RESEARCH ARTICLE

Evaluation of the bioequivalence of a fixed-dose combination tablet of pioglitazone–metformin versus commercial tablets in healthy Japanese male volunteers

Shinzo Hiroi*1,3, Kumi Matsuno2, Masashi Hirayama3, Takaki Hayakawa1, Norihito Yoshioka1 & Koji Kawakami3

Practice Points

- Most patients with Type 2 diabetes mellitus (T2DM) will eventually require use of two or more antidiabetic agents to achieve glycemic control.
- Drugs with different mechanisms of action have proved beneficial in this regard, and promising early results have been reported for the combination of pioglitazone and metformin.
- Simplifying administration via use of a fixed-dose combination tablet may help overcome the issue of poor adherence often associated with combination therapy.
- In healthy adult Japanese males, a fixed-dose combination tablet of pioglitazone–metformin 30/500 mg was bioequivalent to co-administration of commercially available pioglitazone 30 mg plus metformin (2 × 500 mg) tablets.
- A fixed-dose pioglitazone–metformin 30/500 mg tablet provides simpler and more convenient treatment for patients with T2DM and has the potential to enhance compliance and thereby improve glycemic control.

SUMMARY

In chronic asymptomatic diseases such as Type 2 diabetes mellitus (T2DM) poor adherence to therapy is a common problem. Simplification of treatment regimens using fixed-dose combination formulations has the potential to improve patient compliance. In this randomized, crossover, single-dose study we evaluated the bioequivalence of a new fixed-dose combination of pioglitazone–metformin (30/500 mg) and commercial tablets (pioglitazone 30 mg plus metformin 2 × 250 mg) in 84 healthy Japanese male volunteers in a fasted state. The plasma concentration–time curves for unchanged pioglitazone and unchanged metformin were almost identical for the two formulations. The 90% confidence intervals for the ratios of maximum observed concentration (Cmax) and area under the plasma concentration–time curve from time 0 to 72 h (AUC0–72) for unchanged pioglitazone, and for Cmax and AUC0–48 of unchanged metformin, were within the 0.80–1.25 range, which meets the criterion for test-to-reference bioequivalence between the two formulations. In conclusion, the fixed-dose combination of pioglitazone–metformin was bioequivalent to pioglitazone and metformin commercial tablets administered separately. This simplified regimen (one vs three tablets) may be clinically useful in patients with T2DM and should help improve patient compliance leading to better glycemic control and improved patient outcomes.

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International guidelines recommend aggressive management of hyperglycemia associated with Type 2 diabetes mellitus (T2DM) to minimize the impact of microvascular and macrovascular complications. This is supported by findings from pivotal UK Prospective Diabetes Studies (UKPDS) [1,2]. In the early stages of the disease, glycemic control can generally be achieved by lifestyle modifications and/or treatment with a single oral antidiabetic drug, such as metformin. With time, however, T2DM progressively deteriorates and is associated with a secondary failure rate of 30–50% over a 3–5-year period [3,4]; within 3–9 years, patients who fail monotherapy will require the addition of at least one more antidiabetic agent [4]. Various combination regimens have been used in clinical practice to improve glycemic control while trying to preserve pancreatic β-cell function and decrease insulin resistance. Drugs with different mechanisms of action have proven beneficial in this regard, and promising early results have been published for the combination of metformin and pioglitazone [5,6].

Pioglitazone is a thiazolidinedione antihyperglycemic agent that has beneficial effects on β-cell dysfunction, lipid metabolism, endothelial function and cardiovascular markers [7–9]. Metformin is a biguanide antihyperglycemic drug that, following publication of the UKPDS, has become a mainstay in the treatment of T2DM, particularly in overweight individuals [1,2,10,11]. Pioglitazone–metformin combination therapy may provide complementary effects in T2DM as these drugs mediate different pharmacological mechanisms to modulate glycemic control and prevent insulin resistance. Pioglitazone increases peripheral glucose uptake while metformin downregulates hepatic gluconeogenesis [12]. These effects may also reduce several cardiovascular risk factors and markers [12]. Indeed, co-administration of metformin and pioglitazone was shown to significantly improve glycemic control, HDL cholesterol, adiponectin and C-reactive protein in a recent randomized, placebo-controlled, parallel-group trial involving Japanese patients with T2DM [6].

Unfortunately, poor adherence to treatment is particularly common in chronic asymptomatic diseases, such as T2DM [13,14]. Simplification of drug administration via the convenience of a fixed-dose combination tablet may help improve compliance, thereby enhancing treatment efficacy and clinical outcomes [14].

The aim of the current study was to evaluate the bioequivalence of a new fixed-dose combination tablet of pioglitazone–metformin relative to that of commercially available tablets (standard pioglitazone and metformin) in healthy adult Japanese men.

Methods

Study design

A randomized, open-label, single-dose, two-sequence, two-period crossover study was performed to compare the pharmacokinetic properties of pioglitazone and metformin administered as a single fixed-dose combination or the equivalent dosage administered as separate pioglitazone and metformin commercial tablets.

Subjects were randomly allocated to sequence one in which they received a fixed-dose combination tablet of pioglitazone–metformin 30/500 mg followed by one tablet of pioglitazone 30 mg plus two tablets of metformin hydrochloride 250 mg, or to sequence two in which they received one tablet of pioglitazone 30 mg plus two tablets of metformin hydrochloride 250 mg followed by a fixed-dose combination tablet of pioglitazone–metformin 30/500 mg. Subjects fasted for 10 h overnight and for 4 h after taking the tablets with 150 ml of water. The washout period between treatments was 6 days. All subjects remained in the clinical research unit for 5 days during each study period.

Subjects

The subjects were healthy adult Japanese male volunteers, aged 20–35 years, and weighing ≥250 kg with a BMI of ≥18.5 kg/m² but <25 kg/m². Physical examination, vital sign measurements, 12-lead electrocardiogram (ECG) and clinical laboratory tests revealed no clinically significant medical conditions.

Subjects were not permitted to have taken any prescription or nonprescription medications, including vitamins or herbal supplements, within 4 weeks prior to the first administration of study medication or during the study. Grapefruit and caffeine-containing foods and drinks were prohibited for 72 h prior to, and during, the study.
Figure 1. Mean (± standard deviation) plasma concentrations of pioglitazone following administration of a fixed-dose combination of pioglitazone–metformin (30/500 mg) tablet or commercial pioglitazone (30 mg) plus metformin (2 x 250 mg) tablets.

**Pharmacokinetic sample collection & analysis**
Venous blood samples (3 ml) were collected prior to study drug administration and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 h after administration. Samples were centrifuged at 4°C at 3000 rpm for 10 min and the plasma fraction was kept frozen at -30°C until assay. Unchanged pioglitazone and its main metabolites (M-II, M-III and M-IV) and unchanged metformin in plasma were measured with high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). Chromatographic separation was performed on an Agilent 1100 HPLC system, equipped with a HTS-PAL autosampler (Agilent Technologies) by using a Symmetry C18 column (3.9 mm id. × 150 mm).

**Table 1. Mean ± standard deviation pharmacokinetic parameters for pioglitazone administered as a fixed-dose combination tablet of pioglitazone–metformin (30/500 mg) or as commercial pioglitazone tablets (30 mg) co-administered with metformin (2 x 250 mg).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed-dose combination: pioglitazone–metformin</th>
<th>Commercial tablets: pioglitazone + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt; (ng·h/ml)</td>
<td>11,242.1 (3679.0)</td>
<td>11,766.3 (3954.8)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-tlqc&lt;/sub&gt; (ng·h/ml)</td>
<td>10,953.6 (3660.2)</td>
<td>11,458.0 (3924.6)</td>
</tr>
<tr>
<td>MRT&lt;sub&gt;0-tlqc&lt;/sub&gt; (h)</td>
<td>9.896 (4.097)</td>
<td>9.467 (3.374)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>1073.1 (407.6)</td>
<td>1197.6 (455.1)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.506 (1.035)</td>
<td>2.421 (1.014)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng·h/ml)</td>
<td>11,604.3 (3662.9)</td>
<td>12,012.3 (4006.8)</td>
</tr>
<tr>
<td>λ&lt;sub&gt;z&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.1021 (0.0382)</td>
<td>0.1027 (0.0362)</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>10.356 (13.656)</td>
<td>8.506 (6.547)</td>
</tr>
<tr>
<td>CL/F (l/h)</td>
<td>2.87 (1.049)</td>
<td>2.82 (1.103)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>13.896 (14.162)</td>
<td>11.796 (6.636)</td>
</tr>
</tbody>
</table>

AUC: Area under the curve; MRT: Mean residence time.
5 μm; Water, Milford). A 20-μl aliquot of each sample was injected onto the HPLC column and eluted with 20% acetonitrile/IPCC-MS3 (100:0.1) at a flow rate of 0.5 ml/min<sup>1</sup>. Mass spectrometric analysis was conducted on an API4000 mass spectrometer (AB/MDS Sciex). The MS parameters for the positive ion polarity mode were optimized as follows: declustering potential 35 V, collision energy 32 V, needle current 4 μA, probe temperature 300°C, dwell time 500 msec/compound, and analysis time 5.5 min. The ion transitions monitored were mass-to-charge ratio (m/z) 800 to 50. The ion source gas (air), curtain gas (nitrogen) and collision gas (nitrogen) were set at 30 psi, 10 psi and eight units respectively. The lower limits of quantification (LLOQ) were 20 ng/ml for unchanged pioglitazone and its

![Figure 2](image)

**Figure 2.** Mean (± standard deviation) plasma concentrations of metformin following administration of a fixed-dose combination pioglitazone–metformin (30/500 mg) tablet or commercial pioglitazone (30 mg) plus metformin (2 × 250 mg) tablets.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed-dose combination: pioglitazone–metformin</th>
<th>Commercial tablets: pioglitazone + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0–48&lt;/sub&gt; (ng·h/ml)</td>
<td>8641.7 (1699.0)</td>
<td>8790.1 (1892.3)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-tlqc&lt;/sub&gt; (ng·h/ml)</td>
<td>8533.1 (1706.1)</td>
<td>8690.2 (1886.0)</td>
</tr>
<tr>
<td>MRT&lt;sub&gt;0-tlqc&lt;/sub&gt; (h)</td>
<td>5.432 (0.774)</td>
<td>5.382 (0.740)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>1426.0 (387.4)</td>
<td>1446.8 (395.9)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.762 (0.950)</td>
<td>2.512 (0.875)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng·h/ml)</td>
<td>8650.6 (1694.4)</td>
<td>8804.1 (1880.8)</td>
</tr>
<tr>
<td>λ&lt;sub&gt;z&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.1705 (0.0413)</td>
<td>0.1620 (0.0372)</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>4.367 (1.404)</td>
<td>4.667 (2.367)</td>
</tr>
<tr>
<td>CL/F (l/h)</td>
<td>60.17 (12.70)</td>
<td>59.33 (12.45)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>5.845 (1.016)</td>
<td>5.800 (1.035)</td>
</tr>
</tbody>
</table>

AUC: Area under the curve; MRT: Mean residence time.
metabolites, and 10 ng/ml for unchanged metformin. Pharmacokinetic parameters for both pioglitazone and metformin were estimated using noncompartmental analysis by WinNonlin Professional version 5.0.1 (Pharsight Corp., CA, USA).

The maximum observed plasma concentration (C_max) and time to reach C_max (t_max) were measured directly from the plasma concentration–time data. The terminal elimination rate constant (λ_z) was calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration–time curve during the terminal elimination phase. The area under the plasma concentration–time curve from time 0 to 72 h (AUC_0–72) for pioglitazone and its metabolites (M-II, M-III and M-IV) and from time 0 to 48 h (AUC_0–48) for metformin, the AUC from time 0 to time of the last quantifiable concentration (AUC_0–tlqc), and the AUC for the first moment plasma concentration–time curve from time 0 to the time of the last quantifiable concentration (AUMC_0–tlqc) were all determined using the linear trapezoidal rule. AUC from time 0 to infinity (AUC_0–inf) was calculated as AUC_0–inf = AUC_0–tlqc + λ_z / λ_z. Mean residence time (MRT) was calculated as MRT = AUMC_0–inf / AUC_0–inf, while MRT_0–tlqc was calculated as MRT_0–tlqc = AUMC_0–tlqc / AUC_0–tlqc. The terminal elimination half-life was calculated as half-life = ln2 / λ_z, while apparent total clearance after extravascular administration (CL/F) was calculated as CL/F = dose / AUC_0–inf.

Outcome measures
Primary end points were AUC_0–72 and C_max for unchanged pioglitazone and AUC_0–48 and C_max for unchanged metformin. Secondary end points included AUC_0–inf, t_max, and λ_z for unchanged pioglitazone and unchanged metformin. Safety parameters included adverse events, vital signs, bodyweight, 12-lead ECG findings and clinical laboratory tests. Plasma concentrations of the three main metabolites of pioglitazone were also evaluated.

**Statistical analysis**

The sample size for the study was estimated based on the probability of meeting the bioequivalence criterion of test-to-reference ratio limits between 0.80–1.25, assuming an analysis of variance (ANOVA) error term variance of 0.1 for the natural-log transformed C_max and AUC of pioglitazone. If the ratio of the central values (μ_test/μ_reference) for C_max and AUC was between 0.93–1.07, 80 subjects would provide a 90% probability for bioequivalence. Assuming subject drop-outs, a sample size of 84 (42 for each sequence) was chosen. The error term variances for natural-log transformed C_max and AUC of metformin could be assumed less than those for pioglitazone.

Statistical analysis was performed using SAS version 8.2 (SAS Institute). An ANOVA with fixed effects for sequence, period and treatment, and random effect for subject nested within sequence was performed on natural-log transformed pharmacokinetic parameters. The t_max was assessed by ANOVA without natural-log transformation. Within the framework of ANOVA, 90% confidence intervals (CIs) were calculated for the ratio of the least squares (LS) means of the fixed-dose combination tablet (test) to the LS means of coadministered commercial tablets (reference) for each pharmacokinetic parameter. If the 90% CIs for AUC_0–72 for pioglitazone, AUC_0–48 for metformin and C_max were within the range of 0.80–1.25, it was concluded that the test and reference formulations were bioequivalent [15].

Descriptive statistics were also calculated for the plasma concentrations of unchanged pioglitazone, its metabolites and metformin, as well as other pharmacokinetic parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_0–72</td>
<td>0.961</td>
<td>0.903–1.022</td>
</tr>
<tr>
<td>C_max</td>
<td>0.897</td>
<td>0.818–0.984</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_0–48</td>
<td>0.986</td>
<td>0.956–1.016</td>
</tr>
<tr>
<td>C_max</td>
<td>0.987</td>
<td>0.945–1.032</td>
</tr>
</tbody>
</table>
Results
In total, 103 subjects were enrolled into the study; 19 were excluded prior to drug administration (ten did not meet entrance criteria, six had pre-treatment adverse events and three voluntarily withdrew from the study). Thus, a total of 84 subjects received study medication and 82 completed the study; two volunteers withdrew for ‘personal reasons’.

Baseline characteristics were similar between the study groups; overall mean age was 25.1 years (range: 20–35 years), bodyweight was 63.5 kg (range: 50.0–79.0 kg) and BMI was 21.4 (range: 18.5–24.7 kg/m²).

Bioequivalence
Mean plasma concentration–time curves of unchanged pioglitazone and metformin following administration of the fixed-dose combination tablet are shown in Figures 1 & 2, and compared with those after administration of commercial tablets. The most important pharmacokinetic parameters are summarized in Tables 1 & 2 for pioglitazone and metformin, respectively.

The fixed-dose combination tablet provided similar $C_{\text{max}}$ and AUC values for both pioglitazone and metformin compared with those for the commercial tablets. The one-sided t-tests for assessing bioequivalence resulted in 90% CIs for test-to-reference ratios within the range of 0.80–1.25 for both pioglitazone and metformin, thus confirming bioequivalence of the fixed-dose combination tablet and corresponding commercial tablets (Table 3). The $t_{\text{max}}$ of metformin was delayed by 0.25 hours following a single dose of the fixed-dose combination (p < 0.05) and, while this result was statistically significant, it was considered unlikely to be of any clinical relevance. There were no other statistically significant differences between the two formulations for other pharmacokinetic parameters.

Plasma concentration–time profiles and pharmacokinetic parameters for the three main metabolites of pioglitazone were similar following administration of the two formulations (Table 4).

Safety
The fixed-dose combination of pioglitazone–metformin and separate pioglitazone and metformin tablets were both generally well tolerated. Thirty-three adverse events (AEs), all mild in severity, were reported in 25 subjects. The proportion of subjects who experienced AEs was similar for those receiving the pioglitazone–metformin combination (14/84: 16.7%) versus those receiving standard pioglitazone and metformin tablets (11/84: 13.1%). Twenty-nine of the AEs were judged by the investigator to be due to study medication; the most frequent of which were diarrhea and lower abdominal pain (11 events: nine diarrhea, two lower abdominal pain following combination tablet administration; and ten events: seven diarrhea, three lower abdominal pain following standard tablets). There were no clinically significant abnormalities in laboratory tests or other safety parameters during the study.

Discussion
This study confirmed the bioequivalence of a new fixed-dose combination tablet of pioglitazone and metformin with pioglitazone and metformin commercial tablets in healthy Japanese men. The 90% CIs for the differences in $AUC_{0-2}$ and $C_{\text{max}}$ for pioglitazone and $AUC_{0-24}$ and $C_{\text{max}}$ for metformin were within the designated bioequivalent range of 0.80–1.25. The pharmacokinetic properties reported here for pioglitazone and metformin following the fixed-dose combination tablet or corresponding commercial tablets are consistent with those from previous studies in healthy adult volunteers [16–20]. The only statistically significant difference in pharmacokinetic parameters found in this study was a small delay of 0.25 h in the $t_{\text{max}}$ of metformin (p < 0.05) following administration of the fixed-dose combination but it is unlikely that this slight prolongation of $t_{\text{max}}$ would be of any clinical significance.

A recent double-blind, placebo-controlled, parallel-group trial assessed the efficacy of combination therapy with pioglitazone (15 and 30 mg) and metformin (500 and 750 mg) in Japanese patients with T2DM [6]. Improved glycemic control and benefits on markers associated with increased insulin resistance were demonstrated with combination therapy compared with metformin alone. Similar promising clinical findings have also been reported with the combination of pioglitazone and metformin in two studies undertaken in the USA [21,22].

It is thought that the potential for pioglitazone–metformin combination treatment to improve clinical parameters of T2DM may be further enhanced if patient compliance can be increased by using a once-daily fixed-dose combination product [23]. The results of our study, which confirm that
Bioequivalence of pioglitazone–metformin fixed-dose combination versus commercial tablets

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Table 4. Mean ± standard deviation pharmacokinetic parameters for the three main metabolites of pioglitazone (M-II, M-III, M-IV) after administration of a fixed-dose combination of pioglitazone–metformin (30/500 mg) or commercial pioglitazone (30 mg) plus metformin (2 × 250 mg) tablets.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed-dose combination: pioglitazone–metformin</th>
<th>Commercial tablets: pioglitazone + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M-II</td>
<td>M-III</td>
</tr>
<tr>
<td>AUC0–24 (h) (ng·h/ml)</td>
<td>380.6 ± 248.8</td>
<td>8112.7 ± 2454.9</td>
</tr>
<tr>
<td>AUC0–Inf (ng·h/ml)</td>
<td>261.2 ± 194.8</td>
<td>8100.3 ± 2475.0</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>8.103 ± 2.102</td>
<td>30.791 ± 2.969</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>29.5 ± 14.6</td>
<td>180.4 ± 58.4</td>
</tr>
<tr>
<td>AUC0–24 (ng·h/ml)</td>
<td>1244.2 ± 590.0</td>
<td>10,930.6 ± 3879.6</td>
</tr>
<tr>
<td>λz (h–1)</td>
<td>0.0415 ± 0.0243</td>
<td>0.0238 ± 0.0067</td>
</tr>
</tbody>
</table>

The elimination rate constant could not be estimated for 36 subjects receiving pioglitazone–metformin combination therapy and for 29 patients receiving standard combination therapy because values were below the lower limit of quantification or there were insufficient data for the elimination phase (M-II).

AUC: Area under the curve; MRT: Mean residence time.

Table 4: Mean ± standard deviation pharmacokinetic parameters for the three main metabolites of pioglitazone (M-II, M-III, M-IV) after administration of a fixed-dose combination of pioglitazone–metformin (30/500 mg) or commercial pioglitazone (30 mg) plus metformin (2 × 250 mg) tablets.

The fixed-dose combination is bioequivalent to co-administration of standard tablets, provide optimism for the prospect of improved compliance and clinical benefit with the newer fixed-dose formulation. Furthermore, other pharmacokinetic studies have reported no effect of food, gender or race on the bioequivalence of the fixed-dose pioglitazone–metformin tablet formulation [19,20]. This adds weight to the potential clinical utility of the fixed-dose combination pioglitazone–metformin tablets in the treatment of T2DM.

The present study involved administration of single doses of medication and, as such, only limited conclusions can be drawn about safety and tolerability. Both formulations were generally well tolerated in our population of healthy Japanese men, and there was little evidence to suggest that they differed with respect to the prevalence or type of adverse events.

In conclusion, the new fixed-dose combination tablet of pioglitazone–metformin 30/500 mg was shown to be bioequivalent to standard administration of pioglitazone 30 mg and two metformin 250 mg tablets. A combination tablet of the two drugs should provide simpler and more convenient treatment for patients with T2DM and has the potential to enhance compliance and improve glycemic control.

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Financial & competing interests disclosure
Financial support for this study was provided by 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.

Assistance with English language was provided by Content Ed Net, funded by Takeda.

Ethical conduct of research
The study was performed at the Japan-General Clinical Pharmacology Laboratory, Tokyo Heart Center Osaki Hospital, in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline on Good Clinical Practice (GCP). The protocol was approved by the Tokyo

future science group
www.futuremedicine.com
Heart Center Ouiki Hospital Institutional Review Board and all subjects provided written informed consent. 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.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest


- Randomized controlled trial demonstrating greater efficacy and similar safety with fixed-dose pioglitazone–metformin combination therapy compared with individual components in US patients with Type 2 diabetes mellitus.
