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INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report**
Study title	**Efficacy and safety assessment of two schemes of oral administration of once-daily extended release metformin (metformin XR) in type 2 diabetic patients previously treated with metformin in combination with sulfonylurea.** **A 3-month, international, multicentre, randomised, double-blind, double-dummy, parallel group study.**
Study drug	**Metformin XR**
Studied indication	**Type 2 diabetes**
Development phase	**Phase II**
Protocol code	**CL2-05720-005**
Study initiation date	**04 July 2012**
Study completion date	**27 March 2013**
Main coordinator	[redacted] **Czech Republic**
Company / Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Les Laboratoires Servier** **Paveletskaya Sq, 2-3** **15054 Moscow - Russia**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 20 December 2013**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot, 92284 Suresnes Cedex France**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Efficacy and safety assessment of two schemes of oral administration of once-daily extended-release metformin (metformin XR) in type 2 diabetic patients previously treated with metformin in combination with sulfonylurea. A 3-month, international, multicentre, randomised, double-blind, double-dummy, parallel group study.
Protocol No.: CL2-05720-005

National coordinators:
Czech Republic: [redacted] Czech Republic
Hungary: [redacted] Hungary
Poland: [redacted] Poland
Russia: [redacted] Russia
Slovakia: [redacted] Slovakia.

Study centres:
Multicentre study (29 centres in 5 countries). All centres included at least one patient: Czech Republic (10 centres, 93 patients), Hungary (5 centres, 42 patients), Poland (6 centres, 57 patients), Russia (5 centres, 45 patients) and Slovakia (3 centres, 37 patients).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 4 July 2012 Completion date: 27 March 2013	II

Objectives: The purpose of this exploratory study was to assess over 3 months the efficacy and safety of metformin XR given once-daily at 2 different daily times of administration - breakfast *versus* dinner time - in type 2 diabetic patients optimally or sub-optimally controlled on metformin in combination with a sulfonylurea

- Primary objective: efficacy on glycohaemoglobin A1c (HbA1c) value.
- Secondary objectives: efficacy on fasting plasma glucose (FPG) and safety profile including gastrointestinal (GI) tolerance and hypoglycaemic events if any occurred.

Methodology:
Exploratory, international, multicentre, randomised, double blind, double dummy, parallel group, comparative phase II study in type 2 diabetic patients, including:

- 3 to 7-day screening period.
- 2 to 4-week open-label run-in period on metformin XR taken at dinner time.
- 3-month randomised treatment period on either 'Metformin XR Morning' or 'Metformin XR Evening', named "Morning group" or "Evening group".

Five scheduled study visits: pre-selection (ASS1) and selection (ASS2) visits, inclusion/randomisation (M0), intermediate (M2) and end-of-study (M3) visits.
Randomisation (1:1 ratio) with stratification according to previous metformin daily dose ([850-1000 mg], 1500 mg, or [1700-2000 mg]) and country.

Number of patients:
Planned: 250 patients (125 per group).
Included: 274 patients (135 Metformin XR Morning; 139 Metformin XR Evening).

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Diagnosis and main criteria for inclusion:

Main inclusion criteria: Caucasian male or females aged ≥ 35 years; body mass index (BMI) 22-40 kg/m^2; type 2 diabetes diagnosed for ≥ 6 months according to World Health Organisation (WHO) criteria; currently treated with stable doses of metformin (immediate or extended release formulation) at daily dose between 850-2000 mg and a sulfonylurea for ≥ 3 months prior to selection, optimally or sub-optimally controlled with HbA1c < 8% (or between [6.5-8%[if metformin was 850 or 1700 mg/day); without severe diabetic complications; without contra-indications to metformin; with creatinine clearance ≥ 60 mL/min, haemoglobin ≥ 12 g/dL (males) or ≥ 11g/dL (females), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transferase (GGT) ≤ 3 x upper limit of normal range (ULN) and total alkaline phosphatase (ALKP) ≤ 2xULN; used to taking regular meals, with substantial breakfast including solid food.

Antidiabetic treatments other than metformin and sulfonylurea, and systemic (oral, inhaled or intra-venous) corticosteroids were not authorised during the 3 months prior to ASS1 visit and throughout the study. From ASS2 visit, oral drugs known to interact with GI absorption or intestinal transit had to be administered ≥ 2 hours after study drug intake.

Study drug: Metformin XR per os once-daily (1000, 1500 or 2000 mg) at breakfast.
Patients additionally took matching placebo tablet at dinner.

Batch No.: *L0043720, L0044781, L0043732, L0043736, L0043738, L0043817, L0043936, L0044783*

Reference product: Metformin XR per os once-daily (1000, 1500 or 2000 mg) at dinner. Patients additionally took matching placebo tablet at breakfast.

Duration of treatment:

Three successive periods (total study duration ≤ 4.5 months per patient):

- 3 to 7-day screening period (ASS1 to ASS2): Patients continued their current antidiabetic treatment at the same daily dose and administration time as prior to the study.
- 4-week open label run-in period (ASS2 to M0): Previous metformin treatment was replaced by metformin XR given at dinner at the same daily dosage as prior to the study (except for patients previously on 850 or 1700 mg/day who received 1000 or 2000 mg/day, respectively). Run-in period was shortened to 2 weeks for patients previously on metformin XR at 1000, 1500 or 2000 mg/day.
- 3-month randomised double-blind period (M0 to M3).

Criteria for evaluation:

Efficacy measurements:

- Primary criterion: centralised HbA1c (%) at M0 (baseline), M2 and M3. Main analytical approach: change from baseline to last post-baseline value,
- Secondary criterion: centralised FPG level at M0, .2 and M3.

Safety measurements:

- Adverse events (AEs) at each visit with specific attention to GI AEs and hypoglycaemia.
- Laboratory analyses (centralised biochemistry and haematology) at M0 and M3.
- Physical examination and body weight at M0 and M3.
- Vital signs at each visit.

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Statistical methods:

Efficacy analysis:

Efficacy analyses were carried out primarily on the Full Analysis Set (FAS) and confirmed on the Per Protocol Set (PPS). The FAS corresponded to randomised patients who had taken at least one dose of study treatment post-inclusion and who had at least one evaluable baseline value and one evaluable post-baseline value of HbA1c. The PPS corresponded to patients of the FAS without relevant deviation(s) which could affect the evaluation of HbA1c.

- Main criterion (HbA1c; %): The effect of morning intake of metformin *versus* evening intake of metformin on the change from baseline value to last post-baseline value was studied using a general linear model with baseline, previous metformin daily dose ([850-1000 mg], 1500 mg, [1700-2000 mg]) and country as covariates. The estimate of between-group difference, its standard error (SE) and 95% confidence interval (CI) were provided.
- Secondary criterion (FPG; mmol/L): As for the main efficacy criterion, the same analyses using the same methods were performed.

Safety analysis:

All safety analyses were carried out on the Safety Set (SS). The SS corresponded to patients who received at least one dose of study treatment post-inclusion.

Descriptive statistics were provided for AEs, hypoglycaemia, laboratory examinations, physical examinations, vital signs (blood pressure and heart rate) and body weight. Hypoglycemic events were classified according to the European Medicines Agency (EMA) guideline (noteworthy, documented symptomatic or asymptomatic hypoglycemia with blood glucose concentration ≤ 3.9 mmol/L).

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

		Metformin XR Morning	***Metformin XR Evening***	**All**
Included (randomised set)	n	135	139	274
Lost to Follow-up	n	-	-	-
Withdrawn	n (%)	-	6 (4.3)	6 (2.2)
adverse event	n	-	□	1
non-medical reason	n	-	2	2
protocol deviation	n	-	3	3
Completed	n (%)	135 (100)	133 (95.7)	268 (97.8)
Full Analysis Set (FAS)	n (%)	135 (100)	138 (99.3)	273 (99.6)
Per Protocol Set (PPS)	n (%)	123 (91.1)	117 (84.2)	240 (87.6)
Safety Set (SS)	n (%)	135 (100)	139 (100)	274 (100)

% expressed as percentage of patients from the randomised set

A total of 361 patients were pre-selected and 280 were selected for the study. Among them, 274 patients were included and randomly assigned to one of the two groups with a well-balanced distribution. Overall, 6 patients were withdrawn from the study, all from the Evening group, and 268 patients completed the study (see Table).

In the randomised set (RS), mean ± SD baseline characteristics were overall: age 62.6 ± 7.7 years, 57.7% male, BMI 30.4 ± 4.1 kg/m^2, diabetes duration 9.9 ± 6.4 years, HbA1c 6.9 ± 0.6%, FPG 7.8 ± 1.6 mmol/L. Type 2 diabetes was well-controlled, with 62.4% of patients with HbA1c ≤ 7.0%. A majority of patients were treated with high dose of metformin (67% on 1700-2000 mg/day) and sulfonylureas were mainly prescribed as once-daily morning treatments (97.4% of patients, with 45% on gliclazide and 53% on glimepiride).

Most patients (98.5%) reported at least one medical history including hypertension (86.1%) and hyperlipidaemia (44.9%). Therefore, treatments other than drugs used in diabetes were mainly agents acting on the renin-angiotensin system (76.6%), lipid modifying agents (63.5%) and beta-blocking agents (42.3%).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

There was no relevant between-group difference in demographic and other baseline characteristics. Baseline characteristics in the PPS were similar to those observed in the RS.

In the SS, mean exposure and compliance to treatment were similar between breakfast and dinner intakes in either group and no relevant difference was observed between treatment groups: mean values for treatment exposure were 14.6, 28.0 and 87.7 days for the 2-week run-in period, 4-week run-in period and randomised period respectively, with satisfactory overall treatment compliance (> 97%).

EFFICACY RESULTS

Primary assessment criterion

For the FAS, mean HbA1c values were similar in the Morning and Evening groups at baseline (6.84% in both groups) and after 3 months of treatment (7.07% and 7.05%, respectively). Mean (±SD) HbA1c levels slightly increased from baseline to end (+ 0.2 ± 0.5%) similarly in both groups, with a non-clinically relevant estimated between-group difference (± SE) of 0.03% (± 0.06), 95% CI [-0.10, 0.15%] (see Table).

HbA1c – Changes from baseline to End – FAS (N = 273)

	Metformin XR Morning N = 135	***Metformin XR Evening N = 138***
Baseline		
Mean ± SD	6.838 ± 0.589	6.843 ± 0.654
Min ; Max	5.60 ; 8.40	5.20 ; 8.80
End		
Mean ± SD	7.070 ± 0.799	7.049 ± 0.841
Min ; Max	5.40 ; 10.40	5.10 ; 10.20
End - Baseline		
Mean ± SD	0 232 ± 0.510	0.205 ± 0.533
Min ; Max	-1.00 ; 2.20	-1.10 ; 2.30
Statistical analysis		
End - Baseline		
E (SE)[1]	0.028 (0.063)	
95% CI[2]	[-0.096 ; 0.151]	

1 Estimate (Standard Error) of the difference (Metformin XR morning minus Metformin XR evening) between adjusted group means obtained from a general linear model with baseline, previous Metformin dose and country as covariates
2 95% CI of the estimate.

In the subset of patients who had a metformin dose at inclusion of 2000 mg, the largest FAS subset (67% of the FAS overall; 91 and 92 patients in the Morning and Evening groups, respectively), the mean (± SD) baseline HbA1c levels were similar in both groups (6.9 ± 0.6% and 6.9 ± 0.7% for Morning and Evening groups, respectively) and slightly increased over the treatment period as for the overall population: + 0.30% (± 0.55%) and + 0.20% (± 0.54%) in the Morning and Evening groups respectively; the estimated between-group difference (± SE) of 0.098% (± 0.08%), 95% CI [-0.06 ; 0.26%] was not clinically relevant.

Secondary assessment criteria

In the FAS, FPG results were consistent with those observed with HbA1c. Mean ± SD FPG values were similar in the Morning and Evening groups at baseline (8.04 ±1.8 and 7.90 ± 1.8 mmol/L) and at the last post-baseline value (8.8 ± 1.8 and 8.4 ± 2.0 mmol/L respectively). A slight mean (± SD) increase of + 0.7 (± 1.9) mmol/L and + 0.4 (± 1.7) mmol/L was observed in the Morning and Evening groups respectively, with a non-clinically relevant difference (± SE) between groups: 0.31 (± 0.19) mmol/L, 95% CI [-0.06 ; 0.69 mmol/L]. Results were similar in the "metformin 2000 mg" subset with an increase over the treatment period that was slightly higher in the Morning *versus* the Evening groups (+1.0 ± 2.0 *versus* 0.5 ± 1.7 mmol/L) with a non-clinically relevant between-group difference of 0.56 ± 0.25 mmol/L, 95% CI [0.07 ; 1.06 mmol/L]).

Results in the PPS were similar to those observed in the FAS.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Adverse events during the run-in period** (in which all patients received metformin XR in the evening): 48 patients (17.5%) reported 74 AEs, mainly nasopharyngitis (10 patients, 3.6%), hypoglycaemia (7 patients, 2.6%, 8 episodes), and headache, GGT increased and pruritus (all in 3 patients, 1.1%). Hypoglycaemia events were all symptomatic, mild in intensity, with capillary blood glucose values ranging from [3.2 to 5.0 mmol/L]; 4 of these events were not to be considered as hypoglycaemia according to EMA criteria (blood glucose value > 3.9 mmol/L). Trigger factors were reported in all but 1 event. Serious adverse events (SAEs) were reported in 2 patients (1 event of aortic valve stenosis and 1 atrial fibrillation); both were considered unrelated to treatment according to the investigator.
- **Emergent adverse events during the treatment period (after randomisation):** the proportion of patients reporting at least one emergent adverse event (EAE) was similar in the two treatment groups: 26 patients (19.3%) and 29 patients (20.9%) in the Morning and Evening groups respectively. The nature and the distribution of EAEs were similar in the two groups except for the system organ class (SOC) metabolism and nutrition disorders, with a higher proportion of patients reporting hypoglycaemia in the Morning group (11 patients, 8.1%, 25 events) compared to the Evening group (2 patients, 1.4%, 2 events).

  Emergent hypoglycaemia: none were severe**.** Events were symptomatic, of mild intensity, mainly occurring between 1 pm and 6:30 pm (23/27 events).
  Overall 25/27 events (24 in the Morning group *versus* 1 in the Evening group) were documented with glucose values before sugar intake ranging from 2.8 to 4.5 mmol/L:
  - A total of 7 events, all in the Morning group, were not considered as hypoglycaemia according to EMA classification (blood glucose > 3.9 mmol/L): if excluded, patients with confirmed documented hypoglycaemia (blood glucose ≤ 3.9 mmol/l) were 10 (17 events) *versus* 1 (1 event).
  - Only 3 patients (2 patients, 2 events versus 1 patient, 1 event in the Morning and Evening groups respectively) had values below 3 mmol/L.
  - For the 2 events not documented, 1 occurred in the Morning group (blood sampling not done) and 1 in the Evening group (blood glucose value of 13.8 mmol/L measured after sugar intake).

  Most episodes were associated with trigger factors (22/25 events *versus* 1/2 in the Morning and Evening groups respectively, especially missed/delayed meal or meal with no carbohydrates) in patients with well-controlled HbA1c ≤ 7.1% (9/11 *versus* 1/2 patients); Events without trigger factors (4) occurred in very well-controlled patients (2 patients *versus* 1 in the Morning and Evening groups respectively; HbA1c below 6.6%).

  Most hypoglycaemia events occurred in the metformin 2000 mg subset (20/25 events in 8 patients *versus* 1/2 events in 1 patient). The other 6 hypoglycaemia events occurred in 4 patients of the 2 other subsets (2 patients *versus* 1 in 1000 mg and 1 *versus* 0 in 1500 mg subsets). The imbalance in patient numbers between the 3 subsets did not allow assessment of a dose-effect relationship on hypoglycaemia occurrence.

  The frequency of patients affected by hypoglycaemia was lower in patients receiving gliclazide (3.2% overall, 4 patients in the Morning group) compared to those receiving glimepiride (6.2% overall, 7 patients in the Morning group and 2 in the Evening group).

  Gastrointestinal disorders, which are known to be associated with metformin intake, were low and similar in the 2 treatment groups; the most frequently reported EAE was diarrhoea (3 patients, 2.2%, 3 events *versus* 4 patients, 2.9%, 5 events in the Morning and Evening groups respectively).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Other EAEs were reported with a low frequency (similar in both groups) and concerned nasopharyngitis, influenza, hypertension, upper respiratory tract infection and oropharyngeal pain.

Most EAEs (84%) were of mild intensity; One EAE was rated as severe and was an SAE (hypertensive crisis which was not related to treatment according to the investigator). Overall, 4 patients (1.5%; all in the Evening group) experienced 5 EAEs considered to be related to the study drug: diarrhoea in 3 patients and 1 event each of dyspepsia and decreased appetite in 1 patient. Only 1 patient in the Evening group had an event leading to study drug withdrawal (diarrhoea). The majority of EAEs resolved.

There were no deaths during the study.

- **Laboratory tests, other safety evaluation:** There were no clinically relevant changes or differences between groups over time in any of the biochemical or haematological parameters. Emergent potentially clinically significant abnormal (PCSA) values were reported in a low number of patients: 1 in the Morning group (GGT increased) *versus* 7 in the Evening group (potassium, ALAT, GGT, eosinophils and white blood cell [WBC] count increase).

No clinically relevant change was detected for vital signs and weight.

CONCLUSION

This international exploratory study was conducted in 274 type 2 diabetic patients previously treated with metformin on top of sulfonylurea and with optimally or sub-optimally controlled HbA1c. The study showed that the efficacy of metformin XR plus sulfonylurea on HbA1c evolution over the treatment period was similar whatever its time of administration (morning or evening). The incidence of emergent hypoglycaemia, all symptomatic and of mild intensity, was higher in the Morning group than in the Evening group (usual timing of metformin XR administration). Most episodes occurred in patients with well-controlled HbA1c receiving the maximal metformin XR daily dose of 2000 mg, and were associated with trigger factors (mainly poor compliance to lunch intake); no between group difference was observed in the 2 other subsets (metformin XR 1000 or 1500 mg). The nature and incidence of other EAEs was similar in the metformin XR Morning and Evening groups with no unexpected events.

Date of the report: 20 December 2013