Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Takeda Italia Farmaceutici S.p.A.
Via Elio Vittorini, 129
00144 Rome, Italy

Title of Study: Double-blind, randomized, multicenter, parallel-group study to evaluate the effects of pioglitazone on metabolic syndrome in patients with type 2 diabetes treated with metformin

Phase of Development: Phase IIIb

Name of Active Ingredient: (±)-5-[p-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4,thiazolidinedione hydrochloride (pioglitazone)

Name of Finished Product: Pioglitazone

Investigators: 51 principal investigators in Italy enrolled subjects in the double-blind treatment period

Study Site: 51 sites in Italy randomized subjects into the open-label treatment period

Publications Based on the Study (Citations) at Time of Study Completion: None

Study Period:

Date first subject signed informed consent form: 16 January 2007

Date of last subject's last visit/contact (from the Clinical database): 31 July 2008

Objectives:

Primary:

To evaluate the beneficial effect of combining Pioglitazone and metformin on high density lipoprotein cholesterol (HDL-C) after 24 weeks of treatment.

Secondary:

The secondary objectives of this study were:

- To evaluate the effect of combining Pioglitazone and metformin on the risk factors clustered in the International Diabetes Federation (IDF) definition of metabolic syndrome (MS), i.e. the changes in the aggregate of waist circumference, fasting plasma glucose (FPG), triglycerides, HDL-cholesterol, blood pressure (BP). Moreover, individual

metabolic parameters, insulin sensitivity and ß-cell function, inflammatory cytokines, adipokines, endothelial functionality, safety and tolerability were measured.

- To evaluate the safety profile of the investigational medicinal products in terms of adverse events (AEs), laboratory parameters, and overall tolerability.

Methodology: This was a phase IIIb, 24-weeks, double blind, randomised, multicentre, parallel-group study. The study plan included two treatment arms: a) Pioglitazone 15 mg x 3/day (titrated from 15 mg x 2/day in the first 4 weeks) + metformin 850 mg x 3/day; b) Placebo x 3/day (x 2/day in the first 4 weeks) + metformin 850 mg x 3/day.

Six clinic visits in total were planned for this study: enrollment (week -1), randomization (week 0), and 4, 8, 16 and 24 weeks after randomization.

Number of Subjects:

Planned: 400 subjects

Screened: 418 subjects

Enrolled in the double blind treatment period: 213 subjects

Number of patients (total and for each arm):

	Randomised	Safety	Intent-to-treat (ITT)	Per Protocol (PP)	Completers
Total	213	212	206	187	194
Pioglitazone + metformin	110	109	106	93	97
Placebo + metformin	103	103	100	94	97

Diagnosis and Main Criteria for Inclusion: diagnosis of type 2 diabetes mellitus; age ≥ 35 and ≤ 75 years; glycosylated haemoglobin (HbA_{1C}) levels between 6.5-7.5%; treatment with metformin 2.000-3.000 mg daily since at least 3 months; reduced HDL-cholesterol levels: < 40 mg/dl in males and <50 mg/dl in females, irrespective of treatment with statins; central obesity (waist circumference ≥ 94 cm for men and ≥ 80 cm for women); female (childbearing potential) patients with negative response to pregnancy test; female patients had to be postmenopausal, hysterectomised or surgically sterilized using reliable and adequate contraceptive methods (oral contraception or intrauterine device (IUD)); a cooperative attitude and ability to be trained to use correctly the investigational study drugs and to attain the study procedures; written informed consent provided.

Duration of Treatment: 24 weeks

Test Product, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number	Overencapsulation Lot Number
Pioglitazone	15 mg encapsulated tablets	15 mg BID (weeks 1 - 4) 15 mg TID (weeks 5 -24)	Oral	2730013U	N/A
Metformin	850 mg	850 mg TID	Oral	01305	N/A

Reference Therapy, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength	Study Dosage	Mode of Administration	Drug Product Lot Number	Overencapsulation Lot Number
Placebo to Pioglitazone	Encapsulated tablet	N/A	Oral	N/A	N/A

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the change from baseline of HDL-cholesterol measured at 24 weeks.

The secondary efficacy variables included the change in the risk factors clustered in the IDF definition of metabolic syndrome, i.e. the changes in the aggregate of waist circumference, fasting plasma glucose, triglycerides, HDL-cholesterol, blood pressure. Moreover, individual metabolic parameters, insulin sensitivity and ß-cell function, inflammatory cytokines, adipokines, and endothelial function parameters were also evaluated.

Safety:

Safety variables were: adverse events (AEs), laboratory parameters, and overall tolerability of treatments.

Statistical Methods:

Efficacy:

The efficacy summaries and analyses were based on all randomised patients who had taken at least one dose of study drug and with at least one post-baseline follow-up (ITT population). Patients included in the ITT analysis that did not have major protocol violations and completed the overall study period were included in the per-protocol (PP) population. Safety parameters were analysed in all randomized patients who took at least one dose of study drug (safety

population).

The results of primary efficacy variable (HDL-cholesterol) were evaluated by using an analysis of covariance (ANCOVA) model, with basal value as the independent and the value detected after 24 weeks (end of study) as the dependent variable, respectively.

Continuous secondary efficacy variables were analysed by an analysis of variance (ANOVA) for repeated measure (visits) and one grouping factor (treatment). Multiple comparisons were performed either within treatment (versus basal values) or between treatments, using the Bonferroni correction. In order to study the effect of the concomitant administration of statins and the effect of sex on the HDL-cholesterol levels, the dichotomus variables concomitant treatment with stains (No/Yes) and sex (Male/Female) were added as grouping factors to the model used in the analysis of the primary efficacy variable.

Furthermore, the variables included in the IDF definition of metabolic syndrome (waist circumference, fasting plasma glucose, triglycerides, HDL-cholesterol, blood pressure) were evaluated by multivariate analysis (factor analysis).

Safety:

The frequency of adverse events and adverse drug reactions was analysed using Chi square test with Yates correction for 2x2, where applicable. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. For each AE, the System Organ Class (SOC), the Preferred Term (PT), and the PT code were reported.

Laboratory safety parameters (haematology, blood chemistry and urinalysis) were evaluated by parametric methods (ANOVA), with multiple comparisons within treatment (final values versus baseline values) and between treatments. Clinical judgment expressed by the investigator as 1 = normal, 2 = abnormal but not clinically relevant, and 3 = abnormal and clinically relevant, were analysed by non-parametric (McNemar's test and Chi square test).

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

The mean age in the randomized population was 57.0 ± 8.6 years (range 35.9-77.1) in the Pioglitazone group and 57.8 ± 8.2 years (range 37.4-72.9) in the placebo group. The randomized population included 65 males (59.1%) and 45 females (40.9%) in the Pioglitazone group, and 62 males (60.2%) and 41 females (39.80%) in the placebo group. All 213 participating subjects were Caucasians. The mean height in the randomized population was 1.66 ± 0.09 m (range 1.49-1.88) in the Pioglitazone group and 1.65 ± 0.09 m (1.43-1.87) in the placebo group. The mean weight was 88.8 ± 14.0 (range 59.5-149.0) in the Pioglitazone group and 89.0 ± 17.2 kg (range 55.3-157.4) in the placebo group. The mean body mass index (BMI) was 32.4 ± 5.4 kg/m^2 (range 23.6-52.2) in the Pioglitazone group and 32.6 ± 5.3 kg/m^2 (range 24.2-54.5) in the placebo group. The mean waist circumference in the randomized population was 107.4 ± 11.6 cm (range 82-168) in the Pioglitazone group and 107.7 ± 12.2 cm (82-155) in the placebo group.

The presence of at least one disease in the medical history was reported in 80 patients in total (48 (44%) Pioglitazone group vs. 32 (31.1%) placebo group) with the most frequently reported diseases being hypertension (22.9% Pioglitazone vs. 9.4% placebo) and exanthematic child disease (8.3% Pioglitazone vs. 21.9% placebo). The body systems with the most frequent abnormal findings were eyes (4 (3.6%) Pioglitazone vs. 7 (6.8%) placebo (p = 0.464 between groups)), cardiovascular (10 (9.1%) Pioglitazone vs. 7 (6.8%) placebo (p = 0.715)), and gastrointestinal (8 (7.3%) Pioglitazone vs. 6 (%5.8%) placebo (p = 1.000 between groups)). The number of patients taking previous antidiabetic treatments was 31 (28.4%) in the Pioglitazone group and 38 (36.9%) in the placebo group. Metformin was the most frequently taken drug, with 21 patients (67.7%) in the Pioglitazone group and 16 (42.1%) in the placebo group.

Subject Disposition:

A total number of 213 patients were randomized to receive the assigned treatment: 110 patients were assigned to treatment with Pioglitazone plus metformin (named Pioglitazone group hereinafter) and 103 were assigned to receive the placebo treatment plus metformin (named placebo group hereinafter). A total amount of 19 patients, 13 in the Pioglitazone group and 6 in the placebo group, were prematurely withdrawn from the study. Adverse event and consent withdrawn were the most frequent reasons of study discontinuation.

Extent of exposure and compliance:

The mean extent of exposure to study drug in the safety population was 157.1 ± 34.4 days (range 3.0 - 202.0) in the Pioglitazone group and 161.4 ± 30.7 days (range 0.0 - 199.0) in the placebo group.

The mean (±SD) compliance to study medication in the ITT population was 97.1 ± 5.2% (range 71.9 - 107.4) in the Pioglitazone group and 98.3 ± 3.8% (range 82.1 - 109.0) in the placebo group.

Efficacy Results:

Primary efficacy variable (HDL-cholesterol):

In the ITT population, an increase in mean values was observed in both groups. The adjusted means (± standard error (SE)) in the ANCOVA model were 40.72 ± 0.62 mg/dl in the Pioglitazone group and 37.42 ± 0.64 mg/dl in the placebo group. The difference between the Pioglitazone and the placebo group was 3.29 mg/dl (95% confidence interval (CI): 1.53 to 5.06, p = 0.000), thus showing that the difference between groups was statistically significant, in favour of the Pioglitazone group. The results obtained in the PP population were consistent with those observed in the ITT analysis.

A statistically significant increase from baseline was observed both groups at both Visit 4 and Visit 6 (p = 0.000 at both visits in both groups). The mean changes from baseline in the Pioglitazone group were 5.66 mg/dl (95% CI: 4.37 to 6.96) at Visit 4 and 6.31 mg/dl (95% CI: 5.02 to 7.61) at Visit 6, while the mean changes from baseline in the placebo group were 2.50

mg/dl (95% CI: 1.21 to 3.79) at Visit 4 and 3.02 mg/dl (95% CI; 1.73 to 4.31) at Visit 6. The difference between groups was 3.16 mg/dl (95% CI: 1.33 to 4.99) at Visit 4 and 3.29 mg/dl (95% CI: 1.46 to 5.12), thus showing that the difference between groups was statistically significant at both visits, in favour of the Pioglitazone group (p = 0.000 at both visits) (limit for statistical significance: p = 0.025).

The subgroup analyses showed that the changes in HDL-cholesterol levels were independent by sex or by the concomitant treatment with statins. In the analysis that took into account the reference to normal range and clinical judgment, a statistically significant tendency towards normalization was observed in the Pioglitazone group at both Visit 4 and Visit 6 (p = 0.000 at both visits), while the changes in the placebo group were not significant. The comparison between groups showed a statistically significant difference at Visit 6 (p = 0.033), in favour of the Pioglitazone group.

Secondary efficacy variables:

Metabolic syndrome (multivariate analysis):

In the multivariate analysis of the factor score, a statistically significant decrease from baseline was observed in both groups at both Visit 4 and Visit 6. The mean changes from baseline in the Pioglitazone group were -10.4 (95% CI: -15.2 to -5.6) at Visit 4 and -13.2 (95% CI: -18.00 to -8.4) at Visit 6 (p = 0.000 at both visits), while the mean changes from baseline in the placebo group were -4.8 (95% CI: -9.6 to -0.0) at Visit 4 and -4.8 (95% CI: -9.6 to -0.0) at Visit 6 (p = 0.025 at Visit 4 and p = 0.024 at Visit 6). The difference between groups was -5.6 (95% CI: -12.4 to 1.2) at Visit 4 and -8.4 (95% CI: -15.2 to -1.6) at Visit 6, thus showing that the difference between groups was statistically significant at Visit 6 (p = 0.006) in favour of Pioglitazone, while the difference between groups at Visit 4 was not statistically significant (p = 0.063) (limit for statistical significance: p = 0.025).

In the subgroup analyses, the decrease from baseline in factor score was statistically significant in both sexes in Pioglitazone group. In the placebo group, the changes from baseline in factor score were not significant in males, while for female the improvement at Visit 4 was statistically significant. In the comparison between groups, the changes in males were statistically significant, while the difference in females was not. Considering the subgroup of patients without or with a concomitant treatment with statins, the changes from baseline in factor score in the Pioglitazone group were statistically significant in both subgroups, while there were no significant effects in the placebo group. In the comparisons between groups, the difference at Visit 6 was statistically significant (in favour of Pioglitazone) in patients treated with statins.

Waist circumference:

A statistically significant decrease from baseline was observed in both groups at both Visit 4 and Visit 6 (p = 0.000 in both groups at both visits, except p = 0.001 in the placebo group at Visit 4). The difference between groups was -0.2 cm (95% CI: -1.7 to 1.4, p = 0.810) at Visit 4 and 0.9

cm (95% CI: -0.7 to 2.5, p = 0.193) at Visit 6, thus showing that the difference between groups was not statistically significant at both visits (limit for statistical significance: p = 0.025).

Fasting plasma glucose:

A statistically significant decrease from baseline was observed only in Pioglitazone group, both at Visit 4 and Visit 6 (p = 0.000 at both visits), while there were no statistically significant changes in the placebo group. The difference between groups was -15.1 mg/dl (95% CI: -22.9 to -7.3, p = 0.000) at Visit 4 and -14.6 mg/dl (95% CI: -22.4 to -6.8, p = 0.000), thus showing that the difference between groups was statistically significant at both visits, in favour of the Pioglitazone group (limit for statistical significance: p = 0.025).

In the analysis that took into account the reference to normal range and clinical judgment, a statistically significant tendency towards normalisation was observed in the Pioglitazone group at both Visit 4 (p = 0.028) and Visit 6 (p = 0.016), while the changes in the placebo group were not significant. The comparison between groups showed a statistically significant difference, in favour of the Pioglitazone group, at both Visit 4 (p = 0.025) and Visit 6 (p = 0.045).

Triglycerides:

A statistically significant decrease from baseline was observed only in Pioglitazone group at Visit 4 (p = 0.010), while there were no statistically significant changes in Pioglitazone group at Visit 6 and in the placebo group at both Visit 4 and Visit 6. The difference between groups was -17.1 mg/dl (95% CI: -39.9 to 5.7, p = 0.092) at Visit 4 and -7.8 mg/dl (95% CI: -3.07 to 15.0, p = 0.442) at Visit 6, thus showing that the difference between groups was not statistically significant at both visits (limit for statistical significance: p = 0.025).

In the analysis that took into account the reference to normal range and clinical judgment, there were no statistically significant effects in both groups at both Visit 4 and Visit 6. The comparison between groups showed a statistically significant difference at Visit 4 (p = 0.012) due to a tendency towards normalisation in the Pioglitazone group and a tendency towards an increase of abnormal values in the placebo group, while there were no statistically significant differences at Visit 6.

Blood pressure:

No statistically significant changes from baseline were observed in both groups for both diastolic blood pressure (DBP) and systolic blood pressure (SBP), apart from a small but statistically significant decrease of SBP in the Pioglitazone group at Visit 5 (-3.9 mmHg; 95% CI: -7.5 to -0.3, p = 0.006) and at Visit 6 (-3.7 mmHg; 95% CI: -7.3 to -0.2, p = 0.009), as well as a significant decrease of SBP in the Pioglitazone group was observed in the analysis of changes from baseline to the last visit. The comparison between groups did not show statistically significant differences at any time point for both DBP and SBP.

Other metabolic parameters:

- Total cholesterol

A statistically significant increase from baseline was observed in Pioglitazone group at both Visit 4 and Visit 6 (p = 0.000 at both visits), while there were no statistically significant changes from baseline in the placebo group. The difference between groups was 6.4 mg/dl (95% CI: -1.3 to 14.1) at Visit 4 and 13.2 mg/dl (95% CI: 5.5 to 20.9) at Visit 6, thus showing that the difference between groups was statistically significant at Visit 6 (p = 0.000), but not at Visit 4 (p = 0.062). In the analysis that took into account the reference to normal range and clinical judgment, there were no statistically significant effects in both groups at both Visit 4 and Visit 6, as well as there were no statistically significant differences between groups.

- Low density lipoprotein cholesterol (LDL-C)

A statistically significant increase from baseline was observed in Pioglitazone group at both Visit 4 and Visit 6 (p = 0.000 at both visits), while there were no statistically significant changes from baseline in the placebo group. The difference between groups was 6.4 mg/dl (95% CI: -1.0 to 13.8) at Visit 4 and 11.2 mg/dl (95% CI: 3.8 to 18.6) at Visit 6, thus showing that the difference groups was statistically significant at Visit 6 (p = 0.001), but not at Visit 4 (p = 0.052). The significant increases from baseline in Pioglitazone group were irrespective of the presence or absence of a concomitant treatment with statins, while no statistically significant changes from baseline were observed in placebo group. The difference between groups in patients treated with statins was statistically significant at Visit 6.

In the analysis of the LDL-C levels estimated at each visit as a function of total cholesterol, HDL-cholesterol and triglycerides by using an ANCOVA model that used a covariate the same parameters of the function, there were no differences between the adjusted means of Pioglitazone and the placebo group. In the analysis that took into account the reference to normal range and clinical judgment, there were no statistically significant effects in both groups at both Visit 4 and Visit 6, as well as there were no statistically significant difference between groups.

- HbA_{1C}

A statistically significant decrease from baseline was observed in Pioglitazone group at both Visit 4 and Visit 6 (p = 0.000 at both visits), while there were no statistically significant changes from baseline in the placebo group. The difference between groups was -0.19% (95% CI: -0.35 to -0.02) at Visit 4 and -0.45% (95% CI: -0.61 to -0.28) at visit 6, thus showing that the difference between groups was statistically significant at both visits (p = 0.011 at Visit 4 and p = 0.000 at Visit 6).

- Insulin

A statistically significant decrease from baseline to Visit 6 was observed both in the Pioglitazone group (p = 0.000) and in the placebo group (p = 0.015). The difference between groups was -1.733 mU/L (95% CI: -4.538 to 1.072), thus showing that the difference between groups was not statistically significant (p = 0.225). In the analysis that took into account the reference to normal

range and clinical judgment, there were no statistically significant effects in both groups at Visit 6, as well as there were no statistically significant differences between groups.

- Non esterified fatty acids (NEFA)

A statistically significant decrease from baseline to Visit 6 was observed in the Pioglitazone group (p = 0.044), while the change from baseline was not statistically significant in the placebo group. The difference between groups was -0.053 mmol/L (95% CI: -0.125 to 0.019), thus showing that the difference between groups was not statistically significant (p = 0.149).

Insulin Sensitivity:

- Homeostatic Model Assessment of Insulin Resistance (HOMA IR)

A statistically significant decrease from baseline to Visit 6 was observed in the Pioglitazone group (p = 0.000), while the change from baseline was not statistically significant in the placebo group. The difference between groups was -910.5 (95% CI: -1735.5 to -85.5), thus showing that the difference between groups was statistically significant (p = 0.013).

- ß-cells function (Homeostatic Model Assessment of beta-cell function (HOMA-B%))

No statistically significant changes from baseline to Visit 6 were observed both in the Pioglitazone group and in the placebo group. The difference between groups was -102.0 (95% CI: -933.8 to 729.8), thus showing that the difference between groups was not statistically significant (p = 0.783).

Inflammatory cytokines:

- Interleukin-6 (IL6)

No statistically significant changes from baseline to Visit 6 were observed both in the Pioglitazone group and in the placebo group. The difference between groups was -0.144 ng/L (95% CI: -0.280 to 0.568), thus showing that the difference between groups was not statistically significant (p = 0.503).

- Tumour Necrosis Factor-alpha (TNF-α)

No statistically significant changes from baseline to Visit 6 were observed both in the Pioglitazone group and in the placebo group. The difference between groups was -132.0 ng/L (95% CI: -572.7 to 308.7), thus showing that the difference between groups was not statistically significant (p = 0.556).

Adipokines:

- Adiponectin

A statistically significant increase from baseline to Visit 6 was observed in the Pioglitazone group (p = 0.000), while the change from baseline was not statistically significant in the placebo

group. The difference between groups was 5.959 µg/dl (95% CI: 4.757 to 7.160), thus showing that the difference between groups was statistically significant (p = 0.000).

- Leptin

No statistically significant changes from baseline to Visit 6 were observed both in the Pioglitazone group and in the placebo group. The difference between groups was 1.681 µg/dl (95% CI: -0.538 to 3.900), thus showing that the difference between groups was not statistically significant (p = 0.137).

Endothelial function

- Plasminogen Activator Inhibitor-type 1 (PAI-1)

A statistically significant decrease from baseline to Visit 6 was observed in the Pioglitazone group (p = 0.009), while the change from baseline was not statistically significant in the placebo group. The difference between groups was -14.4 µg/L (95% CI: -24.1 to -4.7), thus showing that the difference between groups was statistically significant (p = 0.004).

- high sensitivity C-Reactive Protein (hs-CRP)

A statistically significant decrease from baseline to Visit 6 was observed both in the Pioglitazone group (p = 0.000) and in the placebo group (p = 0.016). The difference between groups was -409.0 mg/L (95% CI: -1206.9 to 388.9), thus showing that the difference between groups was not statistically significant (p = 0.314). In the analysis that took into account the reference to normal range and clinical judgment, there were no statistically significant effects in both groups at Visit 6, as well as there were no statistically significant differences between groups.

- Atherogenic Index of Plasma (AIP)

A statistically significant decrease from baseline was observed in the Pioglitazone group at both Visit 4 and Visit 6 (p = 0.000 at both visits), while there were no statistically significant changes from baseline in the placebo group. The difference between groups was -0.095 (95% CI: -0.154 to -0.037) at Visit 4 and -0.058 (95% CI: -0.116 to 0.001) at Visit 6, thus showing that the difference between groups was statistically significant at Visit 4 (p = 0.000), but not at Visit 6 (p = 0.026).

Safety Results:

Adverse events:

Adverse events were reported in 70 patients in total, 38 (34.9%) in the Pioglitazone group and 32 (31.1%) in the placebo group (p = 0.563 between groups). Adverse events related to study medication were reported in 37 patients in total, 22 (20.2%) in the Pioglitazone group and 15 (14.6%) in the placebo group.

There were no fatal adverse events in both treatment groups. Serious adverse events were reported in 5 patients in total, 4 (3.7%) in the Pioglitazone group and 1 (1.0%) in the placebo

group (p = 0.366 between groups). Only three serious adverse events occurred in one patient in the Pioglitazone group, which consisted of flatulence, nausea and abdominal pain, were considered as related to study medication.

Adverse events that caused permanent study discontinuation were reported in 9 patients in total, 7 (6.4%) in the Pioglitazone group and 2 (1.9%) in the placebo group.

Gastrointestinal complaints were the most common adverse events and were reported with similar frequency in the two groups: diarrhoea, flatulence and abdominal pain were the most frequent adverse events. No substantial differences between groups were observed with reference to any individual event. Peripheral oedema was reported in 3 patients and weight increase was reported in 2 patients in the Pioglitazone group. Only one case of hypoglycaemia was also reported in the Pioglitazone group, as well as there was only one case of increased hepatic enzymes in the same group.

Laboratory tests:

Small but significant reduction in red blood cell (RBC) count, haemoglobin and haematocrit were reported in the Pioglitazone group, with statistically significant differences in the comparison between groups, having this difference little clinical relevance. In the analysis of the number of patients with abnormal values at both baseline and follow-up visits, a statistically significant effect in the Pioglitazone group was observed for RBCs at both week 8 and week 24, and for haemoglobin at week 24. However, the abnormalities in RBCs count, haemoglobin and haematocrit were judged as being clinically significant in a very small amount of cases.

A statistically significant decrease from baseline was observed for alanine amniotransferase (ALT) and gamma Glutamyl Transpeptidease (gamma-GT) in the Pioglitazone group at any time point, with statistically significant difference between groups. The comparison between groups of the proportion of patients with abnormal values of ALT and gamma-GT showed a statistically significant difference, due to a higher number of patients with normal values in the Pioglitazone group compared to placebo. The analysis of changes from baseline of aspartate amniotransferase (AST) did not show significant changes in both groups. Small but significant increases from baseline blood urea nitrogen (BUN) and creatinine were observed in the Pioglitazone group, with significant differences between groups. However, there were no clinically significant abnormalities in any patient in both groups for both BUN and creatinine, as well as there were no significant differences between groups in the distribution of normal and abnormal values for both variables. There were no clinically important changes of urine parameters in both groups.

Body weight and BMI:

There were no substantial changes from baseline in both groups at any time point. In the Pioglitazone group, a small but statistically significant increase from baseline was observed at Visit 6 (mean change: 0.7 kg, 95% CI: 0.10 to 1.27, $p<0.01$), while, in the placebo group, a small but statistically significant decrease from baseline was observed at Visit 4 (mean change: -0.7 kg,

95% CI: -1.30 to -0.14, p<0.01), Visit 5 (mean change: -1.1 kg, 95% CI: -1.66 to -0.49, p<0.01), and Visit 6 (mean change: -1.4 kg, 95% CI: -1.99 to -0.83, p<0.01). The comparison between groups showed a statistically significant difference at both Visit 5 and Visit 6 (p<0.01 at both visits). The results of BMI were consistent with those observed for body weight.

Physical examination:

No clinically significant changes from baseline of abnormal findings were observed in both groups.

Conclusions:

The main results of the present study have shown that:

- Treatment with Pioglitazone combined with metformin was associated with a significantly more marked increase in HDL-cholesterol levels compared to metformin alone (placebo), irrespective of gender and concomitant treatment with statins.
- Pioglitazone was also significantly superior to placebo at week 24 in the improvements of the factor score defined by the multivariate analysis of the overall metabolic syndrome, as well as in its single components fasting plasma glucose and triglycerides levels.
- Pioglitazone was effective in reducing the HbA_{1C} levels at both week 8 and week 24 compared to placebo, and also exhibited positive effects in ameliorating NEFA levels, insulin HOMA IR, adiponectin levels, and endothelial function parameters (including atherogenic or cardiovascular risk factors).
- The rate of patients reporting adverse events, drug-related adverse events, serious adverse events and permanent study discontinuation due to adverse events did not substantially differ between the two treatment groups. Gastrointestinal complaints, which might be caused by the concomitant administration of metformin, were the most common events. Possible adverse effects in the use of thiazolidinediones combined with metformin (e.g. peripheral oedema, increase of hepatic enzyme or hypoglycaemia) were reported in a very small amount of patients.
- Treatment with Pioglitazone was associated with decreases from baseline of RBCs count, haemoglobin and haematocrit, but these changes seemed to have no clinical relevance. There were also no adverse effects in liver function parameters following treatment with Pioglitazone.

Study ID Number:

IT-PIO-108

Other Study ID Number(s):

2006-000725-54 [EudraCT Number]

PIOc/LAN07/TIF [Takeda ID]

U1111-1115-9278 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 25 June 2012