

## RESEARCH ARTICLE

# Bioequivalence of a pioglitazone–glimepiride combination tablet versus coadministered single-dose pioglitazone and glimepiride in healthy Japanese subjects

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### Practice Points

- Combination therapy with pharmacological agents that either stimulate insulin secretion (e.g., sulfonylureas) or improve insulin resistance (e.g., thiazolidinediones) is widely used in patients with Type 2 diabetes mellitus (T2DM).
- Fixed-dose combinations provide greater dosing convenience for patients and have the potential to improve treatment compliance.
- In adult male Japanese volunteers, the fixed-dose combination of pioglitazone–glimepiride 30/3 mg was bioequivalent to coadministration of the individual components at the same doses.
- Fixed-dose pioglitazone–glimepiride 30/3 mg was well tolerated.
- Fixed-dose pioglitazone–glimepiride has the potential to improve medication compliance in patients with T2DM who require combination therapy.

**SUMMARY** For patients with Type 2 diabetes mellitus (T2DM) who require combination antidiabetic drug therapy to achieve glycemic control, fixed-dose combinations have the potential to improve compliance. The objective of this study was to assess the bioequivalence of a fixed-dose combination of pioglitazone (PIO) 30 mg and glimepiride (GLIM) 3 mg relative to coadministered PIO 30 mg and GLIM 3 mg tablets. In an open-label, randomized, two-period, crossover study, 72 healthy Japanese men aged 20–35 years received a single dose of either the combination PIO/GLIM 30/3 mg tablet or coadministered PIO 30 mg and GLIM 3 mg tablets, followed by the alternative formulation after a washout period of  $\geq 6$  days. The primary pharmacokinetic end points were  $C_{\max}$  and  $AUC_{0-72h}$  of unchanged PIO, and  $C_{\max}$  and  $AUC_{0-48h}$  of unchanged GLIM. Bioequivalence was assessed by analysis of variance (ANOVA) using natural log-transformed  $C_{\max}$  and AUC values. The time courses of plasma concentrations of unchanged PIO and GLIM were similar for the fixed-dose combination and coadministered PIO 30 mg and GLIM 3 mg tablets. Application of ANOVA for natural log-transformed data indicated that 90% confidence intervals for the differences between formulations were entirely within the bioequivalence limit of  $\ln(0.80)$  to  $\ln(1.25)$ . Both formulations were equally well tolerated. A fixed-dose combination PIO/GLIM 30/3 mg tablet was bioequivalent to coadministration of PIO 30 mg and GLIM 3 mg in healthy Japanese males, and was as well tolerated.

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As Type 2 diabetes mellitus (T2DM) is characterized by a decline in insulin secretion as well as insulin resistance, combinations of pharmacological agents with complementary modes of action that either stimulate insulin secretion or improve insulin sensitivity are widely used in clinical practice for achieving glucose control in patients not adequately controlled by one agent alone [1,2]. Among agents that stimulate insulin secretion are sulfonylureas such as glimepiride (GLIM), glibenclamide, gliclazide and glipizide, while among agents that improve insulin sensitivity are thiazolidinediones such as pioglitazone (PIO). This latter group of drugs are agonists of peroxisome-proliferator activated receptor  $\gamma$ , a specific nuclear receptor that regulates the transcriptional activity of target genes that play a role in the metabolism of glucose and lipids [3,4]. In patients with T2DM, PIO has been shown to increase insulin sensitivity in hepatic and adipose tissue as well as insulin-stimulated glucose uptake in peripheral tissues [5–7]; it also decreases triglycerides and increases high-density lipoprotein cholesterol [8–10]. Additive effects on glycemic profiles have been demonstrated in randomized clinical trials when PIO was used in combination with sulfonylurea drugs, metformin, repaglinide and insulin [4].

In patients with T2DM who require combination therapy to achieve adequate glycemic control, fixed-dose combinations have the advantage of providing greater dosing convenience for patients, and thereby potentially improving medication compliance. In recent years, several fixed-dose combinations of antidiabetic drugs have been developed, such as those containing PIO and GLIM, rosiglitazone and metformin, metformin and glyburide, and metformin and glipizide. In the USA and Europe, fixed-dose combinations of PIO and GLIM containing 30 mg of PIO with either 2 or 4 mg of GLIM have been approved. A bioequivalence study with the 30/4 mg fixed-dose combination of PIO/GLIM in the USA (predominantly in Caucasian subjects) showed that this combination is bioequivalent to PIO 30 mg and GLIM 4 mg administered concomitantly as commercially available tablets [11]. In Japan, fixed-dose combinations of PIO with a lower dose of GLIM (i.e., as tablets of 15/1 mg and 30/3 mg) have been developed to reduce the risk of hypoglycemia in Japanese patients.

The objective of the present study was to assess the bioequivalence of a fixed-dose combination

tablet containing PIO 30 mg and GLIM 3 mg (test treatment) administered as a single dose relative to coadministration of PIO 30 mg and GLIM 3 mg tablets (reference treatment) in adult Japanese male volunteers. A crossover design for the study was adopted to minimize the influence of interindividual variability.

## Methods

An open-label, randomized, two-period, crossover study was undertaken at a single site in Tokyo, Japan between October 2007 and November 2007 in healthy Japanese men. Subjects received either the test treatment (fixed-dose PIO/GLIM 30/3 mg combination) or the individual components (reference treatment) in the first study period. This was followed by the alternative treatment in the second period after a washout period of  $\geq 6$  days.

### ■ Study participants & medications

Healthy Japanese men aged 20–35 years with a bodyweight of  $\geq 50$  kg, a BMI of  $\geq 18.5$  to  $< 25$  kg/m<sup>2</sup>, and negative tests for hepatitis B and C infection, HIV infection and syphilis were recruited to the study. Exclusion criteria included a current, or history of any, disorder considered inappropriate for participation, a history of drug hypersensitivity or allergy, a history of drug or alcohol abuse, poor peripheral venous access, use of any medicinal product (including over-the-counter drugs and herbal products) within 4 weeks of the first dose of study medication, and consumption of grapefruit juice/products or any food or beverage containing caffeine within 72 h of the first dose of study medication.

Following screening (days -28 to -2), participants underwent a physical examination and were admitted to hospital (on day -1) for a period of 5 days (4 nights). On the morning of day 1 in the first treatment period, subjects were randomized (via a subject allocation code table) to receive either a fixed-dose PIO/GLIM 30/3 mg tablet or coadministration of a PIO 30 mg tablet (Actos; Takeda Pharmaceutical Co.) and a GLIM 3 mg tablet (Amaryl; Sanofi-Aventis) at 9 a.m. after an overnight fast of at least 10 h. At 1 h and 2.5 h after drug administration, subjects also received 20 g of glucose orally to prevent hypoglycemia. Blood samples for determination of plasma drug concentrations were taken prior to drug administration and at 0.25 (for PIO only), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 (for PIO only), 6, 8, 10 (for PIO only), 12, 16

(for GLIM only), 24, 36 (for PIO only), 48 and 72 h (for PIO only) after administration. As the elimination half-lives of active metabolites of PIO are much longer than that of GLIM and its metabolites [4–12], determination of plasma concentrations was extended to 72 h for PIO but was concluded at 48 h for GLIM.

On day 4, subjects were discharged from hospital. After a washout period of  $\geq 6$  days, they were subsequently readmitted to hospital for a further 5 days/4 nights for treatment period 2 when they received the alternative formulation (coadministration of PIO 30 mg and GLIM 3 mg tablets or a combination PIO/GLIM 30/3 mg tablet) and underwent the same assessment procedures as in treatment period 1.

#### ■ Determination of plasma pioglitazone & glimepiride concentrations

Plasma concentrations of unchanged PIO and its principal metabolites (M-II, M-III and M-IV) and unchanged GLIM and its metabolites (M1 and M2) were measured by high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) at Toray Research Center Inc., Tokyo. For determination of plasma drug concentrations, venous blood samples (3 ml) were obtained at each scheduled time point. Each sample was made homogenous by rotating it five to six times. Blood samples were then centrifuged at 4°C at 3000 rpm for 10 min to separate the plasma. Plasma was stored frozen until assayed.

#### Pharmacokinetic parameters

Pharmacokinetic parameters for PIO and GLIM were determined by non-compartmental analysis. The primary end points were the maximum observed plasma concentrations ( $C_{\max}$ ) of unchanged PIO and GLIM, and the area under the plasma concentration–time curve from time 0 to 72 h ( $AUC_{0-72h}$ ) of unchanged PIO and area under the plasma concentration–time curve from time 0 to 48 h ( $AUC_{0-48h}$ ) of unchanged GLIM.

Secondary pharmacokinetic parameters included the area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration ( $AUC_{0-t_{lqc}}$ ), the area under the plasma concentration–time curve from time zero to infinity ( $AUC_{0-\infty}$ ), time to reach maximum plasma concentration ( $t_{\max}$ ), mean residence time (MRT), the apparent terminal elimination rate

constant ( $\lambda_z$ ), apparent elimination half-life, and the apparent clearance (CL/F) of unchanged PIO and unchanged GLIM.

#### Safety assessment

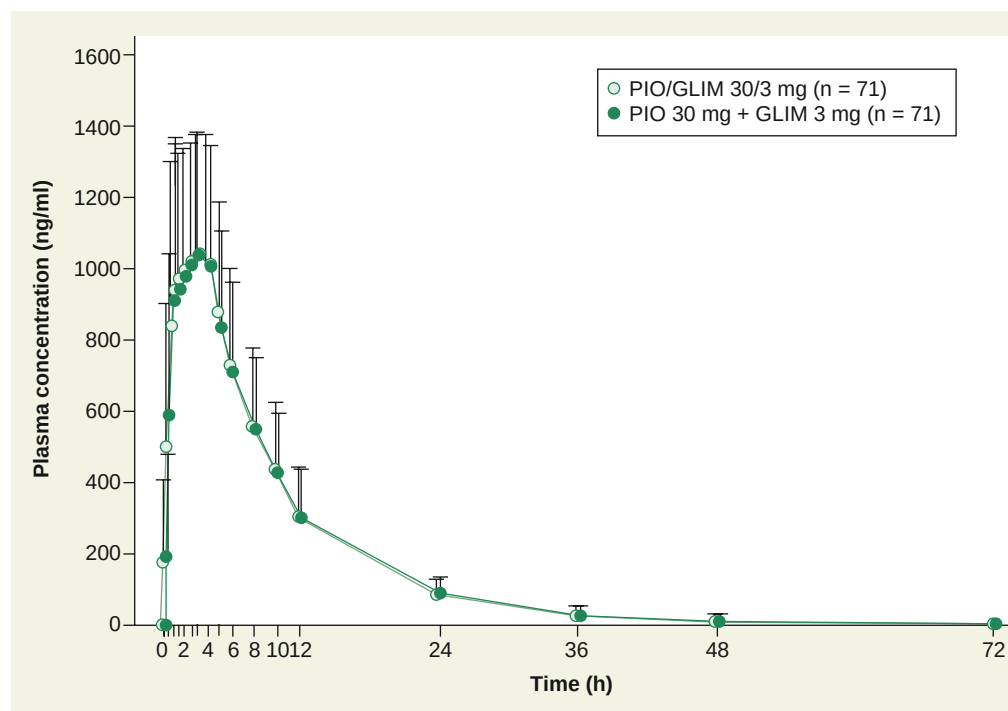
Safety evaluations performed during each treatment period included: monitoring subjects for the occurrence of adverse events; routine laboratory test (hematology, serum chemistry, urinalysis) results; electrocardiographic (ECG) and physical examination findings; vital signs; and changes in bodyweight.

#### Statistical analysis

The pharmacokinetic analysis was performed in the ‘pharmacokinetic data analysis population’ (i.e., all subjects who received study medications and completed the study without protocol deviation), while the safety analysis was performed in the ‘safety data analysis population’ (i.e., all subjects who received at least one dose of study medications). For the pharmacokinetic analysis, descriptive statistics were used to summarize the plasma concentrations of unchanged PIO and its metabolites (M-II, M-III and M-IV) and unchanged GLIM and its metabolites (M1 and M2) at each evaluation point. In addition, plots of mean ( $\pm$  standard deviation) concentration-versus-time curves were produced, and descriptive statistics were used to summarize the pharmacokinetic parameters of each formulation.

Determination of bioequivalence was based on the Japanese Guideline for Bioequivalence Studies of Generic Products [13]. Analysis of variance (ANOVA) was performed using natural log-transformed  $C_{\max}$  and  $AUC_{0-72h}$  values for unchanged PIO, and natural log-transformed  $C_{\max}$  and  $AUC_{0-48h}$  values for unchanged GLIM, with sequence, formulation and treatment period as fixed effects and random effects for subjects nested within sequences. Confidence intervals (CI; confidence coefficient: 90%) for differences between the formulations and treatment periods were then calculated. In addition, differences between the formulations were also examined by applying ANOVA for natural log-transformed  $AUC_{0-\infty}$ ,  $\lambda_z$  and MRT values and non-log transformed  $t_{\max}$  values.

The sample size for the bioequivalence assessment was based on 72 subjects (36 subjects in each group), as the required number of subjects was calculated to be 29 to 35 subjects per group (total of 58 to 70 subjects) when the



**Figure 1. Mean plasma concentrations (and standard deviations) of unchanged PIO over 72 h following single-dose administration of a combination PIO/GLIM 30/3 mg tablet and coadministration of PIO 30 mg and GLIM 3 mg tablets in 71 healthy Japanese males.**

GLIM: Glimepiride; PIO: Pioglitazone.

level of significance, alternative hypothesis and power of the test were set as 0.05,  $\mu = 0.93 - 1.07$  and 90%, respectively, based on two one-sided  $t$  tests [ $H_0: \log(\mu) \leq \log(\theta_1), \log(\mu) \geq \log(\theta_2)$ ;  $H_1: \log(\theta_1) < \log(\mu) < \log(\theta_2)$ ] and assuming that the residual sum of squares of pharmacokinetic parameters in this study was in the range of 0.28–0.30.

### Results

A total of 139 subjects were screened, 86 of whom were enrolled in the study. Of these, 72 subjects received the study medications and 14 were not treated. The mean age of the treated subjects was  $25.0 \pm 3.86$  years (range: 20–34 years), mean body weight was  $62.5 \pm 6.04$  kg (range: 50.3 to 79.0 kg) and mean BMI was  $21.0 \pm 1.61$  kg/m<sup>2</sup> (range: 18.5–24.2 kg/m<sup>2</sup>). The majority were current or ex-smokers (61.1%), consumed alcohol every day or on a few days per week or month (54.2%), and were caffeine consumers (81.9%). During the study, one subject was discontinued due to a protocol violation (concomitant medication for an adverse event), but the remaining 71 subjects completed the study.

### Pharmacokinetic parameters

The time courses of plasma concentrations of unchanged PIO and unchanged GLIM following the fixed-dose combination of PIO/GLIM 30/3 mg were similar to those following coadministration of PIO 30 mg and GLIM 3 mg tablets (Figures 1 & 2). Moreover, the time-courses of plasma concentrations of the M-II, M-III and M-IV metabolites of PIO and the M1 and M2 metabolites of GLIM following administration of the two formulations were also similar (DATA NOT SHOWN).

Mean ( $\pm$  standard deviation) values for the primary pharmacokinetic parameters were similar with the two formulations.  $C_{max}$  values for unchanged PIO and unchanged GLIM were  $1183.2 \pm 364.38$  ng/ml and  $222.5 \pm 64.74$  ng/ml, respectively, following the fixed-dose combination of PIO/GLIM 30/3 mg, as compared with  $1193.9 \pm 380.59$  ng/ml and  $230.4 \pm 83.05$  ng/ml, respectively, following coadministration of PIO 30 mg and GLIM 3 mg. Likewise,  $AUC_{0-t}$  values for unchanged PIO and unchanged GLIM ( $AUC_{0-72h}$  for PIO and  $AUC_{0-48h}$  for GLIM) were also similar for the two formulations –  $11,630.9 \pm 3722.94$  ng•h/ml

and  $1252.1 \pm 382.38$  ng•h/ml, respectively, following the fixed-dose combination of PIO/GLIM 30/3 mg, compared with  $11,574.1 \pm 3894.08$  ng•h/ml and  $1280.0 \pm 423.24$  ng•h/ml, respectively, following coadministration of PIO 30 mg and GLIM 3 mg.

As shown in Table 1, mean ( $\pm$  standard deviation) values for the secondary pharmacokinetic parameters ( $AUC_{0-t_{1/2}}$ ,  $AUC_{0-\infty}$ ,  $t_{max}$ ,  $\lambda_z$ ,  $t_{1/2}$ , CL/F and MRT) for unchanged PIO and unchanged GLIM were also similar for the two formulations.

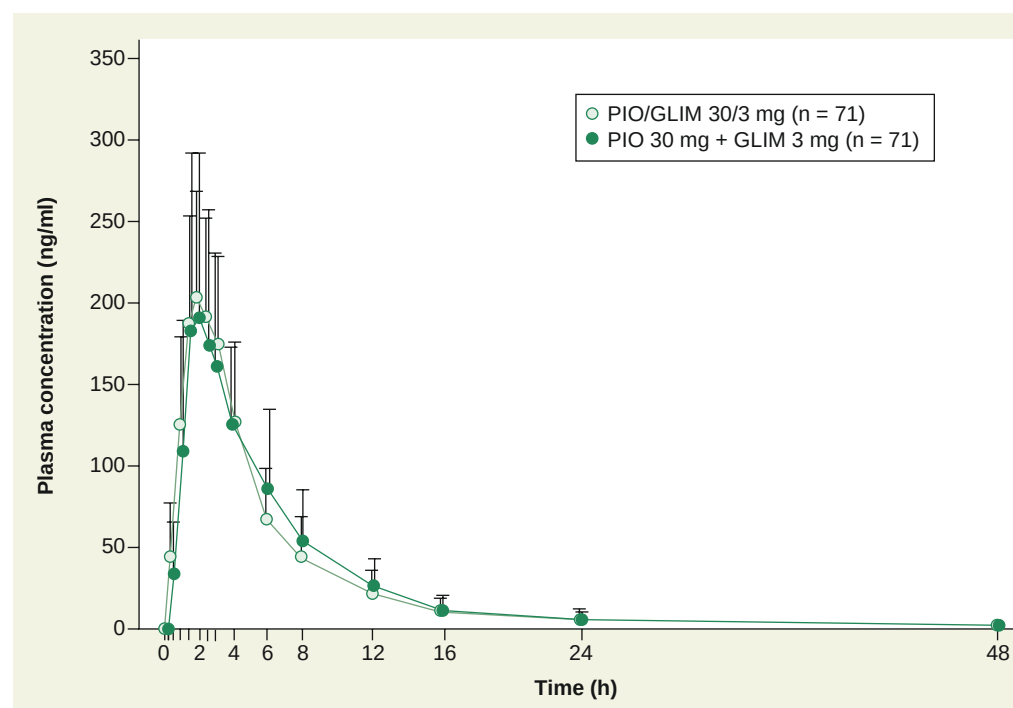
### Evaluation of the bioequivalence of the fixed-dose combination relative to coadministration of the two components

Application of a  $2 \times 2$  crossover ANOVA for natural log-transformed data for  $C_{max}$  and  $AUC_{0-t}$  ( $AUC_{0-72h}$  for unchanged PIO;  $AUC_{0-48h}$  for unchanged GLIM) with sequence, formulation and treatment period as fixed effects and random effects for subjects nested within sequences indicated no significant differences between the first and second treatment periods for unchanged PIO for both  $C_{max}$  and  $AUC_{0-72h}$  ( $C_{max}$ ,  $p = 0.9476$ ;  $AUC_{0-72h}$ ,  $p = 0.9761$ ). For unchanged GLIM, there was a significant

difference between the first and second treatment periods for  $AUC_{0-48h}$  ( $p = 0.0016$ ), but not for  $C_{max}$  ( $p = 0.8507$ ).

The point estimates and 90% CIs for differences between the formulations (fixed-dose PIO/GLIM combination vs the coadministered components) for unchanged PIO and unchanged GLIM are shown in Table 2. The 90% CIs of the differences for  $C_{max}$  and  $AUC_{0-72h}$  for unchanged PIO, and  $C_{max}$  and  $AUC_{0-48h}$  for unchanged GLIM were entirely within the bioequivalence limit of  $\ln(0.80)$  to  $\ln(1.25)$ . Therefore, the fixed-dose PIO/GLIM 30/3 mg combination tablet and the individual component PIO 30 mg and GLIM 3 mg tablets were bioequivalent in this population.

ANOVA was also performed for natural log-transformed  $AUC_{0-\infty}$ ,  $\lambda_z$  and MRT values, and non-log transformed  $t_{max}$  values. For unchanged PIO, there were no statistically significant differences between the formulations for any of these parameters. This was also the case for unchanged GLIM for MRT,  $AUC_{0-48h}$  and  $\lambda_z$ ; however, there was a significant difference between the formulations for  $t_{max}$  ( $p = 0.0008$ ). The difference of the non-log transformed  $t_{max}$



**Figure 2.** Mean plasma concentrations (and standard deviations) of unchanged GLIM over 48 h following single-dose administration of a combination PIO/GLIM 30/3 mg tablet and coadministration of GLIM 3 mg and PIO 30 mg tablets in 71 healthy Japanese males. GLIM: Glimepiride; PIO: Pioglitazone.



of GLIM following the PIO/GLIM 30/3 mg combination tablet was -0.66 h relative to that following coadministration of PIO 30 mg and GLIM 3 mg.

### Tolerability

The safety population comprised 71 subjects who received the fixed-dose combination of PIO/GLIM 30/3 mg and 72 who received coadministered PIO 30 mg and GLIM 3 mg tablets. No adverse events were recorded with the fixed-dose combination, but one subject (1/72; 1.4%) experienced an adverse event with coadministered PIO 30 mg and GLIM 3 mg tablets – a moderate vasovagal syncope that was judged to be drug-related but which resolved. No subjects were withdrawn from the study due to an adverse event, and there were no deaths or any other serious adverse events.

No changes in laboratory tests were considered to be of clinical significance, and there were no clinically relevant abnormal findings in physical examinations, vital signs, bodyweight or ECG findings.

### Discussion

This study used single-dose,  $2 \times 2$  crossover methodology in 72 healthy Japanese adult males to compare the bioequivalence of a fixed-dose PIO/GLIM 30/3 mg combination tablet and coadministered PIO 30 mg and GLIM 3 mg tablets. All 72 subjects received the test medication in the first treatment period, but one subject was subsequently withdrawn from the study due to

use of concomitant medication; 71 subjects therefore completed the study. The time-courses of plasma concentrations of unchanged PIO and its principal metabolites, and of unchanged GLIM and its principal metabolites following the fixed-dose combination tablet, were similar to those following coadministration of PIO 30 mg and GLIM 3 mg tablets. For unchanged PIO, the mean  $C_{\max}$  after the combination and coadministered formulations was 1183.2 and 1193.9 ng/ml, respectively, and the mean  $AUC_{0-72h}$  was 11,630.9 and 11,574.1 ng•h/ml, respectively. For unchanged GLIM, the mean  $C_{\max}$  was 222.5 and 230.4 ng/ml, respectively, and the mean  $AUC_{0-48h}$  was 1252.1 and 1280.0 ng•h/ml, respectively.

On the basis of the current Japanese guideline for establishment of bioequivalence of generic products [13], ANOVA was performed for natural log-transformed  $C_{\max}$  and  $AUC_{0-72h}$  values of unchanged PIO and  $C_{\max}$  and  $AUC_{0-48h}$  values of unchanged GLIM. The point estimate and 90% CIs of the differences between formulations were within the range of  $\ln(0.80)$  to  $\ln(1.25)$ , which is the accepted criterion for bioequivalence. ANOVA was also performed for natural log-transformed  $AUC_{0-\infty}$ ,  $\lambda_z$  and MRT values, and for non-log transformed  $t_{\max}$  as reference parameters. For each of these parameters there was no statistically significant difference between formulations for unchanged PIO, or for  $AUC_{0-\infty}$ ,  $\lambda_z$  and MRT for unchanged GLIM. Although there was a statistically significant difference between formulations for unchanged GLIM

**Table 1. Mean ( $\pm$  standard deviation) pharmacokinetic parameters for unchanged pioglitazone and unchanged glimepiride following single-dose administration of a combination pioglitazone/glimepiride 30/3 mg tablet and coadministration of pioglitazone 30 mg and glimepiride 3 mg tablets in 71 healthy Japanese males.**

| Parameter                          | Unchanged PIO                             |                                   | Unchanged GLIM                            |                                   |
|------------------------------------|-------------------------------------------|-----------------------------------|-------------------------------------------|-----------------------------------|
|                                    | PIO/GLIM 30/3 mg <sup>†</sup><br>(n = 71) | PIO 30 mg + GLIM<br>3 mg (n = 71) | PIO/GLIM 30/3 mg <sup>†</sup><br>(n = 71) | PIO 30 mg + GLIM 3 mg<br>(n = 71) |
| $AUC_{0-t}$ (ng•h/ml) <sup>‡</sup> | 11,630.9 ( $\pm$ 3722.94)                 | 11,574.1 ( $\pm$ 3894.08)         | 1252.1 ( $\pm$ 382.38)                    | 1280.0 ( $\pm$ 423.24)            |
| $AUC_{0-t_{lqc}}$ (ng•h/ml)        | 11,351.8 ( $\pm$ 3729.65)                 | 11,314.3 ( $\pm$ 3883.81)         | 1215.5 ( $\pm$ 388.58)                    | 1249.4 ( $\pm$ 431.91)            |
| $C_{\max}$ (ng/ml)                 | 1183.2 ( $\pm$ 364.38)                    | 1193.9 ( $\pm$ 380.59)            | 222.5 ( $\pm$ 64.74)                      | 230.4 ( $\pm$ 83.05)              |
| $t_{\max}$ (h)                     | 2.59 ( $\pm$ 1.39)                        | 2.36 ( $\pm$ 1.41)                | 2.23 ( $\pm$ 0.74)                        | 2.89 ( $\pm$ 1.54)                |
| $AUC_{0-\infty}$ (ng•h/ml)         | 11,842.2 ( $\pm$ 3607.71)                 | 11,812.1 ( $\pm$ 3907.91)         | 1269.7 ( $\pm$ 426.08)                    | 1278.8 ( $\pm$ 439.54)            |
| $\lambda_z$ (h <sup>-1</sup> )     | 0.107 ( $\pm$ 0.04)                       | 0.108 ( $\pm$ 0.04)               | 0.127 ( $\pm$ 0.058)                      | 0.136 ( $\pm$ 0.054)              |
| Half-life                          | 8.85 ( $\pm$ 9.34)                        | 8.84 ( $\pm$ 8.64)                | 7.53 ( $\pm$ 5.47)                        | 6.28 ( $\pm$ 3.35)                |
| CL/F (l/h)                         | 2.81 ( $\pm$ 1.00)                        | 2.83 ( $\pm$ 1.03)                | 2.58 ( $\pm$ 0.73)                        | 2.57 ( $\pm$ 0.75)                |
| MRT (h)                            | 11.56 ( $\pm$ 9.70)                       | 11.40 ( $\pm$ 8.28)               | 8.21 ( $\pm$ 5.16)                        | 7.34 ( $\pm$ 2.60)                |

<sup>†</sup>Fixed-dose combination tablet.

<sup>‡</sup> $AUC_{0-72h}$  for unchanged pioglitazone;  $AUC_{0-48h}$  for unchanged glimepiride.

GLIM: Glimepiride; MRT: Mean residence time; PIO: Pioglitazone.

**Table 2. ANOVA results for differences between formulations (combination pioglitazone/ glimepiride 30/3 mg tablet and component pioglitazone 30 mg and glimepiride 3 mg tablets) for unchanged pioglitazone and unchanged glimepiride.**

| Drug           | Pharmacokinetic parameter      | Point estimate of differences between formulations <sup>†</sup> | 90% confidence intervals |                         |
|----------------|--------------------------------|-----------------------------------------------------------------|--------------------------|-------------------------|
|                |                                |                                                                 | Lower                    | Upper                   |
| Unchanged PIO  | C <sub>max</sub> , ng/ml       | -0.0034<br>[= ln(0.997)]                                        | -0.0923<br>[= ln(0.912)] | 0.0855<br>[= ln(1.089)] |
|                | AUC <sub>0–72h</sub> , ng•h/ml | 0.0076<br>[= ln(1.008)]                                         | -0.0586<br>[= ln(0.943)] | 0.0739<br>[= ln(1.077)] |
| Unchanged GLIM | C <sub>max</sub> , ng/ml       | -0.0109<br>[= ln(0.989)]                                        | -0.0801<br>[= ln(0.923)] | 0.0583<br>[= ln(1.060)] |
|                | AUC <sub>0–48h</sub> , ng•h/ml | -0.0174<br>[= ln(0.983)]                                        | -0.0447<br>[= ln(0.956)] | 0.0098<br>[= ln(1.010)] |

<sup>†</sup>Fixed-dose combination PIO/GLIM 30/3 mg formulation versus component formulations (PIO 30 mg + GLIM 3 mg).  
GLIM: Glimepiride; PIO: Pioglitazone.

for non-log transformed  $t_{\max}$  (-0.66 h for the combination tablet vs coadministered PIO + GLIM tablets;  $p = 0.0008$ ), this difference is unlikely to be clinically relevant for either glycemic control or the occurrence of adverse events such as hypoglycemia in patients with T2DM. In this regard, Matsuki *et al.* have shown that differences in pharmacokinetic profiles between once-daily and twice-daily doses of GLIM (2 mg once daily vs 1 mg twice daily) each administered for 4 weeks in Japanese patients with T2DM did not result in statistically significant differences in the pharmacodynamic profiles of glycemic parameters such as fasting and postprandial plasma glucose, serum insulin and C-peptide levels [14].

Our findings confirm those of Karim *et al.* who evaluated the bioequivalence of a higher dose combination of PIO/GLIM (30/4 mg) relative to coadministration of commercial PIO 30 mg and GLIM 4 mg tablets in 37 healthy US subjects [11]. Using a four-period, crossover, two-sequence replicate study design, in which participants received both regimens on two different occasions, peak and total exposures (C<sub>max</sub> and AUC) to PIO and GLIM after single doses were similar with intrasubject variabilities of <20%, indicating that the fixed-dose combination was bioequivalent to coadministration of its components [11]. The replicate study design used by these authors has the potential advantage of allowing identification of true outlier subjects (e.g., due to genetic differences in drug metabolism by CYP 2C9) and increases the power of the study when the variability in systemic exposure to a drug is high. However, it also increases the chances

of subjects dropping out of the study and may pose difficulties for statistical analysis when only the initial or repeat administration phases show bioequivalence but the overall study does not. Unlike our study, Karim *et al.* also included female subjects, and showed no significant differences in the systemic exposures of either PIO or GLIM between men and women [11].

Single doses of the fixed-dose combination of PIO/GLIM 30/3 mg were well tolerated in the present study. No adverse events were recorded with this formulation, and only one subject experienced an adverse event with coadministration of the PIO 30 mg and GLIM 3 mg tablets. This subject experienced vasovagal syncope of moderate severity, of which the relationship to study medication could not be ruled out. No clinically significant changes in laboratory tests, physical examinations, vital signs, bodyweight and ECG findings were noted.

In conclusion, the fixed-dose combination PIO/GLIM 30/3 mg tablet was bioequivalent to coadministration of PIO 30 mg and GLIM 3 mg tablets in healthy Japanese men, and was well tolerated. The availability of PIO and GLIM as a fixed-dose combination has the potential to improve medication compliance in patients with T2DM who require combination therapy with these widely used antidiabetic agents.

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### Financial & competing interests disclosure

Financial support for this study was provided by Takeda Pharmaceutical Company Ltd. S Hiroi, K Matsuno, M Hirayama, K Kuriyama are employees of Takeda Pharmaceutical Company Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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### Ethical conduct of research

The study was approved by an Institutional Review Board (IRB) and was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice. Written informed consent forms were obtained from all participating subjects before any study-related procedures were performed. The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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