Oral Testimony to the House Committee on Oversight and Government Reform

My name is Steven E. Nissen, M.D. I am Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic and the Immediate Past-President of the American College of Cardiology (ACC). My testimony does not reflect the views of either Cleveland Clinic or the ACC.

I have been asked to summarize for the Subcommittee the sequence of events and the scientific basis for our manuscript describing the potential cardiovascular risks of Avandia.

In September 2006, a clinical trial called DREAM was published in the British medical journal, the Lancet. In this study, patients at high risk for developing diabetes were assigned to receive either Avandia or an inactive placebo. Avandia did indeed reduce the incidence of new onset diabetes. However, the DREAM study also showed a numerical excess of heart-related adverse events, including 15 heart attacks in the Avandia group, compared with 9 in the placebo group. The number of heart attacks was too few to reach statistical significance, but they were trending in the wrong direction. This was potentially important observation because the reason for giving a drug to prevent diabetes is to reduce the complications of diabetes, the most serious of which is heart disease.

Then, in December 2006, a clinical trial known as ADOPT was published in the New England Journal of Medicine. This study was designed to show whether Avandia had a more durable effect at reducing blood sugar than two generic diabetes medications. The study showed a more long-lasting reduction in blood sugar with Avandia, but heart-related complications were also trending in the wrong direction. The heart attack rate was 33% greater in the Avandia-treated patients, but again, there were too few events to reach statistical significance.

After reviewing DREAM and ADOPT, I was concerned, because these were the only long-term, large scale clinical trials comparing Avandia with other therapies, and both studies showed an excess of heart attacks.

When you have several small or medium sized clinical trials that are insufficient to answer a scientific question, the logical next approach is to combine these trials to try to address the issue. The process is known as a meta-analysis. Using this method, I asked one of my colleagues, a statistician, to combine DREAM and ADOPT, and we noted a 40% excess of heart attacks, which was not statistically significant, but showed an strong trend in the wrong direction, which was approaching statistical significance. This observation was particularly concerning, because heart disease is highly prevalent in diabetics, comprising between 65% and 80% of all diabetic deaths. A diabetes drug that may increase the risk of heart disease would present a potentially important public health concern.

We sought more data to objectively address this scientific question. Eventually, we located on the FDA website, the original group of clinical trials submitted to the Agency to support approval of the drug in 1999. There were 5 clinical trials comparing Avandia to other diabetes drugs or placebo. We again noted that there were more heart-related complications in the Avandia treatment group in these initial clinical trials. But we still did not have enough clinical trial data to form any reasonable scientific conclusions.

Eventually in late April 2007, we discovered a GlaxoSmithKline website that disclosed basic information and summary results for clinical trials conducted by the company. Now we had access to the heart attack and death rates for all 42 relevant Avandia clinical trials completed before or after drug approval. We completed the meta-analysis, which showed a 43% excess incidence of heart attack in Avandia-treated patients, which was statistically significant with a p value of 0.03. A p value of 0.03 means that there is a 97% probability that the results of the study are not due to chance alone. We submitted a manuscript reporting our findings to the New England Journal of Medicine, where the manuscript was peer-reviewed and published on-line on May 21, 2007.

In our manuscript, we were careful to point out the strengths and limitations of our analysis. Because our access to data was limited to publicly available clinical trial data, we could not analyze original patient-level information. In addition, as we pointed out, a meta-analysis is always less convincing than a large prospective trial designed to answer a specific scientific question. Nonetheless, we thought the findings were sufficiently important to warrant prompt publication and concluded that "Until more precise estimates of the cardiovascular risk of this treatment can be delineated in patients with diabetes, patients and providers should carefully consider the potential risks of rosiglitazone in the treatment of type 2 diabetes."

The same 42 trials that we included in our analysis are available to the company and to the FDA. Because both of these organizations have access to raw patient data, they can perform more statistically powerful analyses, which can help clarify the extent of the risk. GSK has reported the basic results of their own patient-level meta-analysis on their clinical trials website, which confirms a statistically significant increase in heart-related complications in patients who received Avandia. The FDA also recently announced that their own internal analysis of patient-level data confirms an "approximately 40%" excess of heart related complications. However, neither the GSK, nor FDA analyses have been published, and it is therefore not possible to directly compare the results for all three analyses.

I look forward to discussing these findings and the policy implications with the Committee during the course of today's hearings.