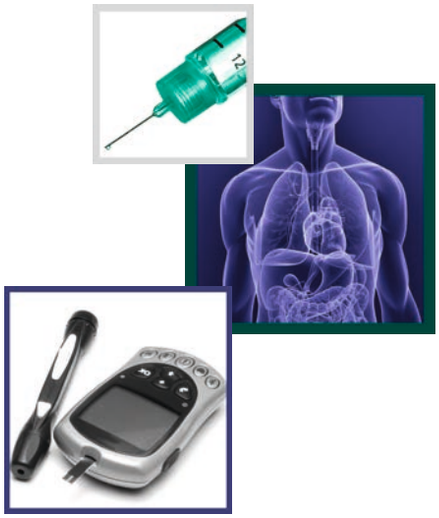
RESEARCH ARTICLE

# Bioequivalence evaluation of pioglitazone orally disintegrating tablet formulation



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**Practice Points**

- Pioglitazone – which has established efficacy in the management of Type 2 diabetes mellitus (T2DM) – has been formulated as an orally disintegrating (OD) tablet.
- A series of studies was conducted in healthy adult males to evaluate the bioequivalence of the pioglitazone OD 30-mg tablet relative to that of a commercially available pioglitazone 30 mg tablet.
- In Japanese volunteers, a pioglitazone OD tablet taken with or without water was bioequivalent to a pioglitazone commercial tablet administered with water, and had low oral mucosal absorption.
- Pioglitazone OD tablets may provide a useful alternative treatment option for patients with T2DM who have difficulty swallowing or are unable to swallow a conventional tablet.
- Ease of use is expected to improve treatment compliance, which is essential for maintaining glycemic control in T2DM.

**SUMMARY** Three studies were performed in healthy Japanese men to compare the bioavailability of an orally disintegrating tablet formulation of pioglitazone (pioglitazone OD tablet) with pioglitazone commercial tablets, and to determine the extent of oral mucosal absorption. In two bioequivalence studies (both n = 64), pioglitazone OD tablets 30 mg were administered without (Study 1) or with water (Study 2), and bioavailability was compared with pioglitazone 30-mg commercial tablets administered with water. In Study 3 (n = 12), the oral mucosal absorption of pioglitazone OD tablet 30 mg was determined by keeping it in the mouth for 2 min. In each study, subjects were randomized into two groups, each receiving the two regimens in a two-sequence, two-period crossover design with a 6-day washout period. Blood samples were collected over 72 h to determine plasma concentrations of unchanged pioglitazone. The 90% confidence interval for the difference in $AUC_{0-72}$ and $C_{max}$ of unchanged pioglitazone following administration of pioglitazone OD tablets with or without water and compared with pioglitazone commercial tablets given with water was always in the range of 0.80–1.25, indicating bioequivalence. Oral mucosal absorption was approximately 4%. In healthy Japanese men, the pioglitazone OD tablet was bioequivalent to pioglitazone commercial tablets, and had low oral mucosal absorption. The pioglitazone OD tablet is expected to provide an alternative treatment option for patients with Type 2 diabetes mellitus who have difficulty swallowing or are unable to swallow a conventional tablet.

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Pioglitazone is an orally active thiazolidinedione antidiabetic agent that acts principally by decreasing insulin resistance; this pharmacological action is attributed to binding to the peroxisome proliferator-activated receptor-γ [1]. In addition to improving glycemic control in patients with Type 2 diabetes mellitus (T2DM), it has been reported that pioglitazone improves lipid metabolism, endothelial function and hypertension, and has beneficial effects on macrovascular end points [1].

Pioglitazone is available as a tablet for once-daily oral administration, which is convenient for many patients. However, patients with some clinical conditions are unable, or find it difficult, to swallow a solid tablet [2,3]. In addition, certain work or social situations can make swallowing a tablet inconvenient. Alternative formulations may therefore be useful for these patients. Relevant to this study, it has been shown that patients have demonstrated a positive preference for oral fast-dissolving tablet formulations (FDTs) compared with conventional oral tablets [4]. FDTs disintegrate rapidly in the mouth and can be taken without water. These characteristics fit in with a modern lifestyle for active patients, for example, during travel when immediate access to water may not be available.

An orally disintegrating tablet formulation of pioglitazone (pioglitazone OD tablets) has recently been developed. The aim of this series of studies was to evaluate the bioequivalence of pioglitazone OD tablets, relative to that of commercially available tablets, in healthy adult Japanese men, and to determine the extent of oral mucosal absorption of pioglitazone from the pioglitazone OD tablet formulation.

## Materials & methods

### Study design

Three randomized, open-label, two-sequence, two-period crossover studies were performed to evaluate the pharmacokinetics of single doses of the pioglitazone OD tablet and the corresponding commercial tablet.

- Study 1: Bioequivalence of pioglitazone OD tablet administered without water
- Study 2: Bioequivalence of pioglitazone OD tablet administered with water
- Study 3: Determination of oral mucosal absorption of pioglitazone OD tablet

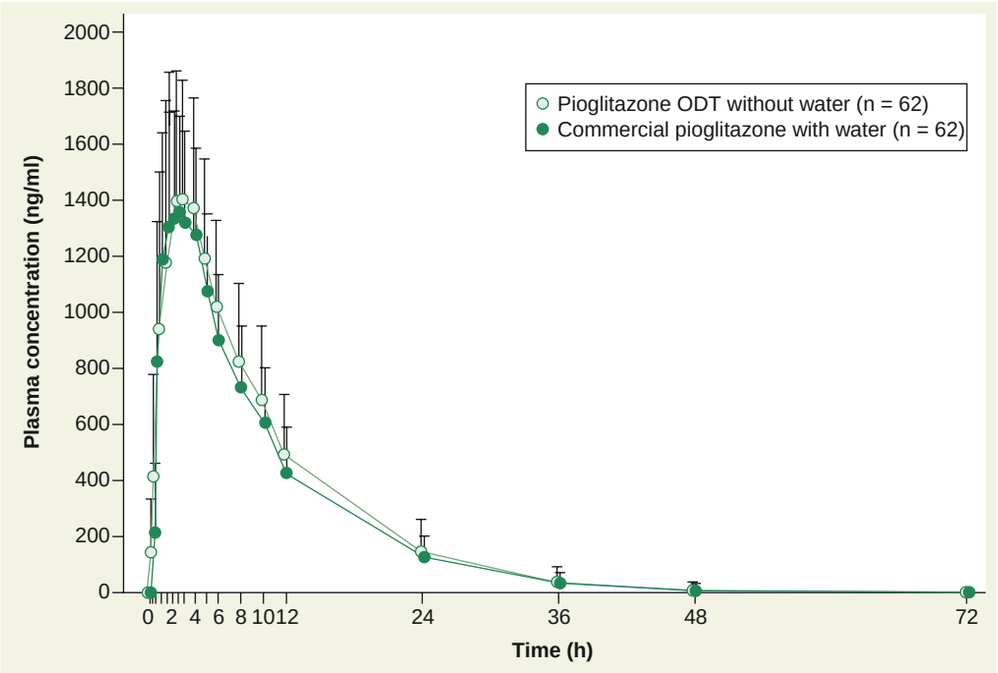


**Figure 1. Mean plasma concentration of pioglitazone following administration of pioglitazone orally disintegrating tablets 30 mg without water and commercial pioglitazone tablets 30 mg with water (Study 1).**
ODT: Orally disintegrating tablet.

**Table 1. Pharmacokinetic parameters for pioglitazone orally disintegrating tablets 30 mg without water compared with commercial pioglitazone tablets 30 mg with water (Study 1).**

| Parameter | Pioglitazone-OD tablet (no water) | Commercial pioglitazone (+water) |
|---|---|---|
| $AUC_{0-72}$ (ng·h/ml) | 16,842.9 (6540.00) | 15,536.7 (4889.06) |
| $AUC_{0-tlqc}$ (ng·h/ml) | 16,512.5 (6522.66) | 15,198.0 (4872.05) |
| $MRT_{0-tlqc}$ (h) | 9.104 (2.1731) | 8.645 (2.2964) |
| $C_{max}$ (ng/ml) | 1548.6 (477.92) | 1468.7 (380.39) |
| $t_{max}$ (h) | 2.726 (1.0852) | 2.105 (1.0368) |
| $AUC_{0-inf}$ (ng·h/ml) | 16,945.3 (6593.21) | 15,666.0 (4920.06) |
| $\lambda_z$ ($h^{-1}$) | 0.1122 (0.02954) | 0.1108 (0.02746) |
| Half-life (h) | 6.727 (2.3160) | 6.788 (2.3785) |
| CL/F (l/h) | 2.00 (0.688) | 2.12 (0.747) |
| MRT (h) | 10.090 (2.5143) | 9.744 (2.7113) |

Mean values (standard deviation) are shown.
AUC: Area under the curve; CL/F: Apparent total clearance after extravascular administration; MRT: Mean residence time; OD: Orally disintegrating.

The studies were all performed at Osaka Pharmacology Clinical Research Hospital (Japan).

Subjects in each study received single oral 30-mg doses of pioglitazone, either as one pioglitazone OD or one commercial tablet, in a fasting state. Two different dosing regimens were investigated for the pioglitazone OD tablet: with 200 ml water (as is recommended for the commercial tablet) or without water to reflect more practical everyday usage. Subjects were hospitalized at the clinical research unit for 5 days and discharged. Following a 6-day washout period, the same subjects returned to the unit to receive the treatment planned for the second crossover period.

To determine oral mucosal absorption of pioglitazone, each subject kept a pioglitazone OD 30 mg tablet in the mouth for 2 min before spitting out the contents, including disintegrated tablet and saliva, and washing their mouths five times with 30-ml portions of water.

## Subjects

Studies 1 and 2 each enrolled 64 subjects, while Study 3 enrolled 12 subjects. The inclusion and exclusion criteria were the same for each study. Participants were healthy adult male Japanese volunteers, aged 20–35 years, and weighing ≥50 kg with a BMI of ≥18.5 $kg/m^2$ but <25 $kg/m^2$. Physical examination, vital sign measurements, 12-lead electrocardiogram (ECG) and clinical laboratory tests revealed no clinically significant medical conditions.

Subjects were prohibited to take any prescription or nonprescription medications, including vitamins or herbal supplements, from 4 weeks before the first administration of study medication until study completion. Grapefruit and caffeine-containing foods and drinks were

**Table 2. Pharmacokinetic parameters for pioglitazone orally disintegrating tablets 30 mg with water compared with commercial pioglitazone tablets 30 mg with water (Study 2).**

| Parameter | Pioglitazone-OD tablet (+water) | Commercial pioglitazone (+water) |
|---|---|---|
| $AUC_{0-72}$ (ng·h/ml) | 15,814.9 (5056.30) | 15,395.7 (4620.05) |
| $AUC_{0-tlqc}$ (ng·h/ml) | 15,520.3 (5036.30) | 15,092.2 (4575.71) |
| $MRT_{0-tlqc}$ (h) | 8.347 (1.4969) | 8.594 (1.6441) |
| $C_{max}$ (ng/ml) | 1521.7 (354.57) | 1466.6 (372.80) |
| $t_{max}$ (h) | 1.935 (0.8707) | 2.298 (1.1031) |
| $AUC_{0-inf}$ (ng·h/ml) | 15,898.6 (5023.32) | 15,493.5 (4621.35) |
| $\lambda_z$ ($h^{-1}$) | 0.1132 (0.02222) | 0.1136 (0.02646) |
| Half-life (h) | 6.362 (1.2685) | 6.565 (2.2457) |
| CL/F (l/h) | 2.08 (0.741) | 2.09 (0.562) |
| MRT (h) | 9.233 (1.5630) | 9.583 (2.0432) |

Mean values (SD) are shown.
AUC: Area under the curve; CL/F: Apparent total clearance after extravascular administration; MRT: Mean residence time; OD: Orally disintegrating.

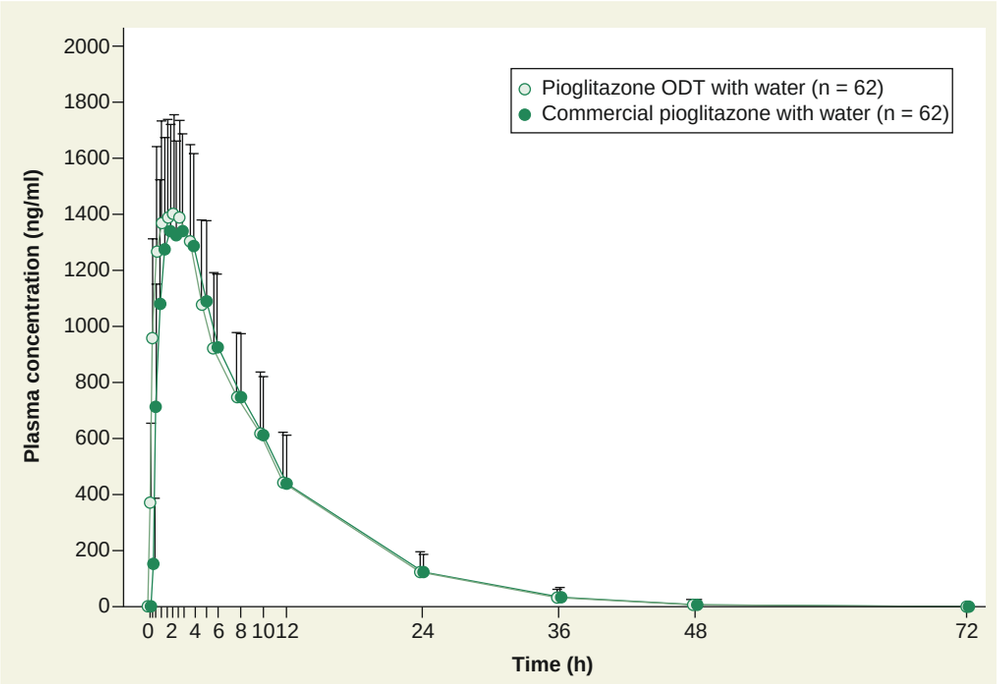


**Figure 2. Mean plasma concentration of pioglitazone following administration of pioglitazone orally disintegrating tablets 30 mg with water and commercial pioglitazone 30-mg tablets with water (Study 2).**

ODT: Orally disintegrating tablet.

also prohibited from 72 h before the study until study completion.

## Pharmacokinetic sample collection & drug concentration determination

Venous blood samples (3 ml) were collected prior to taking the study drug, 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 above -30°C until assay. Plasma concentrations of unchanged pioglitazone and its three major metabolites (M-II, M-III and M-IV) were measured using high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). Chromatographic separation was performed on an Agilent 1100 HPLC system (Agilent Technologies), equipped with a HTS-PAL autosampler (CTC Analytics AG) by using a Develosil C30-UG-5 column (2.0 mm id. × 150 mm, 5 µm; Nomura Chemical Co., Ltd). A 10-µl portion of each sample was injected onto the HPLC column and eluted with methanol/ammonium acetate (10 mmol/l)/formic acid (500:500:1) at a flow rate of 0.25 ml.min$^{-1}$. Mass spectrometric analysis was conducted on an API4000 mass spectrometer (AB/MDS Sciex) with a TurboIonspray source. The MS parameters for the positive ion polarity mode were optimized as follows: ionization voltage: 5000 V; probe temperature: 700°C; dwell time: 150 ms/compound; and analysis time:

**Table 3. Bioequivalence evaluation of unchanged pioglitazone between pioglitazone orally disintegrating tablets administered without (Study 1) or with (Study 2) water and commercial pioglitazone administered with water.**

| Study | Parameter | Point estimate | 90% CI |
|---|---|---|---|
| 1 | $AUC_{0-72}$ | 1.069 | 1.016–1.124 |
| | $C_{max}$ | 1.040 | 0.973–1.112 |
| 2 | $AUC_{0-72}$ | 1.017 | 0.958–1.080 |
| | $C_{max}$ | 1.041 | 0.970–1.117 |

AUC: Area under the curve.

**Table 4. Pharmacokinetic parameters for the three main metabolites of pioglitazone after administration of pioglitazone orally disintegrating tablets 30 mg without water or commercial pioglitazone tablets 30 mg with water (Study 1).**

| Parameter | Pioglitazone ODT (no water) | | | Commercial pioglitazone (+water) | | |
|---|---|---|---|---|---|---|
| | M-II | M-III | M-IV | M-II | M-III | M-IV |
| $AUC_{0-72}$ (ng·h/ml) | 666.8 (392.04) | 11,809.6 (3372.04) | 25,103.8 (5060.23) | 619.8 (325.19) | 11,122.3 (3002.30) | 23,676.3 (4341.39) |
| $AUC_{0\text{-}tlqc}$ (ng·h/ml) | 509.9 (362.19) | 11,809.6 (3372.04) | 25,103.8 (5060.23) | 478.4 (302.45) | 11,113.6 (3025.59) | 23,676.3 (4341.39) |
| $MRT_{0\text{-}tlqc}$ (h)† | 9.587 (3.2549) | 30.079 (2.3205) | 30.224 (2.3478) | 9.003 (3.2391) | 29.708 (2.3768) | 29.882 (2.2428) |
| $C_{max}$ (ng/ml) | 40.5 (13.73) | 271.8 (77.76) | 568.0 (112.73) | 38.5 (11.52) | 251.6 (66.43) | 535.6 (107.02) |
| $t_{max}$ (h)† | 8.279 (2.9616) | 16.742 (6.2958) | 17.032 (7.1677) | 7.475 (3.2094) | 15.645 (6.3918) | 15.097 (6.8202) |
| $AUC_{0\text{-}inf}$ (ng·h/ml)‡ | 1456.0 (873.77) | 14,526.6 (4538.83) | 30,927.2 (7993.89) | 1270.4 (560.01) | 13,749.4 (4002.72) | 28,880.0 (6050.85) |
| $\lambda_z$ ($h^{-1}$)‡ | 0.0441 (0.01899) | 0.0274 (0.00498) | 0.0281 (0.00505) | 0.0466 (0.01996) | 0.0270 (0.00524) | 0.0283 (0.00498) |
| Half-life (h)‡ | 21.387 (23.0671) | 26.199 (5.2975) | 25.683 (6.0510) | 18.830 (11.9439) | 26.939 (6.6344) | 25.426 (5.5472) |
| MRT (h)‡ | 34.407 (33.2947) | 44.637 (8.1532) | 44.564 (9.6492) | 30.200 (17.7120) | 45.141 (10.0981) | 43.895 (8.7322) |

†Plasma concentration of M-II was below the lower limit of quantification (20 ng/ml) at all visits in one subject receiving pioglitazone ODTs and two receiving commercial pioglitazone.
‡Elimination rate constant could not be estimated for 15 subjects receiving pioglitazone ODTs and 14 receiving commercial pioglitazone because values were below the lower limit of quantification or there were insufficient data for the elimination phase (M-II).
Mean values (SD) are shown.
AUC: Area under the curve; MRT: Mean residence time; ODT: Orally disintegrating tablet.

12.0 min. The ion transitions monitored were set at a mass-to-charge ratio (m/z) of 800 to 50. The nebulizer gas (air), heater gas (air), curtain gas (nitrogen) and collision gas (nitrogen) were set to 50 psi, 60 psi, 10 psi and 7 units, respectively. The lower limit of quantification was 20 ng/ml for unchanged pioglitazone and its metabolites.

Pharmacokinetic parameters were determined using noncompartmental analysis by WinNonlin Professional version 5.0.1 (Pharsight Corp.). Maximum observed plasma concentration ($C_{max}$) and time to reach $C_{max}$ ($t_{max}$) were taken directly from the plasma concentration versus time data. The terminal elimination rate constant ($\lambda_z$) was calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration versus time curve during the terminal phase. The area under the plasma concentration versus time curve from 0 to 72 h ($AUC_{0-72}$) and from time 0 to time of the last quantifiable concentration ($AUC_{0\text{-}tlqc}$) were calculated using the linear trapezoidal rule. The area under the plasma concentration versus time from time 0 to infinity ($AUC_{0\text{-}inf}$) was calculated as $AUC_{0\text{-}inf} = AUC_{0\text{-}tlqc} + lqc/\lambda_z$. The terminal elimination half-life was calculated as $\ln 2/\lambda z$, while apparent total clearance after extravascular administration (CL/F) was calculated as $CL/F = Dose/AUC_{0\text{-}inf}$.

## ■ Study end points

Primary end points were $AUC_{0-72}$ and $C_{max}$ for unchanged pioglitazone. Secondary end points included $AUC_{0\text{-}inf}$, $t_{max}$, mean residence time (MRT) and $\lambda_z$ for unchanged pioglitazone. Safety parameters included adverse events, vital signs, bodyweight, 12-lead ECG and clinical laboratory tests. Plasma concentrations of the three main metabolites were also evaluated.

## Statistical analysis

The sample size for Studies 1 and 2 was estimated based on the probability to meet the bioequivalence criterion of test-to-reference ratio limits between 0.80–1.25, assuming an analysis of variance (ANOVA) error term variance of 0.08 for the natural-log transformed $C_{max}$ and AUC of pioglitazone. If the ratio of the central values ($\mu_{test}/\mu_{reference}$) for $C_{max}$ and AUC are between 0.93–1.07, data from at least 58 subjects would provide a 90% probability for bioequivalence. Assuming subject drop-outs, a sample size of 64 (32 for each sequence) was chosen. For Study 3, the sample size of 12 subjects was chosen based on previous studies of absorption via oral mucosa.

For Studies 1 and 2, statistical analyses were performed using SAS version 8.2 (SAS Institute, Carry, NC, USA). 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 subjected to ANOVA without natural-log transformation. Within the framework of ANOVA, 90% confidence intervals were calculated for the ratio of the least squares (LS) means of the pioglitazone OD tablet (test) to the LS means of coadministered commercial tablet (reference) for each pharmacokinetic parameter. If the 90% confidence interval for $AUC_{0-72}$

**Table 5. Pharmacokinetic parameters for the three main metabolites of pioglitazone after administration of pioglitazone orally disintegrating tablets 30 mg with water or commercial pioglitazone tablets 30 mg with water (Study 2).**

| Parameter | Pioglitazone ODT (+water) | | | Commercial pioglitazone (+water) | | |
|---|---|---|---|---|---|---|
| | M-II | M-III | M-IV | M-II | M-III | M-IV |
| $AUC_{0-72}$ (ng·h/ml) | 616.4 (327.80) | 11,441.6 (2780.12) | 24,462.1 (4410.25) | 628.0 (326.40) | 11,686.5 (2930.87) | 24,584.9 (4747.69) |
| $AUC_{0-tlqc}$ (ng·h/ml) | 468.0 (305.82) | 11,441.6 (2780.12) | 24,462.1 (4410.25) | 477.7 (313.53) | 11,686.5 (2930.87) | 24,584.9 (4747.69) |
| $MRT_{0-tlqc}$ (h)† | 8.502 (2.6107) | 29.614 (2.0966) | 29.651 (1.9091) | 8.754 (2.7662) | 29.550 (1.9712) | 29.807 (1.8797) |
| $C_{max}$ (ng/ml) | 38.4 (11.84) | 259.4 (59.65) | 557.7 (104.05) | 39.3 (10.70) | 266.3 (65.01) | 561.6 (110.99) |
| $t_{max}$ (h)† | 7.400 (2.3878) | 16.516 (6.8419) | 14.806 (6.4423) | 7.180 (2.3203) | 15.742 (6.5335) | 15.000 (6.3116) |
| $AUC_{0-inf}$ (ng·h/ml)‡ | 1208.1 (506.13) | 14,149.4 (4353.38) | 29,790.8 (5985.26) | 1517.2 (2831.85) | 14,195.7 (4068.0) | 30,028.4 (6641.21) |
| $\lambda_z$ ($h^{-1}$)‡ | 0.0478 (0.02275) | 0.0275 (0.00561) | 0.0280 (0.00523) | 0.0478 (0.01912) | 0.0281 (0.00475) | 0.0277 (0.00453) |
| Half-life (h)‡ | 18.193 (10.7083) | 26.393 (6.8211) | 25.689 (5.2625) | 22.193 (44.9480) | 25.400 (4.5314) | 25.714 (4.4479) |
| MRT (h)‡ | 29.160 (15.6662) | 44.449 (9.7962) | 43.770 (7.6284) | 35.051 (64.8285) | 43.114 (6.7220) | 43.920 (6.8476) |

†Plasma concentration of M-II was below the lower limit of quantification (20 ng/ml) at all visits in two subjects receiving pioglitazone ODTs and one receiving commercial pioglitazone.
‡Elimination rate constant could not be estimated for 14 subjects receiving pioglitazone ODTs and ten receiving commercial pioglitazone because values were below the lower limit of quantification or there were insufficient data for the elimination phase (M-II).
Mean values (standard deviation) are shown.
AUC: Area under the curve; MRT: Mean residence time; ODT: Orally disintegrating tablet.

and $C_{max}$ were within the 0.80–1.25 interval, bioequivalence was concluded between test and reference formulations [5]. Descriptive statistics were also calculated for the plasma concentrations of unchanged pioglitazone and its three main metabolites, as well as other pharmacokinetic parameters excluding $AUMC_{0-tlqc}$ and $AUMC_{0-inf}$ (area under the first moment of the plasma concentration–time curves).

For Study 3, oral mucosal absorption of pioglitazone OD tablets was determined by comparing $AUC_{0-72}$ and $C_{max}$ of unchanged pioglitazone with those after oral administration of the same dose of commercial tablet. Descriptive statistics were also calculated for plasma concentration, $AUC_{0-72}$ and $C_{max}$ of unchanged pioglitazone, and its three main metabolites.

## Results

In total, 154 subjects were enrolled across the three studies, although 14 did not receive study medication (seven did not meet entrance criteria, three had pre-treatment adverse events, and four were enrolled as potential replacements but were not used). In Study 1, 64 subjects received study medication and 63 completed the study; one withdrew for voluntary reasons. In Study 2, 64 subjects received study medication and 62 completed the study; two were withdrawn – one due to an adverse event and the other due to use of prohibited concomitant medication. All 12 subjects who received study medication in Study 3 completed the study.

Baseline characteristics were similar across the three studies; overall mean age was 22.8 years (range: 20–34 years), mean bodyweight was 62.7 kg (range: 51.1–78.6 kg) and mean BMI was 21.1 kg/m$^2$ (range: 18.5–24.8 kg/m$^2$).

### Bioequivalence of pioglitazone OD tablet (Studies 1 & 2)

Two different dosage regimens for the pioglitazone OD tablet, such as taken without (Figure 1) or with (Figure 2) water, did not influence the plasma concentration over time profiles of unchanged pioglitazone compared with those following the same dose of commercial tablet. Pharmacokinetic parameters from Studies 1 and 2 are summarized in Tables 1 & 2, respectively.

Similar values of $AUC_{0-72}$ and $C_{max}$ for unchanged pioglitazone were observed with pioglitazone OD tablets as with the commercial tablets. The one-sided *t*-tests used to assess bioequivalence resulted in 90% confidence intervals for test-to-reference ratios within the 0.80–1.25 range for unchanged pioglitazone, confirming bioequivalence between the pioglitazone OD tablet and the commercially available tablet, independently of whether the tablets were taken with or without water (Table 3).

Furthermore, no statistically significant findings were observed for other pharmacokinetic parameters of unchanged pioglitazone, with the exception of slight changes in $t_{max}$. Administration of pioglitazone with or without water marginally influenced the rate of gastrointestinal absorption, and this resulted in a slightly prolonged median $t_{max}$ when taking the pioglitazone OD tablet without

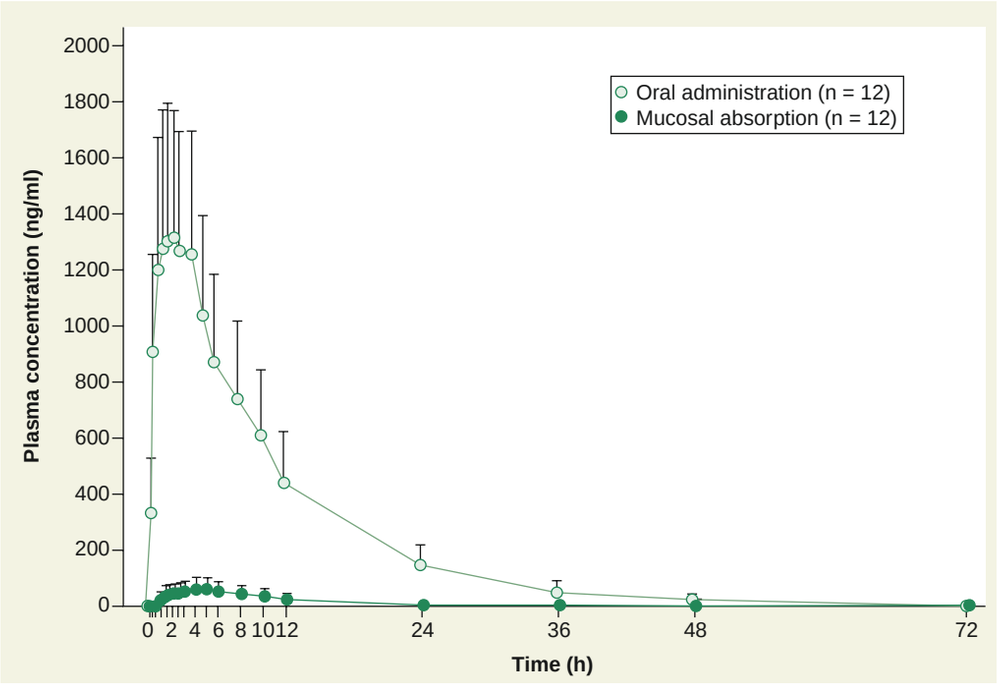


**Figure 3. Mean plasma concentration of pioglitazone after administration of pioglitazone orally disintegrating tablets: mucosal absorption from the oral cavity (tablet kept in mouth) compared with absorption after oral administration (tablet swallowed) (Study 3).**

water compared with that of the corresponding commercial tablet.

Plasma concentration over time profiles and pharmacokinetic parameters for the three main metabolites of pioglitazone were consistent between the pioglitazone OD tablet administered without (Table 4) or with (Table 5) water, and the commercial tablet administered with water.

## Oral mucosal absorption of pioglitazone OD tablet

Oral mucosal absorption of pioglitazone was found to be very low when the pioglitazone OD tablet was kept in the mouth for 2 min (Figure 3). Descriptive statistics are tabulated for $AUC_{0-72}$ and $C_{max}$ of unchanged pioglitazone in Table 6. The mean ± SD relative oral mucosal absorption was estimated to be 3.99 ± 3.09% for $AUC_{0-72}$ and 4.36 ± 2.83% for $C_{max}$.

## Safety

Single 30-mg doses of both the pioglitazone OD and commercial formulations were generally well tolerated. The proportion of subjects who experienced adverse events in each of the three studies was similar for the pioglitazone OD tablet and the corresponding commercial tablet. Adverse events were generally mild in severity, and only two events (dizziness and headache) were judged by the investigator to be possibly related to study medication. After administration of the pioglitazone OD tablet, two events were recorded in two subjects in Study 1 (headache and increased white cell count) and four subjects experienced seven events in Study 2 (headache, hordeolum, blood in urine, red cells in urine, decreased lymphocyte count, increased white cell count and increased neutrophil count). After administration of the commercial tablet, two subjects reported two adverse events in Study 1 (dizziness and myalgia), and four subjects experienced four events in Study 2 (urticaria, epistaxis, increased creatine phosphokinase and white cells in urine). No adverse events were

**Table 6. Key pharmacokinetic parameters for pioglitazone after mucosal absorption and oral administration (Study 3).**

| Parameter | Mucosal absorption† | Oral administration‡ |
|---|---|---|
| $AUC_{0-72}$ (ng·h/ml) | 630.5 (471.92) | 15,996.8 (5443.26) |
| $C_{max}$ (ng/ml) | 64.1 (42.02) | 1467.3 (513.29) |

†Pioglitazone orally disintegrating tablets kept in mouth for 2 min.
‡Pioglitazone orally disintegrating tablets swallowed.
Mean values (standard deviation) are shown.
AUC: Area under the curve.

reported in Study 3. There were no clinically significant abnormalities in laboratory tests or other safety parameters during the studies.

## Discussion

For patients with T2DM, good compliance with antihyperglycemic therapy is essential to achieve and maintain glycemic control [6], which is important for the patient's general health and to help reduce disease-related medical costs [7]. However, many patients do not adhere fully to the prescribed amount of medication [8]. Compared with a conventional tablet, an OD formulation may improve treatment compliance, particularly for medications that need to be taken several times daily [9].

The commercially available pioglitazone tablet formulation is prescribed on a once-daily basis, which is already a convenient dosing regimen for patients. However, the pioglitazone OD tablet may be useful for patients who still have difficulty complying with treatment. For example, patients with disorders such as dysphagia can find it difficult to swallow conventional tablets and may prefer an OD formulation [2]. Other situations where patients may find it difficult to swallow solid tablets or large quantities of water include motion sickness and repeated vomiting [3]. Critically ill patients, or patients who are not able to take anything orally, such as those undergoing surgery, could also benefit from an OD formulation. In addition, elderly patients may prefer the convenience of an OD tablet. The practical aspects of taking medications also need to be considered. For example, in some work and social settings it can be difficult for people to access water at appropriate times in order to take a conventional tablet, a problem that can be overcome with an OD formulation.

In our studies, bioequivalence of the pioglitazone OD tablet formulation was evaluated in healthy volunteers using two different dosing regimens, administered with or without water, compared with the corresponding commercial pioglitazone tablet (30 mg), which was taken with water. Furthermore, oral mucosal absorption was evaluated when the OD tablet was kept in the mouth for 2 min.

The pharmacokinetic properties of the pioglitazone OD tablet and corresponding commercial tablets were generally consistent with the results of previous studies in healthy Japanese volunteers [10–12]. It was found that the two different dosing regimens did not influence the extent or rate of absorption of pioglitazone, and the 90% confidence intervals of the LS mean ratios for $AUC_{0-72}$ and $C_{max}$ were within the 0.80–1.25 bioequivalent range. Relative to the commercial tablet, median $t_{max}$ was slightly longer when the pioglitazone OD tablet was taken without water and the same as when the pioglitazone OD tablet was taken with water. Given that the $HbA_{1c}$ lowering effects of pioglitazone are mediated by cumulative drug effects, it is unlikely that such marginal changes in median $t_{max}$ would be of any clinical significance for the pioglitazone OD tablet.

Since the OD tablet formulation was developed to disintegrate rapidly, some absorption of pioglitazone could potentially occur through the oral mucosa before the tablet is swallowed, and this could alter the pharmacokinetic profile. Therefore, the extent of oral mucosal absorption of pioglitazone was determined for the OD tablet and was found to be very low (approximately 4%).

As the present series of studies involved administration of single doses of medication, only limited conclusions can be drawn about safety and tolerability. However, based on the available data, both formulations appeared to be generally well tolerated, and there was little evidence to suggest that the formulations differed with respect to incidence or type of adverse events.

In conclusion, a newly developed pioglitazone 30-mg OD tablet was confirmed to be bioequivalent to the commercially available pioglitazone 30-mg tablet, independently of whether or not the tablets were taken with water. Furthermore, oral mucosal absorption was found to have minimal impact on the bioavailability of the pioglitazone OD tablet. Thus, this OD tablet formulation of pioglitazone is expected to provide an alternative treatment option for patients with T2DM who have difficulty swallowing or are unable to swallow a conventional tablet.

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## Financial & competing interests disclosure

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*No writing assistance was utilized in the production of this manuscript.*

## Ethical conduct of research

*The protocol was approved by the Osaka Pharmacology Clinical Research Hospital Institutional Review Board. The studies were performed in accordance with the International Conference on Harmonisation (ICH) Technical Requirements for the Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines and in line with ethical principles set out in the Declaration of Helsinki. 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.*

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