

**Statement of Moncef Slaoui, PhD, Chairman
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**Testimony before the House Committee on Oversight and Government Reform
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Mr. Chairman, Ranking Member and Members of the Committee: Good morning, my name is Dr. Moncef Slaoui, and I am the Chairman of Research & Development for GlaxoSmithKline, or GSK. GSK is one of the world's leading research-based pharmaceutical and healthcare companies. I'm here to share with you GSK's extensive and ongoing efforts to research both the safety and the benefits of Avandia®, an important medicine that has been proven to help patients fight the devastating effects of type 2 diabetes.

My colleagues and I at GSK strongly believe that the overall safety of Avandia® is comparable to other available oral anti-diabetes medicines, and that Avandia® provides substantial benefit for diabetic patients. Our commitment to Avandia® patients is demonstrated by our extensive and continuous study of this medicine before and after its approval by regulatory agencies worldwide.

An objective look at GSK's extensive commitment to patients will demonstrate:

- GSK has initiated the most comprehensive and rigorous program of scientific analysis for any oral anti-diabetes medicine available to patients today, with experience in over 52,000 patients. By engaging in this extensive scientific research program over many years, GSK has already undertaken what Congress has suggested all pharmaceutical companies should do; namely, rigorous scientific analysis of a medicine's safety and benefit after it is approved for wider use in patients.
- The data collected from this wide variety of studies – including real-life experience and long-term clinical trials designed to meet the highest standards of sound science – demonstrate that Avandia® has a comparable cardiovascular profile to the two most commonly prescribed oral anti-diabetes medicines, recognizing the risk of congestive heart failure acknowledged for all medicines in the TZD (thiazolidinedione) class.
- Over time, GSK has faithfully and in a timely way reported its findings to regulatory agencies including the Food and Drug Administration (FDA). GSK also made data available to scientists in the public domain in a variety of ways, including postings on the company's Clinical Trial Register.
- Questions about Avandia®'s safety profile are best answered by prospective clinical trials such as ADOPT, DREAM and the RECORD cardiovascular outcomes trial, a large long-term clinical trial in people with diabetes which is specifically designed to look at cardiovascular outcomes.

Our view is that decisions on the safety of medicines should be made on the basis of science and an objective examination of all the data available. The sum of the science, including two recently completed long term prospective clinical trials ADOPT and DREAM as well as the new interim data available from the RECORD trial, establishes that Avandia®, when compared to other widely used anti-diabetes medicines, is not associated with an increased risk of death, including death from a cardiovascular event.

The most important message today for the Committee and the public is this: The cardiovascular profile of Avandia® is comparable to that of the two other oral anti-diabetes medicines that are most widely used in the United States today.

On May 21st, *The New England Journal of Medicine* published an article (“NEJM article”) raising concern about the safety of Avandia®, which has generated controversy among scientists and anxiety among diabetes patients. The article contained the results of a meta-analysis, a type of statistical analysis that is useful for generating hypotheses but which has significant limitations and lacks the rigor required to reach definitive conclusions about adverse events. This is especially so when the analysis deals with an issue that has a very low event rate. Acknowledging these limitations, the editorial accompanying the study stated: “*A few events either way might have changed the findings for myocardial infarction or for death from cardiovascular causes. In this setting, the possibility that the findings might be due to chance cannot be excluded.*”

On May 23rd, *The Lancet*, an independent medical journal, responded to this controversy with an editorial statement. Here is what *The Lancet* said:

Until the results of RECORD are in, it would be premature to overinterpret a meta-analysis that the authors and NEJM editorialists all acknowledge contains important weaknesses. To avoid unnecessary panic among patients, a calmer and more considered approach to the safety of Avandia is needed. Alarmist headlines and confident declarations help nobody.

A similar position has also been taken in a joint statement by the American College of Cardiology, the American Heart Association, and the American Diabetes Association.¹ GSK strongly agrees with these statements and stands firmly behind the safety of Avandia® when used appropriately.

We face a world-wide epidemic of type 2 diabetes. Diabetic patients are at risk for many major complications such as kidney failure, limb amputation, nerve injury, and blindness. Importantly, diabetics are at very high risk for cardiovascular disease, and in fact, it is the main cause of death in these patients. Diabetes gets progressively worse over time, with

¹ Statement from the American College of Cardiology, the American Heart Association, and the American Diabetes Association related to NEJM article, “Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes”
<http://www.acc.org/media/releases/highlights/2007/may07/rosiglitazone.htm>

complications developing over many years. We know from outcome clinical studies that effective treatment of diabetes requires intensive, long term, day-to-day control of blood sugar levels to save lives and significantly reduce the risks of cardiovascular and other complications.

Given the seriousness of diabetes, it is critical to understand how any treatment affects cardiovascular disease in these patients. Since the development and launch of Avandia®, GSK has diligently followed a thorough, long-term program of scientific study, aimed at continuously assessing cardiovascular events in treated patients.

Two specific and different cardiovascular events in diabetic patients will be discussed today: congestive heart failure and ischemic cardiovascular disease.

First, let's discuss congestive heart failure.

Avandia®, and other medicines in its class, increase the risk of the serious problem of congestive heart failure. Diabetics are known to be at risk of developing congestive heart failure, a weakening of the heart's normal pumping power. In this setting, the increased retention of fluid can lead to edema and symptoms of congestive heart failure. Drugs in the same class as Avandia®, including Actos®, can lead to retention of fluid, promotion of edema and hence development of congestive heart failure. Prior to marketing Avandia®, GSK and the FDA recognized the potential for edema and the serious side effect of congestive heart failure. For this reason, the original Avandia® product information label from May 25, 1999, specifically reported that edema had been seen in some patients and that Avandia® was not indicated in patients with moderate or severe symptoms of heart failure.

Since then the label has undergone six changes and warnings as new information has become available from clinical studies regarding congestive heart failure. We are in discussions with the FDA to further enhance the prominence of such heart failure warnings on Avandia®'s label and that of other medicines from the same class.

Now I would like to turn to the question that is our major focus today: Does Avandia® increase the risk of ischemic cardiovascular events, heart attacks and cardiovascular related death in diabetic patients? We believe the data show it does not.

At the time Avandia® was approved, GSK and regulatory agencies believed it was important to develop the highest level of scientific evidence to assess its cardiovascular benefit-to-risk profile. Accordingly, in 2000 and 2001, we started two large, prospective, long-term clinical trials, respectively, the ADOPT and the RECORD studies. Both trials allow us to compare over a period of 3 to 4 years the safety of Avandia® to that of the two most widely used oral anti-diabetes medicines in more than 4000 patients each. Specifically, the primary goal of RECORD is to compare the risk of cardiovascular death and cardiovascular hospitalization, including heart attack, stroke, and congestive heart

failure in patients using Avandia® to the two other most commonly prescribed oral anti-diabetes medicines.

While awaiting the ultimate scientific evidence from the prospective clinical trials including RECORD, and in order to further study Avandia®'s cardiovascular benefit-to-risk profile, GSK has diligently and proactively used other available methods which can provide useful but less definitive information. I will now take you through a chronological description of the key studies and analyses conducted by GSK in this regard.

Let's begin with the meta-analyses that GSK itself has conducted, posted publicly, and communicated to the FDA. GSK performed patient-level meta-analyses of safety data from multiple clinical trials primarily designed to assess end points other than Avandia®'s cardiovascular safety profile. Because of their different focus and the small size of the individual studies, we knew that this approach could NOT yield conclusive information, but rather, could generate hypotheses to be tested using more scientifically robust strategies.

In September, 2005, results from the first meta-analysis became available. This meta-analysis, which pooled data from 37 clinical trials completed prior to September, 2004, compared 6976 patients on Avandia® and 4610 patients on other treatment regimens including no treatment, metformin, sulfonylureas, and insulin. This analysis showed an overall incidence of ischemic cardiovascular events of 2.24% in Avandia® patients versus 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®. The data from this first meta-analysis were officially communicated to the FDA in October, 2005, as well as to the independent Data Safety Monitoring Boards of the various ongoing clinical trials with Avandia®. This potential excess cardiovascular risk prompted GSK to perform a second meta-analysis as well as a separate epidemiologic study, called the Balanced Cohort Study, and both studies were initiated in January, 2006.

The second meta-analysis, that was initiated in January, 2006, was conducted in order to include 5 studies that had finished between September, 2004, and August, 2005. This second analysis included a total of 42 separate randomized clinical trials that compared 8,604 patients on Avandia® and 5,633 patients on other treatment programs. The results were reviewed in March, 2006. The overall incidence of cardiovascular events was 1.99% in Avandia® patients versus 1.51% in the pooled comparison group, with a hazard ratio of 1.31. This equates to a statistically significant excess risk of ischemic events of 31% associated with the use of Avandia®. This hazard ratio is in the same direction as the NEJM article's meta-analysis.

Like meta-analyses, balanced cohort studies do not provide the same high level of scientific evidence that is provided by a large randomized clinical trial. However, they complement the findings of clinical trials because they represent what happens in the

“real world setting.” Using an independent managed care database, the Balanced Cohort Study was a real world observational study that compared diabetic patients who began treatment with Avandia®, with metformin, a sulfonylurea, or combinations between 2000 – 2004. The analysis examined the specific ischemic endpoint of heart attack and coronary revascularization events (such as coronary bypass surgery or angioplasty). This analysis in 33,363 patients showed that the incidence of ischemic cardiovascular events was 1.75 events per 100 patient years for use of Avandia® vs. 1.76 for other treatments. Thus, this study of over 30,000 patients did not confirm that the meta-analyses’ signal of a possible increase in ischemic cardiovascular risk was accurate.

These data were communicated to the FDA in early May, 2006, as well as to other regulatory agencies world-wide, and the results of both this meta-analysis and the Balanced Cohort Study were reviewed with the FDA in a formal submission in early August, 2006. In addition, these data were again communicated with the Data Safety Monitoring Boards of the various ongoing trials using Avandia®, including RECORD. It is important to note that the Data Safety Monitoring Boards are entitled and expected to regularly run an unblinded analysis of the safety of patients enrolled in a clinical trial and decide to either pursue or stop the trial depending on what safety data they saw from the analysis. The decisions of the independent Data Safety Monitoring Boards’ panels to continue the trials conduct unchanged clearly signaled to us that no significant cardiovascular risk was identified in these ongoing large cardiovascular outcome trials.

GSK has and will continue to perform meta-analyses of its databases as further clinical trial data become available because they are helpful in generating hypotheses which can then be further assessed using more accurate scientific strategies. However, GSK also concurs with the NEJM article’s own assessment of the serious limitation of a meta-analysis: *“a meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest.”*

Three such large, long term, prospective clinical trials allow scientifically robust conclusions about the safety of Avandia®. Two of these trials were completed in the later part of 2006 shortly after our second meta-analysis, and the third one, the RECORD trial, is still ongoing.

The ADOPT trial, which GSK launched in 2000, studied 4,360 newly diagnosed diabetic patients over a follow-up period of four to six years. The primary purpose of this randomized controlled trial was to compare the effectiveness of Avandia® versus metformin and glyburide on improvement and maintenance of blood sugar control in 4,360 newly diagnosed diabetics. Avandia® was shown to be significantly superior in maintaining control of blood sugar levels compared to the broadly used oral diabetes medicines metformin and glyburide. This superiority of long-term blood glucose control compared to other classes of diabetic agents has not been tested with the use of Actos®, the other drug in the same class as Avandia®. This study, and many others, has clearly established the benefits of Avandia® in treating diabetes patients. Data from the ADOPT trial were published in the *New England Journal of Medicine* in 2006.

In addition to efficacy, ADOPT also allowed us to compare the cardiovascular benefit-to-risk profile of these widely used oral anti-diabetic medicines. An analysis of cardiovascular deaths, myocardial infarctions, and a composite end point of cardiovascular death, heart attack, and stroke showed that the three medicines are comparable. The ADOPT clinical trial data were submitted to the FDA in February 2007, and recently published in a letter to *The Lancet*.

In September, 2006, the DREAM trial was published in *The Lancet* and the results became available to GSK. This large randomized prospective clinical trial, launched in 2001 by independent investigators, studied nearly 5,300 pre-diabetic patients with 3 year follow-up. It was designed to determine if either ramipril, a drug with well-established benefits on cardiovascular events, or Avandia® delayed the onset of diabetes in comparison with placebo. The trial also collected cardiovascular safety information. The independent investigators reported that the rates of cardiovascular death, heart attack, and stroke were similar in the Avandia® groups versus the placebo groups, whereas congestive heart failure was, as expected, more common.

In February, 2007, once the DREAM database became available to GSK scientists, a further ad hoc refined analysis was performed by GSK and provided to the FDA in May, 2007. These data, which were published in the May 30th letter to *The Lancet*, clearly show that Avandia® has no increased risk of heart attack, stroke, or cardiovascular death as compared to placebo treatment in pre-diabetic patients.

Finally, in May, 2007, GSK decided, in concert with the RECORD study DSMB and Steering Committee and with the knowledge of the EMEA and the FDA, to conduct an unblinded safety interim analysis of the cardiovascular outcome RECORD trial. This interim safety analysis provides the highest quality scientific evidence on the cardiovascular safety of Avandia®. The RECORD trial is a large prospective randomized clinical trial in over 4,400 diabetes patients currently followed up for an average of 4 years. It is designed to specifically examine the risk of adding on Avandia® to either metformin or a sulfonylurea versus combination metformin and sulfonylurea therapy regarding the primary endpoint of cardiovascular death and cardiovascular hospitalization, including heart attack, stroke, and congestive heart failure. The RECORD trial is also specifically designed to examine the risk of death from any cause.

In the RECORD trial, all reported cardiovascular events are independently evaluated and adjudicated by an independent committee that is blinded to which drugs the individual is taking in the study, making these data substantially more accurate than the spontaneously reported – but not adjudicated - serious adverse events reports that make up the events considered in the meta-analyses that I discussed earlier with you. The data from the interim analysis have been submitted as a publication to the *New England Journal of Medicine*.

These interim data show that Avandia®, metformin, and sulfonylurea have a comparable cardiovascular safety profile and are consistent with the results observed in the two other large prospective clinical trials, ADOPT and DREAM. Taken together, data from these three independent prospective clinical trials fail to support the hypothesis generated by any of the meta-analyses.

The totality of the science I have shared with you today establishes that Avandia®, when compared to other widely used anti-diabetes medicines, is not associated with an increased risk of death, including death from a cardiovascular event. Furthermore, all data presented today also show that Avandia®'s overall cardiovascular safety profile is comparable to that of the two most widely used oral anti-diabetes medicines: metformin and the sulfonylureas. We have consistently shared our data with regulators and others to help better inform physicians about the safety of Avandia®, so they can make the right treatment choices for their patients.

In addition to our confidence in the overall safety profile of Avandia®, my colleagues and I believe Avandia® provides substantial benefit for diabetic patients over the long-term in controlling blood sugar. For these patients, having multiple treatment options to manage a progressively debilitating disease like diabetes is critical. Two and three medicines are often needed to help these patients control their blood sugar. If left uncontrolled – as is the case for two-thirds of diabetic patients – the health costs can be catastrophic in terms of heart disease, blindness, amputations, kidney disease and other complications.

Thank you. I look forward to answering any questions you may have.