Document title	**Clinical Study Report Synopsis**
Study title	**The ADVANCE study: Action in Diabetes and Vascular Disease (Preterax and Diamicron MR Controlled Evaluation)** A factorial randomised trial of blood pressure lowering with a fixed perindopril-indapamide combination and an intensive gliclazide MR-based regimen for the prevention of vascular disease among high risk individuals with type 2 diabetes.
Study drug	**S 05590 (Perindopril/Indapamide) (Preterax®)** **S 05702 (Gliclazide 30 mg MR) (Diamicron MR®)**
Claimed indication	**Cardiovascular prevention in diabetic patients (Preterax®)** **Prevention of diabetes complications (Diamicron MR®)**
Development phase	**Phase III**
Protocol code	**CL3-05590-013**
Study initiation date	**06 June 2001 (date of first selection)**
Study completion dates	**31 May 2007 (last visit for the blood pressure lowering arm)** **31 January 2008 (last visit for the glucose control arm)**
Main coordinators	[redacted] **- AUSTRALIA**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 Rue Carnot** **92284 Suresnes Cedex - FRANCE**
	[redacted] **AUSTRALIA**
Responsible medical officers	[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 5 August 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 ® Diamicron MR ®	**Volume:**	
Name of Active Ingredient: Perindopril 2 mg / indapamide 0.625 mg (S 05590) Gliclazide 30 mg MR (S 05702)	**Page:**	

Title of study: The ADVANCE study: Action in Diabetes and Vascular Disease (Preterax and Diamicron MR Controlled Evaluation).
A factorial randomised trial of blood pressure lowering with a fixed perindopril-indapamide combination and an intensive gliclazide 30 mg MR-based glucose control regimen for the prevention of vascular disease among high risk individuals with type 2 diabetes.
Protocol No.: CL3-05590-013
The trial is registered with EUDRACT No. 2005-003281-41.

Main coordinators:
[redacted], Australia.
[redacted], Australia.

Main committes:
- **Management committee (MC)** under the supervision of [redacted] responsible for overseeing all aspects of the conduct of the trial.
- **Data and Safety Monitoring Committee (DSMC)** under the supervision of [redacted]): responsible for ensuring the safety of patients.
- **Enpoint Adjudication Committee (EPAC)** under the supervision of [redacted]): provided final independent adjudication of all suspected primary endpoints and deaths.

Study centres:
Multicentre study involving 216 active centres (which registered at least 1 patient) in 20 countries. Australia (22 centres - 1169 patients), Canada (14 centres - 501 patients), China (49 centres - 3816 patients), Czech Republic (7 centres - 225 patients), Estonia (2 centres - 179 patients), France (9 centres - 230 patients), Germany (2 centres - 371 patients), Hungary (13 centres - 479 patients), India (4 centres - 528 patients), Ireland (5 centres - 526 patients), Italy (1 centre - 22 patients), Lithuania (3 centres - 124 patients), Malaysia (5 centres - 301 patients), Netherlands (10 centres - 726 patients), New Zealand (8 centres - 594 patients), Philippines (4 centres - 189 patients), Poland (17 centres - 661 patients), Russia (7 centres - 186 patients), Slovakia (12 centres - 492 patients), United Kingdom (22 centres - 1558 patients).

Publications:
The ADVANCE Collaborative group. Rationale and design of the ADVANCE study: a randomised trial of blood pressure lowering and intensive glucose control in high-risk individuals with type 2 diabetes mellitus J Hypertens 2001;19:S21-S28.
The ADVANCE Management Committee. Study rationale and design of ADVANCE: Action in diabetes and vascular disease - Preterax and Diamicron MR controlled evaluation Diabetologia 2001;44:1118-1120.
The ADVANCE Collaborative group. Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline Diabet Med 2005;22:882-888.
The ADVANCE Collaborative group. Lessons from the run-in phase of a large study in type 2 diabetes Blood Press 2006;15:340-346.
The ADVANCE Collaborative group: Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial Lancet 2007;370:829-840.
The ADVANCE Collaborative group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes N Engl J Med 2008;358:2560-2572.

Studied period:	**Phase of development of the study:**
Initiation date: 06 June 2001 (date of first selection) Last visit for blood pressure lowering intervention (T1): 31 May 2007 Last visit for glucose control intervention (T2): 31 January 2008	III

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Objectives: The main objectives of this study were to investigate the effects of blood pressure lowering with a perindopril-indapamide combination and of intensive glucose control with a gliclazide 30 mg MR-based regimen on major macrovascular and microvascular disease events among high-risk, hypertensive or non-hypertensive individuals with type 2 diabetes.

Methodology:

The study was a factorial, multicentre, international, randomised controlled trial. The comparison of fixed perindopril-indapamide combination *versus* placebo was double blind and the comparison of the intensive gliclazide 30 mg MR-based glucose control regimen *versus* local standard therapy was conducted according a Prospective Randomised Open study with Blinded Evaluation (PROBE) design. After a 6-week run-in period on perindopril-indapamide combination (2 mg/0.625 mg), patients were randomised to receive one of four treatment options: fixed perindopril-indapamide combination plus intensive gliclazide 30 mg MR-based glucose control, fixed perindopril-indapamide combination plus local standard glucose control, placebo plus intensive gliclazide 30 mg MR-based glucose control, or placebo plus local standard glucose control.

After randomisation, in the BP intervention, patients received the perindopril-indapamide or placebo treatment on top of their usual treatments (except ACE inhibitors other than perindopril, thiazide or thiazide-like diuretics).

In the glucose control intervention, patients from the intensive group could receive additional oral anti-diabetic lowering drugs (except sulphonylurea other than gliclazide 30 mg MR) or insulin to achieve target haemoglobin A1c level ≤ 6.5%. Patients from the standard group were to follow their usual glucose lowering treatments (except those usually treated with gliclazide who were to be treated with another sulphonylurea or glucose lowering drug).

Number of patients:

Planned: 10 000 randomised in four treatment combinations (2500 per group):

- Fixed perindopril-indapamide plus intensive gliclazide 30 mg MR-based glucose control regimen**.**
- Fixed perindopril-indapamide plus local standard glucose control regimen.
- Placebo plus intensive gliclazide 30 mg MR-based glucose control regimen.
- Placebo plus local standard glucose control regimen.

Registered: 12877 patients.

Randomised: 11140 patients:

- To receive continued therapy with either perindopril-indapamide (N = 5569) or matching placebo (N = 5571) (blood pressure lowering intervention).
- And to undergo either a strategy of gliclazide 30 mg MR based-intensive glucose control (N = 5571) or a standard glucose control strategy (N = 5569) (glucose control intervention).

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Diagnosis and main criteria for inclusion:

- Type 2 diabetes mellitus onset at the age of 30 years or older.
- Age 55 years or older at entry.
- A substantially elevated risk of cardiovascular disease, indicated by:
  - A history of major macrovascular disease defined as any one of: stroke, myocardial infarction, hospital admission for transient ischaemic attack, hospital admission for unstable angina, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, peripheral revascularisation or amputation secondary to vascular disease, or
  - A history of major microvascular disease defined as any one of: nephropathy (defined as albumin: creatinine ratio > 300 µg/mg or 33.9 mg/mmol), retinal photocoagulation therapy, proliferative retinopathy, macular oedema or blindness in either eye not known to be due to non-diabetic causes, or
  - A first diagnosis of type 2 diabetes mellitus made 10 years or more before entry, or
  - Another major risk factor for vascular disease defined as any one of: current daily cigarette smoking, total cholesterol greater than 6.0 mmol/L (with or without cholesterol lowering treatment), HDL cholesterol < 1.0 mmol/L, microalbuminuria (defined as albumin:creatinine ratio 30-300 µg/mg or 3.4-33.9 mg/mmol), or
  - Age 65 years or older at entry.
- No definite and specific contraindication or indication for any of the study treatments.

Study drugs:

- Fixed perindopril-indapamide (2 mg/0.625 mg) combination: 1 tablet daily in the morning for the first 3 months and 2 tablets daily in the morning thereafter (forced titration, unless there was a specific contraindication to dose increase).
- Gliclazide 30 mg MR: 1 to 4 tablets (30-120 mg) daily in the morning.
- Batch perindopril-indapamide No.'s:
  H11598, J01607, J05666, J01610, J11634, J07505, J07502, J12585, J12586, K03625, K05555, K09542, L0000381, L0000654, L0002839, L0003919, L0003926, L0004661, L0005244, L0006208, L0006682, L0006815, L0008390, L0009269, L0010109, L0010893, L0011234, L0011849, L0011850, L0011851, L0012028, L0012451, L0014846, L02616, L03525, L03528, L04623, L05588, L07577, L08552, J12590, J12589, L01604, L02584, L04623, L0004242, L0005528.
- Batch gliclazide 30 mg MR No.'s:
  H10610, H11650, J01606, J04605, J05665, J07500, J07503, J10590, K03510, K03511, K03626, K03627, K08546, K09546, L0000534, L0001345, L0001731, L0001742, L0002120, L0002445, L0003316, L0003922, L0004533, L0007842, L0008550, L0009271, L0011440, L01605, L01655, L01656, L03526, L03527, L03532, L03533, L04622, L07575, L07576, L09517, L02592.

Reference product:

Matching placebo for the fixed perindopril-indapamide combination: administered using an identical dosing schedule.

Patients assigned to the standard glucose control regimen continued to follow their usual glucose control program.

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Duration of treatment:

- 6-week perindopril-indapamide (2 mg/0.625 mg) run-in period.
- Blood pressure lowering intervention (BP lowering intervention): average planned duration of 4.5 years double-blind treatment period, extended by 1 year according to Amendment No. 1 (from randomisation to final BP intervention T1 visit) with perindopril-indapamide or matching placebo.
- Glucose control intervention (GC intervention): average planned duration of 4.5 years extended by 1.5 years according to Amendment No. 1 (from randomisation to final GC intervention T2 visit) with gliclazide 30 mg MR-based intensive glucose control strategy or standard glucose control.

From T1 (at the end of the double-blind period), investigators could propose to patients to receive an open perindopril-indapamide treatment until T2, whatever the previous randomised blood pressure lowering treatment received.

Criteria for evaluation:

EFFICACY MEASUREMENTS:

Primary Endpoints, their components, and the causes of deaths were adjudicated by the EPAC.

Primary endpoints

Composites of major macrovascular events (non-fatal stroke, non-fatal myocardial infarction and death from cardiovascular cause) and of major microvascular events (new or substantially worsening nephropathy or new or worsening eye disease) analysed jointly and separately.

Secondary endpoints

Components of the primary endpoints

- Cardiovascular deaths.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- New or worsening nephropathy.
- New or worsening eye disease.

Other endpoints

- Total mortality.
- Total coronary events.
- Major coronary events.
- Peripheral vascular disease.
- All cardiovascular events.
- Hospitalisation of 24 h or longer for any cause.
- All heart failure events leading to death, requiring hospital admission, or requiring withdrawal of study treatment, or resulting in an increase in New York Heart Association class.
- Total renal events (unplanned endpoint defined as a composite of new or worsening nephropathy and new onset microalbuminuria).
- New onset microalbuminuria.
- Major cerebrovascular events.
- All cerebrovascular events.
- Visual deterioration defined as a decrease of two lines in best vision in either eye.
- New or worsening neuropathy.
- Cognitive function decline measured by Folstein Mini-Mental State Examination.
- Dementia.

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Criteria for evaluation (Cont'd):

EFFICACY MEASUREMENTS (Cont'd):

Other efficacy criteria

- Blood pressure (measured 3 times using an Omron automated sphygmomanometer) in the sitting position after 5 minutes rest: measured during the run-in period, at M0, M3, M4, M6, then at 6-month intervals, and at the final T1 and T2 visits (additional measurements for the intensive glucose control group at M0.5, M1 and M2). Blood pressure was considered as an efficacy criterion in the BP lowering intervention of the study and as a safety criterion in the GC intervention.
- HbA1c: measured locally at registration, M6, M12, at yearly intervals and at T1 and T2. Additional measurements were performed at M1, M2, M3 and every 3 months from M6 for patients in the intensive glucose control group. In addition, HbA1c values were standardised. HbA1c was considered as an efficacy criterion in the GC intervention and as a safety criterion in the BP lowering intervention.
- Fasting blood glucose: measured locally at registration, randomisation, every 2 years and at T1 and T2. Patients in the intensive glucose control group had additional measurements at each visit until M6, then at 3-month intervals. Fasting blood glucose was considered as an efficacy criterion in the GC intervention and as a safety criterion in the BP lowering intervention.
- Visual acuity (only for glucose control intervention) at registration, M24, M48, and at final visits (T1, T2).
- Mini-Mental State Examination (MMSE) scores: at registration, M24, M48 and T2.
- Quality of life (EQ-5D): at registration, M24, M48, and at final visits (T1, T2).

SAFETY MEASUREMENTS

- Serious adverse events (including fatal and non-fatal events) and serious suspected adverse reactions to perindopril or/and indapamide and to gliclazide 30 mg MR.
- Mild and severe hypoglycaemia (for the GC intervention).
- Biochemistry: creatinine, sodium, potassium, HDL, LDL, total cholesterol, triglycerides, ALAT at selection, every 2 years and at final visits T1 and T2. Creatinine, sodium and potassium also measured at M4, M12, M36, M60.
- Heart rate in the sitting position after 5 minutes rest and weight during the run-in period, at M0, M3, M4, M6, then at 6-month intervals, and at the final visits T1 and T2 (additional measurements for the intensive glucose control group at M0.5, M1 and M2 visits). The waist and hip circumferences were assessed at registration, then every 2 years, and at final visits (for the GC intervention).
- ECG: at registration, M24 and M48.

Statistical methods:

Efficacy analysis:

Interaction: A preliminary study of the interaction between the BP lowering treatment and the GC strategy was performed before separate analysis of each intervention using a likelihood ratio test (on T1 database) based on Cox models.

Separate analysis of each intervention: data taken into account were all the data until T1 for the analysis of the BP lowering intervention and all the data until T2 for the analysis of the GC intervention.

Endpoints adjudicated by the EPAC were used in the analysis of the primary endpoint.

Main analysis: treatment groups were compared using Cox regression models (hazard ratio and likelihood ratio test).

Time to event was defined as the time between the randomisation date and the first event date. Participants were censored at their date of death (when the death is not a component of the endpoint), the date of their last visit (for those still alive at the end of follow-up), or the date when last known to be alive (for those with unknown vital status).

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Statistical methods (Cont'd):
The perindopril-indapamide and placebo groups were compared on the change in systolic and diastolic blood pressure from randomisation to final value, using a general linear model, with adjustment for value at randomisation. The same analysis was performed to compare the two glucose control strategies on the change in HbA1c and fasting blood glucose.

Safety analysis: Descriptive statistics were provided in the Safety Sets defined for the BP lowering intervention and the GC intervention (except for deaths provided in the Randomised Set).

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

12877 patients with type 2 diabetes were registered in the ADVANCE trial. Of these, 1737 (13.5%) did not proceed to randomisation at the end of the run-in phase. The most frequent reason for non-randomisation was suspected intolerance to perindopril or/and indapamide in 444 registered patients (3.4%), *i.e.* around one third of the patients having reported suspected intolerance during this period. Reported intolerances were cough, dizziness/hypotension and other intolerances: 1.7%, 0.9% and 1.3%. Other reasons for non-randomisation mainly included patient's decision (3.1%) and patient ineligibility (2.8%). At the end of the run-in phase, 11140 patients were randomly assigned, according to a factorial design, as follows:

Factorial randomised treatment assignment

BP int. / **GC int.**	Per-Ind	Placebo	**IG *versus* SG**
Intensive glucose control (IG)	2783	2788	**5571**
Standard glucose control (SG)	2786	2783	**5569**
Per-Ind *versus* placebo	**5569**	**5571**	**11140**

Per-Ind: Perindopril-Indapamide

Baseline characteristics were similar in registered and randomised patients.
There was a good balance between randomised groups in baseline characteristics, whatever the study intervention considered.
At registration in the Randomised Set, the mean age was 65.8 ± 6.4 years, and 42.5% of patients were female. Mean BMI was 28.3 ± 5.2 kg/m². Patients had a mean duration of diabetes of 7.9 years with a mean HbA1c of 7.5% and a mean fasting blood glucose of 8.5 mmol/L. Regarding most frequent risk factors, 59.4% of the patients were ≥ 65 years old, 37.1% of the patients had a duration of type 2 diabetes ≥ 10 years, 13.9% were current smokers, 82.6% were hypertensive (defined as patients with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or with currently treated hypertension at registration). In addition, history of macrovascular disease was reported in 32.2% of the patients and history of microvascular disease in 10.3% of the patients, 26.9% had microalbuminuria and 3.8% had macroalbuminuria.

At registration in the Randomised Set, most patients were taking oral hypoglycaemic agents only (1 agent: 42.8%, 2 agents: 42.1%, and more than 2 agents: 6.1%). Sulphonylurea was taken by 63.7% of the patients (including 7.8% on gliclazide 30 mg MR) and metformin by 60.6% of the patients. 8.9% of the patients were on diet alone and 1.4% on insulin. BP lowering drugs were mainly perindopril (8.4%) and other ACE inhibitors (34.9%), calcium antagonists (30.8%), thiazide (14.3%) or other diuretics (10.5%) and beta-blockers (24.5%).
Main other medications included aspirin (43.9%), other anti-platelets (4.5%), HMG CoA reductase inhibitors (28.2%) and other cholesterol lowering agents (8.4%).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Following the run-in period under perindopril-indapamide treatment, mean SBP decreased from 145.0 ± 21.5 mmHg to 137.4 ± 20.1 mmHg (*i.e.* a mean reduction of 7.7 mmHg) and mean DBP decreased from 80.6 ± 10.9 mmHg to 77.6 ± 10.3 mmHg (*i.e.* a mean reduction of 3.0 mmHg).

Mean duration of follow-up from randomisation was 51.8 ± 8.7 months until the final BP visit (T1) and 57.9 ± 10.3 months until the final glucose visit (T2). 87.7% of the randomised patients were still present in the study at T1 and 85.9% at T2.

Intake of randomised therapy and concomitant treatments in the BP lowering intervention

Mean duration of perindopril-indapamide or matching placebo treatment from randomisation to T1 was 46.1 ± 15.1 months, with no relevant differences between treatment groups. At T1, 73.3% of the patients randomised in the Per-Ind group and 74.4% in the placebo group were receiving randomised therapy *i.e.* 83.1% and 85.2% of the patients with assessment at T1, respectively. Patients received one tablet of perindopril-indapamide (2 mg/0.625 mg) daily for the first 3 months and most of them (more than 90% from M6) received 2 tablets (4 mg/1.250 mg) daily thereafter.

Vital status at T1 was unknown for 15 randomised patients. The disposition of patients is given in the table below.

Disposition of patients from randomisation to T1 (BP lowering intervention)

	Per-Ind (N = 5569)		**Placebo (N = 5571)**		**All (N = 11140)**	
	n	**%**	**n**	**%**	**n**	**%**
Randomised	**5569**		**5571**		**11140**	
Unknown vital status	4	0.1	11	0.2	15	0.1
Death	408	7.3	471	8.5	879	7.9
Alive but not assessed at T1	249	4.5	226	4.1	475	4.3
Completed T1	**4908**	**88.1**	**4863**	**87.3**	**9771**	**87.7**
Completed T1 on treatment	4081	73.3	4143	74.4	8224	73.8

%: Percentage of randomised patients

A total of 1753 patients (15.7% of the randomised patients) permanently discontinued the study treatment before T1 for reasons other than death: 925 (16.6%) in the Per-Ind group and 828 (14.9%) in the placebo group. Main reason for discontinuation was patient's wish (5.3%). More patients withdrew for intolerance to study treatment in the Perindopril-Indapamide group (5.5% of the patients) than in the placebo group (2.4%). Patients withdrew for cough (3.3% *versus* 1.4%, respectively) and dizziness/hypotension (1.3% *versus* 0.4%, respectively). The reason for treatment discontinuation was missing for 363 patients (3.3%) but these patients continued the study until T1 without the study treatment.

The reasons for discontinuation of the BP lowering study treatment are given in the table below.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Reasons for permanent treatment discontinuation (BP lowering intervention)

	Per-Ind (N = 5569)		**Placebo (N = 5571)**		**All (N = 11140)**	
	n	**%**	**n**	**%**	**n**	**%**
Permanently withdrawn from treatment*	**925**	**16.6**	**828**	**14.9**	**1753**	**15.7**
Patient wishes	283	5.1	306	5.5	589	5.3
Intolerance to study treatment	307	5.5	136	2.4	443	4.0
Cough	*182*	*3.3*	*80*	*1.4*	*262*	*2.4*
Dizziness/hypotension	*74*	*1.3*	*22*	*0.4*	*96*	*0.9*
Other intolerance	*55*	*1.0*	*37*	*0.7*	*92*	*0.8*
Missing**	190	3.4	173	3.1	3.3	3.3
Serious adverse event	64	1.1	65	1.2	129	1.2
Non-study ACE inhibitor required	35	0.6	45	0.8	80	0.7
Patient unable to attend clinic	37	0.7	65	1.2	102	0.9
Other	87	1.6	113	2.0	200	1.8

% Percentage of randomised patients

** Reasons other than death; one patient could have several reasons for treatment discontinuation*

*** Continued until T1 without study treatment*

During the BP lowering intervention follow-up, the management of diabetes was similar in the two treatment groups. Fewer patients randomised to Per-Ind group took at least one concomitant blood pressure lowering therapy compared with those allocated to placebo (at T1: 74.0% *versus* 82.7%, respectively, including 44.5% *versus* 54.9% on open background perindopril), very likely because of the anti-hypertensive efficacy of the perindopril-indapamide treatment. The use of lipid modifying drugs, aspirin and other anti-platelet drugs was similar in both treatment groups.

Intake of randomised therapy and concomitant treatments in the glucose control intervention

Mean duration of gliclazide 30 mg MR treatment in the IG group from randomisation to T2 was 52.7 ± 16.0 months. At T2, 75.4% of the patients randomised in the IG group were on gliclazide 30 mg MR, *i.e.* 87.0% of the patients with assessment at T2; 70.5% of the patients on gliclazide 30 mg MR in the IG group received 4 tablets daily (120 mg) and the final average dose was 102.7 ± 29.8 mg *i.e.* approximately 3.4 tablets/day.

Vital status at T2 was unknown for 17 randomised patients. The disposition of patients is given in the table below.

Disposition of patients from randomisation to T2 (GC intervention)

	IG (N = 5571)		**SG (N = 5569)**		**All (N = 11140)**	
	n	**%**	**n**	**%**	**n**	**%**
Randomised	**5571**		**5569**		**11140**	
Unknown vital status	7	0.1	10	0.2	17	0.2
Death	498	8.9	533	9.6	1031	9.3
Alive but not assessed at T2	238	4.3	285	5.1	523	4.7
Completed T2	**4828**	**86.7**	**4741**	**85.1**	**9569**	**85.9**
Completed T2 on gliclazide 30 mg MR	4200	75.4	NA	NA	NA	NA

% Percentage of randomised patients

NA Not Applicable

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

A total of 630 patients (11.3% of the patients randomised in the IG group) permanently discontinued gliclazide 30 mg MR before T2. The main reasons for discontinuation were patient's wish (276 patients: 5.0%), other glucose lowering therapy started (213 patients: 3.8%) and were missing for 95 patients (1.7%) who continued the study without gliclazide 30 mg MR until T2. Among other reasons, hypoglycaemia led to gliclazide 30 mg MR treatment withdrawal in 18 patients (0.3%). The reasons for premature gliclazide 30 mg MR discontinuation are given in the table below.

Reasons for permanent gliclazide 30 mg MR discontinuation (GC intervention)

	IG (N = 5571)	
	n	**%**
Permanently withdrawn from gliclazide 30mg MR*	**630**	**11.3**
Patient wishes	276	5.0
Other glucose lowering therapy started	213	3.8
Missing**	95	1.7
Serious adverse event	57	1.0
Patient unable to attend clinic	46	0.8
Other	103	1.8

% Percentage of randomised patients

** Reasons other than death; one patient could have several reasons for discontinuation;*

***Continued until T2 without gliclazide 30 mg MR*

The use of oral hypoglycaemic drugs and of insulin increased to a greater degree in the IG group than in the SG group. Insulin was prescribed in 41.8% and 25.0% of patients in the IG group and the SG group, respectively, by the end of the follow-up period. The use of blood pressure lowering, lipid modifying and anti-platelet treatments was similar in both groups.

In summary, ADVANCE patients were thoroughly representative of a broad type 2 diabetic population, mostly on one or two oral glucose lowering drugs with risk factors for vascular disease. There were no relevant differences between groups in the two interventions of the study regarding demographics, concomitant medication or any other baseline characteristics.

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EFFICACY RESULTS

The analysis of the interaction between the blood pressure lowering intervention and the glucose control intervention, assessed at the end of the follow-up for the BP lowering intervention (T1) did not show any evidence of interaction for the analysed outcomes (all comparisons were not statistically significant). Consequently, results obtained in one intervention were not modified by those of the other and are presented separately.

Blood pressure lowering intervention

Primary endpoints

There was a significant relative risk reduction (RRR) of 9% in the combined major macrovascular and microvascular events in the Per-Ind group compared to the placebo group (hazard ratio: 0.908, 95% CI: [0.828; 0.996], p = 0.041). The RRR in the macrovascular and microvascular events were 8% (hazard ratio: 0.92, 95% CI: [0.81; 1.04], p = 0.164) and 9% (hazard ratio: 0.91, 95% CI: [0.80; 1.04], p = 0.156) respectively, but were not separately statistically significant.

Incidence of the primary endpoints in the Randomised Set

			Per-Ind (N = 5569)	**Placebo (N = 5571)**
COMBINED MAJOR MACROVASCULAR AND MICROVASCULAR EVENTS				
Number of patients with at least one event		n (%)	861 (15.5%)	938 (16.8%)
Treatment effect	Hazard ratio Estimate [95% CI]		0.908 [0.828 ; 0.996]	
		p value	**0.041**	
MAJOR MACROVASCULAR EVENTS				
Number of patients with at least one event		n (%)	480 (8.6%)	520 (9.3%)
Treatment effect	Hazard ratio Estimate [95% CI]		0.92 [0.81 ; 1.04]	
		p value	0.164	
MAJOR MICROVASCULAR EVENTS				
Number of patients with at least one event		n (%)	439 (7.9%)	477 (8.6%)
Treatment effect	Hazard ratio Estimate [95% CI]		0.91 [0.80 ; 1.04]	
		p value	0.156	

95% CI 95% confidence interval
p value likelihood ratio test from the unadjusted Cox model

Secondary endpoints

Components of the primary endpoints: Among the components of the primary endpoints, cardiovascular deaths were significantly reduced by 18% (hazard ratio: 0.82, 95% CI [0.68 ; 0.98], p = 0.027). Patients died less frequently from a cardiovascular cause in the Per-Ind group than in the placebo group: 211 patients (3.8%) and 257 patients (4.6%), respectively. These deaths were mostly related to coronary diseases: 124 patients (2.2%) in the Per-Ind group *versus* 152 (2.7%) in the placebo group, and cerebrovascular diseases: 33 patients (0.6%) *versus* 47 (0.8%), respectively. Deaths due to heart failure were similarly reported (0.6%) in both groups.

There was no significant reduction in non-fatal myocardial infarction and non-fatal stroke. There was a nearly significant RRR of 18% in new or worsening nephropathy (hazard ratio: 0.82, 95% CI [0.68 ; 1.01], p = 0.055) and no significant reduction in new or worsening eye disease.

Other endpoints: There was a significant RRR of 14% in total mortality in the Per-Ind group compared to the placebo group (hazard ratio: 0.86, 95% CI [0.75 ; 0.98], p = 0.025) mainly driven by the significant RRR in cardiovascular deaths, with no excess in non-cardiovascular death.

There was also a significant RRR in total coronary events of 14% (hazard ratio: 0.86, 95% CI [0.76 ; 0.98], p = 0.020). Total renal events and new onset microalbuminuria were significantly reduced by 21% and 20%, respectively (hazard ratio: 0.79, 95% CI [0.74 ; 0.86], p < 0.001 and 0.80, 95% CI [0.74 ; 0.87], p < 0.001, respectively).

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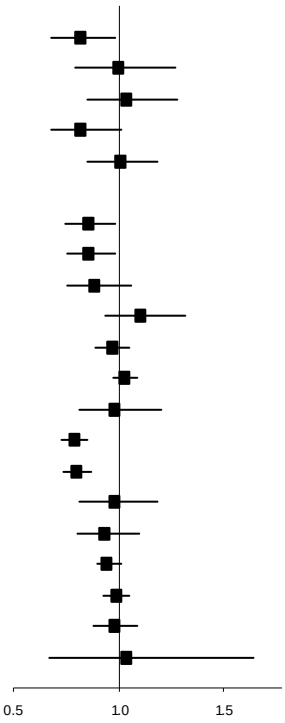
EFFICACY RESULTS (Cont'd)

There was no significant reduction or increased risk in the Per-Ind group on the other endpoints. Results are given in the following table.

Incidence of the secondary endpoints in the Randomised Set

	Per-Ind (N = 5569)	**Placebo (N = 5571)**	**Favours**		**Treatment effect**	
	n (%)	n (%)	**Per-ind**	**Placebo**	Estimate 95%CI	p value
Components of the primary endpoints						
Cardiovascular deaths	211 (3.8)	257 (4.6)			0.82 [0.68 ; 0.98]	**0.027**
Non-fatal myocardial infarction	136 (2.4)	135 (2.4)			1.00 [0.79 ; 1.27]	1.000
Non-fatal stroke	193 (3.5)	184 (3.3)			1.04 [0.85 ; 1.28]	0.686
New or worsening nephropathy	181 (3.3)	216 (3.9)			0.82 [0.68 ; 1.01]	***0.055***
New or worsening eye disease	289 (5.2)	286 (5.1)			1.01 [0.85 ; 1.18]	0.943
Other endpoints						
Total mortality	408 (7.3)	471 (8.5)			0.86 [0.75 ; 0.98]	**0.025**
Total coronary events	468 (8.4)	535 (9.6)			0.86 [0.76 ; 0.98]	**0.020**
Major coronary events	265 (4.8)	294 (5.3)			0.89 [0.76 ; 1.06]	0.185
Peripheral vascular disease	285 (5.1)	255 (4.6)			1.11 [0.94 ; 1.32]	0.219
All cardiovascular events	1057 (19.0)	1080 (19.4)			0.97 [0.89 ; 1.05]	0.439
Hospitalisation > 24h	2271 (40.8)	2221 (39.9)			1.03 [0.97 ; 1.09]	0.389
Heart failure	197 (3.5)	199 (3.6)			0.98 [0.81 ; 1.20]	0.856
Total renal events	1220 (21.9)	1463 (26.3)			0.79 [0.74 ; 0.86]	**< 0.001**
New onset microalbuminuria	1067 (29.0)	1278 (34.5)			0.80 [0.74 ; 0.87]	**< 0.001**
Major cerebrovascular events	215 (3.9)	218 (3.9)			0.98 [0.81 ; 1.18]	0.836
All cerebrovascular events	286 (5.1)	303 (5.4)			0.94 [0.80 ; 1.10]	0.423
Visual deterioration	2446 (43.9)	2514 (45.1)			0.95 [0.90 ; 1.01]	0.100
New or worsening neuropathy	1928 (34.6)	1926 (34.6)			0.99 [0.93 ; 1.05]	0.678
Cognitive function decline	633 (11.4)	640 (11.5)			0.98 [0.88 ; 1.09]	0.715
Dementia	39 (0.7)	37 (0.7)			1.04 [0.67 ; 1.64]	0.850



n number of patients with at least one event,
95% CI 95% confidence interval; p value likelihood ratio test from the Cox model

Blood pressure

From randomisation to T1, SBP decreased from 137.4 ± 20.3 mmHg to 135.6 ± 17.4 mmHg in the Per-Ind group and increased from 137.4 ± 19.9 mmHg to 139.9 ± 17.8 mmHg in the placebo group, corresponding to a mean time-weighted reduction in SBP of 5.6 (0.1) mmHg.

From registration to T1, the overall mean SBP reduction, *i.e.* taking into account the run-in period under open Perindopril-Indapamide treatment, was –9.1 mmHg in the Per-Ind group and –4.2 mmHg in the placebo group.

From randomisation to T1, mean DBP decreased from 77.7 ± 10.4 mmHg to 73.6 ± 10.0 mmHg in the Per-Ind group and from 77.5 ± 10.3 mmHg to 75.1 ± 10.0 mmHg in the placebo group, corresponding to a mean time-weighted reduction in SBP of 2.2 (0.1) mmHg.

From registration to T1, the overall mean DBP reduction was –7.3 mmHg in the Per-Ind group and –5.5 mmHg in the placebo group.

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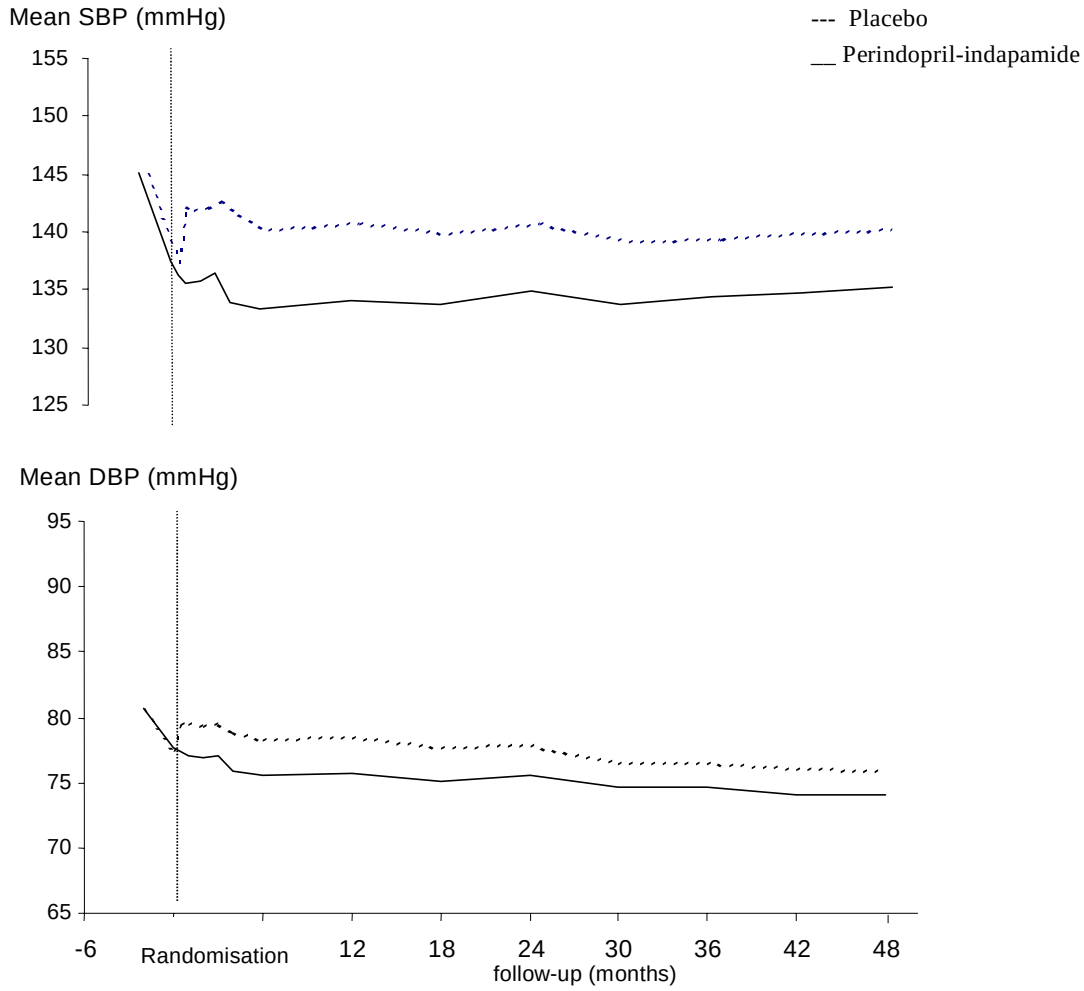
EFFICACY RESULTS (Cont'd)

Mean SBP and DBP in the Randomised Set (BP intervention)



Glucose control intervention

Primary endpoints

There was a significant RRR of 10% in the combined major macrovascular and microvascular events in the IG group compared to the SG group (hazard ratio: 0.90, 95% CI [0.82 ; 0.98], p = 0.013).

As compared with standard glucose control, intensive control resulted in a significant reduction of 14% in the incidence of microvascular events (hazard ratio: 0.86, 95% CI [0.77 ; 0.97], p = 0.014). The RRR of macrovascular events was 6% (hazard ratio: 0.94, 95% CI [0.84 ; 1.06], p = 0.321).

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EFFICACY RESULTS (Cont'd)

Incidence of the primary endpoints in the Randomised Set

			IG (N = 5571)	SG (N = 5569)
COMBINED MAJOR MACROVASCULAR AND MICROVASCULAR EVENTS				
Number of patients with at least one event		n (%)	1009 (18.1%)	1116 (20.0%)
Treatment effect	Hazard ratio Estimate [95% CI]		0.90 [0.82 ; 0.98]	
		p value	**0.013**	
MAJOR MACROVASCULAR EVENTS				
Number of patients with at least one event		n (%)	557 (10.0%)	590 (10.6%)
Treatment effect	Hazard ratio Estimate [95% CI]		0.94 [0.84 ; 1.06]	
		p value	0.321	
MAJOR MICROVASCULAR EVENTS				
Number of patients with at least one event		n (%)	526 (9.4%)	605 (10.9%)
Treatment effect	Hazard ratio Estimate [95% CI]		0.86 [0.77 ; 0.97]	
		p value	**0.014**	

95% CI 95% confidence interval ;
p value likelihood ratio test from the unadjusted Cox model

Secondary endpoints

Components of the primary endpoints

Among components of the microvascular primary endpoint, there was a significant 21% RRR in new or worsening nephropathy (hazard ratio: 0.79, 95% CI [0.66 ; 0.93], p = 0.006), and no significant reduction in new or worsening eye disease or in other components of the primary endpoints. Of note, although non significant, the RRR of cardiovascular deaths was 12%. Cardiovascular deaths affected 253 patients (4.5% of the randomised patients) in the IG group and 289 patients (5.2%) in the SG group, respectively. These deaths were mainly related to coronary diseases: 2.6% *versus* 3.0%, respectively and cerebrovascular diseases: 0.7% *versus* 0.9%, respectively. Deaths due to heart failure were reported in 0.7% of the patients in both groups.

Other endpoints

As compared with standard glucose control, intensive glucose control was associated with a significant 8% reduction in new onset microalbuminuria (hazard ratio: 0.92, 95% CI [0.85 ; 0.99], p = 0.030) and a 11% reduction in total renal events (hazard ratio: 0.89, 95% CI [0.83 ; 0.96], p = 0.001).

More patients in the IG group were hospitalised for any cause (44.9% *versus* 42.8% of those in the SG group (hazard ratio: 1.07, 95% CI [1.01 ; 1.13], p = 0.027). This higher frequency of hospitalisation in the IG group was distributed among several different system organ classes, probably reflecting non-specific effects of more frequent contact with healthcare providers associated with the intensive glucose control strategy. Hospitalisations for severe hypoglycaemia, although slightly more frequent in the IG group than in the SG group, represented an uncommon cause of hospitalisation in both treatment groups (36 patients *versus* 27 *i.e.* 0.7% *versus* 0.5%, respectively).

There were no significant differences between the two groups for any of the other pre-specified secondary endpoints.

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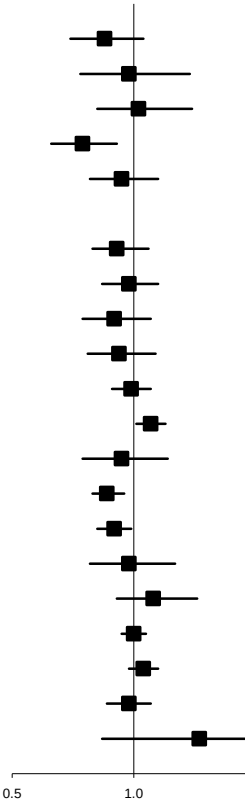
EFFICACY RESULTS (Cont'd)

Incidence of the secondary endpoints in the Randomised Set

	IG (N = 5571)	SG (N = 5569)	Favours	Treatment effect	
	n (%)	n (%)	IG SG	Estimate 95%CI	p value
Components of the primary endpoints					
Cardiovascular deaths	253 (4.5%)	289 (5.2%)		0.88 [0.74, 1.04]	0.123
Non-fatal myocardial infarction	153 (2.8%)	156 (2.8%)		0.98 [0.78, 1.23]	0.864
Non-fatal stroke	214 (3.8%)	209 (3.8%)		1.02 [0.85, 1.24]	0.809
New or worsening nephropathy	230 (4.1%)	292 (5.2%)		0.79 [0.66, 0.93]	**0.006**
New or worsening eye disease	332 (6.0%)	349 (6.3%)		0.95 [0.82, 1.10]	0.497
Other endpoints					
Total mortality	498 (8.9%)	533 (9.6%)		0.93 [0.83, 1.06]	0.278
Total coronary events	560 (10.1%)	572 (10.3%)		0.98 [0.87, 1.10]	0.746
Major coronary events	310 (5.6%)	337 (6.1%)		0.92 [0.79, 1.07]	0.286
Peripheral vascular disease	343 (6.2%)	366 (6.6%)		0.94 [0.81, 1.09]	0.391
All cardiovascular events	1232 (22.1%)	1249 (22.4%)		0.99 [0.91, 1.07]	0.788
Hospitalisation > 24h	2501 (44.9%)	2381 (42.8%)		**1.07 [1.01, 1.13]**	**0.027**
Heart failure	220 (4.0%)	231 (4.2%)		0.95 [0.79, 1.14]	0.597
Total renal events	1474 (26.5%)	1638 (29.4%)		**0.89 [0.83, 0.96]**	**0.001**
New onset microalbuminuria	1289 (34.9%)	1397 (37.9%)		**0.92 [0.85, 0.99]**	**0.030**
Major cerebro-vascular events	238 (4.3%)	246 (4.4%)		0.97 [0.81, 1.16]	0.715
All cerebrovascular events	352 (6.3%)	327 (5.9%)		1.08 [0.93, 1.26]	0.317
Visual deterioration	3033 (54.4%)	3015 (54.1%)		1.00 [0.95, 1.05]	0.961
New or worsening neuropathy	2353 (42.2%)	2311 (41.5%)		1.04 [0.98, 1.10]	0.230
Cognitive function decline	895 (16.1%)	911 (16.4%)		0.98 [0.89, 1.07]	0.650
Dementia	61 (1.1%)	48 (0.9%)		1.27 [0.87, 1.86]	0.212



n Number of patients with at least one event,
95% CI 95% confidence interval; p value likelihood ratio test from the Cox model

HbA1c and fasting blood glucose

During the follow-up period, mean HbA1c level in the IG group progressively decreased to reach 6.5 ± 0.9% at T2. Comparatively, the final mean HbA1c value in the SG group, with target levels based on local guidelines, was 7.3 ± 1.3%. The mean time-weighted reduction in HbA1c was 0.67 (0.02)% in the IG group compared to the SG group. At T2, the target of 6.5% was reached for 64.9% of the patients in the IG group as compared to 28.8% of the patients in the SG group.

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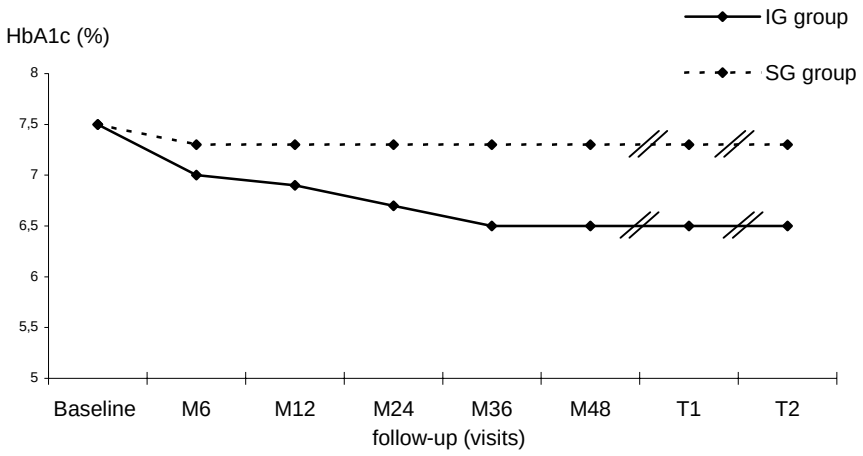
EFFICACY RESULTS (Cont'd)

HbA1c (%) in the Randomised Set (GC intervention)



SG group	N = 5543	N = 5258	N = 5211	N = 4996	N = 4727	N = 4579	N = 4450	N = 4372
IG group	N = 5301	N = 5543	N = 5215	N = 5088	N = 4891	N = 4732	N = 4598	N = 4499

SAFETY RESULTS

Run-in period

Among the 12877 registered patients, 1334 patients (10.4%) reported a suspected intolerance to perindopril or/and indapamide during the run-in period: 5.9% reported cough, 3.2% reported dizziness/hypotension and 3.3% reported other unspecified intolerance. During this period, 250 patients (1.9% of the registered patients) experienced 325 serious adverse events (SAE). The most frequently affected systems were the circulatory system in 80 patients (0.6%) including 18 cases of atrial fibrillation and the endocrine, nutritional, and metabolic diseases in 33 patients (0.3%), mainly related to complications of type 2 diabetes mellitus (27 patients).

Five patients experienced 8 Serious Suspected Adverse Drug Reactions (SSADR) to perindopril or/and indapamide: volume depletion, chronic renal failure and iron deficiency in the same patient, swollen tongue and taste disturbance in the same patient, skin eruption, pruritus and syncope in one patient each.

During the run-in period, among the registered patients, 12 patients (0.1%) died (including 1 patient who died 2 days after the end of the run-in period), 5 patients due to a cardiovascular cause (2 cardiac arrest, 2 sudden deaths cause unknown and 1 acute myocardial infarction) and 7 patients due to a non-cardiovascular cause (3 other ill-defined and unspecified causes of mortality, 1 inflammatory liver disease, 1 umbilical hernia complicated by ileus, 1 pneumonia and 1 septicaemia).

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SAFETY RESULTS (Cont'd)

Blood pressure lowering intervention

Main safety results obtained during the BP intervention follow-up are summarised below:

Summary of safety results in the SSBP (BP lowering intervention)

	Per-Ind (N = 5563)		**Placebo (N = 5569)**	
	n	%	n	%
Patients with at least one Serious Suspected Adverse Drug Reaction*	47	0.8	31	0.6
Patients with at least one Serious Adverse Event	3000	53.9	3071	55.1
Patients who died (Randomised Set)	408	7.3	471	8.5

n number of patients affected
% percentage of patients with at least one event
** to Perindopril or/and Indapamide treatment*

Serious Suspected Adverse Drug Reactions to perindopril or/and indapamide

From randomisation to T1 (+ 15 days), 47 patients (0.8%) in the Per-Ind group and 31 patients (0.6%) in the placebo group experienced SSADR attributed to perindopril or/and indapamide. Disorders of fluid, electrolyte and acid-base balance were the most frequent SSADR: 7 patients (0.1%) in the perindopril-indapamide group and 6 patients (0.1%) in the placebo group. Other relevant events included acute renal failure (5 patients in each group), hypotension (4 patients in each group) and cough (4 patients *versus* 3, respectively).

Serious adverse events

During this period, 54.5% of the patients experienced serious adverse events: 53.9% in the Per-Ind group and 55.1% in the placebo group. The circulatory system was affected in 20.9% of the patients in the Per-Ind group and 21.5% in the placebo group. Main events were angina pectoris (4.7% *versus* 5.3%, respectively) and chronic ischaemic heart disease (4.7% *versus* 4.9%, respectively). Endocrine, nutritional, and metabolic diseases were involved in 13.5% of the patients in the Per-Ind group *versus* 13.0% in the placebo group, who mainly reported complications of type 2 diabetes mellitus (12.0% *versus* 11.9%, respectively). Of note, microalbuminuria and macroalbuminuria were less frequent in the Per-Ind group than in the placebo group (1.6% *versus* 2.6%, respectively, and 2.3% *versus* 3.2%, respectively).

Deaths

A total of 879 patients died from randomisation to T1, 408 patients (*i.*e. 7.3%) in the Per-Ind group and 471 patients (*i.e.* 8.5%) in the placebo group. Out of the 471 patients from the placebo group, 2 patients (No.'s 366 003, 366 025 from the centre 366 prematurely closed) died without any cause of death reported.
197 patients (3.5%) in the Per-Ind group and 212 patients (3.8%) in the placebo group died from a non-cardiovascular cause, mainly due to neoplasm: 115 patients (2.1%) in the Per-Ind group and 139 patients (2.5%) in the placebo group.

Laboratory parameters

Potentially clinically significant high values for creatininemia (> 170 µmol/L) were slightly more frequent in the Per-Ind group (3.9% of the patients) than in the placebo group (3.4%), but with a similar increase over time in mean creatininemia in both groups: +7.1 ± 32.7 µmol/L versus +7.9 ± 33.0 µmol/L, respectively. There were no relevant between-group differences in HbA1c and fasting blood glucose levels or in the other laboratory parameters.

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SAFETY RESULTS (Cont'd)

Vital signs (heart rate, weight)

The mean weight was stable from randomisation to T1 in the Per-Ind group (-0.1 ± 7.0 kg) whereas it slightly increased by 0.5 ± 6.9 kg in the placebo group.

Mean heart rate slightly decreased in both groups from randomisation to T1: -0.8 bpm in the Per-Ind group and -1.9 bpm in the placebo group, with no clinically relevant between-group difference.

ECG

Perindopril-Indapamide intake was not associated with an increased frequency of ECG abnormalities.

Glucose control intervention

Main safety results are summarised below:

Summary of safety results in the SSGC (Glucose control intervention)

	IG (N = 5571)		**SG (N = 5569)**	
	n	%	n	%
Patients with at least one SSADR *(to gliclazide 30 mg MR)*	**32**	**0.6**	**NA**	**NA**
Severe hypoglycaemia*	**150**	**2.7**	**81**	**1.5**
Leading to death	-	-	-	-
Leading to life-threatening situation	23	0.4	14	0.3
Leading to disability	1	< 0.05	1	< 0.05
Leading to hospitalisation	59	1.1	39	0.7
Patients with at least one SAE	**3303**	**59.3**	**3235**	**58.1**
Patients who died (Randomised Set)	**498**	**8.9**	**533**	**9.6**

n number of patients affected
% percentage of patients with at least one event
** included in SAE or SSADR*
NA not applicable

Serious Suspected Adverse Drug Reactions to gliclazide 30 mg MR

From randomisation to T2 (+15 days), 32 patients (0.6%) in the IG group experienced 36 SSADR: severe hypoglycemia (30 patients, 0.5%), mild hypoglycaemia with hospitalisation (1 patient) and allergy (1 patient).

Mild and severe hypoglycaemia

From randomisation to T2, mild hypoglycaemias were more frequently reported in the IG group than in the SG group: 52.5% *versus* 37.6%, respectively, with corresponding annual rates of 129 events per 100 patients-year *versus* 92, respectively.

Severe hypoglycaemias were more frequently reported in the IG group than in the SG group: 2.7% *versus* 1.5% of the patients, respectively. A total of 194 episodes of severe hypoglycemia in the IG group and 104 in the SG group were reported with corresponding annual rates of 0.7 episode per 100 patients-year *versus* 0.4 per 100 patients-year, respectively. The majority of episodes (59.8%) occurred in patients on insulin at the nearest visit before the occurrence of the severe hypoglycaemia.

None of these severe hypoglycaemias led to death. 23 patients (0.4%) in the IG group and 14 patients (0.3%) in the SG group (annual rate 0.1 episode in both groups) had at least one severe hypoglycaemia that led to a life-threatening situation. Severe hypoglycaemias led to hospitalisation in 1.1% of the patients in the IG group versus 0.7% in the SG group, with corresponding annual rates of 0.3 *versus* 0.2 episode, respectively. One patient in each group was affected by hypoglycaemia leading to disability.

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 ® Diamicron MR ®	**Volume:**	
Name of Active Ingredient: Perindopril 2 mg / indapamide 0.625 mg (S 05590) Gliclazide 30 mg MR (S 05702)	**Page:**	

SAFETY RESULTS (Cont'd)

Serious adverse events

From randomisation to T2 (+15 days), SAE were reported in 58.7% of the patients: 59.3% in the IG group and 58.1% in the SG group. The circulatory system was affected in 23.1% of the patients in the IG group and 23.5% in the SG group. Main events were angina pectoris (5.5% *versus* 5.4%, respectively) and chronic ischaemic heart disease (5.7% *versus* 5.0%, respectively). Endocrine, nutritional, and metabolic diseases affected 15.3% of the patients in the IG group *versus* 14.3% in the SG group, who mainly reported complications to their type 2 diabetes mellitus (13.7% *versus* 13.0%, respectively).

Deaths

A total of 1031 patients from the Randomised Set died from randomisation to T2: 498 patients (8.9%) in the IG group, and 533 (9.6%) in the SG group (including 2 patients with no cause of death reported).
243 patients (4.4%) in the IG group and 244 patients (4.4%) in the SG group died from a non-cardiovascular cause, mainly from neoplasm: 142 patients (2.5%) in the IG group and 162 patients (2.9%) in the SG group.

Laboratory parameters

Mean values of laboratory parameters over time were similar in the two glucose control groups.
Total and LDL cholesterol and triglyceridemia slightly decreased over time in both group, and HDL remained stable. Emergent potentially clinically significant abnormal values were sparse in both groups. Abnormal values for high triglycerides were less frequent in the IG group than in the SG group: 23.5% *versus* 28.6%, respectively.

Vital signs

The mean change in weight from registration to T2 was 0.4 ± 7.2 kg in the IG group and –0.7 ± 7.4 kg in the SG group. Mean BMI and waist circumference were stable over time.
Mean SBP slightly decreased over time (from randomisation to T2) in the IG group by –0.9 ± 21.2 mmHg, whereas it slightly increased in the SG group by 0.7 ± 20.5 mmHg and mean DBP decreased over time in both groups: -4.1 ± 11.1 mmHg in the IG group and -3.5 ± 10.8 mmHg in the SG group. Mean heart rate slightly decreased over time in both groups: -1.9 ± 12.5 bpm in the IG group and -1.3 ± 12.6 bpm in the SG group, with no clinically relevant between-group difference.

ECG

Gliclazide 30 mg MR based intensive glucose control strategy was not associated with an increased frequency of ECG abnormalities during the follow-up.

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CONCLUSION

In summary, the routine administration of a fixed combination of perindopril and indapamide to a broad population of type 2 diabetic patients with risk factors for cardiovascular diseases or history of macrovascular or microvascular disease, reduces the risks of total and cardiovascular mortality, of the combined outcome of major macrovascular or microvascular events, and of renal events. The perindopril-indapamide treatment was well tolerated and suitable for use in a wide range of clinical circumstances and settings.

Gliclazide 30 mg MR-based intensive glucose control significantly reduced the risk of combined outcome of major macrovascular or microvascular events, and separately the risk of major microvascular events compared to standard glucose control. There was also a reduction in new or worsening nephropathy and in new onset microalbuminuria. The gliclazide 30 mg MR-based intensive strategy was well tolerated with no weight increase and a low absolute frequency of severe hypoglycaemia.

Such beneficial renal effects of treatments are important in view of the high risk of progression to end stage renal failure and premature death in patients who develop diabetic nephropathy, as well as the emerging evidence of substantial cardiovascular risks associated with progression of renal impairment.

In a broad type 2 diabetic population, the ADVANCE study results demonstrated the beneficial effects on macrovascular and microvascular events of a multifactorial treatment strategy, both:

- **By adding a fixed perindopril-indapamide combination to the standard care, with no need for titration or more monitoring.**
- **And by intensifying blood glucose control with a gliclazide 30 mg MR-based glucose lowering strategy.**

Date of the report: 05 August 2009