Clinical trial results:
A 12-week, Double-blind, Randomized Study to Compare the Efficacy and Safety of Fixed Combinations of Fenofibrate/Simvastatin 145/20 mg and Fenofibrate/Simvastatin 145/40 mg Tablets vs. Matching Monotherapies in Dyslipidemic Subjects at High Risk of Cardiovascular Disease

Summary

EudraCT number	2011-005924-16
Trial protocol	CZ PL
Global end of trial date	28 October 2013

Results information

Result version number	v1 (current)
This version publication date	15 August 2019
First version publication date	15 August 2019

Trial information

Trial identification

Sponsor protocol code	M13-377

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01674712
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbott Laboratories Ireland Ltd
Sponsor organisation address	4051 Kingswood Drive, Citywest Business Campus, Dublin, Ireland, 24
Public contact	Hind Ounis, Abbott Healthcare Products B.V., Hind.Ounis@abbott.com
Scientific contact	Dmitri Kazei, Abbott Healthcare Products B.V., Dmitri.Kazei@abbott.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	28 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the efficacy of the two fixed-combinations (FCs) (fenofibrate/simvastatin 145/20 milligrams [mg] tablet and fenofibrate/simvastatin 145/40 mg tablet) in reducing triglyceride (TG) and increasing high density lipoprotein cholesterol (HDL-C) versus simvastatin 20 mg or 40 mg, and in reducing low density lipoprotein cholesterol (LDL-C) versus fenofibrate 145 mg in subjects with mixed dyslipidemia (type IIb) at high or very high risk of cardiovascular (CV) disease after 12 weeks of treatment.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice ethical and scientific quality standards and the applicable national regulations to assure that the rights, safety, and well being of the participating study subjects were protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2012
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	Argentina: 105
Country: Number of subjects enrolled	Czech Republic: 111
Country: Number of subjects enrolled	Germany: 164
Country: Number of subjects enrolled	Mexico: 39
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Romania: 27
Country: Number of subjects enrolled	Russian Federation: 85
Worldwide total number of subjects	575
EEA total number of subjects	346

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)	389
From 65 to 84 years	186
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with documented mixed dyslipidemia (based on fasting lipids) and assessed to be at high or very high CV risk were recruited to this randomized, double-blind, active-controlled parallel-arm study from June 2012, conducted at 70 centres in 7 countries. The last subject completed in October 2013. Parts A and B were conducted in parallel.

Pre-assignment

Screening details:

576 subjects met all the inclusion and none of the exclusion criteria, 1 subject withdrew consent and 575 were allocated to treatment. Estimation of CV risk was based on European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemias using the Systemic Coronary Risk Estimation chart.

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	Investigator, Subject, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Fenofibrate/Simvastatin 145/20 mg

Arm description:

In Part A subjects were randomized to receive FC fenofibrate/simvastatin 145/20 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 20 mg capsules and placebo fenofibrate 145 mg tablets.

Arm type	Experimental
Investigational medicinal product name	Fenofibrate/Simvastatin 145/20 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one FC tablet containing 145 mg fenofibrate and 20 mg simvastatin daily for 12 +/- 1 weeks.

Investigational medicinal product name	Simvastatin 20 mg placebo capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received one simvastatin 20 mg placebo capsule daily for 12 +/- 1 weeks. The placebo capsules were identical in terms of shape, size and colour as the simvastatin 20 mg capsules containing the active substance.

Investigational medicinal product name	Fenofibrate 145 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one fenofibrate 145 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets

were identical in terms of shape, size, colour and inscriptions as the fenofibrate 145 mg tablets containing the active substance.

Arm title	Simvastatin 20 mg

Arm description:

In Part A subjects were randomized to receive simvastatin 20 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo fenofibrate 145 mg tablets.

Arm type	Active comparator
Investigational medicinal product name	Simvastatin 20 mg capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received one 20 mg simvastatin capsule daily for 12 +/- 1 weeks.

Investigational medicinal product name	Fenofibrate/Simvastatin 145/20 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one fenofibrate/simvastatin 145/20 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets were identical in terms of shape, size and colour as the fenofibrate/simvastatin 145/20 mg tablets containing the active substances.

Investigational medicinal product name	Fenofibrate 145 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one fenofibrate 145 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets were identical in terms of shape, size, colour and inscriptions as the fenofibrate 145 mg tablets containing the active substance.

Arm title	Fenofibrate/Simvastatin 145/40 mg

Arm description:

In Part B subjects were randomized to receive FC fenofibrate/simvastatin 145/40 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 40 mg capsules and placebo fenofibrate 145 mg tablets.

Arm type	Experimental
Investigational medicinal product name	Fenofibrate/Simvastatin 145/40 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one FC tablet containing 145 mg fenofibrate and 40 mg simvastatin daily for 12 +/- 1 weeks.

Investigational medicinal product name	Simvastatin 40 mg placebo capsules
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received one simvastatin 40 mg placebo capsule daily for 12 +/- 1 weeks. The placebo capsules were identical in terms of shape, size and colour as the simvastatin 40 mg capsules containing the active substance.

Investigational medicinal product name	Fenofibrate 145 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one fenofibrate 145 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets were identical in terms of shape, size, colour and inscriptions as the fenofibrate 145 mg tablets containing the active substance.

Arm title	Simvastatin 40 mg

Arm description:

In Part B subjects were randomized to receive simvastatin 40 mg capsules once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo fenofibrate 145 mg tablets.

Arm type	Active comparator
Investigational medicinal product name	Simvastatin 40 mg capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received one 40 mg simvastatin capsule daily for 12 +/- 1 weeks.

Investigational medicinal product name	Fenofibrate/Simvastatin 145/40 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one fenofibrate/simvastatin 145/40 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets were identical in terms of shape, size and colour as the fenofibrate/simvastatin 145/40 mg tablets containing the active substances.

Investigational medicinal product name	Fenofibrate 145 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one fenofibrate 145 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets were identical in terms of shape, size, colour and inscriptions as the fenofibrate 145 mg tablets containing the active substance.

Arm title	Fenofibrate 145 mg

Arm description:

In Part A and in Part B subjects were randomized to receive fenofibrate 145 mg tablets once daily for 12 +/- 1 weeks. In Part A, subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo simvastatin 20 mg capsules. In Part B, subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo simvastatin 40 mg capsules.

Arm type	Active comparator

Investigational medicinal product name	Fenofibrate 145 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one 145 mg fenofibrate tablet daily for 12 +/- 1 weeks.

Investigational medicinal product name	Fenofibrate/Simvastatin 145/20 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects (in Part A) received one fenofibrate/simvastatin 145/20 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets were identical in terms of shape, size and colour as the fenofibrate/simvastatin 145/20 mg tablets containing the active substances.

Investigational medicinal product name	Simvastatin 20 mg placebo capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects (in Part A) received one simvastatin 20 mg placebo capsule daily for 12 +/- 1 weeks. The placebo capsules were identical in terms of shape, size and colour as the simvastatin 20 mg capsules containing the active substance.

Investigational medicinal product name	Fenofibrate/Simvastatin 145/40 mg placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects (in Part B) received one fenofibrate/simvastatin 145/40 mg placebo tablet daily for 12 +/- 1 weeks. The placebo tablets were identical in terms of shape, size and colour as the fenofibrate/simvastatin 145/40 mg tablets containing the active substances.

Investigational medicinal product name	Simvastatin 40 mg placebo capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects (in Part B) received one simvastatin 40 mg placebo capsule daily for 12 +/- 1 weeks. The placebo capsules were identical in terms of shape, size and colour as the simvastatin 40 mg capsules containing the active substance.

Number of subjects in period 1	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg
Started	114	117	115
Completed	104	108	106
Not completed	10	9	9
Consent withdrawn by subject	2	2	5
Administrative	-	1	-

Adverse event, non-fatal	5	6	3
Lost to follow-up	1	-	-
Protocol deviation	2	-	-
Lack of efficacy	-	-	1

Number of subjects in period 1	Simvastatin 40 mg	Fenofibrate 145 mg
Started	116	113
Completed	108	102
Not completed	8	11
Consent withdrawn by subject	4	3
Administrative	-	1
Adverse event, non-fatal	4	6
Lost to follow-up	-	-
Protocol deviation	-	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Fenofibrate/Simvastatin 145/20 mg
Reporting group description:	
In Part A subjects were randomized to receive FC fenofibrate/simvastatin 145/20 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 20 mg capsules and placebo fenofibrate 145 mg tablets.	
Reporting group title	Simvastatin 20 mg
Reporting group description:	
In Part A subjects were randomized to receive simvastatin 20 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo fenofibrate 145 mg tablets.	
Reporting group title	Fenofibrate/Simvastatin 145/40 mg
Reporting group description:	
In Part B subjects were randomized to receive FC fenofibrate/simvastatin 145/40 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 40 mg capsules and placebo fenofibrate 145 mg tablets.	
Reporting group title	Simvastatin 40 mg
Reporting group description:	
In Part B subjects were randomized to receive simvastatin 40 mg capsules once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo fenofibrate 145 mg tablets.	
Reporting group title	Fenofibrate 145 mg
Reporting group description:	
In Part A and in Part B subjects were randomized to receive fenofibrate 145 mg tablets once daily for 12 +/- 1 weeks. In Part A, subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo simvastatin 20 mg capsules. In Part B, subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo simvastatin 40 mg capsules.	

Reporting group values	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg
Number of subjects	114	117	115
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)	78	74	81
From 65-84 years	36	43	34
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	41	42	43
Male	73	75	72

Reporting group values	Simvastatin 40 mg	Fenofibrate 145 mg	Total
Number of subjects	116	113	575

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)	82	74	389
From 65-84 years	34	39	186
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	40	38	204
Male	76	75	371

End points

End points reporting groups

Reporting group title	Fenofibrate/Simvastatin 145/20 mg

Reporting group description:

In Part A subjects were randomized to receive FC fenofibrate/simvastatin 145/20 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 20 mg capsules and placebo fenofibrate 145 mg tablets.

Reporting group title	Simvastatin 20 mg

Reporting group description:

In Part A subjects were randomized to receive simvastatin 20 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo fenofibrate 145 mg tablets.

Reporting group title	Fenofibrate/Simvastatin 145/40 mg

Reporting group description:

In Part B subjects were randomized to receive FC fenofibrate/simvastatin 145/40 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 40 mg capsules and placebo fenofibrate 145 mg tablets.

Reporting group title	Simvastatin 40 mg

Reporting group description:

In Part B subjects were randomized to receive simvastatin 40 mg capsules once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo fenofibrate 145 mg tablets.

Reporting group title	Fenofibrate 145 mg

Reporting group description:

In Part A and in Part B subjects were randomized to receive fenofibrate 145 mg tablets once daily for 12 +/- 1 weeks. In Part A, subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo simvastatin 20 mg capsules. In Part B, subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo simvastatin 40 mg capsules.

Subject analysis set title	Feno/Simv 145/20 mg + Feno/Simv 145/40 mg
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were randomized to receive FC treatment of either fenofibrate/simvastatin 145/20 mg tablets or fenofibrate/simvastatin 145/40 mg tablets once daily for 12 +/- 1 weeks.

Subject analysis set title	Simvastatin 20 mg + Simvastatin 40 mg
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were randomized to receive monotherapy of either simvastatin 20 mg tablets or simvastatin 40 mg tablets once daily for 12 +/- 1 weeks.

Primary: Percentage Change from Baseline in Serum TG, LDL-C and HDL-C Levels at 12 Weeks

End point title	Percentage Change from Baseline in Serum TG, LDL-C and HDL-C Levels at 12 Weeks[1]

End point description:

The baseline value was defined as the mean of the lipid measured in the blood samples collected at the inclusion visit (Visit 1) and at the randomization visit (Visit 2). The endpoint value was defined as the last non-missing value assigned to treatment for the subject. The mean percentage changes from baseline in TG, LDL-C and HDL-C levels after 12 weeks of treatment are presented for the Full Analysis (FA) subject sample which consisted of all subjects who were allocated to treatment, received at least one dose of investigational study drug and had data for at least one post-baseline assessment of any efficacy measurement (TG, HDL-C or LDL-C) before or at Visit 4.

End point type	Primary

End point timeframe:

Baseline (Visits 1 and 2) and after 12 weeks of treatment (Visit 4).

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: Summary descriptive statistics for percentage change from baseline at 12 weeks in the lipid parameters are presented in this endpoint without comparative statistical analyses.

End point values	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg	Simvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	102	97	101
Units: Percentage change				
arithmetic mean (standard deviation)				
TG	-30.562 (± 25.794)	10.703 (± 48.791)	-27.326 (± 35.878)	-2.892 (± 34.286)
LDL-C	1.866 (± 25.400)	-1.973 (± 24.786)	-6.074 (± 26.223)	-8.157 (± 25.826)
HDL-C	9.019 (± 16.816)	0.278 (± 12.101)	8.826 (± 16.497)	2.209 (± 12.480)

End point values	Fenofibrate 145 mg			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: Percentage change				
arithmetic mean (standard deviation)				
TG	-21.630 (± 34.176)			
LDL-C	30.235 (± 35.573)			
HDL-C	7.648 (± 15.710)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage Least Squares (LS) Mean Change from Baseline in Serum TG Level at 12 Weeks

End point title	Percentage Least Squares (LS) Mean Change from Baseline in Serum TG Level at 12 Weeks[2]

End point description:

The baseline value was defined as the mean of the lipid measured in the blood samples collected at the inclusion visit (Visit 1) and at the randomization visit (Visit 2). The endpoint value was defined as the last non-missing value assigned to treatment for the subject. The LS mean percentage change from baseline in TG levels after 12 weeks of treatment are presented for the FA subject sample which consisted of all subjects who were allocated to treatment, received at least one dose of investigational study drug and had data for at least one post-baseline assessment of any efficacy measurement (TG, HDL-C or LDL-C) before or at Visit 4. The LS mean of the percentage change from baseline at 12 weeks was determined using a mixed model repeated measures (MMRM) analysis with treatment group, visit, gender, country and treatment by visit interaction as fixed factors, and the lipid parameter at baseline as covariate.

End point type	Primary

End point timeframe:

Baseline (Visit 2) and after 12 weeks of treatment (Visit 4).

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis tested superiority for the following treatment comparisons for percentage change in TG from baseline at 12 weeks:
- FC fenofibrate/simvastatin 145/20 mg vs Simvastatin 20 mg
- FC fenofibrate/simvastatin 145/40 mg vs Simvastatin 40 mg
- Feno/Simv 145/20 mg + Feno/Simv 145/40 mg vs Simvastatin 20 mg + Simvastatin 40 mg.
Therefore the reporting arm Fenofibrate 145 mg was not included in this endpoint.

End point values	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg	Simvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	102	97	101
Units: Percentage change				
least squares mean (standard error)	-32.484 (± 3.400)	7.766 (± 3.288)	-29.265 (± 3.363)	-5.155 (± 3.303)

End point values	Feno/Simv 145/20 mg + Feno/Simv 145/40 mg	Simvastatin 20 mg + Simvastatin 40 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	203		
Units: Percentage change				
least squares mean (standard error)	-30.874 (± 2.442)	1.305 (± 2.379)		

Statistical analyses

Statistical analysis title	All FC Feno/Simv vs all Simvastatin Monotherapy

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin (fenofibrate/simvastatin 145/20 mg and 145/40 mg) versus simvastatin monotherapy (simvastatin 20 mg and 40 mg). Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Feno/Simv 145/20 mg + Feno/Simv 145/40 mg v Simvastatin 20 mg + Simvastatin 40 mg
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-32.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.61
upper limit	-25.75

Statistical analysis title	Feno/Simv 145/20 mg vs Simvastatin 20 mg

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin 145/20 mg versus simvastatin 20 mg monotherapy. Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Fenofibrate/Simvastatin 145/20 mg v Simvastatin 20 mg
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-40.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.339
upper limit	-31.161

Statistical analysis title	Feno/Simv 145/40 mg vs Simvastatin 40 mg

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin 145/40 mg versus simvastatin 40 mg monotherapy. Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Fenofibrate/Simvastatin 145/40 mg v Simvastatin 40 mg
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-24.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.194
upper limit	-15.025

Primary: Percentage LS Mean Change from Baseline in Serum LDL-C Level at 12

Weeks

End point title	Percentage LS Mean Change from Baseline in Serum LDL-C Level at 12 Weeks[3]

End point description:

The baseline value was defined as the mean of the lipid measured in the blood samples collected at the inclusion visit (Visit 1) and at the randomization visit (Visit 2). The endpoint value was defined as the last non-missing value assigned to treatment for the subject. The LS mean percentage change from baseline in LDL-C levels after 12 weeks of treatment are presented for the FA subject sample which consisted of all subjects who were allocated to treatment, received at least one dose of investigational study drug and had data for at least one post-baseline assessment of any efficacy measurement (TG, HDL-C or LDL-C) before or at Visit 4. The LS mean of the percentage change from baseline at 12 weeks was determined using an MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as fixed factors, and the lipid parameter at baseline as covariate.

End point type	Primary

End point timeframe:

Baseline (Visits 1 and 2) and after 12 weeks of treatment (Visit 4).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis tested superiority for the following treatment comparisons for percentage change in LDL-C from baseline at 12 weeks:
- FC fenofibrate/simvastatin 145/20 mg vs Fenofibrate 145 mg
- FC fenofibrate/simvastatin 145/40 mg vs Fenofibrate 145 mg
- Feno/Simv 145/20 mg + Feno/Simv 145/40 mg vs Simvastatin 20 mg + Simvastatin 40 mg.
Therefore the reporting arms Simvastatin 20 mg and Simvastatin 40 mg were not included in this endpoint.

End point values	Fenofibrate/Simvastatin 145/20 mg	Fenofibrate/Simvastatin 145/40 mg	Fenofibrate 145 mg	Feno/Simv 145/20 mg + Feno/Simv 145/40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	96	97	93	193
Units: Percentage change				
least squares mean (standard error)	-0.352 (± 2.577)	-8.561 (± 2.550)	30.200 (± 2.616)	-4.457 (± 1.852)

Statistical analyses

Statistical analysis title	All FC Feno/Simv vs Fenofibrate Monotherapy

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin (fenofibrate/simvastatin 145/20 mg and 145/40 mg) versus fenofibrate 145 mg monotherapy. Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Fenofibrate 145 mg v Feno/Simv 145/20 mg + Feno/Simv 145/40 mg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-34.657

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.775
upper limit	-28.539

Statistical analysis title	Feno/Simv 145/20 mg vs Fenofibrate Monotherapy

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin 145/20 mg versus fenofibrate 145 mg monotherapy. Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Fenofibrate/Simvastatin 145/20 mg v Fenofibrate 145 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-30.552
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.595
upper limit	-23.509

Statistical analysis title	Feno/Simv 145/40 mg vs Fenofibrate Monotherapy

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin 145/40 mg versus fenofibrate 145 mg monotherapy. Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Fenofibrate/Simvastatin 145/40 mg v Fenofibrate 145 mg
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-38.761
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.797
upper limit	-31.725

Primary: Percentage LS Mean Change from Baseline in Serum HDL-C Level at 12

Weeks

End point title	Percentage LS Mean Change from Baseline in Serum HDL-C Level at 12 Weeks[4]

End point description:

The baseline value was defined as the mean of the lipid measured in the blood samples collected at the inclusion visit (Visit 1) and at the randomization visit (Visit 2). The endpoint value was defined as the last non-missing value assigned to treatment for the subject. The LS mean percentage change from baseline in HDL-C levels after 12 weeks of treatment are presented for the FA subject sample which consisted of all subjects who were allocated to treatment, received at least one dose of investigational study drug and had data for at least one post-baseline assessment of any efficacy measurement (TG, HDL-C or LDL-C) before or at Visit 4. The LS mean of the percentage change from baseline at 12 weeks was determined using an MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as fixed factors, and the lipid parameter at baseline as covariate.

End point type	Primary

End point timeframe:

Baseline (Visits 1 and 2) and after 12 weeks of treatment (Visit 4).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis tested superiority for the following treatment comparisons for percentage change in HDL-C from baseline at 12 weeks:
- FC fenofibrate/simvastatin 145/20 mg vs Simvastatin 20 mg
- FC fenofibrate/simvastatin 145/40 mg vs Simvastatin 40 mg
- Feno/Simv 145/20 mg + Feno/Simv 145/40 mg vs Simvastatin 20 mg + Simvastatin 40 mg.
Therefore the reporting arm Fenofibrate 145 mg was not included in this endpoint.

End point values	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg	Simvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	102	97	101
Units: Percentage change				
least squares mean (standard error)	9.660 (± 1.457)	1.288 (± 1.406)	10.045 (± 1.441)	3.445 (± 1.417)

End point values	Feno/Simv 145/20 mg + Feno/Simv 145/40 mg	Simvastatin 20 mg + Simvastatin 40 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	203		
Units: Percentage change				
least squares mean (standard error)	9.852 (± 1.046)	2.367 (± 1.019)		

Statistical analyses

Statistical analysis title	All FC Feno/Simv vs all Simvastatin Monotherapy

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin (fenofibrate/simvastatin 145/20 mg and 145/40 mg) versus simvastatin monotherapy (simvastatin 20 mg and 40 mg). Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Feno/Simv 145/20 mg + Feno/Simv 145/40 mg v Simvastatin

	20 mg + Simvastatin 40 mg
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	7.486
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.731
upper limit	10.24

Statistical analysis title	Feno/simv 145/20 mg vs simvastatin 20 mg

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin 145/20 mg versus simvastatin 20 mg monotherapy. Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Fenofibrate/Simvastatin 145/20 mg v Simvastatin 20 mg
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	8.372
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.479
upper limit	12.265

Statistical analysis title	Feno/simv 145/40 mg vs Simvastatin 40 mg

Statistical analysis description:

Comparison of FC fenofibrate/simvastatin 145/40 mg versus simvastatin 40 mg monotherapy. Analysis was based on a MMRM analysis with treatment group, visit, gender, country and treatment by visit interaction as factors and lipid parameter at baseline as covariate.

Comparison groups	Fenofibrate/Simvastatin 145/40 mg v Simvastatin 40 mg
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	6.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.707
upper limit	10.492

Secondary: Percentage Change from Baseline in Serum Non-HDL-C, Total Cholesterol (TC), Apolipoprotein A-I (ApoAI), Apolipoprotein B (ApoB) and High-sensitivity C-reactive Protein (hsCRP) at 12 Weeks

End point title	Percentage Change from Baseline in Serum Non-HDL-C, Total Cholesterol (TC), Apolipoprotein A-I (ApoAI), Apolipoprotein B (ApoB) and High-sensitivity C-reactive Protein (hsCRP) at 12 Weeks

End point description:

The baseline value was defined as the last non-missing value collected before first study drug administration at the randomization visit (Visit 2). The endpoint value was defined as the last non-missing value assigned to treatment for the subject. The mean percentage changes from baseline in non-HDL-C, TC, ApoAI, ApoB and hsCRP levels after 12 weeks of treatment are presented for the FA subject sample which consisted of all subjects who were allocated to treatment, received at least one dose of investigational study drug and had data for at least one post-baseline assessment of any efficacy measurement (TG, HDL-C or LDL-C) before or at Visit 4.
n = number of subjects with data analysed for each parameter.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) and after 12 weeks of treatment (Visit 4).

End point values	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg	Simvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	114	110	112
Units: Percentage change				
arithmetic mean (standard deviation)				
Non-HDL-C (n=96, 102, 97, 101, 93)	-7.938 (± 21.031)	0.382 (± 24.739)	-13.722 (± 25.892)	-8.655 (± 21.656)
TC (n=96, 102, 97, 101, 93)	-3.921 (± 15.917)	0.014 (± 18.268)	-8.347 (± 19.304)	-6.515 (± 16.574)
ApoAI (n=94, 101, 95, 100, 93)	3.592 (± 15.153)	2.829 (± 13.664)	5.449 (± 12.209)	2.678 (± 9.990)
ApoB (n=94, 101, 95, 100, 93)	-7.268 (± 22.506)	-1.069 (± 23.109)	-9.427 (± 24.170)	-4.526 (± 24.785)
hsCRP (n=94, 101, 95, 101, 93)	36.777 (± 217.732)	88.114 (± 270.344)	-9.039 (± 64.811)	33.687 (± 170.088)

End point values	Fenofibrate 145 mg			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: Percentage change				

arithmetic mean (standard deviation)				
Non-HDL-C (n=96, 102, 97, 101, 93)	16.003 (± 28.801)			
TC (n=96, 102, 97, 101, 93)	13.540 (± 20.133)			
ApoAI (n=94, 101, 95, 100, 93)	6.122 (± 14.105)			
ApoB (n=94, 101, 95, 100, 93)	15.026 (± 28.617)			
hsCRP (n=94, 101, 95, 101, 93)	60.909 (± 195.658)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Lipid Level Responders for TG, LDL-C and Non-HDL-C at 12 Weeks

End point title	Percentage of Lipid Level Responders for TG, LDL-C and Non-HDL-C at 12 Weeks[5]

End point description:

The percentage of subjects who met the target levels of lipids for TG, LDL-C and non-HDL-C after 12 weeks of treatment is presented (defined as lipid level responders). The target lipid levels were as follows:
TG: < 150 milligrams per deciliter (mg/dL) in very high and high CV risk subjects.
LDL-C: < 70 mg/dL or a >= 50% reduction from baseline in very high CV risk subjects and < 100 mg/dL in high CV risk subjects.
Non-HDL-C: < 100 mg/dL in very high CV risk subjects and < 130 mg/dL in high CV risk subjects.

Percentages are based on the number of subjects with data available in the FA subject sample which consisted of all subjects who were allocated to treatment, received at least one dose of investigational study drug and had data for at least one post-baseline assessment of any efficacy measurement (TG, HDL-C or LDL-C) before or at Visit 4.

End point type	Secondary

End point timeframe:

After 12 weeks of treatment (Visit 4).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary endpoint assessed the effect of treatment with fenofibrate or simvastatin monotherapy and combined fenofibrate and simvastatin treatment on target lipid levels in the following reporting groups only:
- Fenofibrate 145 mg
- Feno/Simv 145/20 mg + Feno/Simv 145/40 mg
- Simvastatin 20 mg + Simvastatin 40 mg

End point values	Fenofibrate 145 mg	Feno/Simv 145/20 mg + Feno/Simv 145/40 mg	Simvastatin 20 mg + Simvastatin 40 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	93	192	202	
Units: Percentage of responders				
number (not applicable)				
TG Responders	33.3	47.9	20.8	
LDL-C Responders	4.5	16.4	19.0	

Non-HDL-C Responders	9.0	28.8	25.2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from randomization (Visit 2) until 30 days after the treatment was completed (Visit 4).

Adverse event reporting additional description:

The Safety subject sample consisted of all subjects who were allocated to treatment and received at least one dose of investigational study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Fenofibrate/Simvastatin 145/20 mg

Reporting group description:

In Part A subjects were randomized to receive FC fenofibrate/simvastatin 145/20 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 20 mg capsules and placebo fenofibrate 145 mg tablets.

Reporting group title	Simvastatin 20 mg

Reporting group description:

In Part A subjects were randomized to receive simvastatin 20 mg capsules once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo fenofibrate 145 mg tablets.

Reporting group title	Fenofibrate/Simvastatin 145/40 mg

Reporting group description:

In Part B subjects were randomized to receive FC fenofibrate/simvastatin 145/40 mg tablets once daily for 12 +/- 1 weeks. Subjects also received placebo simvastatin 40 mg capsules and placebo fenofibrate 145 mg tablets.

Reporting group title	Simvastatin 40 mg

Reporting group description:

In Part B subjects were randomized to receive simvastatin 40 mg capsules once daily for 12 +/- 1 weeks. Subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo fenofibrate 145 mg tablets.

Reporting group title	Fenofibrate 145 mg

Reporting group description:

In Part A and in Part B subjects were randomized to receive fenofibrate 145 mg tablets once daily for 12 +/- 1 weeks. In Part A, subjects also received placebo FC fenofibrate/simvastatin 145/20 mg tablets and placebo simvastatin 20 mg capsules. In Part B, subjects also received placebo FC fenofibrate/simvastatin 145/40 mg tablets and placebo simvastatin 40 mg capsules.

Serious adverse events	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 111 (2.70%)	3 / 117 (2.56%)	3 / 113 (2.65%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	1	1
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple injuries			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 117 (0.85%)	0 / 113 (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
Angina pectoris			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 111 (0.90%)	0 / 117 (0.00%)	0 / 113 (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
Surgical and medical procedures			
Diabetes mellitus management			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	0 / 113 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 111 (0.90%)	0 / 117 (0.00%)	0 / 113 (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
Loss of consciousness			
subjects affected / exposed	0 / 111 (0.00%)	1 / 117 (0.85%)	0 / 113 (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

Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	1 / 113 (0.88%)
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			
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 111 (0.90%)	0 / 117 (0.00%)	0 / 113 (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			
Bursitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	0 / 113 (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			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	0 / 113 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 111 (0.00%)	0 / 117 (0.00%)	0 / 113 (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
Diabetes mellitus			

subjects affected / exposed	0 / 111 (0.00%)	1 / 117 (0.85%)	0 / 113 (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

Serious adverse events	Simvastatin 40 mg	Fenofibrate 145 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 115 (0.87%)	3 / 112 (2.68%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 115 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Diabetes mellitus management			

subjects affected / exposed	1 / 115 (0.87%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			

subjects affected / exposed	0 / 115 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 115 (0.87%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 115 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 115 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Fenofibrate/Simvastatin 145/20 mg	Simvastatin 20 mg	Fenofibrate/Simvastatin 145/40 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 111 (6.31%)	7 / 117 (5.98%)	4 / 113 (3.54%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 111 (3.60%)	0 / 117 (0.00%)	1 / 113 (0.88%)
occurrences (all)	4	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 111 (0.90%)	2 / 117 (1.71%)	2 / 113 (1.77%)
occurrences (all)	1	2	2
Dyspepsia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 117 (0.00%)	0 / 113 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 111 (0.00%)	3 / 117 (2.56%)	0 / 113 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 117 (0.00%)	1 / 113 (0.88%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	1 / 111 (0.90%)	2 / 117 (1.71%)	0 / 113 (0.00%)
occurrences (all)	1	3	0

Non-serious adverse events	Simvastatin 40 mg	Fenofibrate 145 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 115 (7.83%)	12 / 112 (10.71%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 115 (0.87%)	1 / 112 (0.89%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 115 (0.00%)	5 / 112 (4.46%)	
occurrences (all)	0	5	
Dyspepsia			
subjects affected / exposed	4 / 115 (3.48%)	1 / 112 (0.89%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 115 (0.87%)	1 / 112 (0.89%)	
occurrences (all)	2	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 115 (2.61%)	3 / 112 (2.68%)	
occurrences (all)	3	3	
Gastroenteritis			
subjects affected / exposed	0 / 115 (0.00%)	4 / 112 (3.57%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2012	- Withdrawal criteria were clarified to include reasons for study treatment discontinuation: Aspartate aminotransferase and alanine aminotransferase levels after a repeated measurement increase to more than three times the upper limit of normal, diffuse myalgia, myositis, muscle cramps and/or a significant increase in creatine kinase (to more than five times the upper limit of normal) after a repeated measurement indicating myotoxicity. - Amendments were made in relation to justification of the sample size and global study power. The sample size was not changed but the global study power was increased from 90% to 93.2%. The mean difference in percentage change from baseline to 12 weeks treatment the trial was set up to detect HDL-C was updated to 6.5% from 7%.
16 July 2012	- Clarification that the laboratory results for lipid parameters (TG, LDL-C, HDL-C and non-HDL-C) measured at Visits 3 and 4 during the blinded study period would not be provided to the investigators or trial physician, clinical study manager or trial monitors. The investigator was also instructed not to request laboratory tests for these lipid parameters to be done locally for their patients participating in the study. - The rescreening process between Visits 1 and 2 was clarified. Rescreening was not permitted if the safety laboratory results obtained at Visit 1 did not meet the inclusion/randomization criteria, and the subject was considered a screen failure. Rescreening of a subject after at least one week was allowed if one or both lipid criteria values obtained from Visit 1 did not meet the inclusion/randomization criteria. The condition for retesting was the lipid criteria value was outside +/-5% of the range for inclusion, all lipids measured were repeated. Sponsor authorization for retesting was also no longer required. - Recommendations on the contraceptive methods to be used by women of childbearing potential were added to the protocol.
11 December 2012	- Following the split of Abbott into two companies effective as of 1 January 2013, the name of the Sponsor changed from Fournier Laboratories Ireland Limited to Abbott Laboratories Ireland Limited.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported