U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Secondary Statistical Review and Evaluation

PIOGLITAZONE META-ANALYSIS

NDA/Serial Number:	NDA 21-073
Drug Name:	Actos (pioglitazone)
Indication(s):	Treatment of type-2 diabetes
Applicant:	Takeda
Date(s):	Completed: 10 September 2010
Biometrics Division:	Division of Biometrics 7
Statistical Reviewer:	Mark Levenson, Ph.D., Deputy Director (Acting)
Through	Aloka Chakravarty, Ph.D., Director
Medical Division:	Metabolism and Endocrinology Products
Project Manager:	Jena Weber
Subject:	Secondary review of pioglitazone meta-analysis statistical review by Qian Li

This secondary review discusses several statistical aspects of the pioglitazone meta-analysis statistical review by Qian Li (10 September 2010) that I do not concur with. In particular, this review addresses the dose-response findings of the Li pioglitazone meta-analysis review. Overall, it is my conclusion that the dose-response findings of the review are only hypothesis-generating, and there are important statistical aspects that need clarification in order to interpret these findings.

Background

The Li pioglitazone meta-analysis review was one of three meta-analyses of thiazolidinediones (TZDs) conducted by the Office of Biostatistics as part of the overall CDER effort to thoroughly review the cardiovascular risks associated with rosiglitazone. Two of these meta-analyses were conducted in parallel (by Fiona Callaghan and Bradley McEvoy) on rosiglitazone and pioglitazone, respectively, to compare the risks associated with these two drugs to the extent possible based on short-term studies. The summary of the two parallel meta-analyses was provided as part of the briefing material for the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting held on 13-14 July 2010. The review by Li was intended by the Office of Biostatistics to be a thorough exploratory meta-analysis of pioglitazone. The overall approach of the Li meta-analysis was described by Li prior to conducting the analysis. However, the details, including the specific hypotheses and the trials to be included, were based on Li's review of the data. The draft review by Li was received on 20 August 2010.

Statistical Comments

The findings of Li discussed here relate to the dose response in myocardial infarction (MI) and myocardial ischemia (MIS) between the 30 mg and the 45 mg doses of pioglitazone. The dose-response findings were based on 24 trials. These 24 trials had a range of doses among the treatment arms, including placebo, 7.5 mg, 15 mg, 30 mg, and 45 mg. Of these 24 trials, 7 trials had both 30 mg and 45 mg treatment arms. Of these 7 trials, 4 trials had MI or MIS events.

The dose-response findings should be interpreted as hypothesis-generating and do not have the certainty as suggested in the Li review. There are three main reasons for this comment that will be discussed. (1) Some of the findings were based on cross-trial comparisons, which in general may be confounded by differences among trials. (2) The use of term *statistical significance* and nominal p-values were not appropriate, because they were based on multiple reviews of the data. (3) The findings were based on a small amount of data.

Li's first analysis considered all 24 studies in a single model, stratifying by trial and including a linear term for dose. After this analysis, the risk differences between the 30 mg and 45 mg doses were statistically evaluated. Based on a visual inspection of the incidences, Li combined all doses of 30 mg and below and compared the combined group to the 45 mg dose group. The hazard ratios and associated p-values for the two groups were then calculated.

There are two major concerns with these analyses. (1) The analyses involved multiple testing and inspection of the data. The nominal p-values from such analyses are misleading. (2) The analyses

were based on cross-trial comparisons, which are inherently weaker than within-trial comparisons. What that means is that the incidences from a 30 mg treatment arm in one trial were implicitly compared to the incidences from a 45 mg treatment arm in another trial. The incidences given in Li's Summary Section 1.1 were based on such cross-trial comparisons. The stratification by trial in the model was designed to account for cross-trial comparisons but does not fully account for differences in trials that result in different background incidences of events.

Based on directions from myself and others in the Office of Biostatistics, Li conducted an analysis based on the 7 trials that had both 30 mg and 45 mg treatment arms. This analysis generally supported Li's original findings for myocardial ischemia. For myocardial infarction, there were few events but the results did not contradict the original findings.

The revised analysis, although based on more appropriate comparisons, was effectively based on the 4 trials that had both 30 mg and 45 mg treatment arms and events. In these trials there were 11 MI events for the 45 mg dose and 6 MI events for the 30 mg dose.

In conclusion, the difference in event counts between the two doses is intriguing and should be explored further. However, it is my conclusion that the dose-response findings have notable uncertainty associated with them for the reasons given above and should be considered only as hypothesis-generating.

SIGNATURES/DISTRIBUTION LIST

Secondary Statistical Reviewer: Mark Levenson
Date: 10 September 2010

Concurring Reviewer(s): Aloka Chakravarty, Ph.D.

Biometrics VII Division Director, Aloka Chakravarty, Ph.D.

cc:
Jena Weber (Project Manager)
Mary Parks (Clinical Division Director)
Ilan Irony (Clinical Team Leader)
Karen Mahoney (Clinical Reviewer)
Curtis Rosebraugh (Director Office of Drug Evaluation II)
John Jenkins (Director Office of New Drugs)
Janet Woodcock (Director CDER)
Robert O'Neill (Director Office of Biostatistics)
Lillian Patrician (Office of Biostatistics)

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/

MARK S LEVENSON
09/10/2010

ALOKA G CHAKRAVARTY
09/13/2010