Clinical Trial Results Disclosure Synopsis

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

Title of Study: Impact of Pioglitazone, Metformin, and the combination of both on cardiovascular risk in insulin-treated patients with Type 2 Diabetes - The PIOcomb Study

Phase of Development: Phase IIIb

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

Name of Finished Product: Actos®

Investigators: 13 principal investigators enrolled subjects into the double-blind treatment period.

Study Sites: 13 sites in Germany enrolled subjects into the double-blind treatment period.

Study Site 01: KKS GWT-TUD, 01307 Dresden
Study Site 02: 55166 Mainz, Germany
Study Site 03 32545 Bad Oeynhausen, Germany
Study Site 08: 65582 Diez, Germany
Study Site 09: 10409 Berlin, Germany
Study Site 10: 10117 Berlin, Germany
Study Site 12: 76829 Landau, Germany
Study Site14 : 96215 Lichtenfels, Germany
Study Site 15: 45219 Essen, Germany
Study Site 18: 04103 Leipzig, Germany
Study Site 19: 47051 Duisburg, Germany
Study Site 21: 45219 Essen, Germany
Study Site 22: 46537 Dinslaken, Germany

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

Study Period:

Date first subject signed informed consent form: 05 June 2008

Date of last subject's last visit/contact (from the Clinical database): 29 July 2010

Objectives:

Primary:

The aim of this study was to investigate the effect of Pioglitazone (PIO) in comparison to Metformin (MET) and the combination of both on matrix metallo proteinase-9 (MMP-9) in patients with diabetes mellitus type 2 pre-treated with insulin by evaluation of the MMP-9 change after 6 months of treatment compared to baseline.

Secondary:

Investigation of the effects of Pioglitazone in comparison to Metformin, and to a combination of Pioglitazone plus Metformin in type 2 diabetic patients pre-treated with insulin in laboratory parameters in terms of lipid profile, kidney function, inflammatory/metabolic markers, vascular function and other parameters of special interest such as glucose profile, insulin consumption, Homeostasis Model Assessment of insulin Sensitivity (HOMA-S), N-terminal pro-hormone brain natriuretic peptide (NT-proBNP), intima media thickness (IMT), endothelial function, and 24-hour blood pressure profile.

Methodology: Prospective, double-blind, multi-centre, randomized, parallel three-arm study.

Number of Subjects:

Planned: 132 subjects (44 per treatment arm; 1:1:1)
Enrolled and screened: 207 subjects
Enrolled: 207 subjects
Randomized into double-blind treatment period: 121
Analyzed: Safety Set: 121; Full Analysis Set: 113; Per-Protocol Set: 112

Diagnosis and Main Criteria for Inclusion: Male/female, type-2-diabetic patients at an age of 30-75 years treated with or without add-on oral antidiabetics except thiazolidinediones, and pre-treated with insulin for at least 12 weeks prior to study entry. HbA1c 6.5-8.5%; body mass index (BMI) $\geq$ 25 at screening. Signed written consent available.

Duration of Treatment: The treatment phase with test or reference study medication was defined to be 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
Pioglitazone hydrochloride	15 mg tablet	15 mg bid	Oral	2730001H
Metformin hydrochloride	850 mg tablet	850 mg bid	Oral	N/A
Insulin glargine	3 mL; 3.64 mg/mL Pen	Individualized dose	Subcutaneous injection	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	tablet	N/A	oral	Ch.-B.: 2007075401

Criteria for Evaluation:

Efficacy:

Primary: The primary efficacy variable was the change of MMP-9 after 6 months of treatment (visit V6.2) as compared to baseline (visit V2.2). The change was to be calculated using values of MMP-9 after 6 months of treatment minus the MMP-9 results at baseline.

Secondary: Investigation on the effect of Pioglitazone compared to a combination therapy with Metformin and to Metformin alone over 6 months on the parameters circadian blood glucose profile, 24h blood pressure profile, IMT, NT-proBNP, HOMA-S, kidney function (24- hour urine, 8-iso prostaglandine F2 alpha (PGF α)), albumin, creatinine, creatinine/albumin (C/A)-ratio), lipid profile (total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides), metabolic marker (haemoglobin A1c (HbA1c), glucose, insulin, intact proinsulin, C-peptide, adiponectin, high molecular weight (HMW), adiponectin), inflammatory marker (high-sensitivity C-Reactive Protein (hs-CRP), fibrinogen, E-selectin, Nuclear Factor-kappa B (NF κ B), nitrotyrosine, Plasminogen Activator Inhibitor-1 (PAI-1)), insulin consumption, endothelial function (by Laser-Doppler-Flowmetry), body composition in a sub-study (weight, fat%, fat mass, fat free mass, muscle mass, total body water, BMI, bone mass, visceral fat rating, inter- to intracellular water ratio).

Safety:

Incidence of adverse events, changes of safety laboratory parameters, changes in physical

examination and vital signs (with BW, BP, HR, ECG), 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. The primary statistical analysis was the testing of the effect of Pioglitazone in comparison to Metformin and the combination of both on a possible change of MMP-9 after a 6-month (i.e. 24 weeks) treatment compared to baseline. The confirmatory statistical analysis was based on 2-sided t-tests for two independent samples calculated with the parameter estimates of an analysis of covariance (ANCOVA) and using the primary parameter as dependent variable, the treatment group (with two levels) and centre as fixed factors, and the baseline MMP-9 value as covariate. The study included one interim analysis using the two-stage group sequential Pocock design for about 60% of randomized patients. The main analysis was planned after completion of the 24-week visit (V6.2), i.e. when all patients either completed this period after randomization, were lost to follow-up or prematurely discontinued the study within this period. The primary confirmatory analysis was clearly to be distinguished from supporting exploratory analyses of primary and secondary variables. All p-values and confidence levels of additional inferential statistics were to be interpreted in an exploratory sense only. Data of bioelectrical impedance (BIA) from a sub-study at Landau were to be analyzed using only descriptive statistics as well.

Amendments of Clinical Trial Protocol

Changes to the study protocol or the conduct of the clinical trial were defined in a total of 7 officially approved amendments for Germany and 5 corresponding amendments for Austria. A summary of these amendments giving dates and short contents is provided in the following:

Protocol Amendment No. 01 (Germany) from June 26, 2008 raised the patients' allowance, implemented the IMT measurement at visit V2.2 (randomization), and deleted FBG limitation.
Protocol Amendment No. 02 (Germany) from July 25, 2008 lowered the BMI limit and installed one unique study protocol for all participating centres after approval in Germany and Austria.
Protocol Amendment No. 03 (Germany) from September 15, 2008 allowed the inclusion of patients who were pre-treated with another insulin than glargine monotherapy and defined the duration of the screening period with at least 4 weeks.
Protocol Amendment No. 04 (Germany) from November 14, 2008 defined that measurements of IMT and LDF were optional, depending on availability of adequate technical site equipment.
Protocol Amendment No. 05 (Germany) from December 10, 2008 left the adjustment of insulin dosage to the investigator's discretion, introduced additional phone contacts for blood glucose

monitoring and additional blood glucose measurements, and allowed that patients could be randomized after being on a stable glargine monotherapy of at least 14 days.
Protocol Amendment No. 06 (Germany) from February 25, 2009 implemented a bioelectrical impedance analysis of body composition as a sub-study for one centre in Landau/Germany.
Protocol Amendment No. 07 (Germany) from November 10, 2009 implemented a statistical interim analysis after about 60% completed patients, due to an ongoing low recruitment rate.
Protocol Amendment No. A1 (Austria) from July 25, 2008: see Amendment 02, Germany
Protocol Amendment No. A2 (Austria) from September 15, 2008: see Amendment 03,Germany
Protocol Amendment No. A3 (Austria) from November 14, 2008: see Amendment 04, Germany
Protocol Amendment No. A4 (Austria) from December 10, 2008: see Amendment 05, Germany
Protocol Amendment No. A5 (Austria) from February 25, 2009: see Amendment 06, Germany

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

All 121 of the patients of the safety set were of Caucasian origin. When the three treatment groups are compared in this section, the order MET vs. PIO vs. Metformin plus Pioglitazone (MET+PIO) always applies. The average age overall was 63.0 (7.5) (mean ± standard deviation (SD)) and was comparable across all three treatment groups (64.2 (7.3) vs. 61.5 (7.1) vs. 63.3 (7.9)). Seventy-four (74) patients were male (23 vs. 25 vs. 26) and 47 were female (19 vs. 15 vs. 13). Height, weight and BMI were also comparable across all three treatments groups (height: 169.5 (8.3) vs. 167.8 (7.6) vs 170.1 (8.6); weight: 92.5 (17.3) vs. 89.4 (13.8) vs. 91.9 (16.2); BMI: 32.2 (5.3) vs. 31.8 (5.0) vs. 31.7 (4.3)...

Prior medications were recorded at least once in all 121 patients with the most frequently listed (used in over 15%) corresponding to predefined study indication diabetes Type II and findings in medical history (mainly cardiac risk factors). Most frequently listed single diseases in > 15% of the patients (MedDRA preferred terms) were hypertension (84.3%), obesity (47.1%), dyslipidaemia (31.4%), osteoarthritis (21.5%), coronary artery disease (16.5%), hyperlipidaemia (15.7%), and diabetic neuropathy (15.7%).

Subject Disposition:

A total of 121 patients were randomized and treated (the safety set); 8 patients failed to provide evaluable baseline and at least one post-baseline assessment for MMP-9 yielding the full analysis set of 113. To form the per-protocol analysis set, 1 additional subject was excluded due to a protocol violation of taking a not allowed concomitant medication. Thus, the per-protocol set was made up of 112 patients, 38 belonging to the Metformin group, 37 to the Pioglitazone group, and 37 to the Metformin plus Pioglitazone group. A total of 18 cases (14.9%; 5 vs. 8 vs. 5) discontinued the study prematurely.

Efficacy Results: (full analysis set: n=113; 39 MET vs. 37 PIO vs. 37 MET+PIO)

Primary: The results for the MMP-9 change between last observation carried forward (LOCF) and V2.2 were as follows for the 3 treatment groups:

hange of MMP-9 [ng/mL]	Metformin; n=39		Pioglitazone; n=37		MET+PIO; n=37	
	n	mean ± SD (median)	n	mean ± SD (median)	n	mean ± SD (median)
Baseline	39	601.7 ± 317.0 (544.8)	37	535.0 ± 214.9 (533.7)	37	581.8±260.7 (504.5)
LOCF	39	651.3 ± 365.3 (543.3)	37	480.9 ± 232.4 (443.2)	37	514.0 ± 219.5 (474.3)
Change	39	49.6 ± 336.2 (55.9)	37	-54.1 ± 187.1 (-57.2)	37	-67.8 ± 231.4 (-56.5)
Patients with complete observations for original data; n: number of patients; mean: arithmetic mean; SD: standard deviation						

The confirmatory p-value related to the ANCOVA F-test for testing the null-hypothesis of equal treatment means between MET+PIO (group C) and MET (group A) for the change from baseline was p=0.0416 which was statistically not significant at the α =0.0307 significance level of the two-stage group-sequential Pocock design. Thus the multiple test procedure with a-priori ordered hypotheses (Maurer et al; 1995) stopped and the second test on the null-hypothesis of equal treatment means between PIO (group B) and MET (group A) was done. The corresponding exploratory p-value was p=0.0345 again indicating no statistical differences between the groups. The exploratory comparison of MET+PIO (group C) vs. PIO (group B) resulted in p=0.8695. No evidence of differences was seen among pooled centres. The p-value for testing the null-hypothesis of equal overall centre means was p>0.10 for each pairwise comparison. The p-value for testing the covariate effect was p<0.01 for each pairwise comparison indicating a high significant relationship of the change of MMP-9 after 6 months with baseline MMP-9.

In summary, this final analysis revealed that the corresponding variances for the observed changes of MMP-9 were much higher than anticipated in the sample size calculations. Especially due to the high variation no evidence of differences could be statistically detected. However, after calculation of MMP- 9 based on logarithmic transformation for stabilization of variances, a rise of 0.1 ± 0.5 ng/mL (MET) and a decrease of 0.1 ± 0.5 ng/mL for both PIO and MET+PIO was seen. Now, p-values for the between- group comparison (3-group ANCOVA model) reached significance for MET vs. PIO (p=0.0043) and for MET vs. MET+PIO (p=0.0289), according to the overall significance level of α =0.0307 (Pocock design).

Interim analysis: (interim full analysis: n=78; 25 MET vs. 28 PIO vs. 25 MET+PIO)

The interim analysis for 78 (25 vs. 28 vs. 25) evaluable patients revealed that the changes of MMP-9 and the corresponding variances were not as anticipated in sample size calculations. Especially due to the high variation no evidence of differences could be statistically detected, i.e. no evidence of differences for the change of MMP-9 after the 6-month treatment compared to baseline was seen within and between the groups. The ANCOVA results for the between-group differences based on both the original and the rank-transformed data and showed no different tendency, and therefore supported the primary confirmatory analysis and subsequent exploratory analyses.

Per-protocol analysis: (per-protocol set: n=112; 38 MET vs. 37 PIO vs. 37 MET+PIO)

The results of the per-protocol analysis for the primary efficacy variable did not differ in any aspect 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 per-protocol evaluation.

Multicentre analysis: (all patients treated: n=121; 42 MET vs. 40 PIO vs. 39 MET+PIO)

To assess the homogeneity of treatment differences across the centres for the primary efficacy variable, treatment-by-centre interaction was evaluated exploratorily in the ANCOVA model. The appropriate analyses on homogeneity of treatment differences across the centres showed no treatment- by-centre interaction (p=0.5164). Furthermore, no evidence of differences was seen among pooled centres. The p-value from the ANCOVA model for testing the null-hypothesis of equal overall centre means was > 0.10 for each pairwise comparison.

Secondary:

Secondary Efficacy Parameter [Unit]	**absolute values during the study period; baseline*) vs. LOCF (full-analysis-set, n=113); displayed as 'arithmetic means ± standard deviation (medians); *n patients'***					
	A: Metformin (n=39)		**B: Pioglitazone (n=37)**		**C: MET=PIO (n=37)**	
	Baseline	**LOCF**	**Baseline**	**LOCF**	**Baseline**	**LOCF**
MMP-9 – Ln [ng/mL]	6.3 ± 0.6 (6.3); *39*	6.4 ± 0.5 (6.3); *39*	6.2 ± 0.4 (6.3); *37*	6.1 ± 0.5 (6.1); *37*	6.3 ± 0.4 (6.2); *37*	6.2 ± 0.4 (6.2); *37*
Mean blood glucose [mg/dL]	181.7 ± 41.8 (184.4); *28*	144.9 ± 29.1 (146.1); *28*	181.6 ± 49.2 (180.6); *23*	156.9 ± 37.2 (148.2); *23*	193.4 ± 59.4 (173.1); *26*	140.2 ± 36.6 (138.1); *26*
PGFa [ng/mmol]	164 ± 89 (147); *38*	186 ± 99 (168); *38*	171 ± 131 (130); *36*	186 ± 114 (144); *36*	140 ± 46 (133); *37*	162 ± 94 (138); *37*
Crea./Albu. ratio [mmol/mg]	1.14 ± 0.76 (1.18); *33*	1.72 ± 3.12 (0.97); *33*	3.47 ± 14.55 (0.88); *33*	1.19 ± 1.00 (0.93); *33*	1.89 ± 3.14 (0.80); *35*	1.54 ± 1.61 (0.96); *35*
Glomerular Filtration Rate (GFR)[mL/min]	114.2 ± 34.2 (104.5); *39*	115.8 ± 38.9 (108.7); *39*	116.9 ± 33.7 (105.0); *37*	115.3 ± 36.6 (106.7); *37*	118.7 ± 47.3 (106.0); *37*	117.2 ± 47.9 (106.0); *37*
HOMA-S [mmol*mU/L^2]	3.87 ± 3.89 (2.38); *39*	4.14 ± 3.84 (2.64); *39*	4.60 ± 3.93 (2.93); *37*	2.39 ± 1.79 (1.85); *37*	3.40 ± 3.73 (1.97); *35*	1.80 ± 1.30 (1.22); *35*
Total cholesterol [mmol/L]	5.02 ± 0.99 (4.90); *39*	4.82 ± 0.90 (4.90); *39*	4.80 ± 0.89 (4.56); *37*	4.89 ± 0.89 (4.86); *37*	4.71 ± 0.77 (4.68); *37*	4.87 ± 0.86 (4.59); *37*
LDL-cholesterol [mmol/L]	3.21 ± 0.78 (3.11); *38*	3.08 ± 0.78 (3.12); *38*	3.08 ± 0.72 (2.93); *37*	3.10 ± 0.74 (3.01); *37*	3.05 ± 0.62 (3.09); *37*	3.11 ± 0.68 (3.07); *37*

Secondary Efficacy Parameter [Unit]	absolute values during the study period; baseline*) vs. LOCF (full-analysis-set, n=113); displayed as 'arithmetic means ± standard deviation (medians); *n patients'*					
	A: Metformin (n=39)		B: Pioglitazone (n=37)		C: MET=PIO (n=37)	
	Baseline	LOCF	Baseline	LOCF	Baseline	LOCF
HDL-cholesterol [mmol/L]	1.24 ± 0.27 (1.30); *38*	1.29 ± 0.26 (1.28); *38*	1.19 ± 0.39 (1.16); *37*	1.29 ± 0.42 (1.17); *37*	1.19 ± 0.29 (1.18); *37*	1.41 ± 0.36 (1.42); *37*
Triglycerides [mmol/L]	2.03 ± 2.63 (1.54); *39*	1.76 ± 0.70 (1.66); *39*	1.76 ± 0.86 (1.50); *37*	1.70 ± 1.04 (1.35); *37*	1.72 ± 0.80 (1.71); *37*	1.54 ± 0.63 (1.52); *37*
HbA_{1C} [%]	7.33 ± 0.53 (7.30); *39*	7.23 ± 0.66 (7.10); *39*	7.35 ± 0.54 (7.20); *37*	7.19 ± 0.73 (7.20); *37*	7.34 ± 0.55 (7.30); *37*	6.85 ± 0.75 (6.70); *37*
Fasting insulin [µIU/mL]	10.44 ± 9.50 (7.20); *39*	12.43 ± 10.48 (9.20); *39*	10.98 ± 7.71 (9.30); *37*	7.00 ± 4.41 (5.30); *37*	8.49 ± 6.94 (5.90); *35*	6.10 ± 4.25 (4.60); *35*
Fasting glucose [mmol/L]	7.97 ± 1.98 (8.10); *39*	7.32 ± 1.90 (6.79); *39*	8.73 ± 2.58 (8.40); *37*	7.34 ± 1.58 (6.99); *37*	8.21 ± 1.96 (7.81); *37*	6.52 ± 1.48 (6.33); *37*
Fasting int. proinsulin [pmol/L]	9.58 ± 18.04 (4.67); *39*	6.07 ± 5.64 (3.93); *39*	7.58 ± 5.68 (5.53); *37*	5.12 ± 3.43 (3.83); *37*	5.48 ± 3.66 (5.03); *37*	3.52 ± 1.70 (3.31); *37*
C-Peptide [µg/L]	3.05 ± 1.49 (2.92); *39*	3.40 ± 1.48 (3.44); *39*	3.16 ± 1.49 (2.77); *37*	2.99 ± 1.25 (2.82); *37*	2.88 ± 1.29 (2.59); *37*	2.80 ± 1.10 (2.55); *37*
Adiponectin [mg/L]	4.43 ± 2.61 (4.16); *39*	4.33 ± 2.34 (4.00); *39*	4.29 ± 2.69 (3.85); *37*	13.20 ± 8.81 (11.49); *37*	4.83 ± 3.08 (4.11); *37*	13.42 ± 7.69 (10.94); *37*
hs-CRP [mg/L]	4.93 ± 5.04 (2.50); *39*	3.65 ± 3.33 (2.02); *39*	3.73 ± 3.23 (2.67); *37*	3.49 ± 3.47 (1.95); *37*	3.43 ± 3.75 (2.29); *37*	2.71 ± 4.54 (1.51); *37*
hs-CRP (≤10) [mg/L]	3.22 ± 2.43 (2.32); *33*	2.99 ± 2.42 (2.00); *33*	3.30 ± 2.73 (2.49); *35*	2.57 ± 2.07 (1.50); *35*	2.62 ± 1.79 (1.99); *34*	1.78 ± 1.06 (1.46); *34*
Fibrinogen [g/L]	3.89 ± 0.96 (3.62); *38*	3.63 ± 0.85 (3.41); *38*	3.49 ± 0.92 (3.31); *36*	3.45 ± 1.19 (3.28); *36*	3.68 ± 1.15 (3.43); *36*	3.60 ± 1.04 (3.36); *36*

Secondary Efficacy Parameter [Unit]	absolute values during the study period; baseline*) vs. LOCF (full-analysis-set, n=113); displayed as 'arithmetic means ± standard deviation (medians); *n patients'*					
	A: Metformin (n=39)		B: Pioglitazone (n=37)		C: MET=PIO (n=37)	
	Baseline	LOCF	Baseline	LOCF	Baseline	LOCF
E-Selectin [ng/mL]	47.1 ± 18.7 (45.3); *39*	46.5 ± 19.9 (39.2); *39*	48.2 ± 17.4 (43.4); *37*	43.6 ± 16.2 (38.7); *37*	45.7 ± 16.7 (43.8); *37*	42.0 ± 16.1 (41.2); *37*
NFkB [RLU]	1.248 ± 0.756 (0.785); *38*	1.228 ± 0.688 (0.805); *38*	1.024 ± 0.630 (0.745); *36*	0.992 ± 0.588 (0.705); *36*	1.172 ± 0.707 (0.760); *35*	1.154 ± 0.703 (0.750); *35*
PAI-1 [ng/mL]	71.2 ± 23.5 (70.0); *39*	61.2 ± 27.7 (54.4); *39*	71.4 ± 25.7 (76.3); 37	62.0 ± 29.9 (59.7); *37*	70.9 ± 27.8 (76.0); *36*	53.3 ± 30.4 (54.5); *36*
Nitrotyrosine [nmol/L]	294.0 ± 175.6 (307.5); *39*	312.1 ± 185.2 (354.9); *39*	304.7 ± 161.8 (287.3); *37*	298.0 ± 152.2 (330.4); *37*	301.3 ± 175.6 (347.5); *37*	287.4 ± 168.7 (304.2); *37*
Mean insulin consumption; [units]	35.2 ± 17.1 (32.0); *38*	37.7 ± 19.6 (35.2); *38*	34.5 ± 16.9 (33.0); *35*	27.2 ± 14.6 (25.9); *35*	35.4 ± 20.3 (32.4); *37*	29.4 ± 20.9 (24.2); *37*
*): baseline = values of V2.2 (randomization) or screening; Ln: logarithmic transformation; LOCF: last obs. carried forward						

Safety Results: (all patients treated: n=121; 42 MET vs. 40 PIO vs. 39 MET+PIO)

Adverse events were documented in 99/121 (81.8%; 32 vs. 35 vs. 32) treated patients showing 383 (138 vs. 136 vs. 109) single events classified as treatment-emergent adverse events (TEAEs). Most frequently reported were nasopharyngitis in 32/121 patients (26.4%; 10 vs. 10 vs. 12), peripheral oedema in 29/121 (24.0%; 5 vs. 16 vs. 8), hypoglycaemia in 28/121 (23.1%; 9 vs. 8 vs. 11), weight increase in 21/121 (17.4%; 3 vs. 11 vs. 7) and fatigue in 12/121 (9.9%; 5 vs. 1 vs. 6) patients.

In 5/121 patients (4.1%; 2 vs. 3 vs. 0) a number of also 5 (2 vs. 3 vs. 0) coded signs or symptoms referring to TEAEs were documented as serious adverse evenst (SAEs) without relationship to study drug administration in all cases. These events were described as eczema on hands and feet of moderate intensity with hospitalization (MET), severe worsening of dizziness with hospitalization (MET), moderate gastroenteritis with specific drug therapy (PIO), moderate worsening of congenital heart disease (CHD) with hospitalization (PIO), and an acute loss of hearing at the right side with hospitalization (PIO).

Premature discontinuation of the study due to an adverse event according to the entries in the appropriate adverse event (AE)-form occurred in 9/121 patients (7.4%; 1 vs. 5 vs. 3) reporting 13

(4 vs. 5 vs. 4) single events. Cases of death did not occur during the entire study period. The course of events was unique for 135 (52 vs. 49 vs. 33), intermittent for 98 (44 vs. 20 vs. 34), and continuous for 150 (41 vs. 67 vs. 42) events. Regarding severity, 297 (98 vs. 110 vs. 89) events were mild, 85 (39 vs. 26 vs. 20) moderate, and one event (MET) was severe (worsening of dizziness). Relationship to study drug administration was rated as unlikely/not related in 219 (87 vs. 74 vs. 58), as possibly related in 66 (32 vs. 18 vs. 16), as probably related in 15 (3 vs. 9 vs. 3), and as definitely related in 83 (16 vs. 35 vs. 32) single events. Most frequently assessed as related were hyperglycaemia (21.5%), peripheral oedema (21.5%), weight increase (17.4%), fatigue (6.7%), and vertigo (5.8%). The vast majority of events recovered during study (334; 124 vs. 121 vs. 89), 41 events (11 vs. 11 vs. 19) did not, and in 8 events (3 vs. 4 vs. 1) the outcome was unknown.

In terms of laboratory results, a clear trend towards a study therapy related influence on specific parameters can not be derived from the sum of changes assessed as clinically significant by the investigators. The by far most frequently documented change was an decrease of HbA1C and blood glucose levels, which is common for a study collective of diabetic patients. Elevations of liver enzymes, creatinine, or creatine kinase (CK), and a decrease of red blood cells (RBC) or haemoglobin (Hb) occurred only in single cases without marked differences between the treatment groups and were therefore of minor clinical relevance.

The analysis of vital signs revealed a clear increase of weight and leg oedemas, and a slight decrease of systolic and diastolic blood pressure for the treatment groups with Pioglitazone between baseline and last observation. Findings for ECG and the routine physical examination did not differ during the study course.

Overall conclusions:

In patients with type 2 diabetes at high risk for cardiovascular complications and treated with insulin glargine, the addition of Pioglitazone but not of Metformin clinically relevantly reduced the level of inflammatory biomarkers such as MMP-9 and hs-CRP and increased insulin sensitivity and adiponectin independent from glycaemic control. The combination of Pioglitazone with Metformin resulted in better glycaemic (HbA1c) and lipid (LDL-subfractions) control without added effect on inflammation, fibrinolysis, and kidney function. Obvious beneficial influences of Pioglitazone and not of Metformin in the sense of pleiotropic effects occurred for hs-CRP, E-selectin, C-peptide, HOMA-S, adiponectin, intact proinsulin, insulin consumption, HbA1C, and insulin resistance. Therefore, Pioglitazone is assumed to be a rational add-on therapy to basal insulin in type 2 diabetes patients with a noticeable high cardiovascular risk.

As for 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 Pioglitazone and/or Metformin

specific adverse reactions, laboratory tests, and vital signs. Findings like weight increase, peripheral oedema, dizziness, or gastrointestinal problems are consistent with the expected adverse event profile of the used drugs. In contrast, observations such as hypoglycaemia, fatigue, coronary artery disease (CAD), or hypaesthesia can be rated as common in a clinical study considering a collective of diabetic patients with an increased cardiovascular risk.

Significant Changes During Study:

Seven amendments to the protocol were implemented prior to breaking the study blind, which included: the addition of IMT measurement at randomization; lowering of BMI limit; removal of the FPG limitation; IMT and LDF measurements became optional; allowing the inclusion of patients who were pre-treated with an insulin other than glargine monotherapy and defining the duration of the screening period with at least 4 weeks; leaving adjustment of insulin dosage to investigator discretion; and allowing patients to be randomized after being on a stable glargine monotherapy of at least 14 days.

No major changes or modifications of previously planned statistical methods or evaluations were formulated. However, it was decided to calculate the original results of MMP-9 also using logarithmic transformation in order to achieve an appropriate stabilization of the high variances. Furthermore, the initially planned parameter HMW adiponectin was not determined and evaluated.

Study ID Number:

ATS K028

Other Study ID Number(s):

2007-006706-14 [EudraCT Number]

DE-PIO-028 [Takeda ID]

U1111-1113-1888 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012