Document title	**Clinical Study Report Synopsis**
Study title	**Perindopril Amlodipine Regimen *versus* AT1-Receptor Blocker/thiazide: a comparison of Blood pressure Lowering: Efficacy and Safety.** **A randomised, double blind, 9 month study of the efficacy and safety of four uptitrated doses of oral fixed combinations of Perindopril/Amlodipine, including a comparison with uptitrated doses of oral fixed combination of Irbesartan and Hydrochlorothiazide in mild to moderate hypertension.**
Study drug	**S 05985**
Studied indication	**Essential arterial hypertension**
Development phase	**Phase III**
Protocol code	**CL3-05985-006**
Study initiation date	**03 January 2008**
Study completion date	**13 August 2009**
Main coordinator	[redacted] **United Kingdom**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50, rue Carnot** **92284 Suresnes Cedex – France** **Servier Research and Development Limited** **Gallions - Wexham Springs, Framewood Road** **Wexham Springs - SL3 6 RJ Slough - United Kingdom**
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	**Final version of 21 May 2013**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Perindopril Amlodipine Regimen *versus* AT1-Receptor Blocker/thiazide: a comparison of Blood pressure Lowering: Efficacy and Safety.
A randomised, double blind, 9 month study of the efficacy and safety of four uptitrated doses of oral fixed combinations of Perindopril / Amlodipine, including a comparison with uptitrated doses of oral fixed combination of Irbesartan and Hydrochlorothiazide in mild to moderate hypertension.
Protocol No.: **CL3-05985-006**

Coordinator: [redacted] United Kingdom

Study centres: 87 centres were opened in 3 countries and 85 included at least one patient: 3 centres in Ireland (175 included patients), 67 centres in U.K. (2810 included patients), and 15 centres in The Netherlands (287 included patients).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 3 January 2008 Completion date: 13 August 2009	III

Objectives:

- ***Primary objectives*:**
  - *Efficacy*: to assess the efficacy of each dose increase of the Perindopril / Amlodipine combination on blood pressure (BP) control, defined as supine SBP < 140 mmHg **and** DBP < 90 mmHg, or in diabetic patients as supine SBP < 130 mmHg **and** DBP < 80 mmHg, during a 6-month period.
  - *Safety*: to assess the safety of the Perindopril / Amlodipine combination during the 9-month treatment period (allowing a period of exposure at the highest possible dose of up to 6 months).
- ***Secondary objectives***:
  - *Efficacy*: to compare the rate of BP control, the changes in blood pressure parameters (systolic and diastolic blood pressure, pulse pressure and mean blood pressure), the rate of response to treatment, and the new onset of clinical events of special interest (CESI: cardiovascular events, diabetes and glucometabolic impairment, renal impairment), between Perindopril / Amlodipine combination and Irbesartan alone or in combination with Hydrochlothiazide, after a 6-month period.
    Ambulatory blood pressure monitoring (ABPM): an associated study was performed, the objective of which was to assess the effect of the drug regimens on ABPM over a six-month period. This is provided in a separate specific report.
  - *Quality of life*: to compare all patients' well-being with a questionnaire (EQ-5D) prior to randomisation and at final visit.

Methodology: This was a Phase III multicentre, international, randomised, double-blind study in two parallel groups over 9 months in hypertensive patients. The randomisation was balanced, fixed, centralised with an interactive voice or web response system (IRS), and was stratified on centre, age (≤ / > 65 years) and presence of diabetes (yes / no).
The patients received during a 9-month treatment period, according to their randomisation group:

- Either the Perindopril / Amlodipine combination (Per / Amlo), in 4 possible steps of dose.
- Or the Irbesartan / Hydrochlorothiazide combination (Irbe / HCTZ): Irbesartan alone in a first step of dose, then combined with Hydrochlorothiazide, in 3 possible steps of dose.

Supine systolic and diastolic blood pressure (SBP and DBP) were measured at each visit.
In both groups, patients with non-controlled BP were up-titrated monthly step by step to reach the BP targets.
In addition, the associated study on ABPM was conducted in a subgroup of patients (see separate report).

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Number of patients:
Planned: 3000 (1500 by treatment group).
Included in the Randomised Set: 3270 (1617 in in the Perindopril / Amlodipine group and 1653 in the Irbesartan / Hydrochlorothiazide group).

Diagnosis and main criteria for inclusion:
The study was performed in patients:

- Aged at least 18 years, with essential arterial hypertension at selection:
  - For untreated patients: 150 mmHg ≤ SBP < 180 mmHg and/or 95 mmHg ≤ DBP < 115 mmHg, with both pressures lower than the upper limits.
  - For treated patients (with no more than 2 drugs) who in the investigator's opinion require a change in medication because of lack of efficacy or poor tolerability: SBP < 165 mmHg and DBP < 105 mmHg.
- Without history of acute cardio-vascular disease within 3 months before selection, without clinical congestive heart failure, without ventricular rhythm disorders risk, without history of alcohol or drug abuse and without any contra-indication to study drugs.

After 2 weeks on placebo treatment, patients were eligible for randomisation if 150 mmHg ≤ SBP < 200 mmHg and/or 95 mmHg ≤ DBP < 115 mmHg, with both pressures lower than the upper limits.
Any drug with antihypertensive effect was prohibited during the study period (except beta-blockers and alpha-blockers already prescribed for indications other than hypertension, at a dose which should not be changed during the study).

Study drug: Perindopril / Amlodipine, 1 or 2 oral capsules taken o.d. in the morning, according to the following titration steps:

- Step 1: Perindopril 3.5 mg / Amlodipine 2.5 mg.
- Step 2: Perindopril 7 mg / Amlodipine 5 mg.
- Step 3: Perindopril 14 mg / Amlodipine 5 mg.
- Step 4: Perindopril 14 mg / Amlodipine 10 mg.

Reference product: Irbesartan / Hydrochlorothiazide, 1 or 2 oral capsules taken o.d. in the morning, according to the following titration steps:

- Step 1: Irbesartan 150 mg.
- Step 2: Irbesartan 150 mg / Hydrochlorothiazide 12.5 mg.
- Step 3: Irbesartan 300 mg / Hydrochlorothiazide 12.5 mg.
- Step 4: Irbesartan 300 mg / Hydrochlorothiazide 25 mg.

Duration of treatment:

- Run-in period on placebo: 2 weeks.
- Randomised treatment period: 9 months.
  All patients started the randomised study treatment at inclusion (M0 visit), on dose 1.
  At each monthly visit M1, M2, M3, and finally M6:
  - If BP was controlled, patients continued on the same dosage as during the previous period.
  - If BP was non-controlled, treatments were up-titrated to the step above the step received during the previous period.

  M4 was an optional visit, only for patients up-titrated at M3 and with SBP > 160 mmHg at M3. If the SBP at M4 or M6 was > 160 mmHg, patients were withdrawn from the study.

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Criteria for evaluation:

- ***Primary criteria:***
  - *Efficacy*: proportion of patients with controlled blood pressure, measured at trough of study drug.
  - *Safety*: adverse events, specific assessment of orthostatic hypotension and leg oedema, blood biochemistry including fasting blood glucose and hs-CRP, haematology, urinalysis including standard urine strip testing and micro-albuminuria assessment, vital signs.
- ***Secondary criteria:***
  - *Efficacy:* supine SBP, DBP, pulse pressure (PP) and mean blood pressure (MBP), proportion of patients with response to treatment (defined as controlled BP and/or reduction from baseline in SBP ≥ 20 mmHg and/or DBP ≥ 10 mmHg); new onset of clinical events of special interest (CESI), adjudicated by the Adjudication and Safety Committee in 3 categories: cardiovascular endpoints, diabetes and glucometabolic impairment, and renal impairment.
  - *Quality of life*: well-being questionnaire (EQ-5D).

Statistical methods:

EFFICACY ANALYSES

- **Primary criterion: blood pressure control**
  - *Main analysis: Evaluation of the Perindopril / Amlodipine strategy efficiency*
    The variation over each period of evaluation until M6 in the proportion of patients with controlled BP in the FAS (and secondarily in the PPS) was tested using a McNemar test.
  - *Secondary analyses*
    Evaluation of the Perindopril / Amlodipine uptitration efficiency: in order to assess the Perindopril / Amlodipine up-titration efficiency, the rate of patients with controlled BP and its 95% confidence interval were provided at the end of each evaluation period, among patients receiving the highest possible dose over the period.
    Comparison with the Irbesartan / Hydrochlorothiazide strategy: the rates of patients with controlled BP were compared between the Perindopril / Amlodipine and the Irbesartan / Hydrochlorothiazide strategies at the end of the M0-M6 period, using a chi-square test.

    All analyses performed in the Perindopril / Amlodipine strategy were also performed in the Irbesartan / Hydrochlorothiazide strategy. These analyses were performed in the FAS, PPS, and their subgroups.

- **Secondary criteria**:
  - *Supine blood pressure parameters: SBP, DBP, PP, MBP*
    For each parameter and over each period of evaluation, the within-group variation was assessed and tested using a paired Student t-test. The improvement in patients who received the highest possible dose over the period was also assessed, using estimate of the within-group difference and its 95% confidence interval.
    Both strategies were compared on the change over the M0-M6 period using a general linear model with centre, baseline, age (≤ or > 65 years) and presence of known diabetes (IRS stratum) as covariates.
  - *Response to treatment*: the same analyses as for BP control were performed.
  - *CESI*: the incidence of all CESI and of each component (cardiovascular events, diabetes and glucometabolic impairment, and renal impairment) over the 9-month treatment period were compared between groups in the FAS using an unadjusted Cox model.
  - *ABPM associated study*, main analysis: difference between Per/Amlo and Irbe/ HCTZ estimated on the change from baseline to last post-baseline value of mean DBP over 24 hours using a general linear model studying treatment effect with baseline as covariate and age (≤ 65 / > 65), presence of known diabetes (IRS strata) and country (fixed effect) as factors, in patients of the FAS-ABPM.

SAFETY ANALYSES - Descriptive statistics in the Safety Set were provided.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 4501 patients were selected for the study, among whom 3270 were included and randomly assigned to one of the 2 groups. Overall, 71.4% of the randomised patients completed the study and 28.6% were prematurely withdrawn. The rate of withdrawals for adverse event was higher in the Perindopril / Amlodipine group (22.8%) than in the Irbesartan / Hydrochlorothiazide group (14.3%) (difference due to the incidence of oedema peripheral and cough), whereas the rate of withdrawals for lack of efficacy was lower in the Perindopril / Amlodipine group (3.0%) than in the Irbesartan / Hydrochlorothiazide group (5.8%).

Disposition of patients according to the treatment dispensed at inclusion

		Per / Amlo	**Irbe / HCTZ**	**All**
Included and randomised (Randomised Set)	**N**	**1617**	**1653**	**3270**
Lost to Follow-up	n (%)	-	-	-
Withdrawn due to	n (%)	506 (31.3)	428 (25.9)	934 (28.6)
adverse event**	n (%)	368 (22.8)	236 (14.3)	604 (18.5)
lack of efficacy	n (%)	49 (3.0)	96 (5.8)	145 (4.4)
non-medical reason	n (%)	64 (4.0)	67 (4.1)	131 (4.0)
protocol deviation	n (%)	25 (1.5)	29 (1.8)	54 (1.7)
Completed	n (%)	1111 (68.7)	1225 (74.1)	2336 (71.4)
Full Analysis Set (FAS)	n (%)	1605 (99.3)	1628 (98.5)	3233 (98.9)
Per Protocol Set (PPS)	n (%)*	1227 (76.4)	1318 (81.0)	2545 (78.7)
Safety set	n (%)	1617	1653	3270

N Total number of patients included and randomised
n number of patients in each category
% = (n/N) x 100
** % of the FAS*

In the Randomised Set, patients had a mean age of 62.5 ± 9.8 years, with 41.0% aged more than 65 years, and were mostly men (63.2%). Patients had known hypertension for a mean duration of 90.4 ± 88.6 months (approximately 7.5 years), of grade I in 37.5% of patients, grade II in 50.8%, and grade III in 11.7%. Overall, 42.5% of patients presented with isolated systolic hypertension which is a high percentage in an hypertensive population. Most patients (82.7%) were previously treated for their hypertension, mainly with agents acting on the renin-angiotensin system (52.0%), diuretics (30.9%), and calcium channel blockers (29.8%).

A total of 68.0% of patients had metabolic syndrome at baseline, 13.7% were diabetic according to their randomisation stratum, 2.7% had a history of glucometabolic impairment, and 9.2% had a history of leg oedema. Mean SBP value at baseline was 163.6 ± 11.5 mmHg. Mean DBP values at baseline were 82.8 ± 5.3 mmHg in patients presenting with isolated systolic hypertension (ISH) and 97.7 ± 5.4 mmHg in patients presenting with systolic diastolic hypertension (SDH). No relevant difference between treatment groups was detected regarding baseline characteristics. Baseline characteristics in the FAS and in the PPS were comparable to those described in the Randomised Set.

In the Safety Set, the mean treatment duration over the M0-M9 period (period for the safety analysis) was 224.5 ± 80.9 days (approximately 7.4 months). In the FAS, the mean treatment duration over the M0-M6 period (period for the main efficacy analysis) was 160.7 ± 45.8 days (approximately 5.3 months). In both analysis sets, global compliances over the M0-M6 and M0-M9 periods were satisfactory (around 95% in average) and similar between groups.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Perindopril / Amlodipine strategy

- **Primary assessment criterion: blood pressure control**

Evaluation in the FAS of the Perindopril / Amlodipine strategy efficiency (main analysis)

As shown in Table below, the proportion of patients with controlled blood pressure statistically significantly increased in the Perindopril / Amlodipine strategy over each evaluation period until M6, following the up-titration opportunity for patients with non-controlled blood pressure.

The proportion of patients with controlled blood pressure remained stable over the M6-M9 period.

Results in the PPS followed the same trends.

Evaluation of Perindopril / Amlodipine strategy efficiency on blood pressure control over each period in patients ongoing at the beginning of the period in the FAS

Period			Per / Amlo (N = 1605)
M0-M1	All ongoing patients	n (%)	1605 (100.00)
	BP controlled at end	n (%)	342 (21.31)
M1-M2	All ongoing patients	n (%)	1534 (100.00)
	BP controlled at entry	n (%)	328 (21.38)
	BP controlled at end	n (%)	457 (29.79)
	Within-group statistical analysis	E (SE) (1)	8.41 (1.29)
		95% CI (2)	[5.89 ; 10.93]
		p-value (3)	< 0.001
M2-M3	All ongoing patients	n (%)	1468 (100.00)
	BP controlled at entry	n (%)	446 (30.38)
	BP controlled at end	n (%)	538 (36.65)
	Within-group statistical analysis	E (SE) (1)	6.27 (1.34)
		95% CI (2)	[3.65 ; 8.88]
		p-value (3)	< 0.001
M3-M6	All ongoing patients	n (%)	1398 (100.00)
	BP controlled at entry	n (%)	523 (37.41)
	BP controlled at end	n (%)	587 (41.99)
	Within-group statistical analysis	E (SE) (1)	4.58 (1.53)
		95% CI (2)	[1.57 ; 7.58]
		p-value (3)	0.003

(1) Estimate (Standard Error) of the within-group difference between the proportions of patients with controlled blood pressure at entry and at end of the corresponding period

(2) 95% Confidence Interval of the estimate

(3) McNemar test

Evaluation of the up-titration efficiency of the Perindopril / Amlodipine strategy (secondary analysis)

In patients receiving the highest possible dose over each period in the FAS, *i.e.* with previously non-controlled blood pressure, each dose allowed to control between 18.9% and 25.2% of them in the Perindopril / Amlodipine strategy (See Table below). Similar results were observed in the PPS.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Evaluation in Perindopril / Amlodipine strategy of the up-titration efficiency on blood pressure control in patients receiving the highest possible dose over each period in the FAS

Period			**Per / Amlo**
Baseline-M1	**All patients on dose 1**	n (%)	1605 (100.00)
	BP controlled at end	n (%)	342 (21.31)
M1-M2	**All patients on dose 2**	n (%)	1207 (100.00)
	BP controlled at end	n (%)	267 (22.12)
M2-M3	**All patients on dose 3**	n (%)	889 (100.00)
	BP controlled at end	n (%)	168 (18.90)
M3-M6	**All patients on dose 4**	n (%)	682 (100.00)
	BP controlled at end	n (%)	172 (25.22)

- **Secondary assessment criteria**
  - Response to treatment

In the Perindopril / Amlodipine strategy, the proportion of responder patients increased over each evaluation period until M6 as compared to the preceding period, following the up-titration opportunity for patients with non-controlled blood pressure. This increase was statistically significant over all periods. No relevant change was observed over the M6-M9 period.

At last post-baseline assessment over the M0-M6 period, the rate of responders was 71.9% with Perindopril / Amlodipine

  - Blood pressure parameters

As 42.5% of the patients randomised in the study presented with isolated systolic hypertension (ISH), without relevant difference in the distribution between the two groups at baseline, the analysis of DBP, MBP, and PP is presented according to ISH or SDH status.

In the FAS, over each evaluation period until M6, clinically relevant and statistically significant decreases were observed for mean SBP (see Table below). Clinically relevant and statistically significant decreases were observed for mean DBP (see Table below), as well as for mean PP (except between M3 and M6 in patients with ISH) and mean MBP, in patients presenting with ISH and with SDH.

Taking into account only patients receiving the highest possible dose over each period, marked and statistically significant reductions were also observed. Nevertheless, perindopril 14mg / amlodipine 5mg appeared to be the dose which contributed the less to the overall efficacy of the S05985 strategy. Changes observed over the M6-M9 period appeared to be not clinically relevant as expected and due to the fact that the maximum of the effect was already reached at M6.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Evaluation of Perindopril / Amlodipine strategy efficiency on SBP in the FAS

		SBP (mmHg)
		Per / Amlo (N = 1605)
Change from baseline to M1	n	1605
	Mean ± SD	-14.13 ± 12.76
Within-group statistical analysis	E (SE) (1)	-14.13 (0.32)
	95% CI (2)	[-14.75 ; -13.50]
	p-value (3)	< 0.001
Change from M1 to M2	n	1523
	Mean ± SD	-4.36 ± 12.32
Within-group statistical analysis	E (SE) (1)	-4.36 (0.32)
	95% CI (2)	[-4.98 ; -3.74]
	p-value (3)	< 0.001
Change from M2 to M3	n	1460
	Mean ± SD	-2.06 ± 11.11
Within-group statistical analysis	E (SE) (1)	-2.06 (0.29)
	95% CI (2)	[-2.63 ; -1.49]
	p-value (3)	< 0.001
Change from M3 to M6	n	1382
	Mean ± SD	-1.88 ± 12.36
Within-group statistical analysis	E (SE) (1)	-1.88 (0.33)
	95% CI (2)	[-2.54 ; -1.23]
	p-value (3)	< 0.001
Change from baseline to last post-baseline value until M6	n	1605
	Mean ± SD	-22.01 ± 13.44

(1) Estimate (Standard Error) of the within-group difference between means at beginning and end of the corresponding period.
(2) 95% Confidence Interval of the estimate.
(3) Student t-test for paired samples.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Evaluation of Perindopril / Amlodipine strategy efficiency on DBP in ISH and SDH patients in the FAS

		DBP (mmHg)	
		ISH patients	**SDH patients**
Change from baseline to M1	n	679	926
	Mean ± SD	-2.87 ± 6.21	-8.02 ± 6.98
Within-group statistical analysis	E (SE) (1)	-2.87 (0.24)	-8.02 (0.23)
	95% CI (2)	[-3.34 ; -2.41]	[-8.47 ; -7.57]
	p-value (3)	< 0.001	< 0.001
Change from M1 to M2	n	648	875
	Mean ± SD	-2.05 ± 6.42	-2.47 ± 6.77
Within-group statistical analysis	E (SE) (1)	-2.05 (0.25)	-2.47 (0.23)
	95% CI (2)	[-2.54 ; -1.55]	[-2.92 ; -2.02]
	p-value (3)	< 0.001	< 0.001
Change from M2 to M3	n	624	836
	Mean ± SD	-0.90 ± 6.21	-1.13 ± 6.35
Within-group statistical analysis	E (SE) (1)	-0.90 (0.25)	-1.13 (0.22)
	95% CI (2)	[-1.39 ; -0.41]	[-1.56 ; -0.70]
	p-value (3)	< 0.001	< 0.001
Change from M3 to M6	n	593	789
	Mean ± SD	-0.84 ± 6.62	-1.47 ± 6.81
Within-group statistical analysis	E (SE) (1)	-0.84 (0.27)	-1.47 (0.24)
	95% CI (2)	[-1.38 ; -0.31]	[-1.95 ; -1.00]
	p-value (3)	0.002	< 0.001
Change from baseline to last post-baseline value until M6	n	679	926
	Mean ± SD	-6.31 ± 6.41	-12.85 ± 7.22

(1) Estimate (Standard Error) of the within-group difference between means at beginning and end of the corresponding period
(2) 95% Confidence Interval of the estimate
(3) Student t-test for paired samples

Irbesartan / Hydrochlorothiazide strategy

- **Primary assessment criterion: blood pressure control**

Evaluation in the FAS of the Irbesartan / Hydrochlorothiazide strategy efficiency

Similar results were observed within the Irbesartan / Hydrochlorothiazide strategy as in the Perindopril / Amlodipine strategy, although the increase in the proportion of patients with controlled blood pressure over the M3-M6 period was not statistically significant.

The proportion of patients with controlled blood pressure was 20.1% at M1, 36.8% at M2, 44.6% at M3, 48.0% at M6 and remained stable over the M6-M9 period.

Results in the PPS followed the same trends.

Evaluation of the up-titration efficiency of the Irbesartan / Hydrochlorothiazide strategy

In patients receiving the highest possible dose over each period in the FAS, *i.e.* with previously non-controlled blood pressure, each dose allowed to control between 20.1% (Baseline-M1 period) and 31.3% (M1-M2 period) of them. Similar results were observed in the PPS.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **Secondary assessment criteria**
  - Response to treatment

In the Irbesartan / Hydrochlorothiazide strategy, the proportion of responder patients increased over each evaluation period until M6 as compared to the preceding period, following the up-titration opportunity for patients with non-controlled blood pressure. This increase was statistically significant over the M1-M2 and M2-M3 periods. No relevant change was observed over the M6-M9 period.

At last post-baseline assessment over the M0-M6 period, the rate of responders was 73.2% with Irbesartan / Hydrochlorothiazide.

  - Blood pressure parameters

In the FAS, over each evaluation period until M6, clinically relevant and statistically significant decreases were observed for SBP. The mean change for SBP from baseline to the last post-baseline value until M6 was -22.51 ± 14.31 mmHg.

In patients with SDH, clinically relevant and statistically significant decreases were observed for mean DBP, in the FAS, over each evaluation period until M6. The mean change from baseline to the last post-baseline value until M6 was -12.26 ± 8.05 mmHg. The decrease in mean MBP was statistically significant over each period until M6, while the decrease in mean PP was not statistically significant over the M3-M6 period.

In patients with ISH, clinically relevant and statistically significant decreases were observed for mean DBP, mean MBP, and mean PP, in the FAS, over each evaluation period until M3, while changes were not statistically significant over the M3-M6 period. The mean DBP change from baseline to the last post-baseline value until M6 was -6.00 ± 7.09 mmHg.

No clinically relevant change was observed over the M6-M9 period.

Taking into account only patients receiving the highest possible dose over each period, marked and statistically significant reductions were also observed.

Between-group comparison (secondary analysis)

At M1 in the FAS, 21.3% of patients in the Perindopril / Amlodipine group and 20.1% in the Irbesartan / Hydrochlorothiazide group achieved to control their BP, with no statistically significant difference between groups.

At last post-baseline assessment until M6, 39.9% of patients in the Perindopril / Amlodipine group and 44.8% in the Irbesartan / Hydrochlorothiazide group achieved to control their BP, with a statistically significant between-group difference estimated at -4.8%, (95% CI = [-8.24 ; -1.44], p = 0.005). Similar trends were observed in the PPS.

At last post-baseline assessment over the M0-M6 period, the rate of responders was similar between both strategies (71.9% with Perindopril / Amlodipine and 73.2% with Irbesartan / Hydrochlorothiazide).

The between-group comparison of the change from baseline to last post-baseline value until M6, in the FAS, showed no statistically significant difference for SBP and DBP (in patients with SDH as well as in patients with ISH).

Adjudicated clinical events of special interest (CESI) over the M0-M9 period

Emergent CESI occurred with a lower incidence in the Perindopril / Amlodipine group (11.2%) than in the Irbesartan / Hydrochlorothiazide group (13.8%), with respective monthly incidences of 1.6% and 2.0%, and a statistically significant hazard ratio of 0.811 (95% CI [0.666 ; 0.986], p = 0.036), in favour of Perindopril / Amlodipine.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- The between-group difference was mainly related to renal impairment, observed in 0.2% of patients in the Perindopril / Amlodipine group *versus* 2.1% in the Irbesartan / Hydrochlorothiazide group, with respective monthly incidences of 0.0% and 0.3%, and a statistically significant hazard ratio of 0.118 ($p < 0.001$).
- Diabetes and glucometabolic impairment also tended to be less frequent in the Perindopril / Amlodipine group (9.5%) than in the Irbesartan / Hydrochlorothiazide group (11.5%), with respective monthly incidences of 1.4% and 1.6%, although the hazard ratio of 0.826 did not reach statistical significance.
- Similar incidences of cardiovascular events were observed in the Perindopril / Amlodipine group (2.6%) and in the Irbesartan / Hydrochlorothiazide group (2.2%) (respective monthly incidences of 0.4% and 0.3%), with a non statistically significant hazard ratio of 1.227.

Ambulatory Blood Pressure Monitoring (Associated study reported separately)

The ABPM associated study showed a trend towards a greater diastolic and systolic blood pressure lowering effect of the Perindopril / Amlodipine combination than that of the Irbesartan / Hydrochlorothiazide combination, over 24 hours, in hypertensive patients.

SAFETY RESULTS

- Emergent adverse events (EAEs)

Main safety results (Safety Set)

		Per / Amlo (N = 1617)	Irbe / HCTZ (N = 1653)
Patients having reported			
At least one emergent adverse event	n (%)	1344 (83.1)	1301 (78.7)
At least one treatment-related emergent adverse event	n (%)	807 (49.9)	696 (42.1)
At least one serious emergent adverse event (including death)	n (%)	124 (7.7)	127 (7.7)
At least one treatment-related serious emergent adverse event	n (%)	15 (0.9)	16 (1.0)
At least one emergent adverse event leading to treatment discontinuation	n (%)	358 (22.1)	226 (13.7)
Patients who died	n (%)	2 (0.1)	3 (0.2)

During the treatment period, 83.1% of the patients in the Perindopril / Amlodipine group and 78.7% in the Irbesartan / Hydrochlorothiazide group reported EAEs. Similar proportions of patients between groups had EAEs under each dose (in the Per/Amlo and Irbe/HCTZ groups, respectively: 45.4% and 45.2% for dose 1, 39.6% and 43.1% for dose 2, 38.8% and 40.1% for dose 3), except for dose 4 under Perindopril 14 mg / Amlodipine 10 mg, with a higher incidence of EAEs in the Perindopril / Amlodipine group (61.0%) than in the Irbesartan / Hydrochlorothiazide group (50.3%) mainly due to General disorders and administration site condition.

The most frequent emergent adverse events, reported by at least 5.0% of the patients in any group, were:

- With no relevant difference between groups: microalbuminuria in 8.7% of patients in the Perindopril / Amlodipine group and 7.7% of patients in the Irbesartan / Hydrochlorothiazide group, nasopharyngitis in 7.5% and 7.1%, and lower respiratory tract infection in 6.5% and 5.0%.
- More frequent in the Perindopril / Amlodipine group than in the Irbesartan / Hydrochlorothiazide group, as expected:
  - Oedema peripheral (common adverse event with amlodipine), in 18.5% and 4.2% of the patients, respectively, with difference mainly observed under perindopril 14 mg / amlodipine 10 mg (22.2% *versus* 1.2%).
  - Cough (common adverse event with perindopril), in 15.2% and 4.3%, with difference mainly observed under Perindopril 3.5 mg / Amlodipine 2.5 mg (7.7% *versus* 1.7%).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- Less frequent in the Perindopril / Amlodipine group than in the Irbesartan / Hydrochlorothiazide group:
  - Dizziness, in 6.6% and 9.7%, with difference mainly observed under the dose 2 (1.1% *versus* 4.3%).
  - Headache, in 4.7% and 7.5%, with difference spread over all doses.

Orthostatic hypotension, specifically looked for as it is an adverse event likely to occur with antihypertensive treatments, tended to be less frequently reported in the Perindopril / Amlodipine group (1.5%) than in the Irbesartan / Hydrochlorothiazide group (2.1%).

Severe EAEs were reported by 9.2% of the patients in the Perindopril / Amlodipine group, and 7.3% in the Irbesartan / Hydrochlorothiazide group. Treatment-related EAEs were reported in 49.9% of the patients in the Perindopril / Amlodipine group and 42.1% in the Irbesartan / Hydrochlorothiazide group, and consisted mainly of those already described as most frequent emergent adverse events (mainly oedema peripheral and cough in the Perindopril / Amlodipine group and dizziness and headache in the Irbesartan / Hydrochlorothiazide group), with differences between groups in the same lines. Most EAEs recovered or were recovering (68.1% in the Perindopril / Amlodipine group and 69.3% in the Irbesartan / Hydrochlorothiazide group), and 31.2% and 30.1%, respectively, did not recover at the time of the analysis.

Five patients died during the study: 2 (0.1%) in the Perindopril / Amlodipine group (both from brain tumors), and 3 (0.2%) in the Irbesartan / Hydrochlorothiazide group (1 from pneumonia, 1 from respiratory failure, and 1 from ischaemic stroke). No death was related to the study treatment according to the investigator.
In total, 7.7% of patients in the Perindopril / Amlodipine group and 7.7% in the Irbesartan / Hydrochlorothiazide group experienced a serious EAE. The most frequently affected system organ classes were Cardiac disorders, in 19 patients (1.2%) in the Perindopril / Amlodipine group and 14 patients (0.8%) in the Irbesartan / Hydrochlorothiazide group, Surgical and medical procedures, in 18 patients (1.1%) and 13 patients (0.8%), respectively, and Nervous system disorders, in 11 patients (0.7%) and 20 patients (1.2%), respectively.
EAEs leading to premature treatment discontinuation were more frequent in the Perindopril / Amlodipine group (22.1%) than in the Irbesartan / Hydrochlorothiazide group (13.7%), with difference mainly observed under Perindopril 14 mg / Amlodipine 10 mg (14.0% *versus* 4.5%). EAEs involved in the between-group difference were oedema peripheral (6.0% *versus* 0.5%) and cough (6.2% *versus* 0.7%).

- **Laboratory tests**

No relevant difference between groups was detected on mean evolution over time of biochemical and haematological parameters, except for creatinine clearance (-0.2 ± 10.3 mL/min in the Perindopril / Amlodipine group *versus* -4.2 ± 12.3 mL/min in the Irbesartan / Hydrochlorothiazide group) and uric acid (-19.9 ± 50.7 µmol/L *versus* 19.2 ± 58.7 µmol/L).
A lower frequency in the Perindopril / Amlodipine group than in the Irbesartan / Hydrochlorothiazide group of emergent PCSA values was observed for:

- Low creatinine clearance (< 60 mL/min), in 4.1% and 8.2% of the patients, respectively, with no particular dose involved in this difference.
- High uric acid (> 500 µmol/L for women and > 600 µmol/L for men), in 0.4% and 2.5%.
- High triglycerides (> 3 mmol/L), in 2.6% and 6.8%.

No relevant difference between groups was observed for other biochemical as well as for haematological parameters.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Laboratory tests (Cont'd)**

Results of the standard urine strips showed no clinically relevant difference between groups for detection of blood, glucose, leucocytes, and proteins in urinary samples under treatment.

Microalbuminuria was defined as positive when a positive Micral test® was confirmed by an albumin-creatinine ratio > 3.39 mg/mmol (or missing) assessed by the central laboratory. Emergent microalbuminuria was similarly reported in the Perindopril / Amlodipine group and in the Irbesartan / Hydrochlorothiazide group in the Safety Set (29.6% *versus* 27.5%).

- **Vital signs and quality of life**

Clinical examination (weight, BMI, waist circumference, and supine heart rate) did not show any clinically relevant changes over time nor differences between groups.

According to answers to the well-being questionnaire (EQ-5D), most patients had a relatively good quality of life, at baseline and at the end of the study period, without difference between groups. In each group, around 80% of patients had no problem in walking, performing usual activities, no anxiety or depression, around 95% of patients had no problem with self-care, and around two-third of patients did not experience pain/discomfort, at baseline as well as at the last assessment.

CONCLUSION

The study fulfilled its main objective as it demonstrated that the up-titration of the Perindopril / Amlodipine strategy, for patients with non-controlled blood pressure, caused a significant increase of the rate of patients with blood pressure control, over each period. The proportion of patients achieving blood pressure control at the end of the 6-month treatment period was 39.9% in the Perindopril / Amlodipine strategy and 44.8% in the Irbesartan / Hydrochlorothiazide strategy. The rate of responders was the same in both strategies (71.9% and 73.2%, respectively). The mean decreases of SBP and DBP from baseline to last post-baseline value until M6 were similar in both strategies with different interim profiles of response. The perindopril 14mg / amlodipine 5mg dose was the one which seemed to contribute least to the overall efficacy. The Perindopril / Amlodipine strategy was shown to have a significantly lower risk of renal impairment under treatment (0.2%) than the Irbesartan / Hydrochlorothiazide strategy (2.1%). The tolerance of the Perindopril / Amlodipine combination in the study was in accordance with the well-known safety profile of each individual product.

Date of the report: 21 May 2013