I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Report Synopsis**
Study title	**Efficacy and safety of the fixed oral low-dose perindopril arginine 3.5 mg/amlodipine 2.5 mg combination compared with each component (perindopril arginine 3.5 mg and amlodipine 2.5 mg) and with perindopril arginine 5 mg and amlodipine 5 mg. Randomised, double-blind, placebo-controlled study over 8 weeks in hypertensive patients.**
Study drug	**S 05985**
Studied indication	**Essential arterial hypertension**
Development phase	**Phase II**
Protocol code	**CL2-05985-005**
Study initiation date	**19 May 2007**
Study completion date	**30 December 2008**
Main coordinator	[redacted] **- France**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.) 50 rue Carnot 92284 Suresnes Cedex - France**
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 02 August 2012**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

Title of study:
Efficacy and safety of the fixed oral low-dose perindopril arginine 3.5 mg/amlodipine 2.5 mg combination compared with each component (perindopril arginine 3.5 mg and amlodipine 2.5 mg) and with perindopril arginine 5 mg and amlodipine 5 mg.
Randomised, double-blind, placebo-controlled study over 8 weeks in hypertensive patients.
Protocol No.: CL2-05985-005

International coordinator: [redacted] - France)
National coordinators: [redacted] Latvia), [redacted] - Lithuania), [redacted] - Russia), [redacted] - Ukraine) and [redacted] Hungary).

Study centres:
164 centres located in 6 countries included at least one patient:
France – 115 centres (431 included patients), Russian Federation – 20 centres (562 included patients), Ukraine – 9 centres (169 included patients), Lithuania – 8 centres (142 included patients), Hungary – 6 centres (125 included patients), Latvia – 6 centres (152 included patients).

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 15 May 2007 Completion date: 30 December 2008	Phase II study

Objectives:

The primary objectives were:
To demonstrate a statistically significant and clinically relevant greater blood pressure lowering effect with perindopril 3.5 mg/amlodipine 2.5 mg combination than with placebo.
To demonstrate a statistically greater blood pressure lowering effect with perindopril 3.5 mg/amlodipine 2.5 mg combination than with each of monocomponent perindopril 3.5 mg and amlodipine 2.5 mg given separately.
To demonstrate that the blood pressure lowering effect of the perindopril 3.5 mg/amlodipine 2.5 mg fixed low-dose combination was not inferior to those of perindopril 5 mg and amlodipine 5 mg (lowest approved dosage of each component) given separately.

The secondary objectives were:
To demonstrate that the response and normalization rate on the fixed low-dose combination perindopril 3.5 mg/amlodipine 2.5 mg exceed that on placebo by an amount that was statistically significant and clinically valuable.
To show a trend towards better response and normalization rate regarding the low-dose fixed combination perindopril 3.5 mg/amlodipine 2.5 mg as compared to perindopril 5 mg and to amlodipine 5 mg (lowest approved dosage of each component).
To show a trend towards better safety (dose-dependent adverse events) regarding the low-dose fixed combination perindopril 3.5 mg/amlodipine 2.5 mg as compared to perindopril 5 mg and to amlodipine 5 mg (lowest approved dosage of each component).

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

Methodology:
International, multicentric, randomised, double-blind, placebo-controlled phase II study with a factorial design and 6 parallel arms: perindopril 3.5 mg/amlodipine 2.5 mg low-dose combination, perindopril 3.5 mg, amlodipine 2.5 mg, perindopril 5 mg, amlodipine 5 mg, and placebo.
The treatments were allocated via Interactive Voice Response System (IVRS) by non-adaptative, centralised, balanced, stratified randomisation according to centre.

Number of patients:
Planned: 1500 (250 per group)
Included: 1581 *i.e*. 248 in the perindopril (Per) 3.5 mg/amlodipine (Amlo) 2.5 mg group, 250 in the placebo group, 273 in the perindopril 3.5 mg group, 274 in the amlodipine 2.5 mg group, 272 in the perindopril 5 mg group and 264 in the amlodipine 5 mg group.

Diagnosis and main criteria for inclusion:
Men or women, 18 included to 80 excluded years old, suffering from essential mild to moderate uncomplicated hypertension (95 ≤ Diastolic Blood Pressure [DBP] < 110 mmHg and 150 ≤ Systolic Blood Pressure [SBP] < 180 mmHg, measured with a validated automatic device in supine position) after initiation or intensification of appropriate healthy lifestyle modification, requiring antihypertensive treatment institution or a change due to lack of efficacy or poor tolerability.

Patients without known associated clinical conditions (cerebrovascular, heart, renal, peripheral vascular diseases and without advanced retinopathy), without type I and II diabetes, left ventricular hypertrophy and microalbuminuria.
Main other non selection/inclusion criteria: more than 1 antihypertensive drug; liver, psychiatric, endocrine diseases; chronic pancreatitis; ventricular rhythm disorders; symptomatic orthostatic hypotension; connective tissue disorders; angioedema; hypersensitivity to the drugs; pregnancy; obesity; hyperkaliemia; neutropenia; alcoholism or drug abuse.

Study drug:
S 05985 = Perindopril 3.5 mg/amlodipine 2.5 mg low-dose combination.
1 capsule per day, orally, before breakfast.
Batch No.: L0015408, L0020382, L0022393, L0022862.

Reference product:
- Perindopril 3.5 mg (arginine salt).
- Amlodipine 2.5 mg.
- Perindopril 5 mg (arginine salt).
- Amlodipine 5 mg.
- Placebo.

For the 5 treatment groups, 1 capsule per day, orally, before breakfast.

Duration of treatment:
- Run-in period with placebo between selection (SEL) and inclusion (Week 0 [W0]) which lasted at least 2 weeks and no more than 3 weeks.
- 8-weeks double-blind active treatment period from W0 to W8.

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

Criteria for evaluation:
Efficacy measurements:

- Primary efficacy criterion: supine DBP, expressed as the change from baseline to last observation.
- Secondary efficacy criteria:
  - Supine SBP, expressed as the change from baseline to last observation.
  - Response to the treatment corresponding to the percentage of patients at last observation with [SBP < 140 mmHg and DBP < 90 mmHg] and/or SBP decrease ≥ 20 mmHg from baseline and/or DBP decrease ≥ 10 mmHg from baseline.
  - Normalization of blood pressure corresponding to the percentage of patients at last observation with SBP < 140 mmHg and DBP < 90 mmHg.
  - Pulse Pressure and Mean Blood Pressure expressed as the change from baseline to last observation.

Blood pressure efficacy measurements were measured at each visit (SEL, W0, W2, W4 and W8), using a validated automatic device, in supine position after at least 10 minutes of rest. The mean of 3 measurements at 1 minute interval were taken.

Safety measurements:

- Leg oedema (assessed by the patient using a visual analogue scale and by the investigator's clinical exam and measurement of ankle circumference): at W0, W2, W4 and W8 visits.
  A composite endpoint (composite oedema) was used (Amendment No. 2).
- Orthostatic hypotension (calculated): at W0, W2, W4 and W8 visits.
- Adverse events: at W0, W2, W4 and W8 visits.
- Vital signs (weight and heart rate) at SEL, W0, W2, W4 and W8 visits.
- Laboratory parameters (haematology and biochemistry): at W0, W8 (complete tests) and W2 (additional simplified tests) visits.
- Electrocardiogram (ECG): at W0 and W8 visits.

Statistical methods:
EFFICACY ANALYSIS
Primary criterion: supine DBP

Main analyses (Full Analysis Set, FAS)

- 3 superiority comparisons: Per 3.5/Amlo 2.5 *versus* placebo, Per 3.5 and Amlo 2.5, respectively.

The superiority of the Per 3.5/Amlo 2.5 combination was tested on the change from baseline value to last post-baseline value of supine DBP using a general linear model studying treatment effect with baseline and centre (random factor) as covariates.
For the superiority of Per 3.5/Amlo 2.5 on placebo, the estimate and its 95% confidence interval was clinically interpreted according to -2 mmHg.

- 2 non-inferiority comparisons: Per 3.5/Amlo 2.5 *versus* Per 5 and Amlo 5, respectively.

The non-inferiority of the Per 3.5/Amlo 2.5 combination was tested on the change from baseline value to last post-baseline value of supine DBP using a general linear model studying treatment effect with baseline and centre (random factor) as covariates. The non-inferiority limit was set at 2 mmHg.

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

Statistical methods (Cont'd):
EFFICACY ANALYSIS (Cont'd)
Primary criterion: supine DBP (Cont'd)

Sensitivity analyses
A general linear model with country instead of centre as factor was used, for the 3 superiority comparisons and the 2 non-inferiority comparisons.

Other analyses
Similar analyses (main model) were performed in the Per protocol Set (PPS) on the change from baseline to W008 value under treatment and in the Randomised Set (RS).
The value at each visit under treatment and the change from baseline to each post-baseline visit under treatment were described.

Secondary criteria:
For supine SBP, the same analyses as for the main criterion were performed. The non-inferiority limit was set at 3 mmHg.

For response to treatment and normalization rate, the superiority of the Per 3.5/Amlo 2.5 combination on placebo was tested on the last post-baseline value using a chi-2 test. For the comparison between Per 3.5/Amlo 2.5 combination and Per 5 (respectively Amlo 5), the estimate of treatment differences, its standard error and its 95% confidence were provided.
For pulse pressure and mean blood pressure, the treatment group differences between each studied treatment and Per 3.5/Amlo 2.5 combination, and their 95% confidence interval were presented.
Analyses were performed on the FAS and PPS.

Complementary analyses
The superiority of Per 3.5 (respectively Amlo 2.5) *versus* placebo was tested on the mean decrease of supine DBP/SBP (change from baseline to last post-baseline value) and on the rates of responder patients / patients with normalized BP (at the last post-baseline assessment).
The equivalence of Per 3.5 and Amlo 2.5 was tested on the mean decrease of supine SBP (change from baseline to last post-baseline value).

SAFETY ANALYSIS
For parameters assessing leg oedema, for calculated orthostatic hypotension and for specific emergent adverse events, treatment group differences between Per 3.5/Amlo 2.5 combination and Per 5 (respectively Amlo 5) and their 95% confidence interval were presented.
A descriptive analysis in the Safety Set was provided for adverse events, emergent adverse events, vital signs (heart rate and weight), laboratory parameters and ECG clinically significant abnormalities.

Name of Company: I.R.I.S. 50 rue Carnot 92284 Suresnes Cedex - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 2053 patients were selected for the study, 1581 were included with treatment randomly assigned and 1497 completed the study.

No patient was lost to follow-up. A total of 84 patients (5.3%) were withdrawn from the study. The rate of withdrawal was similar in all treatment groups, except for the withdrawal rate due to adverse events (AE) which was lower in the Per 3.5/Amlo 2.5 group (1.2%) than in the other active treatment groups (from 2.2% to 3.3%).

Disposition of patients

(according to the treatment dispensed at inclusion)

		Per 3.5/ Amlo 2.5	*Placebo*	*Per 3.5 mg*	*Amlodipine 2.5 mg*	*Perindopril 5 mg*	*Amlodipine 5 mg*	**All**
Included (randomised)	**n**	**248**	**250**	**273**	**274**	**272**	**264**	**1581**
Withdrawn due to	**n**	**9**	**11**	**16**	**19**	**15**	**14**	**84**
adverse event	n	3	-	6	9	7	8	33
lack of efficacy	n	2	3	3	2	3	3	16
non-medical reason	n	2	5	3	5	3	3	21
other [#]	n	1	1	1	1	1	-	5
protocol deviation	n	1	2	3	2	1	-	9
Completed	**n**	**239**	**239**	**257**	**255**	**257**	**250**	**1497**
Full Analysis Set (FAS)	**n (%)**	246 (15.7)	248 (15.9)	268 (17.1)	270 (17.3)	270 (17.3)	261 (16.7)	**1563 (98.9)[a]**
Per Protocol Set (PPS)	**n (%)**	236 (16.0)	235 (16.0)	248 (16.8)	252 (17.1)	257 (17.4)	245 (16.6)	**1473 (94.2)[b]**
Safety set	**n (%)**	249 (15.7)	251 (15.9)	273 (17.2)	274 (17.3)	272 (17.2)	264 (16.7)	**1583**

*n = number of patients by group; % (n/N)*100 (N Number of patients in a given analysis set) ;[a] % calculated as percentage of the Randomised Set; [b] % calculated as percentage of the FAS.*

[#] protocol requirement.

In the Randomised Set, patients had a mean (± SD) age of 51.7± 11.4 years with 13.3% of patients over 65 years, and the ratio men/women was well-balanced. The BMI was 26.8 ± 2.6 kg/m^2. There was no clinically relevant difference between treatment groups.

The mean duration from the diagnosis of hypertension was 56.0 ± 70.3 months with a median of 30.0 months.

During the year preceding the selection, 61.0% of patients had received treatments for hypertension. The most frequent treatments were agents acting on the renin-angiotensin system (56.3% of the previously treated patients). There were no clinically relevant differences between treatment groups in the distribution of these previous antihypertensive treatments.

The mean supine DBP and SBP, at inclusion, were 100.5 ± 4.0 mmHg and 161.4 ± 7.5 mmHg, respectively. The blood pressure parameters were similar on average in all treatment groups.

In the Safety Set, the mean overall treatment duration was 56.6 ± 9.4 days, very close to the theorical duration (56 days), without relevant difference between treatment groups.

During the treatment period, the mean overall compliance in the Safety Set was satisfactory (98.6 %), without clinically relevant difference between treatment groups.

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Main efficacy criterion: supine DBP, expressed as the change from baseline to last observation

The mean DBP decrease between baseline and the end value was clinically and statistically significantly greater in the Per 3.5/Amlo 2.5 group than in the placebo group and statistically significantly greater in the Per 3.5/Amlo 2.5 group than in the Perindopril 3.5 mg and Amlodipine 2.5 mg groups, in the FAS as well as in the PPS. Results of the sensitivity analysis (adjustment on baseline and country) performed in the FAS confirmed the results of the main analysis (adjustment on baseline and centre).

Supine DBP (mmHg) - FAS (N = 1563) - Change from baseline to END* value - Superiority comparison between treatment groups

		Per 3.5/ Amlo 2.5	***Placebo***	***Perindopril 3.5 mg***	***Amlodipine 2.5 mg***
END*-Baseline	N	246	248	268	270
	Mean ± SD	-13.6 ± 9.2	-9.3 ± 9.2	-9.7 ± 9.9	-10.3 ± 9.7
	Min ; Max	-45 ; 13	-39 ; 15	-34 ; 31	-41 ; 18
Main statistical analysis					
	E (SE) (1)		-4.12 (0.77)	-3.64 (0.76)	-2.97 (0.75)
	95% CI (2)		[-5.63 ; -2.61]	[-5.12 ; -2.16]	[-4.45 ; -1.49]
	p-value (3)		p < 0.001	p < 0.001	p < 0.001

Superiority tests of Per 3.5/Amlo 2.5 as compared to reference treatment (Placebo, Per 3.5 mg, Amlo 2.5 mg).

One-sided type I error rate 0.025.

(1) Estimate (Standard Error) of the difference between baseline and centre adjusted treatment group means Per 3.5/Amlo 2.5 minus reference treatment.

(2) 95% Confidence interval of the estimate.

(3) General linear model with baseline as covariate and centre as random factor.

** Last post-baseline value. For patients with a last post-baseline value not under treatment but with a post-baseline value under treatment, the last post-baseline value under treatment was taken into account.*

The mean supine DBP decrease between baseline and the end value was statistically significantly non-inferior in the Per 3.5/Amlo 2.5 group as compared to that in the Perindopril 5 mg and Amlodipine 5 mg groups, in the FAS as well as in the PPS. Results of the sensitivity analysis (adjustment on baseline and country) performed in the FAS confirmed the results of the main analysis (adjustment on baseline and centre).

Supine DBP (mmHg) - FAS (N = 1563) - Change from baseline to END* value - Non-inferiority comparison between treatment groups

		Per 3.5/ Amlo 2.5	***Perindopril 5 mg***	***Amlodipine 5mg***
END*-Baseline	N	246	270	261
	Mean ± SD	-13.6 ± 9.2	-10.5 ± 9.7	-12.6 ± 8.9
	Min ; Max	-45 ; 13	-45 ; 15	-37 ; 14
Main statistical analysis				
	Estimate (1)		-2.59 (0.75)	-0.76 (0.76)
	95% CI (2)		[-4.07 ; -1.11]	[-2.25 ; 0.73]
	p-value (3)		p < 0.001	p < 0.001

Non-inferiority tests of Per 3.5/Amlo 2.5 as compared to reference treatment (Per 5 mg, Amlo 5 mg).
Non-inferiority limit 2 mmHg.
One-sided type I error rate 0.025.
(1), (2) and (3) see previous table.
** Last post-baseline value. For patients with a last post-baseline value not under treatment but with a post-baseline value under treatment, the last post-baseline value under treatment was taken into account.*

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

EFFICACY RESULTS (Cont'd)

Secondary efficacy criteria

- **Supine SBP**

The mean supine SBP decrease between baseline and the end value was clinically and statistically significantly greater in the Per 3.5/Amlo 2.5 group than in the placebo and statistically significantly greater in the Per 3.5/Amlo 2.5 group than in the Perindopril 3.5 mg and Amlodipine 2.5 mg groups, in the FAS as well as in the PPS. Results of the sensitivity analysis (adjustment on baseline and country) performed in the FAS confirmed the results of the main analysis (adjustment on baseline and centre).

Supine SBP (mmHg) - FAS (N = 1563) - Change from baseline to END* value - Superiority comparison between treatment groups

		Per 3.5/ Amlo 2.5	***Placebo***	***Perindopril 3.5 mg***	***Amlodipine 2.5 mg***
END*-Baseline	N	246	248	268	270
	Mean ± SD	-22.0 ± 14.0	-14.2 ± 16.1	-16.3 ± 17.0	-16.0 ± 15.3
	Min ; Max	-54 ; 16	-62 ; 34	-59 ; 34	-61 ; 25
Main statistical analysis					
	E (SE) (1)		-7.22 (1.21)	-5.01 (1.19)	-5.20 (1.19)
	95% CI (2)		[-9.60 ; -4.84]	[-7.35 ; -2.67]	[-7.53 ; -2.87]
	p-value (3)		p < 0.001	p < 0.001	p < 0.001

Superiority tests of Per 3.5/Amlo 2.5 as compared to reference treatment (Placebo, Per 3.5 mg, Amlo 2.5 mg).
One-sided type I error rate 0.025.
(1), (2) and (3) see first table.
** Last post-baseline value. For patients with a last post-baseline value not under treatment but with a post-baseline value under treatment, the last post-baseline value under treatment was taken into account.*

The mean supine SBP decrease between baseline and the end value was statistically significantly non-inferior in the Per 3.5/Amlo 2.5 group as compared to that in the Perindopril 5 mg and Amlodipine 5 mg groups, in the FAS as well as in the PPS. Results of the sensitivity analysis (adjustment on baseline and country) performed in the FAS confirmed the results of the main analysis (adjustment on baseline and centre).

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

EFFICACY RESULTS (Cont'd)

Secondary efficacy criteria (Cont'd)

Supine SBP (mmHg) - FAS (N = 1563) - Change from baseline to END* value - Non-inferiority comparison between treatment groups

		Per 3.5/ Amlo 2.5	***Perindopril 5 mg***	***Amlodipine 5 mg***
END*-Baseline	N	246	270	261
	Mean ± SD	-22.0 ± 14.0	-18.2 ± 14.8	-21.8 ± 15.4
	Min ; Max	-54 ; 16	-62 ; 18	-58 ; 33
Main statistical analysis				
	Estimate (1)		-2.78 (1.19)	-0.29 (1.20)
	95% CI (2)		[-5.11 ; -0.45]	[-2.64 ; 2.06]
	p-value (3)		p < 0.001	p = 0.003

Non-inferiority tests of Per 3.5/Amlo 2.5 as compared to reference treatment (Per 5 mg, Amlo 5 mg).
Non-inferiority limit 3 mmHg.
One-sided type I error rate 0.025.
(1), (2) and (3) see first table.
** Last post-baseline value. For patients with a last post-baseline value not under treatment but with a post-baseline value under treatment, the last post-baseline value under treatment was taken into account.*

- **Responder and normalization rates**

In the FAS, the rate of responder patients, at the last post-baseline assessment, was statistically significantly greater in the Per 3.5/Amlo 2.5 group than in the placebo group with clinical valuable difference (76.8% *versus* 52.8%, p < 0.001) as well as the rate of patients with normalized BP (43.5% *versus* 26.6%, p < 0.001).

In the FAS, the rates of responder patients and of patients with normalized patients, at the last post-baseline assessment, were greater in the Per 3.5/Amlo 2.5 group than in the Per 5 group (76.8% *versus* 62.6% for responders; 43.5% *versus* 33.3% for normalization) and tended to be greater than in the Amlo 5 group (76.8% *versus* 72.8% for responders; 43.5% *versus* 37.9% for normalization).

Superiority of Per 3.5 (respectively Amlo 2.5) versus placebo and equivalence of Per 3.5 and Amlo 2.5 *(complementary analyses)*

No superiority of Per 3.5 (respectively Amlo 2.5) was demonstrated as compared to placebo either in the mean decrease of supine DBP / SBP between baseline and the last post-baseline measurement or in the rate of responder patients / patients with normalized BP at the last post-baseline assessment.

The mean decrease in the supine SBP, between baseline and the last post-baseline measurement, was statistically and clinically equivalent in the Per 3.5 (-16.3 ± 17.0 mmHg) and Amlo 2.5 groups (-16.0 ± 15.3 mmHg), with an estimated difference between adjusted (baseline and centre) group means of -0.19 mmHg (95% CI [-2.47 ; -2.09], p = 0.008. These results confirm the choice of the doses of 3.5 mg for perindopril and 2.5 mg for amlodipine as subtherapeutic doses with similar effect on SBP.

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

SAFETY RESULTS

Observations related to dose-dependent emergent adverse events

The percentage of patients presenting an emergent leg oedema was lower in the Per 3.5/Amlo 2.5 group than in the Amlo 5 group, for emergent « oedema of lower limbs » reported as AE (1.6% *versus* 4.9%) as well as for leg edema assessed by the investigator at clinical examination (1.6% *versus* 5.3%). Consistently, the percentage of patients presenting with a leg oedema using a composite criterion combining only investigator's assessement criteria (emergent oedema of lower limbs AE, emergent leg oedema at clinical examination or change in ankle circumference from baseline to worst value > 20 mm, complementary analysis) was lower in the Per 3.5/Amlo 2.5 group than in the Amlo 5 group (2.0% *versus* 7.2%). The percentage of patients with a worst change of VAS > 20 mm tended to be lower in the Per 3.5/Amlo 2.5 group (5.6%) than in the Amlo 5 group (7.6%) (complementary analysis). For all these criteria, the percentages were similar in the Per 3.5/Amlo 2.5 and Per 5 groups.

The percentages of patients presenting with a flush tended to be lower in the Per 3.5/Amlo 2.5 group than in the Amlo 5 group (0.4% *versus* 1.9%).

Other specific adverse events

The percentages of patients presenting with orthostatic hypotension, headache or cough were low in each of the Per 3.5/Amlo 2.5, Per 5 and Amlo 5 groups and no clinically relevant difference between the Per 3.5/Amlo 2.5 group and each of the 2 other groups was shown. No case of emergent hypotension was reported during the study.

Overall analysis of emergent adverse events (EAE)

No relevant difference between groups was detected for incidence of emergent adverse events. The most frequently reported emergent adverse events, with percentage of patients affected, (at least 1.5% of the patients in any compared group) are presented thereafter:

	Per 3.5/Amlo 2.5	**Placebo**	**Per 3.5**	**Amlo 2.5**	**Per 5**	**Amlo 5**
ALL	**18.9**	**15.9**	**18.7**	**18.6**	**16.2**	**21.6**
Oedema peripheral	1.6	1.2	2.9	0.7	1.5	4.9
Hyperkalaemia	2.4	-	-	2.2	0.7	0.4
Back pain	0.4	0.4	-	0.7	0.7	1.9
Headache	1.2	1.6	1.8	1.5	1.1	0.4
Bronchitis	0.8	1.6	0.7	1.1	0.4	-
Dyslipidaemia	0.4	0.8	0.4	1.5	0.4	0.8

The intensity was more frequently rated as mild in the Per 3.5/Amlo 2.5 group (79.6%) than in the Per 5 and Amlo 5 groups (58.9% and 51.5%, respectively). Sixteen patients (1.0%) had severe EAEs (ranging from 0% in the Per 3.5/Amlo 2.5 group to 11.8% in the Amlo 5 group). EAEs considered as related to the treatment were mainly (at least 1% of the patients in any compared group) oedema peripheral, hyperkalaemia, headache, cough and flushing.

One patient died during the study (drowning, Per 5 group). Overall, in the Safety Set, 10 patients experienced 10 serious adverse events (including death) (SAE) during the study, which all were emergent and considered by the investigator as not related to the study treatment: 0 in the Per 3.5/Amlo 2.5 group, 1 in the placebo, Per 3.5 and Amlo 2.5 groups, 4 in the Per 5 group and 3 in the Amlo 5 group. Serious non-fatal adverse events led to treatment withdrawal in 4 patients: acute coronary syndrome (Per 3.5 group), angina unstable (Per 5 group), cerebrovascular accident (Amlo 5 group) and renal cancer metastatic (Amlo 5 group). All non-fatal SAEs were recovered except one (renal cancer metastatic).

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: ***Perindopril/Amlodipine*** ***S 05985***	**Page:**	

SAFETY RESULTS (Cont'd)
Overall, emergent adverse events (serious or not) led to treatment stopped in 39 patients. The number of patients with AEs leading to treatment stopped was lower in the Per 3.5/Amlo 2.5 and placebo groups (3 and 2 patients, respectively) than in the other groups (from 7 to 11 patients).

Vital signs
No clinically relevant change or abnormalities were detected for weight or heart rate.

Laboratory tests
Neither clinically relevant changes nor differences between groups, in mean biochemical and haematological values between the baseline and the last assessment on treatment, were observed.

Emergent Potentially Clinically Significant Abnormal (PCSA) values of high potassium and low creatinine clearance were observed in very few patients in any treatment group (from 1 to 3 patients for high potassium and from 2 to 5 patients for low creatinine clearance).

In all, 4 patients presented with emergent PCSA high values of transaminases: 2 in the Per 3.5 group, 1 in the Amlo 2.5 group and 1 in the Amlo 5 group. An AE was reported in all cases and considered as related to the study drug by the investigator in 3 cases. At last (re)test, for the first patient, transaminases values returned to the normal range, for the second patient, transaminases values decreased but were still elevated and for the third patient, transaminases values decreased to out-of-reference-range values. For the fourth patient, no retest was performed.

CONCLUSION
The results of this randomised, double-blind, placebo-controlled study in hypertensive patients are conform with the requirements of the European guidelines (CPMP/EWP/238/95 rev 2) and support the claim of first line therapy for the fixed combination Per 3.5/Amlo 2.5 in the treatment of hypertension.

The study demonstrated that the Per 3.5/Amlo 2.5 fixed combination had a statistically significant greater blood pressure lowering effect than placebo (with clinical relevance) and than each of monocomponent given separately (Per 3.5 and Amlo 2.5), and a statistically significant and clinically valuable greater rate of responders and patients with normalized blood pressure than placebo. The non-inferiority of the effect of the combination was also demonstrated *versus* the lowest approved dosage of each monocomponent (Per 5 and Amlo 5). Moreover, there was a better responder and normalization rate regarding the Per 3.5/Amlo 2.5 combination as compared to Per 5, and there was a trend towards better responder and normalization rate regarding the Per 3.5/Amlo 2.5 combination as compared to Amlo 5. In addition, this study allowed to confirm the appropriate dose selection of each component (Per 3.5 and Amlo 2.5 are subtherapeutic doses and have similar effect on SBP - complementary analysis).
The study also showed a trend towards better safety of the Per 3.5/Amlo 2.5 combination as compared to Per 5 and Amlo 5: lower incidence of dose-dependant adverse events (leg oedema and flush) than with amlodipine 5 mg, lower incidence of serious and severe adverse events, lower incidence of withdrawals due to adverse event.

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