I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy of perindopril / indapamide combination on coronary PET Scan parameters. A 6-month, open non-controlled study in hypertensive patients.**
Study drug	**S05590 perindopril / indapamide Preterax®**
Studied indication	**Essential arterial hypertension**
Development phase	**Phase III**
Protocol code	**CL3-05590-022**
Study initiation date	**15 April 2005**
Study completion date	**21 January 2008**
International coordinator	[redacted] **UK**
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 6 November 2009**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Preterax®	**Volume:**	
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Title of study:
Efficacy of perindopril / indapamide combination on coronary PET Scan parameters. A 6-month, open non-controlled study in hypertensive patients.
Protocol No.: CL3-05590-022

Coordinators
[redacted] Italy
[redacted] - UK

Study centre:
Italy, 1 centre.

Publication (reference): NA

Studied period: Initiation date: 15 April 2005 Completion date: 21 January 2008	**Phase of development of the study:** III

Objectives:
Main objective
To assess the change in Coronary Blood Flow Reserve (CBFR), measured by PET Scan before and after 6 months of treatment with perindopril/indapamide in hypertensive patients with high left ventricular mass (LVM).
Secondary objectives
- To describe the changes between M0 and M6:
  - In resting Myocardial Blood Flow (MBF) measured by PET Scan before dipyridamole infusion.
  - In MBF, after dipyridamole infusion.
  - In LVM using Magnetic Resonance Imaging (MRI).
- To describe the changes in sitting blood pressure (Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Blood Pressure (MBP), Pulse Pressure (PP)) from M0 (baseline) to last observation.
- To describe the clinical and biological safety (adverse events, laboratory tests, ECG, heart rate, weight).

Methodology:
Monocentre, open and non-controlled phase III study, in patients diagnosed with essential hypertension and left ventricular hypertrophy.

Number of patients:
Planned: 20 patients (with completed PET scans at M0 and M6)
Included: 26 patients

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Diagnosis and main criteria for inclusion:

- Outpatients.
- Men or women, 40 to 75 years old.
- Patients with essential hypertension defined as 90 mmHg ≤ DBP < 110 mmHg and 140 mmHg < SBP < 180 mmHg, using a sphygmomanometer automatic device.
- With CBFR < 2.5 (specified by Amendment No. 1: CBFR < 2.5 in the whole left ventricle or in at least in one of the 3 regions (LAD, RCA, CX)), without evidence of regional ischemia suggesting coronary heart disease.
- With Left Ventricular Mass Index at echocardiography (Echo-LVMI) in men > 120 g/m²; women > 100 g/m².
  This criterion changed to Echo-LVMI > 110 g/m² (men) and 95 g/m² (women) for the second half of included patients (13 patients of 26), in compliance with updated Guidelines, result of collaboration between the American Society of Echocardiography and European Society of Echocardiography (Lang, 2006).
- Who had given their written informed consent at the selection visit.

The included patients did not have any contra-indications to perindopril/indapamide and received no forbidden medication. A placebo run-in period of 2 weeks was necessary for wash-out purpose in those previously treated for hypertension.

Study drug: S 5590 tablets of perindopril-indapamide (2 mg/0.625 mg; 4 mg/1.25 mg; 8 mg/2.5 mg).
Dose regimen: 1 tablet/day p.o. (initial daily dose 1 tablet of Per 2/Ind 0.625, with possible adaptation according to sitting BP values at M1 and subsequent visits).
Batch numbers: Per 2/Ind 0.625: L0000649 - L0008390 - L0012451.
Per 4/Ind 1.25 : L0003457 - L0007854 - L0014816.
Per 8/Ind 2.5 : L0003628 - L0007368 - L0014718.

Reference product: Placebo
Dose regimen: 1 tablet/day p.o.

Duration of treatment: Run-in period on placebo: 2 weeks
Active treatment period: 6 months

Criteria for evaluation:

Efficacy measurements:

- PET Scan measurements using ^{13}N-ammonia at M0 and M6: MBF and CBFR were the main efficacy criteria.
- A three-lead ECG was continuously done, while a 12-lead ECG and arterial blood pressure by automatic cuff manometer were recorded every minute during PET acquisitions.
- SBP, DBP, at each visit using an automatic sphygmomanometer, in sitting position.
- Heart MRI at M0 and M6 in order to follow the changes in LVM.
- Biochemical parameters: aldosterone, noradrenalin, insulin, renin activity.

Safety measurements:

- Adverse events, weight at each visit.
- Heart rate and ECG at each visit.
- Complete blood laboratory tests at M0 and M6.
- Simplified laboratory tests at M1 and M3.

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Statistical methods:

Efficacy analyses

The main analyses were performed on the Full Analysis Set (FAS). In accordance with the intention-to-treat principle, the FAS was defined as the included patients having taken at least one dose of study treatment and having non-missing baseline and post-baseline values of the MBF at rest and after dipyridamole.

The evolution between M0 and M6 was studied using a two-sided non-parametric test (Wilcoxon signed rank test) for paired samples for primary and secondary criteria. The estimate of the change from M0 to M6, its 95% confidence interval (CI) and the associated p-value were provided. Value at M0 and M6, change and relative change from M0 to M6 were also described in the FAS. The correlations between the changes from M0 to M6 of efficacy parameters were studied by a scatter plot crossing the two changes. The regression line, the Spearman correlation coefficient and its p-value comparison to 0 were given.

An unplanned parametric approach (two-tailed Student's t-test for paired data) was also used for the primary criteria, as parametric tests are usually used in the literature in coronary PET scans analyses. This analysis was performed using the local reading MBF value for patient No. 022 380 0001 00028 M6 value, for whom the centralised reading MBF value appeared unreliable due to technical problems.

Safety analyses

Descriptive statistics were provided in the Safety Set for all criteria.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 37 patients were screened and selected for the study and 26 were included. Of them, 4 patients were prematurely withdrawn. Two patients withdrew due to adverse events: moderate coronary artery stenosis (serious adverse event not related to the study drug according to the investigator) and moderate pharyngeal inflammation (related to the study drug according to the investigator), and 2 patients due to non-medical reasons. Twenty-two patients completed the study. Overall, 23 patients had at least one protocol deviation at inclusion, and 18 patients had at least one protocol deviation during the study. The most frequent protocol deviations corresponded to exams not done within the time interval planned in the protocol.

Disposition of included patients

Status	**Per/Ind**
	N
Included	**26**
in compliance with the protocol	3
with a protocol deviation before or at inclusion	23
Lost to follow-up	**-**
Withdrawn due to	**4**
adverse event	2
non-medical reason	2
Completed	**22**
in compliance with the protocol	8
with a protocol deviation during the study	14

Main baseline characteristics in the Included Set are presented in the table below. The characteristics of included patients were consistent with the target population defined in the protocol. There were 18 men and 8 women, all Caucasians, with age ranging between 42 and 74 years (mean ± SD = 58.9 ± 9.2 years). All were previously diagnosed with essential arterial hypertension. The mean (± SD) SBP was 161.1 ± 10.5 mmHg and DBP was 95.6 ± 4.8 mmHg. The echo-LVMI ranged between 102 and 175 g/m², with a mean of 125.18 ± 17.90 g/m^2. Relevant medical history other than arterial hypertension was hypercholesterolemia in 6 patients.

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Main baseline characteristics in the Included Set (N = 26)

			Per/ind (N = 26)
Age (years)		Mean ± SD	58.9 ± 9.2
		Min - Max	42 - 74
Sex	Men	n (%)	18 (69.2)
	Women	n (%)	8 (30.8)
BMI (kg/m^2)		Mean ± SD	28.34 ± 3.07
		Min - Max	20.1 - 32.0
SBP (mmHg)		Mean ± SD	161.06 ± 10.51
		Min - Max	140.7 - 178.7
DBP (mmHg)		Mean ± SD	95.61 ± 4.84
		Min - Max	90.0 - 106.3
Duration of arterial hypertension (months)		Mean ± SD	12.0 ± 10.4
		Min - Max	2 - 41

Main concomitant medications during the study treatment period were: antithrombotic agents (6 patients; 23.1%), serum lipid reducing agents (5 patients; 19.2%), thyroid therapy (2 patients; 7.7%).

All patients started to receive Per 2/Ind 0.625 at M0. For more than half of them (14 patients) the dose was increased to Per 4/Ind 1.25 at M1. Out of these 14 patients, 7 were further adapted to Per 8/Ind 2.5 at M3. The treatment duration ranged between 44 and 254 days, with a mean (± SD) of 193.7 (± 54.7) days (*i.e.* approximately 6.4 months). The global compliance to treatment was good: 91.9 ± 18.6%.

EFFICACY RESULTS

At rest, the whole MBF significantly increased from 0.69 ± 0.13 mL/min/g at M0 to 0.88 ± 0.36 mL/min/g at M6 (relative change 27.0 ± 39.4%). The increase was statistically significant (p = 0.011).

After dipyridamole, the whole MBF increased from 1.42 ± 0.32 mL/min/g at M0 to 1.94 ± 0.99 mL/min/g at M6 (relative change: 42.7 ± 76.0%) and was statistically significant using a parametric approach (p = 0.029).

The mean whole CBFR increased from 2.18 ± 0.47 at M0 to 2.37 ± 1.05 at M6 (p = 0.519). The lack of significant change in CBFR, which was calculated as the ratio of the MBF after and before injection of dipyridamole, can be explained by the increase in resting MBF, which partially offset the even larger increase in hyperaemic MBF.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

MBF and CBFR in the FAS (N = 20)

MBF (mL/min/g)	**Mean ± SD**	**Median**	**Min - Max**	**E (1)**	**95% CI (2)**	**p-value (3)**
At rest						
M0	0.69 ± 0.13	0.66	0.53 - 0.96			
M6	0.88 ± 0.36	0.81	0.38 - 2.01			
M6-M0 change	0.19 ± 0.30	0.17	-0.18 - 1.08			
Statistical analysis			Non-parametric	0.16	[0.05 ; 0.29]	**0.006**
			Parametric	0.19	[0.05 ; 0.33]	**0.011**
M6-M0 relative change (%)	27.0 ± 39.4	27.4	-28.3 - 116.1			
After dipyridamole						
M0	1.42 ± 0.32	1.48	0.80 - 2.05			
M6	1.92 ± 1.01	1.62	0.76 - 4.93			
M6-M0 change	0.50 ± 1.02	0.08	-0.77 - 3.34			
Statistical analysis			Non-parametric	0.36	[-0.07 ; 0.89]	0.114
			Parametric	0.53	[0.06 ; 0.99]	**0.029**
M6-M0 relative change (%)	40.6 ± 77.5	5.2	-43.5 - 210.1			
CBRF						
M0	2.18 ± 0.47	2.15	1.36 - 3.13			
M6	2.37 ± 1.05	2.10	1.14 - 4.81			
M6-M0 change	0.18 ± 1.23	0.03	-1.47 - 2.64			
Statistical analysis			Non-parametric	0.18	[-0.40 ; 0.76]	0.708
			Parametric	0.05	[-0.48 ; 0.77]	0.519
M6-M0 relative change (%)	15.0 ± 61.0	1.6	-53.9 - 151.0			

SD standard deviation

(1) Estimate of the change (M6 - M0); non-parametric approach Hodges-Lehman estimator

(2) 95% confidence interval of the estimate; non-parametric approach based on Walsh averages

(3) p value non-parametric approach Wilcoxon signed-rank test; parametric approach paired t-test

The regional MBF and CBFR showed an increase from M0 to M6, similarly to the whole MBF and CBFR.

The mean blood pressure significantly decreased after 6 months of treatment: SBP decreased from 160.8 ± 10.0 mmHg to 136.0 ± 11.7 mmHg ($p < 0.0001$) and DBP decreased from 95.6 ± 5.4 mmHg to 81.1 ± 6.1 mmHg ($p < 0.0001$). Overall, 16 patients (80.0%) were BP responders (Normalisation or SBP decrease ≥ 20 mmHg and/or DBP decrease ≥ 10 mmHg) to treatment at M6.

The MRI-LVMI significantly decreased under Per/Ind treatment from 78.6 ± 16.9 g/m^2 at M0 to 68.3 ± 17.3 g/m^2 at M6 ($p = 0.002$), as shown in the table below.

The whole coronary resistance (unplanned criterion) was calculated as the ratio between mean BP and whole MBF. At rest, the coronary resistance decreased from 167.6 ± 34.4 mmHg/mL/min/g at M0, to 125.1 ± 39.7 mmHg/mL/min/g at M6 ($p < 0.001$).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Left Ventricular Mass Index (g/m²) - FAS (N = 20)

MRI-LVMI (g/m²)	**Mean ± SD**	**Median**	**Min - Max**	**E (1)**	**95% CI (2)**	**p-value (3)**
M0	78.6 ± 16.9	78.6	55 - 123			
M6	68.3 ± 17.3	70.7	37 - 108			
M6-M0 change	-10.3 ± 15.0	-7.3	-51 - 16	-9.7	[-17.1 ; -5.1]	**0.002**
M6-M0 relative change (%)	-12.2 ± 17.5	-9.4	-52 - 26			

SD standard deviation

(1) Estimate of the change (M6 - M0; non-parametric approach Hodges-Lehmann estimator

(2) 95% confidence interval of the estimate; non-parametric approach based on Walsh averages

(3) p value non-parametric approach Wilcoxon signed-rank test

The correlation between changes in efficacy parameters from M0 to M6 gave the following results, indicating that the changes in CBRF and in MBF were not significantly correlated to SBP, DBP or LVM changes.

Correlations between efficacy parameters- Full Analysis Set (N = 20)

Parameters	**Spearman coefficient**	**p-value (3)**
CBFR and SBP measured by Dinamap	0.19	0.421
CBFR and DBP measured by Dinamap	-0.33	0.157
CBFR and LVM Spearman coefficient	-0.19	0.446
LVM and SBP measured by sphygmomanometer	0.27	0.259
LVM and DBP measured by sphygmomanometer	0.25	0.303
MBF at rest and SBP at rest:	0.02	0.918
MBF at rest and DBP at rest	0.36	0.114
MBF after dipyridamole and SBP after dipyridamole	0.12	0.624
MBF after dipyridamole and DBP after dipyridamole	0.10	0.668
MBF at rest and LVM	0.23	0.338
MBF after dipyridamole and LVM	0.18	0.454

Changes in plasma renin activity, aldosterone, noradrenalin and insulin were consistent with the expected effects of the combined treatment with perindopril and indapamide.

SAFETY RESULTS

Six adverse events were reported during the study, of which 5 were emergent: influenza, acute pharyngitis, coronary atherosclerosis, joint pain, hypokaliemia. Two events were considered related to the study treatment according to the investigator: hypokaliemia and acute pharyngitis. A case of coronary atherosclerosis, not considered related to the study treatment according to the investigator, was a serious adverse event and led to premature patient withdrawal.

Regarding laboratory biochemical parameters, 6 patients reported hypokaliemia, including one patient with a potentially clinically significant low level of kaliemia (2.8 mmol/L) at M6 while on Per 2/Ind 0.625.

Vital signs and ECG did not show any clinically relevant abnormality.

In summary, no unexpected events or changes were observed during the study.

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CONCLUSION

The results indicate that long-term therapy with a fixed combination of perindopril-indapamide improves resting and hyperaemic myocardial blood flow without change in coronary blood flow reserve, and reduces coronary resistance in hypertensive patients with left ventricular hypertrophy. These effects did not appear to be correlated to the reduction in blood pressure and in Left Ventricle Mass, suggesting that treatment favourably affects functional and/or structural abnormalities of the coronary circulation present in systemic hypertension. This improved myocardial perfusion might contribute to the improved cardiovascular outcome observed in large randomised trials where this combination was used.

Date of the report: 6 November 2009