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:
Efficacy on systolic and diastolic blood pressure decrease and safety of once-a-day oral 5 milligram (mg) Perindopril arginine salt (titrated to 10 mg).
A 12-week, 2-arm, randomised, double-blind study *versus* once-a-day oral 4 mg Perindopril *tert*-butylamine salt (titrated to 2 x 4 mg) in hypertensive patients.
Protocol No.: **CL3-06490-003**

Coordinator: [redacted]

Study centres:
19 centres located in China, were opened and selected and included at least one patient.

Publication (reference): Not applicable.

Studied period: Initiation date: 29 July 2010 Completion date: 18 May 2011	**Phase of development of the study:** III

Objectives: The aim of this study was to assess the efficacy and the safety of an 8-week administration period of Perindopril arginine salt 5 mg.

- ***Main objective***: To demonstrate that Perindopril arginine salt 5 mg was at least as efficient as perindopril *tert*-butylamine 4 mg in the treatment of hypertensive patients as measured by the change from baseline to week 8 of sitting systolic blood pressure (SBP).
- ***Secondary objectives:***
  - *Efficacy*:
    - To demonstrate that Perindopril arginine salt 5 mg was at least as efficient as perindopril *tert*-butylamine 4 mg in the treatment of hypertensive patients as measured by the change from baseline to week 8 of sitting diastolic blood pressure (DBP).
    - To estimate treatment group differences between Perindopril arginine salt 5 mg and Perindopril *tert*-butylamine salt 4 mg after an 8-week treatment period in:
      - Responders rate (defined as control of blood pressure [BP] and/or SBP decrease ≥ 20 millimetre of mercury (mmHg) from baseline and/or DBP decrease ≥ 10 mmHg from baseline).
      - BP control rate (DBP < 90 mmHg and SBP < 140 mmHg).
      - Change in sitting Pulse Pressure (PP) and in Mean Blood Pressure (MBP = 2/3 DBP + 1/3 SBP).
    - To estimate treatment group differences between perindopril arginine salt (5 or 10 mg) and perindopril *tert*-butylamine (4 or 2 x 4 mg) after a 12-week treatment period in:
      - Change from baseline in sitting SBP, DBP, PP and MBP.
      - BP responders rate and control rate.
    - To estimate treatment group differences between perindopril arginine salt 5 mg and perindopril *tert*-butylamine 4 mg for last post baseline value (W8 for patients with uptitration or W12 for patients without uptitration) in:
      - Change from baseline in sitting SBP, DBP, PP and MBP.
      - BP responders rate and control rate.
    - To describe in each treatment group the BP profile changes using 25-hour ambulatory blood pressure monitoring (ABPM) from baseline to study end.

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- ***Secondary objectives (Cont'd):***
  - *Safety*: To assess the safety and tolerability of each regimen during the 12-week treatment period:
    - All adverse events occurring during the course of the trial were fully documented.
    - BP postural changes, laboratory parameters (haematology, biochemistry), vital signs and electrocardiogram (ECG) abnormalities were recorded.

Methodology: Phase III multi-centric, randomised double-blind study conducted in China, with 2 parallel groups of hypertensive patients.
The patients received during a 12-week treatment period, according to their randomisation group, either Perindopril arginine salt, or Perindopril *tert*-butylamine salt.
Sitting blood pressure (SBP and DBP) was measured at trough of drug activity at each visit, using a validated automatic device.
In addition, 25-hour ABPM assessment was performed at W0 and W12 in patients participating in the ABPM associated study, using the same model of validated ABPM device for W0 and W12 measurements.

Number of patients:
Planned: 352 (176 by group)
Included: 369 *id est* (*i.e).* 186 in the perindopril arginine group and 183 in the perindopril *tert*-butylamine group.

Diagnosis and main criteria for inclusion:
Patients, aged between 18 and 75 years, with essential systolo-diastolic hypertension and who met the following criteria at selection:

- For untreated patients: 95 mmHg ≤ DBP < 110 mmHg and
  150 mmHg ≤ SBP < 180 mmHg
- Or, for treated patients who required a change in medication in the investigator's opinion either because of lack of efficacy or poor tolerability: DBP < 110 mmHg and SBP < 180 mmHg.

Study drug: perindopril arginine salt, one capsule daily containing:

- From W0 to W8: one perindopril arginine 5 mg tablet.
- From W8 to W12: one perindopril arginine 5 mg tablet or 10 mg tablet (patients not controlled at W8).

Reference product: Perindopril *tert*-butylmanine salt, one capsule daily containing:

- From W0 to W8: one Perindopril *tert*-butylamine 4 mg tablet.
- From W8 to W12: one Perindopril *tert*-butylamine 4 mg tablet or two 4 mg tablets (patients not controlled at W8).

Duration of treatment:

- Run-in placebo period (2 weeks).
- Follow-up period (8 weeks): Perindopril arginine 5 mg/day or Perindopril *tert*-butylmanine 4 mg/day.
- Titrated period (4 weeks):
  - Perindopril arginine 5 mg or Perindopril *tert*-butylamine 4 mg/day (patients controlled at W8), or
  - Perindopril arginine 10 mg or Perindopril *tert*-butylamine 2 x 4 mg/day (patients not controlled at W8; with blood pressure control defined as SBP < 140 mmHg and DBP < 90 mmHg).

Criteria for evaluation:

- Primary efficacy criterion: sitting SBP.
- Secondary efficacy criteria: sitting DBP, response to treatment (defined as BP control, and/or SBP decrease ≥ 20 mmHg from baseline, and/or DBP decrease ≥ 10 mmHg from baseline), BP control, pulse pressure, mean blood pressure, 25-hour ABPM parameters.
- Safety criteria (secondary): adverse events, vital signs, orthostatic hypotension, laboratory tests, electrocardiogram.

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Statistical methods:

Efficacy

Efficacy analyses were carried out primarily on the Full Analysis Set and confirmed on the Per Protocol Sets (PPS W8, PPS W12).

Primary criterion: sitting SBP

Main analysis:

The non-inferiority of the Perindopril arginine salt *versus* Perindopril *tert*-butylamine salt was studied on the change from baseline to last post-baseline value over 8 weeks of sitting SBP using a general linear model studying treatment effect with baseline and centre (fixed effects) as covariates. The estimate of treatment difference, its standard error and its 95% confidence interval was also provided. The non-inferiority limit was set at 4 mmHg.

Secondary analyses:

For the change from baseline to last post-baseline value over the study of sitting SBP and for the change from baseline to last post-baseline value under dose 1 (*i.e.* last post-baseline value over 12 weeks for non-titrated patients and last post-baseline value over 8 weeks for titrated patients), the difference between Perindopril arginine salt and Perindopril *tert*-butylamine salt was presented, as well as its 95% confidence interval.

Secondary criteria:

- Sitting DBP

The same analyses as for sitting SBP was performed. The non-inferiority limit was set at 3 mmHg.

- Response to treatment and blood pressure control

For the last post-baseline value over 8 weeks, the last post-baseline value over the study and the last post-baseline value under dose 1 of responders rate and BP control rate, the differences of percentage between Perindopril arginine salt and Perindopril *tert*-butylamine salt were given as well as their 95% confidence intervals.

- Pulse pressure and mean blood pressure

For the change from baseline to last post-baseline value over 8 weeks, the change from baseline to last post-baseline value over the study and the change from baseline to last post-baseline value under dose 1 of PP and MBP, differences between Perindopril arginine salt and Perindopril *tert*-butylamine salt were presented as well as their 95% confidence intervals.

- 25- hour ABPM parameters

All 25-hour ABPM parameters were described at W0 and W12 and the change from baseline to Week 12 was presented by treatment group on the FAS (Full Analysis Set) -ABPM and PPS-ABPM.

Safety

Descriptive statistics were carried out on the Safety Set over 8 weeks and over 12 weeks by treatment group.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 524 patients were selected for the study; 369 patients were included with treatment randomly assigned and 346 patients (93.8%) completed the study.

No patient was lost to follow up. A total of 23 patients (6.2%) were withdrawn: 11 patients due to adverse event, 9 for non-medical reason, 1 due to protocol deviation and 2 for other protocol withdrawal criteria (DBP > 110 mmHg for one patient and SBP > 180 mmHg for the other one). The rate of withdrawal was similar between groups.

Disposition of patients

		Perindopril arginine	**Perindopril *tert*-butylamine**	**All**
Included (Randomised Set [RS])	n	186	183	369
Withdrawn due to	n	11	12	23
adverse event	n	5	6	11
non-medical reason	n	5	4	9
protocol deviation	n	1	0	1
lost to follow-up	n	-	-	-
other protocol withdrawal criteria	n	-	2	2
Completed	n	175	171	346
Safety Set	n	186	183	369
Full Analysis Set (FAS)	n (%)[a]	182 (97.8)	182 (99.5)	364 (98.6)
Per Protocol Set W8 (PPS W8)	n (%)[b]	169 (92.9)	162 (89.0)	331 (90.9)
Per Protocol Set W12 (PPS W12)	n (%)[b]	160 (87.9)	151 (83.0)	311 (85.4)

% a: % of the Randomised Set; % b: % of the FAS

All randomised patients were Chinese. Their mean age was 53.1 ± 9.0 years and most of patients (89.4%) were < 65 years. More than half of the patients were men (54.5%).

The mean duration from the diagnosis of hypertension was 7.6 ± 7.7 years (median = 5.0 years), without relevant difference between groups.

Before study, 285 patients (77.2%) had received treatments for hypertension. The most frequent treatments were calcium channel blockers (49.1% of the previously treated patients), agents acting on the renin-angiotensin system (36.1%) and diuretics (22.5%). Globally, there was no relevant difference between groups in the distribution of the previous antihypertensive treatments except for: calcium channel blockers (55.7% of the previously treated patients in the perindopril arginine group *versus* 42.8% in the perindopril *tert*-butylamine group) and beta-blocking agents (7.9% *versus* 17.9%, respectively).

The mean sitting SBP and DBP, at inclusion, were 160.4 ± 8.2 mmHg and 101.7 ± 4.5 mmHg, respectively, without relevant difference between groups.

During the treatment period, 77 patients of the RS (20.9%) received at least one concomitant treatment: mainly, antithrombotic agents (6.5% of the randomised patients), lipid modifying agents (6.5%) and drugs used in diabetes (5.1%), without relevant difference between groups.

In the Safety Set, the mean global treatment duration was 83.0 ± 15.7 days and similar to the theoretical duration (84 days), without relevant difference between groups.

During the treatment period, the global compliance was satisfactory (97.6% of patients having an overall compliance between 70% and 130%), without relevant difference between groups.

In the RS and the SS, 109 (58.6%) patients of the perindopril arginine group were uptitrated, *i.e.* received 10 mg of study treatment and 116 (63.4%) patients of the perindopril *tert*-butylamine group were uptitrated, *i.e.* received 2 x 4 mg of study treatment.

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SUMMARY - CONCLUSIONS (Cont'd)
STUDY POPULATION AND OUTCOME (Cont'd)

As regards the **ABPM sub-study**, 2 sets were defined: the FAS-ABPM which consisted of 80 patients having ABPM valid both at W0 and W12 visits and the PPS-ABPM which consisted of 67 patients.
Patients of the FAS-ABPM were on average 53.2 ± 8.9 years; most of patients (86.3%) were < 65 years. More than half of the patients were men (58.8%). The mean duration from the diagnosis of hypertension was 7.3 ± 6.8 years. Before study, 63 patients (78.8%) had received treatments for hypertension. At baseline, the mean SBP over 24 hours was on average 144.95 ± 11.48 mmHg and the mean DBP over 24 hours was on average 91.98 ± 9.92 mmHg, without relevant difference between groups.
The mean global treatment duration was 86.2 ± 3.1 days and all patients had an overall compliance between 70% and 130% during the treatment period.

EFFICACY RESULTS
Main efficacy criterion: sitting SBP, expressed as the change from baseline to last post-baseline
- Main analysis: change over 8 weeks

In the FAS, the mean decrease in the sitting SBP, between baseline and the last post-baseline measurement over 8 weeks, in the perindopril arginine group was non-inferior to that in the perindopril *tert*-butylamine group. Similar results were observed in the PPS W8. (See summary table below)

Sitting SBP (mmHg) - Change from baseline to last post-baseline value over 8 weeks - Non-inferiority comparison between treatment groups - During W0-W8 period

	Perindopril arginine	Perindopril *tert*-butylamine
SBP FAS (N = 364)		
W8-Baseline		
N	182	182
Mean ± Standard deviation (SD)	-19.9 ± 17.2	-18.5 ± 14.7
Statistical analysis		
E (SE) (1)	-1.2 (1.6)	
95% Confidence Interval (CI) (2)	[-4.2 ; 1.9]	
p-value (3)	0.0005	
SBP PPS W8 (N = 331)		
W8-Baseline		
N	169	162
Mean ± SD	-20.7 ± 17.1	-18.4 ± 14.0
Statistical analysis		
E (SE) (1)	-2.1 (1.6)	
95% CI (2)	[-5.3 ; 1.1]	
p-value (3)	< 0.0001	

Non-inferiority tests of Per arg salt 5 mg as compared to Per tert but salt 4 mg
Non inferiority limit: 4 mmHg
One-sided type I error rate: 0.025
(1) Estimate (Standard Error) of the difference between baseline and centre adjusted treatment group means: Per arg salt 5 mg minus Per tert but salt 4 mg
(2) 95% Confidence interval of the estimate
(3) General linear model with baseline and centre (fixed effect) as covariates

- Secondary analyses
  - Change over 12 weeks:
    In the FAS, the mean decrease in the sitting SBP, between baseline and the last post-baseline measurement over 12 weeks, in the perindopril arginine group was similar to that in the perindopril *tert*-butylamine group. Similar results were observed in the PPS W12. (See summary table below).

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- Change under dose 1 over 12 weeks:
  In the FAS, the mean decrease in the sitting SBP, between baseline and the last post-baseline measurement (*i.e.* last post-baseline value over 12 weeks for non-titrated patients and last post-baseline value over 8 weeks for titrated patients), in the perindopril arginine group was similar to that in the perindopril *tert*-butylamine group. Similar results were observed in the PPS W12. (See recapitulative table below)
- Change from baseline to each post-baseline visit:
  The mean decrease in the sitting SBP between baseline and W4/W8/W12 measurements, respectively, was similar in the perindopril arginine group and in the perindopril *tert*-butylamine group, in the FAS as well as in the PPS W12.

Sitting SBP (mmHg) - Change from baseline to last post-baseline value over 12 weeks/over 12 weeks under dose 1 - Estimated difference between treatment groups - During W0-W12 period

	Perindopril arginine	Perindopril *tert*-butylamine
End – Baseline SBP FAS (N = 364) over 12 weeks		
N	182	182
Mean ± SD	-19.8 ± 16.2	-19.6 ± 16.3
Statistical analysis		
E (SE) (1)	-0.2 (1.5)	
95% CI (2)	[-3.2 ; 2.9]	
End – Baseline SBP PPS W12 (N = 311) over 12 weeks		
N	160	151
Mean ± SD	-21.4 ± 16.0	-20.0 ± 16.3
Statistical analysis		
E (SE) (1)	-0.8 (1.7)	
95% CI (2)	[-4.2 ; 2.5]	
End – Baseline SBP FAS (N = 364) over 12 weeks under dose 1		
N	182	182
Mean ± SD	-17.5 ± 16.0	-16.6 ± 15.1
Statistical analysis		
E (SE) (1)	-0.9 (1.5)	
95% CI (2)	[-3.8 ; 2.0]	
End – Baseline SBP PPS W12 (N = 311) over 12 weeks under dose 1		
N	160	151
Mean ± SD	-18.8 ± 16.0	-16.4 ± 14.6
Statistical analysis		
E (SE) (1)	-2.1 (1.6)	
95% CI (2)	[-5.2 ; 1.0]	

Estimation of the difference between Per arg salt 5 mg and Per tert but salt 4 mg
(1) Estimate (Standard Error) of the difference between baseline and centre adjusted treatment group means: Per arg salt 5 mg minus Per tert but salt 4 mg
(2) 95% Confidence interval of the estimate

- In each group, there was a statistically significant decrease of the sitting SBP, between W8 and W12, in patients with uncontrolled BP at W8 and uptitrated to Perindopril arginine 10 mg or Perindopril *tert*-butylamine 2x4 mg.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Sitting SBP (mmHg) - FAS (N = 364) - Change from W8 to W12 for uptitrated patients
Description – During W8-W12 period

		Perindopril arginine 10 mg	**Perindopril *tert*-butylamine 2x4 mg**
Baseline	N	109	116
	Mean ± SD	160.2 ± 7.9	160.7 ± 7.7
	Min ; Max	143 ;179	150 ; 180
W8	N	109	116
	Mean ± SD	149.8 ± 12.0	148.7 ± 10.6
	Min ; Max	122.5 ; 183.0	123.5 ; 174.0
W12	N	108	116
	Mean ± SD	146.0 ± 14.5	144.0 ± 13.7
	Min ; Max	104.5 ; 189.0	117.5 ; 173.0
W12 – W8	N	108	116
	Mean ± SD	-3.8 ± 12.8	-4.7 ± 13.5
	Min ; Max	-33.0 ; 31.5	-28.5 ; 35.5
	95% CI	[-6.3 ; -1.4]	[-7.2 ; -2.2]

The difference between W12 and W8 was performed in the completed patient

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Secondary efficacy criteria

- Sitting DBP

In the FAS, the mean decrease in the sitting DBP, between baseline and the last post-baseline measurement over 8 weeks, in the perindopril arginine group was non-inferior to that in the perindopril *tert*-butylamine group. Similar results were observed in the PPS W8. (See recapitulative table below)

Sitting DBP (mmHg) - Change from baseline to last post-baseline value over 8 weeks - Non-inferiority comparison between treatment groups – During W0-W8 period

	Perindopril arginine	Perindopril *tert*-butylamine
DBP FAS (N = 364)		
W8-Baseline		
N	182	182
Mean ± SD	-12.0 ± 10.0	-11.0 ± 8.9
Statistical analysis		
E (SE) (1)	-1.1 (1.0)	
95% CI (2)	[-2.9 ; 0.8]	
p-value (3)	< 0.0001	
DBP PPS W8 (N = 331)		
W8-Baseline		
N	169	162
Mean ± SD	-12.2 ± 10.0	-11.1 ± 9.0
Statistical analysis		
E (SE) (1)	-1.2 (1.0)	
95% CI (2)	[-3.2 ; 0.8]	
p-value (3)	< 0.0001	

Non-inferiority tests of Per arg salt 5 mg as compared to Per tert but salt 4 mg.
Non inferiority limit: 3 mmHg
One-sided type I error rate: 0.025
(1) Estimate (Standard Error) of the difference between baseline and centre adjusted treatment group means: Per arg salt 5 mg minus Per tert but salt 4 mg
(2) 95% Confidence interval of the estimate
(3) General linear model with baseline and centre (fixed effect) as covariates

When taking account the W0-W12 period, the mean decrease of DBP in the perindopril arginine group, between baseline and the last post-baseline value over 12 weeks, was similar to that in the perindopril *tert*-butylamine group, in the FAS as well as in the PPS W12. Similar decreases in the mean DBP were also observed in both groups over the 12 weeks period under dose 1, in the FAS as well as in the PPS W12.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **Sitting DBP (Cont'd)**

Sitting DBP (mmHg) - Change from baseline to last post-baseline value over 12 weeks/over 12 weeks under dose 1 - Estimated difference between treatment groups – During W0-W12 period

	Perindopril arginine	**Perindopril *tert*-butylamine**
End – Baseline DBP FAS (N = 364) over 12 weeks		
N	182	182
Mean ± SD	-12.0 ± 9.4	-11.4 ± 8.5
Statistical analysis		
E (SE) (1)	-0.8 (0.9)	
95% CI (2)	[-2.5 ; 1.0]	
End – Baseline DBP FAS (N = 364) over 12 weeks under dose 1		
N	182	182
Mean ± SD	-10.7 ± 9.4	-9.9 ± 9.0
Statistical analysis		
E (SE) (1)	-0.9 (0.9)	
95% CI (2)	[-2.7 ; 0.9]	

Estimation of the difference between Per arg salt 5 mg and Per tert but salt 4 mg
(1) Estimate (Standard Error) of the difference between baseline and centre adjusted treatment group means: Per arg salt 5 mg minus Per tert but salt 4 mg
(2) 95% Confidence interval of the estimate

In each group, there was a statistically significant decrease of the sitting DBP, between W8 and W12, in patients with uncontrolled BP at W8 and uptitrated to Perindopril arginine 10 mg or Perindopril *tert*-butylamine 2x4 mg.

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

Sitting DBP (mmHg) - FAS (N = 364) - Change from W8 to W12 for uptitrated patients
Description – During W8-W12 period

		Perindopril arginine 10 mg	Perindopril *tert*-butylamine 2x4 mg
Baseline	N	109	116
	Mean ± SD	101.9 ± 4.5	102.1 ± 4.5
	Min ; Max	93 ; 110	95 ; 110
W8	N	109	116
	Mean ± SD	95.6 ± 7.0	95.0 ± 8.1
	Min ; Max	82.0 ; 120.0	69.5 ; 113.0
W12	N	108	116
	Mean ± SD	93.4 ± 8.7	92.7 ± 7.8
	Min ; Max	71.5 ; 116.5	72.0 ; 108.0
W12 – W8	N	108	116
	Mean ± SD	-2.2 ± 8.0	-2.3 ± 8.4
	Min ; Max	-26.5 ; 17.0	-18.0 ; 32.0
	95% CI	[-3.7 ; -0.6]	[-3.8 ; -0.8]

The difference between W12 and W8 was performed in the completed patients

- **Blood pressure control**

In the FAS, the rate of patients with blood pressure control was similar in the perindopril arginine and the perindopril *tert*-butylamine groups over 8 weeks (38.5% and 31.3%, respectively; E [95% CI] = 7.1% [-2.6 ; 16.9]) as well as over 12 weeks (36.3% and 35.7%, respectively; E [95% CI] = 0.5% [-9.3 ; 10.4]). In the PPS, the rate of patients with blood pressure control (last post-baseline assessment) tended to be greater in the perindopril arginine group than in the perindopril *tert*-butylamine group over 8 weeks (PPS W8: 40.2% and 30.2%, respectively; E [95% CI] = 10.0% [-0.2 ; 20.2]), while it was similar over 12 weeks (PPS W12: 38.1% and 35.8%, respectively; E [95% CI] = 2.4% [-8.4 ; 13.1]).

- **Response to treatment**

In the FAS and in the PPS (W8 and W12), the rate of patients with response to treatment was similar in the perindopril arginine and the perindopril *tert*-butylamine groups over 8 weeks (64.3% and 63.2%, respectively, in the FAS) as well as over 12 weeks (65.9% and 64.8%, respectively, in the FAS).

- **Pulse pressure and Mean blood pressure**

In the FAS and in the PPS (W8 and W12), the mean decrease in the PP and MBP, between baseline and the last post-baseline measurement, in the perindopril arginine group was similar to that in the perindopril *tert*-butylamine group, over 8 weeks as well as over 12 weeks and over 12 weeks under dose 1.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- ABPM

Considering ABPM, results should be interpreted cautiously as it was performed in a small subset (N = 80) of the study population (N = 369).

In the FAS-ABPM, the mean SBP and DBP over 24 hours decreased in both treatment groups between baseline and W12 (see table afterwards). This decrease was similar in both groups for SBP as well as for DBP.

The mean SBP and DBP decreased in both groups over the different studied periods: standard/real diurnal periods, daytime period, standard/real nocturnal periods, night-time period, morning period and period of the last 6 hours of measurement before treatment intake.

ABPM - Mean 24 hours SBP and DBP (mmHg) - Change from baseline to W12 value

	Perindopril arginine	**Perindopril *tert*-butylamine**
W12-baseline FAS-ABPM (N = 80)		
SBP over 24 hours		
N	39	41
Mean ± SD	-8.38 ± 10.72	-10.05 ± 17.43
Median	-7.59	-7.92
DBP over 24 hours		
N	39	41
Mean ± SD	-5.46 ± 6.41	-5.87 ± 10.42
Median	-4.66	-5.53

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Name of Active Ingredient: Perindopril arginine salt (S 06490)	**Page:**	

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

Overall (W0-W12 period) summary of safety results - Safety Set

		Perindopril arginine (N = 186)	Perindopril *tert*-butylamine (N = 183)
Patients having reported			
at least one emergent adverse event	n (%)	43 (23.1)	44 (24.0)
at least one treatment-related emergent adverse event	n (%)	18 (9.7)	14 (7.7)
Patients having experienced			
at least one serious emergent adverse event (including death)	n (%)	-	2 (1.1)
at least one treatment-related emergent serious adverse event	n (%)	-	-
Patients withdrawn			
due to an emergent adverse event	n (%)	5 (2.7)	6 (3.3)
due to a serious emergent adverse event	n (%)	-	-
due a treatment-related emergent adverse event	n (%)	3 (1.6)	3 (1.6)
due a treatment-related serious emergent adverse event	n (%)	-	-
Patients who died during the study treatment period	n (%)	-	-

During the treatment period (W0-W12), emergent adverse events were reported in 23.1% of the patients in the perindopril arginine group and 24.0% in the perindopril *tert*-butylamine group.

Consistently with the known adverse events commonly observed with each study treatment, cough was the most frequently reported emergent adverse event whichever the group: 9.1% in the perindopril arginine group and 8.2% in the perindopril *tert*-butylamine group, over 12 weeks. Cough was rated as severe in only 1 case in the perindopril arginine group and 2 cases in the perindopril *tert*-butylamine group. It led unfrequently to treatment discontinuation (2 and 3 cases in the perindopril arginine and perindopril *tert*-butylamine groups, respectively).

The incidence of other emergent adverse events (EAEs) was low, involving mainly metabolism and nutrition disorders as SOC (6.5% in the perindopril arginine group and 4.4% in the perindopril *tert*-butylamine group).

The EAEs considered by the investigator as related to the study treatment were cases of cough except one and one case of fatigue.

Most emergent adverse events were rated as mild or moderate (94.2% of EAEs in the perindopril arginine group and 94.0% in the perindopril *tert*-butylamine group). Severe emergent adverse events were reported by 3 (1.6%) patients in each group.

Most emergent adverse events recovered or were recovering (78.8% in the perindopril arginine group and 78.0% in the perindopril *tert*-butylamine group), and 21.2% and 22.0%, respectively, did no recover. The non-recovered EAEs were considered by the investigator as not related to the study drug.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Emergent adverse events (Cont'd)**

No patient died during the study treatment period. Overall, 2 patients from the perindopril *tert*-butylamine group experienced a serious non-fatal emergent adverse event during the study (acute coronary syndrome and unstable angina). In both cases, the SEAEs recovered, did not lead to study drug withdrawal and were not related to the study drug according to the investigator.

Emergent adverse events led to treatment stop in 11 (3.3%) patients, mainly cough and hypertension. All these EAEs were non-serious. They were reported in 5 patients of the perindopril arginine group and 6 patients of the perindopril *tert*-butylamine group.

- **Laboratory tests, other safety evaluation**

Regarding biology, emergent out-of-reference-range biochemical values on treatment were mainly reported for high values of glucose (13.1% of patients in the perindopril arginine group *versus* 8.7% in the perindopril *tert*-butylamine group), high values of total cholesterol (10.3% *versus* 8.7%, respectively), high values of low-density lipoprotein (LDL) cholesterol (9.7% *versus* 5.2%, respectively), low values of creatinine clearance (9.2% *versus* 7.6%, respectively), high values of triglycerides (8.0% *versus* 9.9%, respectively) and high values of gamma-glutamyl-transferase (GGT) (7.5% *versus* 4.7%, respectively). The most frequently reported emergent potentially clinically significant abnormal (PCSA) values in both groups were high values of triglycerides (4.0% *versus* 6.4%, respectively).
Globally, haematological abnormalities were infrequent in both groups.

The number of patients presenting emergent orthostatic hypotension (defined as at least one orthostatic hypotension between the first treatment intake date [excluded] and the last treatment intake date + 2 days [included], and not present at baseline) was low over 8 weeks as well as over 12 weeks and without difference between groups.

Considering ECG, the investigator reported clinically significant abnormalities at baseline in 7 and 6 patients in the perindopril arginine and perindopril *tert*-butylamine groups, respectively, and in 4 and 5 patients, respectively, at the end of the study.

CONCLUSION

The study fulfilled its main and secondary objectives as it demonstrated that Perindopril arginine salt 5 mg was at least as efficient as Perindopril *tert*-butylamine salt 4 mg in the treatment of hypertensive patient (change from baseline to 8 weeks of sitting SBP and DBP). The proportion of patients achieving blood pressure control after 8-week treatment and the rate of responders were similar with both perindopril salts. Similar results were observed after 12 weeks of treatment, with possible uptitration (10 mg for arginine salt and 2 x 4 mg for *tert*-butylamine salt) for patients with non-controlled BP after 8 weeks. The statistically significant additional SBP and DBP decrease seen after titration to Perindopril arginine salt 10 mg or *tert*-butylamine salt 2 x 4 mg confirmed the interest of these doses in patients not controlled by the previous dose. No unexpected safety concern was identified.

Date of the report: 12 January 2012