

**GLAXOSMITHKLINE LLC’S
WHITE PAPER RESPONSE TO
SENATE FINANCE COMMITTEE’S
“STAFF REPORT ON GLAXOSMITHKLINE AND THE DIABETES
DRUG AVANDIA”**

I. INTRODUCTION

The Senate Finance Committee’s January 2010 “Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia” (“Staff Report”) does not present an accurate, balanced, or complete view of the currently available information on Avandia® (rosiglitazone maleate). Further, the Staff Report mischaracterizes and distorts the efforts that GlaxoSmithKline LLC (“GSK”) took to continue to monitor the safety and efficacy of its diabetes medication. The Staff Report repeatedly cites documents out of context; thereby, crafting a misleading narrative that fails to acknowledge that there is important, relevant safety information pertinent to the understanding of Avandia and its role in helping physicians and patients treat the devastating disease of diabetes.

Most glaringly, the Staff Report does not include discussion of the final results of studies cited in the Report, such as ADOPT, DREAM, and RECORD, nor does it mention numerous other studies reported since the Senate Committee began its inquiry that support the cardiovascular safety of Avandia. In the case of RECORD, final results have been publically available for eight months and, in the case of ADOPT and DREAM, final results were published over three years ago. The absence in the Staff Report of any reference to the final results of these studies, as well as to other important studies on the cardiovascular safety of Avandia, leaves the record incomplete and again does not serve the interests of physicians or patients.

Finally, the Staff Report suggests that GSK did not work to actively monitor the safety of Avandia or inform the Food and Drug Administration (“FDA”) of its investigations. That suggestion is fundamentally flawed and contradicted by the record of extensive, on-going interactions between GSK and the FDA and the FDA’s on-going review of Avandia in light of all the information available to the agency.

Full consideration of the extensive measures GSK undertook to study Avandia prior to marketing approval, and FDA’s determination that the risk-benefit profile of Avandia is favorable, demonstrates that Avandia is an appropriate treatment option for physicians and patients in the treatment of type 2 diabetes.

II. THROUGHOUT THE HISTORY OF AVANDIA, GSK HAS BEEN PROACTIVE IN INVESTIGATING SAFETY DATA AND INFORMING REGULATORY AGENCIES, INCLUDING THE FDA, OF ITS INVESTIGATIONS.

The Staff Report suggests that GSK did not warn patients and the FDA of its ongoing cardiovascular investigations for Avandia, stating that “it can be argued that GSK had a duty to warn patients and the FDA of the Company’s concerns.”¹ In fact, contrary to this suggestion, GSK continuously apprised the FDA of the results of its investigations as they became available and also made the results of its investigations public.

In 2005, GSK took the initiative to design and conduct a retrospective exploratory patient-level analysis of an integrated clinical trial (“ICT”) database to evaluate the association (if any) between Avandia and heart failure and, separately, events of myocardial ischemia, with respect to the various treatment regimens in which Avandia is prescribed. Preliminary results for this first meta-analysis, in 37 randomized clinical trials, were submitted to FDA in October 2005. As this analysis was, by design, retrospective and integrated across a variety of different studies, it was recognized that its results would be hypothesis generating, rather than conclusive.

In early 2006, GSK initiated a second expanded meta-analysis, in order to include 5 additional clinical trials that had finished between September 2004, and August 2005, for a total of 42 randomized clinical trials. These results were submitted to FDA in May 2006. In June 2006, the results of a balanced cohort observational study examining a composite endpoint of hospitalizations for myocardial infarction and/or coronary revascularization comparing Avandia to other anti-diabetic agents became available. This study was conducted in 33,363 patients in a large managed care setting treated with anti-diabetic therapy.

On August 4, 2006, the final results of the ICT analysis of 42 studies, the results of the balanced cohort observational trial, and a proposed update to the prescribing information of Avandia (to describe the observations of the ICT and the balanced cohort study) were submitted as a supplemental New Drug Application (S-022). Following responses to a number of requests during the review cycle of those submissions, GSK met with FDA on May 16, 2007 to present data on myocardial ischemic events and therapy with Avandia. At this meeting, GSK reviewed data from all available sources, including data from long-term trials of DREAM and ADOPT which were completed after the submission of the ICT and observational study, to assess the risk of myocardial ischemic events with Avandia.

On July 30, 2007, the FDA convened an Advisory Committee of outside experts to conduct an independent evaluation of the data. After obtaining input from this Committee, the FDA concluded that the totality of the available evidence does not show that Avandia increases the risk of heart attacks, myocardial ischemia, or cardiovascular death. The FDA determined that Avandia should remain on the market as an available treatment for diabetes, and in

¹ See Staff Report at 1.

November 2007, the Avandia labeling was revised to include these data, and to expressly state that “*the available data on the risk of myocardial ischemia are inconclusive.*”²

Contrary to any suggestion that GSK did not work to actively monitor the safety of Avandia or inform the FDA of its investigations, these key events omitted, in whole or in part, from the Staff Report establish otherwise (Please see Appendix A for complete timeline):³

October 13, 2005: GSK formally submitted to FDA a summary of the results of the meta-analysis of 37 double-blind, controlled clinical trials of Avandia,⁴ as well as a copy of GSK’s analysis plan.

- The preliminary conclusions were that:
 - For MI, there was no consistent pattern with the point estimates for serious events varying between 0.93 and 2.22 with wide confidence intervals. The evidence of fatal ischemic events was very similar between groups (0.16% for RSG and 0.13% for comparators.)

May 9, 2006: GSK submitted the results of the second meta-analysis⁵ to FDA in an Amendment to the pending Supplemental Application (S-021). This Amendment provided FDA with a summary of the results of GSK’s expanded meta-analysis of double-blind, controlled clinical trials of Avandia. This Amendment summarized the results from integration of 42 studies (after inclusion of 5 additional studies with their 2,651 additional patients to the original database of 37 studies). It also referenced the Balanced Cohort Study which was ongoing at the time. See also notation of August 4, 2006.

- The meta-analysis observed that the overall incidence of ischemic cardiovascular events was 1.99% in the Avandia patients vs. 1.51% in the pooled comparison group, with a hazard ratio of 1.31. This equated to a statistically significant excess risk of ischemic events of 31% associated with the use of Avandia.

² See Avandia package insert (revised 11/14/07) (emphasis added).

³ Despite the suggestion in the Staff Report that the labeling for Avandia did not include information pertaining to cardiac risks prior to May 2007, the labeling for Avandia included such information well-before that time. For example, labeling changes were implemented in 1999 to include information pertaining to edema in heart failure patients. In 2001, the label was updated to include information on “cardiac failure and other cardiovascular adverse events” in patients using Avandia and insulin. In 2005 and 2006, warnings were updated pertaining to the risk of congestive heart failure. The revisions in 2006 included data from Study 211, which also specifically reported investigator reports of ischemia (including myocardial infarction and angina).

⁴ The “Avandia Cardiovascular Event Modeling” study.

⁵ The “Avandia Cardiovascular Event Modeling Project” study. This is also described as the “Integrated Clinical Trials Analysis” or “ICT.”

August 4, 2006: GSK submitted to FDA a Supplemental Application (S-022). This sNDA provided the final report of GSK’s meta-analysis of 42 double-blind, controlled clinical trials of Avandia, as well as the final report of the observational Balanced Cohort Study. The sNDA, which also included draft labeling, provided FDA with GSK’s application seeking approval to incorporate the results of these two studies into the labeling for Avandia Tablets.

- The Balanced Cohort Study in 33,363 patients showed that the incidence of ischemic cardiovascular events was 1.75 events per 100 patient years for use of Avandia versus 1.76 for other treatments. This analysis did not confirm the meta-analyses’ suggestion of a possible increase in ischemic cardiovascular risk. The results were later published.⁶ (GSK subsequently conducted the “PharMetrics Study,”⁷ a separate epidemiologic observational study using a different and larger managed care database.)

October 27, 2006: GSK added the final reports of meta-analysis of 42 double-blind, controlled clinical trials of Avandia, as well as the report of the observational Balanced Cohort Study, to the publically available GSK Clinical Trials Register website containing data relating to Avandia.

April 20, 2007: FDA requested a meeting with GSK to hear GSK’s perspective on myocardial ischemic events and the benefit-risk profile of Avandia, based mainly on the expanded meta-analysis in sNDA Supplement (S-022).

May 14, 2007: GSK submitted to FDA a copy of the Safety Interim Analysis Plan for the RECORD study.

May 16, 2007: FDA and GSK met to hear GSK’s perspective on myocardial ischemic events and the benefit-risk profile of Avandia, based mainly on the expanded meta-analysis in sNDA Supplement (S-022).

May 18, 2007: GSK submitted to FDA an Amendment to sNDA Supplement (S-022) to provide revised draft labeling to add a new subsection (on “Myocardial Ischemic Events”) to the Warnings section of labeling for Avandia Tablets.

May 18, 2007: GSK submitted to FDA the interim results of the RECORD trial.

⁶ McAfee AT, et al., 16 *Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents*, PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 711 (2007).

⁷ The “Coronary Heart Disease Outcomes in Patients Receiving AntiDiabetic Agents in the PharMetrics Database” study. This balanced cohort analysis examined the incidence of myocardial infarction and coronary revascularization events in over 400,000 diabetic patients in an independent database. In contrast to the prior study, the head to head comparisons of Avandia versus other oral agents included a comparison of Avandia versus Actos®. This study showed that the incidence of ischemic cardiovascular events was similar for Avandia compared with other antidiabetic agents, and that the incidence was similar for Avandia compared with Actos®.

May 21, 2007: GSK submitted to FDA an Amendment to sNDA Supplement (S-022) to provide a proposal for a Risk Management Plan to address the potential for myocardial ischemic events in patients treated with Avandia.

July 30, 2007: Advisory Committee considered submissions from FDA, GSK, and the public and recommended the continued marketing of rosiglitazone.⁸

III. THE STAFF REPORT IMPROPERLY CASTS AVANDIA AS UNSAFE, IGNORING THE AVAILABLE SCIENTIFIC INFORMATION ON THE PRODUCT.

Since approval by the FDA in 1999 and beyond, GSK has rigorously maintained an extensive and long-term program of scientific study for Avandia, which is the most comprehensive program of scientific analysis for any oral anti-diabetes medicine available to patients today, with experience in well over 52,000 patients. As of March 2009, it is estimated that patient exposure to Avandia is in excess of 14,296,255 patient-years for the treatment of type 2 diabetes, a serious and life-threatening disease that affects more than 23 million people in the United States.⁹ The FDA approved Avandia – and its label – only after determining that Avandia is safe and effective as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The FDA made this determination pursuant to a comprehensive, highly regulated process for approving new drugs and based on an extensive scientific record that included studies of Avandia’s pharmacological action and toxicological effects and the results of numerous clinical investigations, many of which provided important data on cardiovascular risk.

Eight years after approval and after Dr. Steven Nissen published his controversial meta-analysis on May 21, 2007,¹⁰ the FDA again reviewed the safety and efficacy data for Avandia in July of 2007 in a formal Advisory Committee hearing and confirmed that Avandia should remain available for type 2 diabetes patients. The FDA’s confirmation also included review of meta-analyses that GSK conducted and submitted to the FDA in October 2005, May 2006, and August 2006, as well as FDA’s own analysis of the data that GSK submitted. Numerous studies representing tens of thousands of additional patient exposure years to Avandia have concluded since July of 2007 that further support the cardiovascular safety of Avandia.

⁸ GSK acknowledges that the FDA issued a warning letter in March of 2008 for omissions from certain periodic reports that, in many cases, had been submitted to the Agency in other reports and communications. The inadvertent omissions cited in the FDA letter did not compromise the timely reporting of adverse events to the FDA. FDA spokeswoman, Susan Cruzan, herself is quoted as stating that, while GSK did not meet some administrative requirements, information omitted did not change the FDA’s July 2007 evaluation of the safety data for Avandia. Whalen, Jeanne & Corbett-Dooren, Jennifer, FDA Warns Glaxo Over Lack of Reports on Avandia, *Wall Street Journal* (April 9, 2008).

⁹ Am. Diabetes Ass’n, *All About Diabetes*, at <http://www.diabetes.org/diabetes-basics/diabetes-statistics/> (last visited February 20, 2010).

¹⁰ Steven E. Nissen & Kathy Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes*, 356 (24) N. ENG. J. MED. 2457 (2007).

A. The final results of multiple studies demonstrating the ischemic cardiovascular safety of Avandia have been excluded from the Staff Report.

A considerable portion of the Staff Report is devoted to characterizing long-term randomized clinical trials for Avandia, namely, ADOPT, DREAM, and RECORD, as incapable of accurately assessing the cardiovascular safety of the product. Inexplicably, the final results of these trials are not mentioned at all in the Staff Report, despite the fact that the results have been publically available for RECORD since June 2009 and the results of ADOPT and DREAM have been available since late 2006/early 2007. Moreover, five additional randomized clinical trials supporting the cardiovascular safety of Avandia have been omitted from discussion in the Staff Report entirely (APPROACH, VICTORY, VADT, ACCORD, and BARI-2D). Taken together, these studies do not support the initial concerns raised by meta-analyses that Avandia increases the risk of myocardial ischemia or infarction.

1. RECORD

RECORD¹¹ provides the best, most reliable assessment of Avandia's cardiovascular safety. RECORD is a large, long-term, prospective, randomized, controlled trial in 4,447 type 2 diabetic patients. RECORD was designed and intended to evaluate cardiovascular outcomes. The primary outcome in RECORD was cardiovascular hospitalization or cardiovascular death. Pre-specified secondary outcomes included specific cardiovascular events, including cardiovascular death, congestive heart failure, myocardial infarction, and stroke. Outcomes were adjudicated by an independent clinical endpoints committee.

After following patients for an average of 5.5 years, RECORD met its primary objective, demonstrating no increased risk of cardiovascular death or hospitalization in patients randomized to receive a combination of Avandia and standard therapy compared to those treated with the combination of standard therapies, metformin and sulfonylurea (HR¹² 0.99; 95% CI 0.85 – 1.16; p = 0.93). Thus, Avandia was not associated with an increased risk of cardiovascular morbidity or mortality compared to standard glucose-lowering therapies. Secondary analyses showed a non-significant increase in the risk of myocardial infarction in patients taking Avandia (HR 1.14; 95% CI 0.80 – 1.63; p = 0.47), and non-significant reductions in all-cause death, cardiovascular death, stroke, and major cardiovascular adverse events (“MACE,” which includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in Avandia-treated patients.¹³

¹¹ Philip D. Home *et al.*, for the RECORD Study Team, *Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial*, 373 (9681) LANCET 2125 (2009).

¹² A “hazard ratio” (HR) is broadly equivalent to the relative risk, which is the number of times more likely or less likely an event is to happen in one group compared with another. It is the ratio of the absolute risk for each group, and is analogous to the odds ratio when events are rare. BMJ Clinical Evidence Glossary, at <http://clinicalevidence.bmj.com/cweb/resources/glossary.jsp> (last visited February 20, 2010).

¹³ In RECORD, the rate of heart failure, which is distinct from myocardial infarction, was significantly higher in patients treated with rosiglitazone (HR 2.10, CI 1.35.-3.27).

RECORD is a dedicated cardiovascular outcomes study with adjudicated endpoints and does not suffer from the many limitations of the Nissen meta-analysis. According to the authors of the Nissen meta-analysis, among its “important limitations” were: (1) the included trials “were not originally intended to explore cardiovascular outcomes,” (2) most of the included trials “did not centrally adjudicate cardiovascular outcomes,” and (3) the definitions of myocardial infarction “were not available.”¹⁴ Conversely, RECORD is not only a long-term randomized outcomes trial with prospective adjudication of cardiovascular events, its results satisfy the current FDA guidelines for establishing the cardiovascular safety of new anti-diabetic therapies, with the final hazard ratio for the well-accepted endpoint of MACE being 0.93, with a 95% confidence interval that comfortably excludes the proposed FDA margin of 1.3 (MACE 95% confidence interval: 0.74 to 1.15).¹⁵ RECORD demonstrates that Avandia does not increase cardiovascular ischemic risk over comparable therapy.

Citing only documents created years before RECORD was completed and taking them entirely out of context, the Staff Report alleges that the design of RECORD was fundamentally flawed from the outset and had a number of limitations, including: (1) that it was designed as a marketing study to compete with Actos®¹⁶ (pioglitazone HCl); (2) it was underpowered; (3) the chosen endpoints of the study were too inclusive; and (4) the study was not blinded. The Staff Report’s allegations are unwarranted for the following reasons:

- European regulators commissioned the RECORD study and approved its design. It began in 2001 and its initiation bears no relation to Actos or the PROActive study.¹⁷

¹⁴ Nissen, *supra* note 10, at 2469.

¹⁵ FDA Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. This Guidance states that “to establish the safety” of a new antidiabetic therapy, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. One way to demonstrate such safety is by conducting a “single, large safety trial” showing that the upper bound of the 95% confidence interval for cardiovascular events is less than 1.3. With an upper bound of 1.16 for the primary outcome, GSK believes that RECORD satisfies the criteria for cardiovascular safety set forth in the FDA Guidance.

¹⁶ Actos is a registered trademark of Takeda Pharmaceutical Company Limited.

¹⁷ Currently, a second large, long-term cardiovascular outcomes study of Avandia is also under way (Thiazolidinedione Intervention with Vitamin D Evaluation [TIDE]), which includes a comparison of both Avandia (rosiglitazone) and Actos (pioglitazone). The Graham/Gelperin “Benefit-risk assessment of rosiglitazone vs. pioglitazone,” and the Gelperin safety review of TIDE were completed in October 2008. The Graham and Gelperin assessment did not have the benefit of the largest, most comprehensive meta-analysis to date evaluating the effect of rosiglitazone on myocardial infarction. As discussed *infra*, Mannucci et al. analyzed 164 clinical trials and determined that there was “no evidence of increased risk of myocardial infarction or cardiovascular death in patients treated with rosiglitazone.” Although Graham and Gelperin considered the observational data available at the time of their review, investigators have cautioned that unmeasured factors may confound the results of observational data and further cautioned that conclusive evidence can only be ascertained from well-designed cardiovascular outcomes trials. Additional, inconsistent observational data that became available after their review highlights the need for such trials.

(continued...)

- The final results of RECORD included a sufficient event rate to be adequately powered for its primary endpoints of cardiovascular hospitalization or cardiovascular death.¹⁸
- The endpoints chosen in RECORD represent the most conservative approach to analyzing the true cardiovascular risks of Avandia. The chosen endpoints of cardiovascular disease and death are inclusive of myocardial infarction and, therefore, provide information about the risk of myocardial infarction in patients taking Avandia.¹⁹ Additionally, investigators looked specifically at all the components of the primary endpoint, including myocardial infarction, and found no statistically significant difference between Avandia and comparator on any of the individual outcomes, except for heart failure – a long understood issue for the thiazolidinedione class.
- All RECORD cardiovascular outcomes were adjudicated by an independent committee who were blinded to treatment allocation.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Consensus Statement and Algorithm for Glycemic Control in type 2 diabetes noted that following the release of Nissen’s meta-analysis: “Subsequent, *more definitive analyses*, however, have indicated that rosiglitazone has no effect, positive or negative, on the occurrence of cardiovascular disease.”²⁰ This statement was made months after the publication of the final results of RECORD.

(continued...)

RECORD and PROActive are cardiovascular outcome trials of rosiglitazone and pioglitazone, respectively, but there are currently no head-to-head studies assessing cardiovascular endpoints. RECORD and PROActive demonstrated no overall increased cardiovascular risk with rosiglitazone or pioglitazone therapy, but neither trial established a cardiovascular benefit. TIDE is the cardiovascular outcome study directed by FDA to evaluate the comparative cardiovascular safety of rosiglitazone and pioglitazone.

¹⁸ Home, *supra* note 11, at 2131.

¹⁹ *Id.* at 2127.

²⁰ AACE/ACE Consensus Statement, *Glycemic Control Algorithm*, 15(6) ENDOCR PRACT. 541, 554 (2009) (emphasis added).

2. The APPROACH Trial²¹

APPROACH, which is not mentioned in the Staff Report, is a long-term, prospective, randomized, controlled trial evaluating the effect of Avandia compared to glipizide (a sulfonylurea) on progression of atherosclerosis in coronary arteries in patients with type 2 diabetes. Endpoints that were evaluated included various measures of atherosclerosis and cardiovascular outcomes. Cardiovascular outcomes were adjudicated by an independent endpoints committee. Results from APPROACH were reported in 2008 at the annual meeting of the American Heart Association.

After 18 months of follow-up, there was no increase in any measure of atherosclerosis with Avandia, and there was no statistically significant difference in the rate of myocardial infarction, cardiovascular death, stroke, or MACE in patients treated with Avandia compared to patients treated with glipizide.

3. The VICTORY Trial²²

VICTORY, also omitted from the Staff Report, is a long-term, prospective, randomized, placebo-controlled trial evaluating atherosclerosis progression after coronary bypass surgery in patients with type 2 diabetes. Endpoints assessed included atherosclerosis in the vein graft used to bypass the coronary artery blockage, as well as myocardial infarction, transient ischemic attack, stroke, hospitalization, and death. Results from VICTORY were reported in 2008 at the annual meeting of the American College of Cardiology.

After one year of follow-up, atherosclerosis did not progress, and there was not a higher rate of any cardiovascular outcome with Avandia compared to placebo. No patient taking Avandia had a myocardial infarction; one patient taking placebo had a myocardial infarction.

4. The VADT Trial²³

VADT, which is not discussed in the Staff Report, is a large, long-term, prospective, randomized, controlled trial assessing the effect of intense glycemic control compared to standard glycemic control on cardiovascular outcomes in 1,791 veterans with diabetes. The primary endpoint was a composite of myocardial infarction, stroke, cardiovascular

²¹ Richard W. Nesto *et al.*, for the APPROACH Study Team, *Effect of Rosiglitazone versus glipizide on progression of coronary atherosclerosis in patients with type 2 diabetes and coronary artery disease. The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes patients with Cardiovascular History (APPROACH) Trial*. Presented at American Heart Association 2008 Scientific Sessions; November 8-12, 2008; New Orleans, LA.

²² Olivier F. Bertrand *et al.*, for the VICTORY Investigators, *Results of a Multicenter Randomized Double-Blind Placebo-Controlled Study to Assess the Benefit and Safety of Rosiglitazone in Preventing Atherosclerosis After Coronary Bypass Surgery in Type 2 Diabetes*. Presented at the 57th Annual Scientific Sessions of the American College of Cardiology (ACC) March 29, 2008 – April 1, 2008, Chicago, IL.

²³ William C. Duckworth *et al.*, for the Veterans Affairs Diabetes Trial (VADT) Investigators, *Glucose control and vascular complications in veterans with type 2 diabetes*, 360 (2) NEW ENGL. J. MED. 129 (2009).

death, heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic diabetic gangrene. Patients were followed for an average of 5.6 years. Outcomes were adjudicated by an independent endpoints committee.

VADT investigators presented analyses of the cardiovascular safety profile of Avandia at the American Diabetes Association meetings in June 2008. Cardiovascular outcomes analyzed included myocardial infarction, cardiovascular death, and a combined endpoint of myocardial infarction and cardiovascular death. In every analysis, patients taking Avandia were less likely to experience an adverse cardiovascular outcome than patients not taking Avandia.²⁴

5. The ACCORD Trial²⁵

Another study not included in the Staff Report, ACCORD, is a large, long-term, prospective, randomized, controlled trial in 10,251 patients with type 2 diabetes comparing, among other things, intensive glycemic control to standard glycemic control on a variety of different endpoints. Avandia was used in a greater proportion of patients in the intensive treatment group (91.2%) than of patients in the non-intensive treatment group (57.5%). The primary outcome was a composite endpoint of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. Outcomes were adjudicated by an independent adjudication committee.

After 4 years of treatment, the data safety monitoring board for ACCORD recommended stopping the intensive glycemic arm of the trial due to an increased mortality rate compared to the standard glycemic arm. The investigators specifically noted that Avandia use did not explain the increased mortality seen with intensive glycemic control. Further, there were statistically significantly fewer nonfatal myocardial infarctions in the intensive treatment group (HR 0.76, 95% CI 0.62-0.92).

ACCORD investigators presented analyses and data on Avandia at the American Diabetes Association meetings in June 2008. Although the finding was not statistically significant, there was a reduction in mortality in patients taking Avandia. There is no evidence from ACCORD that Avandia had an adverse impact on cardiovascular outcomes.²⁶

²⁴ In some analyses, the beneficial effect of Avandia was statistically significant; in others it was not. Thomas E. Moritz *et al.*, for the VADT Investigators, *Cardiovascular outcomes by glycemic control treatment arm. Glycemic control and Cardiovascular Outcomes – The Veterans Affairs Diabetes Trial (VADT)*. Presented at the 68th Annual Scientific Sessions of the American Diabetes Association, June 6-10, 2008; San Francisco, CA.

²⁵ Hertzel C. Gerstein *et al.*, for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group, *Effects of intensive glucose lowering in type 2 diabetes*, 358 (24) NEW ENGL. J. MED. 2545 (2008).

²⁶ Michael E. Miller, for the ACCORD Study Group, *Relationship between glycemia medications and mortality in ACCORD*. Presented at the 68th Annual Scientific Sessions of the American Diabetes Association, June 6-10, 2008; San Francisco, CA.

6. The BARI-2D Trial^{27 28}

BARI-2D – a study not mentioned in the Staff Report – is a large, long-term, prospective, randomized, controlled trial in 2,386 patients with type 2 diabetes and stable coronary artery disease comparing (among other things) “insulin-providing” medications (sulphonylurea/insulin) with “insulin-sensitizing” medications (metformin/TZD²⁹). Avandia was the predominant TZD used in the insulin-sensitizing group.³⁰ The primary endpoint was all-cause mortality. Pre-specified secondary endpoints included myocardial infarction, cardiac death, and a composite of death, myocardial infarction or stroke (MACE).

After 5 years of follow-up, there was no statistically significant difference in mortality (p = 0.89), myocardial infarction (p = 0.21), cardiac death (p = 0.76), or MACE (p = 0.13) between the insulin-sensitizing group and the insulin-providing group. However, among patients with the most severe coronary artery disease, the authors noted that “the difference in myocardial infarction rates was affected dramatically by the type of initially assigned glycemic strategy.”³¹ Insulin-providing therapy – in patients who underwent coronary artery bypass surgery – “was associated with a higher rate of MI.”³² Additionally, “the combination of prompt revascularization and an insulin-sensitizing strategy was associated with a significantly lower rate of major cardiovascular events...”³³ There is no evidence from BARI-2D supporting an increase in the risk of myocardial infarction from Avandia.

7. ADOPT

While ADOPT is cited in the Staff Report, its importance in examining the ischemic cardiovascular safety of Avandia is overlooked. In connection with the approval of

²⁷ Robert L. Frye *et al.*, for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) Study Group, *A randomized trial of therapies for type 2 diabetes and coronary artery disease*, 360 (24) *NEW ENGL. J. MED.* 2503 (2009).

²⁸ Bernard R. Chaitman *et al.*, for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2d) Study Group, *The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction*, 120 *CIRCULATION* 2529 (2009).

²⁹ The thiazolidinedione (“TZD”) medication class includes Avandia and Actos.

³⁰ Following questions raised about the cardiovascular safety of Avandia, but prior to study completion, the data safety monitoring board and the NHLBI reviewed cardiovascular disease rates in patients receiving Avandia compared to other diabetes drugs. After review, NHLBI issued a statement on June 15, 2007 that data from BARI-2D “contain no observations that would justify a recommendation to terminate Avandia treatment.” (<http://www.nhlbi.nih.gov/new/press/07-rosi-qa.htm>).

³¹ Chaitman, *supra* note 28, at 2536.

³² *Id.*

³³ Frye, *supra* note 27, at 2513.

Avandia, GSK agreed to conduct a Phase 4 (post-marketing) clinical study – the ADOPT trial³⁴ – to further explore the long-term safety and efficacy of the medication. Endpoints of ADOPT included cardiovascular issues.³⁵ The ADOPT trial’s primary objective was to evaluate and compare the effects of long-term therapy with three commonly prescribed antidiabetic medications, Avandia, glyburide/glibenclamide, and metformin, on the improvement and maintenance of glycemic control in over 4,350 patients with recently diagnosed type 2 diabetes.³⁶ The secondary objective included the assessment of cardiovascular safety.³⁷ Notably, as the Commissioner of the FDA stated, the results of the ADOPT trial “do not support an increased ischemic risk of rosiglitazone relative to metformin or glyburide.”³⁸

Since the publication of the primary paper from the ADOPT study, GSK has further analyzed the ADOPT database to ensure no information has been overlooked, examining all major cardiovascular events. This analysis concluded that such events were rare, and that all the treatments studied were comparable. There was no significant difference in myocardial ischemic events among the different therapies.³⁹

8. DREAM

Data from the DREAM trial⁴⁰ give a similar picture of the ischemic cardiovascular safety of Avandia and are not given adequate consideration in the Staff Report.⁴¹ DREAM was designed to determine if Avandia or ramipril (a cardiovascular drug) delayed the

³⁴ The full title of the ADOPT trial is “A Diabetes Outcome Progression Trial.” See Steven E. Kahn et al., for the ADOPT Study Group, *Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy* 355 NEW ENGL. J. MED. 2427, 2438 (2006).

³⁵ *Id.* at 2438.

³⁶ *Id.*

³⁷ FDA Briefing Document for the July 30, 2007 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on Rosiglitazone at 8, complete FDA Briefing Document available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf> [hereinafter “FDA Adv. Comm. Brief”].

³⁸ Statement of FDA Comm’r, Andrew C. von Eschenbach, M.D., before the United States House of Representatives’ Committee on Oversight and Government Reform at 38 (dated 06/06/07); see also FDA Adv. Comm. Brief at 76 (“Overall, ADOPT does not appear to present a significant signal of excess myocardial ischemic event risk, of excess total mortality, or of excess cardiovascular mortality for [Avandia] vs [glyburide/glibenclamide] or [metformin].”).

³⁹ Ronald L. Krall, *Cardiovascular safety of rosiglitazone* 369 THE LANCET 1995 (2007).

⁴⁰ The full title of the DREAM trial is “Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication.” See The DREAM Trial Investigators, *Effect of Rosiglitazone on the Frequency of Diabetes in Patients with Impaired Glucose Tolerance or Impaired Fasting Glucose: A Randomized Controlled Trial* 368 THE LANCET 1096 (2006) [hereinafter “The DREAM Trial”].

⁴¹ FDA Adv. Comm. Brief, *supra* note 37, at 77; The DREAM Trial.

onset of diabetes in pre-diabetic patients.⁴² The trial was also designed to examine cardiovascular event rates, such as cardiovascular deaths, CHF, and ischemic heart disease events, including myocardial infarction and stroke.⁴³ In their initial publication of the DREAM results in 2006, the investigators found no significant difference between the Avandia and placebo groups in the secondary composite endpoint of cardiovascular events (myocardial infarction, stroke, cardiovascular deaths, confirmed heart failure, new angina and revascularization procedures). Both the Avandia and placebo treatment groups had much the same frequency of every component of the composite outcome – including myocardial infarction – except for heart failure.⁴⁴ A further analysis of the DREAM data found that similar numbers of patients in the Avandia, ramipril, and placebo groups experienced cardiovascular events.⁴⁵ In fact, there were fewer myocardial infarction events in patients receiving Avandia alone than in patients receiving placebo alone (OR⁴⁶ 0.83; 95% CI 0.20-3.27).

a. The STARR Trial⁴⁷

STARR, a substudy of 1,425 patients within the DREAM trial also not mentioned in the Staff Report, compared Avandia, ramipril (an ACE inhibitor that is not approved for the treatment of diabetes), and placebo in pre-diabetic patients. Patients were followed for an average of 3 years. Endpoints evaluated included carotid intima medial thickness (“CIMT”)⁴⁸ and other measures of atherosclerosis progression, and cardiovascular events which were adjudicated by an independent endpoints committee.

There was no progression of atherosclerosis by any measure studied for Avandia compared to placebo. In addition, there was no statistically significant difference in major cardiovascular endpoints (a composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, new or unstable angina, coronary or peripheral revascularization, or heart failure) or myocardial infarction in patients taking Avandia compared to patients taking

⁴² See *id.*

⁴³ See *id.*

⁴⁴ *Id.*

⁴⁵ Krall, *supra* note 39.

⁴⁶ An “Odds Ratio” is the ratio of the odds that a case (one with the disease) was exposed to the odds that a control (one without the disease) was exposed. For most purposes the odds ratio from a case-control study is quite similar to a risk ratio from a cohort study. Michael D. Green et al., *Reference Guide on Epidemiology*, in Federal Judicial Center, *Reference Manual on Scientific Evidence, Glossary of Terms*, 333, 387-397 (2d ed. 2000) [hereinafter “*Reference Manual*”].

⁴⁷ Eva M. Lonn et al., for the STARR Investigators, *Effect of ramipril and of rosiglitazone on carotid intima-media thickness in people with impaired glucose tolerance or impaired fasting glucose: STARR (Study of Atherosclerosis with Ramipril and Rosiglitazone)*, 53 (22) J. AM. COLL. CARDIOL. 2028 (2009).

⁴⁸ The carotid artery in the neck carries oxygen and nutrients from the heart and aorta to the brain. The intima media is the inner lining of an artery. Atherosclerosis increases intima medial thickness.

placebo. The authors concluded that “the results for Avandia are not conclusive but suggest a modest beneficial effect on vascular disease progression. This could result in more robust long-term effects on vascular disease progression and possibly on clinical ischemic events, although this hypothesis requires further evaluation.”⁴⁹

Each of these clinical trials and analyses provide important supporting evidence of the ischemic cardiovascular safety of Avandia and, as discussed further below, stand in stark contrast to the limitations of Nissen’s meta-analysis.

B. To the extent that the Staff Report casts the Nissen meta-analysis as evidence of an increased risk of myocardial infarction with Avandia, the suggestion should be rejected.

The Senate Finance Committee’s investigation underlying its report followed shortly on the heels of publication of the meta-analysis written by Nissen and, his co-author, Kathy Wolski. Nissen’s meta-analysis is a retrospective analysis of pooled data largely from short-term Avandia clinical trials primarily designed to assess endpoints other than the cardiovascular safety profile of Avandia. This study reported a statistically significant increased risk of heart attacks associated with Avandia,⁵⁰ but the Nissen meta-analysis has received widespread criticism in the peer-reviewed scientific literature⁵¹ and has been contradicted by other, more robust, meta-analyses.

1. There are many limitations of Nissen’s meta-analysis.

First, the type of study Nissen undertook has serious methodological limitations. A meta-analysis is not a clinical study. It is a retrospective analysis that looks for statistical associations by pooling data from different studies, including studies that can vary in their design, purpose, and endpoints. While the *Reference Manual on Scientific Evidence*⁵² states that

⁴⁹ Lonn, *supra* note 47, at 2034.

⁵⁰ Nissen, *supra* note 10, at 2459.

⁵¹ Editors of The Lancet, *Rosiglitazone: seeking a balanced perspective*, 369 THE LANCET 1834 (2007) (“it would be premature to overinterpret a meta-analysis that the authors and the NEJM all acknowledged contain important weaknesses”); R.W. Bilous, *Rosiglitazone and myocardial infarction: cause for concern or misleading meta-analysis?*, 24 DIAB. MED. 931, 932 (2007) (calling Nissen’s meta-analysis “deeply flawed”); Valentin Fuster & Michael E. Farkouh, *Faster publication isn’t always better*, 4 NATURE CLINICAL PRACTICE: CARDIOVASCULAR MED. 345, 345 (2007) (characterizing Nissen’s analysis as “rushed and incomplete”); *see also* G. A. Diamond et al., *Uncertain effects of Rosiglitazone on the risk of myocardial infarction and cardiovascular death*, 147 ANN. INTERN. MED. 578 (2007) (conducting several meta-analyses on the same data used in the Nissen meta-analysis, and concluding that Nissen’s meta-analysis “probably exaggerated risk estimates,” and led to “confusing and conflicting results about cardiovascular risk associated with rosiglitazone therapy”); Z. T. Bloomgarden, *The Avandia Debate*, 30 DIABETES CARE 2401, 2405-06 (2007) (commenting that Dr. Nissen’s paper violated standard meta-analysis methodology by failing to start with a pre-specified study hypothesis, leading to “data snooping on quite a large scale,” and concluding that it is a “poor basis for making decisions.”).

⁵² *Reference Manual*, *supra* note 46, at 380-81.

“a randomized clinical trial, or true experiment, is considered the gold standard for determining the relationship of an agent to a disease or health outcome,”⁵³ it states that meta-analyses’ “problems have been so frequent and so deep, and overstatements of conclusions so extreme, that one might well conclude that there is something seriously and fundamentally wrong with the method.”⁵⁴ Nissen himself acknowledged in his analysis that “a meta-analysis is always considered less convincing than a large, prospective trial designed to assess the outcome of interest.”⁵⁵

Second, the underlying studies used in Nissen’s meta-analysis reported very few myocardial infarction cases, and the increased myocardial infarction risk the Nissen meta-analysis purports to find is an odds ratio of only 1.43. To put this in context, if a person’s “background” risk of myocardial infarction were 2% (*i.e.*, 2 chances in 100 of getting a heart attack), the risk, if Nissen’s analysis were accurate, would be 2.86% (*i.e.*, 2.86 chances in 100). It does not mean, as some have claimed, that people with diabetes taking Avandia have a 43% risk of having a heart attack. Considering the limitations in the Nissen meta-analysis, its inconsistency with other studies, and lack of validation by the more robust clinical trial data, this small risk is more reason why the Nissen meta-analysis cannot provide reliable proof that Avandia causes heart attacks.⁵⁶

2. The conclusions reached by Nissen have been contradicted by larger, more recent meta-analyses.

Since Nissen’s analysis was published in May 2007, larger, updated, more comprehensive meta-analyses have been done that do not support his hypothesis. Specifically, GSK has updated its ICT,⁵⁷ the earlier version of which Nissen was informed of in the spring of 2007 and was then under consideration by the FDA. Independent investigators (Mannucci, et al.)⁵⁸ also published a comprehensive meta-analysis that included 164 clinical trials, four times more than the 42 trials included in the Nissen meta-analysis. ***Neither the updated ICT nor the Mannucci meta-analysis shows a statistically significant association between Avandia and myocardial infarction or other ischemic cardiovascular events.***

⁵³ *Id.* at 338.

⁵⁴ *Id.* at 381 n.127 (quoting John C. Bailar III, *Assessing Assessments*, 277 SCIENCE 528, 529 (1997)).

⁵⁵ Nissen, *supra* note 10, at 2469.

⁵⁶ *Reference Manual*, *supra* note 46, at 376 (low relative risks must be scrutinized “more closely because there is a greater chance that they are the result of uncontrolled confounding or biases”).

⁵⁷ Study AVD113017, 2008 Update to Integrated Clinical Trials (ICT) analysis for Avandia. Posted to the GSK Clinical Study Register June 8, 2009.

⁵⁸ Edoardo Mannucci *et al.*, *Cardiac safety profile of rosiglitazone: A comprehensive meta-analysis of randomized clinical trials*, INT. J. CARDIOL., e-publication (2009).

As part of GSK’s ongoing pharmacovigilance program, in 2008, GSK updated its ICT dataset to include recently completed studies that were not available for its previous ICT analyses considered by the FDA from October 2005 to July 2007. In the updated analysis, GSK evaluated myocardial ischemia, major adverse cardiovascular events (MACE), and the individual components of MACE (myocardial infarction, stroke, and cardiovascular death). There was no statistically significant increased risk of myocardial ischemia (HR 1.098; p = 0.383), myocardial infarction (HR 1.406; p = 0.143), stroke (HR 0.630; p = 0.155), cardiac death (HR 1.264; p = 0.518) or MACE (HR 1.121; p = 0.525). Thus, GSK’s updated ICT does not support the hypothesis raised by the Nissen meta-analysis.

Mannucci, et al., noted that Nissen failed to include all the clinical trials for Avandia available at the time that Nissen and Wolski conducted their meta-analysis. Thus, to more properly assess the effect of Avandia on cardiovascular outcomes, the authors collected “all available evidence from published or unpublished randomized clinical trials.”⁵⁹ Mannucci, et al., is the largest, most comprehensive meta-analysis of Avandia clinical trials to date. This comprehensive meta-analysis is inconsistent with the hypothesis raised by the Nissen meta-analysis. Treatment with Avandia was not associated with any of the following:

<u>Results of Mannucci Meta-Analysis</u>
Death (OR 0.90, 95% CI 0.73 – 1.12)
Cardiovascular death (OR 0.94, 95% CI 0.69 – 1.29)
Coronary events (OR 1.09, 95% CI 0.90 – 1.31)
Myocardial infarction (OR 1.14, 95% CI 0.90 – 1.45)

The authors concluded, contrary to Nissen, that “there is no evidence of increased risk of myocardial infarction or cardiovascular mortality in patients treated with rosiglitazone.”⁶⁰

Given the significant limitations of the Nissen meta-analysis and the contradicting results from larger meta-analyses conducted by independent investigators and GSK, Nissen’s analysis cannot be accepted as the confirmation the Staff Report urges us to conclude of an increased risk for myocardial ischemic events with Avandia.

⁵⁹ *Id.* at 2.

⁶⁰ Mannucci, *supra* note 58, at 6.

C. Dr. Graham's conclusions cited in the Staff Report are flawed and unreliable and, most importantly, do not represent the formal opinion of the FDA.

As referenced in the Staff Report, Dr. David Graham, an individual within FDA, has suggested that there is an excess risk of cardiovascular events in people treated with Avandia. Dr. Graham's estimates of "excess risk" are based upon numerous false assumptions and incomplete data. Most importantly, Dr. Graham was unable to consider data from the completed RECORD trial, a prospectively, randomized controlled trial designed specifically to evaluate the effect of Avandia on cardiovascular outcomes.

In 2007, Dr. Graham estimated that exposure to Avandia resulted in approximately 83,000 excess cases of serious cardiovascular events, including myocardial infarction and cardiovascular death. These numbers simply do not reflect reality. Implicit in Dr. Graham's estimate is that assumption that Avandia causes such events. In truth, the FDA and the Advisory Committee members fully considered Dr. Graham's 2007 analysis and the totality of available data on the risk of myocardial ischemia with Avandia, concluding that Avandia should remain available to patients with type 2 diabetes.

There is no scientific basis on which to assume that Avandia causes excess myocardial infarction or cardiovascular death. If Dr. Graham's assumptions were true, excess risk would have been clearly demonstrated in the long-term clinical trials. In fact, RECORD established that treatment with Avandia conferred no excess risk of the primary outcome (cardiovascular hospitalization or cardiovascular death) compared to treatment with metformin and sulfonylurea. In addition, there was no statistically significant difference in any of the components of the primary outcome, including cardiovascular death, myocardial infarction, stroke, or MACE outcomes except for heart failure – a long understood issue for the thiazolidinedione class.

In October 2008, Dr. Graham estimated that treatment with Avandia results in an excess of 500 myocardial infarctions and 300 heart failure events per month compared to treatment with Actos. Again, Dr. Graham's methodology is seriously flawed and based on incomplete data. There are no head-to-head trials comparing the effect of Avandia and Actos on cardiovascular outcomes. Dr. Graham compares different meta-analyses for Avandia and Actos, which use different comparisons, different patient populations, and different data collection methods. He also attempts to compare observational studies, which also are filled with different comparator groups, different treatment regimens and different populations. Investigators have cautioned that unmeasured factors may confound the results of observational data and further cautioned that conclusive evidence can only be ascertained from well-designed cardiovascular outcomes trials. Inconsistent findings from observational studies highlight the need for such trials.

RECORD and PROActive are cardiovascular outcome trials of Avandia and Actos, respectively, but there are currently no head-to-head studies assessing cardiovascular endpoints. RECORD and PROActive demonstrated no overall increased cardiovascular risk with Avandia or Actos therapy, but neither trial established a cardiovascular benefit. TIDE is the ongoing head-to head cardiovascular outcome study requested by FDA to conclusively establish the comparative cardiovascular safety of Avandia and Actos.

Based on the many methodological flaws in Dr. Graham's analyses, the Staff Report should not rely on them to support a conclusion that there is an excess ischemic cardiovascular risk for Avandia.

IV. THE EXAMPLES OF GSK'S INTERACTIONS WITH PHYSICIANS CITED IN THE SENATE FINANCE COMMITTEE REPORT WERE NOT INSTANCES OF ATTEMPTS TO CONCEAL SAFETY INFORMATION PERTAINING TO AVANDIA.

The Staff Report notes three sets of interactions GSK employees had with physicians concerning Avandia – involving Dr. John Buse, physicians at the University of Pennsylvania, and Dr. Steven Nissen – as examples of GSK attempting to prevent cardiovascular concerns about its product from becoming known.

As GSK has previously stated, at the time Dr. Buse made his initial comments, GSK was trying to correct inaccuracies about data on Avandia contained in a Continuing Medical Education presentation by Dr. Buse. This 1999 presentation was sponsored by Takeda Pharmaceuticals America, the manufacturer of Actos. When these inaccuracies were first brought to the attention of GSK, GSK believed it was very important to seek a correction to ensure that the data on Avandia were accurately presented to physicians who might be prescribing Avandia and Actos. Ultimately, Dr. Buse clarified and corrected his statements, which the company appreciated. Dr. Buse has publicly indicated that he has long since moved on from the events of 1999, and so has GSK. Specifically, Dr. Buse reflected on his interaction with GSK in a statement he provided to the New York Times on June 2, 2007 that he holds “no ill-will towards GSK” and that the “hint of a cardiovascular safety issue that I was concerned about was so small and in many ways balanced by other bits of evidence.”⁶¹

With respect to allegations concerning two physicians from the University of Pennsylvania, it is difficult for GSK to respond without the benefit of the entire interviews of those physicians, including what questions were asked by Senate investigators and the full reflections of the physicians. GSK acknowledges that it contacted physicians at Penn in 1999 concerning case reports of liver failures. As the Staff Report states, neither physician now believes that there is a link between Avandia and liver failure. GSK was not attempting to downplay safety concerns but rather trying to understand and make sure accurate valid data was presented to physicians.

Finally, the Staff Report accuses GSK employees of having inappropriate interactions with Dr. Nissen concerning studies proposed by him to GSK, as well as in regard to its receipt of his draft manuscript. Dr. Nissen contacted GSK on January 3, 2007 seeking access to patient level data from certain GSK-sponsored clinical trials for a proposed-meta-analysis. GSK wrote back to Dr. Nissen on February 26⁶² and noted that such requests were “readily

⁶¹ John B. Buse, *Statement*, N.Y. TIMES, June 2, 2007.

⁶² GSK102_000000045 (copy of February 26, 2007 letter from GSK to Dr. Nissen produced to Senate Finance Committee).

considered by GSK,” but that it required an outline of the scientific rationale for the proposed analysis, that the analyses be performed by GSK in collaboration and that there be publication with prior GSK review.⁶³ In April and May 2007, GSK and Dr. Nissen were again discussing a research proposal related to rosiglitazone, wherein GSK expressed a willingness to collaborate with Dr. Nissen on the research, and informed him of research done to date, including a GSK meta-analysis similar to the one he was proposing, which was completed, posted publicly on GSK’s website, and sent to and under consideration by FDA.⁶⁴ However, rather than pursue this avenue, Dr. Nissen proceeded with the publication of his manuscript, without GSK’s input.

As GSK has stated repeatedly, on May 3, 2007, GSK received an unsolicited copy of Dr. Nissen’s manuscript. GSK did not provide comments or any input on the manuscript and acted appropriately and responsibly in responding to the situation.

V. CONCLUSION

The Staff Report is neither comprehensive nor detailed in its analysis of safety issues concerning Avandia. The Staff Report did not address Avandia in light of the available scientific data and commentary, in the process ignoring the views of the FDA as a whole, numerous independent physicians who daily prescribe Avandia for their patients, and scientists who continue to study the effect of this medicine. GSK respectfully disagrees with the Committee's decision to publish a Staff Report with such errors of fact, omission, and inference. Government reports that review and analyze the safety and benefits of medicines that treat diseases like diabetes that affect millions of Americans should endeavor to present a fair, balanced and complete picture of the available evidence on the issue.

⁶³ *Id.*

⁶⁴ GSK102_000000401 & GSK102_000000402 (copy of May 2, 2007 letter emailed from GSK to Dr. Nissen produced to the Senate Finance Committee).

APPENDIX A

At the time Avandia® (rosiglitazone maleate) (“Avandia”) was approved, GSK and regulatory agencies believed it was important to develop the highest level of scientific evidence to assess its benefit-to-risk profile. Since the development and launch of Avandia, GSK has followed a rigorous program of scientific analysis to research both the safety and benefits of Avandia. GSK promptly initiated its regulatory post-marketing commitments for Avandia. GSK reported its findings to regulatory agencies, including the FDA, based on emerging clinical trial results and postmarket data regarding the cardiovascular profile of Avandia. GSK also made studies and postmarket data regarding Avandia available to scientists in the public domain in a variety of ways, including on the company’s Clinical Trial Register. The label for Avandia has undergone sequential changes to add cardiovascular safety information as new data has become available.

GSK’s commitment to an extensive scientific research program over many years, as well as GSK’s actions and communications with FDA regarding the cardiovascular safety profile of Avandia, is demonstrated in the following timeline.

AVANDIA TIMELINE

September 22, 1993: GSK submitted the initial Investigational New Drug Application (“IND”) for Avandia (BRL49653C) to enable clinical assessment of the safety and efficacy of the compound in patients with type 2 diabetes mellitus.

November 25, 1998: GSK submitted the original New Drug Application (“NDA”) 21-071 for Avandia Tablets to FDA. The original NDA included data on 4,327 subjects receiving Avandia (alone or in combination with other products), of whom 1,005 received Avandia for at least 12 months.

March 31, 1999: GSK submitted the 120 Day Safety Update Report to NDA 21-071. With this update, the NDA included data on 4,598 subjects receiving Avandia (alone or in combination with other products), of whom 2,061 received Avandia for at least 12 months, to support the initial approval of Avandia tablets in the U.S.

April 15, 1999: FDA provided GSK with a copy of the agenda for a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, as well as a copy of the Medical Officer’s Review⁶⁵ and Pharmacologist’s Summary of NDA 21-071.

⁶⁵ Medical Officer’s review of NDA 21-071-Rosiglitazone (AVANDIA®). HFD 510. April 2, 1999 (updated April 12, 1999).

April 22, 1999: FDA convened the Endocrinologic and Metabolic Drugs Advisory Committee to review Avandia, NDA 21-071.

May 25, 1999: Avandia was approved by the FDA. As part of the approval, GSK committed to design, initiate, sponsor, conduct, finish, and report the results of the “ADOPT” study (a post-approval study of the long-term efficacy and safety of Avandia).

August 20, 1999: GSK submitted to FDA a Preliminary Assessment Report regarding cardiac events observed in clinical studies with the use of Avandia in combination with insulin compared with insulin alone.

September 29, 1999: GSK submitted to FDA the full draft of the ADOPT protocol for FDA’s review and comment (IND 43,468; Serial No. 224). The protocol was subsequently discussed by FDA and GSK and recommended changes were made.

October 27, 1999: GSK submitted to FDA the Supplement sNDA (S-002), Changes Being Effected (“CBE”), to revise labeling describing fluid retention and exacerbation of congestive heart failure (“CHF”). See notation below, **July 11, 2000**, regarding FDA approval date of labeling change.

January 11, 2000: GSK submitted to FDA the final protocol for the ADOPT trial⁶⁶ protocol (also known as BRL49653C/048) to IND 43,468 (Serial No. 238).

February 8, 2000: GSK submitted to FDA the Supplement sNDA (S-004) to support the use of Avandia (4mg and 8mg) in combination with insulin.

May 26, 2000: GSK submitted to FDA the Supplement sNDA (S-006), CBE, to revise the labeling to add further safety data regarding fluid retention and exacerbation of CHF in patients at risk for heart failure, particularly among patients on insulin. See notation below, **February 8, 2001**, regarding FDA approval date of the labeling change.

July 2000: Avandia was approved by the European Commission. As part of the approval, GSK committed to conduct two clinical studies: a cardiovascular structure and function study in patients with New York Heart Association (“NYHA”) Class I and II chronic heart failure (“Study 211”) and a cardiovascular mortality/morbidity study of six years duration with Avandia in combination with either a sulfonylurea or metformin (the “RECORD” trial).

July 11, 2000: FDA approved Avandia product labeling to include in the Precautions section, among other changes, information that, “Since thiazolidinediones can cause fluid retention,

⁶⁶ Study 49653/048, “A Randomized, Double-blind Study to Compare the Durability of Glucose Lowering and Preservation of Pancreatic Beta-Cell Function of Rosiglitazone Monotherapy compared to Metformin or Glyburide/Glibenclamide in Patients with Drug-Naive, Recently Diagnosed Type 2 Diabetes Mellitus (2 Years).”

which can exacerbate congestive heart failure, patients at risk for heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure.”

February 8, 2001: FDA approved Avandia product labeling to include a new Warnings section, among other changes.

- The Warnings section included information that Avandia, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.
- In addition, the Warnings section added information regarding two U.S. trials of type 2 diabetics, in which Avandia plus insulin was compared with insulin therapy alone. Information was provided that, “In these clinical studies an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on AVANDIA and insulin combination therapy compared to insulin and placebo.”
- The Warnings section also included information that, “The use of AVANDIA in combination therapy with insulin is not indicated (see Adverse Reactions).”

February 8, 2001: FDA also provided GSK with an Approvable Action letter for the indication of the use of Avandia (4mg and 8mg) in combination with insulin requesting that additional information regarding cardiovascular events and fluid retention be provided.

July 2001: GSK partially funded the “DREAM” trial which was sponsored and carried out by independent investigators.⁶⁷ The DREAM trial was designed to determine if Avandia or ramipril (a cardiovascular drug) delayed the onset of diabetes in pre-diabetic patients compared with placebo and followed nearly 5,300 patients for an average of three years. The trial was also designed to examine cardiovascular event rates, including cardiovascular deaths, CHF, and ischemic heart disease events including myocardial infarction and stroke. See notation on **September 23, 2006**, regarding publication of results.

June 7, 2002: GSK submitted to FDA the Supplement sNDA (S-008), CBE, to revise the labeling to add further safety data regarding new information from postmarket reports of patients with unusually rapid weight gain; such patients should be assessed for excessive edema and CHF. See notation below, **December 3, 2002**, regarding FDA approval date of the labeling change.

⁶⁷ The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial was funded by the Canadian Institutes of Health Research (MCT41548), as well as Sanofi-Aventis, GlaxoSmithKline, and King Pharmaceuticals and all results were analyzed at the Population Health Research Institute at McMaster University, Hamilton, Ontario, Canada.

August 26, 2002: GSK submitted an amendment to the Avandia and insulin combination Supplement sNDA (S-004).

December 3, 2002: FDA approved Avandia product labeling to include in the Precautions section information that, “In postmarketing experience, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.”

January 3, 2003: GSK submitted to FDA a “15-day ADR Report: Initial Written Report” for an event of myocardial infarction which occurred in a patient enrolled in IND 43,468, Study 048 (the ADOPT trial). In the regulatory report that accompanied this submission, which was also sent to investigators for Institutional Review Board notification, GSK provided an analysis from the GlaxoSmithKline safety database regarding myocardial infarction.

February 27, 2003: FDA approved the indication of the use of Avandia (4mg and 8mg) in combination with insulin. The FDA and GSK discussed and agreed that the labeling adequately described information regarding increased incidence of CHF and other cardiovascular events associated with the use of Avandia (4mg and 8mg) in combination with insulin.

December 5, 2003: The GSK Global Safety Board reviewed the proposal to include information regarding non-CHF cardiac events in the Global Data Sheet (“GDS”)⁶⁸ for the Avandia plus insulin combination. The Global Safety Board requested relative risk be calculated for pooled non-CHF cardiovascular events in these patients.

January 20, 2004: The WHO Collaborating Center for International Drug Monitoring communicated with GSK regarding an analysis of thiazolidinediones and cardiac disease based on the experience with Avandia, pioglitazone (Actos®), and troglitazone as reported to the WHO database.⁶⁹ The WHO Programme communication explicitly stated, “From the definition it is clear that the signal is early, and a caveat document (encl.) is sent with the signal information to guide its use. Such early warning signals mostly need further work and evaluation before they should be used in public health action or information.”

February 12, 2004: GSK approved an amendment to the GDS regarding Avandia to include information related to non-CHF cardiovascular events for the Avandia plus insulin indication.

⁶⁸ The GDS is an internal GSK tool used to harmonize regulatory labeling across geographies.

⁶⁹ The report, “Thiazolidinediones and cardiac disease,” was published in the WHO ‘SIGNAL’ document and distributed to the 72 national centres of the WHO Programme for International Drug Monitoring.

April 2004: GSK formed an internal working group to consider approaches for analysis of cardiovascular events (both CHF and non-CHF, including ischemic events) across the Avandia randomized clinical trials dataset (all treatments).

June 2004: From June 2004, through December 2004, this internal working group met to develop a formal protocol and statistical plan.

June 30, 2004: The GSK Global Safety Board reviewed preliminary results of Study 211. The Global Safety Board agreed that analyses of relative risk of CHF and ischemic events for Avandia versus control subjects should be completed.

December 2, 2004: The GSK Global Safety Board reviewed and provided guidance regarding the development of the proposed protocol and statistical plan by the internal working group.

December 2, 2004: GSK submitted to FDA the final study report for Study 211 (IND 43,468; Serial No. 0481).

April 8, 2005: The GSK Global Safety Board reviewed the proposed protocol developed by the internal working group to conduct a meta-analysis of cardiovascular events (both CHF & non-CHF, including ischemic events) across 37 randomized clinical trials from the Avandia randomized clinical trials dataset.

June 21, 2005: GSK submitted to FDA the Supplement sNDA (S-016) to revise the labeling to add further safety data regarding new information regarding the observations of Study 211. See notation below, **April 21, 2006**, regarding FDA approval date of the labeling change.

August 11, 2005: GSK approved the final analysis plan to conduct a meta-analysis of cardiovascular events (both CHF & non-CHF, including ischemic events) across 37 trials from the Avandia randomized clinical trials dataset.

September 30, 2005: The GSK Global Safety Board reviewed the results of the meta-analysis of cardiovascular events (both CHF and non-CHF, including ischemic events) across 37 trials.

- The meta-analysis showed an overall incidence of ischemic cardiovascular events of 2.24% in Avandia patients vs. 1.71% in the pooled comparison group. This equates to a non-statistically significant estimate of excess risk of ischemic cardiovascular events of 29% associated with the use of Avandia.

October 7, 2005: GSK advised FDA of the availability of results from the meta-analysis of 37 double-blind, controlled clinical trials of Avandia. GSK transmitted to FDA a summary of information regarding this meta-analysis.

October 13, 2005: GSK formally submitted to FDA a summary of the results of the meta-analysis of 37 double-blind, controlled clinical trials of Avandia,⁷⁰ as well as a copy of GSK's analysis plan. These documents were submitted to IND 43,468 (Serial No. 0533).

December 15, 2005: On December 15, 2005, and April 26, 2006, GSK submitted to FDA the Supplement sNDA (S-019), CBE, to revise the labeling to add safety data regarding new postmarket report information regarding macular edema. See notation below, **June 16, 2006**, regarding FDA approval date of the labeling change. This supplement also contained proposed revision of labeling based on cardiovascular events in the October 13, 2005, meta-analysis submission. FDA administratively split this review of supplements on April 6, 2006, assigning S-021 to applications regarding new language of cardiac events.

December 23, 2005: GSK added the final study results of the Study 211 to the GSK Clinical Trials Register website containing data relating to Avandia. The results of the study were also later published in the *Journal of the American College of Cardiology*.⁷¹

January 2006: GSK initiated a second expanded meta-analysis, in order to include 5 additional clinical trials that had finished between September 2004, and August 2005, for a total of 42 randomized clinical trials. The results were available for review by GSK in March 2006.

January 2006: GSK retained i3 Drug Safety (Ingenix) to conduct a separate epidemiologic observational study, the "Balanced Cohort Study," to examine the specific endpoint of myocardial infarction and coronary revascularization events in over 30,000 diabetic patients using an independent managed care database.⁷²

March 27, 2006: GSK submitted to FDA information including the related datasets of the GSK meta-analysis of 37 clinical trials and the results of a full logistic and an exact logistic regression analysis in tabular format.

March 31, 2006: FDA informed GSK that there was an ongoing initiative at FDA to review the cardiovascular safety of thiazolidinedione drugs.

April 21, 2006: FDA approved Avandia product labeling to include in the Warnings section, among other changes, information based on Study 211 that observed that patients with NYHA Class I or II CHF treated with Avandia had a numerical increase in cardiovascular events compared with non-Avandia therapies.

⁷⁰ The "Avandia Cardiovascular Event Modeling" study.

⁷¹ Dargie HJ, et al., 49 *Journal of the American College of Cardiology*, 1696 (2007).

⁷² The "Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents" study.

- “Although no treatment difference in cardiac ejection fractions was observed, more cardiovascular adverse events were observed with AVANDIA treatment compared to placebo during the 52-week study.”
- The modified Warnings section presents the cardiovascular adverse events in these patients with NYHA Class I and II CHF including adjudicated CHF events and cardiovascular hospitalizations, and non-adjudicated ischemic adverse events.

May 9, 2006: GSK submitted the results of the second meta-analysis⁷³ to FDA in an Amendment to the pending Supplemental Application (S-021). This Amendment provided FDA with a summary of the results of GSK’s expanded meta-analysis of double-blind, controlled clinical trials of Avandia. This Amendment summarized the results from integration of 42 studies (after inclusion of 5 additional studies with their 2,651 additional patients to the original database of 37 studies). It also referenced the Balanced Cohort Study which was ongoing at the time. See also notation of **August 4, 2006**.

- The meta-analysis observed that the overall incidence of ischemic cardiovascular events was 1.99% in the Avandia patients vs. 1.51% in the pooled comparison group, with a hazard ratio of 1.31. This equated to a statistically significant excess risk of ischemic events of 31% associated with the use of Avandia.

June 16, 2006: FDA approved Avandia product labeling to include in the Precautions section, among other changes, information regarding macular edema based on postmarket reports.

August 4, 2006: GSK submitted to FDA a Supplemental Application (S-022). This sNDA provided the final report of GSK’s meta-analysis of 42 double-blind, controlled clinical trials of Avandia, as well as the final report of the observational Balanced Cohort Study. The sNDA, which also included draft labeling, provided FDA with GSK’s application seeking approval to incorporate the results of these two studies into the labeling for Avandia Tablets. On August 7th, the FDA notified GSK that it assigned the sNDA Supplement number (S-022).

- The Balanced Cohort Study in 33,363 patients showed that the incidence of ischemic cardiovascular events was 1.75 events per 100 patient years for use of Avandia versus 1.76 for other treatments. This analysis did not confirm the meta-analyses’ suggestion of a possible increase in ischemic cardiovascular risk. The results were later published.⁷⁴

⁷³ The “Avandia Cardiovascular Event Modeling Project” study. This is also described as the “Integrated Clinical Trials Analysis.”

⁷⁴ McAfee AT, et al., *supra* note 6.

(GSK subsequently conducted the “PharMetrics Study,”⁷⁵ a separate epidemiologic observational study using a different and larger care database.)

September 23, 2006: The results of the DREAM trial conducted by independent investigators were published in *The Lancet*.⁷⁶ Avandia was shown to be significantly superior to placebo in delaying the onset of diabetes.

- The publication reported that Avandia was associated with a higher risk of congestive heart failure events compared with placebo.
- There was no significant difference between Avandia and placebo regarding either the composite of all cardiovascular events, and there was no significant difference between Avandia and placebo regarding cardiovascular deaths or ischemic cardiovascular events, including myocardial infarction and stroke.
- The DREAM database was not made available by the independent investigators to GSK until February 2007.

October 24, 2006: GSK submitted responses to FDA’s requests for information about the Balanced Cohort Study.

October 27, 2006: GSK added the final reports of meta-analysis of 42 double-blind, controlled clinical trials of Avandia, as well as the report of the observational Balanced Cohort Study, to the GSK Clinical Trials Register website containing data relating to Avandia.

November 2, 2006: GSK submitted to FDA a response to a request for information about an earlier epidemiology study previously carried out by i3 Drug Safety (Ingenix) on thiazolidinediones.⁷⁷ GSK submitted the protocol and study report from i3 Drug Safety (Ingenix).

⁷⁵ The “Coronary Heart Disease Outcomes in Patients Receiving AntiDiabetic Agents in the PharMetrics Database” study. This balanced cohort analysis examined the incidence of myocardial infarction and coronary revascularization events in over 400,000 diabetic patients in an independent database. In contrast to the prior study, the head to head comparisons of Avandia versus other oral agents included a comparison of Avandia versus Actos®. This study showed that the incidence of ischemic cardiovascular events was similar for Avandia compared with other antidiabetic agents, and that the incidence was similar for Avandia compared with Actos®.

⁷⁶ The DREAM Trial Investigators, *supra* note 40.

⁷⁷ “Balanced Cohort Study of TZDs and other Anti-Diabetic Therapies and Coronary Heart Disease Outcomes” study. This study was published, Johannes CB et al. *Pharmacoepidemiology and Drug Safety*. 2007; 16:504.

November 8, 2006: GSK submitted to FDA a response to a request for additional data from the expanded meta-analysis including comparator group information and cardiovascular Serious Adverse Events (“SAEs”).

December 7, 2006: GSK submitted to FDA a response to a request for a dataset from the expanded meta-analysis including information on any patient who died.

December 7, 2006: The results of the ADOPT trial were published in *The New England Journal of Medicine*.⁷⁸ This randomized prospective clinical trial compared the effectiveness of monotherapy with Avandia versus metformin and the sulfonylurea, glyburide, on improvement and maintenance of blood sugar control in 4,360 newly diagnosed diabetics who were followed for an average of four years.

- Glyburide was associated with a lower risk of congestive heart failure compared with Avandia, whereas there was no significant difference between Avandia and metformin.
- There was no significant difference between Avandia and the comparator drugs regarding ischemic cardiovascular events, including fatal and nonfatal myocardial infarction and stroke, or deaths.
- See notations for **February 28, 2007**, and **April 16, 2007** regarding GSK submissions to FDA.

January 18, 2007: GSK submitted to FDA a response to the request for a table of additional information on each of the 42 studies in the expanded meta-analysis dataset.

February 2007: The DREAM database was provided by the independent investigators to GSK. An additional analysis of the DREAM database by GSK, which was published in a letter to the Editor of *The Lancet*,⁷⁹ also observed that similar numbers of patients treated with Avandia alone (as opposed to the combination of Avandia and ramipril) and placebo experienced cardiovascular death, myocardial infarction, and stroke. See notation for **April 16, 2007** regarding GSK submissions to FDA.

February 28, 2007: GSK submitted a Supplemental NDA to FDA in order to provide the Final Study Report for the ADOPT study consistent with the post-marketing commitment to support the use of Avandia as monotherapy in type 2 diabetes mellitus.

⁷⁸ Kahn, *supra* note 34.

⁷⁹ Krall, *supra* note 39.

March 7, 2007: FDA requested information about the ongoing cardiovascular outcome trial RECORD.

April 16, 2007: GSK submitted to FDA a response to a request for information on reports of ischemic heart disease in the ADOPT and DREAM studies.

April 19, 2007: GSK added the final study results of the ADOPT trial to the GSK Clinical Trial Register website.⁸⁰

April 20, 2007: FDA requested a meeting with GSK to hear GSK's perspective on myocardial ischemic events and the benefit-risk profile of Avandia, based mainly on the expanded meta-analysis in sNDA Supplement (S-022).

May 11, 2007: GSK submitted to FDA copies of three letters from the Data Safety Monitoring Board ("DSMB") for the RECORD study.

May 13, 2007: GSK submitted to FDA a copy of the charter of the DSMB for the RECORD study.

May 14, 2007: GSK submitted to FDA a copy of the Safety Interim Analysis Plan for the RECORD study.

May 16, 2007: FDA and GSK met to hear GSK's perspective on myocardial ischemic events and the benefit-risk profile of Avandia, based mainly on the expanded meta-analysis in sNDA Supplement (S-022).

May 18, 2007: GSK submitted to FDA the interim results of the RECORD trial. These interim results were also published.⁸¹

May 18, 2007: GSK submitted to FDA an Amendment to sNDA Supplement (S-022) to provide revised draft labeling to add a new subsection (on "Myocardial Ischemic Events") to the Warnings section of labeling for Avandia Tablets.

May 21, 2007: GSK submitted to FDA an Amendment to sNDA Supplement (S-022) to provide a proposal for a Risk Management Plan to address the potential for myocardial ischemic events in patients treated with Avandia.

⁸⁰ The DREAM trial is not posted on the GSK Clinical Trial Register website because it was not sponsored by GSK.

⁸¹ Home PD, et al., 357 *The New England Journal of Medicine*, 1 (2007).

June 4, 2007: Non-approvable letter sent to GSK. FDA concluded that pooled data require further analysis to adequately convey potential risk for increased cardiac ischemia. FDA identified subgroups of patients (e.g., patients using nitrates, ACE-inhibitors, insulin, or metformin) that may be particularly vulnerable to ischemic events. Further analyses of subgroups needed. Letter specifically requested data from studies included in Nissen meta-analysis not included in ICT; withdrawals/discontinuation data from ADOPT; use of nitrates and ACE-inhibitors at baseline in ADOPT and DREAM; primary datasets for DREAM trial; and data from on-going RECORD and BARI-2D.

July 30, 2007. Advisory Committee considered submissions from FDA, GSK, and the public and recommended the continued marketing of rosiglitazone.

August 14, 2007: Boxed Warning on CHF added to label for thiazolidinediones.

November 14, 2007: Boxed Warning on Myocardial Ischemia

- Boxed Warning states that available data on the risk of myocardial ischemia were “inconclusive”.