2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Coversyl	**Volume:**	
Name of Active Ingredient: Perindopril (S 9490)	**Page:**	

Title of study: The EUROPA study: EURopean trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease.
Effects of perindopril on mortality / morbidity in patients with stable coronary artery disease without clinical heart failure. A three year, double-blind, multicentre, randomised trial.
Protocol No.: CL3- 09490-144

Main coordinators: [redacted]

Study centres: Multicentre study involving 425 active centres (which included at least 1 patient) in 24 countries. Austria (3 centres - 17 included patients), Belgium (5 centres - 197 included patients), Czech Republic (33 centres - 2176 included patients), Denmark (8 centres - 130 included patients), Estonia (4 centres - 115 included patients), Finland (10 centres - 176 included patients), France (24 centres - 211 included patients), Germany (10 centres - 134 included patients), Greece (24 centres - 511 included patients), Hungary (12 centres - 285 included patients), Ireland (7 centres - 277 included patients), Italy (52 centres - 891 included patients), Latvia (5 centres - 94 included patients), Lithuania (8 centres - 300 included patients), The Netherlands (34 centres - 2072 included patients), Norway (1 centre - 57 included patients), Poland (43 centres - 1251 included patients), Portugal (6 centres - 66 included patients), Slovakia (15 centres - 399 included patients), Spain (36 centres - 831 included patients), Sweden (4 centres - 141 included patients), Switzerland (2 centres - 22 included patients), Turkey (5 centres - 102 included patients), United Kingdom (74 centres - 1775 included patients).

Publication (reference): Fox KM., The EURopean trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised double-blind, placebo controlled, multicentre trial (the EUROPA study). Lancet, 2003 Sept 6; 362: 782-88.

Studied period:	**Phase of development of the study:**
- Initiation date: 22 October 1997 - Completion date: 20 May 2003	Phase III

Primary objective:
To examine the effect of the ACE inhibitor perindopril on the combined endpoint cardiovascular mortality, non-fatal acute myocardial infarction and cardiac arrest with successful resuscitation in patients with coronary artery disease and without clinical signs of heart failure.

Secondary objectives:
- To evaluate the ability of perindopril to reduce the rate of the following events:
- Total mortality, non-fatal acute myocardial infarction, unstable angina pectoris and cardiac arrest with successful resuscitation.
- Cardiovascular mortality, non-fatal acute myocardial infarction and stroke.
- Cardiovascular mortality, non-fatal acute myocardial infarction and revascularisation.
- Cardiovascular mortality and non-fatal acute myocardial infarction.
- Cardiovascular mortality, non-fatal acute myocardial infarction and unstable angina pectoris.
- Fatal and non-fatal acute myocardial infarction and unstable angina pectoris.
- Non-fatal and fatal acute myocardial infarction
- Total mortality.
- Cardiovascular mortality.
- Unstable angina pectoris.
- Cardiac arrest with successful resuscitation.
- Stroke.
- Revascularisation (coronary artery bypass graft and percutaneous coronary intervention).
- Heart failure.

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Coversyl	**Volume:**	
Name of Active Ingredient: Perindopril (S 9490)	**Page:**	

Methodology:
Multicentre multinational European, double blind, randomised, parallel group, placebo-controlled trial.

Number of patients:
Planned: 10500 patients,
Included: 12230 patients, 6122 in perindopril group and 6108 in placebo group.

Diagnosis and main criteria for inclusion:
Male or female patients, aged 18 years or more, with stable documented coronary artery disease, without clinical evidence of heart failure. Patients were to tolerate perindopril 8 mg o.d. during the run-in period. All concomitant treatments were allowed except ACE inhibitors and angiotensin II receptor inhibitors. Potassium-sparing diuretics were authorised only in the case of persistent hypokalaemia.

Study drug: Perindopril (S 9490) 4 mg tablet.
During the 4-week run-in period: 4 mg o.d. during the first 2 weeks and 8 mg o.d. during the following 2 weeks if the previous dose was well tolerated (patients aged 70 years or older were given 2 mg o.d. i.e. ½ tablet the first week then 4 mg o.d. during the second week if the lower dose was well tolerated).
During the double-blind treatment period: 8 mg o.d. Investigators were allowed to decrease the dose to 4 mg o.d. if necessary.
Mode of administration: orally once daily in the morning.

Reference product: placebo tablet
Patients received 2 tablets once daily in the morning during the double-blind treatment period (with possibility to decrease to 1 tablet o.d. if judged necessary by investigator).

Duration of treatment:
- Open 4-week perindopril run-in period
- Double-blind treatment period of at least 3 years with perindopril 8 mg o.d. or placebo (or half dose if not tolerated) with follow-up visits at M3, M6 and every 6 months thereafter. Patients were to continue their treatment until a cutoff date based on event collection (treatment duration around 4 years).

Criteria for evaluation:

EFFICACY MEASUREMENTS:
Primary endpoint: Composite endpoint of cardiovascular mortality, non-fatal acute myocardial infarction and cardiac arrest with successful resuscitation.
Secondary endpoints:
Composite endpoint of total mortality, non-fatal acute myocardial infarction, unstable angina and cardiac arrest with successful resuscitation (initially the primary endpoint) and the individual components of the primary and first secondary outcome, revascularisation (PTCA and CABG), stroke and hospital admission for heart failure.

SAFETY MEASUREMENTS:
- Hospitalisations and serious suspected adverse drug reactions (SSADRs)
- Anginal status (Canadian Cardiovascular Society classification) and heart failure status (New York Heart Association classification) assessed at each visit.
- Systolic and diastolic blood pressures (mmHg) (measured twice with a standard sphygmomanometer) and heart rate (bpm), measured at each visit in the sitting position after at least 5 minutes of rest.
- Biochemistry: potassium (mmol/L), sodium (mmol/L), creatinine (µmol/L) measured during the run-in period and at randomisation, and subsequently at yearly intervals.

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Coversyl	**Volume:**	
Name of Active Ingredient: Perindopril (S 9490)	**Page:**	

Statistical methods:

EFFICACY ANALYSIS

The log-rank test was used in an intention-to-treat (ITT) analysis for the time to first occurrence of a primary endpoint. The cumulative distribution of events over time was examined using the Kaplan-Meier method. Cox's proportional-hazards model was used to estimate the relative risk reduction for the primary and secondary clinical endpoints. Event rates were compared between treatment groups using 95% confidence intervals. The relative risk was also presented at yearly timepoints (1, 2, 3, 4 years).

A descriptive analysis of the primary endpoint was performed in predefined subgroups of patients. All analyses were based on intention to treat.

No endpoints occurring after April 30, 2003 were taken into account in the analysis.

For patients who did not experience a given endpoint during the study, the time to event was right-censored at the last visit when the patient did not die during the study. When the patient died during the study, the date of death was used as the point of censoring, as far as death was not part of the endpoint. For mortality endpoints or composite endpoints with a mortality component, the time-to-event was right-censored at the date of death when the cause of death was not part of the endpoint of interest.

SAFETY ANALYSIS

Descriptive statistics were provided in the Safety Set, except for blood pressure data, that was analysed in the ITT Set. Reasons for hospital admission were coded using the ICD9-CM dictionary. The number and percentage of patients hospitalised was described by system organ class, by diagnosis associated with hospital admission. The number and percentage of patients for whom a pharmacovigilance form was issued was also given.

Systolic and diastolic blood pressure and heart rate were described by visit. Summary statistics were given for biochemical parameters (plasma sodium, potassium and creatinine) by visit. The number and percentage of patients with values out of the reference range by visit and with at least one value out of the reference range throughout the study was calculated. Baseline (screening visit 1) values were crossed with the first out-of-reference range values under treatment, in order to estimate the number and percentage of patients with emergent abnormalities.

STUDY POPULATION AND OUTCOME

Thirteen thousand six hundred and fifty-five (13655) patients with documented coronary artery disease and no clinical signs of heart failure were registered in the EUROPA trial. Among them, 8775 (64.3%) had a history of myocardial infarction, 8302 (60.8%) of angiography with substantial stenoses, 7550 (55.3%) of previous revascularisation and 1670 (12.2%) of diabetes mellitus.

Run-in perindopril was well tolerated; 1425 (10.4%) of patients were excluded. Hypotension, high creatinine, high potassium or other intolerance were reported as the reason for non-randomisation in 771 patients (5.6% of registered patients).

Overall 12218 patients were randomised, 6110 patients were assigned to perindopril and 6108 patients to placebo. Baseline characteristics were similar in randomised patients and registered but non-randomised patients. There were no relevant differences between groups regarding demographics or any other baseline characteristics. Patients in both groups were similar in terms of the history of coronary artery disease and how it was documented; there were no differences either in blood pressure, heart rate, or anginal and heart failure status (Canadian Cardiovascular Society and New York Heart Association classifications respectively). At randomisation, 81% of patients had no angina, 17% had mild angina and 2% had moderate or severe angina, and no patients had clinical signs of heart failure.

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Coversyl	**Volume:**	
Name of Active Ingredient: Perindopril (S 9490)	**Page:**	

STUDY POPULATION AND OUTCOME (Cont'd)

There were no differences between groups regarding concomitant treatments. At randomisation, 92.3% of randomised patients were taking platelet inhibitors, 61.7% beta-blockers, and 57.6% lipid-lowering therapy.
The study population was consistent with the profile of CAD patients currently managed in the health care setting.
The mean duration of follow-up was 4.2 years. The follow-up duration and the total patient-years were similar in both groups. No relevant differences were observed regarding treatment duration and compliance. At 3 years, in the perindopril group, 4855 (95.3%) patients out of 5095 patients for whom the information was available were still receiving study medication (i.e. 79.5% of the patients randomised to perindopril). In the placebo group, 5018 (95.5%) patients out of 5,256 patients for whom information was available were still receiving study medication (82.1% of the patients randomised to placebo). Most patients continued receiving 2 tablets daily: at three years, 93.3% of the patients treated with perindopril received 8 mg perindopril once daily and 96.7% of the patients treated with placebo received 2 tablets daily.
The disposition of patients and reasons for permanent discontinuation of the study treatment are given in the following table.

		Perindopril	**Placebo**	**All**
Registered *(entered the run-in period)*	n	-	-	**13655**
Excluded	n	-	-	**1425**
Entered the double blind period [1]	n	-	-	**12230**
Not randomised	n	**7**	**5**	**12**
Randomised	n	**6110**	**6108**	**12218**
Completed	n	**6107**	**6108**	**12215**
Incomplete follow-up	n	**3**	**0**	**3**
Withdrawn from treatment	n (%)	**1391 (22.8)**	**1266 (20.7)**	**2657 (21.8)**
Cough	n (%)	162 (2.7)	32 (0.5)	194 (1.6)
Hypotension	n (%)	60 (1.0)	17 (0.3)	77 (0.6)
Kidney failure	n (%)	20 (0.3)	16 (0.3)	36 (0.3)
Intolerance, unspecified	n (%)	144 (2.4)	80 (1.3)	224 (1.8)
Study endpoint	n (%)	376 (6.2)	460 (7.5)	836 (6.8)
Hypertension	n (%)	22 (0.4)	46 (0.8)	68 (0.6)
Refused to continue	n (%)	261 (4.3)	257 (4.2)	518 (4.2)
Other reason	n (%)	345 (5.6)	356 (5.8)	701 (5.7)
Missing	n	1	2	3
Registered Set (RGS)	n	-	-	**13655**
Non-Randomised Set (NONRS)	n (%)	-	-	1437
Intention-to-treat Set (ITT) [2]	n (%)	**6110** (100)	**6108** (100)	**12218** (100)
Safety set (SS) [3]	n (%)	**6122**	**6107**	**12229**

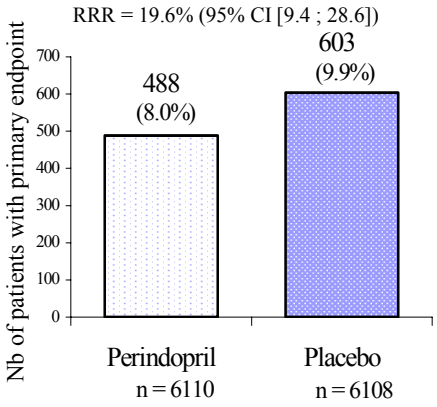
%: percentage of randomised patients (ITT Set)
[1] Twelve patients were included but not randomised (perindopril: 7, placebo: 5). They were assessed for safety only.
[2] ITT Set = 100% of the randomised patients. Patients were analysed according their assigned treatment.
[3] Safety Set. Patients were analysed according the treatment they actually received. One patient was randomised but died the same day and was excluded from the Safety Set.

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Coversyl	**Volume:**	
Name of Active Ingredient: Perindopril (S 9490)	**Page:**	

EFFICACY RESULTS

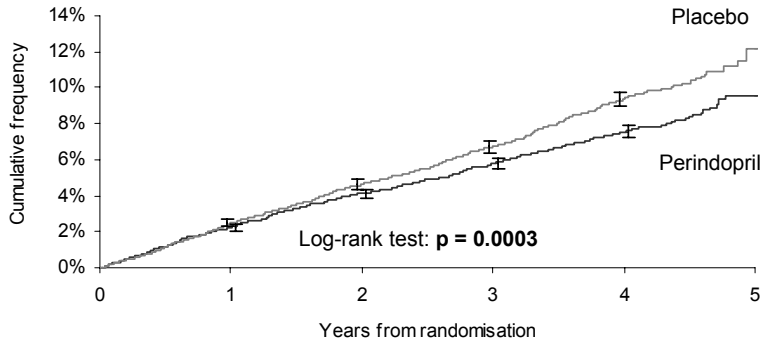
Primary endpoint: *Main analysis*

Number of patients who experienced a primary endpoint event
(CV death, non-fatal AMI or cardiac arrest with successful resuscitation) in the ITT Set



Among patients treated with perindopril, 488 (8.0%) experienced a primary endpoint event, compared with 603 (9.9%) in the placebo group, corresponding to a **1.9% absolute risk reduction**, and a **19.6% relative risk reduction** (95% CI [9.4 ; 28.6], **p = 0.0003**). The Number Needed to Treat, i.e. the estimated number of patients needed to be treated with perindopril rather than placebo for one additional patient to benefit was 54. The benefit began to appear at 1 year (relative risk reduction 10%) and gradually increased throughout the trial (significant difference from 3 years on).

Cumulative event curve of time to occurrence of the composite endpoint cardiovascular mortality, non-fatal acute myocardial infarction and resuscitated cardiac arrest (Intention-to-treat)



Primary endpoint: *Secondary analyses*

The beneficial effect of perindopril on the primary endpoint was consistent across all predefined subgroups, although it was not statistically significant in some of the smaller subgroups. Outcome was improved in all age-groups among patients with and without hypertension, diabetes mellitus, or previous myocardial infarction. Treatment benefit was found whatever the concomitant treatment the patients were receiving, in particular in patients taking lipid-lowering therapy and beta-blockers.

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Coversyl	**Volume:**	
Name of Active Ingredient: Perindopril (S 9490)	**Page:**	

EFFICACY RESULTS 'cont'd)

Secondary endpoints

Compared with placebo, treatment with perindopril was associated with reductions in all secondary endpoints. In particular, there was a significant 14.0% relative risk reduction for the composite endpoint total mortality, non-fatal acute myocardial infarction, unstable angina and cardiac arrest with successful resuscitation (95% CI [6.0 ; 21.3], **p = 0.0009**) which was the initial primary endpoint. Results for the other secondary endpoints are given in the following table:

Incidence of secondary endpoints and relative risk reductions in the ITT Set

	Perindopril n (%)	**Placebo** n (%)	**Relative risk reduction** [95% CI]	***p Cox***
Total mortality, non-fatal AMI, UAP and cardiac arrest with successful resuscitation	904 (14.8)	1043 (17.1)	14.0% [6.0 ; 21.3]	**0.0009**
Cardiovascular mortality and non-fatal AMI	484 (7.9)	596 (9.8)	19.3% [9.0 ; 28.4]	**<0.001**
Cardiovascular mortality, non-fatal AMI and stroke	552 (9.0)	664 (10.9)	17.4% [7.5 ; 26.2]	**<0.001**
Cardiovascular mortality, non-fatal AMI and revascularisation	887 (14.5)	996 (16.3)	11.3% [2.9 ; 19.0]	**0.009**
Cardiovascular mortality, non-fatal AMI and UAP	753 (12.3)	885 (14.5)	15.5% [6.8 ; 23.3]	**<0.001**
Fatal and non-fatal AMI and UAP	601 (9.8)	716 (11.7)	16.5% [7.0 ; 25.1]	**0.001**
Non-fatal and fatal AMI	320 (5.2)	418 (6.8)	23.9% [12.0 ; 34.2]	**<0.001**
Total mortality	375 (6.1)	420 (6.9)	11.0% [-2.3 ; 22.6]	0.101
Cardiovascular mortality	215 (3.5)	249 (4.1)	13.9% [-3.4 ; 28.2]	0.108
Unstable angina pectoris	342 (5.6)	367 (6.0)	7.1% [-7.6 ; 19.8]	0.326
Cardiac arrest with successful resuscitation	6 (0.1)	11 (0.2)	45.6%[-47.0 ; 79.9]	0.230
Stroke	98 (1.6)	102 (1.7)	4.3% [-26.3 ; 27.4]	0.759
Revascularisation	577 (9.4)	601 (9.8)	4.2% [-7.4 ; 14.5]	0.465
Heart failure	63 (1.0)	103 (1.7)	39.2% [16.8 ; 55.5]	**0.002**

SAFETY RESULTS

Hospitalisations:

There were significantly less patients hospitalised (including short hospitalisations for coronary angiography or PTCA) with perindopril: 2513 patients (41.0%) in the perindopril group and 2621 patients (42.9%) in the placebo group were hospitalised at least once (95% CI = **[-3.6% ; -0.1%]**).

In the perindopril group, there were less patients hospitalised for cardiovascular diseases: 1284 (21.0%) perindopril patients compared to 1383 (22.6%). There were also less hospital admissions for cardiovascular operations: 660 perindopril patients (10.8%) *versus* 683 (11.2%) placebo patients. There were 3189 hospital admissions related to cardiovascular system organ classes in the perindopril group and 3479 in the placebo group.

The incidence of hospital admissions due to non-cardiovascular events was similar in both treatment groups.

Serious suspected adverse drug reactions:

Only serious suspected adverse drug reactions (SSADRs) were to be reported.

During the perindopril run-in period, 12 patients (0.09%) experienced serious adverse drug reactions: hypotension (7 cases), syncope (3 cases) were the most frequently observed. There were also 2 cases of angioneurotic oedema and one sudden death.

During the double blind period, a total of 112 patients were issued at least one pharmacovigilance form: 65 (1.1%) perindopril patients and 47 (0.7%) placebo patients). Among these, 28 patients experienced serious suspected adverse drug reactions: sixteen (0.3%) perindopril patients experienced serious adverse drug reactions. Hypotension (6 episodes) was the most frequent SSADR. There were three cases of syncope or loss of consciousness, two cases of angioneurotic oedema, one case of pancreatic adenocarcinoma and one sudden cardiac death.

Twelve (0.2%) out of the 6107 patients receiving placebo experienced serious adverse events, including one case of pancreatic adenocarcinoma.

Name of Company: I.R.I.S. 6 place des Pléiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Coversyl	**Volume:**	
Name of Active Ingredient: Perindopril (S 9490)	**Page:**	

SAFETY RESULTS (cont'd)

Blood pressure and heart rate:
Mean systolic blood pressure was reduced from 137 to 128 mmHg and mean diastolic blood pressure from 82 to 78 mmHg during the perindopril run-in period. After randomisation, systolic and diastolic blood pressures among patients treated with perindopril were maintained and the mean SBP and DBP over the double-blind treatment period were respectively 4.9 ± 16.3 mmHg and 2.4 ± 8.7 mmHg higher in the placebo group. Blood pressures remained quite stable throughout the double-blind period in both groups.
No relevant change in heart rate was observed within or between groups throughout the study.

Anginal and heart failure status (Canadian Cardiovascular Society and NYHA classifications) :
The percentage of patients in each class of anginal status or heart failure status remained constant throughout the study with more than 80% of the patients in class I of anginal pain and without heart failure. These results showed that the EUROPA patients remained clinically stable.

Laboratory parameters
Laboratory parameters remained stable in both groups throughout the study, and there were no clinically relevant changes in mean sodium potassium or creatinine between baseline and any visit with perindopril or with placebo.
No relevant differences between the two groups were observed as regards emergence of abnormal values of sodium, potassium or creatinine, although there were slightly more patients with emergent hyperkalaemia with perindopril than with placebo (2.2% versus 1.4% respectively).

CONCLUSION
Thirteen thousand six hundred and fifty-five (13655) patients with stable coronary artery disease and without apparent heart failure were registered in the EUROPA study, and 12218 patients were randomly assigned to perindopril 8 mg once daily or to placebo. There were no relevant differences between groups regarding demographics or any other baseline characteristics.
After a mean 4.2 years of follow-up, 603 (9.9%) placebo and 488 (8.0%) perindopril patients experienced a primary endpoint event, corresponding to a 19.6% relative risk reduction with perindopril (95%CI [9.4 ; 28.6]), p = 0.0003). These benefits were consistent in all predefined subgroups and secondary endpoints, in all age-groups, among patients with and without hypertension, diabetes mellitus, or previous myocardial infarction, and in particular in patients receiving lipid-lowering therapy or beta-blockers.
Overall, perindopril 8 mg was well tolerated in the EUROPA study population. The adherence to the study drug was similar in both arms of the study, and the study profile was that expected with perindopril, with no unexpected serious adverse drug reactions in the study population. EUROPA patients were thoroughly representative of the population of interest, i.e. patients with coronary artery disease and no clinical heart failure, but otherwise unselected. Concomitant therapy was in keeping with current recommendations for the management of coronary artery disease. The results of the EUROPA study, consistent throughout the study population, can be generalised to all patients with coronary artery disease.