Clinical trial results:
Efficacy and Safety of Fixed-Dose Combination atorvastatin/amlodipine/perindopril versus Fixed-Dose Combination of atorvastatin/ amlodipine in Patients with Hypertension and Dyslipidemia.

Summary

EudraCT number	2014-005378-12
Trial protocol	BG IT
Global end of trial date	08 September 2016

Results information

Result version number	v1 (current)
This version publication date	24 September 2017
First version publication date	24 September 2017

Trial information

Trial identification

Sponsor protocol code	CL3-05153-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1166-2705

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50, rue Carnot, Suresnes, France, 92284
Public contact	Clinical study Department, Institut de Recherches Internationales Servier, + 33155724366, clinicaltrials@servier.com
Scientific contact	Clinical study Department, Institut de Recherches Internationales Servier, + 33155724366, clinicaltrials@servier.com
Sponsor organisation name	Les Laboratoires Servier Representative Office Paveletskaya
Sponsor organisation address	Paveletskaya square 2, building 3, Moscow, Russian Federation,
Public contact	Les Laboratoires Servier Representative Office Paveletskaya, Les Laboratoires Servier Representative Office Paveletskaya, 7 4959374767,
Scientific contact	Les Laboratoires Servier Representative Office Paveletskaya, Les Laboratoires Servier Representative Office Paveletskaya, 7 4959374767,

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	08 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 September 2016
Global end of trial reached?	Yes
Global end of trial date	08 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of oral fixed-dose combination atorvastatin/amlodipine/perindopril versus the reference drug atorvastatin/amlodipine in lowering office sitting systolic blood pressure (SBP) after 12 weeks of treatment versus baseline (W012-W000).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2015
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: 91
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Mexico: 27
Country: Number of subjects enrolled	Poland: 148
Country: Number of subjects enrolled	Russian Federation: 371
Country: Number of subjects enrolled	Ukraine: 138
Worldwide total number of subjects	854
EEA total number of subjects	206

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)	633
From 65 to 84 years	221
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Five patients (1 in Argentina; 1 in Mexico, 2 in Poland and 1 in Russian Federation) who were randomised were not subsequently included.

Pre-assignment

Screening details:

M/F, hypertensive and dyslipidaemic patients, aged 40 to 79 years, naive of treatment, or uncontrolled with antihypertensive monotherapy and/or statin, with inclusion criteria 150 ≤ SBP < 180 mmHg and 95 ≤ DBP < 110 mmHg or isolated systolic hypertension and with 130 ≤ LDL-c < 190 mg/dL with risk of 10-year Atherosclerotic CV Disease ≥ 5%.

Period 1

Period 1 title	W000-W012 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Treatment allocated by a centralized (Interactive System Response) balanced non-adaptive randomisation process, with stratification on country .
S 5153 was supplied as tablets as its matching placebo. Atorvastatin/amlodipine was supplied as capsules as it matching placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	S 5153

Arm description:

Tablets of S 5153 (atorvastatin/amlodipine/perindopril) with doses of 10/5/5 mg, 20/5/5 mg and 20/10/10 mg.

Arm type	Experimental
Investigational medicinal product name	S 5153
Investigational medicinal product code	S 5153
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

-Wash-out period: 2 weeks (3 weeks maximum) without antihypertensive or lipid lowering drugs and without any IMP intake.
At inclusion, the patients randomised to the S 5153 group were allocated a kit comprising tablets of S 5153 10/5/5 mg and capsules of placebo.
At W4, the dose of statin was titrated to 20 mg, as allowed by the level of 10-year ASCVD risk of the patients. Dose of antihypertensive drugs was titrated according to their BP and maintained for 8 weeks until W12 visit (as specified in Amendment No. 2, the up-titrated drug was to be taken from the day of W4 visit, after BP measurement):
-- If BP was not controlled (SBP≥ 140 mmHg or DBP ≥ 90 mmHg), patients were dispensed with a kit of S 5153 20/10/10 mg.
-- If BP was controlled (SBP< 140 mmHg and DBP < 90 mmHg), patients were dispensed with a kit of S 5153 20/5/5 mg.

Arm title	Atorvastatin/amlodipine

Arm description:

Capsules of atorvastatin/amlodipine with doses of 10/5 mg, 20/5 mg and 20/10 mg.

Arm type	Active comparator

Investigational medicinal product name	Atorvastatin/amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Wash-out period: 2 weeks (3 weeks maximum) without antihypertensive or lipid lowering drugs and without any IMP intake.
-At inclusion, the patients randomised to the atorvastatin/amlodipine group were allocated a kit comprising capsules of atorvastatin/amlodipine 10/5 mg and tablets of placebo.
At W4, the dose of statin was titrated to 20 mg, as allowed by the level of 10-year ASCVD risk of the patients. Dose of antihypertensive drug was titrated according to their BP and maintained for 8 weeks until W12 visit (as specified in Amendment No. 2, the up-titrated drug was to be taken from the day of W4 visit, after BP measurement):
-- If BP was not controlled (SBP≥ 140 mmHg or DBP ≥ 90 mmHg), patients were dispensed with a kit of atorvastatin/amlodipine 20/10 mg.
-- If BP was controlled (SBP< 140 mmHg and DBP < 90 mmHg), patients were dispensed with a kit of atorvastatin/amlodipine 20/5 mg.

Number of subjects in period 1	S 5153	Atorvastatin/amlodipine
Started	429	425
Completed	402	401
Not completed	27	24
Adverse event, serious fatal	-	2
Randomised but not included	3	2
Non medical reason	8	7
Adverse event, non-fatal	9	9
Protocol deviation	7	4

Baseline characteristics

Reporting groups	
Reporting group title	S 5153
Reporting group description:	
Tablets of S 5153 (atorvastatin/amlodipine/perindopril) with doses of 10/5/5 mg, 20/5/5 mg and 20/10/10 mg.	
Reporting group title	Atorvastatin/amlodipine
Reporting group description:	
Capsules of atorvastatin/amlodipine with doses of 10/5 mg, 20/5 mg and 20/10 mg.	

Reporting group values	S 5153	Atorvastatin/amlodipine	Total
Number of subjects	429	425	854
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)	315	318	633
From 65-84 years	114	107	221
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	58.1	57.7	
standard deviation	± 8.7	± 8.9	-
Gender categorical Units: Subjects			
Female	241	234	475
Male	188	191	379
Type of dyslipidaemia Units: Subjects			
Hypercholesterolaemia	242	235	477
Mixed dyslipidaemia	187	190	377
Hypertension duration Units: months			
arithmetic mean	79.2	73.9	
standard deviation	± 92.2	± 83.2	-
10-year ASCVD risk Units: percent			
arithmetic mean	15.7	15.7	
standard deviation	± 8.8	± 9.4	-
Dyslipidaemia duration Units: months			
arithmetic mean	32.8	31	

standard deviation	± 50.1	± 45.8	-
Sitting SBP			
Units: mmHg			
arithmetic mean	163.1	163.7	
standard deviation	± 7.5	± 7.1	-
Sitting DBP			
Units: mmHg			
arithmetic mean	95.2	95.7	
standard deviation	± 10.4	± 9.5	-
LDL-Cholesterol			
Units: mmol/L			
arithmetic mean	4.02	4.03	
standard deviation	± 0.42	± 0.43	-

End points

End points reporting groups

Reporting group title	S 5153
Reporting group description:	
Tablets of S 5153 (atorvastatin/amlodipine/perindopril) with doses of 10/5/5 mg, 20/5/5 mg and 20/10/10 mg.	
Reporting group title	Atorvastatin/amlodipine
Reporting group description:	
Capsules of atorvastatin/amlodipine with doses of 10/5 mg, 20/5 mg and 20/10 mg.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
In accordance with the intention-to-treat principle and the Section 5.2.1 of ICH E9 guideline (CPMP/ICH/363/96/step 5, 1998), all patients of the RS having taken at least one dose of IMP and having at least an analysable value at baseline and at least one analysable post-baseline value of mean sitting SBP over W0-W12 period.	

Primary: Change in office sitting SBP from baseline to last post-baseline value

End point title	Change in office sitting SBP from baseline to last post-baseline value
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to last post-baseline value over W000-W012 period.	

End point values	S 5153	Atorvastatin/amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	420		
Units: mmHg				
arithmetic mean (standard deviation)	-31.7 (± 13.8)	-31.6 (± 13.6)		

Statistical analyses

Statistical analysis title	Ancova
Statistical analysis description:	
Between group comparison (S 5153 versus atorvastatin/amlodipine) on the change in office sitting SBP using ANCOVA model, adjusted on fixed, categorical effects of treatment and country, as well as the continuous fixed covariate of baseline.	
Comparison groups	S 5153 v Atorvastatin/amlodipine

Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.83

Secondary: Change in office sitting DBP from baseline to last post-baseline value

End point title	Change in office sitting DBP from baseline to last post-baseline value

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to last post-baseline value over W000-W012 period.

End point values	S 5153	Atorvastatin/amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	420		
Units: mmHg				
arithmetic mean (standard deviation)	-15.9 (± 12.1)	-15.3 (± 11.1)		

Statistical analyses

Statistical analysis title	Ancova

Statistical analysis description:

Between group comparison (S 5153 versus atorvastatin/amlodipine) on the change in DBP using ANCOVA model, adjusted on fixed, categorical effects of treatment and country, as well as the continuous fixed covariate of baseline.

Comparison groups	S 5153 v Atorvastatin/amlodipine

Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.58

Post-hoc: Change in office sitting SBP from baseline to last post-baseline value in patients with grade 2 systolic-diastolic hypertension at baseline

End point title	Change in office sitting SBP from baseline to last post-baseline value in patients with grade 2 systolic-diastolic hypertension at baseline

End point description:

End point type	Post-hoc

End point timeframe:

Change from baseline to last post-baseline value during W000-W012 period.

End point values	S 5153	Atorvastatin/amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	117		
Units: mmHg				
arithmetic mean (standard deviation)	-36.5 (± 10.8)	-34.5 (± 12.5)		

Statistical analyses

Statistical analysis title	Ancova

Statistical analysis description:

Between group comparison (S 5153 versus atorvastatin/amlodipine) on the change in office sitting SBP using ANCOVA model, adjusted on fixed, categorical effects of treatment and country, as well as the continuous fixed covariate of baseline.

Comparison groups	S 5153 v Atorvastatin/amlodipine

Number of subjects included in analysis	241
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.101
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.08
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	1.4

Post-hoc: Change in office sitting DBP from baseline to last post-baseline value in patients with grade 2 systolic-diastolic hypertension at baseline

End point title	Change in office sitting DBP from baseline to last post-baseline value in patients with grade 2 systolic-diastolic hypertension at baseline

End point description:

End point type	Post-hoc

End point timeframe:

Change from baseline to last post-baseline value during W000-W012 period.

End point values	S 5153	Atorvastatin/amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	117		
Units: mmHg				
arithmetic mean (standard deviation)	-24.5 (± 10)	-21.7 (± 9.8)		

Statistical analyses

Statistical analysis title	Ancova

Statistical analysis description:

Between group comparison (S 5153 versus atorvastatin/amlodipine) on the change in DBP using ANCOVA model, adjusted on fixed, categorical effects of treatment and country, as well as the continuous fixed covariate of baseline.

Comparison groups	S 5153 v Atorvastatin/amlodipine

Number of subjects included in analysis	241
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.016
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.38
upper limit	-0.55
Variability estimate	Standard error of the mean
Dispersion value	1.23

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events that occurred, worsened or became serious between the first study drug intake and the last study drug intake + 7 days (both included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	S 5153
Reporting group description: -	
Reporting group title	Atorvastatin/amlodipine
Reporting group description: -	

Serious adverse events	S 5153	Atorvastatin/amlodipine	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 425 (1.41%)	3 / 423 (0.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood potassium increased			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			

subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
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 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			

subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (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: 0 %

Non-serious adverse events	S 5153	Atorvastatin/amlodipine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 425 (17.18%)	96 / 423 (22.70%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Brachiocephalic arteriosclerosis			
subjects affected / exposed	0 / 425 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Haematoma			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	11 / 425 (2.59%)	23 / 423 (5.44%)	
occurrences (all)	13	23	
Peripheral swelling			
subjects affected / exposed	2 / 425 (0.47%)	3 / 423 (0.71%)	
occurrences (all)	2	3	
Asthenia			
subjects affected / exposed	1 / 425 (0.24%)	2 / 423 (0.47%)	
occurrences (all)	1	2	
Drug intolerance			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	

Soft tissue inflammation			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 425 (0.47%)	0 / 423 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	0 / 425 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Rhinitis allergic			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Psychiatric disorders			
Middle insomnia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 425 (2.12%)	8 / 423 (1.89%)	
occurrences (all)	9	8	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 425 (1.88%)	4 / 423 (0.95%)	
occurrences (all)	8	4	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 425 (0.94%)	3 / 423 (0.71%)	
occurrences (all)	4	3	
Creatinine renal clearance decreased			
subjects affected / exposed	3 / 425 (0.71%)	1 / 423 (0.24%)	
occurrences (all)	3	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 425 (0.47%)	2 / 423 (0.47%)	
occurrences (all)	2	2	
Blood potassium increased			

subjects affected / exposed	2 / 425 (0.47%)	1 / 423 (0.24%)	
occurrences (all)	2	1	
Blood creatinine increased			
subjects affected / exposed	1 / 425 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Blood pressure decreased			
subjects affected / exposed	0 / 425 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 425 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Ankle fracture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Radius fracture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Accidental overdose			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Overdose			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	2	
Rib fracture			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Thermal burn			

subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	1 / 425 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Sinus tachycardia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 425 (0.47%)	6 / 423 (1.42%)	
occurrences (all)	2	6	
Dizziness			
subjects affected / exposed	2 / 425 (0.47%)	1 / 423 (0.24%)	
occurrences (all)	2	1	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Haemorrhagic diathesis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Dyspepsia			
subjects affected / exposed	2 / 425 (0.47%)	3 / 423 (0.71%)	
occurrences (all)	2	3	
Food poisoning			
subjects affected / exposed	1 / 425 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 425 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	2 / 425 (0.47%)	0 / 423 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	1 / 425 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Swelling face			

subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 425 (0.24%)	2 / 423 (0.47%)	
occurrences (all)	1	4	
Back disorder			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Periostitis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	0 / 425 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 425 (1.88%)	13 / 423 (3.07%)	
occurrences (all)	8	13	
Respiratory tract infection			
subjects affected / exposed	3 / 425 (0.71%)	0 / 423 (0.00%)	
occurrences (all)	3	0	
Respiratory tract infection viral			

subjects affected / exposed	2 / 425 (0.47%)	1 / 423 (0.24%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	1 / 425 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 425 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	0 / 425 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Pulpitis dental			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Viral pharyngitis			
subjects affected / exposed	0 / 425 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 425 (0.47%)	7 / 423 (1.65%)	
occurrences (all)	2	7	
Hypercholesterolaemia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2015	-Amendment No. 1 was applicable in all countries. It mainly concerned: - Precisions on the upper limits of biological parameters of triglycerides and kaliaemia, above which the patient was not to be selected or included. - Precisions on the measurements of the blood pressure - Notification of approval of Triveram® (S 5153) in Europe. - Precisions on ERIN notifications. - Precisions on e-CRF completion.
10 February 2016	Amendment No. 2 was applicable in all countries. It mainly concerned: - Precisions on the limits of blood pressure values for selection. - Notification of approved SmPC of Triveram. - Precision that the first study drug intake should be the day after randomisation, at home, before breakfast. - Blood pressure measurement: if the difference between 2 consecutive SBP measurements was larger than or equal to 15 mmHg, then the set of 3 measurements should not be considered as valid and all 3 measurements were to be repeated after an additional 5 minutes of rest.
15 April 2016	Amendment No. 3 was applicable in all countries. It modified the estimated standard deviation (from 11.9 mmHg to 13.0 mmHg) and consequently re evaluated the number of patients to be included in the study (from 700 to 830).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported