Clinical Trial Results Disclosure Synopsis

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

Title of Study: Comparison Of The Effects Of Pioglitazone Vs. Placebo When Given In Addition To Standard Insulin Treatment In Patients With Type 2 Diabetes Mellitus And Renal Failure - The Pioren 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®, 30 mg

Investigators: 12 principal investigators enrolled subjects into the double-blind treatment period.

Study Sites: In total, 22 study sites existed as listed below. However, some sites did not recruit, screen or treat patients. Active sites that performed at least one screening were study sites 01, 02, 03,04, 05, 07, 08, 10, 11, 12, 15, 19, 20, and 22. These active sites can be divided into sites,which only screened (study sites 08 and 15) and sites, which actually randomized patients (study sites 01, 02, 03, 04, 05, 07, 10, 11, 12, 19, 20, and 22).

Study Site 01: Klinik für Nephrologie und Dialyseverfahren
Paulmannshöher Straße 14
58515 Lüdenscheid
Germany

Study Site 02: Dialysezentrum Schwetzingen
Bodelschwinghstr. 10/3
68723 Schwetzingen
Germany
Study Site 03: KfH-Nierenzentrum
Freiligrathstr. 12
55131 Mainz

Germany
Study Site 04: Carolinenstrasse 6
55218 Ingelheim
Germany
Study Site 05: Dialysezentrum Alzey
Am Damm 17
55232 Alzey
Germany
Study Site 06: Nephrologische Praxis
Buckesfelderstraße 105a
58509 Lüdenscheid
Germany
Study Site 07: Klinik für Nephrologie und Allgemeine Innere Medizin
Städtisches Klinikum Solingen
Gotenstraße 1
42653 Solingen
Germany
Study Site 08: Dialysezentrum Wiesbaden
Geisenheimerstr. 10
65197 Wiesbaden
Germany
Study Site 09 KfH Nephrologisches Zentrum
Osterfelderstraße 155a
46242 Bottrop
Germany
Study Site 10: Dialysezentrum Karlstraße
Karlstraße 17-19
40210 Düsseldorf
Germany
Study Site 11: Diabetes- und Nierenzentrum Dormagen
Florastr. 8
41539 Dormagen
Germany
Study Site 12: KfH-Nierenzentrum
Schleusenweg 22
60528 Frankfurt
Germany
Study Site 13: Dialyse Zentrum Dinkelsbühl
Luitpoldstraße 16
91550 Dinkelsbühl
Study Site 14: Krankenhaus der Barmherzigen Brüder
Nordallee 1

54292 Trier
Germany
Study Site 15: Gemeinschaftspraxis & Dialysezentrum
Mörikestr.5
74076 Heilbronn
Germany
Study Site 16: KfH-Dialysezentrum, Haus 91
Fermersleber Weg 25
39112 Magdeburg
Germany
Study Site 17: KfH-Nierenzentrum im Cusanus Krankenhaus
Karl-Binz-Weg 12
54470 Bernkastel-Kues
Germany
Study Site 18: Dialysepraxis
Im Klauenfuß 2/2
74172 Neckarsulm
Germany
Study Site 19: KfH-Nierenzentrum Eberswalde
Rudolf-Breitscheidstraße 100
16225 Eberswalde
Germany
Study Site 20: KfH-Nierenzentrum Moabit
Turmstraße 20A
10559 Berlin
Germany
Study Site 21: KfH-Nierenzentrum Rosenheim
Pettenkoferstraße 10
83022 Rosenheim
Germany
Study Site 22: Gemeinschaftspraxis
Innere Medizin und Nephrologie
Elisabethenstraße 13
64732 Bad König
Germany

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

Study Period:

Date first subject signed informed consent form: 04 August 2008

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

Objectives:

Primary:

The primary objective of the study was to analyze the change in the daily insulin dose (basal and prandial) after 24 weeks of treatment with either pioglitazone (PIO) or placebo (PLA) when given in addition to insulin.

Secondary:

Secondary efficacy objective was to investigate the effect of PIO vs. PLA from start of treatment (V2) to 12 weeks of treatment (V5) and to end of treatment (24 weeks, V7) when given in combination with standard insulin care on the following parameters: reduction of the daily insulin dose of ≥30%, various laboratory parameters (HbA1c, glucose, insulin, C-peptide, intact proinsulin, adiponectin, relaxin, fetuin A, carbonyl protein, angiotensin, hs-CRP, calcification markers (MPO, Matrix Gla Protein), lipids (cholesterol, HDL, LDL, triglycerides), MMP-9, MCP-1, E-selectin, oxidized low density lipoprotein (ox LDL), pioglitazone in serum, intact parathyroid hormone, NT-proBNP), and the change in the ultra filtrate volumes during the course of the study. Laboratory efficacy parameters were measured using blood collected prior to dialysis at visit 2 (baseline), visit 5 (12 weeks later), and visit 7 (24 weeks later). At visit 5 these variables were also determined after dialysis.

Another objective was the safety surveillance including assessment of adverse events (AE) and safety laboratory parameters.

Methodology: This phase II study was designed as a prospective, randomized, double-blinded parallel multi-centre study.

Number of Subjects:

Planned: 20 subjects per treatment arm
Screened: 52 subjects
Enrolled in the double-blind treatment period: 39 subjects
Analyzed: Intention-to-treat (ITT) Set: 39 patients were randomized, Pioglitazone (PIO) group (20) and placebo (PLA) group (19); Full Analysis Set (FAS): 36 subjects (PIO: 19, PLA: 17); Per Protocol Set (PPS): 26 subjects (PIO: 15, PLA: 11)

Diagnosis and Main Criteria for Inclusion:

Type 2 diabetes mellitus (T2DM) patients with renal failure and on dialysis.

Duration of Treatment: The duration of study participation for patients completing the study was 26 weeks (2-14 days run-in phase and 24 weeks treatment phase). The estimated duration of the total study was initially 12 months. The actual duration was about 23 months.

Study Medication	Product Dose Strength and	Study Dosage	Mode of Administration	Drug Product Lot Number

	Form			
Pioglitazone	30 mg tablet	30 mg	Oral	0803025

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

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	0803025

Criteria for Evaluation:

Efficacy:

Primary: The primary variable was the change in daily insulin doses after administration of either PIO or PLA for 24 weeks.

Secondary: Secondary efficacy variables were the number of patients with a reduction of the daily insulin dose of ≥30%, various laboratory parameters (HbA1c, glucose, insulin, C-peptide, intact proinsulin, adiponectin, relaxin, fetuin A, carbonyl protein, angiotensin, hs-CRP, calcification markers (MPO, Matrix Gla Protein), lipids (cholesterol, HDL, LDL, triglycerides), MMP-9, MCP-1, E-selectin, ox LDL, pioglitazone in serum, intact parathyroid hormone, NT-proBNP), and the change in the ultra filtrate volumes during the course of the study. Laboratory efficacy parameters were measured using blood collected prior to dialysis at visit 2 (baseline), visit 5 (12 weeks later), and visit 7 (24 weeks later). At visit 5 these variables were also determined after dialysis.

Safety:

Safety of all patients was assessed by monitoring i) adverse events (AE), ii) laboratory safety parameters (blood cell count, inflammation markers, hepatic and renal parameters, and electrolytes), iii) electrocardiograms, iv) vital signs, and v) pregnancy in women with childbearing potential.

Statistical Methods:

Efficacy:

The primary efficacy variable was analyzed by descriptive statistics (mean, standard deviation, minimum value, 1. quartile, median, 3. quartile, maximum value) and inferential statistics (analysis of covariates (ANCOVA), student's t-test, Wilcoxon rank test, confidence intervals

within treatment group and between treatment groups). Secondary efficacy parameters were analyzed by the same descriptive statistics, by confidence intervals and two-sided student's t-tests.

The following analysis sets were used:

Intention-to-treat set: All patients who had been randomized.

Full analysis set: All randomized patients who received study medication and who provided one post baseline value for the daily insulin dose.

Per protocol set: All randomized patients who administered study medication and passed all visits without major protocol violations.

Primary and secondary efficacy variables were analyzed for the FAS and PPS. Demographic data are displayed for the PPS, the FAS, and ITT set. The ITT set was used for evaluation of medical history, physical examination, concurrent diseases, concomitant medications, and safety issues ((S)AEs, laboratory safety parameters).

Amendments of Clinical Trial Protocol
There were four amendments modifying the initial plan of the trial (see chapter 5.1).

Amendment 01, dated June 19, 2008
Main points of this amendment were i) the change of the sponsor's project leader, ii) minor, partially formal changes in the schedule of trial events, iii) removal of one inclusion and one exclusion criterion, iv) conversion of the original safety parameter NT-proBNP to an efficacy parameter, v) documentation of the ultra filtrate volume of the last six consecutive dialyses and calculation of the mean value, vi) measurement of capillary blood glucose at the study site and the distribution of diaries for recording blood glucose (BG) values and insulin doses at all treatment visits (V3-V6), and vii) postponement of trial dates.

Amendment 02, dated October 15, 2008
This amendment introduced alterations of two inclusion criteria. The maximal age was raised to 80 years and the acceptable range of HbA1c was widened ($\geq$6 and <10). Please see sections 9.3.1 and 9.3.2 for further details regarding changes in the inclusion and exclusion criteria.

Amendment 03, dated April 27, 2009
This amendment addressed the following four issues. i) Fasting status at patient visits had not to be strictly kept, allowing recruitment of patients with afternoon dialysis shifts. ii) The exclusion criterion No. 2 was modified and judgement of the acuteness of an infection was left to the investigator's discretion. iii) The exclusion criterion No. 9 was modified to the investigator's discretion. iv) An echocardiography was allowed as optional measure to judge the patient's heart function.

Amendment 04, dated November 11, 2009
By this amendment, an interim analysis due to ongoing low recruitment rate was scheduled and the statistical methods section was modified by inclusion of use of the t-test.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

All 39 patients of the ITT set were of Caucasian origin. The gender distribution of all patients belonging to the ITT set, the FAS, and the PPS was very similar. However, between treatment group comparisons revealed differences in the gender distribution, which was especially pronounced in the PPS (73.3% vs. 63.7% males, PIO vs. PLA group).

The age of the patients ranged for the entire study population from 50 to 80 years. For the ITT set the average age was 68.9 ± 6.8 years (mean ± standard deviation (SD)) in the PIO group and 69.6 ± 9.4 years in the PLA group. The average age of the FAS of both treatment groups varied to some extent (PIO: 68.4 ± 6.6 years vs. PLA: 69.9 ± 9.3).

The mean values for height and weight was higher for the patients of the PIO group (height: 169.1 ± 8.0 cm, weight: 90.0 ± 12.9 kg) vs. the PLA group (height: 163.2 ± 16.6 cm, weight: 83.4 ± 11.2 kg; table 11.3). A slightly higher body mass index (BMI) value was observed in the PIO group (31.5 ± 4) as compared to the PLA group (30.3 ± 4.6). The average systolic and diastolic blood pressure was similar in both treatment groups with 143.4 ± 19.5 and 72.7 ± 13.3 mm Hg, respectively, in the PIO group and 144.6 ± 22.8 and 73.2 ± 12.3 mm Hg, respectively, in the PLA group. The same is valid for the radial pulse, which averaged out at 74.4 ±14.1 beats per minute in the PIO group and at 73.7 ± 9.6 in the PLA group.

The most prominent findings in the medical history for the ITT set of the entire study population were diseases with the preferred term (PT) “arteriovenous shunt operation” (7.8%), “angioplasty” (4.2%), “catheter placement” (4.2%), “toe amputation” (3.6%), and “leg amputation” (3.0%). All patients had a history of kidney disease and hypertension.

Duration of T2DM showed good conformity in the average duration of T2DM in patients of both treatment groups for all three analysis sets. Patients of the PIO group had a higher number of concurrent diseases (CD) as compared to the PLA group (269 vs. 251). Apart from T2DM and “renal failure chronic” the most frequent CDs relative to all CDs assessed on the PT level were “nephrogenic anaemia“ (6%), “hypertension” (4.8%), and “hyperparathyroidism secondary” (4.4%), “coronary artery disease“ (3.7%), “diabetic nephropathy” (3.5%), and “hyperlipidaemia” 2.9%).

Subject Disposition:

In total, 52 patients were screened in 14 study centers; 13 subjects failed to comply with inclusion/exclusion criteria yielding the ITT set of 39 patients. Three patients were erroneously randomized (and excluded prior to visit 3) as they did not meet all inclusion criteria. Therefore, the FAS consisted of 36 patients (19 x PIO, 17 x PLA). To form the PPS, five patients of the FAS were excluded because of an increase in the ultra filtrate volume >30% (2x PIO, 3x PLA).

One patient each was excluded due to discomfort (PIO), lost to follow up (PIO), a fasting blood glucose (FBG) >270 mg/dL (PLA), withdrawal of consent (PLA) or an adverse event (PLA). Thus, the PPS was made up of 26 patients, 15 belonging to the PIO group and 11 to the PLA group.

Efficacy Results:

The following efficacy results refer to the FAS.

Daily insulin doses dropped stronger in the PIO (-35%) than in the PLA (-10%) group after 24 weeks. Application of ANCOVA and student's t-test was not possible due to violation of prerequisites (comparable normal distribution and variance). Wilcoxon rank test indicates statistical significance of this effect (p=0.003).

The following section describes effects of PIO administration on secondary objectives. Data is presented as mean ± standard deviation.

As judged by between treatment group 95% confidence intervals the post baseline values of the next five parameters were statistically significant different at V5 and V7 with the exception of the MCP-1 level (only at V5).

- Insulin reduction ≥30% (five (V5) and eight (V7) patients of the PIO group in comparison to no (V5) and one (V7) patient of the PLA group).
- The HbA1c value (in %) dropped in the PIO group (7.4±0.9 (V2), 6.8±0.8 (V5), 6.8±1.0 (V7)), whereas it remained constant (V5 vs. V2) or increased (V7 vs. V2) in the PLA group (7.7±0.9 (V2), 7.7±0.9 (V5), 7.9±1.0 (V7).
- Adiponectin concentrations (in µg/mL) rose strongly upon PIO administration (9.2±6.2 (V2), 17.6±6.9 (V5), 16.5±6.8 (V7)) and decreased slightly after PLA intake (9.8±5.9 (V2), 8.5±4.2 (V5), 8.4±5.2 (V7)).
- E-selectin levels (in ng/mL) decreased upon PIO intake (45±16 (V2), 38±7 (V5), 38±10 (V7)) and increased after PLA administration (46±18 (V2), 49±18 (V5), 53±18 (V7)).
- MCP-1 levels were almost unchanged upon PIO administration (566±115 (V2), 549±144 (V5), 557±126 (V7)). In the PLA group, a slight increase was present at V5 and a considerable one at V7 (641±177 (V2), 676±158 (V5), 941±931 (V7)).

The following six parameters showed a different tendency in the course of the study between the PIO and PLA group.

- Glucose levels (in mg/dL) decreased upon PIO administration from 153±45 (V2) to 148±76 (V5) and 116±44 (V7), while it increased after intake of PLA from 157±44 (V2) to 163±51 (V5) and 172±82 (V7).
- Triglyceride levels (in mg/dL) also decreased in the PIO group (356±229 (V2), 246±128 (V5), 249±121 (V7)) and increased in the PLA group (237±108 (V2), 260±89 (V5), 282±174 (V7)).

- Intact PTH (in ng/L) also decreased in the PIO group (325±389) (V2), 243±164 (V5), 237±175 (V7)) and increased in the PLA group (273±178 (V2), 430±641 (V5), 359±185 (V7)).
- LDL levels (in mg/dL) increased in the PIO group (97±48 (V2), 107±29 (V5), 101±37 (V7)) and decreased in the PLA group (108±40 (V2), 105±40 (V5), 73±36 (V7)).
- Carbonyl protein levels (in nmol/mL) also increased in the PIO group (11±5 (V2), 14±6 (V5), 14±7 (V7)). In the PLA group levels remained almost constant (16±7 (V2), 15±8 (V5), 16±9 (V7)).
- Oxidized LDL levels (in ng/mL) also increased in the PIO group in the course of the study (59±45 (V2), 137±228 (V5), 100±129 (V7)), whereas they decreased in the PLA group (68±55 (V2), 41±0 (V5), 50±23 (V7)).

Ten parameters did not show a pronounced change in any of the groups at V5 and V7.

- HDL levels (in mg/dL) slightly increased in the PIO group (31±9 (V2), 35±7 (V5), 33±9 (V7)) and remained constant (V5 vs. V2) or decreased (V7 vs. V2) in the PLA group (34±10 (V2), 34±6 (V5), 26±9 (V7)).
- The ultra filtrate volume (in mL) remained almost unchanged at V5 and increased slightly to V7 (2504±855 (V2), 2501±1030 (V5), 2618±938 (V7)). In comparison to the PIO group, stronger increases were assessed for the PLA group at V5 and V7 (2743±999 (V2), 2916±1101 (V5), 3105±1100 (V7)).
- Intact proinsulin levels (pmol/L) remained initially (V5) constant after PIO intake and increased subsequently (14±13 (V2), 15±15 (V5), 18±22 (V7)). The level in the PLA group decreased first (V5) and increased afterwards at V7 (24±26 (V2), 21±11 (V5), 26±20 (V7)).
- Insulin levels (µU/mL) decreased slightly in the PIO group (33±24 (V2), 32±33 (V5), 31±31 (V7)). In the PLA group an initial decrease (V5) was followed by a rise at V7 (39 ±48 (V2), 24±13 (V5), 62±76 (V7)).
- C-peptide levels (in pmol/L) in the PIO group initially declined at V5 and remained unchanged at V7 vs. V2 (6.7±6.6 (V2), 5.3±4.0 (V5), 6.8±7.6 (V7)). In the PLA group the value was unaltered at first (V5 vs. V2) and increased subsequently (8.4±5.5 (V2), 8.1±2.7 (V5), 11.5±6.5 (V7)).
- MMP-9 levels (in ng/mL) increased during study conduct in the PIO group (679±367 (V2), 718±440 (V5), 768±468 (V7)). In the PLA group levels were at first quite constant (V5) and increased afterwards (815±488 (V2), 822±485 (V5), 1009±565 (V7)).
- NT-proBNP levels (in pg/mL) were decreased in the PIO group at V5 and increased subsequently (5134±8826 (V2), 4478±6947 (V5), 8086±13973 (V7)), while they increased considerably in the PLA group throughout the study (5052±7354 (V2), 7394±8800 (V5), 10326±16915 (V7)).

- Angiotensin levels (in pmol/L) increased in the PIO group initially and declined subsequently (26±32 (V2), 34±41 (V5), 21±7 (V7)). The levels in the PLA group were increased at V5 vs. V2 and at V7 vs. V2 (23±20 (V2), 26±36 (V5), 28±37 (V7)).
- MPO levels (in ng/mL) increased at first in the PIO group (V5) and declined afterwards at V7 vs. V2 (75±85 (V2), 96±194 (V5), 60±53 (V7)). An increase at both visits was observed in the PLA group (45±28 (V2), 48±23 (V5), 53±41 (V7)).
- Matrix gla protein levels (in nmol/L) remained constant in the PIO group (15±7 (V2), 15±7 (V5), 15±6 (V7)). In the PLA group the level remained initially constant, too, and decreased subsequently (15±8 (V2), 15±8 (V5), 13±7 (V7)).

Finally, there was a fourth group of parameters that showed tendentially similar changes in both treatment arms.

- Cholesterol levels (in mg/dL) decreased in the PIO (205±61 (V2), 192±30 (V5), 190±48 (V7)) and PLA (196±53 (V2), 192±58 (V5), 156±50 (V7)) group.
- hs-CRP levels (in mg/L) increased in the PIO (3.1±2.3 (V2), 3.5±2.8 (V5), 3.8±2.8 (V7)) and PLA (3.9±2.6 (V2), 4.1±2.4 (V5), 4.4±1.4 (V7)) group.
- Feutin A levels (in g/L) decreased in the PIO (0.57±0.15 (V2), 0.55±0.19 (V5), 0.53±0.15 (V7)) and PLA (0.60±0.24 (V2), 0.54±0.14 (V5), 0.51±0.14 (V7)) group.
- Relaxin levels (in pg/mL) declined in the PIO (24±58 (V2), 21±34 (V5), 20±37 (V7)) as well as in the PLA group (27±35 (V2), 16±18 (V5), 21±34 (V7)).

Pioglitazone quantification (sum of the PIO peak and those of its M3 and M4 metabolites) yielded mean values of 56.4 and 28.24 ng/mL for the PLA group for pre and post dialysis at visit 5. These larger than the expected values are possibly due to unreliable methodology used for this analysis.

Statistical analysis of changes during the study (endpoint vs. baseline) within both treatment groups by student's t-tests showed for the PIO group statistically significant decreases in the HbA1c and E-selectin value as well as a statistically significant increase in the adiponectin level. No statistically significant changes were observed for the PLA group.

In summary, PIO in comparison to PLA had beneficial metabolic effects with regard to an improved metabolic control (HbA1c, fasting glucose) despite a significant reduction of insulin requirements. Further improvements were indicated by an improved lipid profile (triglycerides, HDL) and reduction in other risk proteins (E-selectin, intact PTH). The tendentially lower NT-proBNP level in the PIO group and similar increases in the ultra filtrate volumes in both groups during the course of the study indicate the absence of a negative impact of PIO on heart failure.

Safety Results:

A total of 129 adverse events occurred during this study. There was no difference in the number of hypoglycemic events observed in the study between the two groups (PIO: 5 vs. PLA: 3). In general, a slightly higher number of AEs was observed in the PLA (68) group vs. the PIO (61)

group. The majority of the AEs belonged to the system organ classes “gastrointestinal disorders”, “investigations”, “infections and infestations”, and “musculoskeletal and connective tissue disorders” making up 56% of the AEs. No AE concerning fractures did occur. With regard to severity 78 AEs were classified as “mild” (PIO: 37, PLA: 41), 45 as “moderate” (PIO: 23, PLA: 22), and six as “severe” (PIO: 1, PLA: 5). One AE was judged as “definitely” treatment-related. However, this AE affected a patient receiving placebo. Eight (PIO: 3, PLA: 5), 11 (PIO: 7, PLA: 4), and 109 (PIO: 51, PLA: 58) AEs were rated as “probably”, “possibly”, and “unlikely” related to treatment, respectively. Twenty-two AEs (PIO: 12, PLA: 10) were classified as serious and affected 11 patients (PIO: 5, PLA: 6). All SAEs were rated as not related to study medication intake.

Altogether 764 abnormal results (PIO: 415, PLA: 349) were obtained for laboratory safety parameters. Breaking down abnormal laboratory values to a single visit revealed a very similar number of abnormal values for the PIO (5.9) and PLA (6.0) group. Not clinically significant (NCS) abnormal values prevailed vs. clinically significant (CS) in the PIO group (217 vs. 198 CS), whereas in the PLA group CS abnormal values predominated (207 CS vs. 142 NCS). Comparing means of laboratory safety parameters in the course of the study revealed by tendency treatment emerging effects on levels of platelets, hematocrit, alkaline phosphatase, creatinine kinase, potassium, aspartate aminotransferase (ASAT), and glucose at V5 and V7 vs. baseline. By contrast, almost no impact of treatment was observed with regard to mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), C-reactive protein (CRP), and Gamma-Glutamyl Transferase (γ-GT). Additionally, a third class of parameters (red and white blood cells, hemoglobin, billirubin, creatinine, mean corpuscular hemoglobin (MCH), and alanine aminotransferase (ALAT)) existed, which showed between treatment group differences only at V5 or V7 vs. baseline. Vital signs (weight, body mass index, waist and hip circumference, systolic and diastolic blood pressure, pulse) did not change significantly in the course of the study in either treatment group. At the end of the study electrocardiogram (ECG) findings were improved in three patients of the PIO group and one of the PLA group, possibly indicating a beneficial effect of PIO. From the number of dropouts in the treatment groups due to premature termination of study participation (PIO: four patients corresponding to 21%, PLA: six patients corresponding to 35%) it can be inferred that PIO was well tolerated from T2DM patients with renal malfunction requiring hemodialysis.

Human chorion gonadotropin was not analyzed because all female patients were sterilized or post-menopausal.

Conclusions

Addition of pioglitazone to insulin therapy in hemodialysis patients was well tolerated and had similar effects on ultra filtrate volume in comparison to placebo. During the study, there was no indication of an elevated risk for congestive heart failure in the pioglitazone group. Despite a significant reduction in daily insulin dose and without negative influence on hypoglycemia risk or on biomarkers of heart failure, treatment with pioglitazone resulted in improved glycemic and lipd metabolism and had further beneficial effects on biomarkers of chronic systemic

inflammation and cardiovascular risk in patients with late stage kidney failure requiring hemodialysis. These changes in efficacy parameters indicate a positive influence of pioglitazone administration on disease prognosis even in late stage diabetes.

Significant Changes During Study:

Four amendments to the protocol were implemented prior to breaking the study blind, which included changes to eligibility criteria (the maximal age was raised to 80 years and the acceptable range of HbA1c was widened (≥6 and <10); one exclusion criterion was modified to a history of significant cardiovascular (e.g. congestive heart failure (CHF) New York Heart Association (NYHA) stage III – IV), respiratory, gastrointestinal, hepatic (e.g. ALAT > 2.5 times the normal reference range), hematological disease at the investigator's discretion. An echocardiography was allowed as optional measure to judge the patient's heart function), and conversion of the original safety parameter NT-proBNP to an efficacy parameter.

Changes in the Planned Analyses included:

Parameters were defined that could only be measured after an at least eight (glucose, total bilirubin, potassium, C-peptide, intact proinsulin, insulin) or four (cholesterol, triglycerides, HDL, LDL, and oxLDL) hours fasting period. To assure that this prerequisite was met patients fasting status was documented at each visit together with the time of the last meal. Samples not fulfilling the above mentioned prerequisites were excluded from interpretation.

Analysis of the secondary efficacy parameter hs-CRP was performed by considering only values ≤10 mg/L as these values are linked to arterial inflammation in comparison to higher values that are caused by other sources of inflammation.

Study ID Number:

DE-PIO-029

Other Study ID Number(s):

2007-006744-21 [EudraCT Number]

DE-PIO-029 [Takeda ID]

U1111-1114-1645 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012