



## Clinical trial results:

**A phase III, two-armed, randomised, double blind, parallel study to compare the efficacy and safety in high CHD-risk patients with mixed dyslipidaemia of a 12-week administration of a fixed dose combination of Fenofibrate 160 mg and Pravastatin 40 mg (PRAVAFENIX®) versus Atorvastatin 20 mg.**

### Summary

EudraCT number	2012-000575-17
Trial protocol	BG LV HR
Global end of trial date	16 March 2015

### Results information

Result version number	v1 (current)
This version publication date	26 March 2016
First version publication date	26 March 2016

### Trial information

#### Trial identification

Sponsor protocol code	FENOPRA-III-12-1
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Laboratoires SMB S.A.
Sponsor organisation address	Rue de la Pastorale, 26-28, Brussels, Belgium, 1080
Public contact	CLINICAL DEPARTMENT, LABORATOIRES SMB S.A., 32 2 412 09 93, clinique@smb.be
Scientific contact	CLINICAL DEPARTMENT, LABORATOIRES SMB S.A., 32 2 412 09 93, clinique@smb.be

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	07 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2015
Global end of trial reached?	Yes
Global end of trial date	16 March 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of the present study is to demonstrate the non-inferiority of the efficacy of Fenofibrate 160 mg/Pravastatin 40 mg fixed combination (PRAVAFENIX®) versus Atorvastatin 20 mg, in high CHD-risk patients with mixed dyslipidaemia not at goals on Atorvastatin 10 mg regarding TG (between 150 mg/dl and 600 mg/dl) and HDL-C (< 40 mg/dl for male and < 50 mg/dl for female).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Guidelines, Directive 2001/20/EC of the European Parliament and the most recent version of the declaration of Helsinki (64th WMA General Assembly, Fortaleza, October 2013).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 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	Romania: 100
Country: Number of subjects enrolled	Georgia: 14
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 241
Country: Number of subjects enrolled	Bosnia and Herzegovina: 1
Country: Number of subjects enrolled	Croatia: 16
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Latvia: 34
Worldwide total number of subjects	430
EEA total number of subjects	174

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)	319
From 65 to 84 years	111
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 7 countries between October 2012 and March 2015. 82 sites were activated and 75 sites were active and screened at least one patient. The patients were randomized (Fenofibrate 160 mg/Pravastatin 40 mg fixed dose combination or Atorvastatin 20 mg) after a run-in period of 8 weeks under atorvastatin 10 mg.

### Pre-assignment

Screening details:

- Obtain signed ICF
- Confirmation of mixed dislipidaemia
- Demographic data, Medical history, Physical Examination, Vital signs
- Review Diet compliance
- Contraceptive method
- Laboratory test
- Prior & Concomitant medication review
- Review of inclusion/exclusion criteria

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Atorvastatin 20 mg

Arm description: -

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

Dosage and administration details:

Atorvastatin 20 mg (ATORSTATINEG® or TOTALIP®), one blinded capsule, taken once a day orally.

<b>Arm title</b>	Pravafenix 160/40 mg
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fenofibrate 160 mg / Pravastatin 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Fenofibrate 160 mg/Pravastatin 40 mg fixed dose combination (PRAVAFENIX®), one capsule, taken once a day orally.

<b>Number of subjects in period 1</b>	Atorvastatin 20 mg	Pravafenix 160/40 mg
Started	215	215
Completed	209	207
Not completed	6	8
Consent withdrawn by subject	3	1
Adverse event, non-fatal	-	4
Other	1	-
Protocol deviation	2	3

## Baseline characteristics

### Reporting groups

Reporting group title	Efficacy Phase
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Reporting group description: -

Reporting group values	Efficacy Phase	Total	
Number of subjects	430	430	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	319	319	
From 65-84 years	111	111	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	58.62		
standard deviation	± 10.22	-	
Gender categorical			
Units: Subjects			
Female	215	215	
Male	215	215	

## End points

### End points reporting groups

Reporting group title	Atorvastatin 20 mg
Reporting group description: -	
Reporting group title	Pravafenix 160/40 mg
Reporting group description: -	

### Primary: Mean percent change in plasma non-HDL cholesterol at week 12 compared to the baseline

End point title	Mean percent change in plasma non-HDL cholesterol at week 12 compared to the baseline
End point description:	
End point type	Primary
End point timeframe:	
Week 12 compared to the baseline value.	

End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	173		
Units: percent				
arithmetic mean (standard deviation)	-2.79 (± 25.42)	7.83 (± 30.29)		

### Statistical analyses

Statistical analysis title	A student t-test
Comparison groups	Pravafenix 160/40 mg v Atorvastatin 20 mg
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.94
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.94
Variability estimate	Standard deviation

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**Secondary: Mean percent change in HDL-C at W12 compared to baseline**

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End point title	Mean percent change in HDL-C at W12 compared to baseline
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End point description:

End point type	Secondary
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End point timeframe:

Week 12 compared to baseline in HDL-C.

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End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	173		
Units: percent				
arithmetic mean (standard deviation)	11.86 (± 33.6)	18.1 (± 25.78)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Mean percent change in LDL at week 12 compared to baseline**

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End point title	Mean percent change in LDL at week 12 compared to baseline
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End point description:

End point type	Secondary
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End point timeframe:

Week 12 compared to baseline

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End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	173		
Units: percent				
arithmetic mean (standard deviation)	5.46 (± 35.38)	26.88 (± 38.14)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Mean percent change in cholesterol at week 12 compared to baseline**

End point title	Mean percent change in cholesterol at week 12 compared to baseline
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End point description:

End point type	Secondary
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End point timeframe:

Week 12 compared to baseline

End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	173		
Units: percent				
arithmetic mean (standard deviation)	0.15 (± 20.75)	9.65 (± 23.32)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Mean percent change in TG at week 12 compared to baseline**

End point title	Mean percent change in TG at week 12 compared to baseline
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End point description:

End point type	Secondary
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End point timeframe:

Week 12 compared to baseline

End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	173		
Units: percent				
arithmetic mean (standard deviation)	-11.62 (± 36.47)	-26.4 (± 36.6)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Mean percent change in ApoA1 at week 12 compared to baseline**

End point title	Mean percent change in ApoA1 at week 12 compared to
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baseline
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End point description:

End point type	Secondary
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End point timeframe:

Week 12 compared to baseline

End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	168		
Units: percent				
arithmetic mean (standard deviation)	1.7 (± 16.83)	8.63 (± 16.36)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean percent change in ApoB at week 12 compared to baseline

End point title	Mean percent change in ApoB at week 12 compared to baseline
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End point description:

End point type	Secondary
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End point timeframe:

Week 12 compared to baseline

End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	168		
Units: percent				
arithmetic mean (standard deviation)	-1.75 (± 23.9)	8.7 (± 27.19)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean percent change in ApoB/ApoA1 ratio at week 12 compared to baseline

End point title	Mean percent change in ApoB/ApoA1 ratio at week 12 compared to baseline
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End point description:

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End point type	Secondary
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End point timeframe:

Week 12 compared to baseline

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End point values	Atorvastatin 20 mg	Pravafenix 160/40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	168		
Units: percent				
arithmetic mean (standard deviation)	-1.96 (± 25.08)	1.64 (± 26.48)		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Efficacy period (12 weeks).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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### Reporting groups

Reporting group title	Atorvastatin 20 mg (arm 1)
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Reporting group description: -

Reporting group title	Pravafenix 160/40 mg (arm 2)
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No adverse event reach the incidence of 5% in any of the study groups.

Serious adverse events	Atorvastatin 20 mg (arm 1)	Pravafenix 160/40 mg (arm 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 215 (0.47%)	0 / 215 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
ISCHAEMIC CARDIOMYOPATHY			
subjects affected / exposed	1 / 215 (0.47%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atorvastatin 20 mg (arm 1)	Pravafenix 160/40 mg (arm 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 215 (0.00%)	0 / 215 (0.00%)	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2012	The purpose of the protocol version 2.0 was to notify a change concerning the secondary packaging for the run-in treatment. In fact the run-in treatments were packaged in bottles and not in boxes as mentioned in the protocol version 1.0.
19 June 2013	<p>Further to the comments from the Latvian authorities, the protocol and the ICF have been adapted to exclude the oral anticoagulants from the permitted therapies.</p> <p>Oral anticoagulants should be titrated down when initiating treatment with the test treatment PRAVAFENIX® due to potential interaction with fenofibrate. The risk of interactions existed with vitamin K antagonists i.e. oral anticoagulants, namely warfarin, acenocoumarol and phenprocoumon.</p> <p>Titration of the anticoagulant was not feasible in the study as the study medication was blinded during the efficacy phase and statin (the other arm) did not require anticoagulant down titration.</p> <p>To avoid the appearance of any safety issue, it was preferred to non include patients taking oral anticoagulants.</p>
13 September 2013	<p>The sponsor encountered a significant problem to buy the sufficient quantity of AtorstatinEG® (comparator) with an adequate expiry date needed for the replacement of current treatment at sites (scheduled for October 2013). The expiry date of available batches (Mid 2014) did not allow sufficient flexibility in patient recruitment. Therefore the sponsor decided to change the comparator from AtorstatinEG® to Totalip®.</p> <p>The molecule remained the same "Atorvastatin" but the commercial name was different. Totalip® and AtorstatinEG® were generic drugs of the originator Lipitor®. All these tablets were immediate release film-coated tablets with Atorvastatin Calcium salt as Active Ingredient.</p> <p>Posology and route of administration (oral administration, once a day, with or without food) were identical for all the drug formulations.</p> <p>For the run-in phase of the trial the sponsor used tablets of Totalip® 10mg instead of tablets of AtorstatinEG® 10mg but for the efficacy phase of the trial the sponsor used also tablets of Totalip® 10 mg (the blinded capsule will contain 2 tablets of 10mg). Tablet of Totalip® 20 mg cannot be used due to the high size of the tablet.</p> <p>Blinding was not affected by using two 10 mg tablets as the capsules were also filled with microcrystalline cellulose. In-vitro dissolution profiles of blinded capsules (containing either 1 tablet of AtorstatinEG® 20mg or 2 tablets of Totalip® 10 mg) compared to the unblinded tablets were identical.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported