Clinical trial results:
AN 8-WEEK, OPEN-LABEL, PHASE 1 STUDY TO EVALUATE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF ATORVASTATIN IN CHILDREN AND ADOLESCENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Summary

EudraCT number	2008-002774-34
Trial protocol	NL Outside EU/EEA
Global end of trial date	13 May 2009

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	A2581172

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00739999
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer Inc., Pfizer ClinicalTrials.gov Call Center, 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer Inc., Pfizer ClinicalTrials.gov Call Center, 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000073-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 August 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To develop population pharmacokinetic models for atorvastatin and its active metabolites (o-hydroxyatorvastatin and p-hydroxyatorvastatin) in children and adolescents with heterozygous familial hypercholesterolemia (HeFH), and to examine the influence of covariates on the pharmacokinetic parameters.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2008
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	Norway: 11
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Canada: 19
Worldwide total number of subjects	39
EEA total number of subjects	20

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)	18
Adolescents (12-17 years)	21
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 3 medical centres and participated in the study between 02 December 2008 and 13 May 2009. The enrolment in Norway, Greece and Canada.

Pre-assignment

Screening details:

Forty-five subjects were screened, and 39 subjects were assigned to study treatment.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Atorvastatin (5 mg, 10 mg): Tanner Stage 1

Arm description:

Age 6 - 10 years, at Tanner Stage 1. Initial dose through Week 4; after Week 4 dose may have been doubled if target low-density lipoprotein cholesterol (LDL-C) was not attained.

Arm type	Experimental
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Initial dose 5 mg/day through Week 4; after Week 4 dose may have been doubled to 10 mg/day if target low-density lipoprotein cholesterol (LDL-C) was not attained.

Arm title	Atorvastatin (10 mg, 20 mg): Tanner Stage 2+

Arm description:

Age 10 - 17 years, at Tanner Stage 2+. Initial dose through Week 4; after Week 4 dose may have been doubled if target LDL-C was not attained.

Arm type	Experimental
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Initial dose 10 mg/day through Week 4; after Week 4 dose may have been doubled to 20 mg/day if target LDL-C was not attained.

Number of subjects in period 1	Atorvastatin (5 mg, 10 mg): Tanner Stage 1	Atorvastatin (10 mg, 20 mg): Tanner Stage 2+
Started	15	24
Completed	15	24

Baseline characteristics

Reporting groups	
Reporting group title	Atorvastatin (5 mg, 10 mg): Tanner Stage 1
Reporting group description:	
Age 6 - 10 years, at Tanner Stage 1. Initial dose through Week 4; after Week 4 dose may have been doubled if target low-density lipoprotein cholesterol (LDL-C) was not attained.	
Reporting group title	Atorvastatin (10 mg, 20 mg): Tanner Stage 2+
Reporting group description:	
Age 10 - 17 years, at Tanner Stage 2+. Initial dose through Week 4; after Week 4 dose may have been doubled if target LDL-C was not attained.	

Reporting group values	Atorvastatin (5 mg, 10 mg): Tanner Stage 1	Atorvastatin (10 mg, 20 mg): Tanner Stage 2+	Total
Number of subjects	15	24	39
Age categorical Units: Subjects			
6-8 years	7	0	7
9-10 years	6	3	9
11-14 years	2	14	16
15-17 years	0	7	7
Gender categorical Units: Subjects			
Female	7	12	19
Male	8	12	20

End points

End points reporting groups

Reporting group title	Atorvastatin (5 mg, 10 mg): Tanner Stage 1
Reporting group description:	
Age 6 - 10 years, at Tanner Stage 1. Initial dose through Week 4; after Week 4 dose may have been doubled if target low-density lipoprotein cholesterol (LDL-C) was not attained.	
Reporting group title	Atorvastatin (10 mg, 20 mg): Tanner Stage 2+
Reporting group description:	
Age 10 - 17 years, at Tanner Stage 2+. Initial dose through Week 4; after Week 4 dose may have been doubled if target LDL-C was not attained.	
Subject analysis set title	Stayed at 5 mg: Tanner Stage 1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Atorvastatin 5 mg/day	
Subject analysis set title	Titrated to 10 mg: Tanner Stage 1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Atorvastatin: initial dose 5 mg/day through Week 4; after Week 4 dose was doubled to 10 mg/day if target LDL-C was not attained and study drug was well tolerated.	
Subject analysis set title	Stayed at 10 mg: Tanner Stage 2+
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Atorvastatin 10 mg/day	
Subject analysis set title	Titrated to 20 mg: Tanner Stage 2+
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Atorvastatin: initial dose 10 mg/day through Week 4; after Week 4 dose was doubled to 20 mg/day if target LDL-C was not attained and study drug was well tolerated.	
Subject analysis set title	Atorvastatin (5 mg, 10 mg, 20 mg): Tanner Stages 1 and 2+
Subject analysis set type	Full analysis
Subject analysis set description:	
Tanner Stage 1: Initial dose 5 mg/day through Week 4; after Week 4 dose may have been doubled to 10 mg/day if target LDL-C was not attained and study drug was well tolerated; Tanner Stage 2+: Initial dose 10 mg/day through Week 4; after Week 4 dose may have been doubled to 20 mg/day if target LDL-C was not attained and study drug was well tolerated.	

Primary: Parent-metabolite Population Pharmacokinetic (PK) Model for Atorvastatin and Its Metabolites: Atorvastatin Apparent Clearance (CL/F)

End point title	Parent-metabolite Population Pharmacokinetic (PK) Model for Atorvastatin and Its Metabolites: Atorvastatin Apparent Clearance (CL/F)
End point description:	
Parent-metabolite population PK model built using sparse blood samples from both Tanner Stage 1 and Tanner Stage 2+. Blood sampling times: Weeks 2 and 6: single sample between 4 and 12 hours postdose; Weeks 4 and 8: predose, 1 hour, and 2 hours postdose. Plasma samples were analyzed for atorvastatin and active hydroxyacid metabolite (o-hydroxyatorvastatin) concentrations using a validated, sensitive, and specific high-performance liquid chromatography tandem mass spectrometric method. Data presented are the result of the model used. Pharmacokinetic (PK) concentration population: all enrolled and treated subjects who had greater than or equal to (>=) 1 PK concentration assessed. Active hydroxyacid metabolite p-hydroxyatorvastatin was not included in the model as originally planned as greater than (>) 80% of samples were below detectable level at the doses used in this trial.	
End point type	Primary
End point timeframe:	
Week 2, Week 4, Week 6, Week 8	

End point values	Atorvastatin (5 mg, 10 mg): Tanner Stage 1	Atorvastatin (10 mg, 20 mg): Tanner Stage 2+		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	24		
Units: liter per hour (L/hr)				
number (not applicable)	553	543		

Statistical analyses

Statistical analysis title	Atorvastatin Apparent Clearance (CL/F)

Statistical analysis description:

Atorvastatin apparent clearance (CL/F) was described as a function of body weight using an allometric equation. The estimated parameter given is an extrapolation of the model for subjects who weigh 70 kg. Measures of parameter estimation uncertainty (95% CI) were determined by non-parametric bootstrap analysis.

Comparison groups	Atorvastatin (5 mg, 10 mg): Tanner Stage 1 v Atorvastatin (10 mg, 20 mg): Tanner Stage 2+
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	non-linear mixed-effects model
Point estimate	699
Confidence interval	
level	95 %
sides	2-sided
lower limit	570
upper limit	881

Primary: Parent-metabolite Population Pharmacokinetic (PK) Model for Atorvastatin and Its Metabolites: Apparent Volume of Distribution of the Central Compartment (Vc/F)

End point title	Parent-metabolite Population Pharmacokinetic (PK) Model for Atorvastatin and Its Metabolites: Apparent Volume of Distribution of the Central Compartment (Vc/F)[1]

End point description:

Parent-metabolite population PK model built using sparse blood samples from Tanner Stages 1 and 2+. Sampling times: Weeks 2 + 6: single sample between 4 -12 hours postdose; Weeks 4 + 8: predose, 1 + 2 hours postdose. Plasma samples analyzed for atorvastatin and active hydroxyacid metabolite (o-hydroxyatorvastatin) concentrations using validated, sensitive, specific high-performance liquid chromatography tandem mass spectrometric method. Vc/F value based on 70 kg body weight. Parameter estimation uncertainty (95% CI) by non-parametric bootstrap analysis. Data presented are result of model used.
PK concentration population: all enrolled and treated subjects who had >= 1 PK concentration assessed. Active hydroxyacid metabolite p-hydroxyatorvastatin was not included in the model as originally planned as > 80% of samples were below detectable level at the doses used in this trial.

End point type	Primary

End point timeframe:

Week 2, Week 4, Week 6, Week 8

Notes:

[1] - 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: Inferential statistical analysis was not performed since descriptive statistical analysis was planned for this endpoint.

End point values	Atorvastatin (5 mg, 10 mg, 20 mg): Tanner Stages 1 and 2+			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: liters				
number (confidence interval 95%)	1020 (209 to 2210)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Pharmacodynamic Responses of Low-density Lipoprotein Cholesterol (LDL-C)

End point title	Absolute Change From Baseline in Pharmacodynamic Responses of Low-density Lipoprotein Cholesterol (LDL-C)

End point description:

Low-density lipoprotein cholesterol (LDL-C) measured in millimoles per liter (mmol/L); assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). Change from baseline is equal to (=) value at observation minus baseline value. Pharmacodynamic (PD) analysis population: all enrolled subjects who received >= 1 dose of study drug and had >= 1 PD parameter measurement.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	4.87 (± 0.48)	6.37 (± 1.1)	5.11 (± 0.65)	6.23 (± 1)
Week 2	-1.75 (± 0.72)	-1.62 (± 0.46)	-1.95 (± 0.52)	-1.9 (± 0.72)
Week 4	-2.07 (± 0.5)	-1.94 (± 0.56)	-2.24 (± 0.57)	-2.27 (± 1.04)
Week 6	-1.89 (± 0.42)	-2.57 (± 0.7)	-2.12 (± 0.74)	-2.55 (± 1.02)
Week 8	-1.8 (± 0.63)	-2.71 (± 0.6)	-1.99 (± 0.58)	-2.6 (± 1.01)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pharmacodynamic Responses of Low-density Lipoprotein Cholesterol (LDL-C)

End point title	Percent Change From Baseline in Pharmacodynamic Responses of Low-density Lipoprotein Cholesterol (LDL-C)

End point description:

Low-density Lipoprotein Cholesterol (LDL-C): percent (%) change from baseline by treatment over time = [LDL-C at observation minus LDL-C at Week 0] divided by LDL-C at Week 0 multiplied by (*) 100. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: percent change in LDL-C				
arithmetic mean (standard deviation)				
Week 2	-36.27 (± 14.72)	-25.7 (± 7.76)	-38.14 (± 9.35)	-30.27 (± 9.22)
Week 4	-42.33 (± 8.24)	-30.27 (± 5.72)	-43.66 (± 7.78)	-35.13 (± 12.01)
Week 6	-38.87 (± 7.84)	-40.01 (± 6.34)	-41.22 (± 11.34)	-39.73 (± 10.4)
Week 8	-36.78 (± 11.16)	-42.7 (± 6.45)	-38.45 (± 7.84)	-40.39 (± 11.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Total Cholesterol (TC)

End point title	Absolute Change From Baseline in Total Cholesterol (TC)

End point description:

Total Cholesterol measured in millimoles per liter (mmol/L); assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). Change from baseline = value at observation minus baseline value. PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	6.76 (± 0.46)	8.58 (± 1.06)	6.92 (± 0.71)	8.4 (± 1.1)
Week 2	-1.89 (± 0.79)	-2.04 (± 0.69)	-2.11 (± 0.53)	-2.28 (± 0.82)
Week 4	-2.27 (± 0.63)	-2.24 (± 0.49)	-2.37 (± 0.61)	-2.66 (± 1.29)
Week 6	-2.03 (± 0.53)	-2.86 (± 0.79)	-2.28 (± 0.73)	-2.95 (± 1.19)
Week 8	-1.89 (± 0.44)	-3.2 (± 0.65)	-2.26 (± 0.69)	-3.22 (± 1.14)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total Cholesterol (TC)

End point title	Percent Change From Baseline in Total Cholesterol (TC)

End point description:

Total cholesterol (TC): percent (%) change from baseline by treatment over time = [TC at observation minus TC at Week 0] divided by TC at Week 0 * 100. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: percent change in TC				
arithmetic mean (standard deviation)				
Week 2	-28.06 (± 11.23)	-24.11 (± 8.97)	-30.6 (± 7.49)	-26.78 (± 7.59)
Week 4	-33.37 (± 7.81)	-26.12 (± 4.24)	-33.98 (± 7.13)	-30.54 (± 11.6)
Week 6	-29.99 (± 8)	-33.12 (± 6.83)	-32.8 (± 8.97)	-34.06 (± 9.94)
Week 8	-27.8 (± 5.56)	-37.17 (± 5.28)	-32.43 (± 8.53)	-37.45 (± 9.89)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Triglycerides (TG)

End point title	Absolute Change From Baseline in Triglycerides (TG)

End point description:

Change from baseline in triglycerides measured in millimoles per liter (mmol/L); assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). Change from baseline = value at observation minus baseline value. PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	0.76 (± 0.15)	0.95 (± 0.27)	1.03 (± 0.37)	1.2 (± 0.5)
Week 2	0.05 (± 0.34)	-0.08 (± 0.28)	0.05 (± 0.68)	0 (± 0.47)
Week 4	-0.05 (± 0.29)	-0.26 (± 0.3)	-0.1 (± 0.51)	-0.1 (± 0.37)
Week 6	0.4 (± 0.62)	-0.04 (± 0.24)	-0.12 (± 0.42)	-0.04 (± 0.32)
Week 8	0.02 (± 0.28)	-0.16 (± 0.37)	-0.31 (± 0.43)	-0.28 (± 0.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Triglycerides (TG)

End point title	Percent Change From Baseline in Triglycerides (TG)

End point description:

Triglycerides (TG): percent (%) change from baseline by treatment over time = [TG at observation minus TG at Week 0] divided by TG at Week 0 * 100. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: percent change in TG				
arithmetic mean (standard deviation)				
Week 2	5.66 (± 38.26)	-6.87 (± 29.08)	28.37 (± 85.32)	-0.56 (± 32.19)
Week 4	-6.2 (± 32.55)	-21.43 (± 30.42)	1.27 (± 50.81)	-7.6 (± 25.75)
Week 6	57.06 (± 78.73)	-1.27 (± 23.91)	-4.43 (± 32.52)	-2.72 (± 24.8)
Week 8	1.69 (± 31.48)	-9.88 (± 33.31)	-20.94 (± 39.24)	-21.11 (± 23.85)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C)

End point title	Absolute Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C)

End point description:

Change from baseline in high-density lipoprotein cholesterol measured in millimoles per liter (mmol/L); assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). Change from baseline = value at observation minus baseline value. PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	1.35 (± 0.12)	1.45 (± 0.29)	1.17 (± 0.18)	1.18 (± 0.23)
Week 2	0.08 (± 0.24)	-0.1 (± 0.29)	-0.05 (± 0.26)	-0.01 (± 0.2)
Week 4	-0.02 (± 0.05)	0 (± 0.19)	0.02 (± 0.21)	-0.01 (± 0.28)
Week 6	-0.12 (± 0.29)	-0.01 (± 0.18)	0.04 (± 0.14)	-0.03 (± 0.23)
Week 8	0.04 (± 0.22)	-0.07 (± 0.21)	0.08 (± 0.25)	-0.08 (± 0.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C)

End point title	Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C)

End point description:

High-density lipoprotein cholesterol (HDL-C): percent (%) change by treatment over time = [HDL-C at observation minus HDL-C at Week 0] divided by HDL-C at Week 0 * 100. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: percent change in HDL-C				
arithmetic mean (standard deviation)				
Week 2	5.38 (± 17.32)	-6.45 (± 21.01)	-4.11 (± 19.96)	-0.77 (± 17.66)
Week 4	-1.99 (± 3.9)	1.59 (± 13.18)	1.04 (± 17.38)	1.77 (± 23.22)
Week 6	-10.18 (± 22.7)	-0.64 (± 10.35)	3.28 (± 11.63)	-2.78 (± 21.49)
Week 8	2.5 (± 15.02)	-2.84 (± 14.49)	5.99 (± 21.02)	-5.19 (± 17.76)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Apolipoprotein A-1 (Apo A-1)

End point title	Absolute Change From Baseline in Apolipoprotein A-1 (Apo A-1)

End point description:

Change from baseline in Apolipoprotein A-1 measured in grams per liter (g/L); assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). Change from baseline = value at observation minus baseline value. PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: g/L				
arithmetic mean (standard deviation)				
Baseline	1.42 (± 0.2)	1.45 (± 0.2)	1.29 (± 0.2)	1.24 (± 0.15)
Week 2	0.01 (± 0.17)	-0.08 (± 0.23)	-0.09 (± 0.22)	-0.01 (± 0.15)
Week 4	-0.09 (± 0.14)	-0.06 (± 0.13)	-0.06 (± 0.21)	0.07 (± 0.29)
Week 6	-0.14 (± 0.18)	-0.02 (± 0.11)	-0.07 (± 0.19)	-0.04 (± 0.23)
Week 8	-0.03 (± 0.12)	-0.05 (± 0.13)	-0.04 (± 0.24)	-0.07 (± 0.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein A-1 (Apo A-1)

End point title	Percent Change From Baseline in Apolipoprotein A-1 (Apo A-1)

End point description:

Apolipoprotein A-1 (Apo A-1): percent (%) change from baseline by treatment over time = [Apo A-1 at observation minus Apo A-1 at Week 0] divided by Apo A-1 at Week 0 * 100. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: percent change in Apo A-1				
arithmetic mean (standard deviation)				
Week 2	1.69 (± 11.21)	-5.24 (± 15.86)	-5.96 (± 16.76)	-0.53 (± 11.9)
Week 4	-5.15 (± 8.2)	-3.3 (± 8.11)	-3.73 (± 16.43)	7.54 (± 25.24)
Week 6	-9.9 (± 14.01)	-0.97 (± 7.04)	-4.21 (± 14.81)	-2.82 (± 18.2)
Week 8	-1.24 (± 8.49)	-3.37 (± 9.35)	-2.6 (± 20.22)	-4.82 (± 16.13)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Apolipoprotein B (Apo B)

End point title	Absolute Change From Baseline in Apolipoprotein B (Apo B)

End point description:

Change from baseline in Apolipoprotein B measured in grams per liter (g/L); assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]). Change from baseline = value at observation minus baseline value. PD analysis population.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: g/L				
arithmetic mean (standard deviation)				
Baseline	1.09 (± 0.13)	1.49 (± 0.24)	1.26 (± 0.14)	1.52 (± 0.18)
Week 2	-0.23 (± 0.13)	-0.31 (± 0.19)	-0.39 (± 0.14)	-0.42 (± 0.16)
Week 4	-0.33 (± 0.11)	-0.4 (± 0.13)	-0.44 (± 0.1)	-0.47 (± 0.22)
Week 6	-0.27 (± 0.15)	-0.53 (± 0.17)	-0.42 (± 0.15)	-0.52 (± 0.18)
Week 8	-0.3 (± 0.08)	-0.59 (± 0.15)	-0.41 (± 0.17)	-0.49 (± 0.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein B (Apo B)

End point title	Percent Change From Baseline in Apolipoprotein B (Apo B)

End point description:

Apolipoprotein B (Apo B): percent (%) change from baseline by treatment over time = [Apo B at observation minus Apo B at Week 0] divided by Apo B at Week 0 * 100. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]).

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: percent change in Apo B				
arithmetic mean (standard deviation)				
Week 2	-21.92 (± 13.97)	-19.88 (± 10.96)	-30.81 (± 10.27)	-27.46 (± 8.89)
Week 4	-29.89 (± 8.94)	-26.56 (± 5.33)	-34.69 (± 6.1)	-30.42 (± 11.86)
Week 6	-24.58 (± 12.96)	-35.26 (± 6.85)	-33.26 (± 10.38)	-33.61 (± 9.59)
Week 8	-27.39 (± 5.97)	-39.59 (± 5.83)	-31.94 (± 11.64)	-31.26 (± 18.57)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Very Low-density Lipoprotein-cholesterol (VLDL-C)

End point title	Absolute Change From Baseline in Very Low-density Lipoprotein-cholesterol (VLDL-C)

End point description:

Change from baseline in very low-density lipoprotein-cholesterol (VLDL-C) measured in millimoles per liter (mmol/L). Change from baseline = value at observation minus baseline value. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]).

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	0.54 (± 0.15)	0.76 (± 0.3)	0.65 (± 0.11)	0.99 (± 0.31)
Change at Week 2	-0.22 (± 0.12)	-0.31 (± 0.38)	-0.12 (± 0.29)	-0.38 (± 0.33)
Change at Week 4	-0.18 (± 0.24)	-0.3 (± 0.27)	-0.14 (± 0.24)	-0.39 (± 0.35)
Change at Week 6	-0.01 (± 0.17)	-0.28 (± 0.32)	-0.2 (± 0.17)	-0.36 (± 0.28)
Change at Week 8	-0.13 (± 0.32)	-0.42 (± 0.28)	-0.35 (± 0.14)	-0.55 (± 0.32)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Very Low-density Lipoprotein-cholesterol (VLDL-C)

End point title	Percent Change From Baseline in Very Low-density Lipoprotein-cholesterol (VLDL-C)

End point description:

Very low-density lipoprotein-cholesterol (VLDL-C): percent (%) change from baseline by treatment over time = [VLDL-C at observation minus VLDL-C at Week 0] divided by VLDL-C at Week 0 * 100. Assessments were performed in the fasting state (minimum 10-hour fast [optional at Weeks 2 and 6]).

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	10	9	15
Units: percent change in VLDL-C				
arithmetic mean (standard deviation)				
Week 2	-42.2 (± 25.17)	-28.49 (± 43.5)	-14.5 (± 41.19)	-39.95 (± 37.24)
Week 4	-30.66 (± 48.66)	-31.86 (± 37.62)	-21.1 (± 37.56)	-36.35 (± 28.79)
Week 6	4.1 (± 36.46)	-25.59 (± 44.9)	-29.2 (± 25.11)	-35.08 (± 25.06)
Week 8	-12.31 (± 57.38)	-50.29 (± 21.44)	-53.61 (± 19.21)	-52.38 (± 29.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Flow-Mediated Dilatation at Week 8

End point title	Absolute Change From Baseline in Flow-Mediated Dilatation at Week 8

End point description:

Brachial artery flow-mediated dilatation (FMD) = (max minus baseline diameter divided by baseline diameter) x 100%. Standardized image acquisition: brachial artery images recorded for one minute at rest, blood pressure cuff inflated to 250 mm Hg for 5 minutes with brachial artery imaged continuously throughout cuff inflation, cuff released to produce reactive hyperaemia and the brachial artery imaged

continuously for 3 minutes after release. Total duration of measurement approximately 25 minutes. Change from baseline = value at observation minus baseline value. PD analysis population. Flow-mediated dilation (FMD) was measured at centers with established FMD facilities. PD analysis population. Flow-mediated dilation (FMD) was measured at centers with established FMD facilities.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	7	5	12
Units: FMD				
arithmetic mean (standard deviation)				
Baseline	4.34 (± 3.15)	7.41 (± 3.3)	5.05 (± 3.86)	3.67 (± 2.51)
Change at Week 8	-0.16 (± 2.32)	-1.14 (± 1.47)	-0.32 (± 4.83)	1.35 (± 2.73)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Flow-Mediated Dilatation at Week 8

End point title	Percent Change From Baseline in Flow-Mediated Dilatation at Week 8

End point description:

Brachial Flow-Mediated Dilatation (FMD) = (max minus baseline diameter divided by baseline diameter) x 100%.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Stayed at 5 mg: Tanner Stage 1	Titrated to 10 mg: Tanner Stage 1	Stayed at 10 mg: Tanner Stage 2+	Titrated to 20 mg: Tanner Stage 2+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	7	5	12
Units: percent change in FMD				
arithmetic mean (standard deviation)	-17.19 (± 23.67)	-20.77 (± 37.03)	-9.77 (± 63.2)	1.49 (± 28.64)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 8	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	All Subjects (5 mg, 10 mg): Tanner Stage 1
Reporting group description: Atorvastatin: subjects who stayed at initial dose of 5 mg/day for duration of study and subjects who titrated after Week 4 to 10 mg/day if target LDL-C was not attained and study drug was well tolerated.	
Reporting group title	All Subjects (10 mg, 20 mg): Tanner Stage 2+
Reporting group description: Atorvastatin: subjects who stayed at initial dose of 10 mg/day for duration of study and subjects who titrated to 20 mg/day after Week 4 if target LDL-C was not attained and study drug was well tolerated.	

Serious adverse events	All Subjects (5 mg, 10 mg): Tanner Stage 1	All Subjects (10 mg, 20 mg): Tanner Stage 2+	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All Subjects (5 mg, 10 mg): Tanner Stage 1	All Subjects (10 mg, 20 mg): Tanner Stage 2+	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 15 (60.00%)	13 / 24 (54.17%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Blood creatinine increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 15 (13.33%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Musculoskeletal pain			

subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Gastritis viral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Tonsillitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Viral rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			

subjects affected / exposed	3 / 15 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Hand fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported