Clinical trial results:
Safety and efficacy of fixed dose combination of Indapamide SR 1.5 mg / Amlodipine versus Valsartan / Amlodipine over 12-week of treatment with conditional titration based on the blood pressure control, in patients with uncontrolled essential hypertension after 1 month of Amlodipine 5 mg run-in treatment. An international, randomized, double-blind, multicenter controlled study.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-001690-84
Trial protocol	GB HU LT LV BG PL
Global end of trial date	27 February 2015

Results information

Result version number	v1 (current)
This version publication date	15 July 2016
First version publication date	15 July 2016

Trial information

Trial identification

Sponsor protocol code	CL3-05520-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1139-9138

Notes:

Sponsors

Sponsor organisation name	Institut de Recherche Internationale Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France,
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Sponsor organisation name	Les Laboratoires Servier Representative Office Paveletskaya
Sponsor organisation address	Paveletskaya square 2, builiding 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,
Sponsor organisation name	Servier United Kingdom

Sponsor organisation address	Framewood road, Slough, United Kingdom,
Public contact	Servier United Kingdom, Servier United Kingdom, 44 1753663456,
Scientific contact	Servier United Kingdom, Servier United Kingdom, 44 1753663456,

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	27 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2015
Global end of trial reached?	Yes
Global end of trial date	27 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To demonstrate better efficacy of fixed-dose combination strategy Indapamide SR 1.5 mg/Amlodipine versus Valsartan/Amlodipine fixed-dose in lowering office systolic blood pressure at W12.

Protection of trial subjects:

Controlled hypertension was defined according to the hypertension management guidelines (WHO/ISH, 2003; ESC, 2009) and was in accordance with the recent guideline of The task force for the management of arterial hypertension of the ESH and of the ESC (2013), as the blood pressure values were under the following targets: SBP < 140 mmHg and DBP < 90 mmHg.A run-in period of 4 weeks was dedicated to confirm the essential uncontrolled hypertension under patient’s amlodipine 5 mg treatment.

Study treatment should be prematurely and definitively discontinued for a participant for one of the following reasons:
- Patients who at the W6 visit had the SBP >= 180 mmHg or DBP >= 110 mmHg (mean of the last 2 out of 3 measurements).
- Onset of adverse event, which presented a risk for the patient according to the investigator or requires prescription of a treatment incompatible with the protocol.
- Onset of an adverse event which, according to the investigator, made it unsafe for the patient to continue with the study treatment. This included clinically significant abnormal biochemical and haematological parameters, or clinically significant ECG abnormality (except LVH).
- ALAT or ASAT>= 1.5 times the upper limit of normal laboratory range.
- Pregnancy.
- Major protocol deviation preventing the analysis of the main endpoint, or which, in the opinion of the investigator, made it unsafe for the patient to continue to take the study medication and to stay in the study.
- Non- medical reason (patient’s personal decision to stop treatment).

Background therapy: -

Evidence for comparator:

Among a wide number of fixed dual combination marketed worldwide for the treatment of hypertension, valsartan/amlodipine already registered since 2007 in Europe is one of the most commonly prescribed.

Actual start date of recruitment	04 July 2013
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	Poland: 60
Country: Number of subjects enrolled	Bulgaria: 67
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Latvia: 34
Country: Number of subjects enrolled	Lithuania: 31
Country: Number of subjects enrolled	Romania: 41
Country: Number of subjects enrolled	Argentina: 51
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Russian Federation: 56
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Ukraine: 66
Country: Number of subjects enrolled	Vietnam: 30
Worldwide total number of subjects	473
EEA total number of subjects	240

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)	355
From 65 to 84 years	114
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

An Open label run-in period (4 weeks) was dedicated to confirm the essential uncontrolled hypertension under treatment with amlodipine 5 mg over 4 weeks, in order to check the baseline evaluations. Only eligible patients having still an uncontrolled hypertension under amlodipine 5 mg were randomised to Investigational Medicine Products (IMP).

Period 1

Period 1 title	Double-blind treatment period (12 weeks) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Indapamide/Amlodipine

Arm description:

Indapamide slow release 1.5mg / Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Indapamide slow release 1.5mg / Amlodipine 10 mg, at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

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

Dosage and administration details:

Indapamide SR 1.5 mg/amlodipine 5 mg single pill fixe dose combination administered orally as one tablet daily, and possibly from W6 in case of up-titration for non-controlled patients: Indapamide SR 1.5 mg/amlodipine 10 mg single pill fixe dose combination administered orally as one tablet daily

Arm title	Valsartan/Amlodipine

Arm description:

Valsartan 80 mg/Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Valsartan 160 mg/Amlodipine 5 mg, at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

Arm type	Active comparator
Investigational medicinal product name	Valsartan/Amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Valsartan 80 mg/amlodipine 5 mg single pill fixe dose combination administered orally as one capsule daily, and possibly from W6 in case of up-titration for non-controlled patients: Valsartan 160 mg/amlodipine 5 mg single pill fixe dose combination administered orally as one capsule daily.

Number of subjects in period 1	Indapamide/Amlodipine	Valsartan/Amlodipine
Started	237	236
Completed	220	223
Not completed	17	13
Adverse event, non-fatal	3	-
non-medical reasons	7	5
Protocol deviation	7	7
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Indapamide/Amlodipine

Reporting group description:

Indapamide slow release 1.5mg / Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Indapamide slow release 1.5mg / Amlodipine 10 mg, at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

Reporting group title	Valsartan/Amlodipine

Reporting group description:

Valsartan 80 mg/Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Valsartan 160 mg/Amlodipine 5 mg, at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

Reporting group values	Indapamide/Amlodipine	Valsartan/Amlodipine	Total
Number of subjects	237	236	473
Age categorical			
Results of demographic data are provided in the Full Analysis Set.			
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)	182	173	355
From 65-84 years	53	61	114
85 years and over	2	2	4
Age continuous			
Units: years			
arithmetic mean	57.4	57.3	
standard deviation	± 10.7	± 11.9	-
Gender categorical			
Results of demographic data are provided in the Full Analysis Set.			
Units: Subjects			
Female	116	116	232
Male	121	120	241

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the intention-to-treat principle and ICH E9 guideline, this set corresponded to all patients of the RS who received at least one dose of study treatment and who had at least one baseline analysable value and one post-baseline analysable value for Supine Systolic Blood Pressure.

Reporting group values	Full Analysis Set		
Number of subjects	465		
Age categorical			
Results of demographic data are provided in the Full Analysis Set.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	348		
From 65-84 years	113		
85 years and over	4		
Age continuous			
Units: years			
arithmetic mean	57.3		
standard deviation	± 11.3		
Gender categorical			
Results of demographic data are provided in the Full Analysis Set.			
Units: Subjects			
Female	228		
Male	237		

End points

End points reporting groups

Reporting group title	Indapamide/Amlodipine

Reporting group description:

Indapamide slow release 1.5mg / Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Indapamide slow release 1.5mg / Amlodipine 10 mg, at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

Reporting group title	Valsartan/Amlodipine

Reporting group description:

Valsartan 80 mg/Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Valsartan 160 mg/Amlodipine 5 mg, at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the intention-to-treat principle and ICH E9 guideline, this set corresponded to all patients of the RS who received at least one dose of study treatment and who had at least one baseline analysable value and one post-baseline analysable value for Supine Systolic Blood Pressure.

Primary: Office supine systolic blood pressure over 12 weeks (W0-W12)

End point title	Office supine systolic blood pressure over 12 weeks (W0-W12)

End point description:

The change in the office supine systolic blood pressure (SBP) over 12 weeks (W0-W12) was measured. The between group comparison was performed in the Full Analysis Set on the change from Baseline (W0) to last post baseline value at W12 of SBP using an analysis of covariance (ANCOVA) model performed. Analysis included the fixed, categorical effect of treatment with modality Indapamide/A mlodipine and Valsartan/Amlodipine, and categorical fixed effects of country, as well as the continuous fixed covariate of baseline.

End point type	Primary

End point timeframe:

Office supine systolic blood pressure was measured over 12 weeks (W0-W12)

End point values	Indapamide/Amlodipine	Valsartan/Amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	232		
Units: mmHg				
arithmetic mean (standard deviation)	-20.84 (± 14.85)	-19.72 (± 16.13)		

Statistical analyses

Statistical analysis title	Office supine systolic blood pressure

Statistical analysis description:

Analysis of the between-group difference in the change of the office supine blood pressure over 12 weeks (W0-W12), using an analysis of covariance (ANCOVA) model performed. Analysis included the

fixed, categorical effect of treatment with modality Indapamide/Amlodipine and Valsartan/Amlodipine, and categorical fixed effects of country, as well as the continuous fixed covariate of baseline.

Comparison groups	Indapamide/Amlodipine v Valsartan/Amlodipine
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.67
upper limit	1.56
Variability estimate	Standard error of the mean
Dispersion value	1.33

Statistical analysis title	Office supine systolic blood pressure

Statistical analysis description:

The non-inferiority analysis using a margin of 3 mmHg, of Ind/Aml as compared to Val/Aml strategy was performed on the change from baseline to the last-post baseline value over the W0-W12 period for office SBP and DBP (ISH and SDH gathered) in the FAS.

Comparison groups	Indapamide/Amlodipine v Valsartan/Amlodipine
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	non-inferiority[1]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.67
upper limit	1.56
Variability estimate	Standard error of the mean
Dispersion value	1.33

Notes:

[1] - The objective of superiority was not reached in this study. However, as both strategies (Ind/Aml and Val/Aml) provided a clinically relevant antihypertensive effect, there was a scientific interest of assessing the extent of difference between treatments, exploring the non-inferiority of Ind/Aml against Val/Aml stategy (registered since January 2007 in Europe and worldwide), for which the well-known anti-hypertensive effect was obtained in the present study.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind 12 weeks period

Adverse event reporting additional description:

Emergent aderse events are presented. They were defined as all adverse events which occurred between the first study drug intake date (included) and the last study drug intake date + 7 days (included), or which occurred strictly before the first study drug intake date and which worsened (in terms of intensity) or became serious.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Ind/Amlo

Reporting group description:

Indapamide slow release 1.5mg / Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Indapamide slow release 1.5 mg / Amlodipine 10 mg, at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

Reporting group title	Val/Amlo

Reporting group description:

Valsartan 80 mg / Amlodipine 5 mg single pill fixe dose combination as starting dose, possibly up-titrated to the next dose of the treatment strategy to Valsartan 160 mg / Amlodipine 5 mg , at visit W6, for all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office blood pressure measurement).

Serious adverse events	Ind/Amlo	Val/Amlo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 236 (0.85%)	2 / 236 (0.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Myocardial ischaemia			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Ind/Amlo	Val/Amlo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 236 (19.49%)	27 / 236 (11.44%)	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 236 (1.27%)	1 / 236 (0.42%)	
occurrences (all)	3	1	
Chest pain			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Puncture site oedema			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 236 (0.00%)	2 / 236 (0.85%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences (all)	1	1	
Alcohol abuse			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 236 (0.42%)	2 / 236 (0.85%)	
occurrences (all)	1	2	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 236 (0.42%)	2 / 236 (0.85%)	
occurrences (all)	1	2	
Blood bilirubin increased			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Blood potassium increased			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences (all)	1	1	
Blood pressure increased			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Blood triglycerides increased			

subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Blood uric acid increased			
subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	4 / 236 (1.69%)	0 / 236 (0.00%)	
occurrences (all)	4	0	
Excoriation			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Intentional overdose			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Spinal column injury			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Bundle branch block right			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Palpitations			

subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 236 (2.12%)	0 / 236 (0.00%)	
occurrences (all)	5	0	
Headache			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 236 (0.00%)	2 / 236 (0.85%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	3 / 236 (1.27%)	0 / 236 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 236 (0.42%)	2 / 236 (0.85%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Hepatocellular injury			

subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences (all)	1	1	
Joint swelling			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Costochondritis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	3 / 236 (1.27%)	1 / 236 (0.42%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	1 / 236 (0.42%)	2 / 236 (0.85%)	
occurrences (all)	1	2	
Rhinitis			

subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	4 / 236 (1.69%)	3 / 236 (1.27%)	
occurrences (all)	4	3	
Hyperglycaemia			
subjects affected / exposed	2 / 236 (0.85%)	0 / 236 (0.00%)	
occurrences (all)	2	0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 236 (0.00%)	2 / 236 (0.85%)	
occurrences (all)	0	2	
Hyperuricaemia			
subjects affected / exposed	3 / 236 (1.27%)	0 / 236 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	12 / 236 (5.08%)	2 / 236 (0.85%)	
occurrences (all)	14	2	
Hypochloraemia			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences (all)	1	0	
Impaired fasting glucose			
subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2013	This amendment to be applied in Argentina was implemented in order to comply with local regulation in Argentina. It concerned the addition of an urinary pregnancy test at W0, W6, and W12 visits, for all women except those who were menopausal or who had a hysterectomy or surgical sterilisation. The result should be verified as being negative and result had to be known before any treatment dispensation at W0, W6 and W12 visits.
18 November 2013	This substantial amendment was set up in all counries on request of country coordinators. The objective was to provide an adequate version, which was better adapted to each country's conditions, to respect the regular patient's follow up recommendations for each country and ensure the maximal safety of the patients. The secondary objective and secondary efficacy criteria were completed. It was specified that during the study the e-GFR should be calculated by the investigator using the e-CRF calculator. Of the methods already authorised by the current version of the protocol and approved in all countries, in reality 3 of them were used in the clinical practice and were chosen to be followed in this protocol. The additional formula for e-GRF was described. As the information about the method of creatinine measurement was frequently missing, if the investigator decided to use the MDRD the MDRD 186 formula and conversion factor 0.95 was applied to all patients. This version took into account the recently published ESH/ESC 2013 guidelines for the management of arterial hypertension, as they confirmed all data previously described in the initial version of the protocol background information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported