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 Patients with Type 2 Diabetes Mellitus and Coronary Heart Disease at High Risk for Vascular Complications: A Placebo-Controlled Study - PIOCARD

Phase of Development: Phase III

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

Name of Finished Product: Actos®

Investigators: 7 principal investigators enrolled subjects in the double-blind treatment period

Study Sites: 7 sites in Germany enrolled patients in the double-blind treatment period.

Study Site 1
Institute of Clinical Research and Development (ikfe GmbH), Clinical Department, Parcusstraße 8, D-55116 Mainz, Germany

Study Site 2
Medizinische Universitätskliniken, Abt.1 (Endokrinologie und Stoffwechsel), Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany

Study Site 3*
Johannes Gutenberg-Universität Mainz (II. Med. Klinik und Poliklinik), Langenbeckstr. 1 D-55131 Mainz, Germany
*Please note that there was no patient screening and enrolment at this study site

Study Site 4
Universitäres Herz- und Gefäßzentrum Hamburg GmbH, Wördemanns Weg 25-27, D-22527 Hamburg, Germany

Study Site 5*
Medizinische Hochschule Hannover, Kardiologie und Angiologie, Carl-Neuberg-Str. 01, D-30625 Hannover, Germany
*Please note that there was no patient screening and enrolment at this study site

Study Site 6*
Med. Univ.- Klinik und Poliklinik II, Sigmund-Freud-Str.25, D-53105 Bonn, Germany
*Please note that there was no patient screening and enrolment at this study site

Study Site 7
Kardiologische Gemeinschaftspraxis, Leipziger Str. 137, D-09113 Chemnitz, Germany

Study Site 8
CCB, Cardioangiologisches Centrum Bethanien, Im Prüfling 23, D-60389 Frankfurt a. M., Germany

Study Site 9
ikfe Berlin GmbH, Große Hamburger Str. 5 – 11, D-10115 Berlin, Germany

Study Site 10
Heinz-Meise-Str. 101, D-36199 Rotenburg a. d. Fulda, Germany

Publication Based on the Study (Citation) at Time of Study Completion: Forst T, Karagiannis E, Lübben G, Hohberg C, Schöndorf T, Dikta G, Drexler M, Morcos M, Dänschel W, Borchert M, Pfützner A. Pleiotrophic and anti-inflammatory effects of pioglitazone precede the metabolic activity in type 2 diabetic patients with coronary artery disease. Atherosclerosis. 2008;197(1):311–317

Study Period:

Date first subject signed informed consent form: 24 February 2005

Date of last subject's last visit/contact (from the Clinical database): 25 September 2006

Objectives:

Primary:

The primary objective was to evaluate the effects of Pioglitazone on the up regulated inflammatory system in patients with type 2 diabetes with angiographically proven coronary heart disease (CHD). Primary efficacy parameter was Matrix Metalloproteinases-9 (MMP-9) on day 28 (final visit, visit 7) versus MMP-9 on day 0 (baseline, visit 2).

Secondary:

The secondary objective was to investigate the effect of Pioglitazone in comparison to Placebo

on laboratory and clinical markers for atherosclerosis.

Methodology: Prospective, multi-centre, Placebo-controlled, double-blinded, randomised, parallel, two-arm study.

Number of Subjects:

Planned: It was planned to enroll 160 patients in order to achieve 150 patients for each group with 75 patients.

Screened: 145 subjects

Randomised: 93 subjects

Analyzed: The trial terminated earlier (44/47) instead of 2 x 75 patients planned because of the significant reduction in MMP9 in the treatment group compared to the control group. In this trial, 91 patients (Treatment/Control: 44/47) were in the full analysis set (FAS) and 88 patients (Treatment/Control: 42/46) in per-protocol analysis set (PAS) respectively. The trial was terminated after demonstration of the significant improvement of the primary parameter MMP-9 in favor of pioglitazone vs. control. Therefore, the study ended with fewer patient numbers than originally planned. All patients enrolled in active treatment of this study were treated to the end of protocol procedures. None of the therapies were interrupted early as consequence of the early termination decision. Data generated after the interim analysis by treatment of enrolled patients was considered in the final analysis, in which all data of the complete trial was analyzed for all planned parameters.

Diagnosis and Main Criteria for Inclusion: Male or female patients aged 20 to 80 years; diagnosis of type 2 diabetes and angiographically proven coronary heart disease with high sensitive C-reactive protein (hs-CRP) level of > 2 mg/l (amended to > 1 mg/l).

Duration of Treatment: The mean duration of study participation for patients completing the study was 27 days ± 4 days. The duration of the total study was 19 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	45 mg tablet	45 mg QD	Oral	0511004

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	Tablet	N/A	Oral	0511004

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the change in the natural log value of MMP-9 on day 28 versus on day 0.

The secondary efficacy variables (e.g. cardiovascular risk markers like hs-CRP, monocyte chemoattractant protein – 1 (MCP-1), intact proinsulin, metabolic markers like adiponectin, fasting blood glucose, lipids) were evaluated by the method of descriptive statistics where the absolute values and changes from baseline were compared between the treatment groups, if appropriate. Between-group treatment differences were calculated with two-sided confidence interval of 95%.

Safety:

Safety assessments included adverse event reports, clinical laboratory parameters and premature withdrawals.

Statistical Methods:

Efficacy:

The primary study parameter was evaluated by one-sided t-test and analysis of covariance (ANCOVA) for the full analysis set (FAS) and per-protocol set (PAS).

The secondary efficacy variables were evaluated by the method of descriptive statistics where the absolute values and changes, when appropriate, from baseline were compared between the treatment groups. Between-group treatment differences were calculated with two-sided confidence interval of 95% in FAS and PAS.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

In this trial, 79 out of 92 (85.9%) patients were male and 13 out of 92 patients (14.1%) were female. All (100%) of the patients were of Caucasian origins. The age ranged between 44 to 78 years. The mean age was 65 ± 7 years. The mean BMI was 30.1 ± 4.1.

Subject Disposition:

93 patients were randomised, including one patient who did not consume any dose of study medication. Therefore, 92 patients were in the ITT. 88 patients completed the study.

Efficacy Results:

Primary Efficacy

The statistical analysis of primary efficacy variable (MMP-9 on day 28 vs. MMP-9 on day 0, Baseline value) shows a significant reduction in MMP-9 in the Pioglitazone group compared to the Placebo group in the PAS. The result was based on the two-sample Wilcoxon test and confirmed by an ANCOVA analysis.

Time course of MMP-9 during Pioglitazone and Placebo Treatment (FAS)

MMP-9 (ng/ml)	Placebo		Pioglitazone	
	n	Mean ± SD	n	Mean ± SD
Baseline	47	419.1	44	423 ± 266*
3 Days	47	403 ± 217	44	373 ± 262*
7 Days	47	372 ± 170	42	367 ± 251*
10 Days	46	400 ± 250	42	338 ± 222*
14 Days	46	386 ± 206	42	361 ± 240*
28 Days	47	427 ± 166	44	392 ± 286 #
n is the number of patients, Mean is arithmetic mean and SD is standard deviation; * $p < 0.05$ versus baseline; # $p < 0.05$ Pioglitazone vs. Placebo				

Secondary Efficacy

Secondary parameters analyzed showed significant results of pioglitazone treatment versus placebo treatment and/or versus Baseline respectively, for the cardiovascular risk parameters hs-CRP, MCP-1, Intact proinsulin, soluble cluster of differentiation 40 ligand (sCD-40L), and the metabolic markers adiponectin, fasting blood glucose, high density lipoprotein (HDL), and triglycerides. No significances were detected in this trial for the other investigated parameters of interleukin-6 (IL-6), haemoglobin A1c (HbA1c), total cholesterol, low density lipoprotein (LDL), P-selectin, homeostatic model assessment – sensitivity and Beta cell function (Homa-S/B) scores, Insulin, soluble intercellular adhesion molecules (ICAM) 1, soluble vascular cell adhesion molecule (sVCAM) 1, tissue plasminogen activator (tPA), macrophage migration inhibitory factor (MIF), tumor necrosis factor-alpha (TNF-α), angiotensin-II, and Complement factor C3.

Laboratory measurements at baseline and after 28 treatment days

Parameter	Placebo		Pioglitazone	
	Baseline	28 Days	Baseline	28 Days
Interleukin-6 (pg/ml)	3.3 ± 0.4	3.3 ± 0.4	4.7 ± 9.8	4.8 ± 10.7
hs-CRP (mg/l)	2.7 ± 1.7	3.1 ± 2.3	3.0 ± 2.2	1.9 ± 1.8*#
Glucose (mg/dl)	137.6 ± 37.8	133.2 ± 26.3	145.7 ± 37.4	129.2 ± 42.1*
MCP-1 (pg/ml)	455.1 ± 132.4	470.6 ± 146.1	438.6 ± 117.7	412.9 ± 115.3*#
HbA1c (%)	6.8 ± 0.7	6.7 ± 0.7	7.2 ± 1.2	7.1 ± 1.2

Parameter	Placebo		Pioglitazone	
	Baseline	28 Days	Baseline	28 Days
Intact proinsulin (pmol/L)	29.7 ± 28.9	25.7 ± 20.1*	33.7 ± 39.4	20.7 ± 19.8*#
Adiponectin (µg/ml)	8.9 ± 4.7	8.8 ± 4.3	8.6 ± 3.3	23.4 ± 10.0*#
SCD40 ligand (ng/ml)	1.21 ± 1.12	1.13 ± 0.98	1.47 ± 1.66	1.00 ± 1.02*
Total cholesterol (mg/dl)	184 ± 43	184 ± 37	180 ± 37	182 ± 39
Low density lipoprotein (mg/dl)	87 ± 35	89 ± 34	94 ± 28	94 ± 28
High density lipoprotein (mg/dl)	43.8 ± 8.9	44.7 ± 9.6	45.3 ± 9.1	47.8 ± 9.5*#
Triglycerides (mg/dl)	251 ± 215	244 ± 155	192 ± 119	169 ± 97*#
P-Selectin (ng/ml)	102 ± 29	103 ± 30	102 ± 28	99 ± 28$^{p=0.053}$
HOMA-S	8.3 ± 9.4	7.0 ± 5.4	6.3 ± 4.0	4.9 ± 5.5
Mean ± standard deviation; where * $p < 0.05$ versus baseline; # $p < 0.05$ Pioglitazone vs. Placebo				

Parameter	Placebo		Pioglitazone	
	Baseline	28 Days	Baseline	28 Days
Insulin (µU/ml)	21.7 ± 16.4	20.1 ± 12.4	16.9 ± 9.0	13.9 ± 9.9
HOMA-B	108.2 ± 60.4	104.7 ± 50.7	83.46 ± 52.0	92.25 ± 63.9
slCAM1 (ng/ml)	297.7 ± 56.3	300.9 ± 61.2	306.5 ± 81.8	302.8 ± 80.2
sVAM1 (ng/ml)	757.3 ± 204.7	767.7 ± 214.3	881.2 ± 384.6	936.6 ± 447.8
t-PA (ng/ml)	15.08 ± 4.94	15.23 ± 5.25	16.28 ± 6.05	14.90 ± 6.63
MIF (ng/ml)	9.94 ± 4.07	10.59 ± 5.10	10.29 ± 5.18	9.38 ± 3.44
TNF-α (pg/ml)	15.63 ± 0.0	15.63 ± 0.0	18.60 ± 14.92	18.34 ± 13.98
Angiotensin II (ng/l)	9.0 ± 8.1	12.7 ± 24.8	11.5 ± 16.8	7.8 ± 8.4
Complement factor C3 (mg/dl)	162.1 ± 40.1	168.5 ± 50.2	164.1 ± 47.9	152.3 ± 32.8

Safety Results:

In the all treated patients group, adverse events were reported in 34 out of 44 patients in the Pioglitazone group (77.3%) and 22 out of 48 patients in the Placebo group (45.8 %). No serious

adverse event was reported in the trial. All changes of safety parameters (e.g. haematologic parameters like haemoglobin, small blood cell count, standard hepatic and renal parameters, parameters of cardiac function like troponin T) were moderate and classified as clinically not relevant.

Conclusion:

Pioglitazone showed an immediate effect on surrogate parameters of plaque stability and low grade inflammation in type 2 diabetic patients with proven cardiovascular disease. It also exerts an overall improvement of several cardiovascular risk parameters, including metabolic, inflammatory and lipid markers in a 4 weeks treatment.

There were no relevant changes in safety parameters of Haematology (haemoglobin, Erythrocyte count, Haematocrit, MCG, MCV, MCHC, platelets, leukocytes, basophils, eosinophils, neutrophils, lymphocytes and monocytes), hepatic (ASAT/ALAT and γ-GT), renal (Creatinine) or cardiac function (Troponin T and Creatine Kinase (CK-MB)), or parameters of homeostasis (Na+, K+, and Cl-).

Significant Changes During Study:

- 18-Mar- 2005: Exclusion criterion 10 for was changed from ’A history of significant cardiac insufficiency (NYHA stage I – IV), respiratory, or hepatic insufficiency’ to ‘A history of symptomatic cardiac insufficiency (NYHA stage II – IV), respiratory, or hepatic insufficiency’.
- 12-May-2005: Inclusion criterion 3 was changed from hs-CRP > 2 mg/l to hs-CRP > 1 mg/l.
- It was planned to enroll 160 patients in order to achieve 150 patients for each group with 75 patients. In this trial, 91 patients (Treatment/Control: 44/47) were in the full analysis set (FAS) and 88 patients (Treatment/Control: 42/46) in per-protocol analysis set (PAS) respectively. The described reduction of patient numbers did not however interfere, weaken or bias the significant results in regard to the primary efficacy, which were clearly evident already after the planned interim analysis with half of the planned patient data sets (80 of 160 planned patients). By the early termination, the statistical power of the trial decreased moderately by the reduced data set. However, since the significant results cannot be augmented beyond, a higher number of patients would not have increased evidence. Eventually, further patient enrollment would not or only moderately decrease the given variances of this analysis, while exposing patients to unnecessary medical procedures.

Study ID Number:

ATS-K-016

Other Study ID Number(s):

2004-004226-28 [EudraCT Number]

DATE OF DISCLOSURE SYNOPSIS: 20 June 2012