Clinical trial results:
Efficacy and safety of fixed-dose combination Perindopril 5 mg / Indapamide 1.25 mg / Amlodipine 5 mg versus Perindopril 5 mg / Indapamide 1.25 mg single pill in patients with uncontrolled essential hypertension after 1 month of treatment by Perindopril 5 mg / Indapamide 1.25 mg single pill with conditional titration based on blood pressure control up to Perindopril 10 mg/ Indapamide 2.5 mg / Amlodipine 10 mg. An international, multicentre, randomised, double blind, 4-month superiority study.

Summary

EudraCT number	2012-001658-24
Trial protocol	SK CZ HU BG PL
Global end of trial date	28 July 2015

Results information

Result version number	v1 (current)
This version publication date	06 August 2016
First version publication date	06 August 2016

Trial information

Trial identification

Sponsor protocol code	CL3-06593-006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de recherches Internationale Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France,
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 33 0155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 33 0155724366, 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	28 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2015
Global end of trial reached?	Yes
Global end of trial date	28 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To demonstrate the superiority effect of fixed-dose combination Perindopril / Indapamide / Amlodipine in single-pill versus bi-therapy in single pill in lowering office systolic blood pressure at the end of one month of treatment.

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 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 1 month was dedicated to confirm the essential uncontrolled hypertension in patients under Perindopril 5 mg/Indapamide 1.25 mg single pill treatment.
Study treatments should be prematurely and definitively discontinued for a participant for one of the following reasons:
-Patients having at any visit whatever the dosage of study treatment used : SBP >= 180 mmHg and/or DBP >= 110 mmHg.
-Patients who were up-titrated at any visit and had at the following visit SBP >= 160 mmHg or DBP >= 100 mmHg.
- Patients having not controlled BP at the clinical visit M6; M9; M12 confirmed by the HBPM measurements performed by the patient at home: SBP >= 135 mmHg or DBP >= 85 mmHg (within 4 days before the clinical visit).
- Onset of adverse event which presented a risk for the patient or made it unsafe for the patient to continue with the study treatment.
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 decision personal).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 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: 7
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Argentina: 61
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Romania: 38
Country: Number of subjects enrolled	Russian Federation: 114
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Ukraine: 116
Country: Number of subjects enrolled	Vietnam: 15
Worldwide total number of subjects	454
EEA total number of subjects	125

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)	386
From 65 to 84 years	66
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

-A 4 weeks open label run-in period from selection was dedicated to confirm the essential non-controlled hypertension on Perindopril 5 mg/Indapamide 1.25 mg. Only eligible patients having still an uncontrolled hypertension were randomised to IMPs.

Period 1

Period 1 title	Double-blind treatment period (4 months)
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	Starting with Perindopril/Indapamide/Amlodipine

Arm description:

The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg administered orally. Then, the patients could receive, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as: SBP 140 >= mmHg or DBP>= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg):
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Arm type	Experimental
Investigational medicinal product name	Perindopril/Indapamide/Amlodipine
Investigational medicinal product code	S06593
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study treatment was to be administered orally with water as one capsule daily in the morning before breakfast. The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg. Then, the patients with blood pressure not controlled (SBP >= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg) could receive, depending on the blood pressure values an uptitration from M1:
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Of note, all patients received during the 1-month run-in period perindopril 5 mg/indapamide 1.25 mg.

Arm title	Starting with Perindopril/Indapamide

Arm description:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination administered orally. Then, the patients could receive the test drug, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as : SBP >= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg).
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Arm type	Active comparator

Investigational medicinal product name	Prindopril/Indapamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination administered orally with water as one capsule daily in the morning before breakfast. Then, the patients with blood pressure not controlled (SBP >= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg) could receive the test drug, depending on the blood pressure values an uptitration from M1:
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.
Of note, all patients received during the 1-month run-in period perindopril 5 mg/indapamide 1.25 mg.

Number of subjects in period 1	Starting with Perindopril/Indapamide/Amlodipine	Starting with Perindopril/Indapamide
Started	227	227
Completed	200	197
Not completed	27	30
Adverse event, serious fatal	1	-
Adverse event, non-fatal	6	2
non-medical reasons	9	5
patients not included	-	2
Protocol deviation	2	5
Other protocol withdrawal criteria	9	16

Period 2

Period 2 title	Overall period M0-M15 including M4-M15
Is this the baseline period?	No
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	Starting with Perindopril/Indapamide/Amlodipine M0-M15

Arm description:

The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg administered orally. Then, the patients could receive, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as: SBP 140 mmHg or DBP 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg):
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

From M4, all patients with BP controlled on Per10/Ind2.5/Aml5 or Per10/Ind2.5/Aml10 could enter in

the extension period (M4-M15) and remained on this treatment dose.

Arm type	Experimental
Investigational medicinal product name	Perindopril/Indapamide/Amlodipine
Investigational medicinal product code	S06593
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study treatment was to be administered orally with water as one capsule daily in the morning before breakfast. The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg. Then, the patients with blood pressure not controlled (SBP >= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg) could receive, depending on the blood pressure values an uptitration from M1:
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

From M4, all patients with BP controlled on Per10/Ind2.5/Aml5 or Per10/Ind2.5/Aml10 could enter in the extension period (M4-M15) and remained on this treatment dose.
Of note, all patients received during the 1-month run-in period perindopril 5 mg/indapamide 1.25 mg.

Arm title	Starting with Perindopril/Indapamide M0-M15

Arm description:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination administered orally . Then, the patients could receive the test drug, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as : SBP>= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg).
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

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

Dosage and administration details:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination was administered orally with water as one capsule daily in the morning before breakfast. Then, the patients not controlled (SBP >= 140 mmHg or DBP >=90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg) could receive the test drug, depending on the blood pressure values an uptitration from M1:
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.
Of note, all patients received during the 1-month run-in period perindopril 5 mg/indapamide 1.25 mg.

Number of subjects in period 2	Starting with Perindopril/Indapamide/Amlodipine M0-M15	Starting with Perindopril/Indapamide M0-M15
Started	200	197
Completed	40	54
Not completed	160	143
Adverse event, serious fatal	1	-
patients completed M0-M4 and not entering M4-M15	159	143

Baseline characteristics

Reporting groups

Reporting group title	Starting with Perindopril/Indapamide/Amlodipine

Reporting group description:

The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg administered orally. Then, the patients could receive, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as: SBP 140 >= mmHg or DBP>= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg):
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Reporting group title	Starting with Perindopril/Indapamide

Reporting group description:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination administered orally. Then, the patients could receive the test drug, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as : SBP >= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg).
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Reporting group values	Starting with Perindopril/Indapamide/Amlodipine	Starting with Perindopril/Indapamide	Total
Number of subjects	227	227	454
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)	194	192	386
From 65-84 years	32	34	66
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	54.5	54.9	
standard deviation	± 9.8	± 9.9	-
Gender categorical Units: Subjects			
Female	88	113	201
Male	139	114	253

Subject analysis sets

Subject analysis set title	Full Analysis Set (main office study)
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the the intention-to-treat principle, this set corresponded to all randomised patients who received at least one dose of study treatment and who had at least one analysable baseline value and one analysable post-baseline value at M1 for Systolic Blood Pressure (SBP).

Subject analysis set title	FAS-ABPM
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the intention-to-treat principle, the FAS-ABPM (ambulatory blood pressure monitoring) was defined as : all patients of Randomised Set ABPM* who received at least one dose of study treatment and who have at least one valid ABPM at baseline and one valid post-baseline ABPM for mean 24h systolic blood pressure at M1.
The ABPM was a sub-study of the main study.
* Randomised Set ABPM defined as a randomised patients in the main study who had performed at least one ABPM measurement.

Subject analysis set title	FAS-HBPM
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the intention-to-treat principle, the FAS-HBPM (Home Blood Pressure Monitoring) was defined as : all patients of RS-HBPM* who received at least one dose of study treatment and who had at least one valid HBPM at baseline and one valid post-baseline HBPM for mean HSBP over the 4 days preceding the study visit at M1.
* defined as all randomised patients in the main study who had performed at least one HBPM measurement.

Reporting group values	Full Analysis Set (main office study)	FAS-ABPM	FAS-HBPM
Number of subjects	449	276	263
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)	382	236	226
From 65-84 years	65	39	36
85 years and over	2	1	1
Age continuous Units: years			
arithmetic mean	54.7	55.1	54.6
standard deviation	± 9.8	± 9	± 9.6
Gender categorical Units: Subjects			
Female	198	112	121
Male	251	164	142

End points

End points reporting groups

Reporting group title	Starting with Perindopril/Indapamide/Amlodipine

Reporting group description:

The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg administered orally. Then, the patients could receive, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as: SBP 140 >= mmHg or DBP>= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg):
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Reporting group title	Starting with Perindopril/Indapamide

Reporting group description:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination administered orally. Then, the patients could receive the test drug, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as : SBP >= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg).
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Reporting group title	Starting with Perindopril/Indapamide/Amlodipine M0-M15

Reporting group description:

The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg administered orally. Then, the patients could receive, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as: SBP 140 mmHg or DBP 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg):
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

From M4, all patients with BP controlled on Per10/Ind2.5/Aml5 or Per10/Ind2.5/Aml10 could enter in the extension period (M4-M15) and remained on this treatment dose.

Reporting group title	Starting with Perindopril/Indapamide M0-M15

Reporting group description:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination administered orally . Then, the patients could receive the test drug, depending on the blood pressure values an uptitration from M1 (not controlled BP defined as : SBP>= 140 mmHg or DBP >= 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg).
- Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixed dose combination.
- Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Subject analysis set title	Full Analysis Set (main office study)
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the the intention-to-treat principle, this set corresponded to all randomised patients who received at least one dose of study treatment and who had at least one analysable baseline value and one analysable post-baseline value at M1 for Systolic Blood Pressure (SBP).

Subject analysis set title	FAS-ABPM
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the intention-to-treat principle, the FAS-ABPM (ambulatory blood pressure monitoring) was defined as : all patients of Randomised Set ABPM* who received at least one dose of study treatment and who have at least one valid ABPM at baseline and one valid post-baseline ABPM for mean 24h systolic blood pressure at M1.
The ABPM was a sub-study of the main study.
* Randomised Set ABPM defined as a randomised patients in the main study who had performed at least one ABPM measurement.

Subject analysis set title	FAS-HBPM
Subject analysis set type	Full analysis

Subject analysis set description:

Based on the intention-to-treat principle, the FAS-HBPM (Home Blood Pressure Monitoring) was defined as : all patients of RS-HBPM* who received at least one dose of study treatment and who had at least one valid HBPM at baseline and one valid post-baseline HBPM for mean HSBP over the 4 days preceding the study visit at M1.
* defined as all randomised patients in the main study who had performed at least one HBPM measurement.

Primary: Office supine systolic blood pressure at M1 visit

End point title	Office supine systolic blood pressure at M1 visit

End point description:

To study the effect of fixed-dose combination P5/I1.25/A5 in single-pill versus P5/I1.25 in single pill in lowering office SBP at the end of one month of treatment, a between group comparison was performed on the change of supine SBP from baseline to M1 post-baseline value, using an analysis of covariance (ANCOVA) model.

End point type	Primary

End point timeframe:

The change in office supine systolic blood pressure was calculated between baseline and M1

End point values	Starting with Perindopril/Indapamide/Amlodipine	Starting with Perindopril/Indapamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	224		
Units: mmHg				
arithmetic mean (standard deviation)	-19.18 (± 14.5)	-17.29 (± 16.4)		

Statistical analyses

Statistical analysis title	Change in office systolic blood pressure M0-M1

Statistical analysis description:

To study the superiority effect of fixed-dose combination P5/I1.25/A5 in single-pill versus P5/I1.25 in single pill in lowering office SBP over M0-M1, a between group comparison was performed in the FAS on the change of supine SBP from baseline to M1 post-baseline value, using an analysis of covariance (ANCOVA) model. This analysis included the fixed, categorical effect of treatment and the fixed categorical effect of country as well as the continuous, fixed covariate of baseline.

Comparison groups	Starting with Perindopril/Indapamide/Amlodipine v Starting with Perindopril/Indapamide
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.16
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	1.32

Statistical analysis title	Change over M0-M1 including adjustment on gender

Statistical analysis description:

At study entry, the relevant imbalance between-groups in the gender distribution that is likely due to chance, with a greater proportion of women in the starting Per/Ind group as compared to the starting Per/Ind/Aml group, justifying to perform a post-hoc sensitivity analysis adjusted on gender. The same model as the main analysis (ANCOVA adjusted on treatment, baseline and country), additionally adjusted on gender, was used.

Comparison groups	Starting with Perindopril/Indapamide/Amlodipine v Starting with Perindopril/Indapamide
Number of subjects included in analysis	449
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.63
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	1.32

Statistical analysis title	Change over M0-M1/sustained hypertension/FAS-ABPM

Statistical analysis description:

The between-group comparison of the office SBP in patients with sustained hypertension (uncontrolled hypertension confirmed at both office and 24-hour ABPM [mean 24h ASBP ≥ 130 mmHg or mean 24h ADBP ≥ 80 mmHg]) was performed on the change from baseline to last post-baseline value at M1 using an analysis of covariance (ANCOVA) adjusted on treatment, baseline, country (fixed effects), in the FAS-ABPM.

Comparison groups	Starting with Perindopril/Indapamide/Amlodipine v Starting with Perindopril/Indapamide
Number of subjects included in analysis	449
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.52
upper limit	-0.72
Variability estimate	Standard error of the mean
Dispersion value	1.73

Notes:

[1] - This analysis was performed in the FAS-ABPM (N = 276)

Statistical analysis title	Change M0-M1/sustained hypertension/gender adj.

Statistical analysis description:

The between-group comparison of the office SBP in patients with sustained hypertension (uncontrolled hypertension confirmed at both office and 24-hour ABPM [mean 24h ASBP ≥ 130 mmHg or mean 24h ADBP ≥ 80 mmHg]) was performed on the change from baseline to last post-baseline value at M1 using an analysis of covariance (ANCOVA) adjusted on treatment, baseline, country (fixed effects),and gender in the FAS-ABPM.

Comparison groups	Starting with Perindopril/Indapamide/Amlodipine v Starting with Perindopril/Indapamide
Number of subjects included in analysis	449
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.62
upper limit	-1.96
Variability estimate	Standard error of the mean
Dispersion value	1.69

Notes:

[2] - This analysis was performed in the FAS-ABPM (N = 276)

Primary: 24H Ambulatory Systolic Blood Pressure over M0-M1 (ABPM sub-study)

End point title	24H Ambulatory Systolic Blood Pressure over M0-M1 (ABPM sub-study)

End point description:

The 24h Ambulatory Systolic Blood Pressure (ASBP) was the main endpoint of the Ambulatory Blood pressure Monitoring (ABPM) sub-study. The change over M0-M1 was provided in the FAS-ABPM.

End point type	Primary

End point timeframe:

M0-M1

End point values	Starting with Perindopril/Indapamide/Amlodipine	Starting with Perindopril/Indapamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	142		
Units: mmHg				
arithmetic mean (standard deviation)	-8.73 (± 13.03)	-4.86 (± 12.93)		

Statistical analyses

Statistical analysis title	24h ASBP change over M0-M1

Statistical analysis description:

To demonstrate efficacy of P5/I1.25/A5 as compared to P5/I1.25 at M1 in measurement of mean 24h Ambulatory Systolic Blood Pressure (ASBP) measured after 24h continuous SBP measures, a between group comparison was performed in the FAS-ABPM on the change from baseline to M1 post-baseline value, using an analysis of covariance (ANCOVA) model. This analysis included the fixed, categorical effect of treatment and the continuous, fixed covariate of baseline.

Comparison groups	Starting with Perindopril/Indapamide/Amlodipine v Starting with Perindopril/Indapamide
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.39
upper limit	-1.09
Variability estimate	Standard error of the mean
Dispersion value	1.35

Primary: Home systolic blood pressure global over M0-M1 (HBPM sub-study)

End point title	Home systolic blood pressure global over M0-M1 (HBPM sub-study)

End point description:

The Home systolic blood pressure (HSBP) global (i.e. morning and evening, mean of the 4 days preceding the visit) was the main endpoint of the Home Blood Pressure Monitoring (HBPM) sub-study. The change over M0-M1 was provided in the FAS-HBPM.

End point type	Primary

End point timeframe:

M0-M1

End point values	Starting with Perindopril/Indapamide/Amlodipine	Starting with Perindopril/Indapamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	128		
Units: mmHg				
arithmetic mean (standard deviation)	-10.28 (± 12.69)	-4.95 (± 14.01)		

Statistical analyses

Statistical analysis title	HSBP change over M0-M1

Statistical analysis description:

To demonstrate efficacy of P5/I1.25/A5 as compared to P5/I1.25 at M1 in measurement of Home Systolic Blood pressure HSBP (morning and evening, means 4 days preceding the visit), a between group comparison was performed in the FAS-HBPM on the change from baseline to M1 post-baseline value, using an analysis of covariance (ANCOVA) model. This analysis included the fixed, categorical effect of treatment and the continuous,fixed covariate of baseline.

Comparison groups	Starting with Perindopril/Indapamide/Amlodipine v Starting with Perindopril/Indapamide
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.36
upper limit	-1.89
Variability estimate	Standard error of the mean
Dispersion value	1.39

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind 1 month period (M0-M1) for each group
and overall period M0-M15 including extension M4-M15 for overall patients

Adverse event reporting additional description:

Emergent adverse events are presented (EAE) . EAE on treatment on the whole study (overall, M0-M15) 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 worsened or became serious.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Starting with Per/Ind/Aml [M0-M1]

Reporting group description:

The study treatment was to be administered orally with water as one capsule daily. The starting dose at inclusion was perindopril 5 mg/indapamide 1.25 mg/ Amlodipine 5 mg. Then, the patients could receive, depending on the blood pressure titration from M1:
- - Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg fixed dose combination.
- - Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Of note, all patients received during the 1-month run-in period perindopril 5 mg/indapamide 1.25 mg.

Reporting group title	Starting with Per/Ind [M0-M1]

Reporting group description:

Perindopril 5 mg / Indapamide 1.25 mg (as starting dose) fixed dose combination administered orally with water as one capsule daily. Then, the patients could receive the test drug, depending on the blood pressure titration from M1:
- - Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg fixe dose combination.
- - Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg fixed dose combination.

At M3, patients still uncontrolled with Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg could switch to Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg fixed dose combination.

Reporting group title	All patients [M0-M15]

Reporting group description:

This group includes all patients included in the study and that entered or not in the M4-M15 period, whatever the Perindopril/Indapamide/Amlodipine or Perindopril/Indapamide starting group.

Serious adverse events	Starting with Per/Ind/Aml [M0-M1]	Starting with Per/Ind [M0-M1]	All patients [M0-M15]
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 227 (3.08%)	1 / 225 (0.44%)	9 / 452 (1.99%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Meningioma benign			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Nerve root injury cervical			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Intraocular lens implant			

subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenic infarction			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
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			
Ascites			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleurisy			

subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
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			
Renal infarct			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endocarditis bacterial			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Starting with Per/Ind/Aml [M0-M1]	Starting with Per/Ind [M0-M1]	All patients [M0-M15]
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 227 (23.79%)	49 / 225 (21.78%)	111 / 452 (24.56%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Pancreatic neoplasm			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Prostatic adenoma			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	1 / 452 (0.22%)
occurrences (all)	0	1	1
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Arteriosclerosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	2 / 452 (0.44%)
occurrences (all)	1	0	2
Hypotension			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	4 / 452 (0.88%)
occurrences (all)	0	0	4
Orthostatic hypotension			
subjects affected / exposed	2 / 227 (0.88%)	0 / 225 (0.00%)	3 / 452 (0.66%)
occurrences (all)	2	0	3
Surgical and medical procedures			
Continuous positive airway pressure			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	4 / 227 (1.76%)	0 / 225 (0.00%)	6 / 452 (1.33%)
occurrences (all)	4	0	6
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 227 (0.88%)	1 / 225 (0.44%)	6 / 452 (1.33%)
occurrences (all)	2	1	6
Emphysema			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Nasal septum deviation			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Psychiatric disorders			
Terminal insomnia			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	1 / 452 (0.22%)
occurrences (all)	0	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	2 / 452 (0.44%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Blood creatinine increased			

subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Blood glucose increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	8 / 452 (1.77%)
occurrences (all)	0	1	8
Body temperature increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	3 / 452 (0.66%)
occurrences (all)	0	0	3
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	3 / 452 (0.66%)
occurrences (all)	0	1	3
Foot fracture			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	1 / 452 (0.22%)
occurrences (all)	0	1	1
Spinal compression fracture			

subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Cardiac disorders			
Aortic valve calcification			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Aortic valve incompetence			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Bradycardia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Supraventricular extrasystoles			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Tricuspid valve incompetence			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Nervous system disorders			
Acoustic neuritis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	2
Cerebral ischaemia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 227 (0.44%)	2 / 225 (0.89%)	4 / 452 (0.88%)
occurrences (all)	1	2	5
Dysgeusia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Headache			

subjects affected / exposed	2 / 227 (0.88%)	3 / 225 (1.33%)	7 / 452 (1.55%)
occurrences (all)	2	3	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	1 / 452 (0.22%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	2 / 452 (0.44%)
occurrences (all)	0	0	2
Duodenitis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	2 / 452 (0.44%)
occurrences (all)	1	0	2
Duodenogastric reflux			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Food poisoning			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	3 / 452 (0.66%)
occurrences (all)	0	0	3
Gastritis			
subjects affected / exposed	1 / 227 (0.44%)	1 / 225 (0.44%)	2 / 452 (0.44%)
occurrences (all)	1	1	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Gingival hypertrophy			

subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Hiatus hernia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Pancreatolithiasis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	2 / 452 (0.44%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Pruritus generalised			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	1 / 452 (0.22%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	2 / 452 (0.44%)
occurrences (all)	1	0	2
Intervertebral disc protrusion			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Spinal osteoarthritis			

subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Spinal pain			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	4 / 452 (0.88%)
occurrences (all)	1	0	4
Cystitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	2 / 452 (0.44%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	6 / 452 (1.33%)
occurrences (all)	0	1	6
Pharyngitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Pulpitis dental			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Pyelonephritis chronic			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	3 / 452 (0.66%)
occurrences (all)	1	0	3

Upper respiratory tract infection			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 227 (0.44%)	1 / 225 (0.44%)	5 / 452 (1.11%)
occurrences (all)	1	1	5
Hyperglycaemia			
subjects affected / exposed	0 / 227 (0.00%)	1 / 225 (0.44%)	5 / 452 (1.11%)
occurrences (all)	0	1	5
Hyperkalaemia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	1 / 452 (0.22%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 225 (0.00%)	5 / 452 (1.11%)
occurrences (all)	0	0	5
Hyperuricaemia			
subjects affected / exposed	0 / 227 (0.00%)	2 / 225 (0.89%)	14 / 452 (3.10%)
occurrences (all)	0	2	14
Hypokalaemia			
subjects affected / exposed	0 / 227 (0.00%)	2 / 225 (0.89%)	11 / 452 (2.43%)
occurrences (all)	0	2	12
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 227 (0.44%)	0 / 225 (0.00%)	3 / 452 (0.66%)
occurrences (all)	1	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2012	This amendement was was applicable in all countries involved in the study. The main changes followed the coordinators' opinion, and concerned mainly the modification of some selection / inclusion criteria.
16 January 2013	This amendement was only applicable in Argentina, to comply with local regulation. A urinary pregnancy test was included at study entrance and then regularly, i.e. at all visits. Results had to be known before any dispensation of the study medication.
01 July 2013	This amendement was applicable in all countries involved in the study. The main changes were: - For registration purpose, a 11-month double-blind follow-up extension period was added in order to collect 1 year safety data of a minimum of 100 patients treated with the highest doses of fixed-dose combination (Perindopril 10 mg / Indapamide 2.5 mg / Amlodipine 10 mg), and to confirm the sustained efficacy of this treatment over one year. Thus, a 4 month double-blind superiority study followed by a double-blind follow-up extension period until M15 were implemented instead of the 12-weeks double-blind period initially planned in the study protocol. The title, the objectives, and the design of the study were accordingly modified. - The design was adapted to keep the investigators and the Sponsor blinded with regard to the treatment group allocated to the patients over the efficacy / safety 4-month titration period and its follow-up extension. - - For safety reasons and to have a better follow-up of the patients over the 11-month extension period, HBPM measurements had been added for all patients in the study, and performed at M4 and M15. Moreover, for the patients who took part to the extension period, even if not involved in the sub-studies during the titration period, the ABPM was to be performed only at M15 during the week before the last visit with the objective to obtain the 24 hours profile. - - In order to detect possible differences between right and left arms, at the request of the investigators, it was decided to simplify the definition of the dominant arm for the BP measurement. At the first visit, the investigator was asked to take only 1 measurement of SBP and DBP (instead of 3) in supine position in both right and left arms. - - The 2013 ESH/ECS guidelines for management of arterial hypertension were implemented.
04 February 2014	This amendement was only applicable in Ukraine in order to: postpone the Last Visit Last Patient (LVLP) date due to the extension of the recruitment period In accordance with the most recent quality information submitted to authorities, the storage conditions for the Therapeutic Units to be used in the study were included in this protocol version. No special storage was any more required. -There was a discrepancy regarding the measurement time of the complete laboratory test at selection visit (ASSE). It had been harmonized throughout the protocol to become: "the complete laboratory test at ASSE visit will be performed during the week after selection and preferably between day 5 to 7". This precision was given in order to obtain the laboratory results around one week after starting the run-in treatment period and to allow a better monitoring of the biological parameters to detect possible modifications induced by the treatment (Perindopril 5 mg / Indapamide 1.25 mg).

04 June 2014	This amendement was applicable in all country involved in the study. The purpose of this amendment was to remove the extension period that was added following Amendment No. 3. Indeed, in the countries where the registration was foreseen, the Health Authorities did not require 1 year safety data collection with the highest dose of this combination to reach a Marketing Authorisation. Consequently, the benefit/risk ratio of the study drug being sufficient at the time of the study, the extension part was no more justified. The study title, the study objectives, and the study design were accordingly modified. All patients had to perform the final M4 visit except patients who were already on going in the extension part of the study. For patients already ongoing in the extension period, the study was to be stopped at the next visit planned in the previously approved protocol (M6, M9, M12 or M15). At this final visit, patients were to perform all examinations requested for the withdrawal, including complete laboratory tests, weight and ECG. However, if the consent of the Amendment No. 6 was not obtained, patients were to stop the study at the visit (M6, M9, M12 or M15 visit) and to perform only assessment scheduled at the visit in accordance with the current signed ICF. The other patients who were not yet entered in the extension period were to perform the final visit at M4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported