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BRIEF REPORT

Metformin extended-release versus immediate-release: An international, randomized, double-blind, head-to-head trial in pharmacotherapy-naïve patients with type 2 diabetes

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This international, randomized, double-blind trial (NCT01864174) compared the efficacy and safety of metformin extended-release (XR) and immediate-release (IR) in patients with type 2 diabetes. After a 4-week placebo lead-in, pharmacotherapy-naïve adults with glycated haemoglobin (HbA1c) at 7.0% to 9.2% were randomized (1:1) to receive once-daily metformin XR 2000 mg or twice-daily metformin IR 1000 mg for 24 weeks. The primary endpoint was change in HbA1c after 24 weeks. Secondary endpoints were change in fasting plasma glucose (FPG), mean daily glucose (MDG) and patients (%) with HbA1c <7.0% after 24 weeks. Overall, 539 patients were randomized (metformin XR, N = 268; metformin IR, N = 271). Adjusted mean changes in HbA1c, FPG, MDG and patients (%) with HbA1c <7.0% after 24 weeks were similar for XR and IR: -0.93% vs -0.96%; -21.1 vs -20.6 mg/dL (-1.2 vs -1.1 mmol/L); -24.7 vs -27.1 mg/dL (-1.4 vs -1.5 mmol/L); and 70.9% vs 72.0%, respectively. Adverse events were similar between groups and consistent with previous studies. Overall, metformin XR demonstrated efficacy and safety similar to that of metformin IR over 24 weeks, with the advantage of once-daily dosing.

KEYWORDS

glycated haemoglobin, metformin extended-release, once-daily dosing, randomized clinical trial, type 2 diabetes

1 | INTRODUCTION

Metformin, a first-line treatment for patients with type 2 diabetes, is available as an immediate-release (IR) formulation, typically administered several times daily with meals, and an extended-release (XR) formulation, administered once daily.^{1–6} The pharmacokinetic properties of metformin IR are generally comparable to those of the XR formulation.⁷ However, peak plasma concentrations (C_{max}) for metformin IR occur ~3 hours after a single oral 1000-mg dose (mean C_{max} [standard deviation (SD)], 1321 [234] ng/mL), whereas peak plasma concentrations of metformin XR 2000 mg occur within 7 to 8 hours after dosing (mean C_{max} [SD], 1780 [288] ng/mL).⁷ Both

formulations are well tolerated and are effective in reducing glycated haemoglobin (HbA1c) levels as compared to placebo in patients with type 2 diabetes.^{8,9} Previous studies have shown greater patient adherence^{10,11} and indicate improved gastrointestinal (GI) tolerability with metformin XR compared with metformin IR.^{11–13}

Despite widespread use of both metformin IR and XR preparations, only 2 head-to-head clinical trials comparing the safety and efficacy of metformin IR and metformin XR have been conducted, one in the USA and the other in China.^{11,12} However, both studies included patients who had previously received metformin.^{11,12} The Chinese study had an open-label design, comprising a relatively small number of patients and comparing the 2 metformin formulations at

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1500 mg/d over 12 weeks.¹¹ The US study was larger and of a longer duration than the Chinese study and compared metformin XR (at different dosages) with metformin IR at a dose of 1500 mg/d. In the US study, patients previously treated with metformin and a sulphonylurea were permitted.¹² The aim of this trial was to evaluate the efficacy, safety and tolerability of the same 2000 mg daily doses of once-daily metformin XR versus twice-daily metformin IR in pharmacotherapy-naïve patients with type 2 diabetes.

2 | METHODS

2.1 | Study design

This was an international, randomized, parallel-group, double-blind trial (ClinicalTrials.gov identifier: NCT01864174) conducted at 148 sites (June 2013 to June 2016) in North America (USA, Canada, Puerto Rico), Europe (Czech Republic, Germany, Hungary, Poland, Romania, UK) and South Africa. Eligible patients entered a 4-week, single-blind, placebo lead-in period, followed by a 24-week, randomized, double-blind treatment period. Patients were randomized (1:1) to receive either once-daily metformin XR (Glucophage[®] XR, Bristol-Myers Squibb) 2000 mg (with evening meals) or twice-daily metformin IR (Glucophage[®], Bristol-Myers Squibb) 1000 mg (every morning and evening with meals) for 24 weeks. During the double-blind treatment period, metformin XR and IR were titrated from 500 to 2000 mg/d over the first 3 weeks of treatment. Patients who were unable to tolerate 2000 mg/d were down-titrated and re-challenge was attempted, if possible, before week 12. The study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation, and the study protocol was approved by the Institutional Review Board/Independent Ethics Committee at each participating institution.

2.2 | Patients

Patients (≥ 18 years old) who had type 2 diabetes and inadequate glycaemic control with diet and lifestyle advice alone (ie, pharmacotherapy-naïve, defined as no prior pharmacotherapy for glucose lowering within 90 days prior to enrolment and no more than 14 days of glucose-lowering medication) were eligible for inclusion. Key inclusion criteria were: HbA1c, 7.0% to 9.2% at screening; body mass index (BMI) ≤ 45.0 kg/m²; fasting plasma glucose (FPG) < 250 mg/dL (13.9 mmol/L); C-peptide ≥ 1.0 ng/mL at enrolment. Key exclusion criteria were: history of ketoacidosis, lactic acidosis or hyperosmolar non-ketotic coma; marked polyuria; polydipsia with $> 10\%$ weight loss during last 3 months prior to screening/enrolment; and elevated serum creatinine levels. Patients provided written informed consent before participating in the study, which followed the ethical principles of the Declaration of Helsinki.

2.3 | Study assessments

The primary efficacy endpoint was mean change in HbA1c from baseline to week 24, which was also examined by baseline HbA1c subgroup ($< 8\%$, ≥ 8 to $< 9\%$ and $\geq 9\%$). The secondary efficacy endpoints

were mean change in FPG and mean daily glucose (MDG) levels from baseline to week 24 (or last observation carried forward [LOCF] for MDG) and percentage of patients achieving a therapeutic glycaemic response (HbA1c $< 7.0\%$) at week 24. MDG was self-monitored using a 7-point fingerstick blood-glucose test. Mean change in body weight and waist circumference, and mean percentage change in fasting serum lipids from baseline to week 24 were also assessed. Safety assessments included incidence of adverse events (AEs), clinical laboratory evaluations (haematology, blood chemistry, liver function tests, urinalysis) and vital signs. Hypoglycaemia was also assessed; all episodes consistent with the clinical definition of hypoglycaemia as assessed by the investigator were documented. Reasons for discontinuation because of hypoglycaemia included, but were not limited to, a documented fingerstick glucose value ≤ 54 mg/dL (≤ 3.1 mmol/L).

2.4 | Statistical analyses

Given a sample size of 235 patients/group, the study would provide 90% power to demonstrate non-inferiority in change from baseline to week 24 in mean HbA1c (assumed SD, 1.0%; non-inferiority margin, 0.3%; 2-sided $\alpha = 0.05$). Assuming that approximately 10% of patients would not have a post-baseline value, approximately 524 patients would be required for randomization.

The primary efficacy endpoint was analysed using a longitudinal repeated-measures model, which adjusted for baseline HbA1c, treatment group, time, baseline-by-time interaction and time-by-treatment group interaction. Changes in FPG were assessed using the same model. For MDG, changes from baseline to week 24/LOCF were analysed using an analysis of covariance (ANCOVA) model. For the percentage of patients with HbA1c $< 7.0\%$ at week 24, data were analysed using logistic regression,^{14,15} with adjustments for baseline HbA1c. These analyses were performed using data from patients who received at least 1 dose of double-blind study drug during the randomized treatment period (randomized data set). Values prior to initiation of rescue medication were used for analysis of these data. The treated data set includes all patients who received at least 1 dose of double-blind study drug during the treatment period, regardless of rescue.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Of the 1736 patients enrolled, 794 (45.7%) were eligible to enter the placebo lead-in period, of whom 568 patients were randomized (1:1) to receive either once-daily metformin XR (N = 283) or twice-daily metformin IR (N = 285) (Figure S1). The most common reason for study non-eligibility or non-randomization was no longer meeting study criteria (Figure S1). Of those patients who were randomized, 29 were excluded because of study site non-compliance. Thus, the randomized data set became metformin XR (N = 268) and metformin IR (N = 271). Overall, 245 patients in both groups completed the

double-blind period of the study. Baseline demographics and disease characteristics are shown in Table S1.

3.2 | Extent of exposure

Patients receiving once-daily metformin XR and twice-daily metformin IR had similar exposure and total daily doses of study drug (Table S2). Down-titration because of metformin intolerance was implemented in 37 and 108 patients receiving metformin XR and IR, respectively. However, for patients who were down-titrated, up-titrations/rechallenges with higher doses were attempted before week 12. Eight patients received rescue medication (metformin XR, $n = 3$; metformin IR, $n = 5$) (Table S2).

3.3 | Efficacy

Baseline mean (standard deviation) HbA1c was 7.58% (0.6) for metformin XR and 7.76% (0.5) for metformin IR. The adjusted mean change (standard error [SE]) in HbA1c from baseline to week 24 was similar between treatment arms (metformin XR, -0.93% [0.05]; metformin IR, -0.96% [0.05]), resulting in a non-significant difference of 0.03% between groups (95% confidence interval, -0.10 to 0.17) (Figure 1). A subgroup analysis using baseline HbA1c supported this finding (Table S3). Baseline adjusted changes in mean (SE) FPG and MDG levels, and percentage of patients with HbA1c $<7.0\%$ at week 24/LOCF were similar between treatment arms (Table 1), as were changes in body weight, waist circumference and serum lipid profiles (Table S4).

3.4 | Safety and tolerability

Overall, 50.2% (142/283) and 47.4% (135/285) of patients in the metformin XR and IR groups reported at least 1 treatment-emergent AE, respectively (Table S5). Of these, 10.6% and 8.8% were considered treatment-related, respectively. Serious AEs (SAEs) were reported for 2.8% (8/283) and 3.5% (10/285) of patients receiving metformin XR and IR, respectively; only 1 case per group was considered treatment-related. The most common reason for discontinuation because of AEs was GI disorders (metformin XR, 1.4%; metformin IR, 1.4%). The most frequently reported AEs were GI in nature, ie,

diarrhoea, nausea and vomiting (Table S5). There were no clinically meaningful changes in vital signs or standard laboratory variables, including creatinine, hepatic panel and urinalysis parameters.

3.5 | Hypoglycaemia

After 24 weeks of treatment, no hypoglycaemia events were reported in patients receiving once-daily metformin XR compared with 3 patients (1.1%) receiving twice-daily metformin IR. There were 5 events in total: 2 classified as "probable symptomatic hypoglycaemia" and 3 as "relative hypoglycaemia" (according to American Diabetes Association recommendations).

4 | DISCUSSION

Few head-to-head trials have been conducted to establish therapeutic equivalency of metformin IR and XR formulations.^{11,12} We report an international, 24-week, head-to-head trial of metformin XR and IR conducted in pharmacotherapy-naïve patients with type 2 diabetes. The results demonstrate that once-daily metformin XR 2000 mg and twice-daily metformin IR 1000 mg monotherapy have similar efficacy and safety profiles.

The primary efficacy endpoint demonstrated the non-inferiority of metformin XR compared with metformin IR, which was confirmed in subgroup analysis by baseline HbA1c. Results from the 3 secondary efficacy endpoints, change from baseline to week 24 in FPG and MDG and proportion of patients achieving a therapeutic glycaemic response of HbA1c $<7.0\%$ at week 24, supported this finding. In the previously reported 24-week head-to-head study,¹² the mean decrease in HbA1c from baseline to week 24 for once-daily metformin XR 2000 mg was -1.06% , similar to the value reported in this study. Patients in the metformin IR group received a lower dose than was used here (500 mg in the morning and 1000 mg in the evening vs 1000 mg twice daily) and experienced a mean decrease in HbA1c of -0.70% .

Once-daily metformin XR and twice-daily metformin IR were well tolerated, as reported in the literature^{11,12} and product labelling.¹ Notably, the most common AE was diarrhoea in both treatment groups. The frequency of nausea was slightly higher with metformin XR than with metformin IR (4.6% vs 2.8%, respectively), which

FIGURE 1 Adjusted^a mean change (SE) in HbA1c (%) from baseline to week 24 for patients receiving twice-daily metformin IR or once-daily metformin XR (randomized data set)^b. ^aAdjusted for baseline HbA1c, treatment group, time, baseline-by-time interaction and time-by-treatment group interaction and ^bexcluding data after rescue medication. Abbreviations: HbA1c, glycated haemoglobin; IR, immediate release; SE, standard error; XR, extended release

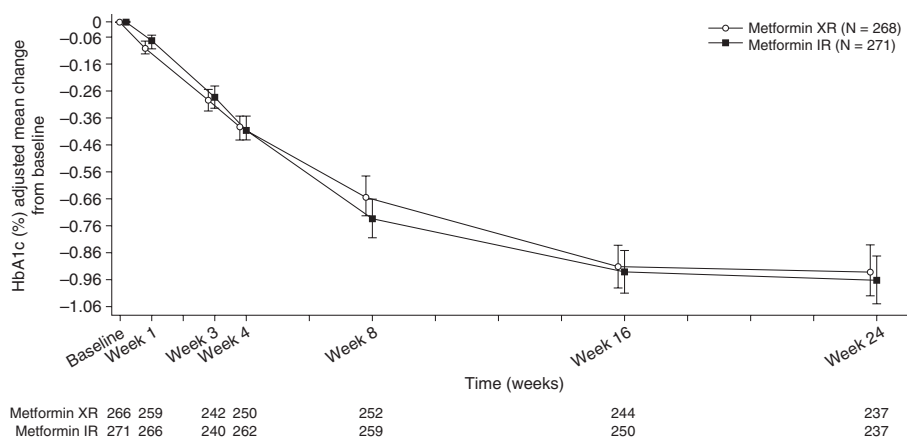


TABLE 1 Adjusted mean changes in secondary efficacy endpoints from baseline to week 24 (randomized data set)^a

Secondary efficacy endpoint	Metformin XR 2000 mg QD (N = 268)	Metformin IR 1000 mg BID (N = 271)	Difference (95% CI)
FPG, mg/dL			
Baseline, mean (SD)	153.8 (30.7)	157.9 (33.0)	-
Week 24, mean (SD)	131.9 (31.2)	134.9 (27.9)	-
Adj mean change from baseline (SE) ^b	n = 228	n = 229	
	-21.1 (1.8)	-20.6 (1.8)	-0.5 (-5.5 to 4.5)
MDG, mg/dL			
Baseline, mean (SD)	161.4 (29.8)	169.9 (31.5)	-
Week 24 (LOCF), mean (SD)	139.3 (26.2)	140.4 (26.0)	-
Adj mean change from baseline (SE) ^c	n = 211	n = 218	
	-24.7 (1.6)	-27.1 (1.6)	2.4 (-2.0 to 6.8)
Patients achieving HbA1c <7.0%			
Week 24, patients (%)	n = 237	n = 237	
	174 (73.4)	166 (70.0)	-
Week 24, adjusted % (SE)	70.9 (2.8)	72.0 (2.9)	-1.1 (-8.7 to 6.5)

Abbreviations: Adj, adjusted; BID, twice daily; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IR, immediate release; LOCF, last observation carried forward; MDG, mean daily glucose; QD, once daily; SD, standard deviation; SE, standard error; XR, extended release.

n values are number of randomized patients who had non-missing baseline values and values at week 24.

Data are adjusted mean changes from baseline, except for the responder rate (reported as percentage of patients achieving HbA1c <7.0% at week 24; percentage adjusted for baseline HbA1c).

^a Excluding data after rescue medication.

^b Metformin XR vs metformin IR, -1.2 vs -1.1 mmol/L.

^c Metformin XR vs metformin IR, -1.4 vs -1.5 mmol/L.

contrasts with the previous head-to-head trials^{11,12}; however, overall, nausea was reported by few patients in both groups. Moreover, AEs and SAEs leading to study discontinuation were reported for fewer than 5% of patients in both treatment groups.

In this study, down-titration because of metformin intolerance¹ was necessary in almost 3 times as many patients treated with metformin IR compared with metformin XR. The reduced requirement for down-titration from 2000 mg/d with metformin XR, in addition to the once-daily dosing regimen, may help to improve the patient and physician experience. Patients in this study were highly selected (a large proportion of patients did not meet the study criteria) and were motivated to comply with medication; however, outside of a controlled study setting, the potential patient compliance benefits of once-daily vs twice-daily dosing are more likely to become apparent.

In conclusion, this international head-to-head trial has demonstrated the therapeutic equivalence of metformin XR and metformin IR over a 24-week period in pharmacotherapy-naïve patients with type 2 diabetes, and confirms metformin XR as an important treatment option for patients in whom dosing frequency could affect medication compliance and compromise treatment outcomes.

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Conflict of interests

N. A. and A. S. report no conflicts of interest. C. M. reports advisory/consultancy activities for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly & Company, Novartis AG, Hanmi Pharmaceutical, Intrexon, Janssen Pharmaceutical, MannKind Corporation, Medtronic, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Pfizer, Roche Diagnostics and UCB Pharma; speaker's bureau activities for AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, Merck Sharp & Dohme, Novartis AG, Novo Nordisk and Sanofi; and has received research support from Abbott, Eli Lilly & Company, Intrexon, Merck Sharp & Dohme, Novartis AG, Novo Nordisk, Roche Diagnostics and Sanofi. E. M. reports advisory/consultancy activities for AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, GlaxoSmithKline, Intarcia Therapeutics, Inc., Janssen Pharmaceutical, Laboratoires Servier, Merck Sharp & Dohme, Novo Nordisk and Sanofi. A. F. H. P. reports advisory/consultancy activities for AstraZeneca, Berlin-Chemie, Novo Nordisk, Eli Lilly & Company and Sanofi. J. Z., E. J. and N. I. are employees and stockholders of AstraZeneca. C.B. reports advisory/consultancy activities for Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Elcelyx, Eli Lilly & Company, Johnson & Johnson, Merck Sharp & Dohme, Novo Nordisk, Poxel and Sanofi.

Author contributions

All authors fulfill the authorship criteria of the International Committee of Medical Journal Editors by substantial contribution to the conception and design, to acquisition of the data, or to the analysis

and interpretation of the data. All authors have made a substantial contribution to drafting the article or reviewing it critically. All authors have given final approval of this version of the article to be published.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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