Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**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 simple pill with conditional titration based on blood pressure control up to Perindopril 10 mg / Indapamide 2.5 mg / Amlodipine 10 mg. An international, multicentre, randomized, double blind, 4-month superiority study.** ***The initial 12-weeks superiority study had been amended twice regarding the study design: firstly to add an extension period until M15 visit for patients controlled with Perindopril 10 mg / Indapamide 2.5 mg / Amlodipine 5 or 10 mg at the end of the titration period (M4), and secondarily to delete this extension period (except for patients already ongoing in this period).***
Test drug code	**S 06593 (Perindopril arginine / Indapamide / Amlodipine)**
Indication	**Essential hypertension**
Development phase	**III**
Protocol code	**CL3-06593-006**
Study initiation date	**22 January 2013**
Study completion date	**28 July 2015**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Les Laboratoires Servier - Representative Office** **Paveletskaya Square 2, building 3** **Moscow 115 054 – Russia**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**04 July 2016**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** **S06593 (Perindopril arginine / Indapamide / Amlodipine)**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: 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.

The initial 12-week superiority study had been amended twice regarding the study design: firstly to continue the study until M4 for all patients and to add an extension period until M15 visit for patients controlled with Perindopril 10 mg/ Indapamide 2.5 mg / Amlodipine 5 or 10 mg at the end of the titration period (M4), and secondarily to delete this extension period (except for patients already ongoing in this period).

Protocol No.: CL3-06593-006

EudraCT No.: 2012-001658-24

The description of the study protocol given hereafter includes the modifications of the 6 substantial amendments to the protocol.

Name of international coordinator: [redacted]

Study centres:

Multinational, multicentre study = 59 centres located in 13 countries included 452 patients distributed as follows: Argentina (4 centres - 61 patients included), Brazil (1 centre - 3 patients), Bulgaria (5 centres - 35 patients), Czech Republic (4 centres - 7 patients), Hungary (7 centres - 20 patients), Mexico (2 centres - 18 patients), Poland (1 centre - 7 patients), Romania (5 centres - 38 patients), Russian Federation (14 centres - 113 patients), Singapore (1 centre - 1 patient), Slovakia (5 centres - 18 patients), Ukraine (7 centres - 116 patients), Vietnam (3 centres - 15 patients).

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 22 January 2013 (date of first visit first patient) Completion date: 28 July 2015 (date of last visit last patient**)**	III

Objectives:

The **primary objective** was to demonstrate the superiority effect of fixed-dose combination Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg in single-pill *versus* Perindopril 5 mg/Indapamide 1.25 mg single pill in lowering office supine systolic blood pressure at the end of one month of treatment (M1).

Secondary objectives:

Efficacy*:

- To assess the effect of fixed-dose combination Perindopril/Indapamide/Amlodipine in single-pill in Standing Systolic Blood Pressure (SBP), Supine and Standing Diastolic Blood Pressure (DBP), Supine Mean Blood Pressure (MBP), Supine Pulse Pressure (PP), response to the treatment and normalisation of blood pressure achieved at M1 (as per Amendment No. 6).
- To assess the effect of fixed-dose combination Perindopril/Indapamide/Amlodipine in single-pill in Supine and standing SBP and DBP, supine MBP, PP, overall control BP and response rates achieved in M0-M2, M0-M3, periods whatever the dose at the period (added by Amendment No. 6).
- To assess the effect of fixed-dose combination Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 10 mg in single-pill and of Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg uptitration strategy at Month 2 visit (M2) in term of percent of responders and normalisation of blood pressure as compared to the previous dose (M1).

Objectives (Cont'd):
Secondary objectives (Cont'd):
Efficacy* (Cont'd):

- To assess the effect of fixed-dose combination Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 5 mg (P10/I2.5/A5) and Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg (P10/I2.5/A10) uptitration strategy at Month 3 visit (M3) in term of percent of responders and normalisation of blood pressure as compared to the previous dose.
- Only for patient who at M3 switched from P10/I2.5/A5 to P10/I2.5/A10, to assess at M4 the effect of fixed-dose combination Perindopril 10 mg/Indapamide 2.5 mg/Amlodipine 10 mg, in term of percent of responders and normalisation of blood pressure as compared to the previous dose. To assess value at the visit (descriptive analysis) for other patients who performed M4 (added by Amendment No. 6).

Safety*:
To assess the safety and tolerability of each dose of Perindopril 5 mg and 10 mg/Indapamide 1.25 mg and 2.5 mg/Amlodipine 5 mg and 10 mg during the study (as per Amendment No. 6)*.

** Of note, some modifications implemented by Amendment No. 3, related to efficacy and safety criteria during the extension period, were then deleted by Amendment No. 6 as this period was removed.*

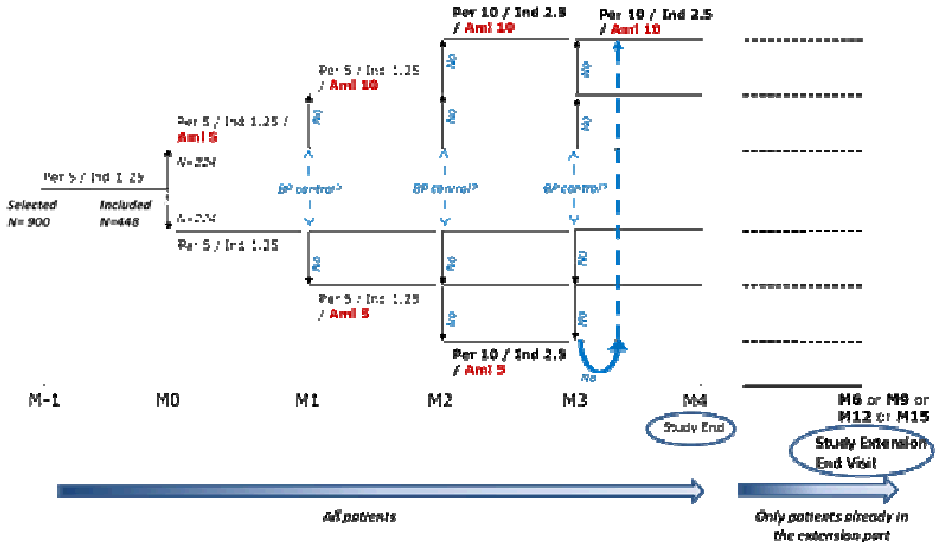
Two sub-studies were proposed: Ambulatory Blood Pressure Monitoring (ABPM) and Home Blood Pressure Measurements (HBPM).

Sub-studies objectives for ABPM and HBPM are detailed in the specific protocol provided separately for each sub-study and submitted for approval to concerned Ethics Committees and Health Authorities.

Results relative to ABPM and HBPM are presented in separate clinical reports.

Methodology:
This study was international, multicentre, randomised, double blind, Phase III, over a 4-month period superiority study, comparing single-pill combination of fixed dose combination of Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg *versus* 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 5 or 10 mg, in patients with uncontrolled hypertension after 1 month of treatment with Perindopril 5 mg/Indapamide 1.25 mg. A fixed, centralised randomisation, stratified according to the country by Interactive Response System (IRS) was used.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Study design (including amendments)



Patients starting with P5/Ind1.25 still uncontrolled under P10//I2.5/Aml5 could switch at M3 to P10//I2.5/Aml10

Number of patients:
Planned (office part of the study): 448 patients (224 in each treatment group).

Included: 452: 227 in the starting with Perindopril/Indapamide/Amlodipine (starting Per/Ind/Aml) group and 225 in the starting with Perindopril/Indapamide (starting Per/Ind) group.

Diagnosis and main criteria for inclusion:
Men or women of any ethnic origin ≥ 18 years old or legal national majority who signed informed consent form, with a confirmed essential uncontrolled hypertension after 1 month of Perindopril 5 mg/Indapamide 1.25 mg active run-in treatment, defined by office SBP ≥ 150 and < 180 mmHg and DBP ≥ 95 and < 110 mmHg, measured with a validated automatic device in supine position after at least 10 minutes of rest (mean of the two last values of three measurements at 1 minute interval).

Test drug:
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, patients with uncontrolled blood pressure (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, and SBP < 180 mmHg and DBP < 110 mmHg) 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.

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.

Batch Nos. L0048232, L0043775, L0050936, L0053508, L0054770, L0048319, L0044070, L0051240, L0053511, L0054772, L0048325, L0044932, L0050790, L0052044, L0053595, L0054502

Comparator (Reference product):
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 uncontrolled blood pressure 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.
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.

Duration of treatment:
Run-in period (1 month): the run-in period was dedicated to confirm the essential uncontrolled hypertension under treatment with perindopril 5 mg/indapamide 1.25 mg. Only eligible patients having still an uncontrolled hypertension after 1-month treatment were randomised to Investigational Medicine product (IMP).
Double-blind treatment period (4 months), with 4 visits at M1, M2, M3 and M4. At M1, M2 and M3 all uncontrolled patients were up-titrated to the next dose of the treatment strategy, or were withdrawn from the study depending on their blood pressure. As per amendment, all patients performed the final visit (M4), except those who were already ongoing in the extension part of the study when the amendment was set up.
Extension period (initially planned to cover M4-M15 stopped by amendment): for patients who already started this extension period, the study was to be stopped at the next visit planned and patients were to complete this visit with all examinations requested for the withdrawal, including complete laboratory tests weight and ECG. Consequently, the study extension end visit could be visit M6, M9, M12, or M15.

Criteria for evaluation
Efficacy measurements:
Primary efficacy endpoint

- Supine SBP (Office BP Measurement): change from baseline to post-baseline value over the M0-M1 period (main expression).

Secondary efficacy endpoints

- Office BP Measurement at each visit:
  - Supine DBP and Standing SBP, DBP.
  - Supine Mean Blood Pressure (MBP), defined as MBP = 2/3 DBP + 1/3 SBP.
  - Supine Pulse Pressure (PP), defined as PP = SBP – DBP.
  - Response to the treatment defined as SBP < 140 mmHg and DBP < 90 mmHg and/or SBP decrease ≥ 20 mmHg from baseline and/or DBP decrease ≥ 10 mmHg from baseline.
  - Normalisation of blood pressure (*i.e.* BP control) corresponding to the percentage of patients with SBP < 140 mmHg and DBP < 90 mmHg.

Safety measurements:

- Emergent adverse events at all study visits.
- Orthostatic hypotension (calculated) at all study visits.
- Complete laboratory examinations: performed in fasting conditions, during the week (preferably between day 5 to 7) after selection, within 7 days before M4 visit, at premature withdrawal visit, and at the extension study end visit for patients already ongoing in the extension part of the study (within 7 days before or 3 days after the visit): biochemistry (sodium, potassium, calcium, chloride, uric acid, urea, creatinine, creatinine clearance, fasting blood glucose levels, total protein, triglycerides, total cholesterol, ASpartate Amino Transferase (ASAT), ALanine Amino Transferase (ALAT), Gamma-Glutamyl Transferase (GGT)), and haematology (haemoglobin, haematocrit, erythrocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, leucocytes and platelets), and urine check for proteinuria (at selection).
  Results should be available at least for inclusion visit and for M4 visit.
- Simplified laboratory test performed at inclusion (W0), and within 7 days after M2 and M3 visits: sodium, potassium, uric acid, creatinine and creatinine clearance.
- Vital signs: physical examination at all study visits, height (at selection), weight (at selection and M4, or extension study end visit M6 or M9 or M12 or M15), heart rate (at all visits).
- 12-lead electrocardiogram available for inclusion visit and visit M4. For patients already in the extension part of, the final ECG was also performed at the extension study end visit (within 7 days before the visit or within 3 days after the visit).

Statistical methods:
Analysis Set:
The Full Analysis Set (FAS) used for the efficacy analysis was: based on the intention-to-treat principle, all randomised patients who received at least one dose of study treatment and who had at least one analysable value at baseline and one analysable post-baseline value at M1 for Systolic Blood Pressure.

Efficacy analysis:
Primary endpoint:
The primary efficacy endpoint was the supine SBP at M1 visit. The main analysis corresponded to the between group comparison on the change from baseline to last post-baseline value at M1 of SBP using an analysis of covariance (ANCOVA) adjusted on treatment, baseline, country (fixed effects).
Secondary expressions were (within group comparisons): change from baseline to last post-baseline value over M0-M2 and M0-M3, change from M0 to M1, change from M1 to M2 and from M2 to M3 (for titration effect), change over one month in patients randomised in P5/I1.25/A5 group having switched to P10/I2.5/A10 at M2 or M3.

Statistical methods (Cont'd):
Efficacy analysis (Cont'd):
Unplanned analyses:

- Post-hoc analysis including adjustment on gender

At study entry, there was some unexpected 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), while it is recommended that patients of both genders should be included in clinical studies for antihypertensive drugs in a balanced way (EMA/238/1995/Rev.3), justifying to perform for efficacy endpoints a post-hoc sensitivity analysis adjusted on gender. Indeed, it is important to demonstrate that any observed treatment effect is not misrepresented due to imbalances at baseline.
In addition to the already known difference between men and women regarding the BP status, especially taking into account the menopause or hormonal status in women, the better BP decrease in women with the use of anti-hypertensive treatment has been evidenced (Kloner 1996, Abad-Santos 2005, Kreutz 2014, Kario 2015, Chor 2015, Wang 2016).
The sensitivity analysis was performed on the change from baseline to post-baseline value over M0-M1 period for the comparison between the treatment groups of office supine SBP, DBP, standing SBP and DBP, as well as for supine MBP, PP, the response to treatment, and normalisation of BP at M1. The same model as the main analysis (ANCOVA adjusted on treatment, baseline and country), additionally adjusted on gender, was used (quantitative parameters only). For BP response and control, a logistic regression adjusted on gender, treatment and country was used.

- Post-hoc analysis in patients with sustained hypertension

The between-group comparison of the office SBP and DBP in patients with sustained hypertension (uncontrolled hypertension confirmed at both office and 24-hour ABPM [mean 24h ASBP $\geq$ 130 mmHg or mean 24h ADBP $\geq$ 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 (defined as all patients of RS-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 of mean 24h SBP at M1). The same analysis including adjustment on gender was performed.

Secondary endpoints:

- Mean supine DBP, MBP, PP, mean standing SBP and DBP at 3 minutes expressed in term of analysis as the main primary efficacy criterion.
- Response to treatment and normalisation of BP: expressed as number and percentage of patients.

Study outcome and safety analysis: Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of patients during the M0-M4 and M4-M15 periods

Status		Starting with Per/Ind/Aml	Starting with Per/Ind	All
Selected for the run-in period	**n**	**-**	**-**	**674**
Excluded during the run-in period / not included	n	-	-	222
Randomised	**n**	**227**	**227***	**454***
Included	**n (%)**	**227 (100)**	**225 (99.1)**	**452 (99.6)**
In compliance with the protocol	n (%)	163 (71.8)	164 (72.2)	327 (72.0)
With a protocol deviation before or at inclusion	n (%)	64 (28.2)	61 (26.9)	125 (27.5)
M0-M4				
Withdrawn due to	**n (%)**	**27 (11.9)**	**28 (12.3)**	**55 (12.1)**
Other protocol withdrawal criteria	n (%)	9 (4.0)	16 (7.0)	25 (5.5)
Non-medical reason	n (%)	9 (4.0)	5 (2.2)	14 (3.1)
Adverse event	n (%)	7 (3.1)	2 (0.9)	9 (2.0)
Protocol deviation	n (%)	2 (0.9)	5 (2.2)	7 (1.5)
Completed**	**n (%)**	**200 (88.1)**	**197 (86.8)**	**397 (87.4)**
In compliance with the protocol	n (%)	165 (72.7)	167 (73.6)	332 (73.1)
With a protocol deviation after inclusion	n (%)	35 (15.4)	30 (13.2)	65 (14.3)
Entering the extension period (M4-M15)				
In compliance with the protocol	n (%)	37 (16.3)	48 (21.1)	85 (18.7)
With a protocol deviation before or at inclusion	n (%)	4 (1.8)	6 (2.6)	10 (2.2)
Withdrawn due to	**n (%)**	**1 (0.4)**	**-**	**1 (0.2)**
Adverse event	n (%)	1 (0.4)	-	1 (0.2)
Completed extension period	**n (%)**	**40 (17.6)**	**54 (23.8)**	**94 (20.7)**
In compliance with the protocol	n (%)	36 (15.9)	47 (20.7)	83 (18.3)
With a protocol deviation after inclusion	n (%)	4 (1.8)	7 (3.1)	11 (2.4)
Full Analysis Set (FAS)	**n (%)**	225 (99.1)	224 (98.7)	449 (98.9)
Per Protocol Set (PPS)	**n (%)*** **	212 (94.2)	211 (94.2)	423 (94.2)
Safety Set (SS)	**n (%)**	**227 (100)**	**225 (99.1)**	**452 (99.6)**

n: number of patients

%: expressed as percentage of the randomised patients

**: Two patients not included were erroneously randomised*

***: Completed = patients who completed the main study part (i.e. patients who completed M0-M3 period as planned in the initial study protocol, and patients who completed the M0-M4 period as the M0-M3 period was extended following Amendment No. 3, and the 95 patients who entered in the extension period)*

****: expressed as percentage of the FAS*

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

A total of **454 patients were randomised** (452 included) with a well-balanced distribution reached between-groups (227 patients in the Per/Ind/Aml and 227 patients in the starting Per/Ind group). Two patients not included were erroneously randomised (in the starting Per/Ind group). Of the randomised patients, 12.1% were withdrawn (11.9% *versus* 12.3%, respectively) during the M0-M4 period, including 7 patients (3.1%) in the starting Per/Ind/Aml group and 2 (0.9%) in the starting Per/Ind group withdrawn for adverse events. Finally, 397 patients, 87.4% of the randomised patients completed the M0-M4 treatment period (200 patients, 88.1% and 197 patients, 86.8%, respectively), including the 95 patients (20.9%) ongoing for the extension period.

Of these 95 patients (18.1% in the starting Per/Ind/Aml group and 23.8% in the starting Per/Ind group), one patient, in the starting Per/Ind/Aml group, was withdrawn over the M4-M15 period due to adverse event (sudden death).

Finally, over the M0-M15 period, 396 out of the 454 patients (87.2%) completed the study, according to the protocol.

Overall, 27.5% reported protocol deviations before or at inclusion, with similar frequency in both treatment groups (28.2% *versus* 26.9%, respectively). They were mainly in relation with biochemistry results (9.3% in both groups). After inclusion, 24.0% reported protocol deviations (25.6% *versus* 22.5%, respectively), mainly those due to study drug administration (13.7% and 11.5%, respectively), mostly due to duration not respected between inclusion visit and next visit (7.9% and 5.7%).

No relevant between-group difference was detected.

BASELINE CHARACTERISTICS

Demographic and other baseline characteristics of the patients were in line with the selection/inclusion criteria of the study protocol. In the Randomised Set, patients were in average 54.7 ± 9.8 years old, with no relevant between-group difference, and most of them (85.0%) were between 18 and 64 years old. More than half of the patients were men (55.7%), but there was an unexpected higher proportion of women in the starting Per/Ind group than in the starting Per/Ind/Aml group (49.8% *versus* 38.8%). BMI was on average 27.0 ± 2.5 kg/m², and 8 patients, 1.8% had a BMI ≥ 30 kg/m² (of whom 2 patients were considered as having protocol deviations at inclusion).

All patients presented at selection an essential hypertension in average since 79.0 ± 86.3 months (74.6 ± 83.9 months, median: 48.0 months *versus* 83.4 ± 88.6 months, median: 57.0 months, respectively). Most of the patients (89.4%) received at least one treatment for essential hypertension before entry in the study, mainly Agents acting on the renin-angiotensin system (77.1% *versus* 78.0%, respectively). Overall, 46.3% of patients were on monotherapy and 53.7% on bi-therapy. No relevant between-group difference was observed.

Most of the patients (79.5%) reported additional medical history, mainly related to Metabolism and nutrition disorders (41.9% in the starting Per/Ind/Aml group and 36.1% in the starting Per/Ind group), including mostly dyslipidaemia (17.2% *versus* 17.6%, respectively).

Regarding risk factors, 15.0% had smoking habit and 29.1% had alcohol habit consumption, with no relevant between-group difference.

In the Randomised Set, at selection, mean supine SBP and DBP were: 163.9 ± 7.4 mmHg and 101.0 ± 3.7 mmHg, respectively, with no relevant between-group difference. At baseline, the office supine SBP and DBP were in average: 162.3 ± 7.4 mmHg and 101.1 ± 3.8 mmHg, PP: 61.2 ± 8.0 mmHg, and MBP: 121.5 ± 3.7 mmHg, with no relevant between group-difference. The office standing SBP and DBP at 3 min were similar in both treatment groups at inclusion (160.5 ± 10.9 mmHg and 101.4 ± 6.9 mmHg, respectively).

EXTENT OF EXPOSURE

The global compliance was in average 99.1 ± 3.1% over M0-M1 and 98.5 ± 4.7% over M0-M4, with similar results in both treatment groups, in the FAS. Over M0-M1, all patients had an overall compliance between 70% and 130% (inclusive). Over the M0-M4 treatment period, 99.1% of the patients had an overall compliance between 70% and 130%. No relevant between-group difference was observed.

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Due to:

- The relevant between-groups imbalance in the gender distribution (with a greater proportion of women in the starting Per/Ind group as compared to the starting Per/Ind/Aml group: 49.6% versus 38.7%, p = 0.002, in the FAS, post-hoc analysis).
- The greater decrease in the office SBP over M0-M1 in women than men (women: -21.56 ± 15.52 mmHg in the starting Per/Ind/Aml group and -20.74 ± 16.85 mmHg in the starting Per/Ind group, men: -17.68 ± 13.67 mmHg in the starting Per/Ind/Aml group and -13.90 ± 15.26 mmHg in the starting Per/Ind group), although the SBP values at baseline were similar (women: 162.16 ± 7.52 mmHg in the starting Per/Ind/Aml group and 163.34 ± 8.12 in the starting Per/Ind group, men: 161.69 ± 6.82 mmHg and 162.27 ± 7.49 mmHg).
- The already known difference between men and women regarding the BP status and the better BP decrease in women with the use of anti-hypertensive treatment evidenced.
- The EMEA guidelines 2013 recommendation (EMA/238/1995/Rev.3) that patients of both genders should be included in a balanced way.

*A **post-hoc sensitivity analysis including adjustment on gender** was performed for all efficacy endpoints over the M0-M1 period, as well as for all analyses presented hereafter.*

- Primary assessment endpoint

Main analysis

Over the M0-M1 period, the office supine SBP markedly decreased from baseline to post-baseline value in both treatment groups by -19.18 ± 14.50 mmHg in the starting Per/Ind/Aml group *versus* -17.29 ± 16.40 mmHg in the starting Per/Ind group, in the FAS. The between-group difference was in favour of the starting Per/Ind/Aml group but was not statistically significant (E (SE) = -2.56 (1.32) mmHg, 95% CI = [-5.16 ; 0.04], p = 0.054). After including adjustment on gender, the between group difference in the mean supine SBP decrease over M0-M1 was statistically significant in favour of the starting Per/Ind/Aml group (E = -3.05 (1.32) mmHg; 95% CI = [-5.63; -0.46], p = 0.021).

When considering patients with sustained hypertension (uncontrolled hypertension confirmed at both office and 24-hour ABPM, 116/134 patients (86.6%) and 126/142 patients (88.7%)), a statistically significant decrease in the office SBP was observed: by -20.76 ± 13.61 mmHg in the starting Per/Ind/Aml group *versus* -16.78 ± 16.31 mmHg in the starting Per/Ind group (E (SE) = -4.12 (1.73) mmHg, 95% CI = [-7.52 ; -0.72], p = 0.018, in the FAS ABPM, post-hoc analysis, and including adjustment on gender E (SE) = -5.29 (1.69), 95 % CI = [-8.62 ; -1.96], p = 0.002).

Office supine SBP (mmHg) - Change from baseline to M1
Comparison between groups - Over M0-M1 period - FAS (N = 449)

Office supine SBP (mmHg)		Starting with Per/Ind/Aml (N = 225)	Starting with Per/Ind (N = 224)
Baseline	n	225	224
	Mean ± SD	161.87 ± 7.09	162.80 ± 7.81
	95% CI	[160.94 ; 162.80]	[161.77 ; 163.83]
	Min ; Max	150.0 ; 178.5	150.0 ; 179.5
END M1	n	225	224
	Mean ± SD	142.69 ± 13.46	145.51 ± 15.60
	95% CI	[140.93 ; 144.46]	[143.45 ; 147.56]
	Min ; Max	107.5 ; 183.5	102.5 ; 193.5
END M1 - Baseline	n	225	224
	Mean ± SD	-19.18 ± 14.50	-17.29 ± 16.40
	95% CI	[-21.09 ; -17.27]	[-19.45 ; -15.13]
	Min ; Max	-63.0 ; 16.5	-72.0 ; 34.5
Statistical analysis	E (SE) (1)	-2.56 (1.32)	
	95% CI (2)	[-5.16; 0.04]	
	p (3)	0.054	
Including adjustment on gender	E (SE) (4)	-3.05 (1.32)	
	95% CI (2)	[-5.63 ; -0.46]	
	p (3)	0.021	

N: total number of patients in each treatment group; n: number of patients affected; (1) Estimate (Standard Error) of the difference in adjusted mean changes from baseline to M1 last post-baseline value P5/I1.25/A5 - P5/I1.25 using a General Linear Model with treatment, baseline and country as covariates; (2) 95% Confidence Interval of the estimate; (3) p value associated to the estimate; (4) Estimate (Standard Error) of the difference in adjusted mean changes from baseline to M1 post-baseline value P5/I1.25/A5 - P5/I1.25 using a General Linear Model with treatment, baseline,country, and gender as covariates

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- Primary assessment endpoint (Cont'd)

Moreover, results of SBP from ABPM and HBPM measurements showed a statistically significant effect in favour of Per/Ind/Aml, in non-adjusted and adjusted on gender analyses (see Table hereafter).

SBP (mmHg) from ABPM and HBPM sub-studies - Change from baseline to M1
Comparison between groups - Over M0-M1 period - FAS-ABPM (N = 276) and FAS-HBPM (N = 263)

SBP (mmHg)			**Starting with Per/Ind/Aml**	**Starting with Per/Ind**
Mean 24 h ASBP (mmHg)	FAS-ABPM	N	134	142
M1 - Baseline		Mean ± SD	-8.73 ± 13.03	-4.86 ± 12.93
		95% CI	[-10.96 ; -6.50]	[-7.01 ; -2.72]
		Min ; Max	-59.0 ; 18.7	-54.1 ; 33.7
Statistical analysis		E (SE) (1)	-3.74 (1.35)	
		95% CI (2)	[-6.39 ; -1.09]	
		p (3)	0.006	
Including adjustment on gender		E (SE) (4)	-4.48 (1.33)	
		95% CI (2)	[-7.11; -1.85]	
		p (3)	< 0.001	
HSBP (mmHg) global (morning and evening) mean 4 days preceding the visit	FAS-HBPM	N	135	128
M1 - Baseline		Mean ± SD	-10.28 ± 12.69	-4.95 ± 14.01
		95% CI	[-12.44 ; -8.12]	[-7.40 ; -2.50]
		Min ; Max	-41.0 ; 18.2	-52.2 ; 32.3
Statistical analysis		E (SE) (1)	-4.62 (1.39)	
		95% CI (2)	[-7.36; -1.89]	
		p (3)	0.001	
Including adjustment on gender		E (SE) (4)	-4.91 (1.37)	
		95% CI (2)	[-7.61 ; -2.21]	
		p (3)	< 0.001	

ASBP: Ambulatory Systolic Blood Pressure; HSBP: Home Blood Pressure Systolic Blood Pressure; N: total number of patients in each considered treatment group; (1) Estimate (Standard Error) of the difference in adjusted mean changes from Baseline to M1 post baseline value P5/I1.25/A5 - P5/I1.25 using a General Linear Model with treatment and baseline as covariates; (2) 95% Confidence Interval of the estimate; (3) p-value associated to General Linear Model; (4) Estimate (Standard Error) of the difference in adjusted mean changes from Baseline to M1 post baseline value P5/I1.25/A5 - P5/I1.25 using a General Linear Model with treatment, baseline and gender as covariates

SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- **Primary assessment endpoint (Cont'd)**

Secondary analyses

The within-group analysis showed that the decrease in the office SBP was statistically significant in both treatment groups over M0-M2 and M0-M3 in the FAS:

- M0-M2: E (SE) = -25.79 (0.92) mmHg; 95% CI = [-27.61 ; -23.98] in the starting Per/Ind/Aml group and E (SE) = -24.47 (1.00) mmHg; 95% CI = [-26.44 ; -22.51] in the starting Per/Ind group, both $p < 0.001$.
- M0-M3: E (SE) = -28.19 (0.98) mmHg; 95% CI = [-30.11 ; -26.27] and E (SE) = -26.82 (0.97) mmHg; 95% CI [-28.72 ; -24.91], respectively, both $p < 0.001$.

In patients not controlled at M1 (M2 respectively), and uptitrated to the highest dose, a statistically significant decrease was observed in the office SBP, in the FAS:

- Over M1-M2: E (SE) = -11.66 (1.06) mmHg ($p < 0.001$) in patients who switched from Per5/Ind1.25/Aml5 to Per5/Ind1.25/Aml10 (144/225 patients, 64.0%), and E (SE) = -11.61 (1.02) mmHg ($p < 0.001$) in patients who switched from Per5/Ind1.25 to Per5/Ind1.25/Aml5 (133/224 patients, 72.8%).
- Over M2-M3: E (SE) = -7.53 (1.24) mmHg ($p < 0.001$) in patients who switched from Per5/Ind1.25/Aml10 to Per10/Ind2.5/Aml10, 65/225 patients, 28.9%, and E (SE) = -7.73 (1.03) mmHg ($p < 0.001$) in patients who switched from Per5/Ind1.25/Aml5 to Per10/Ind2.5/Aml5, 90/224 patients, 40.2%).

Note that all patients that were uptitrated from M1 received triple combination whatever the starting group (with Per/Ind/Aml or Per/Ind).

For patients initially randomised in the starting Per/Ind/Aml group and having switched on P10/I2.5/A10 at M2 or M3, a statistically significant decrease in the supine SBP was observed one month after the switch: E (SE) = -8.17 (1.14) mmHg ($p < 0.001$).

For patients initially randomised in the starting Per/Ind group who were up-titrated, then switched from P10/I2.5/A5 to P10/I2.5/A10 at M3, a statistically significant decrease in the supine SBP was observed over one month, from M3 to M4, E (SE) = -9.17 (1.50) mmHg ($p < 0.001$).

Sensitivity analyses performed in the PPS showed same trends.

- **Secondary assessment endpoints**

The ***office supine DBP*** decreased between baseline and the last post-baseline measurement until M1 in both treatment groups. This decrease was statistically significantly greater in the starting Per/Ind/Aml group than in the starting Per/Ind group: -13.16 ± 9.98 mmHg *versus* -10.11 ± 9.65 mmHg, respectively (E (SE) = -2.82 (0.88) mmHg; 95% CI [-4.54; -1.09], p = 0.001).
The office DBP over M0-M1 was also statistically significant when considering the adjustement on gender ($p < 0.001$). When considering patients with sustained hypertension (uncontrolled hypertension confirmed at both office and 24-hour ABPM, 116/134 patients (86.6%) and 126/142 patients (88.7%)), a statistically significant decrease in the office DBP was observed: by -12.85 ± 8.61 mmHg in the starting Per/Ind/Aml group versus -9.79 ± 9.40 mmHg in the starting Per/Ind group (E (SE) = -3.19 (1.11) mmHg, 95% CI = [-5.37 ; -1.01], p = 0.004, in the FAS ABPM, post-hoc analysis, and after including adjustment on gender : E (SE) = -3.71 (1.11) mmHg, 95% CI = [-5.89 ; -1.54], $p < 0.001$).

Moreover, results issued from the ABPM study showed a statistically significant between-group difference in the mean 24h ADBP decrease over M0-M1, in favour of the starting Per/Ind/Aml group after including adjustement on the gender (p = 0.039).

Results issued from the HBPM study showed a statistically significant between-group difference in mean HDBP (global) over the 4 days preceding the visit in favour of the starting Per/Ind/Aml group (E (SE) = -3.02 (0.90) mmHg, 95% CI = [-4.78; -1.25], $p < 0.001$; and after including adjustment on the gender: E (SE) = -3.12 (0.90) mmHg, 95% CI =[-4.89 ; -1.35], $p < 0.001$, see HBPM clinical report NP34561). The results were also in favour of the starting Per/Ind/Aml group when considering 4 days preceding the visit for all periods.

The within-group analysis showed that the decrease in the office DBP was statistically significant in both treatment groups over M0-M2 and M0-M3 in the FAS:

- Over M0-M2: E (SE) = -16.68 (0.58) mmHg; 95% CI = [-17.82; -15.54] in the starting Per/Ind/Aml group and E (SE) = -14.83 (0.63) mmHg; 95% CI [-16.06; -13.59] in the starting Per/Ind group, both $p < 0.001$
- Over M0-M3: E (SE) = -17.99 (0.61) mmHg; 95% CI = [-19.19; -16.79] and E (SE) = -15.23 (0.59) mmHg; 95% CI [-16.39; -14.07], respectively, both $p < 0.001$.

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **Secondary assessment endpoints (Cont'd)**

In patients uptitrated to the highest possible dose at M1 (M2 respectively), the mean office supine DBP statistically significantly decreased in each treatment group, in the FAS:

- Over M1-M2: E (SE) = -6.50 (0.70) mmHg in patients who switched from Per5/Ind1.25/Aml5 to Per5/Ind1.25/Aml10, and E (SE) = -7.00 (0.72) mmHg in patients who switched from Per5/Ind1.25 to Per5/Ind1.25/Aml5, both $p < 0.001$).
- Over M2-M3: E (SE) = -4.05 (0.89) mmHg in patients who switched from Per5/Ind1.25/Aml10 to Per10/Ind2.5/Aml10, and E (SE) = -3.40 (0.72) mmHg in patients who switched from Per5/Ind1.25/Aml5 to Per10/Ind2.5/Aml5, both $p < 0.001$).

For patients initially randomised in the starting Per/Ind/Aml group who switched on P10/I2.5/A10 at M2 or M3, a statistically significant decrease in the supine DBP was observed one month after having switched (E (SE) = -4.16 (0.82) mmHg, $p < 0.001$).

For patients initially randomised in the starting Per/Ind group who switched from P10/I2.5/A5 to P10/I2.5/A10 at M3, a statistically significant decrease in the supine DBP was observed from M3 to M4 (E (SE) = -7.57 (1.03) mmHg, $p < 0.001$).

The other following **main secondary efficacy endpoints** also showed a decrease over M0-M1 in both treatment groups in the FAS, with statistically significant greater decrease in the starting Per/Ind/Aml group than in the starting Per/Ind group:

- ***Office standing SBP at 3 min***: -17.9 ± 16.7 mmHg group *versus* -14.4 ± 18.5 mmHg, respectively ($p = 0.004$, and after including adjustment on gender $p = 0.001$).
- ***Office standing DBP at 3 min***: -10.8 ± 11.7 mmHg *versus* -8.0 ± 12.1 mmHg, respectively ($p = 0.003$, and after including adjustment on gender $p = 0.001$).
- ***Office supine MBP***: -15.2 ± 10.2 mmHg *versus* -12.5 ± 10.9 mmHg ($p = 0.004$, and after including adjustment on gender $p < 0.001$).

The ***office supine PP*** decreased over M0-M1 in both treatment groups, on average by -6.0 ± 12.2 mmHg in the starting Per/Ind/Aml group *versus* -7.2 ± 12.1 mmHg in the starting Per/Ind group, with no statistically significant difference between treatment groups (as well as for the analysis including adjustment on gender).

Most of the patients ***responded to treatment*** at M1, with a statistically significant greater proportion of responders in the starting Per/Ind/Aml group than in the Per/Aml group: 72.0% *versus* 52.7%, respectively ($p < 0.001$, and after including adjustment on gender $p < 0.0001$).

The ***blood pressure control*** was reached at M1 by 32.0% of the patients in the starting Per/Ind/Aml group *versus* 24.6% in the starting Per/Ind group, with no statistically significant between-group difference, but reaching statistical significance in favour of starting Per/Ind/Aml group after including adjustment on gender $p = 0.005$. At the last M4 visit, more than 80% of the patients achieved to control their blood pressure whatever the starting group: 82.2% in the starting Per/Ind/Aml group and 81.7% in the starting Per/Ind group.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

The Table hereafter summarises the main results of adverse events in the Safety Set.

Overall summary for adverse events over the M0-M1 and M0-M15 periods in the Safety Set

		Over M0-M1		Over M0-M15
		Starting with Per/Ind/Aml (N = 227)	**Starting with Per/Ind (N = 225)**	**ALL (N = 452)**
Patients having reported at least one:				
Emergent adverse event	n (%)	20 (8.8)	17 (7.6)	115 (25.4)
Treatment-related emergent adverse event	n (%)	9 (4.0)	5 (2.2)	37 (8.2)
Emergent hypotension	n (%)	2 (0.9)	-	7 (1.6)
Emergent orthostatic hypotension	n (%)	2 (0.9)	-	3 (0.7)
Serious emergent adverse event	n (%)	3 (1.3)	1 (0.4)	9 (2.0)
Treatment-related emergent serious adverse event	n (%)	-	-	-
Patients with treatment withdrawal due to:				
Emergent adverse event	n (%)	3 (1.3)	2 (0.9)	8 (1.8)
Emergent serious adverse event	n (%)	-	1 (0.4)	-
Treatment-related emergent adverse event	n (%)	3 (1.3)	1 (0.4)	6 (1.3)
Treatment-related emergent serious adverse event	n (%)	-	-	-
Patients who died	n (%)	-	-	2 (0.4)

N: Number of patients by group
n: number of affected patients
*%: (n*100/N)*

Over M0-M1, emergent AEs were reported with a similar frequency in both groups: 20 patients (8.8%) in the starting Per/Ind/Aml group *versus* 17 patients (7.6%) in the starting Per/Ind group.

The SOCs most frequently affected were in the starting Per/Ind/Aml group: Nervous system disorders (4 patients 1.8% *versus* 5 patients, 2.2%, respectively), Infections and infestations (4 patients, 1.8% *versus* 2 patients, 0.9%, respectively), and General disorders and administration site conditions and Vascular disorders (4 patients, 1.8% *versus* none, respectively). In the starting Per/Ind group the most frequently reported SOCs were: Metabolism and nutrition disorders (2 patients, 0.9% *versus* 6 patients, 2.7%), and Nervous system disorders (see above). No relevant between-group difference was observed.

Consistently with the amlodipine SmPC, the following expected EAEs were more frequently reported in the starting Per/Ind/Aml group than in the starting Per/Ind group: oedema peripheral (4 patients, 1.8% *versus* none, respectively) and orthostatic hypotension (2 patients, 0.9% *versus* none). The other EAEs listed in the SmPC and reported were:

- Cough, due to perindopril (2 patients, 0.9% *versus* 1 patient, 0.4%, respectively).
- Hypokalaemia, due to the indapamide diuretic mechanism of action (none *versus* 2 patients, 0.9%, respectively).

In the starting Per/Ind group, headache was the only preferred term reported in more than 2 patients (2 patients, 0.9% in the starting Per/Ind/Aml group *versus* 3 patients, 1.3% in the starting Per/Ind group).

Most of the EAEs were rated mild 48 (77.4%) and 3 (4.8%) were severe.

Treatment-related EAEs were reported in 9 patients (4.0%) in the starting Per/Ind/Aml group *versus* 5 patients (2.2%) in the starting Per/Ind group, mainly peripheral oedema in the starting Per/Ind/Aml group (4 patients, 1.8% in the starting Per/Ind/Aml group only) and hypokalaemia in the starting Per/Ind group (2 patients, 0.9% in the starting Per/Ind group only). Other treatment-related EAEs reported in at least 2 patients in any group were cough (2 patients, 0.9% in the starting Per/Ind/Aml group *versus* 1 patient, 0.4% in the Per/Ind group) and orthostatic hypotension (2 patients, 0.9% *versus* none). None of the treatment-related EAEs was serious.

EAEs led to patient's treatment withdrawal during the M0-M1 period in 3 patients, 1.3% in the starting Per/Ind/Aml group (cough, oedema peripheral and erectile dysfunction) and 2 patients, 0.9% in the starting Per/Ind group (cough in 1 patient, meningioma benign and grand mal convulsion in 1 patient). Of them, 2 were serious and not considered as treatment-related (meningioma benign and grand mal convulsion); the other events were considered as treatment-related and non-serious.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Over M0-M4, EAEs were reported in 25.1% of patients in the starting Per/Ind/Aml group and 21.8% in the starting Per/Ind group, with a similar profile of EAEs to the one described over M0-M1, excepted for the SOC Metabolism and nutrition disorders, which was the most frequently reported over M0-M4 in both groups (7.5% in the starting Per/Ind/Aml group and 8.9% in the starting Per/Ind group) due to protocol planned laboratory assessments performed after M1.
In the starting Per/Ind/Aml group all EAEs were reported in less than 2% of patients excepted hypokalaemia and oedema peripheral, both reported in 2.6%. In the starting Per/Ind group only hyperuricaemia was reported in more than 2% of patients (4.4%).

Most frequent treatment-related EAEs were foreseeable, as they are already described in the SmPC related to amlodipine and indapamide: oedema peripheral (2.6%) and hypokalaemia (2.2%) in the starting Per/Ind/Aml group. None of the treatment-related EAEs were reported in more than 2% of patients in the starting Per/Ind group. No particular event led to study withdrawal.
Regarding the treatment dose groups, less than 5% of the patients were affected by any EAE, whatever the treatment dose group. The safety profile was similar whatever the treatment dose received.

The EAEs reported during the whole study were in line with events reported in the SmPC for indapamide, perindopril and amlodipine. Hypokalaemia is listed as very common (≥ 10%) with indapamide, oedema common (≥ 1%) with amlodipine, cough common (≥ 1%) with perindopril; and orthostatic hypotension is commonly reported with anti-hypertensive treatments.

Over M0-M15, EAEs affected 25.4% of the patients. The SOC most frequently affected was Metabolism and nutrition disorders (8.6%), and the most frequently reported EAEs were hyperuricaemia (3.1%) and hypokalaemia (2.4%). The other EAEs were reported in less than 2% of patients. None of the treatment-related EAEs was reported in more than 2% of patients except for hypokalaemia (2.2%). Less than 2% of EAEs reported over M0-M15 led to treatment discontinuation.
During the overall study period (M0-M15), most EAEs recovered or were recovering (63.7%, 128 events).
Two events were fatal: sudden death and staphylococcal sepsis.

Hypotension and orthostatic hypotension during the whole M0-M15 study
Orthostatic hypotension, listed in the SmPC, was uncommon in this study. Over M0-M1, 2 patients reported emergent orthostatic hypotensions in the starting Per/Ind/Aml group. During the M0-M4 period after M1, 3 other patients reported hypotension in the starting Per/Ind/Aml group; 1 patient reported orthostatic hypotension and 1 reported hypotension in the starting Per/Ind group.
Emergent calculated orthostatic hypotension (defined according to a mathematic rule) was detected in 3 patients in the starting Per/Ind/Aml group over the M0-M1 period, in 3 patients in each group over the M0-M4 period, and in 7 patients overall during the M0-M15 period.

Serious EAE during the whole M0-M15 study
A total of 9 patients (2.0%) experienced 22 serious EAEs (including the Sponsor's upgrade) during the study:

- Over M0-M1, 4 patients (0.9%) experienced 7 SEAEs: 3 patients in the starting Per/Ind/Aml group had 5 SEAEs and 1 patient in the starting Per/Ind group had 2 SEAEs.
- Over M0-M4 after M1, 5 patients (1.1%) experienced a total of 14 SEAEs: 4 patients in the starting Per/Ind/Aml group had 13 SEAEs and 1 patient in the starting Per/Ind group had 1 SEAE.
- After M4, over M0-M15: one additional patient experienced an SEAE.

Overall, SEAEs concerned no particular SOC or PT and none was considered related to the study drug. A total of 3 emergent SAEs in 2 patients led to study drug withdrawal (tendon rupture, and in one patient: and in one patient grand mal convulsive and meningioma benign).

Two patients died during the study, both on treatment and considered as not treatment-related: staphylococcal sepsis during the M0-M4 period (while the patient was on P10/I2.5/A10), and one patient from sudden death after M4, with no persistent medical history nor cardiovascular disease, diabetes, or dyslipidaemia. During the study, this patient did not have any adverse event reported.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Laboratory tests**

Neither clinically relevant change over time nor relevant between-group difference was observed for biochemistry and haematological parameters, over M0-M4 and M0-M15, in the Safety Set.

During the M0-M4 treatment period in the starting Per/Ind/Aml group, emergent PCSA for biochemical values were reported in less than 5% of the patients for each parameter. For haematology, PCSAs values affected less than 2% of the patients, whatever the parameter.
In the starting Per/Ind group, emergent PCSA for biochemical values were also reported in less than 5% of the patients for each parameter. For haematology, emergent PCSA values were sparse for all parameters, except for low haematocrit, reported in 5 patients, 2.4%.

During the M0-M15 treatment period, emergent PCSA for biochemical values were reported in less than 5% of the patients for each parameter. For haematology, PCSAs values affected less than 2% of the patients, whatever the parameter.

- **Other safety evaluations**

For **vital signs,** neither relevant change over time neither between-group difference was observed for the heart rate over the M0-M1 treatment period.
No relevant changes over time were observed for heart rate, weight and BMI during the M0-M4 period in the Per/Ind/Aml and the starting Per/Ind groups, and during the M0-M15 period overall in the Safety Set.

ECG abnormalities were detected at last post-baseline visit on treatment over M0-M4 in 6 patients, 2.8% in the starting Per/Ind/Aml group and in 5 patients, 2.3% in the starting Per/Ind group. Over M0-M15, significant ECG abnormalities were detected at last post baseline visit in 10 patients (2.3%).

CONCLUSION

This international randomised double-blind Phase III study, conducted in 454 patients with essential uncontrolled hypertension, aimed to demonstrate the superiority effect of Perindopril/Indapamide/Amlodipine *versus* Perindopril/Indapamide (as fixed combinations) in lowering office supine SBP, after one month of treatment.

At study entry, a relevant greater proportion of women in the starting Per/Ind group as compared to the starting Per/Ind/Aml group likely due to chance was observed. Taking into account the known influence of gender on anti-hypertensive therapy efficacy, it was important to demonstrate that any observed treatment effect was not misrepresented due to imbalances at baseline. Therefore post-hoc sensitivity analyses including adjustment on gender were performed for efficacy analysis.

After 1 month of treatment, a large decrease in the office supine SBP was observed with both treatment groups (-19.18 ± 14.50 mmHg in the starting Per/Ind/Aml group *versus* -17.29 ± 16.40 mmHg in the starting Per/Ind group). The greater decrease observed in starting Per/Ind/Aml group compared to the starting Per/Ind group close to significance (p = 0.054), was statistically significant in favour of the starting Per/Ind/Aml group once including adjustment on gender (p = 0.021).

When considering patients with sustained hypertension (uncontrolled hypertension confirmed at both office and 24-hour ABPM) a statistically significant greater decrease in the office SBP was obtained with the starting Per/Ind/Aml group, on non-adjusted (post-hoc analysis), and including adjustment on gender analysis.

Results for SBP obtained with ABPM and HBPM measurements (from sub-studies) confirmed also a statistically significant superiority of the group starting with Per/Ind/Aml in comparison with the group starting with Per/Ind, over M0-M1, in the non-adjusted analysis, even more pronounced in the gender adjusted analysis.

Regarding office supine DBP, a statistically significant decrease after 1 month of treatment was reached in favour of the starting Per/Ind/Aml group (also when considering the adjustment on gender). Other secondary efficacy endpoints showed also a greater effect of the Per/Ind/Aml strategy in comparison with the Per/Ind strategy (standing SBP and DBP, supine MBP).
A greater and statistically significant difference (non-adjusted and gender adjusted analysis) was observed in terms of responders to the treatment after one month in the starting Per/Ind/Aml group than in the starting Per/Ind group (72.0% *versus* 52.7%, respectively). After one month of treatment, 32.0% of the patients in the starting Per/Ind/Aml group and 24.6% in the starting Per/Ind group achieved to control their blood pressure. The non-controlled patients could be uptitrated at M1, M2 and or M3 with triple therapy whatever the starting group. This up-titration allowed a large decrease of office supine SBP and DBP that was statistically significant within each strategy. At the end of the study, whatever the starting treatment group, more than 80% of the patients achieved to control their blood pressure.

Over the whole study period (M0-M15), no safety concern was raised in any treatment group, and the safety profile was in accordance with the known Summary of the Products Characteristics. In particular, peripheral oedema and orthostatic hypotension were reported in less than 2% of the overall patients over the whole study period.

The safety profile was similar whatever the treatment dose received.

Date of the report: 04 July 2016

Version of the report: Final version