STATISTICAL REVIEW AND EVALUATION

PIOGLITAZONE META-ANALYSES

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Drug Name:	Pioglitazone
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Footnotes: There are two sets of pioglitazone meta-analyses from two statistical reviewers, one from this reviewer and the other from Dr. McEvoy. Both of them were conducted in parallel for the preparation of the Advisory Committee (AC) meeting to discuss Avandia cardiovascular risk held on July 13 and 14, 2010. The pioglitazone meta-analyses that Dr. McEvoy conducted used the same methods that have been used in the Avandia meta-analyses. I took novel approaches which had been discussed several times in the preparation of the pioglitazone meta-analyses within the Avandia review team in the Division of Biometric 7 (DB7) in the Office of Biostatistics.

The main analyses of my meta-analyses were completed and the results, including the finding of significant dose-response trends of increased risk in certain cardiovascular events, were discussed within the DB7 review team on and before June 7th, 2010. After noticing that only Dr. McEvoy's draft pioglitazone meta-analyses were sent for circulation, I reminded Dr. Levenson on June 7th that I also had a review and would be finalized within a couple of days (All materials for the meeting were due on June 15). I was told then by Dr. Levenson that my review was not needed for the AC meeting nor was due by June 15, 2010 and that Dr. McEvoy will add the dose-response analyses in his review.

As I believe that different statistical methods of conducting meta-analyses using clinical trials should be discussed and debated openly, I expressed the interest of publishing my meta-analyses to the Office of Biostatistics. I was advised that my meta-analyses should be first discussed within DB7 and the medical division. The first draft of this document was sent to DB7 for comment on August 11, 2010.

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1. Summary

Forty blinded phase II-IV clinical studies are used to evaluate the cardiovascular effect of pioglitazone in this review. The studies are divided, not mutual exclusively, into 5 groups for 1) dose-response relationship assessment, 2) comparison with placebo, 3) comparison with placebo co-administered with tailored background therapies, 4) comparison with metformin, and 5) comparison with sulfonylurea. The cardiovascular effect is evaluated using endpoints including all-cause mortality, cardiovascular death (CVD), stroke, myocardial infarction (MI), myocardial ischemic events (MIS), and congestive heart failure (CHF). A composite endpoint consisting of MI, stroke, and cardiovascular death is also evaluated.

1.1 Dose-response assessment and comparison with placebo

Dose-response analyses based on information from 24 of the 40 studies including over 9,000 patients show that there are visible dose-response trends of increased risk of MIS, MI, and CHF in pioglitazone. Among the 24 studies, the planned treatment duration of 23 studies was 6 months and under. The dose-response trends for MIS and MI events were primarily driven by the differences between pioglitazone 30 and 45 mg. The risk increase in MIS in pioglitazone 45 mg from 30 mg was statistically significant. The incidence rate of MIS for pioglitazone 45 mg was 4.19 per 100 patient-years, while the incidence rate for pioglitazone 30 mg was 1.98 per 100 patient-years (similar to the placebo rate). The incidence rate of MI for pioglitazone 45 mg was 1.60 per 100 patient-years, while the rate for 30 mg was 0.69 per 100 patient-years (also close to the placebo rate). The risk of CHF increased as the dose levels of pioglitazone increased.

Among the placebo-controlled studies, studies are further divided by add-on therapies. They are mono-therapy with no add-ons, insulin add-on, metformin add-on, sulfonylurea add-on, and two add-on agents that have not yet been approved in US (alogliptin and voglibose). The majority of the placebo-controlled studies used fixed doses of pioglitazone and is included in the dose-response assessment. The additional 4 studies that are included in this placebo-controlled group used titrated pioglitazone doses. There is little information in each add-on group in terms of sample size and number of events, which made it inadequate for the assessment of consistency of cardiovascular effect among add-on groups. Overall, the pioglitazone dose level is primarily 30 mg and below in the placebo-controlled studies. Higher risk of CHF was observed in pioglitazone compared with placebo. Although the data in the placebo-controlled studies are not sufficient to draw meaningful conclusion, the results are consistent with the findings in the dose-response assessment.

1.2 Relative effect versus other treatments for type 2 diabetes

The relative cardiovascular effect of pioglitazone is assessed in comparison to sulfonylurea, metformin, or placebo co-administered with background therapies which were tailored to individual needs in the meta-analyses.

More than 6,500 patients from nine sulfonylurea-controlled studies are used to evaluate the cardiovascular effect of pioglitazone in comparison with sulfonylurea. The pioglitazone dose levels in these studies were all titrated up to 45 mg. The treatment duration lasted from 6 months to more than 3 years. Over the entire treatment period, other than the significantly higher risk of CHF in the pioglitazone treatment group compared with that in sulfonylurea, there was no distinguishable difference between pioglitazone and sulfnoylurea in other cardiovascular events.

About 2,300 patients from 3 metformin-controlled studies are used to evaluate the cardiovascular effect of pioglitazone in comparison with metformin. The dose levels of pioglitazone included 15 mg fixed dose and titrated doses from 15 mg to 45 mg. Few cardiovascular events occurred over the treatment duration from 6 months to 2 years, perhaps due to the fact that the majority of patients were naïve to diabetic treatments. No significant difference between pioglitazone and metformin is observed except that the occurrence of stroke in pioglitazone appeared to be lower than that in metformin.

PROactive was a randomized, double-blinded, and placebo-controlled study which included over 5,000 patients who were at high risk for macrovascular events. The study added background treatments of type 2 diabetes that were tailored to individual patients' need to achieve the optimal glycemic control. The dose levels of pioglitazone were titrated from 15 mg to individual patient's maximum tolerated dose level up to 45 mg. Patients in pioglitazone had significantly lower rates of MIS and MI, however, higher rate of CHF, compared to placebo over 3 years of treatment.

1.3 Risk assessment over the first 6 months of treatment

Because of increased cardiovascular risk in pioglitazone 45 mg which is observed in studies with treatment duration of 6 months and under, the cardiovascular effect is also assessed by 6-month intervals. Only the PROactive study and sulfonylurea-controlled studies are discussed as they had not only a large sample size, but a reasonable number of events and treatment duration longer than 6 months. The dose levels of pioglitazone in these studies were a mixture of 15 mg to 45 mg.

In the first 6 months of the PROactive study, the cardiovascular risk in pioglitazone was similar to that in the placebo arm in almost all events except the CHF events. After Month 6, the risk of cardiovascular events in MIS, MI, stroke, even CHF began to decline in the pioglitazone treatment. Although the decline also occurred in MIS, MI and CHF in the placebo arm, the decline was relatively slower compared to that in the pioglitazone arm. It is possible that dropouts or changes in the patient sample over time may contribute to the decline of risk in the pioglitazone treatment. However, it is unlikely to be the sole factor for the larger decline in the pioglitazone arm compared to placebo since the dropout rates of this study were low and reasonably balanced in both treatment arms.

In the sulfonylurea-controlled studies, pioglitazone had numerically higher risk in almost all cardiovascular events (except MIS) compared to that in sulfonylurea in the first 6 months of treatment. This difference was particularly visible in the composite endpoint consisting of MI, stroke, and CVD. The risk ratio of pioglitazone to sulfonylurea was

above 2 in this composite endpoint with a p-value of 0.05. The risk of all cardiovascular events began to decline after Month 6 in the pioglitazone arm, whilst the risks of MI, stroke and the composite endpoint increased over time in the sulfonylurea arm. The interpretation of the changes of risk over time becomes difficult due to high dropout rates in both treatments: 20% in pioglitazone and 16% in sulfonylurea in the first 6 months of treatment.

1.4 Conclusion

Dose-response analysis using studies over 6-months treatment duration indicated that the risk of CHF increased as the dose of pioglitazone increased. The risk was visible with pioglitazone 15 mg in comparison to placebo. In long term studies, pioglitazone had significantly higher risk of CHF compared to sulfonylurea or placebo co-administered with tailored background treatments to type 2 diabetes. The risk was consistently higher than controls over time, although the risk of CHF was reduced after the first 6 months of treatment in pioglitazone.

Pioglitazone 45 mg showed significantly higher risk of MIS compared to pioglitazone 30 mg over 6 months of treatment duration (p-value=0.001). The risk of MIS in pioglitazone 45 mg was more than 2-fold of the risk in pioglitazone 30 mg. The risk of MI in pioglitazone 45 mg was also close to 2-fold of the risk in pioglitazone 30 mg over 6 months of treatment, although the increase was not statistically significant at the level of 0.05 (p-value=0.117). No overwhelming evidence suggests that pioglitazone 30 mg or under had higher risk in MIS and MI. Assessing risk over time, we observe consistent risk reduction in MIS and MI in the PROactive study and the group of studies with the sulfonylurea control after 6-month treatment in pioglitazone using doses titrated up to 45 mg. Such changes altered the relative risk compared with controls. The protective effect of pioglitazone in MIS and MI compared with placebo was not observed in the first 6 months of treatment in the PROactive study, but was observed after. In the first 6 months of treatment, pioglitazone did not do well in MI in comparison to sulfonylurea. However, over the entire treatment period which lasted over 3-years, the problems that were seen in the first 6 months of treatment became less visible.

The events of stroke were less frequent compared with the events of MIS, MI, and CHF. Although we observe trend of increased risk of stroke with increased pioglitazone dose levels, the trend is uncertain because only few events were available. The risk profile of stroke that is observed in the PROactive study and the studies with the sulfonylurea control is similar to that of MI.

No meaningful difference was observed in all-cause mortality and CVD between pioglitazone and various controls.

2. Background

Pioglitazone is a member of thiazolidinedione (TZD) family which was approved in 1999 by the Food and Drug Administration (FDA) for glycemic control in type 2 diabetes.

Due to concerns of cardiovascular risk of rosiglitazone, another member of TZD family approved for the treatment of type 2 diabetes, the cardiovascular effect of pioglitazone has also been evaluated.

This review discusses a comprehensive approach to evaluating the cardiovascular effect of pioglitazone. The evaluation includes assessing the dose-response relationship of cardiovascular effect in pioglitazone, excess risk in comparison to placebo, as well as the relative risk in comparison to other popular type 2 diabetic treatments, such as metformin, sulfonylurea, or background therapy. We also investigate changes of the cardiovascular effect over time, as well as the impact of premature discontinuations of study treatment.

The approach differs from the previously publicly presented meta-analyses in pioglitazone in many ways, as the focus here is to understand the cardiovascular effect of pioglitazone. There are differences in how to quantify risk. This review uses a measurement that takes both sample sizes and treatment duration into consideration. The most important difference is in selecting information to be included in the meta-analyses.

One of the important debates in meta-analyses is what information should be included, as different sets of information may lead to different analysis results. In our meta-analyses, we do not exclude a study unless we have objective scientific reasons. In this principle, instead of selecting only the approved doses of pioglitazone, which are 30 and 45 mg, we requested data of all dose levels in case that unapproved doses may contain valuable information. We include studies that consist of several doses of pioglitazone without comparators, as such studies may help gain understanding of the dose-response relationship. We include studies with not-yet-approved agents as add-on with the understanding that the add-ons, like those add-ons of the approved agents, may complicate the understanding of the cardiovascular effect. The complication is that the add-on may introduce possible treatment by add-on interaction in directions that either increase or mitigate the risk. We do not exclude studies based on study duration as it is important to include studies of short duration to evaluate when the effect kicked in as well as long treatment duration to assess how the effect changes overtime.

This review is divided into the following sections: The third section discusses methodologies including data sources and analysis strategies; the fourth section investigates dose-response relationship of cardiovascular effect in pioglitazone and comparison with placebo; the fifth section evaluates the relative cardiovascular effect compared with currently used popular type 2 diabetes treatments, sulfonylurea and metformin. A large scale randomized, double-blind and placebo-controlled study named PROactive that co-administered tailored background therapies is also analyzed in this section.

3. Methods

3.1 Data Sources

To avoid potential selection bias, this reviewer requested data of all clinical trials that include pioglitazone from Takeda, the sponsor of pioglitazone. We intend to collect all trial level information which includes all Takeda and non-Takeda sponsored trials for the purpose of controlling systematic selection biases. However, due to difficulty of obtaining data of non-Takeda sponsored studies, the data are limited to Takeda-sponsored studies. Only one non-Takeda sponsored study was provided by Takeda. We requested three levels of information: the trial level, treatment level, and patient level information. The data request was sent to Takeda in January 2010. The request provides information on data set structures, data variables, as well as definitions of endpoints such as MIS, MI, stroke, and CHF. The trial level information includes study synopses and data of trial characteristics. The treatment level information includes summary statistics of each treatment arm on sample size, treatment duration, number of events, efficacy information, etc. The patient level information consists of 4 datasets, patient demographic information, concomitant and previous use of cardiovascular medication, cardiovascular events, as well as certain general serious adverse events.

The sponsor identified 67 phase II to IV studies that included pioglitazone treatment arms and were completed by December 2009. Among them, 45 are randomized and double-blinded and 3 are randomized but single-blinded (patient-blinded). Of these 48 studies, 40 studies (including 3 single-blinded studies) are used to evaluate the cardiovascular effect of pioglitazone in this review. The 3 single-blinded studies are included as there is not a better reason to exclude them other than the suspicion of data quality. As far as the concern of data quality, double-blinded studies may not be immune from such suspicion in safety assessment as there is less incentive to collect high quality data to show differences in safety.

Of the 8 randomized and double-blinded studies that are not used in the meta-analyses, there are either no patient level information available (2 studies) or comparisons are not relevant to pioglitazone, in that all arms contain the same dose of pioglitazone (5 studies). One study that is not included in the meta-analyses is the study that compares pioglitazone directly to rosiglitazone. This study will be briefly mentioned at the end of Section 5.

The 40 studies that are used for the meta-analyses are further grouped based on study design and purpose of evaluation: 24 studies are used in the dose-response assessment; 23 studies are used for comparison with placebo, which include mono-therapy or add-on therapies primarily with insulin, metformin and sulfonylurea; 3 studies are metformin-control; and 9 studies are sulfonylurea-conrol. The studies in each group are not mutually exclusive.

3.2 Endpoints

The endpoints assessed include fatal and non-fatal MIS, MI, strokes, all cause mortality, CVD, and CHF. These events are defined by the FDA medical reviewers using the coding system of Medical Dictionary for Regulatory Activity (MedDRA) at the level of the preferred terms. The preferred terms are listed in Appendix I. The events were retrospectively identified by the sponsor, based on FDA's instruction, from the safety data collected as part of a standard adverse event reporting process during clinical studies. A composite endpoint consisting of CVD, nonfatal MI, and nonfatal stroke is also used in the meta-analyses.

3.3 Statistical methods

The meta-analysis strategy was thought through before data became available. As most of the clinical studies for diabetes treatments had high dropout rates, patients were not equally exposed to treatments. The number of events that could be observed depends directly on the duration of exposure and follow-up. Therefore a simple rate as the number of events divided by the total number of patients may not be adequate in expressing the risk level. In addition, the cardiovascular effect may change over time. To adequately reflect the level of cardiovascular risk that will take treatment duration as well as sample size into consideration, and at the same time provide flexibility to evaluate the risk over different treatment period, we use the incidence rates, expressed as number of events per 100 patient-years to represent the risk level. Consequently, survival analysis is used for reasons mentioned above in analyzing relative treatment effects which are expressed as hazard ratios. The analyses in this review are based on the first event that was experience by a patient. Multiple events, such as recurring events of one type as well as different types of events, are also analyzed using Anderson-Gill and Wei-Lin-Weissfeld models. As these analyses do not reveal more than what is observed in the analyses of the first event, the results of multivariate survival analyses are not reported in this review. The summary of recurrent events can be found in Appendix II where summary information of cardiovascular events are displayed by studies.

4. Cardiovascular effect relative to placebo

4.1 Dose response assessment

Twenty-four studies that contain either multiple arms of fixed pioglitazone dose levels or placebo are used to assess dose-response relationship in cardiovascular effect. These studies include mono-therapy studies where the treatments are either pioglitazone or placebo and studies where other diabetic therapies are added to pioglitazone or placebo. The add-ons include sulfonylurea, metformin, insulin, as well as other not-yet-approved agents including alogliptin (2 studies), voglibose (1 study) and TAK-536 (1 study). The doses of pioglitazone range from 7.5 mg to 60 mg. Since only 5 patients received 60 mg

for about 2 weeks and no event was reported from the 5 patients, the 60 mg of pioglitazone was not included in the dose-response analysis. The treatment duration of all studies except one is 6 months or less. Over 90% were non-naïve diabetic patients. On average, patients had 8 years of history of diabetes ranging from newly diagnosed to 55 years of diabetic treatment. The average age is 56 years old ranging from 18 to 87 years of age. About 19% of patients used statin at baseline and the percentage increased to 22% during treatment. Aspirin use was 20% at baseline and 22% during treatment. Nitrate use was low at baseline (2%) and during treatment period (3%). The summary information of study sample size, treatment duration, as well as counts of events by treatment is provided in Appendix II, Table A1.

Statistical tests are performed using the Cox proportional hazard model stratified by studies. Two studies, Studies OPI-525 and 322OPI-001, are further stratified based on the add-on dose levels. Linear trend test results, i.e., testing if the cardiovascular effect is increasing in proportion to dose levels of pioglitazone, are provided in Table 4.1 for each endpoint. The incidence rates that are displayed in Table 4.1 are the results of pooling all 24 studies. From Table 4.1, we observe the following:

- Visual inspection suggests that the linear trend does not appear to be a good fit for MIS and MI.
- Although the linear trend is statistically significant in MIS, the significant trend test is primarily driven by the risk difference between pioglitazone 30 and 45 mg. As there is no visible difference between placebo and pioglitazone 30 mg and under in MIS, all dose levels of 30 mg and below are combined. The hazard ratio between pioglitazone 45 mg and the combined dose group is 2.2 (p-value=0.001) based on the proportional hazard model stratified by studies.
- Although no linear trend is detected in MI, a large risk difference in MI between pioglitazone 30 and 45 mg is also observed. As there is no visible difference between placebo and pioglitazone 30 mg and under in MI, all dose levels of 30 mg and below are combined. The hazard ratio between pioglitazone 45 mg and the combined dose group is 2.0 with a p-value of 0.117 based on the stratified proportional hazard model. This analysis suggests possible higher risk of MI in pioglitazone 45 mg compared with 30 mg.
- This dose-response relationship assessment confirms the known fact that the risk of CHF in pioglitazone increases with the increase of pioglitazone dose level.
- Events for stroke, as well as all-cause mortality and cardiovascular death, are sparse in this set of data that it is not possible to make reliable comparisons.

To obtain a direct comparison between pioglitazone 30 and 45 mg, 7 studies that have both pioglitazone 30 and 45 mg are identified, from the 24 studies, to perform the comparison using only the pioglitazone 30 and 45 mg arms. The analyses use the Cox proportional hazard model which is stratified by studies and add-on dose levels. The results which are also reported in Table 4.1 are consistent with the results that are obtained from the analyses of the 24 studies. It is worth to note that there is very little information on pioglitazone 45 mg outside the 7 studies. There is nothing unusual about the 7 studies except that some of the studies had relatively larger sample sizes compared with that of the rest of the studies.

Table 4.1: CV events and rates by dose.

Pioglitazone doses	Sample Size (patient-years)	Number of Events (Rate/100 Patient-year)					
		MIS	MI	Stroke	CHF	CVD	Death
Dose-response analysis using 24 studies							
0	2336(849)	17(2.00)	7(0.82)	1(0.12)	6(0.71)	3(0.35)	3(0.35)
7.5mg	129 (35)	2(5.71)	1(2.86)	0(0.00)	1(2.86)	0(0.00)	0(0.00)
15mg	1391 (490)	6(1.22)	1(0.20)	2(0.41)	6(1.22)	1(0.20)	1(0.20)
30mg	3486 (1310)	26(1.98)	9(0.69)	7(0.53)	25(1.90)	3(0.23)	5(0.38)
45mg	2072 (811)	34(4.19)	13(1.60)	6(0.74)	23(2.84)	3(0.37)	4(0.49)
p-values for linear trend*		**0.028**	**0.713**	**N/A**	**0.064**	**N/A**	**N/A**
Comparison between pioglitazone 30mg and 45 mg using 7 studies							
30mg	1718 (671)	10(1.49)	6(0.89)	6(0.89)	17(2.53)	2(0.30)	3(0.45)
45mg	1720 (664)	27(4.07)	11(1.66)	5(0.75)	23(3.46)	2(0.30)	3(0.45)
Hazard Ratio (45mg vs. 30mg)		**2.74**	**1.86**		**1.36**		
p-values*		**0.006**	**0.224**	**N/A**	**0.343**	**N/A**	**N/A**

* N/A indicates that asymptotic analyses results are not displayed due to small number of events.

4.2 Placebo-controlled studies

The 23 placebo-controlled studies are grouped based on add-on therapies. All placebo-controlled studies except 4 studies used fixed pioglitazone doses and are also included in the dose-response assessment. Only four studies used pioglitazone titrated doses. Similar to the group of studies for dose-response assessment, the treatment duration was 6 months and less for all studies except one. As opposed to the group of studies for dose-response assessment, there are few data on pioglitazone 45 mg fixed dose.

There are 8 placebo-controlled studies without any add-on. The summary information of the 8 studies can be found in Table A2 in Appendix II. About 90% patients were non-naïve patients. Eight of the 9 studies included fixed doses of pioglitazone 7.5, 15, 30, and 45 mg. One study contains two arms of titrated dose, one from 7.5 to 30 mg and the other from 15 to 45 mg. As events are sparse and it is difficult to separate dose levels in the titrated dose of pioglitazone, all pioglitazone doses are combined. The combined pioglitazone group represents a total exposure of 338 patient-years, of which 45 patient-years were from 45 mg fixed doses.

Four placebo-controlled studies have insulin as an add-on. The summary information of the four studies can be found in Table A3 in Appendix II. Among the four studies, Study OPI-502 is not strictly an insulin add-on study. This study added either pioglitazone or placebo to patients who were using either insulin alone or insulin with metformin for glycemic control. The insulin level may be reduced during the double-blind treatment period to assess the reduction in insulin by adding pioglitazone in glycemic control. The dose level of pioglitazone was titrated from 30 mg after 8-week treatment to 45 mg for additional 12-week treatment. The rest of the 3 studies are fixed dose studies all using pioglitazone 15 to 30 mg. All dose levels of pioglitazone are combined due to sparse information. The combined pioglitazone group primarily represents dose levels of 30 mg and below. About 90% patients were non-naïve patients.

Five placebo-controlled studies have metformin as an add-on. The summary information of the 5 studies can be found in Table A4 in Appendix II. Among the 5 studies, 4 studies are fixed dose studies all using pioglitazone 30 mg except Study 322OPI-001. Study 322OPI-001 used fixed pioglitazone 15, 30, and 45 mg. One study titrated pioglitazone from 15 mg for initial 12-week treatment followed by pioglitazone 30 mg for 16 weeks. All doses are combined due to sparse information. The combined pioglitazone group represents a total exposure of 387 patient-years, of which 57 patient-years were from 45 mg fixed dose. About 50% patients were non-naïve patients in this placebo-controlled group with metformin add-on.

Another four placebo-controlled studies have sulfonylurea as an add-on. The summary information of the four studies can be found in Table A5 in Appendix II. Among the 4 studies, 3 studies used fixed dose of pioglitazone ranging from 15, 30, and 45 mg. Study F-PIO-100 started with pioglitazone 30 mg with the choice of titration up to 45 mg later. This study in fact is metformin and sulfonylurea add-on. All dose levels of pioglitazone are combined with a total exposure of 250 patient-years, of which 16 patient-years exposed to 45 mg fixed doses. Close to 70% patients were non-naïve patients.

Three placebo-controlled studies used add-ons that have not yet been approved in US. Study 322OP-002 and part of Study 320OPI-001 are alogliptin add-on studies and Study CCT-102 is a voglibose add-on study. The summary information on cardiovascular events of the three studies is displayed in Table A1. As Study CCT-102 was small in sample size and exposure and no events reported, voglinose add-on is not further discussed in this section. The two alogliptin add-on studies used fixed doses of pioglitazone ranging from 15 to 45 mg. Since there is fair amount of data on pioglitazone 45 mg (120 patient-years), the 45 mg doses are separated from the rest of the doses.

The cardiovascular events of the placebo-controlled studies are summarized in Table 4.2 separated by add-ons. Due to the facts that the events are sparse, sample sizes are small, and doses of pioglitazone are mixed with various fixed and titrated doses (primarily 30 mg and below), the assessment is focused on the patterns of event rates among various add-ons. Although the treatment differences of cardiovascular effect between pioglitazone and placebo varied among different add-ons, the risks of cardiovascular events in pioglitazone other than the CHF events do not appear to be alarmingly higher than placebo. Higher risk of CHF is observed in pioglitazone group compared with placebo in the mono-therapy, insulin add-on, and metformin add-on groups. The observations in the placebo-controlled studies are consistent with that in the dose-response assessment.

Table 4.2 Analyses on cardiovascular events in placebo controlled trials

Treatment/ Sample Size (patient-years)		Number of Events (Rate /100 Patient-years)						
		MIS	MI	Stroke	CHF	CVD	Death	Composite
Monotherapy								
Pio	1144(338)	4 (1.18)	1 (0.30)	1(0.30)	6(1.78)	0	0	2(0.59)
Plc	545(154)	4 (2.60)	4 (2.60)	0	0	1(0.65)	10.65)	4(2.60)
Insulin add-on								
Pio	697(298)	8(2.68)	1(0.34)	0	7(2.35)	0	0	1(0.34)
Plc	512(249)	9(3.61)	2(0.80)	0	1(0.40)	1(0.40)	1(0.40)	2(0.80)
Metformin add-on								
Pio	948(387)	7(1.81)	2(0.52)	0	3(0.78)	1 (0.26)	1 (0.26)	2(0.52)
Plc	746(269)	2(0.74)	0	1 (0.37)	1(0.37)	0	0	1(0.37)
Sulfonylurea add-on								
Pio	804(250)	7(2.80)	2(0.80)	1(0.40)	3(1.20)	2(0.80)	2(0.80)	2(0.80)
Plc	480(164)	2(1.22)	2(1.22)	0	4(2.45)	2(1.22)	2(1.22)	2(1.22)
Alogliptin								
Pio 45mg	260 (120)	7(5.83)	2(1.67)	1(0.83)	1(0.83)	0	0	3(2.50)
Pio ≤30mg	684 (316)	5(1.58)	2(0.63)	1(0.32)	0	1(0.32)	0	2(0.63)
Plc	421 (186)	4(2.15)	1(0.54)	0	0	0	0	1(0.54)

5. Cardiovascular effect relative to other diabetic treatments

5.1 PROactive – a placebo-controlled study with tailored background diabetic therapies

PROactive was conducted in 19 European countries and evaluated 5238 patients with advanced type 2 diabetes and at high risk for macrovascular events. Patients were randomized in 1:1 ratio to pioglitazone or placebo in addition to any existing anti-diabetes therapies and cardiovascular medications. Pioglitazone was titrated from 15 mg to maximum tolerated dose up to 45 mg. Patients continued on the highest tolerated dose throughout the treatment period for up to 3.5 years. Concomitant anti-diabetes and cardiovascular medications were adjusted throughout the study to achieve and maintain the target A1C levels and reducing cardiovascular risk.

The patient population consisted of 66% males, predominately Caucasian, and overweight, had an average age of 62 years, mean diabetes history of 9.5 years, and serious comorbidities that required multiple therapies. About 96% patients are non-naïve; 48% took statin at the baseline and 60% during the treatment; 76% used aspirn at baseline and 83% during the treatment; 42% used nitrate at the baseline and 47% during the treatment. About 28% (21% dropped from study) and 16% (12% dropped study) patients experienced edema in the pioglitazone and placebo arms, respectively.

The summary information of this study can be found in Table A6 in Appendix II. Analysis results of the cardiovascular events are summarized in Table 5.1. The results of the average risk over the entire treatment period are presented in bold along with the overall hazard ratios and p-values generated from the proportional hazard model. The risk is also reported by an interval of 6 months. Subgroup analyses by nitrate, aspirin, and statin use are also displayed in this table. From Table 5.1, we observe the following:

- The risk of MIS in the pioglitazone group was statistically significantly lower compared to the placebo group over the entire treatment period. Examining the risk by 6-month interval, there was no risk difference in the first 6-month period between pioglitazone and placebo. The risk difference between the two treatment groups was primarily driven by the larger risk reduction after 6-month treatment in the pioglitazone group compared to that in placebo.
- Similar pattern is also observed in the MI events. The risk of MI in the pioglitazone group was statistically significantly lower compared to the placebo group over the entire treatment period. Again, there was no risk difference in the first 6-month period between pioglitazone and placebo. The risk difference between the two treatment groups was primarily driven by the large risk reduction after 6-month treatment in the pioglitazone group.
- Similar pattern is again observed in the stroke event, except that the risk difference was not statistically significantly different.
- The risk of CHF was statistically significantly higher in the pioglitazone group compared to that in the placebo group. The risk increase averaged over the entire treatment period was 38%. This actual risk increase might be even higher than the observed for the following reasons: all patients with CHF had edema; more patients developed edema in the pioglitazone group; and higher percentage of patients who experienced edema had dropped out the study prematurely.
- No meaningful difference was observed in all-cause mortality and cardiovascular deaths, although in the pioglitazone treatment, the risk of death including cardiovascular deaths appears to be increasing over years in numerically higher rates compared with placebo.
- Based on the subgroup analyses grouped by either nitrate, aspirin, or statin use, the treatment differences were not driven by a particular subgroup. Examining all subgroup analyses displayed in Table 5.1, treatment by statin-use interaction was observed in the CVD and all-cause mortality events.

Table 5.1 Analyses for cardiovascular events for Study EC444

Trt /Sample Size (patient-years)	Number of Events (Rate /100 Patient-years)						
	MIS	MI	Stroke	CHF	CVD	Death	Composite
Pio **2605 (6477)**	**356 (5.64)**	**93 (1.44)**	**73 (1.13)**	**249 (3.84)**	**118 (1.82)**	**162 (2.50)**	**163 (2.52)**
0-6 months	124 (9.97)	28 (2.22)	17 (1.34)	70 (5.57)	19 (1.50)	24 (1.89)	45 (3.57)
6-12 months	69 (6.04)	14 (1.17)	13 (1.09)	53 (4.53)	17 (1.41)	22 (1.82)	27 (2.28)
12-18 months	43 (4.00)	13 (1.14)	13 (1.13)	36 (3.24)	19 (1.64)	24 (2.07)	26 (2.30)
18-24 months	54 (5.27)	16 (1.45)	12 (1.09)	35 (3.29)	22 (1.96)	33 (2.94)	28 (2.58)
24-30 months	47 (4.85)	14 (1.32)	10 (0.94)	36 (3.55)	21 (1.94)	28 (2.58)	22 (2.11)
30-36 months	18 (2.86)	7 (1.00)	8 (1.14)	19 (2.86)	19 (2.66)	29 (4.05)	14 (2.04)
Plc **2633 (6557)**	**439 (6.70)**	**131 (2.00)**	**87 (1.33)**	**184 (2.81)**	**119 (1.81)**	**168 (2.56)**	**206 (3.14)**
0-6 months	125 (9.96)	29 (2.27)	16 (1.25)	44 (3.46)	25 (1.95)	28 (2.18)	44 (3.46)
6-12 months	83 (7.21)	24 (1.99)	16 (1.32)	32 (2.67)	24 (1.97)	30 (2.46)	39 (3.26)
12-18 months	76 (7.02)	23 (1.99)	17 (1.46)	34 (2.97)	14 (1.19)	24 (2.03)	39 (3.40)
18-24 months	64 (6.25)	23 (2.06)	15 (1.33)	29 (2.64)	23 (2.01)	34 (2.97)	35 (3.17)
24-30 months	66 (6.25)	19 (1.77)	14 (1.30)	29 (2.76)	18 (1.64)	31 (2.81)	29 (2.75)
30-36 months	25 (4.07)	12 (1.72)	9 (1.28)	14 (2.06)	13 (1.81)	18 (2.50)	19 (2.78)
HR p-values	***0.82 (0.002)***	***0.71(0.011)***	***0.84(0.284)***	***1.38 (0.001)***	***0.99 (0.951)***	***0.97 (0.752)***	***0.79 (0.026)***
Subgroup by nitrate use							
Yes Pio 1239(3044)	256 (8.41)	68 (2.23)	35 (1.15)	163 (5.35)	64 (2.10)	86 (2.83)	100 (3.29)
Plc 1242(3104)	331 (10.66)	95 (3.06)	40 (1.29)	130 (4.19)	64 (2.06)	86 (2.77)	130 (4.19)
No Pio 1366(3433)	100 (2.91)	25 (0.73)	38 (1.11)	86 (2.51)	54 (1.57)	76 (2.21)	63 (1.84)

Plc 1391(3454)	108 (3.13)	36 (1.04)	47 (1.36)	54 (1.56)	55 (1.59)	82 (2.37)	76 (2.20)
Subgroups by aspirin use							
Yes Pio 2181(5448)	325 (5.97)	85 (1.56)	65 (1.19)	220 (4.04)	96 (1.76)	129 (2.37)	147 (2.70)
Plc 2158 (5402)	382 (7.07)	115 (2.13)	75 (1.39)	157 (2.91)	82 (1.57)	120 (2.22)	181 (3.35)
No Pio 424 (1030)	31 (3.01)	8 (0.78)	8 (0.78)	29 (2.82)	22 (2.14)	33 (3.20)	16 (1.55)
Plc 475 (1155)	57 (4.94)	16 (1.38)	12 (1.04)	27 (2.34)	37 (3.20)	48 (4.16)	25 (2.16)
Subgroup by statin use							
Yes Pio 1588(3938)	278 (7.06)	72 (1.83)	41 (1.04)	160 (4.06)	62 (1.57)	83 (2.11)	110 (2.79)
Plc 1583(4002)	344 (8.60)	95 (2.37)	48 (1.20)	124 (3.10)	42 (1.05)	66 (1.65)	139 (3.47)
No Pio 1017(2540)	78 (3.07)	21 (0.83)	32 (1.26)	89 (3.50)	56 (2.20)	79 (3.11)	53 (2.09)
Plc 1050(2555)	95 (3.72)	36 (1.41)	39 (1.53)	60 (2.35)	77 (3.01)	102 (3.99)	67 (2.62)

5.2 Metformin-controlled studies

There are 3 metformin-controlled studies. The summary information of the 3 studies can be found in Table A7 in Appendix II. Among the 3 studies, Study OPIMET-008 is a fixed dose study administrating pioglitazone 30 mg with relatively short treatment duration (20 weeks on average) in naïve patients. Study EC404 also recruited all naïve patients and administrated pioglitazone 30 mg for 12 weeks and titrated upward to 45 mg for 40 weeks. EC409, with metformin-control and sulfonylurea add-on, recruited all non-naïve patients and started with pioglitazone 15 mg and titrated up to 45 mg. The summary information of cardiovascular events for each study is also available in Table A7 in Appendix II. The average duration of diabetes was 4.5 years. Overall, 26% patients were non-naïve diabetic patients. About 5% patients used nitrate at baseline and 7% during treatment; About 13% patients used aspirin at baseline and 16% during treatment; The statin use at baseline was 9% and 12% during treatment. Eighty-five (7.7%) patients developed edema during pioglitazone treatment and 20 (1.8%) of these prematurely discontinued; while as 25 (2.2%) developed edema in the metaformin treatment group and 6 (0.5%) of these prematurely discontinued.

The summary of the cardiovascular events is provided in Table 5.2. Overall, no increased risk was observed in pioglitazone for all type of cardiovascular events except cardiovascular deaths, which is numerically higher in pioglitazone. The number of events is not large enough to make meaningful assessment by treatment period in every 6 months.

Table 5.2 Analysis on CV events for studies with metformin control

Trt/Sample Size	Number of Events (Rate /100 Patient-years)						
(patient-years)	MIS	MI	Stroke	CHF	CVD	Death	Composite
Pio 1105 (1130)	**20 (1.77)**	**8 (0.71)**	**2 (0.18)**	**6 (0.53)**	**6 (0.53)**	**6 (0.53)**	**10 (0.85)**
0-6 months	10 (1.94)	2 (0.39)	1 (0.19)	5 (0.97)	2 (0.39)	2 (0.39)	3 (0.58)
6-12 months	6 (1.40)	3 (0.70)	1 (0.23)	1 (0.23)	2 (0.46)	2 (0.46)	4 (0.93)
12-18 months	3 (1.20)	2 (0.80)	0	0	2 (0.78)	2 (0.78)	2 (0.80)
18-24 months	1 (0.85)	1 (0.85)	0	0	0	0	1 (0.85)
Met 1127 (1170)	**26 (2.22)**	**9 (0.77)**	**9 (0.77)**	**7 (0.60)**	**3 (0.26)**	**6 (0.51)**	**18 (1.54)**
0-6 months	15 (2.86)	5 (0.95)	2 (0.38)	2 (0.38)	1 (0.19)	1 (0.19)	7 (1.33)
6-12 months	7 (1.61)	1 (0.23)	3 (0.68)	2 (0.45)	0	2 (0.45)	4 (0.91)
12-18 months	1 (0.39)	1 (0.38)	1 (0.38)	3 (1.14)	0	1 (0.37)	2 (0.77)
18-24 months	3 (2.37)	2 (1.55)	3 (2.33)	0	1 (0.77)	1 (0.77)	5 (3.91)
HR (p-values)	***0.80(0.436)***	***0.94(0.895)***	***0.23(0.060)***	***0.87(0.797)***	***2.04(0.313)***	***1.02(0.975)***	***0.59(0.177)***

5.3 Sulfonylurea-controlled studies

There are 9 sulfonylurea-controlled studies, one of which (Study EC410), has metformin as an add-on therapy. Several studies, including Studies OPI-504, OPI-506, OPI-516, OPI-518, and OPI-520, allowed either metformin or insulin, or both as concomitant therapies. In addition to the variation of concomitant use of diabetic medication, the patient population varied among studies. Studies EC405/EC415 and OPI-501 recruited only naïve patients. Study EC204 had naïve status missing. The rest of the studies recruited about 90% non-naïve patients. Study OPI-504 recruited patients with type 2 diabetic and history of CHF. The average length of diabetes was about 5.7 years and 67% were non-naïve patients. About 12% patients used nitrate at baseline, although not everyone continued, about 12% used during treatment; About 31% patients used aspirin at baseline and 37% during treatment; Similarly, about 31% used statin at baseline and 37% during treatment. 413 (13%) patients in pioglitazone group developed edema and 139 (4%) of these discontinued study prematurely, 223 (7%) patients in the sulfonylurea group developed edema and 74 (2%) of these discontinued treatment prematurely.

Overall, 3235 and 3245 patients were in the sulfonylurea and pioglitazone treatment groups, respectively. Among these patients, 4233 and 4068 patient-years are treated with sulfonylurea and pioglitazone, respectively. It can be seen that there were less patient-years with more patients in the pioglitazone group compared with that in the sulfonylurea group. This reflected more patients were dropped out the studies earlier in the pioglitazone group. Analysis shows more patients in pioglitazone dropped out in the first 6 months of treatment than that in sulfonylurea, 20% (655 out of 3263) and 16% (522 out of 3248) in pioglitazone and sulfonylurea, respectively.

The results on cardiovascular events are summarized in Table 5.3. Over the entire treatment period, pioglitazone showed statistically significantly higher risk in developing CHF compared with sulfonylurea. The hazard ratio is 1.60 with p-value=0.004. No large difference is observed on the other events over the entire treatment period. However, breaking the risk by 6-month intervals, we see the followings:

- There were large risk reductions in MIS in both treatment groups after 6-month treatment.
- The risk of MI in pioglitazone in the first 6-month treatment period is higher than that of sulfonylurea. Similar observation was seen in stroke, although less certain as the number of events is sparse.
- Although the risk of CHF in pioglitazone is higher than that in sulfonylurea, there were large risk reductions in both treatment groups after 6-month treatment.
- The risk of death in both all-cause mortality and cardiovascular death was numerically higher in the first 6 months of treatment.
- The risk in the composite endpoint in pioglitazone was more than 2-fold higher than that in the sulfonylurea treatment in the first 6 months of treatment. The p-value for the risk ratio was 0.050. The average risk ratio was reduced to 1.15 as more events occurred later in sulfonylurea.
- The high dropout rates in both treatment arms (20% and 16% in pioglitazone and sulfonylurea, respectively) and the difference in drop out rates between the two arms

in the first 6 months add a layer of difficulties in the interpretation of the observed cardiovascular risk.

Table 5.3 Analysis of CV events for studies with sulfonylurea control

Treatment/Sample Size(patient-years)	Number of Events (Rate /100 Patient-years)						
	MIS	MI	Stroke	CHF	CVD	Death	Composite
PIO **3263 (4068)**	**141 (2.64)**	**28 (0.52)**	**14 (0.26)**	**97 (1.82)**	**19 (0.36)**	**25 (0.47)**	**41 (0.77)**
0-6 months	76 (5.24)	14 (0.96)	6 (0.41)	64 (4.40)	13 (0.88)	17 (1.16)	20 (1.37)
6-12 months	29 (2.52)	8 (0.68)	3 (0.26)	17 (1.46)	4 (0.34)	5 (0.43)	11 (0.94)
12-18 months	14 (1.82)	4 (0.51)	1 (0.13)	5 (0.64)	1 (0.13)	1 (0.13)	5 (0.64)
18-24 months	12 (2.55)	1 (0.21)	1 (0.21)	4 (0.83)	1 (0.21)	2 (0.41)	2 (0.41)
24-30 months	8 (2.51)	1 (0.30)	2 (0.61)	3 (0.92)	0	0	2 (0.61)
30-36 months	2 (0.99)	0	1 (0.47)	4 (1.90)	0	0	1 (0.47)
SU **3248 (4220)**	**150 (2.82)**	**26 (0.49)**	**13 (0.24)**	**67 (1.26)**	**23 (0.43)**	**27 (0.51)**	**38 (0.71)**
0-6 months	78 (5.28)	8 (0.54)	2 (0.13)	46 (3.10)	11 (0.74)	13 (0.87)	10 (0.67)
6-12 months	35 (2.92)	6 (0.49)	4 (0.33)	11 (0.91)	6 (0.49)	6 (0.49)	10 (0.82)
12-18 months	21 (2.61)	5 (0.61)	3 (0.36)	5 (0.61)	2 (0.24)	3 (0.36)	8 (0.98)
18-24 months	7 (1.42)	1 (0.20)	1 (0.20)	3 (0.60)	1 (0.20)	1 (0.20)	2 (0.40)
24-30 months	4 (1.20)	3 (0.88)	2 (0.59)	2 (0.59)	2 (0.59)	2 (0.59)	5 (1.48)
30-36 months	5 (2.33)	3 (1.37)	1 (0.45)	0	1 (0.45)	2(0.90)	3 (1.38)
HR (p-values)	***0.97(0.818)***	***1.16(0.595)***	***1.14(0.743)***	***1.60(0.004)***	***0.85(0.604)***	***0.95(0.861)***	***1.15(0.540)***

5.4 Comparison between pioglitazone and rosiglitazone

One study, Study GLAI, compares pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. This study is a randomized and double-blind study enrolled 369 and 366 patients in the pioglitazone and rosiglitazone arms, respectively. Patients in the pioglitazone arm took 30 mg for 12 weeks followed by 45 mg for another 12 weeks; Patients in the rosiglitazone arm took 4 mg for 12 weeks and 8 mg for another 12 weeks. The total treatment duration was 24 weeks. The cardiovascular events in this study are summarized in Table 5.4. Because of risk differences between pioglitazone 30 and 45 mg, the events are also summarized by 12 weeks. Because of small sample size and sparse events, no meaningful conclusion can be made between the two drugs on cardiovascular events.

Table 5.4 Analysis on CV events for studies with metformin control

Trt/Sample Size (patient-years)	Number of Events (Rate /100 Patient-years)						
	MIS	MI	Stroke	CHF	CVD	Death	Composite
Pio 369 (154)	**3**	**1**	**0**	**0**	**0**	**1**	**1**
0-12 wks (30mg)	0	0	0	0	0	1	0
12-24wks (45mg)	3	1	0	0	0	0	1
Rosi 366(149)	**8**	**2**	**1**	**1**	**1**	**2**	**3**
0-12 wks (4 mg)	5	0	1	0	0	1	1
12-24wks (8 mg)	3	1	0	1	1	1	1

Appendix I: Definitions of cardiovascular endpoints using the MedDRA preferred terms

Preferred terms that are used to define myocardial ischemia:

- Acute coronary syndrome
- Acute myocardial infarction
- Angina pectoris
- Angina unstable
- Arteriospasm coronary
- Cardiac arrest
- Cardiac death
- Coronary artery occlusion
- Coronary artery reocclusion
- Coronary artery thrombosis
- Coronary bypass thrombosis
- Electrocardiogram ST segment elevation
- Electrocardiogram ST-T segment elevation
- Myocardial infarction
- Myocardial ischemia
- Papillary muscle infarction
- Postinfarction angina
- Prinzmetal angina
- Silent myocardial infarction
- Subendocardial ischemia
- Sudden cardiac death
- Sudden death
- Ventricular asystole
- Ventricular fibrillation
- Ventricular tachycardia

Preferred terms that are used to define congestive heart failure:

- Acute pulmonary edema
- Cardiac failure
- Cardiac failure acute
- Cardiac failure chronic
- Cardiac failure congestive
- Cardiac failure not otherwise specified (NOS)
- Cardiogenic shock
- Congestive cardiac failure
- Cor pulmonale acute
- Cor pulmonale chronic
- Cor pulmonale NOS
- Left ventricular failure
- Pulmonary congestion
- Pulmonary edema
- Pulmonary edema NOS
- Right ventricular failure

Ventricular failure NOS

Preferred terms that are used to define strokes:

- Basilar artery thrombosis
- Brain stem infarction
- Brain stem stroke
- Brain stem thrombosis
- Carotid arterial embolus
- Carotid artery thrombosis
- Cerebellar infarction
- Cerebral artery embolism
- Cerebral artery thrombosis
- Cerebral infarction
- Cerebral thrombosis
- Cerebrovascular accident
- Embolic cerebral infarction
- Embolic stroke
- Hemorrhagic cerebral infarction
- Hemorrhagic stroke
- Hemorrhagic transformation stroke
- Ischemic cerebral infarction
- Ischemic stroke
- Lacunar infarction
- Lateral medullary syndrome
- Moyamoya disease
- Postprocedural stroke
- Stroke in evolution
- Thalamic infarction
- Thrombotic cerebral infarction
- Thrombotic stroke
- Wallenberg syndrome

Preferred terms that are used to define myocardial infarction:

- Acute myocardial infarction
- Coronary artery thrombosis
- Myocardial infarction
- Papillary muscle infarction
- Postprocedural myocardial infarction
- Silent myocardial infarction

Appendix II: Summary information of studies by study groups

Note that recurrent events are reported in parentheses. Events that occurred after the first dose of study medication and within 30 days after the last dose are counted in the following tables.

Table A1: Summary information of studies used in dose-response assessment.

Study	Treatment	N	Trtment duration (in wks)	Patient-Year	MI	MIS	STK	CHF	CVD	Death
PNFP-001										
	Pio 45 mg	80	19.44	29.82	0	0	0	0	0	0
	Pio 30 mg	87	18.84	31.44	0	0	0	3(4)	0	0
	Pio 15 mg	81	17.50	27.19	0	0	0	1(2)	0	0
	Pio 7.5 mg	81	17.96	27.91	1	2	0	1	0	0
	Placebo	79	16.18	24.52	1	1(4)	0	0	0	0
AD-4833/ CPH-010 (patient –blinded)										
	Pio 30mg	49	7.66	7.20	0	0	0	0	0	0
	Pio 15mg	44	7.85	6.63	0	0	0	0	0	0
	Pio 7.5mg	48	7.98	7.35	0	0	0	0	0	0
	Placebo	47	8.10	7.30	0	0	0	0	0	0
AD-4833/ CPH-010A (patient –blinded)										
	Pio 60mg	5	2.00	0.19	0	0	0	0	0	0
	Pio 30mg	6	1.83	0.21	0	0	0	0	0	0
	Pio 15mg	5	2.00	0.19	0	0	0	0	0	0
AD-4833/ CCT-001										
	Pio 45mg	69	11.85	15.68	0	0	0	0	0	0
	Pio 30mg	67	11.55	14.84	0	0	0	0	0	0
	Pio 15mg	71	11.73	15.97	0	0	0	0	0	0
	Placebo	66	12.09	15.30	0	0	0	0	0	0
AD-4833/ CCT-011										
	Pio 30	77	11.71	17.30	0	0	1	0	0	0
	Placebo	75	11.80	16.98	0	0	0	0	0	0
AD-4833/ CPH-030A										
	Pio 30 mg	23	11.99	5.29	0	0	0	0	0	0
	Placebo	10	11.96	2.29	0	0	0	0	0	0
AD-4833/ PNFP-026										
	Pio 30 mg	101	14.33	27.75	0	0	0	0	0	0
	Placebo	96	13.18	24.27	1	2	0	0	0	0
EC204										
	Pio 30 mg	89	21.85	37.30	0	(2)3	0	1	0	0
	Placebo	88	21.59	36.44	1	1	0	0	0	0
AD-4833/ OCT-003 (single-blind study)										
	Pio 45mg+SU	70	11.98	16.09	0	0	0	0	0	0
	Pio 30mg+SU	68	11.28	14.70	0	0	0	0	0	0
	Pio 15mg+SU	72	11.89	16.42	0	0	0	0	0	0
	SU	66	11.71	14.82	0	0	0	0	0	0
PNFP-010										
	Pio 30 mg + Su	189	15.43	55.93	2	5	0	0	1	1
	Pio 15 mg + Su	184	15.01	52.97	0	1	0	3	0	0
	Placebo + Su	187	15.20	54.52	2	2	0	4	2	2

PNFP-341										
	Pio 45 mg + Su	351	20.16	135.71	2	7(9)	1	8	0	0
	Pio 30 mg + Su	351	20.91	140.78	2	2	1	6(7)	1	1
AD-4833/CCT-012										
	Pio 30 mg + Su	76	11.23	16.37	0	0	0	0	0	0
	Su	73	11.40	15.97	0	0	0	0	0	0
PNFP-342										
	Pio 45 mg + Met	416	19.73	157.40	0	2	0	5	0	0
	Pio 30 mg + Met	411	20.12	158.60	2	3	2	3	0	0
PNFP-027										
	Pio 30 mg + Met	168	14.94	48.14	0	0	0	1	0	0
	Met	160	13.94	42.78	0	0	0	0	0	0
XT010										
	Pio 30 mg + Met	157	15.23	45.85	0	0	0	0	0	0
	Met	158	15.11	45.78	0	0	0	1	0	0
OPIMET-008										
	Pio 30 mg + Met	201	21.58	83.20	0	0	0	0	0	0
	Met	210	20.80	83.79	0	1	0	0	0	0
PNFP-014										
	Pio 30 + Insulin	188	15.71	56.65	0	3	0	3	0	0
	Pio 15 + Insulin	191	15.05	55.13	1	1	0	2(4)	0	0
	Placebo + Insulin	187	15.27	54.77	0	2	0	0	0	0
PNFP-343										
	Pio 45 mg + Insulin	345	20.18	133.51	6	9	3	7(10)	1	2
	Pio 30 mg + Insulin	345	20.29	134.22	2	4(5)	2(3)	4(5)	1	2
AD-4833/ CCT-101										
	Pio 30 mg +insulin	66	14.93	18.89	0	0	0	0	0	0
	Insulin	66	14.68	18.58	0	1	0	0	0	0
GLAT										
	Pio 30 mg +insulin	142	46.75	127.33	0	4	0	2	0	1
	Insulin	147	48.11	135.63	1	3	0	2	1	1
322OPI-001 (alogliptin study)										
	SYR 12.5 +Pio15	130	24.41	60.86	0	2	0	0	0	0
	SYR 12.5 +Pio30	130	24.61	61.36	0	0	0	0	0	0
	SYR 12.5 +Pio45	130	23.83	59.42	1	2	0	1	0	0
	SYR 12.5 +Placebo	128	22.76	55.88	0	0	0	0	0	0
	SYR 25 +Pio 15	130	23.94	59.69	0	1	0	0	0	0
	SYR 25+Pio 30	130	24.12	60.15	0	0	1	0	0	0
	SYR 25+Pio 45	130	24.18	60.29	1	5	1	0	0	0
	SYR 25+Placebo	129	23.20	57.39	1	3	0	0	0	0
	SYR Plcbo+Pio 15	129	22.27	55.09	0	1	0	0	0	0
	SYR Plcbo+Pio 30	129	22.20	54.93	0	1	0	1	0	0
	SYR Plcbo+Pio 45	129	23.04	56.99	1	4	0	2	1	1
	SYR Plcbo+Pio Plc	129	20.61	50.99	0	1	1	0	0	0
322OPI-002 (alogliptin study)										
	SYR 25+Pio 30 mg	164	23.7	74.5	1	2	0	1	0	0
	SYR 25	164	23.2	73.1	0	1	0	0	0	0
OPI525										
	PIO 15mg + Placebo	118	20.26	45.84	0	0	1	0	1	1
	PIO 45mg + Placebo	118	22.58	51.10	0	2	0	0	0	0
	PIO 15mg + TAK 5	118	21.58	48.83	0	0	1	0	0	0
	PIO 45mg + TAK 5	117	21.35	47.90	0	1	0	0	1	1
	PIO 15mg + TAK40	113	21.02	45.55	0	0	0	0	0	0
	PIO 45mg + TAK40	114	21.97	48.04	2	4	1	0	0	0
CCT-102 (Voglibose study)										
	Pio 30 mg +Vog	67	15	18.8	0	0	0	0	0	0
	Vog	65	15	18.2	0	0	0	0	0	0

Table A2: Study information for studies with placebo-controlled monotherapy.

STUDY	Treatment	dose	N	Treatment duration in weeks	Patient-years	MI	MIS	Stroke	CHF	CV death	Death
AD-4833/ PNFP-001											
	Placebo		79	16.18	24.52	1	3(4)	0	0	0	0
	Pio	7.5	81	17.96	27.91	1	2	0	1	0	0
	Pio	15	81	17.50	27.19	0	0	0	1(2)	0	0
	Pio	30	87	18.84	31.44	0	0	0	3(4)	0	0
	Pio	45	80	19.44	29.82	0	0	0	0	0	0
AD-4833/ PNFP-012											
	Placebo		84	17.13	27.60	1	1	0	0	1	1
	Pio 7.5/15/30		87	19.41	32.38	0	0	0	0	0	0
	Pio 15/30/45		89	19.84	33.87	0	0	0	0	0	0
AD-4833/ PNFP-026											
	Pio	30	101	14.33	27.75	0	0	0	0	0	0
	Placebo		96	13.18	24.27	1	2	0	0	0	0
AD-4833/ CCT-001											
	Pio	15	71	11.73	15.97	0	0	0	0	0	0
	Pio	30	67	11.55	14.84	0	0	0	0	0	0
	Pio	45	69	11.85	15.68	0	0	0	0	0	0
	Placebo		66	12.09	15.30	0	0	0	0	0	0
AD-4833/ CCT-011											
	Pio	30	77	11.71	17.30	0	0	1	0	0	0
	Placebo	0	75	11.80	16.98	0	0	0	0	0	0
AD-4833/ CPH-010 (patient-blinded)											
	Pio	15	44	7.85	6.63	0	0	0	0	0	0
	Pio	30	49	7.66	7.20	0	0	0	0	0	0
	Pio	7.5	48	7.98	7.35	0	0	0	0	0	0
	Placebo	0	47	8.10	7.30	0	0	0	0	0	0
AD-4833/ CPH-030A											
	Pio	30	23	11.99	5.29	0	0	0	0	0	0
	Placebo	0	10	11.96	2.29	0	0	0	0	0	0
EC204											
	Pio	30	89	21.85	37.30	0	2(3)	0	1	0	0
	Placebo	0	88	21.59	36.44	1	1	0	0	0	0

Table A3: Summary information for placebo-controlled trials with insulin add-on

Study	Treatment	dose	Sample size	Treatment duration in weeks	Patient-years	MI	MIS	Stroke	CHF	CV death	Death
PNFP-014											
	Pio+ins	15	191	15.05	55.13	1	1	0	2(4)	0	0
	Pio+ins	30	188	15.71	56.65	0	3	0	3	0	0
	ins	0	187	15.27	54.77	0	2	0	0	0	0
AD-4833/CCT-101											
	Pio+ins	30	66	14.93	18.89	0	0	0	0	0	0
	ins		66	14.68	18.58	0	1	0	0	0	0
GLAT											
	Pio+ins	30	142	46.75	127.33	0	4	0	2	0	1
	ins	0	147	48.11	135.63	1	3	0	1(2)	1	1
OPI-502*(insulin reduction trial)											
	Pio	30 to 45	110	18.83	39.73	0	0	0	0	0	0
	Placebo	0	112	19.21	41.27	1	3(5)	0	0	0	0

Table A4: Summary information for placebo-controlled trials with metformin add-on

STUDY	Treatment	dose	Sample Size	Treatment duration in weeks	Patient-years	MI	MIS	Stroke	CHF	CV death	Death
PNFP-027											
	Pio+m	30	168	14.94	48.14	0	0	0	1	0	0
	m	0	160	13.94	42.78	0	0	0	0	0	0
AD-4833/CCT-100											
	Pio+m	15/30	84	26.54	42.76	1	1	0	0	0	0
	m		89	26.49	45.21	0	0	0	0	0	0
XT010											
	Pio+m	30	157	15.23	45.85	0	0	0	0	0	0
	m		158	15.11	45.78	0	0	0	1	0	0
OPIMET-008											
	m		210	20.80	83.79	0	1	0	0	0	0
	Pio+m	30	201	21.58	83.20	0	0	0	0	0	0
322OPI-001											
	Pio	15	129	22.27	55.09	0	1	0	0	0	0
	Pio	30	129	22.20	54.93	0	1	0	1	0	0
	Pio	45	129	23.04	56.99	1	4	0	1(2)	1	1
	Placebo		129	20.61	50.99	0	1	1	0	0	0

Table A5: Summary information for placebo-controlled trials with sulfonylurea add-on

STUDY	Treatment	dose	Sample Size	Trtment duration in weeks	Patient-years	MI	MIS	Stroke	CHF	CV death	Death
PNFP-010											
	Pio+su	15	184	15.01	52.97	0	1	0	3	0	0
	Pio+su	30	189	15.43	55.93	2	5	0	0	1	1
	su	0	187	15.20	54.52	2	2(3)	0	4	2	2
AD-4833/CCT-012											
	Pio+su	30	76	11.23	16.37	0	0	0	0	0	0
	su	0	73	11.40	15.97	0	0	0	0	0	0
AD-4833/OCT-003 (single-blind)											
	Pio+su	15	72	11.89	16.42	0	0	0	0	0	0
	Pio+su	30	68	11.28	14.70	0	0	0	0	0	0
	Pio+su	45	70	11.98	16.09	0	0	0	0	0	0
	su		66	11.71	14.82	0	0	0	0	0	0
F-Pio-100 (Placebo control with M+SU add-on)											
	Pio+m+su	30/45	145	27.99	77.83	0	1	1	0	1	1
	m+su		154	26.86	79.34	0	0	0	0	0	0

Table A6 Summary information for Study EC444.

STUDY	Treatment	Sample size	Treatment duration in wks	Patient-years	MI	MIS	Stroke	CHF	CV death	Death
EC444	Pio	2605	129.8	6482.3	93(107)	356(457)	73(76)	333	118	162
	Placebo	2633	130.0	6562.2	131(146)	439(582)	87(93)	274	119	168

Table A7 Summary information for Studies wth metformin control

STUDY	Treatment	Sample size	Treat duration in weeks	Patient-years	MI	MIS	Stroke	CHF	CV death	Death
OPIMET-008										
	metformin	210	20.80	83.79	0	1	0	0	0	0
	Pio 30 mg	189	20.16	73.09	1	1	0	0	0	0
EC404										
	metformin	597	46.35	530.74	4	13 (17)	2	4	1	2
	Pio 30 or 45 mg	597	46.28	529.94	3	9 (11)	1	4	3	3
EC409* (with sulfonylurea add-on)										
	m+su	320	90.73	556.84	5	12 (13)	7	3 (7)	2	4
	Pio 15 to 45 mg+su	319	86.27	527.83	4	10 (13)	1	2	3	3

Table A8 Summary information for studies with sulfonylurea control

STUDY	TREATMENT	Sample size	Treatment duration in weeks	patient-year	MI	MIS	Stroke	CHF	CV death	De ath
OPI-501: naïve patients according to synopsis										
	SU	251	52.86	254.46	2	7	0	2	1	2
	Pio 15/30/45 mg	251	50.69	244.03	2	3	0	1	0	0
OPI-504: 100% non-naïve status										
	SU	256	20.78	102.00	2	26(31)	0	30(36)	7	8
	Pio 30/45 mg	262	18.52	93.05	5	20(24)	1	46(70)	10	13
OPI-506: 100% non-naïve patients										
	SU	1046	93.09	1867.49	12	36(47)	8(10)	16(17)	5	6
	Pio up to 45 mg	1051	87.23	1758.26	7(8)	38(50)	8	22(25)	1	1
OPI-516: 90% non-naïve patients										
	SU	273	56.31	294.84	3	44(59)	1	7(13)	2	3
	Pio titration to 45mg	270	56.50	292.57	5	30(36)	0	7(8)	3	3
OPI-518: 90% non-naïve patients										
	SU	228	59.74	261.23	2	7(8)	1	0	0	0
	Pio 15 or 30 to 45mg	230	56.52	249.32	0	2(3)	0	1	0	1
OPI-520: 88% non-naïve patients										
	SU	149	45.55	130.17	2	16(19)	0	6	2	2
	Pio up to 45 mg	151	43.75	126.70	2	14(18)	0	10(15)	1	2
EC204: missing naïve status										
	SU	93	24.26	43.27	0	1	0	0	0	0
	Pio 30/45 mg	89	21.85	37.30	0	2(3)	0	1	0	0
EC405/EC415: 100% naïve patients										
	SU	626	60.65	728.14	2	8(9)	1	4	4	4
	Pio 30/45 mg	624	61.73	738.83	2	18(23)	3	4	3	3
EC410 (SU control with M add-on): 100% non-naïve patients										
	SU+ Met	313	90.24	541.73	1	5	2	2	2	2
	Pio 15/30/45+ Met	317	87.33	530.92	5	14(16)	2	5	1	2

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21073	ORIG-1	TAKEDA PHARMACEUTICALS NORTH AMERICA INC	ACTOS (PIOGLITAZONE HCL)15/30/45MG TABS

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/s/

QIAN H LI
09/10/2010

MARK S LEVENSON
09/10/2010

I do not concur with several statistical aspects of this review. My secondary review addresses these aspects. Additionally, I do not concur with the note on due date, and I feel it is not pertinent to the review.