >=6, <=8 using WHO/Dutch criteria. (Synopsis and Section 4.1). - Update to Protocol Section 5.6.1 Excluded Medications and/or Procedures to allow up to 10% of study participants to be on stably dosed PCSK9 inhibitors (at least 3 months). - Added that for participants undergoing PCSK9 inhibitor treatment that the baseline and week 12 visits occur within 5 days of the next scheduled PCSK9 inhibitor dose (Sections 6.4.1 and 6.4.5).
04 July 2017	Amendment 4 (Norway) - Change to allow rosuvastatin doses up to 40 mg. (Synopsis, Sections 1.2.1, 4.1, and 6.2). - Change to Inclusion Criteria #4 to allow up to 10% of study participants with probable HeFH based on a score of >=6, <=8 using WHO/Dutch criteria. (Synopsis and Section 4.1). - Update to Protocol Section 5.6.1 Excluded Medications and/or Procedures to allow up to 10% of study participants to be on stably dosed PCSK9 inhibitors (at least 3 months). - Added that for participants undergoing PCSK9 inhibitor treatment that the baseline and week 12 visits occur within 5 days of the next scheduled PCSK9 inhibitor dose (Sections 6.4.1 and 6.4.5).
02 August 2017	Amendment 4.1 (The Netherlands) - Restored Inclusion Criteria #4 to diagnosis of HeFH only. Removed possible inclusion of 10% of study participants with probable HeFH (Synopsis and Section 4.1).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported