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: Triplixam®** **Name of Active Ingredient: perindopril / indapamide / amlodipine (S06593)**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study:

Evaluation of the clinical efficacy and safety of **perindopril 5 mg / indapamide 1.25 mg / amlodipine 5 mg** fixed combination in single-pill after 2 months of treatment *versus* free combination, **perindopril 4 mg** / **indapamide 1.25 mg** + **amlodipine 5 mg** given separately at the same time, with conditional titration based on blood pressure control in patients with essential hypertension uncontrolled after 1 month with perindopril 4 mg / indapamide 1.25 mg bi-therapy. A national, multicentre, randomised, double-blind, 7 months study.

Protocol No.: CL3-06593-018

The description of the study protocol given hereafter includes the modifications of the n°1 and 2 substantial amendments to the protocol.

National coordinator

[redacted]

Study country:

37 centres located in China included a total of 532 patients.

Publication (reference):

Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 06 May 2019 (date of first visit first patient) Completion date: 23 February 2022 (date of last visit last patient)	**III**

Objectives:

Primary objective

To assess the non-inferiority of perindopril 5 mg / indapamide 1.25 mg / amlodipine 5 mg fixed combination in lowering office sitting Systolic Blood Pressure (SBP), after 2 months of treatment (M002), compared to a free combination of the components perindopril 4 mg / indapamide 1.25 mg in a single pill and amlodipine 5 mg pill given separately at the same time, in patients with essential hypertension, uncontrolled after 1 month with perindopril 4 mg / indapamide 1.25 mg bi-therapy.

Secondary objectives

Efficacy on Office blood pressure:

- To assess the effect of fixed combination *versus* free combination in lowering of other office sitting BP parameters (Diastolic Blood Pressure (DBP), Mean Blood Pressure (MAP), Pulse Pressure (PP), response to the treatment, blood pressure control rates) and in lowering of standing SBP and DBP, after 2 months of treatment (M002),
- To assess in each arm the up-titration effect (sitting SBP, DBP, MAP, PP, response to the treatment, blood pressure control rates and standing SBP, DBP) for each higher dose (after 2 months of treatment with each higher dose):
  - over M002-M004 period in patients remaining uncontrolled at the dose of perindopril 5 mg / indapamide 1.25 mg / amlodipine 5 mg or perindopril 4 mg / indapamide 1.25 mg + amlodipine 5 mg, and uptitrated at visit M002 to perindopril 10 mg / indapamide 2.5 mg / amlodipine 5 mg or perindopril 4 mg / indapamide 1.25 mg (x2) + amlodipine 5 mg,
  - over M004-M006 period in patients remaining uncontrolled at the dose of perindopril 10 mg / indapamide 2.5 mg / amlodipine 5 mg or perindopril 4 mg / indapamide 1.25 mg (x2) + amlodipine 5 mg and uptitrated at visit M004 to perindopril 10 mg / indapamide 2.5 mg / amlodipine 10 mg or perindopril 4 mg / indapamide 1.25 mg (x2) + amlodipine 5 mg (x2).

Efficacy on Ambulatory Blood Pressure Monitoring (ABPM)

- To assess the effect of fixed combination and free combination on ambulatory BP parameters after 2 months of treatment (from M000 to M002) in the sub-group of patients participating to the ABPM part of the study.
- To explore the effect of fixed combination and free combination on ambulatory BP parameters after 1-day treatment omission at M006 (in the sub-group of patients with a 48-hour ABPM recording).

Safety:

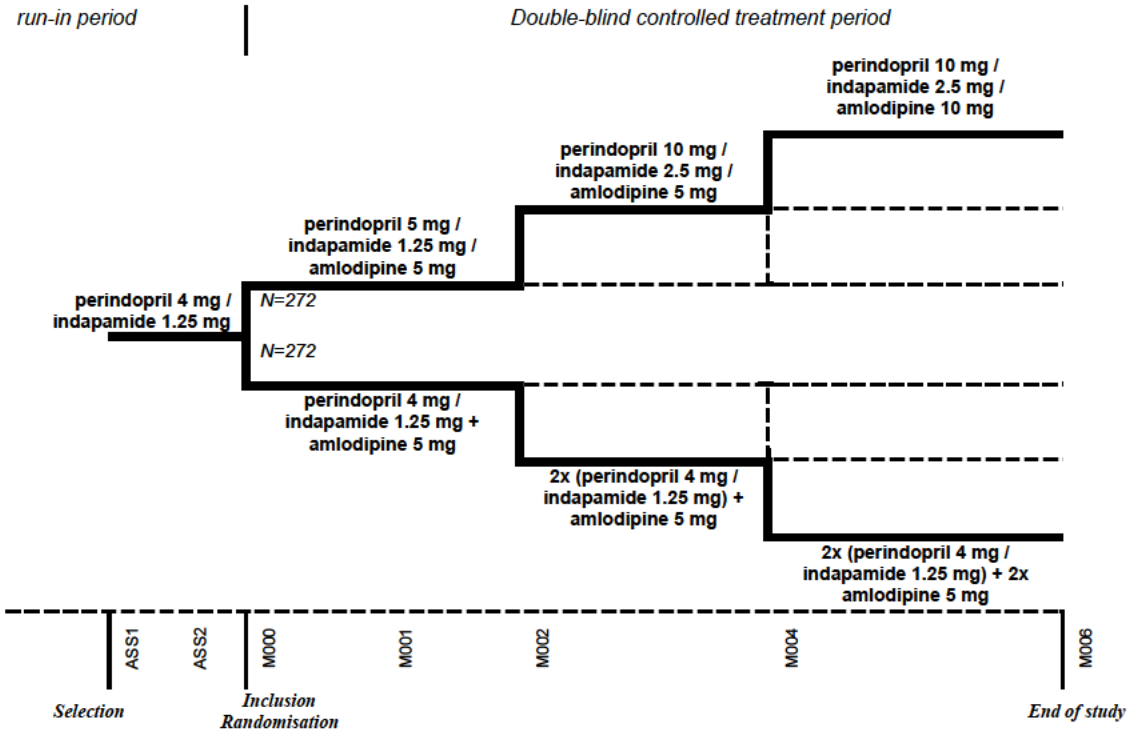
- To assess the safety and tolerability of fixed combination and free combination during the study.

Methodology:

This was a multicentre, randomised, double-blind, phase III study conducted over 7 months in patients with essential hypertension. A one-month run-in period on assigned bi-therapy was followed by 6 months of randomised triple therapies, with conditional titration based on blood pressure (BP) control. The primary BP endpoint was assessed after 2 months of randomised treatment and non-inferiority analysis was performed. The remaining 4 months were to assess the up-titration strategy and safety. A fixed, centralised randomisation by Interactive Response System (IRS) stratified patients according to study centre.

The uptitrations of the study drug doses could occur for patients who did not achieve target BP (SBP ≥140 mmHg and/or DBP ≥90 mmHg) at the M002 and/or M004 visits.

The ABPM assessment was performed at M000, M002 and M006 (optional) visits in a subgroup of dedicated sites that accepted to participate. In these sites, ABPM assessment was proposed to all patients.



This study was performed in strict accordance with Good Clinical Practice.

Number of patients:

Planned: 544 included patients (272 randomised in each group)
At least 270 patients participating in the 24-ABPM part of the study.

Included: 532 patients (263 in the Per/Ind/Aml group and 269 in the Per/Ind + Aml group)
74 patients participated in the 24-ABPM part of the study (33 in the Per/Ind/Aml group and 41 in the Per/Ind + Aml group).

Diagnosis and main criteria for inclusion:
The participants were Asian men and women of at least 18 years old, treated for essential systolic and diastolic hypertension, having a body mass index (BMI) not exceeding 30 kg/m² and having on the day of the selection visit an uncontrolled hypertension (SBP ≥ 140 and < 180 mmHg and DBP ≥ 90 and < 110 mmHg) while being treated with any anti-hypertensive monotherapy at maximal dose or any dual therapy at starting dose according to investigator's routine practice, for at least 1 month prior to the visit. At the inclusion visit, after one month of run-in therapy, patients were again required to have SBP ≥ 140 and < 180 mmHg and DBP ≥ 90 and < 110 mmHg for randomisation.

Study drugs:
Run-in IMP: perindopril tert-butylamine 4 mg / indapamide 1.25 mg (Batch manufacturing No: L0071219, L00738, L0075599, L007678, L0071377, L0074841, L0075781, L0077505).
During run-in, patients were to take orally each morning before breakfast one capsule containing 1 tablet of perindopril 4 mg / indapamide 1.25 mg.

Test drug IMP (S06593): 3 dose strengths:

- Perindopril arginine 5 mg / indapamide 1.25 mg / amlodipine 5 mg (Batch manufacturing No: L0071126, L0073906, L0075729, L0076755, L0071515, L0074387, L0075782, L0077979).
- Perindopril arginine 10 mg / indapamide 2.5 mg / amlodipine 5 mg (Batch manufacturing No: L0071127, L0073904, L0076754, L0071519, L0074805, L0076811).
- Perindopril arginine 10 mg / indapamide 2.5 mg / amlodipine 10 mg (Batch manufacturing No: L0071128, L0073905, L0076753, L0071523, L0074808, L0076812).

All patients randomised on test drug arm were to take orally each morning before breakfast one capsule containing 1 tablet of S06593.
The starting dose at inclusion was perindopril 5 mg / indapamide 1.25 mg / amlodipine 5 mg. At M002, then M004, if needed on basis of their SBP and DBP results, patients could be uptitrated (assigned a higher dose via the IRS): perindopril 10 mg / indapamide 2.5 mg / amlodipine 5 mg, then, perindopril 10 mg / indapamide 2.5 mg / amlodipine 10 mg, respectively.

Comparator (Reference products and/or placebo):

- Perindopril tert-butylamine 4 mg / indapamide 1.25 mg + amlodipine 5 mg.
- Perindopril tert-butylamine 4 mg / indapamide 1.25 mg (x2) + amlodipine 5 mg.
- Perindopril tert-butylamine 4 mg / indapamide 1.25 mg (x2) + amlodipine 5 mg (x2).

All patients randomised on the comparator arm were to take each morning before breakfast 2 capsules orally: 1 capsule containing 1 or 2 tablets of perindopril 4 mg / indapamide 1.25 mg and 1 capsule containing 1 or 2 tablets of amlodipine 5 mg.
The starting dose at inclusion was perindopril 4 mg/indapamide 1.25 mg + Amlodipine 5 mg. At M002, then M004, if needed on basis of their SBP and DBP results, patients could be uptitrated (assigned a higher dose via the IRS): perindopril 4 mg / indapamide 1.25 mg (x2) + amlodipine 5 mg, then perindopril 4 mg / indapamide 1.25 mg (x2) + amlodipine 5 mg (x2), respectively.

To maintain the blind treatment allocation, patients randomised to the study drug (run-in IMP and study drug IMP) also took one capsule of placebo each morning.

Duration of treatment:
Run-in period: 1 month
Active treatment period: 6 months
(1 month corresponded to 28 calendar days)

Criteria for evaluation:
Efficacy measurements
Primary efficacy endpoint: Office sitting SBP change from baseline to last post-baseline value over M000-M002 period with each treatment strategy.

Secondary efficacy endpoints

- Office BP measurement at each visit:
  - Sitting DBP and standing SBP, DBP.
  - Sitting Mean Arterial Blood Pressure (MAP), defined as MAP = 2/3 DBP + 1/3 SBP.
  - Sitting Pulse Pressure (PP), defined as PP = SBP – DBP.
  - Response to the treatment, defined as sitting SBP < 140 mmHg and DBP < 90 mmHg and/or SBP decrease ≥ 20 mmHg from baseline and/or DBP decrease ≥ 10 mmHg from baseline.
  - BP control, defined as sitting SBP < 140 mmHg and DBP < 90 mmHg.
- ABPM parameters at each visit over the M000-M002 period in the sub-group of participating patients:
  - Mean ambulatory SBP, DBP and heart rate (HR) over 24 hours and ambulatory blood pressure control.

Exploratory measurements (optional)

Exploratory ABPM parameters in the sub-group of participating patients:

- Mean ambulatory SBP, DBP and HR over 24 hours at M006 and ambulatory blood pressure control.
- Ambulatory SBP, DBP and HR hourly mean over the first 24 hours and on 24-48h at M006.

Safety measurements

- Emergent adverse events.
- Orthostatic hypotension (calculated, from sitting to standing position).
- Complete and simplified laboratory examinations.
- Physical examination, height (at selection), weight, HR.
- 12-lead electrocardiogram.

Statistical methods:

Analysis Sets:

Randomised Set (RS): All included patients to whom a therapeutic unit was randomly assigned using IRS.

Full Analysis Set (FAS): In accordance with the intention-to-treat principle, all patients of the RS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value of SBP over M000-M002 period.

Per Protocol Set (PPS): All patients of the FAS without relevant deviation(s), that could affect the evaluation of IMP effect on the primary efficacy endpoint.

Safety Set (SS): All patients having taken at least one dose of IMP.

Safety Set Run-In (SSR): All patients having taken at least one dose of run-in IMP.

ABPM set: All patients of the RS having taken at least one dose of IMP and having valid mean 24-hour SBP values at both baseline and M002.

Efficacy analysis:

Primary endpoint: Change from baseline to last post-baseline in office sitting SBP value over M000-M002 period in the FAS. The main analysis was to demonstrate the non-inferiority of S06593 *versus* the free combination comparator, using an analysis of covariance (ANCOVA) model including the fixed, categorical effects of treatment and centre, as well as the continuous, fixed covariate of baseline. Missing data were imputed using a Last Observation Carried Forward (LOCF) approach. The non-inferiority margin was set at 4 mmHg.

The supplementary analyses were performed (without adjusting on the centre) and included: an Intercurrent Event (ICE) approach in the RS, analyses on the PPS (*i.e.,* the primary analysis for the primary efficacy endpoint performed in the FAS was repeated in the PPS) and on Completers at M002 in the FAS (*i.e.,* patients with no missing data at M002) as well as an analysis with the addition of recruitment source as covariate in the FAS.

Secondary endpoints: Other sitting office BP parameters (DBP, MAP, PP), standing SBP and DBP, expressed as change from baseline to last post-baseline value over M000-M002 period with an ANCOVA model for quantitative endpoints and on the last post-baseline value at M002 with logistic regression for qualitative endpoints. Missing data were imputed using LOCF approach. Secondary endpoints analyses were done in the FAS and PPS.
The response to treatment and BP control: expressed as number and percentage of patients.
The intra group analyses were performed to evaluate the titration efficiency.

ABPM endpoints: Only descriptive statistics were provided.

Study patients: disposition, baseline characteristics and treatments analysis: Descriptive statistics were provided.

Safety analysis: Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 1392 patients were screened and 1053 were selected to enter the run-in phase of the study during which they received the bi-therapy perindopril 4 mg / indapamide 1.25 mg. After one month of treatment, a total of 532 patients were considered eligible for inclusion and were randomised. A well-balanced distribution was reached between-groups (263 patients in the Per/Ind/Aml group and 269 patients in the Per/Ind + Aml group).

The table below gives the disposition of patients by group as well as the analysis sets.

Of the randomised patients, 18.6% were withdrawn during the study (47 patients, 17.9% in the Per/Ind/Aml group *versus* 52 patients, 19.3% in the Per/Ind + Aml group), mostly due to non-medical reason (25 patients, 9.5% *versus* 23 patients, 8.6%, respectively). A total of 433 patients (81.4% of the randomised patients) completed the study (216 patients, 82.1% and 217 patients, 80.7%, respectively). No relevant between-group difference was detected.

Disposition of patients by group

	Fixed [Per/Ind/Aml] (N = 263)	**Free [Per/Ind + Aml] (N = 269)**	**ALL (N = 532)**
	n (%)	**n (%)**	**n (%)**
Included/randomised	**263**	**269**	**532**
Withdrawn due to	**47 (17.9)**	**52 (19.3)**	**99 (18.6)**
Non-medical reason	25 (9.5)	23 (8.6)	48 (9.0)
Treatment failure	11 (4.2)	13 (4.8)	24 (4.5)
Adverse event	9 (3.4)	15 (5.6)	24 (4.5)
Protocol violation	2 (0.8)	1 (0.4)	3 (0.6)
Completed	**216 (82.1)**	**217 (80.7)**	**433 (81.4)**
Full Analysis Set (FAS)	256 (97.3)	264 (98.1)	520 (97.7)
Per Protocol Set (PPS)	230 (87.5)	240 (89.2)	470 (88.3)
Ambulatory Blood Pressure Monitoring (ABPM)	33 (12.5)	41 (15.2)	74 (13.9)
Safety set (SS)	262 (99.6)	269 (100)	531 (99.8)

% Expressed as percentage of the patients in the randomised set.

BASELINE CHARACTERISTICS

The demographic and other baseline characteristics of the randomised patients were in line with the selection/inclusion criteria of the study protocol. There were no relevant differences between the treatment groups for baseline demographic characteristics.

In the Randomised Set (RS), patients were on average 55.7 ± 8.8 years old, and most of them (82.1%) were between 18 and 64 years old. More than half of the patients were men (60.7%). As recruitment source, patients were mainly addressed by the referral company (74.6%) rather than by direct recruitment at the centre (25.4%).
At baseline, the sitting HR was on average 78.1 ± 11.1 beats per minute (bpm), and the BMI was on average 26.1 ± 2.5 kg/m². Most of the patients (67.1%) had their BMI within the [25 ; 30[kg/m² range.

All patients had at selection an essential hypertension, with a mean duration from diagnosis slightly longer in the Per/Ind/Aml group than in the Per/Ind + Aml group: 118.1 ± 90.2 months *i.e.,* about 9.8 ± 7.5 years (median: 96.0 months *i.e.,* 8.0 years) *versus* 93.3 ± 78.8 months *i.e.,* about 7.8 ± 6.6 years (median: 71.0 months *i.e.,* 5.9 years), respectively. Almost all patients (96.8%) had previously received at least one treatment for essential hypertension before entry in the study, mainly calcium channel blockers (60.8% *versus* 61.7%, respectively). Most of the patients (73.1%) reported additional medical history, frequently related to metabolism and nutrition disorders (42.6% *versus* 47.6%, respectively), and most often hyperlipidaemia (with a slightly lower frequency in the Per/Ind/Aml group than in the Per/Ind + Aml group: 25.1% *versus* 32.0%, respectively).

Regarding risk factors, 25.9% of the patients had a smoking habit and 26.1% had a habit of alcohol consumption.

The concomitant treatments at inclusion (other than those received for essential hypertension) were reported in 14.3% of the patients and comprised mainly lipid modifying agents (7.3% overall).

At baseline, the mean office sitting SBP and DBP were: 150.4 ± 8.5 mmHg and 97.2 ± 4.9 mmHg, sitting MAP: 114.9 ± 4.5 mmHg and sitting PP: 53.2 ± 9.5 mmHg, with no relevant difference between groups. All patients had uncontrolled BP at baseline.

The demographic and other baseline characteristics described in the PPS (N = 470; 88.3% of the RS) were similar to those in the RS.

The ABPM analysis set was small (N = 74 patients, with 33 patients in the Per/Ind/Aml group and 41 patients in the Per/Ind + Aml group). Therefore, interpretations of ABPM data should be carried out with caution.

The demographic data and other baseline characteristics described in the ABPM Set (13.9% of the RS) were fairly similar to those of the RS, except a lower frequency of male patients in the Per/Ind/Aml group than in the Per/Ind + Aml group (60.6% *versus* 75.6%, respectively), and a higher frequency of patients addressed by referral company in the Per/Ind/Aml group than in the Per/Ind + Aml group (72.7% *versus* 58.5%, respectively). Other main demographic and baseline characteristics analysed in the ABPM set showed no clinically relevant difference compared to those observed in the RS.

EXTENT OF EXPOSURE

The treatment duration over the M000-M002 period was on average 58.0 ± 10.4 days (median: 57.0 days), and over the M000-M006 period it was on average 154.4 ± 37.5 days (median: 168.0 days). No relevant between-group difference was observed.
The global compliance was on average 97.6 ± 7.8% over M000-M002 and 97.5 ± 7.9% over M000-M006.

EFFICACY RESULTS

- **Primary efficacy endpoint**

Primary analysis

A robust decrease in the office sitting SBP was observed in the FAS (N = 520) in both treatment groups from baseline to the last post-baseline value over M000-M002 period. This decrease was similar in both treatment groups with a mean change ± SD of -14.99 ± 14.46 mmHg in the Per/Ind/Aml group *versus* -14.49 ± 12.87 mmHg in the Per/Ind + Aml group. Considering the pre-defined non-inferiority margin of 4 mmHg, the non-inferiority of Per/Ind/Aml group compared to Per/Ind + Aml was statistically demonstrated (one sided p-value < 0.001), with an estimate (SE) of the adjusted between-group difference of 0.23 (1.08) mmHg, (95% CI = [-1.90 ; 2.36]).

Office sitting SBP – Primary Analysis - Change from baseline to last post-baseline value - Comparison between groups - During the M000–M002 period – FAS (N=520)

		Fixed [Per/Ind/Aml] (N = 256)	Free [Per/Ind + Aml] (N = 264)
Descriptive Statistics			
Baseline	n	256	264
	Mean ± SD	150.75 ± 8.80	150.06 ± 8.16
	Median	148.50	147.70
	Min ; Max	140.0 ; 179.5	140.0 ; 179.3
Last post-baseline value (period M000 - M002)*	n	256	264
	Mean ± SD	135.76 ± 13.49	135.57 ± 12.59
	Median	135.25	134.25
	Min ; Max	95.7 ; 173.5	105.0 ; 176.7
Last post-baseline value (period M000 - M002)* - Baseline	n	256	264
	Mean ± SD	-14.99 ± 14.46	-14.49 ± 12.87
	Median	-13.20	-16.50
	Min ; Max	-58.3 ; 29.5	-44.5 ; 22.0
Statistical analysis			
Primary statistical analysis	E (SE) (1)	0.23 (1.08)	
	95% CI (2)	[-1.90 ; 2.36]	
	p-value (3)	< 0.001	

Non-inferiority test of Fixed [Per/Ind/Aml] as compared to Free [Per/Ind + Aml] / Non-inferiority limit 4 mmHg
(1) Estimate (Standard Error) of the adjusted difference from baseline to M002 between treatment groups means Perindopril 5 mg / indapamide 1.25 mg / amlodipine 5 mg minus Perindopril 4 mg / indapamide 1.25 mg + amlodipine 5 mg using a General Linear Model including the fixed, categorical effects of treatment, centre, as well as the continuous, fixed covariate of baseline
(2) Two-sided 95% Confidence Interval of the estimate
(3) One-sided associated p-value of the non-inferiority (to be compared to 0.025)
Missing data handling missing data was imputed using LOCF approach
** Considered in the analysis due to the LOCF approach to handle missing data*
An estimate < 0 is in favour of Perindopril 5 mg / indapamide 1.25 mg / amlodipine 5 mg.

This result was confirmed in the 4 ***supplementary analyses***:

- Analysis with intercurrent event approach: E (SE) of -0.44 (1.13) mmHg (95% CI = [-2.65 ;1.78]).
- Analysis in the PPS: E (SE) of -0.44 (1.11) mmHg (95% CI = [-2.62 ; 1.75]).
- Analysis in the completers at M002 (N = 245 in the Per/Ind/Aml group and 248 in the Per/Ind + Aml group): E (SE) of -0.34 (1.12) mmHg (95% CI = [-2.54 ; 1.85]).
- Analysis with the addition of recruitment source as covariate: E (SE) of -0.09 (1.10) mmHg (95% CI = [-2.26 ; 2.08]).

- **Secondary efficacy endpoints**

Office blood pressure endpoint

The ***sitting DBP*** (at office) markedly decreased between baseline and last post-baseline value over the M000-M002 period in both treatment groups in the FAS. The decrease was similar in both groups with a mean change ± SD of -8.56 ± 8.22 mmHg in the Per/Ind/Aml group *versus* -8.74 ± 7.74 mmHg in the Per/Ind + Aml group, with an estimate (SE) of the adjusted between-group difference of 0.32 (0.67) mmHg, (95% CI = [-1.00 ; 1.64]).

Blood pressure control was reached at last post baseline value over the M000-M002 period by 46.9% of the patients in the Per/Ind/Aml group and 50.4% in the Per/Ind + Aml group (E (SE) = -0.14 (0.18)%, 95% CI = [-0.48 ; 0.20]).

Most patients were considered as ***treatment responders*** at last post baseline value over M000-M002 period in both groups: 57.8% in the Per/Ind/Aml group *versus* 61.7% in the Per/Ind + Aml group (E (SE) = -0.16 (0.18), 95% CI = [-0.51 ; 0.19]).

As regards ***up-titration*** efficiency, in patients not controlled at M002 (M004 respectively), the up-titrations to the highest possible dose at each step, in both groups led to further clinically meaningful decreases in mean sitting ***SBP*** and ***DBP*** in the FAS:

- Over M002-M004 period:
  - The estimates of change in SBP were: E (SE) = -9.03 (1.10) mmHg in patients who were uptitrated (118/256 patients, 46.1%) from P5/I1.25/A5 to P10/I2.5/A5 and E (SE) = -7.21 (1.17) mmHg in patients who were uptitrated (115/264 patients, 43.6%) from P4/I1.25 + A5 mg to P4/I1.25[x2] + A5.
  - The estimates of change in DBP were: E (SE) = -5.93 (0.71) mmHg in patients who were uptitrated from P5/I1.25/A5 to P10/I2.5/A5 and E (SE) = -4.14 (0.70) mmHg in patients who were uptitrated from P4/I.25 + A5 mg to P4/I1.25[x2] + A5.
- Over the M004-M006 period:
  - The estimates of change in SBP were: E (SE) = -6.08 (1.55) mmHg in patients who were uptitrated (45/256 patients, 17.6%) from P10/I2.5/A5 to P10/I2.5/A10 and E (SE) = -4.93 (1.72) mmHg in patients who were uptitrated (49/264 patients, 18.6%) from P4/I1.25[x2] + A5 to P4/I1.25[x2] + A5[x2].
  - The estimates of change in DBP were: E (SE) = -3.61 (0.90) mmHg in patients who were uptitrated from P10/I2.5/A5 to P10/I2.5/A10 and E (SE) = -4.51 (1.02) mmHg in patients who were uptitrated from P4/I1.25[x2] + A5 to P4/I1.25[x2] + A5[x2].

In patients with uncontrolled BP and treated at the highest possible dose at M002 (M004 respectively), the rate of patients with ***blood pressure control*** at M004 (M006 respectively) was:

- At M004: 50.0% in the Per/Ind/Aml group and 43.5% in the Per/Ind + Aml group.
- At M006: 46.7% and 36.7%, respectively.

The ***response to treatment*** at M004 (M006 respectively), in patients who were uptitrated to the highest possible dose at M002 (M004 respectively) was meaningfully increased in both treatment groups of the FAS:

- At M004: 75/118 patients (63.6%) who were uptitrated at M002 were considered as responders in the Per/Ind/Aml group and 68/115 patients (59.1%) were considered as responders in the Per/Ind + Aml group.
- At M006: 32/45 patients (71.1%) who were uptitrated at M004 to the highest dose were considered as responders in the Per/Ind/Aml group and 32/49 patients (65.3%) were considered as responders in the Per/Ind + Aml group.

The other following **main secondary efficacy endpoints** also showed a decrease from baseline to last post-baseline value over the M000-M002 period in both treatment groups in the FAS, without clinically relevant difference between groups:

- ***Sitting MAP:*** -10.70 ± 9.64 mmHg *versus* -10.66 ± 8.75 mmHg, with an E (SE) = 0.20 (0.78) mmHg (95% CI= [-1.32 ; 1.73]).
- ***Sitting PP:*** -6.44 ± 9.93 mmHg *versus* -5.75 ± 9.14 mmHg, with an E (SE) = -0.48 (0.71) mmHg (95% CI = [-1.88 ; 0.91]).

ABPM parameters

Given the small number of patients having taken part in the ABPM analysis, interpretations of the ABPM data analysis should be carried out with caution.

The results from 24-hour ambulatory BP monitoring indicated that after 2 months of treatment the mean systolic and diastolic blood pressure analysed over different periods of the nychthemeron (24 hours, standard daytime, standard night-time, real daytime, real night-time) were lowered with similar trends in both treatment groups (Table below describes 24-hour mean ambulatory SBP and DBP over the M000-M002 period). Ambulatory BP values confirmed the robust decreases observed with office BP.

Mean ambulatory SBP and DBP (mmHg) over 24-hour – Change from baseline to M002 – ABPM set (N=74)

		Fixed [Per/Ind/Aml] (N = 33)	Free [Per/Ind + Aml] (N =41)
Mean ambulatory SBP over 24-hour	n	33	41
Baseline	Mean ± SD	136.53 ± 13.95	134.84 ± 13.91
M002	Mean ± SD	123.68 ± 9.40	123.49 ± 10.78
M002-Baseline	Mean ± SD	-12.85 ± 15.41	-11.36 ± 10.61
Mean ambulatory DBP over 24-hour	n	33	41
Baseline	Mean ± SD	88.18 ± 9.04	87.35 ± 8.53
M002	Mean ± SD	80.49 ± 6.51	80.42 ± 5.77
M002-Baseline	Mean ± SD	-7.69 ± 9.12	-6.92 ± 6.35

The mean over 24 hours is the mean of the first 24h hourly means

SAFETY RESULTS

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

Overall summary for adverse events in the Safety Set

		M000-M002		M000-M006	
		Fixed [Per/Ind/ Aml] (N = 262)	Free [Per/Ind + Aml] (N=269)	Fixed [Per/Ind/ Aml] (N = 262)	Free [Per/Ind + Aml] (N= 269)
Patients having reported at least one:					
TEAE	n (%)	108 (41.2)	118 (43.9)	176 (67.2)	177 (65.8)
Treatment-related TEAE	n (%)	53 (20.2)	64 (23.8)	110 (42.0)	108 (40.1)
Serious TEAE	n (%)	2 (0.8)	2 (0.7)	12 (4.6)	9 (3.3)
Treatment-related serious TEAE	n (%)	-	1 (0.4)	-	2 (0.7)
TEAE leading to treatment withdrawal	n (%)	3 (1.1)	5 (1.9)	8 (3.1)	15 (5.6)
Serious TEAE leading to treatment withdrawal	n (%)	-	-	1 (0.4)	4 (1.5)
Treatment-related TEAE leading to treatment withdrawal	n (%)	3 (1.1)	3 (1.1)	7 (2.7)	10 (3.7)
Treatment-related serious TEAE leading to treatment withdrawal	n (%)	-	-	-	1 (0.4)
On-treatment patients who died*	n (%)	-	-	-	-

** One patient reported a cerebral infarction (not related to the run-in IMP), with paranasal sinus inflammation and pneumonia during the run-in period leading to his death 16 days later (the patient was on the run-in treatment for 12 days). One patient in the Per/Ind + Aml group reported upper gastrointestinal haemorrhage leading to his death after the randomised treatment period (the death occurred 77 days after his last IMP intake).*

Adverse events during the M000-M002 period

Over M000-M002, TEAEs were reported with a similar frequency in both groups: 108 patients (41.2%) in the Per/Ind/Aml group *versus* 118 patients (43.9%) in the Per/Ind + Aml group.

The **SOCs** most frequently affected in the Per/Ind/Aml group were Metabolism and nutrition disorders (25.2%) as well as Investigations (8.0%).

The **most frequent treatment emergent adverse events** in the Per/Ind/Aml group were hyperuricaemia (10.7%), hypokalaemia (6.1%), hypercholesterolaemia (5.0%) and hypertriglyceridaemia (4.6%).

As regards **intensity** over 90% of TEAEs were rated mild, without relevant difference between the treatment groups. The percentage of TEAEs rated as **severe** was 1.1% of the TEAEs (2 events) in each group.

The percentage of patients with at least one TEAE considered to be **related to the treatment** was similar in both groups (20.2% *versus* 23.8%, respectively). In the Per/Ind/Aml group, these were mostly hyperuricaemia (9.2%), hypokalaemia (5.3%), hypercholesterolaemia (1.9%), hypertriglyceridaemia (1.5%), blood glucose increased (1.9%), and cough (1.9%).

The 4 **serious** TEAEs, which occurred during the M000-M002 period were ankylosing spondylitis and ankle fracture in the Per/Ind/Aml group (2 patients, 0.8%) and intervertebral disc protrusion and cough variant asthma in the Per/Ind + Aml group (2 patients, 0.7%). Among them, one was considered as treatment-related (cough variant asthma) and none led to study drug withdrawal.

The TEAEs which led to **treatment withdrawal** during the M000-M002 period were reported in 3 patients, 1.1% in the Per/Ind/Aml group *versus* 5 patients, 1.9% in the Per/Ind + Aml group.

Clinical laboratory results and vital signs during the M000-M002 period
During M000-M002 period, emergent **Potentially Clinically Significant Abnormal** (**PCSA**) **biochemical values** were sparse in both groups and for each parameter, except for high values of triglycerides: 11 patients (4.3%) and 7 patients (2.7%), respectively.

As regards **vital signs**, neither clinically relevant within-group changes nor differences between groups were observed in mean values for weight, BMI, or HR.

Adverse events during the M000-M006 period
Over the randomised treatment period (up to M006), TEAEs were reported with a similar frequency in both groups, affecting 67.2% of patients in the Per/Ind/Aml group *versus* 65.8% in the Per/Ind + Aml group.

The most frequently affected **SOCs** and **preferred terms** were in line with those reported in the M002 analysis.

Over 90% of TEAEs were rated mild in both groups; 5 events in each group (1.2%) were rated as **severe**.

The percentage of patients with at least one TEAE considered to be **related to the treatment** was similar in both groups: 42.0% in the Per/Ind/Aml group *versus* 40.1% in the Per/Ind + Aml group. These events were essentially the same as reported in the M002 analysis: in the Per/Ind/Aml group, hyperuricaemia (17.9%), hypokalaemia (13.0%), cough (5.0%), hypertriglyceridaemia (3.8%), blood glucose increased (3.8%) and hypercholesterolaemia (3.4%).
These most frequently reported treatment-related TEAEs are already described in the SmPC for indapamide, perindopril and amlodipine: hyperuricemia and hypokalaemia with indapamide and cough with perindopril.

The **serious** TEAEs that occurred during the M000-M006 period were reported in 12 patients (4.6%) in the Per/Ind/Aml group *versus* 9 patients (3.3%) in the Per/Ind + Aml group. These events concerned mostly nervous system disorders or musculoskeletal and connective tissue disorders. Among the serious TEAEs, three (in 2 patients) were considered as treatment-related (all in the Per/Ind + Aml group): cerebral infarction, demyelination and cough variant asthma. Serious TEAEs led to treatment withdrawal in 1 patient (0.4%) in the Per/Ind/Aml group (cerebral infarction) and in 4 patients (1.5%) in the Per/Ind + Aml group (5 events: cerebral ischaemia, spondylolisthesis, hepatic cirrhosis, cough variant asthma and hepatitis B).

TEAEs **led to treatment withdrawal** in 8 patients (3.1%) in the Per/Ind/Aml group *versus* 15 patients (5.6%) in the Per/Ind + Aml group.

No **death** was reported during the randomised treatment period. However, one patient reported a cerebral infarction (not related to the run-in IMP), with paranasal sinus inflammation and pneumonia during the run-in period leading to the patient's death 16 days later (the patient was on the run-in treatment for 12 days) and one death occurred after the treatment period in a patient randomised to the Per/Ind + Aml group; the causal event of upper gastrointestinal haemorrhage (not related to the IMP) occurred 74 days after patient's last IMP intake and resulted in death three days later.

Clinical laboratory results and vital signs during the M000-M006 period

Emergent **PCSA** biochemical values were sparse in both groups and for each parameter, except for high values of triglycerides (15 patients, 5.9% and 11 patients, 4.2%, respectively) and high value of gamma glutamyl transferase (4 patients, 1.6% and 7 patients, 2.7%, respectively).

Emergent PCSA haematological values were not detected in the Per/Ind/Aml group and were sparse in the Per/Ind + Aml group.

As regards **vital signs**, neither clinically relevant changes nor differences between groups in mean values over time were detected for weight, BMI, and HR during the M000-M006 period.

The emergent **orthostatic hypotension** (calculated) over the M000-M006 period was detected in 6 patients (2.4%) in the Per/Ind/Aml group and in 5 patients (1.9%) in the Per/Ind + Aml group.

CONCLUSION

This national multicentre randomised double-blind phase III study with conditional up-titration, conducted in 532 patients with essential uncontrolled hypertension, demonstrated the non-inferiority of the perindopril 5 mg / indapamide 1.25 mg / amlodipine 5 mg fixed combination as compared to the free combination of the components perindopril 4 mg / indapamide 1.25 mg + amlodipine 5 mg in lowering office sitting SBP after 2 months of treatment, with an estimate of the between-group difference of 0.23 (1.08) mmHg, 95%CI = [-1.90 ; 2.36]; p < 0.001). Robust decreases in SBP were observed in both groups: -14.99 ± 14.46 mmHg in the Per/Ind/Aml group *versus* -14.49 ± 12.87 mmHg in the Per/Ind + Aml group. The robust decrease in office sitting SBP after 2 months of treatment highlights the interest of a tri-therapy compared to the bi-therapy treatment of the run-in.

Both treatments also, and to a similar extent after 2 months of treatment, markedly reduced office sitting DBP, as well as pulse pressure and mean arterial blood pressure.

The results of the ambulatory BP measurements confirmed the robust decreases observed in office BP with markedly lower day and night-time values.

Roughly 50% of patients attained office BP control at M002 and thus, of the on-going patients about 50% in each group were uptitrated to the next dose. This titration provided an additional benefit on reducing sitting SBP/DBP and increasing the proportions of patients having their BP controlled and those considered as treatment responders.

No safety concern was raised in either treatment group; the safety profiles were similar between groups and were in accordance with the current Summaries of the Products Characteristics.

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