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2.0 SYNOPSIS

STUDY INFORMATION:

Name of Sponsor: Takeda Development Centre Europe Ltd.

Title of Study: An Observational Study of Patient Cohorts Who Previously Received Long-Term Treatment With Pioglitazone or Placebo in Addition to Existing Antidiabetic Medications

Name of Active Ingredient: None

Name of Finished Product: None

Investigators: One lead investigator; primary investigators in 18 European countries

Study Sites: 321 sites in Europe

Publications Based on the Study: Erdmann E, Song E, Spanheimer R, van Troostenburg de Bruyn AR, Perez A. Observational follow-up of the PROactive study: a 6-year update. Diabetes Obes Metab 2014;16(1):63-74.

Study Period:
Date first subject signed informed consent form: 02 November 2004

Date of last subject's last visit/contact (from the Clinical database): 10 March 2015

Date of last subject's last procedure for collection of data for primary endpoint: 10 March 2015

Phase of Development: Phase 4 (observational)

Objectives:

Primary: To investigate whether prior long-term treatment with pioglitazone has any effect on the composite endpoint of all-cause mortality, nonfatal myocardial infarction (MI), cardiac intervention, stroke, major leg amputation (above the ankle), bypass surgery, or revascularization in the leg; and to compare the incidence, nature, and pattern of newly diagnosed malignancies between the subject cohorts (previously treated with pioglitazone vs previously treated with placebo).

Methodology: This was a 10-year, European, multicenter, observational study of cohort subjects who were previously enrolled in the PROactive study (EC444; a 3-year study [mean duration of follow up was 34.5 months]) and treated with pioglitazone or placebo in addition to their existing antidiabetic medication and other cardiovascular medication. This study assessed total mortality and macrovascular morbidity as well as the incidence, nature, and pattern of newly reported malignancies in subjects with type 2 diabetes (T2DM). No treatment was prescribed by this protocol, and subjects were managed in accordance with normal medical practice. The total duration of the study was 10 years, and data were analyzed every 2 years. Subjects were assessed at nominal visits every 6 months. This report summarizes the final analyses of the 10-year observational study period (EC445), as well as analyses of combined data from rhe PROactive study, for a combined total duration of follow-up of 13 years.

Number of Subjects:

Planned: 3600 subjects
Screened: Not applicable
Enrolled: 3599 subjects
Analyzed: 3599 subjects

Diagnosis and Main Criteria for Inclusion: To qualify for study participation, subjects must have been adults with T2DM who completed the prospective pioglitazone clinical trial in macrovascular events (PROactive study).

Duration of Treatment: Not applicable

Test Product, Dose and Mode of Administration, and Lot Number: Not applicable

Reference Therapy, Dose and Mode of Administration, and Lot Number: Not applicable

Criteria for Evaluation:

Outcome Variables:

The primary outcome measure was the time to the occurrence of any of the following composite events:

- All-cause mortality.
- Nonfatal MI.
- Cardiac intervention including coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI).
- Stroke.
- Major leg amputation (above the ankle).
- Bypass surgery or revascularization in the leg.

Safety:

No safety parameters other than the incidence, nature, and pattern of newly diagnosed malignancies were monitored.

Statistical Methods:

Outcome Variables:

All analyses performed in this study were considered exploratory in nature, and findings of hypothesis tests were summarized by citing the observed significance level (p-value) and confidence interval without any attempt to adjust for the multiplicity of tests.

Two analyses were planned for the primary efficacy endpoint, based on subject's original treatment in PROactive: (1) Considering the period of observation from the date of entry into this observational study, (EC445) the treatment groups were compared with respect to the time to first occurrence of any event within the primary composite outcome. This analysis did not account for actual antidiabetic medication during the follow-up period. The primary outcome for this observational study is not identical to the primary endpoint for the PROactive study (EC444), which included acute coronary syndrome, and required that potential endpoint events be centrally adjudicated. Nevertheless, this analysis is achievable as the events that constitute the primary outcome are also identifiable within the PROactive database. (2) Considering the period of observation from the date of randomization in PROactive to the end of this observational study (EC444/EC445), the treatment groups were assessed with respect to the time to the first occurrence of any event within the primary composite outcome. Again, this assessment did not account for actual antidiabetic medication during the period of follow-up. In each case, survival curves were calculated for each treatment group using the Kaplan-Meier method. Estimates of the hazard ratio were calculated using Cox model regression methods.

Secondary outcomes were analyzed as: time to the first occurrence of the composite of death from any cause, nonfatal MI, or stroke; time to all-cause death; time to nonfatal MI; time to cardiac intervention; time to stroke; time to major leg amputation; time to bypass surgery or revascularization of leg; incidence of recurrent MI or recurrent stroke during the observational study period; and time to cardiovascular death. Frequencies of death were calculated for each treatment group and compared to determine whether there was evidence of a difference between treatments as to the cause of death. An exploratory analysis of the primary and main secondary outcomes was also performed excluding subjects who took pioglitazone during the observational study period (EC445).

Safety:

No formal statistical analysis was planned for safety data. Summaries of information pertaining to malignancies were provided for the overall incidence rate, by type of malignancy (including relative risks and corresponding 95% confidence intervals where the frequency of malignancies was sufficient), and according to thiazolidinedione (TZD) exposure. Some of the additional information recorded during this observational study (EC445) was not available for malignancies that were reported during the PROactive study (EC444); separate summaries of this data are therefore presented for only those events occurring during the observational study period. A distinction was also made between new and recurrent malignancies during this time, and subjects with recurrent or multiple malignancy reports were listed individually. Additional summaries of the reported malignancies were prepared as necessary

following inspection of the data for each report, including investigation of ongoing exposure to TZDs. Post hoc analyses of time to bladder cancer were performed using Cox proportional hazards models with explanatory variables for treatment, age, gender and smoking status (current /past vs never), and post-hoc analyses of time to prostate cancer were performed using Cox proportional hazards models with exploratory variables for treatment and age.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

Baseline and demographic data of subjects enrolled in this observational study (EC445) were collected at the time of entry into the PROactive study (EC444)**.** Sixty-five percent of subjects were male, 98.7% were Caucasian, mean age was 61.6 years, and mean body mass index was approximately 31 kg/m². Most subjects (42.6%) had a mean duration of T2DM of ≥10 years**.** There were no clinically meaningful differences between the PROactive treatment groups for demographic characteristics.

Subject Disposition:

A total of 5238 subjects enrolled in the PROactive study (EC444), and 4873 subjects (93.0%) attended the final PROactive visit. Of these, 3599 subjects (73.9%) enrolled in this observational study (EC445) and comprise the population observed for the subsequent 10 years: 1820 subjects who had received pioglitazone and 1779 subjects who had received placebo during the PROactive study. A total of 1871 subjects (52.0%) completed the Month 120 (10-year) study visit.

Outcome Variable Results:

Based on the original randomization treatment during the PROactive study (EC444), without accounting for TZD use during the observational study period (EC445), there were no statistically significant differences between pioglitazone and placebo groups in the incidence of the primary composite endpoint during the 13 years of both study periods (EC444/EC445) combined (hazard ratio [HR]=0.94 [95% CI: 0.87, 1.01] p=0.1001) or during the 10-year observational study period (EC445) (HR=0.96 [95% CI: 0.88, 1.04], p=0.3444). These results were expected given that all subjects were on standard of care during the observational study period.

Also based on treatment during the PROactive study, there were no statistically significant differences between the pioglitazone and placebo groups in the incidence of the main secondary composite outcome events during the 13 years of both study periods combined (EC444/EC445) (HR=0.94 [95% CI: 0.87, 1.03], p=0.1699) or during the 10-year observational study period (EC444) (HR=0.98 [95% CI: 0.89, 1.07], p=0.6211).

There were no statistically significant differences between the PROactive treatment groups for individual primary outcome components during the 13 years of both study periods combined (EC444/EC445) or during the 10-year observational study period (EC445), except for major leg amputations, which was significantly lower in the pioglitazone group (4.1%) compared with the placebo group (5.6%) (HR=0.74 [95% CI: 0.55, 0.99], p=0.0460) during the 10-year observational study period.

There were also no statistically significant differences between the PROactive treatment groups in the incidence of recurrent MI, recurrent stroke, cardiovascular mortality, or death due to a cardiovascular event or nonfatal MI during the 13 years of both study periods combined (EC444/EC445) or during the 10-year observational study period (EC445).

Following the end of treatment in the PROactive study (EC444) and throughout the 10-year observational study period (EC445), there were no differences between groups in mean glycosylated hemoglobin (HbA1c) values. After showing a significant decrease with pioglitazone treatment during the PROactive study, mean HbA1c values in the PROactive pioglitazone group increased during the observational study period to values similar to those in the PROactive placebo group.

When considering TZD use during the observational study period (EC445), the incidence of the primary composite outcome (all-cause mortality, nonfatal MI, stroke, cardiac intervention [PCI or CABG], major leg amputation [above the ankle], and bypass surgery/leg revascularization) was similar between the PROactive pioglitazone/No TZD Use and PROactive placebo/No TZD Use groups and both were higher compared with the groups that used TZDs during the observational study period. Any TZD use in the observational study period was associated with a lower

incidence of primary composite endpoint events compared to no TZD use, although the smaller sample size makes it difficult to draw meaningful conclusions.

Similarly, the incidence of main secondary composite outcomes (all-cause mortality, nonfatal MI, and stroke) was also similar between the PROactive pioglitazone/No TZD Use and PROactive placebo/No TZD Use groups and both groups were higher compared with the groups that used TZDs during the observational study period (EC445).

The incidence of deaths was lower in the PROactive pioglitazone group with TZD use in the 10-year observational study period (EC445) compared with the PROactive pioglitazone/No TZD Use group. The incidence of stroke was comparable in the PROactive pioglitazone/No TZD Use and PROactive placebo/No TZD Use groups but both were higher compared with the groups that used TZDs during the observational study period.

Safety Results:

Mean duration of exposure to TZDs during the 10-year observational study period (EC445) was similar between the PROactive pioglitazone and placebo groups (approximately 4.4 vs 4.0 years, respectively).

Based on treatment received in the PROactive study (EC444), the incidence of malignancies reported during both study periods combined (13 years; EC444/EC445) was similar between groups: 12.5% of subjects in the pioglitazone group and 12.2% of subjects in the placebo group. The relative risk (RR), pioglitazone vs placebo, was 1.02 (95% CI: 0.89, 1.18). Results were similar during the 10-year observational period (EC445): 12.9% of subjects in the pioglitazone group vs 13.2% of subjects in the placebo group; RR=0.98 (95% CI: 0.83, 1.16). By any TZD use during both study periods combined (13 years; EC444/EC445), the incidence of malignancies reported was similar for subjects who received any TZDs (12.5%) and for subjects who never received TZDs (12.2%).

Based on treatment during the PROactive study (EC444) and TZD use during the observational study period (EC445), the incidence of malignancies reported during the 10-year observational study period was the same for both PROactive pioglitazone/no TZD and PROactive placebo/No TZD Use groups (13.3%). In general, the incidence of malignancies reported during this period was lower for subjects who received pioglitazone, regardless of their treatment in the PROactive study.

During the PROactive study (EC444), bladder cancer was reported in 14 pioglitazone subjects (0.5%) and 5 placebo subjects (0.2%). In the analysis based on treatment in the PROactive study, which did not account for pioglitazone use during the 10-year observational study period (EC445), bladder cancer was reported in 14 subjects in the pioglitazone group (0.8%) and 21 subjects in the placebo group (1.2%). During both study period combined (13 years; EC444/EC445), bladder cancer was reported in 27 subjects in the PROactive pioglitazone group (1.0%) and 26 subjects in the placebo group (1.0%). Note that a subject originally randomized to pioglitazone reported 1 event of bladder cancer during the PROactive study and another event of bladder cancer during the 10-year observational study period and was only counted once in the combined 13-year analysis.

In the post hoc analysis of bladder cancer by pioglitazone use in either the PROactive study (EC444) or during the 10-year observational study period (EC445), the number of subjects who reported bladder cancer during the 13 years of both study periods combined (EC444/EC445) was 29 (1.0%) in the Any Pioglitazone Use group vs 24 (1.0%) in the No Pioglitazone Use group. The 29 subjects that reported bladder cancer in the any pioglitazone use group includes 27 subjects that reported bladder cancer in the PROactive pioglitazone group plus an additional 2 subjects from the PROactive placebo group that took pioglitazone during the observational period before the onset of bladder cancer. There was no statistically significant difference between the Any Pioglitazone Use and No Pioglitazone Use groups in the time diagnosis of bladder cancer during the 13 years of both study periods combined (HR=0.93 [95% CI: 0.54, 1.60] p=0.8047).

During the PROactive study (EC444), SAEs of prostate cancer were reported in 9 (0.5%) pioglitazone male subjects and 5 (0.3%) placebo male subjects. In the analysis based on treatment in the PROactive study, which did not account for pioglitazone use during the 10-year observational study period (EC445), prostate cancer was reported in 44 (3.7%) male subjects in the pioglitazone group compared with 29 (2.5%) male subjects in the placebo group. During both study periods combined (13 years; EC444/EC445), prostate cancer was reported in 53 (3.1%) male subjects in the pioglitazone group compared with 33 (1.9%) male subjects in the placebo group. Note that a subject originally randomized to placebo reported an event of prostate cancer during the PROactive study and another event of prostate cancer during the 10-year observational study period and is only counted once in the combined 13-year

analysis. Including the nonserious cases of prostate cancer in the PROactive study (EC444), during both study periods combined (13 years; EC444/EC445), prostate cancer was reported in 58 (3.3%) male subjects in the pioglitazone group compared with 35 (2.0%) male subjects in the placebo group.

In the post hoc analysis of prostate cancer by pioglitazone use in either the PROactive study (EC444) or during the 10-year observational study period (EC445), the number of male subjects who reported prostate cancer during the 13 years of both study periods combined (EC444/EC445) was 58 (3.1%) in the Any Pioglitazone Use group vs 28 (1.8%) in the No Pioglitazone Use group. The HR for the time to diagnosis of prostate cancer during the 13 years of both study periods combined was 1.55 (95% CI: 0.99, 2.43; p=0.0572). Including the nonserious cases of prostate cancer in the PROactive study (EC444), the number of male subjects who reported prostate cancer during the 13 years of both study periods combined (EC444/EC445) was 63(3.4%) in the Any Pioglitazone Use group vs 30 (1.9%) in the No Pioglitazone Use group (HR=1.57, 95% CI: 1.02, 2.43; p=0.0408).

CONCLUSIONS:

The results of the final 10-year analyses (EC445) were very similar to the previous interim analyses.

Any TZD use in the observational study period was associated with a lower incidence of primary and secondary composite outcome events; regardless of treatment during the PROactive study (EC444). Consistent with the results of the 2-, 4-, 6-, and 8 year interim reports, the statistically significant treatment group difference during the PROactive study in favor of pioglitazone for the main secondary composite outcome (all-cause mortality, nonfatal MI, or stroke) was no longer observed 10 years after pioglitazone treatment ceased. In the subgroup of subjects who continued on pioglitazone, the cardiovascular trend of benefit appeared to persist for the main secondary outcome.

During the combined study periods (13 years; EC444/EC445), there was no statistically significant difference in the time to bladder cancer events between subjects who received any pioglitazone and those who received no pioglitazone. These data suggest that there is no residual risk of developing bladder cancer after stopping treatment with pioglitazone.

During the combined study periods (13 years; EC444/EC445), prostate cancer was reported more frequently in subjects who received any pioglitazone compared to those who received no pioglitazone. These results should be interpreted with caution, as the observational study period (EC445) was not blinded and results may have been subject to detection bias, as pioglitazone-treated subjects may have been more likely to visit a urologist and have PSA testing due to the interest in bladder cancer. Additionally, age, which is a risk factor for prostate cancer, may have impacted the results as the mean and median age at onset of prostate cancer was higher in the pioglitazone group compared with those in the placebo group.

The overall pattern and incidence of malignancies reported during this 10-year observational study (EC445) did not change from that observed in the PROactive study (EC444), suggesting that exposure to pioglitazone in PROactive did not increase the risk for the development of new malignancies.

The results from this observational study support the positive benefit-risk profile of pioglitazone.

DATE OF REPORT: 15 July 2015