Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Takeda Pharma Vertieb GmbH & Co. KG
Jägerstr.27, 10117 Berlin, Germany

Title of Study: Effects of Pioglitazone in Combination with Glimepiride in Comparison to Glimepiride Monotherapy on Metabolic Control in Patients with Type 2 Diabetes mellitus

Phase of Development: Phase IIIb

Name of Active Ingredient: [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]-2,4-] (pioglitazone hydrochloride)

Name of Finished Product: Actos®

Investigators: 17 principal investigators enrolled patients.

Study Sites: 22 study centers in Germany including 17 active centres, i.e. centres which screened at least one patient, in Germany.

Center 001 :IKFE GmbH
Geschäftsführer Forschung und
Entwicklung
Parcusstrasse 8
55116 Mainz

Center 002 :IKFE GmbH
Große Hamburger Str. 5-11
10115 Berlin

Center 003 :IKFE GmbH
Heinz-Meisestr. 101
36199 Rotenburg

Center 004 : Elisenstr. 28
63739 Ashaffenburg

Center 005 : Jarekstr. 1
88400 Biberach an der Riß

Center 006 : Ludwigstr. 11

85049 Ingolstadt

Center 007 : Rathausplatz 9
91126 Rednitzhembach

Center 008 : Venloer Str. 247
50823 Köln

Center 009 : Sammetwiesen 17
34621 Frielendorf-Verna

Center 010 : Diabetologe DDG
Eichendorffstr. 12 d
97072 Würzburg

Center 011 : Diabetologe DDG
Studienzentrum (ZKSN)
Langendorfer Str. 82a
56564 Neuwied

Center 012 :Pühlstr. 37
55624 Rhaunen

Center 013 : Neugasse 20a
67169 Kallstadt

Center 014 : Neugasse 20a
67169 Kallstadt

Center 015 :kfhm (Klinische Forschung Hannover-Mitte)
Bahnhofstr. 4
30159 Hannover

Center 016 : Hoher Wall 25
44137 Dortmund

Center 017 : Stralsunder Str. 16
(Studienzentrum)
60323 Frankfurt

Center 018 : Grühlingsstollen 3
66299 Friedrichsthal

Center 019 : Prenzlauer Allee 146
10409 Berlin

Center 020 : SiegResearch Pharma
Frankfurter Str. 29
57074 Siegen

Center 021: Diabetologische Praxis
Koblenzer Str. 89
56727 Mayen

Center 022: Brombeerweg 6
78048 Villingen-Schwenningen

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

Study Period:

Date first subject signed informed consent form: 06 December 2006

Date of last subject's last visit/contact (from the Clinical database): 16 December 2008

Objectives:

Primary:

The primary objective of the study was to investigate the effects of Pioglitazone in combination with Glimepiride in comparison to Glimepiride alone on beta-cell function in type 2 diabetic patients. The primary endpoint of the study was the change in Homeostatic model assessment–Beta cell (HOMA-B) from baseline to the end of treatment (V10).

Secondary:

The secondary objective of the study was to investigate the effect of Pioglitazone in combination with Glimepiride vs. Glimepiride monotherapy on the change from baseline to study end (V10) in haemoglobin A1c (HbA1c), glucose, insulin, proinsulin, C-peptide, lipids, high sensitivity C-reactive protein (hs-CRP), Adiponectin, HOMA-Sensitivity (HOMA-S), and HOMA-B/Proinsulin.

Methodology: This study was designed as a prospective, comparative, randomised, double-blind, parallel, two-arm, multicentre, phase IIIb trial.

Number of Subjects:

Planned: 100 subjects (50 per treatment group)
Screened: 122 subjects
Randomized in the double-blind treatment period: 91 subjects

Analyzed: APT population: 91; APTv7 population: 82; PP population: 46

Analysis populations:

All patients treated (APT) population: All patients treated (i.e. all patients as randomised according to the intention-to-treat (ITT) principle).

APTv7 population: All patients in the APT who had baseline values of fasting glucose and fasting insulin and at least one post-baseline assessment under treatment of fasting glucose and fasting insulin between week 12 (i.e. V7 or early termination and treatment duration of at least 84 days) and week 24 (i.e. V10)). The primary analysis was based on the APTv7 population. The APT population was added as sensitivity analysis to ensure that there does not exist a bias due to early dropouts.

Per Protocol (PP) population: All patients in the APTv7 without any major protocol violations, who completed the study regularly (i.e. intake of at least 80% of study medication during the treatment period and last intake of study medication one day before regular visit V10).

Diagnosis and Main Criteria for Inclusion: Type 2 diabetic patients of either sex aged 30 to 75 years with at least 3 months of pre-treatment with Glimepiride monotherapy (1-3 mg/day) and characterized by insufficiently controlled glucose metabolism (HbA1c > 6.5% but < 8.5% and/or fasting plasma glucose (FPG) > 7 mmol/L).

Duration of Treatment: The duration of study participation for patients completing the study was 6 to 7 months (screening period, 6 months treatment period). The duration of the total study was planned to be 18 months.

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
Pioglitazone	30 mg tablet	30 mg QD	Oral	Ch.-B. 9230017B / 2740005B
Pioglitazone	45 mg tablet	45 mg QD	Oral	Ch.-B. 1250004A / 2250078C
Glimepiride	2 mg tablet	2 mg QD	Oral	Ch.-B. 6I54 / 0707281B
Glimepiride	4 mg tablet	4 mg QD	Oral	Ch.-B. 6H19 / 0702248C
Glimepiride	1 mg tablet + 4 mg tablet	5 mg QD	Oral	Ch.-B. 6I30 / 0701190C (Glimepiride 1 mg) Ch.-B. 6H19 / 0702248C (Glimepiride 4 mg)
Glimepiride	2 mg tablet + 4 mg tablet	6 mg QD	Oral	Ch.-B. 6I54 / 0707281B (Glimepiride 2 mg) Ch.-B. 6H19 / 0702248C (Glimepiride 4 mg)

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

Study Medication	Product Dose Strength	Study Dosage	Mode of Administration	Drug Product Lot Number
Placebo to Pioglitazone 30 mg	Tablet	N/A	Oral	Ch.-B. 2005068501 / 2005068501
Placebo to Pioglitazone 45 mg	Tablet	N/A	Oral	Ch.-B. 2005083901 / 2007075601
Placebo to Glimepiride 1 mg	Tablet	N/A	Oral	Ch.-B. 4627 / 6224
Placebo to Glimepiride 2 mg	Tablet	N/A	Oral	Ch.-B. 4632 / 6580

Criteria for Evaluation:

Efficacy:

Primary efficacy variable:

Change in beta-cell function as assessed by the HOMA-B score after 24 weeks of treatment (V10) as compared to baseline (V2).

Secondary efficacy variables:

Change from baseline (V2) to study end (V10) in

- HbA1c
- Glucose (fasting, area under the curve (AUC) during oral glucose tolerance test (OGTT))
- Insulin (fasting, AUC during OGTT)
- Proinsulin (fasting, AUC during OGTT)
- C-peptide (fasting, AUC during OGTT)
- Lipids (triglycerides, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, total cholesterol)
- hs-CRP
- Adiponectin
- HOMA-S
- HOMA-B/Proinsulin

Safety:

The assessment of safety is mainly addressed by

- Occurrence of adverse events (AEs)
- Change in clinical laboratory parameters (haematology, clinical chemistry)
- Rate of premature withdrawals

Statistical Methods:

Efficacy:

Demographic and baseline characteristics were summarised descriptively for the all patients treated analysis sets (APT and APTv7) and the per protocol set (PP).

The primary efficacy variable, the change in HOMA-B between baseline and V10 (ΔHOMA-B), was analysed for the APTv7 population (primary analysis set), the APT and the PP.

The following hypotheses were tested in a confirmatory manner using a one-sided t-test at the significance level of 0.025:

H0: $\mu Pio+SU \leq \mu SU$

H1: $\mu Pio+SU > \mu SU$

with μPio+Sulfonylurea (SU) as expected value of ΔHOMA-B under the combination therapy (Pioglitazone + Glimepiride) and μSU as expected value of ΔHOMA-B under Glimepiride monotherapy.

The secondary efficacy variables were evaluated using descriptive statistics primarily (absolute values at each time point and changes from baseline). In addition, two-sided 95% confidence intervals for between-group treatment differences were calculated using appropriate methods for

continuous or categorical variables. Analyses for the secondary efficacy parameters were performed for the APT, APTv7 and PP populations. All inferential analyses for the secondary efficacy parameters are to be interpreted in the exploratory sense.

Safety:

The safety variables were analysed for patients in the all patients treated set (APT). Safety was mainly assessed from the incidence of AEs, the changes of clinical laboratory parameters and the rate of premature withdrawals. The AEs were displayed in summary tables using descriptive statistics. They were grouped by MedDRA system organ class (SOC) and preferred term (PT) and analysed with regard to their severity and relationship to study treatment. Laboratory data were presented in tabulated statistical summaries of the raw data and changes from screening values as well as in shift tables using the ranges of reference values. Pertinent values in the data listings were flagged. The number of patients who discontinued the study prematurely were tabulated by reason for discontinuation. No statistical tests were performed.

Descriptive statistics for all recorded and derived variables used appropriate descriptive summary tables (continuous data: sample size, mean, standard deviation (SD), minimum, median, maximum; categorical data: sample size, absolute and relative frequency).

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

Of the 91 patients in the APT population, 52 (57.1%) were male and 39 (42.9%) were female. Both treatment groups had a slightly higher proportion of male patients. All patients were Caucasians except for two patients in the Glimepiride group who were of Asian origin. The average age was comparable across both treatment groups (61.9 (42, 75) (mean (min, max)) Pioglitazone + Glimepiride vs. 59.8 (41, 75) Glimepiride). Height and weight were also comparable across the two treatment groups (height: 169.3 (153, 186) vs. 171.4 (154, 190); weight: 94.9 (65, 159) vs. 91.8 (64, 144).

All patients in the APT population pre-treated their study disease with Glimepiride monotherapy within the last 3 months prior to study start. The most common concurrent conditions were diabetes mellitus type 2 (all patients in both treatment groups), hypertension (79.2% vs. 67.4% of patients in the Pioglitazone + Glimepiride and Glimepiride groups, respectively), hyperlipidaemia (27.1% vs. 37.2% of patients, respectively), and obesity (27.1% vs. 18.6% of patients, respectively). The most common concurrent medications reported were ACE inhibitors and diuretics, platelet aggregation inhibitors, HMG COA reductase inhibitors, and beta blocking agents.

Subject Disposition:

	Group A (Pioglitazone + Glimepiride)	**Group B Glimepiride**	**Total**
Screened			122
Randomised	48	43	91
Completed	32	18	50

	Group A (Pioglitazone + Glimepiride)	Group B Glimepiride	Total
Withdrawn due to AEs	5	2	7

Efficacy Results:

Analysis of the primary efficacy variable of the study (change in beta-cell function assessed by HOMA-B score between baseline and the last value under treatment in the APTv7 population) resulted in a distinctly higher effect in the Glimepiride group (+16.78%) as compared to the Pioglitazone + Glimepiride group (-4.79%). As the one-sided hypothesis setting for the primary variable expected a stronger increase under Pioglitazone + Glimepiride than under Glimepiride, the null hypothesis H0 of non-superiority of the combination therapy could not be rejected. There was no statistically significant difference between the two treatment groups. The result of the one-sided t-test ($p = 0.9681$) was confirmed by the results of the non parametric van Elteren and Wilcoxon two-sample tests (p-values of 0.9233 and 0.9667, respectively). Analyses of the APT and PP populations yielded similar results which can be interpreted confirmatorily as well.

Regarding the secondary efficacy parameters, however, a physiological and patho- physiological consistent chain of observations was made. The Pioglitazone + Glimepiride group showed a tremendous reduction in glucose (fasting values and those stimulated by OGTT) and HbA1c values, whereas only a minimal improvement in fasting glucose and HbA1c, and even a worsening regarding the area under the curve for glucose values during OGTT was detected in the Glimepiride monotherapy group. A major difference was observed between both treatment groups in regard of insulin sensitivity (HOMA-S doubled) and adiponectin concentrations (more than doubled) in the Pioglitazone + Glimepiride group and both parameters failed to do so in the Glimepiride group. On the other hand, parameters of pancreatic beta-cell function consistently declined with Pioglitazone + Glimepiride (fasting and stimulated insulin, C-Peptide, and proinsulin), and again failed to do so in the Glimepiride monotherapy group.

These secondary efficacy results had strong influence on the primary efficacy variable, as the HOMA-B score is calculated as a ratio of fasting insulin (multiplied by factor 20) and fasting glucose (subtracted by a blood sugar value of 3.5 mmol/L). Thus, HOMA-B scores, as indicator of beta-cell function, were to decline in the Pioglitazone + Glimepiride group in parallel with insulin and C-peptide.

Regarding lipid metabolism, no negative effects were observed with the combination treatment. There was a statistically significant slight increase in HDL cholesterol levels in the Pioglitazone + Glimepiride group compared to the Glimepiride group. However, this increase in the protective HDL lipoprotein fraction is rather a positive modulation of lipid metabolism. Therefore, it is appropriate to state that pioglitazone treatment had no negative influence on the cholesterol system.

Up to the last value under treatment the mean hs-CRP levels showed a decrease which was more pronounced in the Pioglitazone + Glimepiride group (-1.43 mg/L) than in the Glimepiride group

(-0.49 mg/L). Statistical comparison of changes between the treatment groups revealed no significant differences (p=0.7081, two-sided t-test).

Overall, descriptive results of the APTv7, APT and PP populations were similar with somewhat differing statistical results in the PP population due to a smaller sample size of this analysis set.

Safety Results:

Overall, the number of patients experiencing AEs was similar between the two treatment groups: After the start of study treatment a total of 109 AEs in 33 patients (68.8%) in the Pioglitazone + Glimepiride group and 80 AEs in 27 patients (62.8%) in the Glimepiride group were reported.

AEs from the Medical Dictionary for Regulatory Activities (MedDRA) SOCs 'infections and infestations' (26/91 patients, 28.6%), 'metabolism and nutrition disorders' (23/91 patients, 25.3%) and 'musculoskeletal and connective tissue disorders' (12/91 patients, 13.2%) were reported most frequently with a slightly higher incidence in the Pioglitazone + Glimepiride group. Otherwise, comparison of the treatment groups regarding the frequency of distinct MedDRA SOCs revealed no relevant differences.

No patient died in the study. A total of 6 serious AEs (SAEs) occurred in 4 patients: 2 events in 2 patients of the Pioglitazone + Glimepiride group, and 4 events in 2 patients of the Glimepiride group. None of the SAEs was judged as being related to the study medication.

The percentage of patients with AEs considered related to study medication (defined as definite, probable or possible) was also similar between the two treatment groups, i.e. 12/48 patients (25.0%) of the Pioglitazone + Glimepiride group and 8/43 patients (18.6%) in the Glimepiride group. Most of the related events reported in the Pioglitazone + Glimepiride group were commonly observed under pioglitazone hydrochloride and/or sulfonylurea. A slightly higher rate of hypoglycaemic events was observed in the Pioglitazone + Glimepiride group (8 events in 5 patients) as compared to the Glimepiride monotherapy (2 events in 2 patients).

The number of patients withdrawn due to AEs was low. Five early withdrawals in the Pioglitazone + Glimepiride group were due to related AEs and two early withdrawals in the Glimepiride group were due to a related AE and an unrelated SAE. A distinctly higher proportion of patients in the Glimepiride group (21/43 patients, 48.8%) had withdrawn due to lack of efficacy as compared to the Pioglitazone + Glimepiride group (8/48 patients, 16.7%).

No apparent differences between the treatment groups were observed in either mean changes from screening to the last value or numbers of individual patients with clinically significant abnormalities in any haematological or clinical chemistry parameters.

Conclusion:

In conclusion, the present study shows that the addition of Pioglitazone to Glimepiride treatment in type 2 diabetics is a safe, well-tolerated and highly efficient antidiabetic approach. Fasting and stimulated glucose levels were considerably lowered and HbA1c values were considerably improved - close to normoglycaemic conditions - in patients on combination therapy, whereas

the group receiving Glimepiride monotherapy did not show any relevant improvement in glycaemic control. HOMA-S, the indicator of insulin sensitivity at insulin- receptor site, considerably improved in agreement with the understanding of the pharmacological action of thiazolidinediones. Increases in adiponectin levels paralleled (or even triggered) improvements in insulin sensitivity with Pioglitazone. However, HOMA-B scores, indicators of pancreatic beta-cell function and primary endpoint variable in the present study, did not follow the hypothetical expectations. HOMA-B rather slightly declined with Pioglitazone combination and considerably increased with the Glimepiride monotherapy. This difference is physiologically plausible, when anticipating that endocrine pancreatic function was attenuated in the Pioglitazone combination group in a glucose-regulated feedback loop to prevent from hypoglycaemic decompensation. The reductions in insulin, C-peptide and proinsulin with Pioglitazone were even requesting the decline in HOMA-B scores in the present study. In contrast to sulfonylureas, which don't follow any glucose-controlled regulation, the observation of excellent metabolic control with Pioglitazone and the functional down-regulation of beta-cell activity in the present study both highlight the positive value of thiazolidinediones in modern antidiabetic therapy.

Significant Changes During Study:

Four amendments to the protocol were implemented and all of the changes have been taken into account in this report.

Amendment 1 (Final revised protocol, dated 26 October 2006)
Due to an internal audit of the final revised version of the study protocol, dated 27 September 2006, several formal changes were performed that were considered as not substantial.
This version of the study protocol was not approved by the authorities as the changes were considered as substantial and were requested to be submitted as such.

Amendment 2 (Final revised protocol, dated 21 December 2006)
Due to experiences during the initiation visits at the involved study centres it was decided to ease the selection criterion regarding renal disease from serum creatinine > 1.2 mg/dL to > 1.8 mg/dL. Otherwise, the inclusion of - especially male - patients with already slightly increased, non-pathological creatinine values would not have been possible.
The change refers to section 4.3.3 of the study protocol ('exclusion criteria').
The change was restricted to one selection criteria and the definition of the patient population without affecting the safety of the patients. It did not inflict the primary parameter and endpoint of this study.
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Amendment 3 (Final revised protocol, dated 07 February 2007)
Due to a request from the Federal Institute for Drugs and Medical Devices (BfArM) concerning the calculation of the glomerular filtration rate a further revision of the study protocol was necessary.
Therefore, in section 5.2 of the study protocol ('trial procedures') a new section 5.2.3 was

added:
“5.2.3 Estimation of the Glomerular Filtration Rate
Renal function will be judged by the estimation of the glomerular filtration rate according to the Cockroft-Gault formula. The Cockroft Gault formula may be used to calculate an estimated creatinine clearance, which in turn estimates GFR.
Cockroft-Gault formula for **female** patients:
[ ] ([ ]) [ ]
serum creatinine[***mg / dl***]
age years weight kg
GFR ml / min .
×
− ×
= ×
72
140
0 85
Cockroft-Gault formula for **male** patients:
[ ] ([ ]) [ ]
serum creatinine[***mg / dl***]
age years weight kg
GFR ml / min
×
− ×
=
72
140
Serum creatinine and body weight will be determined at visits V1, V4, V6-V10. The calculated GFR values will be documented in the central laboratory. The central laboratory will inform the investigator about values considered to be clinically significant abnormalities. Patients displaying an estimated GFR < 40 ml/min need to be withdrawn from further study participation (see section 7.6. Premature Discontinuation/Patient Replacement).”
Additionally, due to the experiences during the first months of recruitment it was decided to ease the selection criterion regarding the forbidden pre-treatment with thiazolidines to 12 months prior to study participation.
The change refers to section 4.3.3 of the study protocol (‘exclusion criteria’):
• criterion no. 12 “Pretreatment with thiazolidinediones” was changed to “Pretreatment with thiazolidinediones within the last 12 months”
The change was restricted to one selection criteria and the definition of the patient population without affecting the safety of the patients. It did not inflict the primary parameter and endpoint of this study.
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Amendment 4 (Final revised protocol, dated 05 March 2007)
Due to experiences during the first months of the study concerning a possibly increased risk for the occurrence of hypoglycaemia in patients treated with a Glimepiride dosage > 4 mg it was decided to delete the withdrawal criterion "Dose titration from mid to high dose cannot be performed".
The change refers to section 5.2.9 of the study protocol ('titration steps of study medication').
The following paragraphs were added:
"Dose titration from mid to high dose at V4 may be omitted in case the investigator considers this dose increase might put the patient at risk of symptomatic or severe hypoglycaemia. In this case all procedures scheduled for V4 will be performed and the investigator will supply the patient with the study drug (dosage mid) for V5. If possible, dosage mid should be kept constant until the remainder of the study."
"In order to prevent hypoglycaemic episodes resulting from the intake of 5 mg Glimepiride, dose reduction from mid to low dose is allowed for patients
• taking mid dose after omitting dose titration at V4
• requiring a second dose reduction step after first dose reduction from high to mid dose
As dosage low will not be provided at any visit after V2, the blisters provided for dosage mid may be adjusted to dosage low by cutting off row C. Since 1 mg placebo Glimepiride in group A and 1 mg Glimepiride in group B will be omitted by cutting off row C, this dose reduction is limited to patients belonging to group B.

Changes in the planned analysis included:

The final statistical analysis plan (SAP) was finalized prior to database closure.

The APT population was added as sensitivity analysis to ensure that there does not exist a bias due to early dropouts. Primary analysis was based on the APTv7 population (equals ITT population of the study protocol). "All patients treated – Safety" population was renamed to "All patients treated (APT)" as to deal with same population for safety and efficacy analysis. Full analysis set (Intent-to-Treat) renamed to "All patients treated – V7 (APTv7)" as to be consistent with naming of efficacy population APT.

Unless otherwise specified there was no substitution of missing data, i.e. missing data will not be replaced, missing data will be handled as 'missing' in the statistical evaluation. Considering last-observation-carried-forward approach (LOCF), the last available value under treatment was used for the efficacy analysis in the all patients treated – V7 (APTv7). For the efficacy analysis in the all patients treated population (APT) the last available value (even if it is the baseline value) of the parameter was be used. Missing baseline values were not to be replaced. For descriptive statistics the last value under treatment for the APTv7 or last value for APT, respectively, was conducted in addition to the regular visits.

Regarding subgroup analysis, as treatment effect is assumed to be best under high titration dose the primary efficacy variable was evaluated for the subgroup of patients in the APTv7 and PP

populations who achieved high titration dose of study medication one day before the assessment of the last value under treatment.

Original sample size calculation and hypothesis formulation was not consistent, therefore, it was modified to ensure a total of 78 patients in the full analysis dataset and with a calculated drop-out rate of 25% a total number of 100 patients will be included in the study.

For all laboratory parameters under OGTT some of the timepoints were not analysed by the central laboratory and therefore were not included in the analysis.

The formula mentioned in the SAP for the calculation of the secondary efficacy parameter 'HOMA-S' erroneously did not include the factor 100 to achieve percentage units. Therefore, the following formula was used for analyses instead:

- HOMA-S [%] = (22.5*100)/(glucose [mmol/L] * insulin [μ U/mL])

Study ID Number:

ATS K020 (D-Pio 112)

Other Study ID Number(s):

2006-002271-41 [EudraCT Number]

D-PIO-112 [Takeda ID]

U1111-1114-3221 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012