Clinical Trial Results Disclosure Synopsis

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

Title of Study: Effect of Pioglitazone compared to a combination therapy with Ramipril and to a Ramipril monotherapy on low grade inflammation and vascular function in patients with increased cardiovascular risk and an activated inflammation. A randomized, double-blinded phase II study.

Phase of Development: Phase II

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

Name of Finished Product: Actos®

Investigators: 17 principal investigators enrolled subjects for screening.

Study Sites: 17 sites in Germany enrolled subjects into the double-blind treatment period.

Study Site 01: Ikfe GmbH, 55116 Mainz
Study Site 02: Ikfe GmbH, 10115 Berlin
Study Site 03: KKS GWT-TUD, 01307 Dresden
Study Site 05: KF Berlin-Buch GmbH, 13125 Berlin
Study Site 06: KF Berlin-Mitte GmbH, 10117 Berlin
Study Site 07: KF Hannover GmbH, 30159 Hannover
Study Site 08: 59368 Werne
Study Site 09: 45138 Essen
Study Site 11: 99444 Blankenhain
Study Site 12:91365 Weilersbach
Study Site 13: 78549 Spaichingen
Study Site 16: 73326 Deggingen
Study Site 17: 12524 Berlin
Study Site 18: 01129 Dresden
Study Site 19: 50823 Köln
Study Site 22: 78628 Rottweil
Study Site 23: 34270 Schauenburg

The study centres 04 (88400 Bieberach), 10 (22177 Hamburg), 14 (12687 Berlin), 15 (28844 Weyhe), 20 (50389 Wesseling), and 21 (72336 Balingen) did not enrol any study patient. In the study centres 07 (30159 Hannover) and 12 (91365 Weilersbach), 22 and 2 patients, respectively, were screened and enrolled but not randomized for the treatment with study medication.

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

Study Period:

Date first subject signed informed consent form: 07 March 2007

Date of last subject's last visit/contact (from the Clinical database): 21 May 2008

Objectives:

Primary:

The aim of this study was to investigate the effect of Pioglitazone (PIO) compared to a combination therapy with Ramipril (PIO + Rami) and to Ramipril (Rami) alone on low grade inflammation and vascular function in patients with increased cardiovascular risk and an activated inflammation, by evaluation of the high-sensitivity C-reactive Protein (hs-CRP) change after 12 weeks of treatment compared to baseline.

Secondary:

Investigation of the effects of Pioglitazone compared to a combination therapy with Ramipril and to Ramipril alone on laboratory parameters such as lipids, inflammatory markers, parameters of vascular function and other parameters of special interest.

Methodology: Prospective, double-blind, multicentre, randomized, parallel three-arm study

Number of Subjects:

Planned: 250 subjects screened to achieve 144 randomized subjects (48 per treatment arm; 1:1:1)
Enrolled and screened: 440 subjects
Randomized into the double-blind treatment period: 172 subjects
Analyzed: Safety Set: 172; Full analysis Set: 149; Per-Protocol Set: 140

Diagnosis and Main Criteria for Inclusion:

Male and female, non-diabetic, hypertensive patients with an age of 30-75 years, a hs-CRP value in the range $\geq$ 1.0 mg/l and < 10.0 mg/l, and a stable pre-treatment with an angiotensin converting enzyme (ACE) inhibitor for at least 12 weeks. A signed written consent had to be available prior to enrolment.

Duration of Treatment: The treatment phase with test or reference study medication was defined to be 13 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
Pioglitazone	15 mg tablet	15 mg	Oral	31138C
Pioglitazone	30 mg tablet	30 mg	Oral	33398A
Ramipril	2.5 mg	2.5 mg	Oral	N/A
Ramipril	5 mg	5 mg	Oral	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
Placebo to Pioglitazone	Tablet	N/A	Oral	2005084001, 2005068501
Placebo to Ramipril	Tablet	N/A	Oral	N/A

Criteria for Evaluation:

Efficacy:

Primary: The primary efficacy variable was the change of hs-CRP after 12 weeks of treatment (visit V5.2) as compared to baseline (visit V1.2). The change was to be calculated using values of hs-CRP after 12 weeks of treatment minus the hs-CRP values at baseline.

Secondary: Investigation on the effect of Pioglitazone compared to a combination therapy with Ramipril and to Ramipril alone over 12 weeks on several laboratory parameters such as lipid metabolism (high density lipoprotein (HDL), low density lipoprotein (LDL), oxidized low density lipoprotein (oxLDL), total cholesterol, triglycerides, adiponectin), glucose tolerance and insulin sensitivity (fasting glucose, fasting insulin, glycosylated haemoglobin (HbA1c), intact proinsulin, C-peptide, Homeostatic Model Assessment-sensitivity (HOMA-S), Homeostatic Model Assessment-insulin secretion (HOMA-B), Oral Glucose Tolerance Test (oGTT)), inflammation and vascular function (hs-CRP, monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), endothelin 1-21, soluble intercellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule (sVCAM), P-Selectin, asymmetric dimethylarginine (ADMA), nitrotyrosine), and parameters of special interest (placental growth factor, relaxin, osteoprotegrin, plasminogen activator inhibitor-1 (PAI-1), 11-dehydroxy-thromboxan B2, per-ox-assay, myeloperoxidase, 24-hour blood pressure (BP) profile).

Safety: Incidence of adverse events, changes in safety laboratory parameters, changes in physical examination and vital signs (with BP self monitoring), and the rate of premature withdrawals.

Statistical Methods:

Data were summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements. Standard descriptive summary statistics were done for continuous variables (i.e. arithmetic mean, standard deviation, minimum/maximum value, lower/median/upper quartile, number of non-missing values). Categorical data were displayed in frequency tables using counts and percentages. Individual patient data listings were presented parameterwise and were sorted by treatment group, centre, patient number and visit. Summary tables were displayed by treatment group and for the total of the sample. The safety analyses were done for the all patients treated set, efficacy analyses were conducted for the full analysis set (primary set) and for two per-protocol analysis sets. For definition of the full analysis set, hs-CRP values > 10 mg/l after baseline were excluded from the statistical analyses due an agreement for the final statistical analysis plan (SAP) after blinded review of efficacy results since high hs-CRP values were distorted by study-specific not relevant infections in most of the cases (e.g., nasopharyngitis or cystitis).

However, in addition, patients with hs-CRP values > 10 mg/l at their individual last observation were excluded from a second per-protocol set, in order to confirm the robustness of efficacy results derived from evaluation of the full-analysis and the initial per-protocol set of patients.

All inferential statistical analyses for the primary and the secondary efficacy parameters were interpreted in the exploratory sense only, using a pooled-centre analysis for the main efficacy evaluation (3 sites). The evaluation of the primary efficacy variable based on a general model for analysis of covariance (ANCOVA) with the fixed effect factors for treatment group and centre, and with the baseline hs-CRP value as covariate. An 'unpooled' analysis and an analysis without factor 'centre' were calculated additionally for hs-CRP. The natural logarithmic transformation was done for the hs-CRP values due to a skewed distribution.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

All 172 (62 Pioglitazone vs. 53 Ramipril Vs. 57 Pioglitazone + Ramipril) of the patients in the safety set were of Caucasian origin. When the three treatment groups are compared in this section, the order Pioglitazone vs. Ramipril vs. Pioglitazone plus Ramipril always applies. The average age overall was 60.0 (8.7) (mean ± standard deviation (SD)) and was comparable across all three treatment groups (59.6 (9.2) vs. 60.2 (8.8) vs. 60.4 (8.3)). Eighty-three (83) patients were male (27 vs. 29 vs. 27) and 89 were female (35 vs. 24 vs. 30). Height, weight and body mass index (BMI) were also comparable across all three treatment groups (height: 168 (7.8) vs. 169 (9.0) vs 169 (8.5); weight: 86.2 (14.9) vs. 86.9 (13.9) vs. 88.1 (16.8); BMI: 30.5 (5.0) vs. 30.3 (4.3) vs. 30.7 (5.0).

Prior medications were recorded at least once in all 172 patients with the most frequently listed preparations (in about 10% of the patients) corresponding to the pre-defined study indication of increased cardiovascular risk with activated inflammation and findings in medical history (mainly hypertension). Most frequently listed single diseases (in > 5% of the patients) were osteoarthritis (25.0%), hypercholesterolaemia (19.8%), obesity (17.4%), goitre (14.5%), back pain (12.8%), hyperlipidaemia (12.2%), hyperuricaemia (9.9%), benign prostatic cancer (9.3%),

cervicobrachial syndrome (8.1%), arterial sclerosis (8.1%), lipid metabolism disorder (7.0%), gastritis (6.4%), sleep apnoea syndrome (6.4%), hypothyroidism (6.4%), and varicose veins (5.8%).

Subject Disposition:

A total of 440 patients were screened and enrolled by 17 participating German study centres. Thereof, 172 (62 Pioglitazone vs. 53 Ramipril vs. 57 Pioglitazone + Ramipril) patients at 15 study centres were randomized and treated with at least one dose of study medication yielding the safety set. Twenty-three (23) patients failed to provide one evaluable hs-CRP baseline value < 10mg/l and at least one post-baseline assessment for hs-CRP ≤ 10mg/l yielding the full analysis set of 149 (52 vs. 44 vs. 53). Moreover, a total of 32 cases presented major protocol violations and were excluded as well from the all-patients-treated set, leading to 140 (48 vs. 42 vs. 50) patients allocated to the per-protocol analysis set. A total of 46 patients (26.7%; 20 vs. 15 vs. 11) discontinued the study prematurely.

Efficacy Results: (Full Analysis Set: n=149, 52 vs. 44 vs. 53)

Primary Efficacy Parameter (pooled-centre analysis):

The results for the hs-CRP change between last observation carried forward (LOCF) and V1.2 were as follows for the 3 treatment groups:

Change of hs-CRP [mg/L]	**Pioglitazone; n=52**		**Ramipril; n=44**		**PIO + Ramipril; n=53**	
	n	**mean ± SD (median) geom. mean**	**n**	**mean ± SD (median) geom. mean**	**n**	**mean ± SD (median) geom. mean**
Baseline	52	3.54 ± 2.54 (2.70) 2.52	44	2.90 ± 2.26 (2.35) 2.03	53	2.98 ± 2.15 (2.50) 2.32
LOCF	52	2.65 ± 2.02 (2.15) 1.91	44	3.47 ± 2.62 (2.36) 2.52	53	2.50 ± 1.98 (2.17) 1.84
Change	52	-0.89 ± 1.98 (-0.50)	44	0.58 ± 2.13 (0.23)	53	-0.49 ± 2.11 (-0.60)
Patients with complete observations for original data; n: number of patients; mean: arithmetic mean; SD: standard deviation						

The development of hs-CRP under study therapy provided a clear decrease between baseline and individual last observation for both Pioglitazone and the combination treatment. Exploratory simultaneous 95% confidence limits according to Tukey-Kramer for the antilogs of the LS-means per group and for the antilogs of the differences between the LS-means revealed significant differences (i.e., value '1' not included) for Pioglitazone monotherapy (p=0.0211) and for the combined treatment (p=0.0282) at the exploratory significance level of α =0.05, as well as for the pairwise comparison of Pioglitazone with Ramipril monotherapies in favour of

Pioglitazone (p=0.0128) and for the comparison of the combined treatment with Ramipril alone in favour of the combination therapy (p=0.0163). The p-value for testing the null-hypothesis of equal overall centre means was p=0.0735 and the p-value related to the ANCOVA F- test for testing the global null-hypothesis of equal treatment means for the change from baseline with log- transformed data was p=0.0066.

Secondary Efficacy Parameters (pooled-centre analysis):

A summarizing overview of the secondary efficacy results is shown in the listing below providing the mean change with standard dev. (median) between baseline (V1.2) and the individual study end (LOCF or V5.2):

Parameter (V1.2 vs. LOCF)	**Unit**	**Pioglitazone; n=52**		**Ramipril; n=44**		**PIO + Ramipril; n=53**	
		n	**mean ± SD (median)**	**n**	**mean ± SD (median)**	**n**	**mean ± SD (median)**
hs-CRP (V3)	mg/L	44	-0.77 ± 2.28 (-0.49)	36	0.19 ± 1.71 (-0.07)	49	-0.70 ± 1.27 (-0.55)
hs-CRP (V4)	mg/L	40	-0.64 ± 2.16 (-0.76)	33	-0.01 ± 1.15 (-0.11)	43	-0.81 ± 1.66 (-0.68)
hs-CRP (V5.2)	mg/L	48	-0.88 ± 1.78 (-0.50)	42	0.55 ± 2.16 (0.23)	46	-0.43 ± 2.23 (-0.53)
Glucose (=G)	mg/dL	52	-2.7 ± 10.5 (-2.5)	43	1.6 ± 7.8 (1.0)	53	-3.4 ± 9.3 (-3.0)
Insulin (=I)	mU/L	52	-2.8 ± 4.8 (-2.4)	43	0.5 ± 3.5 (0.0)	53	-5.4 ± 11.1 (-3.0)
AUC(I)	hmU/L	41	-55.8 ± 72.6 (-43.3)	36	-4.8 ± 43.2 (-1.5)	43	-41.3 ± 39.2 (-33.9)
AUC(G)	hmg/dL	41	-18.1 ± 47.7 (-25.5)	36	-5.8 ± 47.9 (-4.3)	43	-29.8 ± 46.6 (-25.5)
AUC(I)/AUC(G)	dU/L	41	-0.16 ± 0.26 (-0.12)	36	0.00 ± 0.15 (-0.01)	43	-0.10 ± 0.13 (-0.11)
HbA_{1C}	%	52	-0.03 ± 0.25 (-0.10)	44	0.02 ± 0.54 (0.00)	52	-0.15 ± 0.27 (-0.10)
HOMA-S	mU x mmol	52	-0.78 ± 1.39 (-0.67)	43	0.15 ± 1.03 (0.06)	53	-1.44 ± 2.83 (-0.73)
HOMA-B	mU/mmol	52	-25.7 ± 61.6 (-15.4)	43	4.4 ± 30.5 (1.8)	53	-43.6 ± 100.1 (-22.3)
MCP-1	pg/mL	52	-13.9 ± 64.9 (-9.3)	44	-7.7 ± 80.2 (-20.0)	52	-6.6 ± 71.8 (-16.4)
MMP-9	ng/mL	52	-48.0 ± 126.6 (-	44	-1.3 ± 224.1 (-	52	-59.8 ± 210.1 (-

Parameter (V1.2 vs. LOCF)	Unit	Pioglitazone; n=52		Ramipril; n=44		PIO + Ramipril; n=53	
		n	mean ± SD (median)	n	mean ± SD (median)	n	mean ± SD (median)
			49.3)		12.9)		59.1)
P-Selectin	ng/mL	52	-8.7 ± 35.7 (-6.1)	44	1.6 ± 32.1 (3.6)	52	4.9 ± 40.0 (-5.4)
Tot. cholesterol	mg/dL	52	0.8 ± 21.8 (-1.0)	43	1.2 ± 35.8 (-2.0)	53	2.9 ± 26.1 (7.0)
HDL	mg/dL	51	1.5 ± 4.9 (1.0)	43	-0.6 ± 6.5 (0.0)	53	2.0 ± 7.0 (2.0)
LDL	mg/dL	52	-2.8 ± 20.4 (-3.5)	43	2.9 ± 24.3 (-2.0)	53	0.8 ± 18.5 (-3.0)
Triglycerides	mg/dL	52	-13.6 ± 54.5 (-17.5)	43	0.5 ± 39.9 (0.0)	53	-8.9 ± 53.4 (-4.0)
Adiponectin	mg/L	52	8.51 ± 5.91 (8.04)	44	0.09 ± 2.63 (0.37)	52	8.86 ± 6.37 (8.24)
24-hour SBP	mmHg	42	7.2 ± 13.1 (7.0)	37	2.2 ± 9.1 (3.0)	42	0.0 ± 9.7 (0.5)
24-hour DBP	mmHg	42	3.0 ± 7.3 (4.0)	37	0.9 ± 5.5 (2.0)	42	-1.4 ± 5.4 (-1.5)
24-hour HR	bpm	42	0.4 ± 6.3 (0.0)	37	-0.1 ± 5.9 (0.0)	42	2.8 ± 8.7 (2.0)
n: number of patients; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate							

Results of secondary efficacy parameters for the three treatment groups can be summarized as follows:

- hs-CRP results at the single study visits (V3, V4, V5.2) did not differ relevantly from the results for the primary comparison between baseline (V1.2) and LOCF. However, there was no distinct increase of hs-CRP for Ramipril monotherapy at the visits V3 and V4 as it could be observed for V5.2 or LOCF.
- Glucose tolerance and insulin sensitivity were clearly more improved under Pioglitazone alone and for the combination therapy. Regarding the parameters glucose, insulin, oGTT, HOMA-S, and HOMA-B consistent significant differences were observed for the comparison of both groups with Ramipril alone.
- As for inflammation and vascular function hs-CRP, MCP-1, MMP-9, and p-selectin showed an obvious reduction again mainly for Pioglitazone alone and the combination therapy. A significant difference was only seen for the comparison of Pioglitazone with Ramipril in terms of MMP-9 (decrease; p=0.0489).
- Regarding lipid metabolism the most noticeable effects occurred with Pioglitazone alone for adiponectin and HDL (increase), as well as for LDL and triglycerides (decrease). Statistically significant differences were calculated for the comparison of Pioglitazone with Ramipril monotherapy in terms of triglycerides (decrease; p=0.0367) and adiponectin (increase;

p<0.0001), and for the comparison of Pioglitazone plus Ramipril with Ramipril alone in terms of adiponectin (increase; p<0.0001).

- Changes of the 24-hour BP-profile revealed increases for SBP and DBP in the Pioglitazone and in the Ramipril group, whereas a slight decrease occurred in the combined treatment group. These within- group differences were statistically significant for the Pioglitazone and the combined treatment group. Furthermore, the between-group difference for Pioglitazone vs. combination therapy was statistically significant both for SBP (p=0.0048) and DBP (p=0.0026). The remaining within- and between-group comparisons including heart rate did not show clinically relevant or statistically significant differences.

The observed increase of blood pressure with findings of hypertension and hypertensive crisis in several patients is thus most likely caused by the replacement of the stable antihypertensive pre-treatment with ACE-inhibitors by the respective study medication at the time of randomization.

Per-protocol analysis (Set 1: n=140, 48 vs. 42 vs. 50; Set 2: n=133, 46 vs. 41 vs. 46; pooled-centres):

The results of the per-protocol analyses (PP-Sets 1 and 2) for the primary efficacy variable as well as for the secondary efficacy parameters did not differ relevantly from the outcome of the evaluation based on the full-analysis set. Hence, the direction of the exploratory results obtained for the main efficacy analysis was clearly supported by the two per-protocol analyses.

Multicentre analyses (Full Analysis Set: n=149; 52 vs. 44 vs. 53):

Additional supportive ANCOVA analyses were done for the model with unpooled centres and moreover excluding the factor 'centre' completely from the model, i.e. merely with the fixed effect factor treatment group and with the baseline hs-CRP value as covariate. The pertinent results were as follows:

In the latter analysis, the exploratory p-value related to ANCOVA F-test for testing the null-hypothesis of equal treatment means for the change from baseline with the log-transformed data was p=0.0095. Exploratory simultaneous 95% confidence intervals (CIs) according to Tukey-Kramer for the antilogs of the differences between LS-means revealed a significant difference for the pairwise comparison of Pioglitazone with Ramipril monotherapy in favour of Pioglitazone (p = 0.0181), and for the comparison of the combination therapy with Ramipril monotherapy in favour of the combination therapy (p = 0.0210).

In the unpooled analysis, the p-value related to ANCOVA F-test for testing the null-hypothesis of equal treatment means for the change from baseline with the log-transformed data was p=0.0532. Exploratory simultaneous 95% CIs according to Tukey-Kramer for the antilogs of the differences between LS-means revealed no significant differences for the pairwise within- and between-group comparisons in hs-CRP.

Safety Results: (All-Patients-Treated Set: n=172; 62 vs. 53 vs. 57)

Adverse events were documented in 134/172 (77.9%; 54 vs. 39 vs. 41) treated patients showing 359 (147 vs. 99 vs. 113) single events classified as treatment emergent adverse events (TEAEs).

Most frequently reported events were nasopharyngitis in 30/172 patients (17.4%; 9 vs. 9 vs. 12), headache in 24 (14.0%; 12 vs. 3 vs. 9), hypertension in 17 (9.9%; 7 vs. 5 vs. 5), peripheral oedema in 15 (8.7%; 10 vs. 2 vs. 3), arteriosclerosis in 11 (6.4%; 3 vs. 5 vs. 3), upper abdominal pain in 9 (5.2%; 4 vs. 3 vs. 2), and hypertensive crisis in 7 patients (4.1%; 2 vs. 4 vs. 1).

In 7/172 patients (4.1%; 3 vs. 1 vs. 3) a total number of 15 (6 vs.1 vs. 8) coded signs or symptoms referring to TEAEs were documented as serious adverse events (SAEs) mainly due to hospitalization. Thus, 344 (141 vs. 98 vs. 105) events were non-serious. All treatment emergent serious adverse events (TESAEs) were described as isolated episodes, except for hypertensive crisis (2 patients). The TESAEs were allocated to injuries in 3 patients (2 vs. 0 vs. 1), to musculoskeletal and vascular disorders in 2 patients each (0 vs. 1 vs. 1 and 1 vs. 0 vs. 1, respectively), and to gastrointestinal, general and nervous system disorders in one patient each (all Pioglitazone plus Ramipril). In 2 patients (Ramipril and Pioglitazone plus Ramipril) the documented TESAEs (arthralgia and malaise/loss of consciousness/subdural haematoma, respectively) were rated as possibly related to study drug administration.

Premature discontinuation of the study due to an adverse event according to the entries in the appropriate AE-form occurred in 37/172 patients (21.5%; 16 vs. 12 vs. 9 cases) reporting 49 (20 vs. 15 vs. 14) single events. Cases of death did not occur during the entire study period.

The course of single events was determined as unique for 58 (23 vs. 15 vs. 20), as intermittent for 114 (46 vs. 36 vs. 32) and as continuous for 187 (78 vs. 48 vs. 61) events. Regarding severity 266 (108 vs. 81 vs. 77) events were assessed as mild, 88 (37 vs. 17 vs. 34) as moderate, and only 5 (2 vs. 1 vs. 2) as severe. Relationship to the administration of study medication was rated as unlikely/not related in 220 (84 vs. 61 vs. 75), as possibly related in 99 (47 vs. 23 vs. 29), as probably related in 21 (6 vs. 8 vs. 7), and as definitely related in 19 (10 vs. 7 vs. 2) single events. The majority of events was classified as recovered during study (279; 117 vs. 71 vs. 91) whereas 67 (24 vs. 26 vs. 17) events did not yet recover or recovered with persistent damage (2; 0 vs. 0 vs. 2). Patient distribution for highest relationship was 'unlikely/not related' in 61 cases (35.5%, 23 vs. 17 vs. 21), 'possibly related' in 44 (25.6%, 21 vs. 10 vs. 13), 'probably related' in 16 (9.3%, 5 vs. 6 vs. 5), and 'definitely related' in 13 cases (7.6%; 5 vs. 6 vs. 2). The events mainly assessed as related to study drug were headache, hypertension/hypertensive crisis, peripheral oedema, vertigo/dizziness, upper abdominal pain, and weight increase.

Regarding laboratory results no clear trend towards a study therapy related influence on specific parameters could be derived from the sum of changes assessed as clinically significant by the investigators. Among the evaluation of vital signs clinically relevant changes both during the study course and between the treatment groups did not occur. Nevertheless, a slight decrease during study therapy was seen for systolic and diastolic blood pressure under treatment with the combination regimen.

Overall conclusions:

The 12-week treatment with Pioglitazone in hypertensive patients with increased cardiovascular risk and activated inflammation showed a clear mean decrease of hs-CRP in the studied period of at least more than 15% both for the Pioglitazone monotherapy and for the combination with

Ramipril. Moreover, both groups offer clearly positive results in terms of several established clinical and laboratory markers for cardiovascular diseases and risk factors. Obvious beneficial influences in the sense of pleiotropic effects were seen for the parameters of inflammation and vascular function (hs-CRP, MCP-1, MMP-9), glucose tolerance/insulin sensitivity (glucose, insulin, adiponectin, HOMA-S, HOMA-B), and lipid metabolism (HDL, LDL, triglycerides, adiponectin). The observed effects were statistically significant versus Ramipril monotherapy for the primary pooled-centre analysis on hs-CRP (full-analysis set), as well as for the per- protocol and the centre-independent evaluation, and regarding most of the secondary efficacy variables.

In terms of safety issues the study did not reveal any potential new or unexpected sign or symptom allocated to the study drugs in comparison to the known range of thiazolidinedione- and/or ACE-inhibitor specific adverse reactions. Observations like hypotension, peripheral oedema, headache, dizziness and gastrointestinal problems are consistent with the expected adverse event profile of the used drugs. In contrast, findings such as anxiety, nervousness, hyperhidrosis, diabetes, and general indisposition can be rated as usual for a clinical trial considering a patient collective with an increased cardiovascular risk.

Significant Changes During Study:

There was one amendment to the study protocol from September 10, 2007 which included the following modifications: the inclusion criteria “HOMA-S score > 2” was deleted due to high screen failure rate; part of the definition of the full analysis set was changed from “at least one post-baseline assessment of hs-CRP ≤ 10 mg/l” to “at least one post-baseline assessment of hs-CRP”; not all previously planned secondary efficacy parameters were determined by the central laboratory, but samples remained available for further testing if necessary; parameters initially determined were: hs-CRP; oGTT; HOMA-S; HOMA-B; HbA1c; 24-hour BP-profile; adiponectin; MCP-1; MMP-9; P-selectin; triglycerides; total cholesterol; HDL; LDL; fasting insulin; fasting glucose.

Changes to the planned analyses were as follows: individual change per patient for a specific parameter was calculated as the value at visit 5.2 minus the value at baseline (V1.2) in order to receive negative results for possible decreases; main efficacy evaluation was conducted on the basis of an exploratory pooled centre analysis of all sites due to low recruitment in all but 2 centres and skewed distribution; 'unpooled' analysis and an analysis without the factor 'centre' were calculated additionally only for the primary efficacy variable hs-CRP; patients with hs-CRP values > 10 mg/l at their last observation were excluded from a second per-protocol set.

Study ID Number:

ATS K023

Other Study ID Number(s):

2006-004028-35 [EudraCT Number]

D-PIO-110 [Takeda ID]

U1111-1115-9194 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012