I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**Long term double-blind comparison of gliclazide MR (30 to 120 mg daily per os) and rosiglitaz one (4 to 8 mg daily per os) given in combination with metformin in type 2 diabetic patients.** **A 2-year international, multicentre, randomised, double-blind, parallel group study followed by a 2-year double-blind extension.** **E**valuation in **N**oncontrolled patients of the addition of **D**iamicron MR **O**r **R**osiglitazone for **S**ustaining **E**fficacy. **The ENDORSE study.**
Study drug	**S05702** **Gliclazide MR**
Indication	**Type 2 diabetes**
Development phase	**Phase III**
Protocol code	**CL3-05702-013**
Study initiation date	**10 November 2006**
Study completion date	**12 March 2008**
Main coordinator	[redacted] **- Italy**
Company / 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 accord ance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 03rd of June 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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

Title of study:
Long term double-blind comparison of gliclazide MR (30 to 120 mg daily per os) and rosiglitazone (4 to 8 mg daily per os) given in combination with metformin in type 2 diabetic patients.
A 2-year international, multicentre, randomised, double-blind, parallel group study followed by a 2-year double-blind extension.
Evaluation in **N**oncontrolled patients of the addition of **D**iamicron MR **O**r **R**osiglitazone for **S**ustaining **E**fficacy.
The **ENDORSE** study.
Protocol No.: CL3-05702-013

Coordinator: [redacted] - Italy.

Study centres:
Multicentre: 20 countries – 129 study centres having included at least 1 patient; 8 in Australia (29 patients), 6 in Austria (12 patients), 3 in Belgium (4 patients), 7 in Bulgaria (28 patients), 9 in Canada (17 patients), 10 in Czech Republic (46 patients), 6 in France (6 patients), 8 in Germany (27 patients), 11 in Hungary (58 patients), 4 in Latvia (23 patients), 4 in Lithuania (16 patients), 5 in Poland (15 patients), 7 in Romania (32 patients), 18 in the Russian Federation (142 patients), 8 in Slovakia (49 patients), 4 in Slovenia (15 patients), 10 in Spain (50 patients) and 1 in the United Kingdom (1 patient). No patients were enrolled in Portugal and the Netherlands.

Publication (reference): Not applicable.

Study period:	**Phase of development of the study:**
Initiation date: 10 November 2006. Date of early study termination: 04 December 2007. Completion: 12 March 2008.	III

Objectives:
To compare the efficacy and the safety profiles of gliclazide MR and rosiglitazone given in combination with metformin in type 2 diabetic patients not optimally controlled on metformin monotherapy.
Primary objective: To compare the efficacy of the two bitherapies administered at optimal dosage on mean weighted glycosylated haemoglobin (HbA1c) over 2 years.

Secondary objectives: To compare the two bitherapies over 2 and 4 years on:
Other metabolic efficacy criteria (HbA1c expressed differently, fasting plasma glucose [FPG]), pancreatic beta (β) cell function, cardiovascular risk profile, safety profile, health status of the patients assessed through health related quality of life questionnaire (EQ-5D) and economic outcomes.
To evaluate the additional benefit of tritherapy when bitherapy fails.

Methodology:
Prospective, international, multicentre, randomised, double blind, parallel group, comparative (gliclazide MR versus rosiglitazone, on top of metformin) study over 2 years followed by a 2-year double blind extension.
Switch to tritherapy (not allowed within the first year) if HbA1c was > 7.5% at 2 consecutive planned visits despite bitherapy prescribed at least 2 months at maximal tolerated dose. In this case, the patient would have received the alternative treatment according to the initial randomisation in a blind manner.
Non-adaptative, centralised, balanced randomisation with stratification on country and baseline HbA1c level

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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

(< or ≥ 8.0%, with at least 50% of patients in the last stratum).

Number of patients:
Due to the publication on rosiglitazone cardiovascular safety by Nissen in May 2007 followed by restrictive recommendations of European Medicines Evaluation Agency (EMEA) regarding rosiglitazone use in patients suffering from ischaemic heart disease in October 2007, the recruitment for this study became no longer feasible. Subsequently, the Advisory Board and I.R.I.S. have decided to prematurely terminate the study. All the study centres were informed of this decision on 04 December 2007.
Planned: 2500 patients (1250 patients per group).
Included: 570 patients (284 patients in the gliclazide MR group and 286 patients in the rosiglitazone group).

Diagnosis and main criteria for inclusion:
Type 2 diabetic outpatients diagnosed for at least 6 months according to the World Health Organisation (WHO) criteria, male or female aged ≥ 35 years, body mass index (BMI) 24 - 38 kg/m^2 inclusive, currently on monotherapy with metformin at maximal tolerated dose of at least 1500 mg/d prescribed for at least 4 months (stable dose), not optimally controlled with HbA1c in the range [7.5 - 9.0%], not having been treated with 2 anti-diabetic drugs within the previous year (except if both prescribed at low dose and stopped at least 4 months prior to selection), not having been treated with insulin for more than one month in the previous year (not acceptable within the 4 months prior to selection), or being at risk of rapidly requiring chronic insulin therapy, without severe diabetic complications, without contra-indication to gliclazide MR, rosiglitazone or metformin, with creatinine clearance ≥30 mL/min, alanine aminotransferase (ALAT) ≤ 2.5 the upper limit of normal (ULN), haemoglobin level ≥11 g/dL (men) and ≥10 g/dL (women), without heart failure or history of cardiac failure (New York Heart Association [NYHA] grade I to IV), with relatively stable weight (+/- 10% in the previous 6 months).

Study drug (in addition to metformine ≥ 1500 mg/d):
Gliclazide MR (30, 60, 90 or 120 mg) tablets masked in capsules, once daily (o.d) at breakfast, orally, in combination with metformin (stable dose identical to prior the study).

- From M0 (start dose: 30 mg o.d) to M3 included (titration period), dose could be adjusted each month (by one step) to obtain a FPG level ≤ 7.8 mmol/L.
- From M3 (excluded) to M48, dose level was adapted to obtain an HbA1c level ≤ 6.5%; possibility to decrease the dose at any moment in case of safety issue.
- From M12, if bitherapy given at optimal dose for at least 2 months failed to control HbA1c, the patient initially randomised in the gliclazide MR group could receive rosiglitazone as 3rd oral antidiabetic drug (start dose 4mg then dose increase using the same rules as those defined for bitherapy). Possibility to decrease the dose of the 3rd treatment in case of safety issue.

Batch Numbers: L0012030, L0012379, L0012509, L0013979, L0015880, L0016249, L0018741, L0019624, L0012093, L0012870, L0013578, L0013981, L0015613, L0015987, L0016662, L0017039, L0018352, L0018876 and L0018878.

Reference product (in addition to metformine ≥ 1500 mg/d):
Rosiglitazone (4 or 8 mg), tablets masked in capsules, once daily at breakfast, orally in combination with metformin (stable dose, identical to prior the study).
- From M0 (start dose: 4 mg o.d) to M3 included (titration period), the adjustment of dose was possible from M2 to obtain a FPG level ≤ 7.8 mmol/L.
- From M3 (excluded) to M48, dose level was adapted to obtain an HbA1c level ≤ 6.5%. Possibility to decrease the dose at any moment in case of safety issue.
- From M12, if bitherapy given at optimal dose for at least 2 months failed to control HbA1c, the patient initially randomised in the rosiglitazone group could receive gliclazide MR as 3rd oral antidiabetic drug (start dose 30mg then dose increase using the same rules as those defined for bitherapy). Possibility to decrease the dose of the 3rd treatment in case of safety issue.

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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

Duration of treatment:

Total study duration per patient was to be 49 months. This duration included:

- Selection period (1 month): Patients continued their current metformin treatment.
- Active period: 2 years followed by a 2-year double-blind extension period. Study drug and metformin were provided.

Criteria for evaluation:

Efficacy (Centralised measurements, assessed in fasting conditions)

Primary criterion: HbA1c (%) Assayed by High Performance Liquid Chromatography (HPLC) and certified by National Glycohaemoglobin Standardisation Program (NGSP): At M0, every month until M3 then every 3 months from M3 to M48*; in case of tritherapy, every month within the 3 first months then every 3 months.

Secondary criteria

- Fasting plasma glucose (mmol/L) at M0, every month until M3, every 3 months from M3 to M48*; in case of tritherapy, every month within the 3 first months then every 3 months,
- Fasting insulin, pro-insulin and C-Peptide (Homeostatic Model Assessment [HOMA] index) at M0 then every 6 months from M12 until M48*,
- Fasting lipids (Total Cholesterol, low density lipoprotein [LDL]-cholesterol, high density lipoprotein [HDL]-cholesterol, triglycerides, apolipoprotein [Apo] A1, Apo B) every 6 months from M0 to M48*,
- High sensitive C-reactive protein (hsCRP), fibrinogen, Brain Natriuretic Peptide (BNP), urinary albumin/creatinin ratio: every year from M0 to M48*,
- Criteria only assessed in subpopulations:
    - Tumour necrosis factor (TNF)-α, high sensitive interleukin (hsIL)-6, plasminogen activator inhibitor (PAI)-1, tissue plasminogen activator (t-PA), E-selectin, intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM), oxidised LDL, nitrotyrosine, urinary isoprostanes, total radical-trapping antioxidant parameters (TRAP): at M0 then every year until M48*,
    - Postprandial profile of glucose, insulin, C-peptide: at M0 then every year until M48 (ancillary study),
    - Intima Media Thickness (IMT) assessment: at M1, M6, M24, M48 (and in any case of premature discontinuation if previous one ≥ 1 year) (ancillary study).

Safety

Adverse events (AE) at each visit with specific attention to

- hypoglycaemic events (glucose meter provided to be used in case of symptoms suggestive of hypoglycaemia),
- peripheral oedema, weight gain, suspected symptoms of heart failure,
- suspected cardiovascular events leading to hospitalization and all deaths.

- Physical examination, vital signs (heart rate, blood pressure), body weight at each visit, waist circumference every 6 months from M0,
- laboratory examination (centralised biochemistry and haematology) every 6 months from M0 to M48*,
- Pregnancy test at M0,
- 12-Lead electrocardiogram (ECG) each year from M0 to M48*,
- Ophthalmologic exam (fundoscopy): at baseline (if not performed in the previous 3 months) and during the study if needed,
- In menopausal women ≥ 1 year: hip and spine bone mineral density (BMD): at M1, M24, M48 (and in case of premature discontinuation if previous assessment was ≥ 1 year); bone markers (bALP, P1NP, S-CTX): at M0, M6, M12 and M24, oestradiol at M0 (in order to characterize the population).

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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

Others

- Health related quality of life questionnaire (EQ-5D) at M0, M6, M12, M24, M36, M48*.
- Economic outcomes throughout the study via a patient diary.
- Serum bank for any further investigations required: extra fasting serum stored at the central laboratory at M0, M6, M12, M24, M36, M48* (no genetic analyses).

** also in case of premature discontinuation*

Statistical methods:

Due to the premature termination of the study, the last visit completed by patients having the longest duration of follow-up was M12. Consequently, the statistical analyses planned in the study protocol were modified as described below.

Efficacy analysis:

Main analytical approach of the main criterion HbA1c: the weighted mean HbA1c was calculated up to the patient discontinuation from the study and not over 2 years (maximum = M12). The main analysis estimated the difference between the two treatment groups using a linear general model with baseline HbA1c and country as covariates on the Full Analysis Set (FAS) and in Per Protocol Set (PPS). Due to the different number of patients in each country, countries were pooled in 9 groups. The estimate of treatment difference, its standard error and its 95% confidence interval (CI) are presented. The sensitivity to adjustment factors was assessed.

The following secondary approaches were studied:

- Percentage of patients reaching HbA1c ≤ 6.5,]6.5;7],]7;7.5], > 7.5% at each visit and at study end, value at the visit, change from baseline to the last value under treatment or to the last value during the study using a linear general model with country and baseline HbA1c as covariates on the FAS and PPS. The estimate of treatment difference, its standard error and its 95% CI were provided. A within group analysis was performed using a two-sided Student's t test for paired samples.
- The treatment effect for HbA1c was also described in subgroups, using the same approaches as for the total population: HbA1c at baseline (< 8 % / ≥ 8 %), age at selection (≤ 65 years / > 65 years), creatinine clearance at baseline (≤ 80 mL/min / > 80 mL/min), BMI at baseline (≤ 30 kg/m² / > 30 kg/m²), dose of metformin at baseline (1500 mg or 1700 mg / 2000 mg / 2550 mg or 3000 mg).

The following analytical approaches of the main efficacy criterion HbA1c were not studied: time to end of adequate control over 4 years, time to switch to tritherapy over 4 years, maximal effect and time to maximal effect on HbA1c (%) over 2 and 4 years, Percentage of patients reaching HbA1c ≤ 6.5%, 7.0% and 7.5% over 2 and 4 years, mean HbA1c (%) over 4 years. All references to tritherapy were suppressed as no patient started on tritherapy during the study.

Secondary efficacy criteria:

- Fasting plasma glucose: change from baseline to the last value under treatment and to the last value during the study. A comparison between treatments groups was performed using a linear general model with country and baseline HbA1c as covariates on the FAS and PPS. A within group analysis was performed using a two-sided Student's t test for paired samples. A descriptive analysis was performed on other secondary efficacy criteria, such as insulin, pro-insulin, pro-insulin/insulin ratio and C-peptide in the FAS and PPS.
- The HOMA was not assessed; the lipid parameters, the specific cardiovascular markers were not analysed as efficacy parameters but as safety parameters.

Safety analysis:

- Descriptive analyses were carried out on the Safety Set. Hypoglycaemic events were classified according to the EMEA. IMT, Hip and Lumber spine BMD were described at baseline only (no post-baseline value).
- Peripheral oedema, heart failure and other cardiovascular events: no adjudication was performed.

Health status and Economic outcomes: no analyse was carried out.

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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

SUMMARY - CONCLUSIONS

Study population and outcome:

	Gliclazide MR	Rosiglitazone	Whole population
Included	284	286	570
Withdrawn	28	32	60
due to adverse event	13	9	22
due to non-medical reason	7	15	22
due to protocol deviation	6	4	10
due to lack of efficacy	1	3	4
lost to follow-up	1	1	2
Completed	256	254	510
Randomised Set (RS)	284	285	569
Full Analysis Set (FAS)	274	276	550
Per Protocol Set (PPS)	187	183	370
Safety Set (SS)	280	285	565
Sub-SS Menopause	121	131	252

Overall, 570 patients were included and 569 randomised (1 patient had treatment allocation without the interactive voice response system [IVRS]). Two patients were lost to follow-up (one in each group). The frequency of withdrawal was well balanced between treatment groups. The FAS respectively represented 96.5% and the PPS 67.3% of the Randomised Set (RS).

The RS consisted of 264 (46.4%) males and 305 (53.6%) females. The baseline characteristics were comparable between groups with a mean age of 58.2 ± 8.2 years (80.7% < 65 years old). Mean duration of Diabetes was 6.07 ± 4.98 years, mean BMI was 31.66 ± 3.75 kg/m^2 (65.6% > 30 kg/m^2), mean creatinine clearance was 99.29 ± 29.33 mL/min (29.3% ≤ 80 mL/min). At inclusion HbA1c was 8.11 ± 0.42% (57.8% ≥ 8.0%) and FPG was 10.06 ± 1.98 mmol/L.

A total of 560 patients (98.4%) reported at least one medical history including hypertension (80.7%), dyslipidaemia (52.9%), macrovascular complications (21.1%), microvascular complications (19.3%) without difference between groups. At inclusion, 520 patients (91.4 %) received at least one concomitant treatment. Treatments were mainly agents acting on the renin-angiotensin system (63.4%), lipid modifying agents (39.4%), beta blocking agents (27.2%), antithrombotic agents (25.7%), calcium channel blockers (19.2%) and diuretics (19.0%).

Due to the premature discontinuation of the study, treatment duration for patients in the FAS ranged between 17 and 375 days. Overall, patients received study drug for a mean (± standard deviation [SD]) of 188 ± 93.6 days with compliance with the study drug of 97.4 ± 9.7%. From M1, 59% of the patients had their dose increased in the gliclazide MR group and 74.1% in the rosiglitazone group. Dose adaptation carried on at each visit; the final dose distribution for gliclazide MR group and rosiglitazone group was respectively: dose 1 (30 mg/4 mg; 31.0% and 19.6%), dose 2 (60 mg/4 mg; 23.7% and 18.5%), dose 3 (90 mg/8 mg; 16.4% and 19.9%), dose 4 (120 mg/8 mg; 28.8% and 42.0%).

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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

Efficacy results

1. Primary assessment criteria

Mean weighted HbA1c (%) during the study (FAS)

		Gliclazide MR (n = 274)	Rosiglitazone (n = 276)
Baseline	Mean ± SD	8.12 ± 0.42	8.12 ± 0.41
End	Mean ± SD	7.30 ± 0.64	7.61 ± 0.69
Statistical analysis	E (SE)[1]	-0.31 (0.05)	
	95% CI[2]	[-0.41; -0.21]	
	p-value[3]	< 0.001	

CI Confidence interval; FAS Full Analysis Set; SD Standard deviation; SE Standard error.
1 Estimate (Standard Error) of the difference gliclazide MR minus rosiglitazone adjusted group means.
2 95% CI of the estimate. 3 Analysis of covariance with baseline and country as covariates with fixed effect and treatment as factor

In both treatment groups, the mean weighted HbA1c was lower than at baseline. The main efficacy analysis performed in the FAS and confirmed in the PPS demonstrates the superiority of gliclazide MR on rosiglitazone both associated to metformin: E (SE) = -0.31 (0.05)%, 95% CI [-0.41 ; -0.21], $p < 0.001$ in the FAS and E (SE) = -0.31 (0.06)%, 95% CI [-0.44 ; -0.19], $p < 0.001$ in the PPS. This superiority has been observed whatever the dose level of metformin at baseline (1500 mg or 1700 mg / 2000 mg / 2550 mg or 3000 mg) with an increased difference with the highest dose of 2550 mg or 3000 mg of metformin, E (SE) = -0.45 (0.10)%, 95% CI [-0.64 ; -0.26], $p < 0.001$.
Due to the premature discontinuation of the study, 174 patients from the FAS withdrew between M6 and M9, thus the time course of the changes at each visit were mainly representative till M6. They differed between treatment groups with a more pronounced decrease in the gliclazide MR group from M1. The superiority of the combination gliclazide MR + metformin over rosiglitazone + metformin was also demonstrated with the change from baseline to the last value under treatment [E (SE) = -0.25 (0.06)%, 95% CI [-0.36 ; -0.13], $p < 0.001$] (results in the FAS confirmed in the PPS).

At study end, in the FAS, the percentage of patients reaching the HbA1c goal of ≤ 6.5% and ≤ 7.0% was higher in the gliclazide MR group than in the rosiglitazone group (respectively 19.3% and 27.4% for gliclazide MR; 8.0% and 21.0% for rosiglitazone). In the PPS, the percentage was higher for the HbA1c goal ≤ 6.5% in the gliclazide MR group (22.5%) than in the rosiglitazone group (9.3%); it was quite equal for the HbA1c goal ≤ 7.0% (27.8% and 27.3% respectively).

The sensitivity analysis confirmed these results on all the subgroups tested, namely defined by HbA1c at baseline, age at selection, creatinine clearance at baseline, BMI at baseline and dose of metformin at baseline, where the decrease of the mean weighted HbA1c was comparable to that of the whole population.

2. Secondary assessment criteria

Fasting Plasma Glucose: In the FAS, in both treatment groups, the mean FPG significantly decreased from baseline to last value under treatment: E (SE) = -1.42 (0.13) mmol/L with 95% CI [-1.67 ; -1.16] in the gliclazide group and E (SE) = -1.36 (0.13) mmol/L with 95% CI [-1.61 ; -1.12] in the rosiglitazone group. The difference between groups adjusted on baseline HbA1c and country was not statistically significant:
E (SE) = -0.01 (0.15) mmol/L with 95% CI [-0.32 ; 0.29]. These results were comparable for all the sub-groups tested.
No relevant data could be observed on insulin, pro-insulin or C-peptide values.

3. Safety results

Overall, 198 patients (35%) of the 565 patients in the Safety Set reported at least one Emergent Adverse Event (EAE): 99 patients (35.4%) with 241 events in the gliclazide MR group and 99 patients (34.7%) with 183

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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

events in the rosiglitazone group. The number of patients affected by EAE was similar in both groups but the number of EAE was higher in the gliclazide MR group, due to the higher number of recorded hypoglycaemia: 75 events *versus* 5 events in the rosiglitazone group (not expected in this group). According to EMEA classification for hypoglycaemia, only 7 minor episodes in 6 patients (2.1%) and 12 suggestive episodes in 9 patients (3.2%) were indeed recorded; no major hypoglycaemia occurred.

The majority of the events were considered to be mild, not related to the study drug administration by the investigator and totally recovered by the end of the study. No patient died during the study.

Outside hypoglycaemia, the most frequent EAEs by system class in the gliclazide MR and rosiglitazone groups were respectively: infections and infestations (9.3% and 9.5% of patients), musculoskeletal (10.0% and 7.7% of patients), gastrointestinal (5.7% and 4.2% of patients).

In the rosiglitazone group, 8 (2.8%) patients experienced 9 emergent cardiac disorders; among them 4 were considered as treatment-related by the investigator: acute myocardial infarction, cardiac failure, coronary artery disease and myocardial ischaemia. One emergent cardiac disorder occurred in the gliclazide MR group: palpitations which were not considered as treatment-related.

No relevant differences were observed between groups on the evolution of body weight or oedema occurrence during the study.

Overall, 14 out of 565 patients (2.5%) experienced at least one emergent serious adverse event (ESAEs): 8 patients (2.9%) in the gliclazide MR group (not considered treatment-related): benign salivary gland neoplasm, colon cancer, prostate cancer, uterine leiomyoma, erysipelas, acute cholecystitis, carotid artery stenosis and chronic eosinophilic pneumonia; 6 patients (2.1%) in the rosiglitazone group (3 considered treatment-related): acute myocardial infarction, cardiac failure, coronary artery disease, erysipelas, impaired hearing and urinary retention.

Summary of emergent adverse events

Number and percent of patients with at least one	Gliclazide MR (n = 280)	Rosiglitazone (n = 285)
Emergent adverse event	99 (35.4%)	99 (34.7%)
hypoglycaemia	30 (10.7%)	5 (1.8%)
cardiac disorder	1 (0.4%)	8 (2.8%)
Treatment-related emergent adverse event	34 (12.1%)	26 (9.1%)
Emergent serious adverse event	8 (2.9%)	6 (2.1%)
Treatment-related serious adverse event	-	3 (1.1%)
Death	-	-
Patient withdrawn		
due to adverse event (including hypoglycaemia)	11 (3.9%)	8 (2.8%)
due to hypoglycaemia	3 (1.1%)	-

Nineteen patients (3.4%) prematurely discontinued their participation from the study due to the occurrence of an EAE: 11 patients (3.9%) in the gliclazide MR group and 8 patients (2.8%) in the rosiglitazone group. Among them, 3 patients withdrew due to hypoglycaemia and 2 for diarrhoea in the gliclazide MR group and 2 patients withdrew for anaemia, 1 for cardiac failure, 2 for skin disorders in the rosiglitazone group.

Laboratory tests: a decrease from baseline to last observation under treatment was noted in the haemoglobin levels of patients with a more pronounced decrease in the rosiglitazone group (-8.5 ± 9.9 g/L) than in the gliclazide group (-2.9 ± 8.9 g/L). No other notable changes from baseline to last value were recorded. Regarding lipids, the changes versus baseline for HDL- and LDL-cholesterol were minor: -0.03 ± 0.18 mmol/L

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:	**Volume:**	
Name of Active Ingredient: ***Gliclazide MR***	**Page:**	

and 0.10 ± 0.78 mmol/L respectively for the gliclazide group and 0.05 ± 0.20 mmol/L and 0.41 ± 0.83 mmol/L respectively for the rosiglitazone group.

No clinically significant changes were observed for any of the vital signs including ECG parameters, weight and blood pressure.

Due to the great between-patients variability observed on bone markers measurements, in the menopausal women sub-set, it was not possible to establish valid conclusions.

CONCLUSIONS

This international, double-blind, randomized, controlled study was conducted to compare the long term efficacy and safety profiles of gliclazide MR and rosiglitazone given in combination with metformin in type 2 diabetic patients not optimally controlled on metformin monotherapy.
Due to premature study discontinuation, the duration of follow-up was variable among patients with a majority of patients going till month 6. The superiority of gliclazide MR versus rosiglitazone (both associated to metformin) was demonstrated in the control of HbA1c whereas no between-group differences were observed on FPG.
The safety of gliclazide MR was satisfactory on all studied safety parameters. Only few (2.1%), minor hypoglycaemia occurred during the study. No major hypoglycaemia arose.
In the rosiglitazone group, 2.8% of patients experienced emergent cardiac disorders with 4 considered as treatment-related.
No patient died during the study.

Date of the report: 03rd of June 2009