111TH CONGRESS
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STAFF REPORT ON GLAXOSMITHKLINE AND THE DIABETES DRUG AVANDIA

PREPARED BY THE STAFF OF THE

COMMITTEE ON FINANCE
UNITED STATES SENATE

MAX BAUCUS, *Chairman*
CHUCK GRASSLEY, *Ranking Member*

JANUARY 2010

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CONTENTS

EXECUTIVE SUMMARY

This staff report was developed over the last 2 years by U.S. Senate Committee on Finance investigators who reviewed over 250,000 pages of documents provided by GlaxoSmithKline (GSK/the Company), the Food and Drug Administration (FDA), the University of North Carolina, and others. Committee investigators also conducted numerous interviews and phone calls with GSK, the FDA, and anonymous whistleblowers.

Committee staff began this investigation in May 2007 after a study was published in the *New England Journal of Medicine,* showing a link between the diabetes drug Avandia (rosiglitazone) and heart attacks. However, the reviewed evidence suggests that GSK knew for several years prior to this study that there were possible cardiac risks associated with Avandia. As a result, it can be argued that GSK had a duty to warn patients and the FDA of the Company's concerns. Instead, GSK executives attempted to intimidate independent physicians, focused on strategies to minimize or misrepresent findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that a competing drug might reduce cardiovascular risk.

When an independent scientist sought to publish a study in 2007 pointing out the cardiovascular risk of Avandia, GSK acquired a leaked copy of that study from one of its consultants prior to the study being published. The company's own experts analyzed the study, found it to be statistically reliable, and then attacked the soundness of that study in press releases and public comments. GSK also sought to counter the study's findings by quickly releasing preliminary results from its own study on Avandia, even though the company's internal communications established that its study was not primarily designed to answer questions about cardiovascular risk.

INTRODUCTION

For the past 4 years, the staff of the Senate Committee on Finance (Committee) has been examining allegations that pharmaceutical companies attempt to manipulate science to improve the marketability of drugs, potentially at the expense of public safety. These allegations include intimidating scientists, ghostwriting studies for academic researchers, suppressing studies that may show that a drug could be dangerous, and selecting data to publish results that favor one product over another.

In November 2007, the Committee reported on the intimidation of Dr. John Buse, a professor of medicine at the University of

North Carolina (UNC) who specializes in diabetes.[1] Based partly on internal documents from GSK, the Committee reported on what appeared to be an orchestrated plan by GSK to stifle the opinion of Dr. Buse in 1999. At that time, Dr. Buse argued at several medical conferences and in letters to the FDA that GSK's diabetes drug Avandia may cause cardiovascular problems.[2]

According to GSK emails made available to the Committee, GSK executives labeled Dr. Buse a "renegade" and silenced his concerns about Avandia by complaining to his superiors at UNC and threatening a lawsuit. The call to Dr. Buse's superiors was made by Dr. Tachi Yamada, then GSK's head of research. In discussions with Committee investigators, Dr. Yamada denied that his call was meant to intimidate Dr. Buse. Instead, Dr. Yamada argued that he had made the call to determine if Dr. Buse was making legitimate statements or if he was possibly on the payroll of a GSK rival.

Dr. Yamada also made a call to the University of Pennsylvania (Penn) regarding two physicians who were about to publish a case study that Avandia may have caused liver problems in one of their patients.[3] Committee investigators contacted the two Penn physicians. Both physicians chose to remain anonymous because of concerns about possible retaliation by pharmaceutical companies.[4]

In hindsight, both physicians agree that Avandia probably does not cause liver problems. However, in 1999 Avandia was a new drug and the two physicians wanted to publish a report on their patient who had liver failure while on Avandia. Both physicians also said that the calls placed by GSK officials, including Dr. Yamada, were highly unprofessional and had a chilling effect on their professional activity.[5]

Commenting on the calls by GSK, one of the two physicians told Committee investigators, "It was really ridiculous. It was a case report and I had no intention of bringing down GSK. I just wanted people to know." The physician added, "It left a really bad taste in my mouth. After that happened, I said that I would never work for a drug company."[6]

Also commenting on the calls from GSK, the other physician told Committee investigators, "I have never encountered anything like this in my career. I don't even know how [GSK] knew that we were publishing. It's the kind of thing you imagine happening on TV."[7]

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[1] Committee Staff Report to the Chairman and Ranking Member, Committee on Finance, United States Senate, November 2007, "The Intimidation of Dr. John Buse and the Diabetes Drug Avandia."

[2] *Id.*

[3] According to GSK internal emails, Dr. Yamada placed a call to senior officials at the University of Pennsylvania Medical School after receiving the following email on August 4, 1999, from a GSK executive:

> Tachi, I need you to place another call to your contacts at U Penn. The situation is that Dr. NAME REDACTED is apparently on the Takeda speaker's circuit. He is reported to be speaking about the case and implicating Avandia. Obviously, this is not in anyone's best interest.

The following day, Dr. Yamada responded:

> What exactly do you want me [sic] ask for? Obviously, we are not going to be able to prevent Dr. NAME REDACTED from speaking on behalf of Takeda. I would be happy to speak with either NAME REDACTED (Dept. Chair) or NAME REDACTED (Hepatology Chief) but we need to be clear on the message we want to send.

[4] Staff interviews, December 2007.

[5] *Id.*

[6] *Id.*

[7] *Id.*

In an interview with Committee investigators, Dr. Yamada stated that he had no intention of intimidating the two physicians at Penn, and that he had merely placed the call because he was concerned that Avandia may cause liver problems.

In a December 2007 floor speech, Senator Grassley revealed that Dr. Steve Haffner, a professor of medicine at the University of Texas Health Sciences Center, San Antonio, and a consultant for GSK, leaked to GSK the draft of a study critical of Avandia that was to appear in the *New England Journal of Medicine (NEJM).*[8] Dr. Haffner was entrusted with a confidential copy of the manuscript draft because he was peer-reviewing the study for the *NEJM*. The study's lead author, Dr. Steven Nissen, professor of cardiology at the Cleveland Clinic, found that Avandia was associated with a 43-percent increased risk of heart attacks, one of the main health outcomes physicians hoped to avoid by treating diabetic patients with medication.[9]

According to documents produced by GSK, the leaked manuscript was widely disseminated within the Company, and allowed GSK to launch a public relations plan to protect Avandia, a multi-billion dollar product.[10] The Committee staff reviewed documents showing that over 40 executives at GSK received and/or learned of the results in the leaked study, including then CEO Dr. Jean-Pierre Garnier; head of research, Dr. Moncef Slaoui; Vice President of Corporate Media Relations, Nancy Pekarek; and GSK Senior Advisor, Sir Colin Dollery.[11]

Before Dr. Nissen's study on Avandia was published, GSK's statistical experts were examining the study for potential flaws. In addition, GSK officials were drafting "key messages" to undermine the main conclusion of the Nissen study. GSK had already published several large trials on Avandia (rosiglitazone) including studies named ADOPT and DREAM. After Nissen's study was published, GSK began publicly referencing those trials, as well as another trial called RECORD, in what appeared to be an effort to further repudiate any link between Avandia and heart attacks. RECORD is a study GSK had been conducting for several years. GSK later published the interim results of the RECORD trial in what appeared to be an attempt to cast doubt on Nissen's results.

However, internal GSK emails indicate that GSK executives, not the study's independent steering committee, made the final decision to publish the RECORD trial results. Further, based on a review of emails, it can be argued that the authors of the RECORD trial appeared more concerned about countering claims that Avandia may be associated with heart attacks, than in trying to understand the underlying science. While circulating a draft of a manuscript on the RECORD trial, one of the authors wrote to his

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[8] Stephanie Saul, "Doctor accused of leak to drug maker," *The New York Times,* January 30, 2008.

[9] Steven E. Nissen et. al. "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes" the *New England Journal of Medicine,* May 21, 2007.

[10] In 2006, global sales of Avandia reached nearly $3.4 billion. Citation: Gardiner Harris, "Report Backs Up Warnings About Drug Avandia," *The New York Times,* July 27, 2007.

[11] Letter from Daniel F. Donovan III, counsel to GSK, to Senator Grassley, dated May 23, 2008.

colleagues, "[W]hat's to stop [Nissen] adding the events from RECORD to his meta-analysis and re-enforcing his view?" [12]

Further, after the authors of the RECORD study submitted their paper to the *NEJM,* one of the peer reviewers and several of the *NEJM* editors replied, "an explanation for the continued use of [Avandia] is needed in this manuscript." [13]

Committee investigators also learned that GSK was aware since at least 2004 that the RECORD trial was statistically inadequate, or "underpowered" [14] to answer questions regarding cardiovascular safety. Such "inconclusive" results could be favorable to GSK and the marketing strategy for Avandia. Further, experts were advising GSK since 2004 about the possible biological mechanisms related to why Avandia may cause an increased risk for heart attacks. However, GSK appeared eager to design studies to prove that Avandia was safer than its competitor ACTOS (pioglitazone), which is manufactured by Takeda.

At a July 30, 2007, safety panel on Avandia, Food and Drug Administration (FDA) scientists presented an analysis estimating that Avandia use was associated with approximately 83,000 excess heart attacks since the drug came on the market.[15] Had GSK considered Avandia's potential increased cardiovascular risk more seriously when the issue was first raised in 1999 by Dr. Buse, as well as by some of their own consultants in later years, some of these heart attacks may have been avoided.

RESPONSE TO THE NISSEN STUDY

In March 2007, GSK held a meeting with company officials and academic advisors to discuss several studies on Avandia and its cardiac risks and benefits.[16] Several presentations were made about studies on Avandia's possible cardiac risk. During the discussion of a GSK meta-analysis (integrated study) and a study GSK commissioned by Ingenix, GSK noted that the academic advisors stated the following:

> Dr. NAME REDACTED commented that the [cardiovascular] effect seen in the Integrated Clinical Trials Analyses with rosiglitazone was small but real, and that it is counter to the proposed [cardiovascular] benefits associated with Avandia. Dr. NAME REDACTED agreed, noted that all data point to rosiglitazone having a hazard ratio greater than unity. . . . Dr. NAME REDACTED summarized the discussion on the Integrated Clinical Trials data by stating that rosiglitazone causes weight gain and edema, leading to a greater number of events.[17]

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[12] Email from John McMurray to Nigel Jones et al., dated May 29, 2007.

[13] Letter from the *New England Journal of Medicine* to Philip H. Home, M.D., dated June 1, 2007.

[14] A study is underpowered if it does not meet the statistical requirements to adequately measure a medical outcome or study endpoint.

[15] FDA, "Assessment of the cardiovascular risks and health benefits of rosiglitazone," presented July 30, 2007. Estimate presented publicly at FDA advisory committee meeting.

[16] Internal GSK report, "GSK Diabetes Franchise Cardiology Advisory Board," meeting held March 1–2, 2007, report dated March 16, 2007.

[17] *Id.*

Moreover, during the discussion of the DREAM [18] trial, a cardiologist from Stanford stated:

> [T]he diabetes prevention afforded by rosiglitazone was very impressive, but there was no cardioprotective benefit. **He then asked what the point of diabetes prevention is if there is no cardiovascular benefit.**[19] [Emphasis added]

When discussing ADOPT,[20] the academic advisors concluded that, "The data in ADOPT and DREAM as well as in the CV Clinical Trials are consistent in indicating a signal for heart failure and ischemic events." According to GSK interal documents, GSK's experts were discussing problems with DREAM as early as 2006.[21]

Around this same time, Dr. Steven Nissen began studying the potential cardiac risks of Avandia, by reviewing data found in previously published studies. He placed several requests to GSK asking for patient level data on several studies published about Avandia. However, GSK would provide the requested data only if Dr. Nissen agreed to use a GSK statistician for the analysis.[22] Dr. Nissen refused to use the Company's statistician, citing a need to maintain independence.[23]

On May 2, 2007, Dr. Nissen submitted an analysis of 42 published and unpublished clinical trials on Avandia to the *NEJM* for peer review and publication. *NEJM* then sent confidential copies of the study to several independent experts, including Dr. Steve Haffner, to peer review the Nissen study. According to *NEJM*, peer reviewers must acknowledge in writing that the material they are reviewing is confidential, not to be shared with others, and is to be destroyed or returned to the medical journal after a review is completed.[24]

However, the very next day, May 3, 2007, Dr. Haffner faxed Dr. Nissen's unpublished study to a GSK executive. Dr. Haffner wrote "confidential" on the fax cover sheet and checked a box marked "urgent." [25]

LEAKED MANUSCRIPT AND A SCRAMBLED DEFENSE

One day after receiving the unpublished study from Dr. Haffner, GSK produced a detailed, 8-page analysis of Dr. Nissen's paper,

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[18] DREAM is an acronym for "The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication." DREAM is an international, multi-center, randomized, double-blind diabetes trial involving 5,269 patients from 21 countries. The DREAM study was conducted by the Population Health Research Institute and published in the middle of 2006.

[19] Internal GSK report, "GSK Diabetes Franchise Cardiology Advisory Board," meeting held March 1–2, 2007, report dated March 16, 2007.

[20] ADOPT is an acronym for "A Diabetes Outcome Progression Trial." ADOPT is a randomized, double-blind, parallel-group study conducted on ~3,600 drug-naive patients designed to measure the efficacy of rosiglitazone in controlling the glycemic levels of Type 2 diabetes patients.

[21] Internal GSK slide show, "DREAM: Results of the Rampiril Arm," undated but several slides state "updated Sept 6/06." One particular slide titled, "DREAM vs. Previous Trials," notes that DREAM "was low power to detect differences in CVD events (short duration, low risk participants)." The summary and conclusions slide on DREAM finds that the study had "too few events to draw any conclusion re the effect on other CV events or death."

[22] Internal GSK emails, dated May 3, 2007. "I have made oit [sic] clear in my letter of Feb 26 [to Dr. Nissen] that analyses should be conducted by GSK personnel pursuant to prospectively agreed analyses plan."

[23] Multiple staff discussions with Dr. Steven Nissen, from June 2007 to the present.

[24] Email from *NEJM* editor to Committee staff, dated December 18, 2007.

[25] Steven Haffner, fax to Alex Cobitz, dated May 3, 2007.

weeks before the paper's public release.[26] The GSK statistician attempted to find deficiencies in Nissen's meta-analysis but noted, "The selection of trials therefore appears to be thorough, though others more familiar with the trials can comment more knowledgeably." [27]

The GSK statistician also performed a regression analysis [28] on each study that Dr. Nissen used in his meta-analysis to see if the effects of myocardial infarction and/or cardiovascular death would still appear. The statistician stated, "These results are very similar to the conclusion from the [Nissen] paper using the Peto method.[29] As such there is no statistical reason for disregarding the findings as presented." [30]

The GSK statistical analysis was circulated to senior executives within GSK. These executives then discussed several large trials, such as RECORD, DREAM and ADOPT that GSK could use to combat Dr. Nissen's analysis. RECORD was an ongoing trial that had not been published. On the other hand, DREAM and ADOPT were published and were included in Dr. Nissen's analysis. GSK, as well as the FDA, had also performed their own meta-analyses. Both meta-analyses were consistent with Dr. Nissen's results.[31]

On May 8, 2007, Dr. Moncef Slaoui, head of research at GSK, wrote an email to several company executives.[32] Commenting on the meta-analyses, he wrote:

> —FDA, Nissen and GSK all come to comparable conclusions regarding increased risk for ischemic events, ranging from 30 percent to 43 percent!
>
> —FDA and Nissen (but no final data from GSK [to] date) reach the conclusion of an [hazard ratio] for death (CHF + IHD) of 1.72 or 1.75! [33]

Dr. Slaoui also noted in this email that a GSK commissioned study by Ingenix did not find any significant problems with rosiglitazone. Ingenix had performed an epidemiological study of Avandia. While medical experts place greater importance on a clinical trial over an epidemiological study, Dr. Slaoui sought to highlight the Ingenix results. He also expressed concern that a beneficial effect was observed (6 to 16 percent) in the PROactive [34] study of ACTOS in high-risk cardiovascular disease patients.[35]

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[26] Internal GSK document, "Report on the article by SE Nissen & K Wolski 'Effect of rosiglitazone on the risk of myocardial infarction and cardiovascular death.'" Research Statistic Unit, GSK, DRAFT May 4, 2007.

[27] *Id.*

[28] A statistical method that allows data to be simultaneously adjusted for differences in the distribution of a wide variety of measured risk factors that may exist between patients in a study treated with one therapy compared to those treated with another or with placebo.

[29] Peto Method is a widely used way of combining odds ratios in meta-analysis.

[30] Internal GSK document, "Report on the article by SE Nissen & K Wolski 'Effect of rosiglitazone on the risk of myocardial infarction and cardiovascular death.'" Research Statistic Unit, GSK, DRAFT May 4, 2007.

[31] Internal GSK email from Moncef Slaoui to multiple GSK executives, dated May 8, 2007.

[32] *Id.*

[33] *Id.*

[34] PROactive—"PROspective PioglitAzone Clinical Trial In MacroVascular Events Study." The PROactive Study was initiated as a randomized, double-blind, placebo-controlled cardiovascular outcome study to determine the effects of pioglitazone on reducing the risk of a wide variety of cardiovascular events as well as to determine its ability to control blood glucose levels of patients with Type 2 Diabetes. The study was commissioned by Takeda pharmaceuticals, a company that competes directly with GSK and produces a similar diabetes medication called ACTOS.

[35] Internal GSK email from Moncef Slaoui to multiple GSK executives, dated May 8, 2007.

Dr. Slaoui asked, "How can we reinforce the value of the [Ingenix] study? The FDA criticizes the fact that we excluded cases of sudden cardiac death."[36] He then asked his team to strategize further on the issue:

> [W]hat studies could we offer the FDA to further assess the contradictory data between the integrated study and the two others? can we expand Record? Propose something else (very high risk patients? ok? ethical?), compare to Actos for superiority on some end points?[37]

By May 9, 2007, GSK began drafting "key messages" to counteract the findings of the Nissen study.[38] In an email, GSK's Vice President for Corporate Media Relations noted, "The Nissen analysis is one way of looking at the data, but it doesn't reflect all we know about the safety of this medicine. . . . [W]e are not seeing a proven link between Avandia and increased cardiovascular deaths. . . ."[39]

On May 9, 2007, Sir Colin Dollery, a senior consultant to GSK, laid out many of the problems with Avandia in an email to Dr. Slaoui and others. He wrote:

> To a great extent, the numbers are the numbers, the [Nissen] analysis is very similar to our own. . . . We cannot undermine the numbers but I think they can be explained so we must concentrate on effective risk management.[40]

Later in the email, Sir Dollery noted that the PROactive study on ACTOS (pioglitazone) is undermining Avandia (rosiglitazone). He wrote:

> The main argument here lies in that pioglitazone [ACTOS] causes a small reduction of LDL [Low-Density Lipoprotein] and rosiglitazone causes a small elevation. . . . [W]e should search for evidence that the use of statins in diabetics generally and with rosiglitazone in particular has risen steeply over the time the thiazolidenediones have been on the market. We can then argue that any problem that existed with LDL is now controlled or controllable. It would also be worth obtaining the evidence that the use of antihypertensives in diabetics has also been increasing rapidly.[41]

On fluid retention and links with cardiovascular disease, Sir Dollery mentioned a possible mechanism to explain how Avandia may cause heart attacks. He wrote:

> If [fluid retention is] substantial in patients with an impaired myocardium it can lead to [cardiac heart failure] and to cardiac ischemia by decreasing myocardial efficiency in the face of existing coronary disease. . . . If there is criticism of GSK it might be that we were a bit slow off

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[36] *Id.*
[37] *Id.*
[38] Internal GSK email from VP Corporate Media Relations, US GlaxoSmithKline, dated May 9, 2007.
[39] *Id.*
[40] Internal GSK email from Colin Dollery to Moncef Slaoui and other GSK officials, dated May 9, 2007.
[41] *Id.*

> the [mark] in making firm recommendations about the use of diurectics . . .[42] and recognizing that the sodium retention is mediated via distal renal tubular ENaC.[43]

On May 21, 2007, *NEJM* published online Dr. Nissen's meta-analysis that found a link between Avandia and heart attacks. That same day, GSK responded, "GSK strongly disagrees with the conclusions reached in the *NEJM* article, which are based on incomplete evidence and a methodology that the author admits has significant limitations."[44] Instead, GSK highlighted the results of company sponsored trials like RECORD as "the most scientifically rigorous way to examine the safety and benefits of a medicine."[45]

In a subsequent letter to *The Lancet,* GSK maintained that the RECORD trial is "compelling evidence" for the safety of Avandia.[46]

On May 23, 2007, a GSK official emailed members of the RECORD steering committee, the group of independent academics overseeing the study, to alert them of a teleconference to be held the following day.[47] GSK officials also emailed internal talking points to help guide their discussion with the steering committee. However, it appears that prior to receiving input from the steering committee, GSK had already decided to publish the RECORD results. Later that same day, a GSK official wrote, ". . . we've decided to disclose the results. . . ."[48]

The following day, GSK officials discussed potential problems if the academics on the RECORD steering committee raised concerns about publishing the interim results of the RECORD trial.[49] In an email, one GSK official wrote:

> [I]f the Steering Committee [SC] are reluctant to publish—Frank and I will argue the case that there is a balance to be drawn between very negative press coverage and specific reassurance for the patients in the study. However if the SC believe that publishing interim data will fatally damage their ability to bring the study to a completion—Frank and I will bring that opinion with reasons back to GSK, before pursuing the line—that a decision has been made—live with it.[50]

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[42] Diuretics are blood pressure medications that cause the body to excrete water and sodium (salt).

[43] Internal GSK email from Colin Dollery to Moncef Slaoui and other GSK officials, dated May 9, 2007.

[44] GlaxoSmithKline press release, "GlaxoSmithKline responds to NEJM article on Avandia," published online May 21, 2007.

[45] *Id.*

[46] Ronald Krall M.D., Chief Medical Officer, GlaxoSmithKline, "Cardiovascular Safety of Rosiglitazone," *The Lancet,* letter published online May 30, 2007. "The most compelling evidence comes from RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes), an open-label, 6-year, cardiovascular outcomes trial (with prospectively defined cardiovascular endpoints) in 4458 patients that started in 2000."

[47] Email to GSK officials and RECORD steering committee, dated May 23, 2007.

[48] Internal GSK email, dated May 23, 2007.

[49] Internal GSK email, dated May 24, 2007.

[50] *Id.*

A few hours after this email, the acting chair of the RECORD steering committee, contacted the *NEJM* to inquire about publishing the interim results.[51] The editor of the *NEJM* responded that the journal would be interested in publishing the study.[52]

By May 29, 2007, several authors of the RECORD study began passing around a manuscript, discussing the results, and offering suggestions for improvement. The third author on the RECORD study wrote, "We do not find more myocardial infarctions with rosiglitazone treatment, but again there is a tendency supporting the Nissen argument. It is important to stress that it does not affect cardiovascular death." [53]

That same day, a senior author of the RECORD study, wrote:

> There are several striking issues:
>
> (1) The HR ratio (and 95 percent CI) for MI in RECORD is not inconsistent with Nissen's—and he had more events; what's to stop him adding the events from RECORD to his meta-analysis and re-enforcing his view? . . .
>
> (2) Same is for CV death, although the number of events in RECORD and in the meta-analysis are similar and at least in RECORD the HR is in the other direction!
>
> (3) Manuscript looks to downplay the 239 percent INCREASE in HF. I have taken the liberty of doing some rewording.[54]

Once a study is submitted to a journal, the journal editors then send the article to several experts for peer-review. After the review, the editors send the peer-review comments back to the author. On June 1, 2007, the RECORD authors received a reply from *NEJM* regarding their earlier submitted manuscript. The *NEJM* editors summarized the issues presented by all 8 peer reviewers, many of whom were highly critical of the study in their reply.[55]

Reviewer A, along with other reviewers, asked that the authors "modify the language in multiple locations in the manuscript to tone down your conclusions." [56] The editor also noted, "[I]n the opinion of all the readers, the data that you present are completely compatible with the results of the meta-analysis by Nissen and the meta-analysis for myocardial ischemic events posted on the GSK Web site." [57]

Regarding the comments of Reviewer B, the editors wrote that for myocardial infarction the "estimates in the RECORD trial and the Nissen meta-analysis" overlap in their confidence intervals, meaning that they found a similar trend for heart attacks.[58] They continued, "The editors feel strongly that your data do not support

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[51] Email from Acting Chair of the RECORD trial to Editor at *NEJM,* dated May 24, 2007. The Acting Chair wrote, "We the Steering Committee of the RECORD Study would like to submit a brief report of the current interim findings of this ongoing trial concerning the key cardiovascular outcomes."

[52] Email from Editor at *NEJM* to the acting chair of RECORD trial, dated May 24, 2007.

[53] Email between members of the RECORD trial, dated May 29, 2007.

[54] Email between members of the RECORD trial, dated May 29, 2007.

[55] Letter from the *New England Journal of Medicine* to Philip H. Home, M.D. dated June 1, 2007.

[56] *Id.*

[57] *Id.*

[58] *Id.*

the statement that the RECORD results for MI contradict the Nissen meta-analysis; this statement must be removed or modified."[59]

Reviewer C noted that the RECORD trial is not blinded,[60] and pointed out "the serious problem of the low event rate, especially for MI events, in this study."[61] He continued to ask, "Do you have an explanation for the very low event rate?" This reviewer also noted the "need to greatly tone down your language to reflect the substantial level of uncertainty in the data."[62]

Reviewer D questioned the need for keeping rosiglitazone on the market. "The editors also agree that an explanation for the continued use of rosiglitazone is needed in this manuscript."[63]

The *NEJM* published the interim analysis of the RECORD study on July 5, 2007. The GSK study authors concluded that the data was "insufficient" to find a link between Avandia and heart attacks.[64]

However, an editorial by the *NEJM* questioned the RECORD study, as well as several of GSK's studies of Avandia such as DREAM and ADOPT. The authors of the editorial wrote, "The DREAM trial and ADOPT focused largely on marketing questions and failed to address questions of myocardial infarction-related risk or benefit directly." In addition, the editorial noted that the RECORD trial had "several weaknesses in design and conduct" including a lack of blinding when treatment was assigned. The authors also pointed out that events of myocardial infarction would have been a preferred clinical endpoint for the study. Studies are normally designed to evaluate certain clinical endpoints or disease symptoms such as heart attack, tumor size, or depression. The authors also added that the RECORD study was not powered (or designed) to detect a myocardial infarction as an endpoint.[65]

On June 6, 2007, the House of Representatives Committee on Oversight and Government Reform held a hearing on Avandia. Despite mounting criticism of the RECORD trial, Dr. Slaoui again highlighted the study in his sworn testimony. "I will say that we found the RECORD data which we published yesterday in the *New England Journal of Medicine* very reassuring, recognizing that it is interim and therefore not fully conclusive."[66]

That same day, GSK dismissed the idea that Dr. Nissen's study spurred the publication of the RECORD interim results. Instead, the Company placed blame on the media. In talking points created for its sales force, GSK stated, "Because of the widespread media

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[59] *Id.*

[60] A blinded study is a study done in such a way that the patients or subjects do not know what treatment they are receiving to ensure that the results are not affected by a bias on the part of patients, doctors, or the sponsors who are paying for the study.

[61] Letter from the *New England Journal of Medicine* to Philip H. Home, M.D. dated June 1, 2007.

[62] *Id.*

[63] *Id.*

[64] Philip D. Home et al., "Rosiglitazone Evaluated for Cardivascular Outcomes—An Interim Analysis," the *New England Journal of Medicine,* July 5, 2007. The study authors concluded, "Rosiglitazone was associated with an increased risk of heart failure. The data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction."

[65] Bruce M Psaty, et al. "The Record on Rosiglitazone and the Risk of Myocardial Infarction," the *New England Journal of Medicine,* July 5, 2007.

[66] House of Representatives, Committee on Oversight and Government Reform, "Hearing on FDA's Role on the Evaluation of Avandia's Safety," June 6, 2007, preliminary transcript, page 168 (*see also http://oversight.house.gov/documents/20071114160344.pdf*).

coverage of the *NEJM* [Nissen] meta-analysis and the confusion it has created, the RECORD Steering Committee decided it was important to publish the interim analysis in the interests of patient safety."[67]

Regarding its competitor Takeda, which sells ACTOS, GSK advised its sales force if asked questions about the PROactive study:

> Please do not discuss Actos or the Proactive study with your physicians. For questions regarding Actos or the Proactive study, healthcare providers should contact Takeda. GSK's focus is on Avandia. Communicate the key points from the interim analysis of RECORD to your physicians.[68]

THE RECORD TRIAL AS A MARKETING TOOL FOR COMPETITION

Despite attempts to highlight the RECORD study, it appears that GSK knew for years that the study was "underpowered," i.e., the study did not provide sufficient data to test for cardiovascular safety. And executives appeared more concerned about designing a study to limit competition from ACTOS. Such evidence can be found in a GSK slide presentation, emails, and other documents created in 2004 to 2006.

For instance, in an undated slide show, apparently created in 2004, GSK noted that RECORD does not have sufficient "power."[69] The slide presentation also noted that GSK was trying to create studies to counter the PROactive study on ACTOS that Takeda planned to release.[70]

Slide number 6 titled, "PROactive: Potential Impact," noted that GSK's challenge was to "maintain share in growing market over next 2–3 years."[71]

Slide number 8 reads:

Situation Summary:

- We have a gap
  —In 2005 Actos will have some [cardiovascular] outcome data
- To keep our share of the growing class
  —Additive benefit to RECORD of non-inferiority result
- However this gap may be permanent
  —RECORD has a lower event rate than expected

PROPOSAL

Fill this gap with an outcome study reporting in 2007

Slide number 10 compared the potential impact of a new GSK study to counter the marketing danger of PROactive and the potential impact on sales in UK pounds in 2010. The slide reads: "Timely CV Outcomes data would more than fill the RECORD 'potential gap' and would have twice the impact on our sales than PRO-

[67] GSK's RECORD Study Questions, dated June 6, 2007, for GSK Internal Use Only.
[68] *Id.*
[69] GSK Internal Slide Show, "European Commercial Need for a Post-ACS Study Proposal," undated.
[70] *Id.*
[71] *Id.*

active."[72] The final slide pointed out that GSK should do a "kick off study only after review of results from Proactive in Sept 2005 and assessing benefits/risks."[73]

A second instance is found in a June 2005 email where GSK executives discussed the need for a study to counter PROactive. In the email, a GSK official wrote, "Clearly no patients will be recruited until [we] have made a decision based on the go-no go criteria from the PROactive data. However, there is a great deal of EU commercial push to initiate this study in 2005."[74]

A third case is found in an internal GSK document outlining an upcoming meeting for December 2004. Several points were discussed about RECORD and PROactive. Regarding RECORD, the document noted that RECORD has "low events rates." This means that the study did not have the statistical "power" to give sufficient cardiovascular event data. The document also stated, "PROactive results to be coming soon—need to be able to respond to a variety of different outcomes. Communications plan in place for various possible outcomes of PROactive."[75]

A fourth instance is found in a briefing document for a June 2005 meeting on Avandia's cardiovascular plan. The document notes several "important limitations of RECORD."[76]

—the study will not be available until 2009

—the current observed rate for the primary endpoint is very much lower (approximately 3.5 percent per annum) than that anticipated in the original protocol (11 percent per annum).[77]

A fifth case is found in another GSK email. On July 26, 2005, GSK officials began emailing each other about potential problems with RECORD and how the PROactive study by Takeda on ACTOS will create problems for Avandia. One official wrote:

> Ron Krall [then GSK Chief Medical Officer] has asked Lawson [unknown GSK executive] to provide an urgent update to David Stout [then GSK President of Global Pharmaceutical Operations] regarding RECORD. In particular he has asked for our "intent to manage information flow in Europe to manage the competitive situation." Clearly we can provide a summary of the communications around PROactive but I wonder if you could put a few sentences together regarding the communications piece around RECORD.[78]

A sixth incident is documented in July 2005, when GSK officials continued expressing concerns about cardiovascular problems with Avandia and potential problems arising from the PROactive study which focused on positive findings with ACTOS. GSK held a meeting on July 18, 2005 to discuss the need for a study to compete

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[72] *Id.*
[73] *Id.*
[74] Internal GSK email, dated June 16, 2005.
[75] Internal GSK document, untitled, unknown date.
[76] Internal GSK document, "Briefing Document for 27 June 2005 PMB Avandia Cardiovascular Modeling Plan."
[77] *Id.*
[78] Internal GSK email, dated July 26, 2005.

with PROactive.[79] The briefing document from this meeting discussed the "European Commercial Need" for a study:

> A recently completed evidence gap analysis completed by the Metabolic Centre of Excellence has identified the need for the rapid generation of clinical endpoint data to support the superiority of rosiglitazone [Avandia] for the prevention of future cardiovascular clinical events in patients with [type 2 diabetes mellitus]. Publication of the PROactive data may result in important commercial disadvantage in Europe. We therefore have the opportunity to start a CV outcomes study with the aim of getting superiority data in 2007.[80]

The document also noted that GSK's studies provided insufficient data on cardiovascular outcomes:

> The primary endpoint in RECORD is powered for non-inferiority and taking into account the low observed event rate, it is unlikely that this study will demonstrate any potential for [Avandia] combination to be superior in terms of the primary endpoint compared to SU+MET combination therapy. DREAM and ADOPT are collecting CV safety data, but these are low risk populations and it is unlikely that [Avandia] will be superior to controls for the prevention of CV events.[81]

CONCERNS ABOUT AVANDIA RAISED PRIOR TO 2007

In June 2004, GSK's leader for a cardiac safety study called the "Avandia 211 Cardiac Heart Failure Study"[82] reported on a meeting with a consulting academic. The academic was the chairman of the independent clinical endpoint committee for the Avandia 211 study.[83] The study leader's report of the academic consultant's feedback on Avandia 211 follows:

> With regard to CV mortality and morbidity data, [the academic consultant] said that the results were 'almost identical' to the results he had seen from a previous glitazone study as a member of the DSMB with increased CV events, hospitalizations, and ischaemic events. [The academic consultant] said that he felt this was a class effect as a result of reduced oxygen carrying capacity as a result of haemodilution to fluid-retention.[84]

The report of the Avandia 211 meeting noted that the academic consultant said he would not stop prescribing Avandia, as the study was too small, and that he "would continue to use [Avandia]

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[79] Internal GSK document, "MDC Briefing Document: Ad-hoc meeting 18th July 2005. AVD104821: rosiglitazone in post-acs patients."
[80] *Id.*
[81] *Id.*
[82] Internal GSK slide show titled "Avandia 211 CHF study: Senior Review of Additional Analysis," undated.
[83] Internal GSK report, "Avandia 211 CHF study—Review of Study Results, Feedback from Professor NAME REDACTED," dated June 3, 2004.
[84] *Id.*

as a second or third line therapy whilst taking appropriate precautions."[85]

Later that month, several GSK representatives met with the advisory board for study protocol 211.[86] The meeting notes state:

> There was disappointment verbalized about the morbidity and mortality table that showed that there were ten ischemia-related adverse events in the rosiglitazone group versus five events in the placebo group. . . . Dr. NAME REDACTED found [it] unusual that there was an increase in edema and cardiac events despite the fact that there was significant improvement in glycemic control in the rosiglitazone arm of the trial. He thought the glycemic control and pleitrophic [sic] effects of rosiglitazone would have predicted a different outcome than what was observed.[87]

In late 2005, GSK published a draft retrospective analysis of cardiovascular events in Avandia clinical trials discussing the underlying cause for the increase in ischemia.[88] In a section of the analysis that examined myocardial ischemia, the authors mention a "hypothesis that small degrees of fluid retention may be an important contributor to the development of worsening myocardial ischemia in high risk patients."[89]

After GSK reviewed the evidence found in this analysis, it appears that the Company was aware of the potential cardiovascular risks associated with Avandia in late 2004 or early 2005. In 2005, GSK commissioned an "observational" trial study that was conducted in two parts: the first part in 2005 and the second in 2006. The results of these studies support the further investigation of the cardiovascular risks associated with Avandia.

The first study included 11,586 subjects randomly placed in clinical trials before September 20, 2004. The analysis of the trials was completed during the fall of 2005, giving a hazard ratio for myocardial ischemia of 1.29, meaning that rosiglitazone increased the risk of heart-related ischemia by 29 percent. This number was statistically significant.

GSK's second observational study involved analyzing 14,237 patients by the summer of 2006. The results found a hazard ratio of 1.31, meaning that Avandia increased the risk of myocardial ischemia by 31 percent.[90]

CONCLUSION

In preparing this report, Committee investigators reviewed over 250,000 pages of documents provided by GSK, the FDA, the University of North Carolina, and others. Anonymous whistleblowers who contacted Senator Grassley's investigators provided hundreds of other pages. For well over a year, Committee investigators also

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[85] *Id.*

[86] GSK Internal Meeting Minutes, "Summary of the feedback from the Advisory Board Meeting held on June 23rd, 2004, the Philadelphia Airport Marriot to discuss Study Protocol 211."

[87] *Id.*

[88] Internal GSK document titled, "Rosiglitazone: Further Interim Results from Retrospective Analysis of Cardiovascular Events in Clinical Trials DRAFT," undated.

[89] *Id.*

[90] GlaxoSmithKline, Studies ZM2005/00181/01 and HM2006/00497/00/WEUSRTP866; *http://ctr.gsk.co.uk/Summary/rosiglitazone/studylist.asp.*

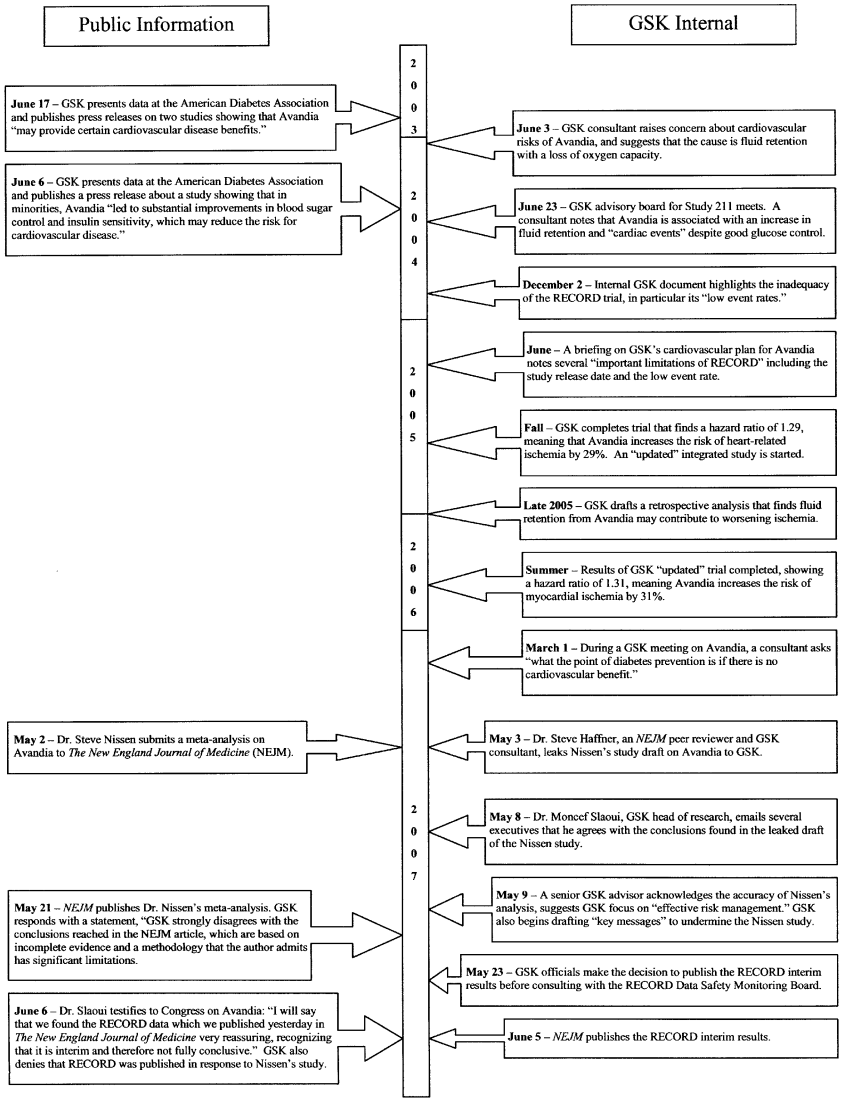
conducted numerous interviews and phone calls with GSK, the FDA and anonymous whistleblowers.

The totality of evidence suggests that GSK was aware of the possible cardiac risks associated with Avandia years before such evidence became public. Several years prior to Nissen's study, it can be argued that GSK was on notice that Avandia may have problems. Based on this knowledge, GSK had a duty to sufficiently warn patients and the FDA of its concerns in a timely manner. Instead, GSK executives intimidated independent physicians, focused on strategies to minimize findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that the rival drug ACTOS (pioglitazone) might reduce cardiovascular risk.

In recent years, pharmaceutical companies have committed acts that forced them to pay the largest criminal fines in American history.[91] In cases involving Pfizer, Eli Lilly, Bristol Myers Squibb and four other drug companies, these fines and penalties have totaled over $7 billion since May 2004.[92] In particular, Pfizer has been fined multiple times in the past 6 years for illegal off-label promotion of their drugs. In its latest plea agreement, which took place last September, Pfizer paid $2.3 billion in fines and penalties for off-label promotion of Bextra. This settlement was the largest criminal fine in U.S. history.[93] Such an environment requires diligent oversight by the FDA to protect the citizens of this country and to ensure the safety of American medicine.

[91] David Evans, "Pfizer Broke the Law by Promoting Drugs for Unapproved Uses," *Bloomberg,* November 9, 2009.
[92] *Id.*
[93] *Id.*

APPENDIX I: VISUAL TIMELINE OF PUBLIC AND INTERNAL INFORMATION



APPENDIX II: TIMELINE

2004—A slide appears to show that the RECORD trial is statistically inadequate to answer questions on cardiovascular safety. The slide show also points out that GSK is creating studies to counter Takeda's PROactive study on ACTOS, a competitor to Avandia.

2004—GSK experts advise the company as to the possible biological mechanisms behind the cardiovascular risk associated with Avandia.

September 2004—GSK commissions an observational study to examine over 11,000 subjects for an "initial" analysis of linkages between Avandia and myocardial ischemia.

June 3, 2004—GSK's clinical manager reports on feedback from a consultant who expressed concern over the cardiovascular risks of Avandia. The consultant says that he does not intend to discontinue Avandia use in patients, but will push it to a backup position behind similar, rival drugs.

December 2, 2004—Internal GSK document highlights the inadequacy of the RECORD trial, in particular its "low event rates."

June 2005—A briefing document on GSK's cardiovascular plan for Avandia notes several "important limitations of RECORD" including the study release date and the low event rate.

July 18, 2005—GSK holds a meeting to discuss the need for a study to compete with PROactive, in particular to address the "European commercial need" for a study.

Fall 2005—GSK presents the initial observational trial of Avandia, showing that the hazard ratio was 1.29, meaning that Avandia increased the risk of heart-related ischemia by 29 percent. An "updated" observational study is commissioned.

Late 2005—GSK drafts a retrospective analysis discussing the underlying cause for the increase in ischemia due to Avandia.

Early 2006—GSK experts discuss problems with the DREAM study.

Summer 2006—The results of the GSK "updated" trial were presented, showing that the hazard ratio of these results was 1.31, meaning that Avandia increases the risk of myocardial ischemia by 31 percent.

May 2, 2007—Dr. Steven Nissen submits his meta-analysis on Avandia to the *New England Journal of Medicine (NEJM)* for peer review and publication.

May 3, 2007—Dr. Steve Haffner, an *NEJM* peer reviewer and consultant for GSK, leaks Nissen's study draft on Avandia to GSK.

May 8, 2007—Moncef Slaoui, head of research for GSK, writes an email to several executives agreeing with the conclusions found in the Nissen article.

May 9, 2007—GSK begins drafting "key messages" to combat the Nissen study.

May 9, 2007—Sir Colin Dollery, a senior GSK advisor, acknowledges the accuracy of Nissen's analysis and suggests that the company concentrate on "effective risk management."

May 21, 2007—*NEJM* publishes Dr. Nissen's meta-analysis and on the same day GSK responds with a statement of disagreement.

May 23, 2007—A GSK official emails members of the RECORD steering committee requesting a meeting to discuss the publication of the study's interim results. Emails show that GSK executives were intent on publishing the interim results regardless of whatever opinion the steering committee voiced.

May 29, 2007—RECORD interim results were submitted to *NEJM* for peer review and publication.

June 1, 2007—The RECORD authors received a reply from *NEJM* regarding their first draft which included a summary of the highly critical comments made by the panel of 8 experts.

June 6, 2007—Dr. Moncef Slaoui testifies in a congressional hearing on Avandia and FDA regulation. He states, "I will say that we found the RECORD data which we published yesterday in the *New England Journal of Medicine* very reassuring, recognizing that it is interim and therefore not fully conclusive." That same day GSK dismisses the idea that the RECORD results had been published in response to Dr. Nissen's study.

APPENDIX III: RELEVANT DEFINITIONS

ACTOS (pioglitazone)—once-a-day prescription medication for Type 2 diabetes that helps the body control blood sugar (glucose) levels. ACTOS is produced by Takeda Pharmaceuticals and is Avandia's primary competitor.

ADOPT—"A Diabetes Outcome Progression Trial." ADOPT is a randomized, double-blind, parallel-group study conducted on 3,600 recently diagnosed diabetic patients who had not been taking a diabetes medication. ADOPT was designed to measure the efficacy of rosiglitazone in controlling glucose in diabetics.

Antihypertensives—medications for treating high blood pressure.

Avandia (rosiglitazone)—GlaxoSmithKline's brand name for rosiglitazone, an oral diabetes drug which controls glucose levels.

Blinded study—a study done in such a way that both treating physicians (investigators) and the patients (study subjects) do not know what treatment they are receiving, to ensure that the results are not affected by investigator or treatment subject bias.

Cardiovascular disease or CVD—diseases that involve the heart or blood vessels (arteries and veins). Generally refers to heart attack and stroke.

Diuretics—blood pressure medications that cause the body to excrete water and sodium (salt).

DREAM—"The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication." DREAM is an international, multicentre, randomized, double-blind trial involving 5,269 patients from 21 countries. The DREAM study was published in the middle of 2006.

DSMB—Data Safety Monitoring Board.

Edema—excessive accumulation of fluid in tissue spaces that causes swelling, particularly in the ankles and lower legs.

Event Rate—proportion of patients in whom an event is observed.

GlaxoSmithKline or GSK—company formed in 2000 by the merger of Glaxo Wellcome with SmithKline Beecham.

Ghostwriting—when an individual(s) writes a report which is then officially accredited to another person with more medical prestige.

Glycemic Control—to stabilize glucose levels in the body.

Haemodilution—condition affecting the proportion of red blood cells relative to the plasma, brought about by an increase in the total volume of plasma.

Hazard Ratio—formula used to estimate relative risk.

Ingenix—health care information and research company which writes studies and reports for pharmaceutical companies.

Ischemia—inadequate blood supply (circulation) to a local area due to blockage of blood flow to that area.

Lipids—fat-soluble (lipophilic), naturally-occurring molecules. Generally, LDL transports cholesterol and triglycerides from the liver to peripheral tissues.

Low-density Lipoprotein or LDL—a lipid that is associated with heart disease. Sometimes called "bad" cholesterol.

Meta-Analysis—method of summarizing previous research by reviewing and combining results from multiple clinical trials.

Myocardial Infarction—more commonly known as a "heart attack."

Patient-Level Data—captures encounters of the individual patient with the healthcare system over time.

Peto Method—method of combining odds ratios that has become widely used in meta-analysis.

Pioglitazone—diabetes drug which controls glucose in diabetics. Takeda-Lilly markets pioglitazone as ACTOS.

PROactive—"PROspective PioglitAzone Clinical Trial In Macro-Vascular Events Study." The PROactive Study was initiated as a randomized, double-blind, placebo-controlled cardiovascular outcome study to determine the effects of pioglitazone on reducing the risk of a wide variety of cardiovascular events as well as to determine its ability to control blood glucose levels of patients with Type 2 Diabetes. The study was commissioned by Takeda pharmaceuticals, a company that competes directly with GSK and produces a similar diabetes medication called ACTOS.

RECORD—Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes. The RECORD trial was a GSK sponsored trial of Avandia.

Regression Analysis—a statistical method that allows data to be simultaneously adjusted for differences in the distribution of a wide variety of measured risk factors that may exist between patients in a study treated with one therapy compared to those treated with another or with placebo.

Retrospective Analysis—study that looks backward in time, usually using medical records and interviews with patients who already have or had a disease. Such an analysis is generally referred to as "observational" or "epidemiologic" because it is not a prospectively designed randomized clinical trial. In the hierarchy of scientific evidence, these analyses provide weaker evidence than clinical trials or meta-analyses of clinical trials.

Rosiglitazone (RSG)—diabetes drug which controls glucose in diabetics. GlaxoSmithKline sells rosiglitazone as the brand Avandia.

Statins—class of drugs used to lower LDL ("bad") cholesterol by inhibiting the body's production of them.

Thiazolidinedione or TZD—drug class used for therapy in Type 2 diabetes. Members of this class include Rosiglitazone (Avandia), Pioglitazone (Actos), and Troglitazone (Rezulin), which was withdrawn from the market due to an increased incidence of liver problems.

Underpowered—a study that does not meet the statistical requirements to adequately measure a medical outcome or study endpoint.

APPENDIX IV: DOCUMENTS NOT PUBLICLY AVAILABLE	
Footnote No.	Description
3	Internal GSK emails between Tachi Yamada and David Pernock, Aug. 4 and 5, 1999.
9	Steven E. Nissan et. al. "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes," *The New England Journal of Medicine*, May 21, 2007.
12	Email from John McMurray to Nigel Jones et. al., dated May 29, 2007.
13, 55	Letter from *The New England Journal of Medicine* to Philip H. Home, M.D. dated June 1, 2007.
15	FDA, "Assessment of the cardiovascular risks and health benefits of rosiglitazone," presented July 30, 2007.
16, 19	"GSK Diabetes Franchise Cardiology Advisory Board," meeting held March 1-2, 2007, report dated March 16, 2007.
21	Internal GSK slides titled "DREAM: Diabeted Reduction Assessment with ramipril and rosiglitazone Medication," undated but some slides state "updated Sept 6/06."
22	Internal GSK email, dated May 3, 2007. "I have made oit [sic] clear in my letter of Feb 26 [to Dr. Nissen]that analyses should be conducted by GSK personnel pursuant to prospectively agreed analyses plan."
26, 30	Internal GSK document, "Report on the article by SE Nissen & K Wolski 'Effect of rosiglitazone on the risk of myocardiàl infarction and cardiovascular death.'" Research Statistic Unit, GSK, DRAFT May 4, 2007.
31, 36	Internal GSK email from Moncef Slaoui to multiple GSK executives, dated May 8, 2007.
38	Internal GSK email from VP Corporate Media Relations, US GlaxoSmithKline, dated May 9, 2007.
40	Internal GSK email from Colin Dollery to Moncef Slaoui and other GSK officials, dated May 9, 2007.
44	GlaxoSmithKline press release, "GlaxoSmithKline Responds to *NEJM* Article on Avandia," published online May 21, 2007.
46	Ronald Krall M.D., Chief Medical Officer, GlaxoSmithkline, "Cardiovascular Safety of Rosiglitazone," *The Lancet*, letter published online May 30, 2007.
47	Email to GSK officials and RECORD steering committee, dated May 23, 2007.
48 - 50	Internal GSK emails, dated May 23 and 24, 2007.
51	Email from the Acting Chair of the RECORD trial to Editor at *NEJM*, dated May 24, 2007.

52	Email from Editor at *NEJM* to the acting chair of the RECORD trial, dated May 24, 2007.
53	Email between members of the RECORD trial, dated May 29, 2007.
54	Email between members of the RECORD trial, dated May 29, 2007.
55, 61	Letter from *The New England Journal of Medicine* to Philip H. Home, M.D. dated June 1, 2007.
64	Philip D. Home et. al., "Rosiglitazone Evaluated for Cardiovascular Outcomes - An Interim Analysis," *The New England Journal of Medicine*, July 5, 2007.
65	Bruce M. Psaty, et. Al., "The Record on Rosiglitazone and the Risk of Myocardial Infarction," *The New England Journal of Medicine*, July 5, 2007.
66	House of Represenatives, Committee on Oversight and Government Reform, "Hearing on the FDA's Role on the Evalutaion of Avandia's Safety," June 6, 2007, preliminary transcript, page 168.
67	GSK's RECORD Study Questions, dated June 6, 2007.
69	GSK Internal Slide Show, "European Commercial Need for a Post-ACS Study Proposal," undated, but some slides suggest creation in 2004.
74	Internal GSK email, dated June 16, 2005.
75	Internal GSK document, untitled, unknown date.
76	Internal GSK document, "Briefing Document for 27 June 2005 PMB: Avandia Cardiovascular Modeling Plan."
78	Internal GSK email, dated July 26, 2005.
79	Internal GSK document, MDC Briefing Document: Ad-hoc meeting 18th July 2005.
82	Internal GSK slide show titled, "Avandia 211 CHF study: Senior Review of Additional Analysis," undated.
83	Internal GSK report, "Avandia 211 CHF study - Review of Study Results, Feedback from Professor NAME REDACTED," dated June 3, 2004.
86	GSK Internal Meeting Minutes, "Summary of the feedback from the Advisory Board Meetiong held on June 23rd, 2004, the Philadelphia Airport Marriot to discuss Study Protocol 211."
88	Internal GSK document titled, "Rosiglitazone: Further Interim Results from Retrospective Analysis of Cardiovascular Events in Clinical Trials DRAFT," undated.

FOOTNOTE 3

From: Tachi Yamada
Date Sent: 8/5/1999 12:09:43 AM
To: David M Pernock
CC: David M Stout
Subject: Re:

David

What exactly do you want me ask for? Obviously, we are not going to be able to prevent [redacted] from speaking on behalf of Takeda. I would be happy to speak to either [redacted] (Dept. Chair) or [redacted] (Hepatology Chief) but we had better be clear on the message we want to send.

Tachi

David M Pernock@SB on 04-Aug-1999 18:06

To: Tachi Yamada, David M Stout
cc:
Subject:

Tachi,

I need you to place another call to your contacts at U Penn. The situation is that [redacted] (gastroenterologist) is apparently on the Takeda speaker's circuit. He is reported to be speaking about the case and implicating Avandia.
Obviously this is not anyone's best interest.

FOOTNOTE 9

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

N Engl J Med 2007;356:2457-71.

THIAZOLIDINEDIONE DRUGS ARE WIDELY used to lower blood glucose levels in patients with type 2 diabetes mellitus. In the United States, three such agents have been introduced: troglitazone, which was removed from the market because of hepatotoxicity, and two currently available agents, rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda). The thiazolidinediones are agonists for peroxisome-proliferator–activated receptor γ (PPAR-γ). PPAR-γ receptors are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose primarily by increasing insulin sensitivity in peripheral tissues.[1,2] Rosiglitazone was introduced in 1999 and is widely used as monotherapy or in fixed-dose combinations with either metformin (Avandamet, GlaxoSmithKline) or glimepiride (Avandaryl, GlaxoSmithKline).

The original approval of rosiglitazone was based on the ability of the drug to reduce blood glucose and glycated hemoglobin levels.[3] Initial studies were not adequately powered to determine the effects of this agent on microvascular or macrovascular complications of diabetes, including cardiovascular morbidity and mortality.[3] However, the effect of any antidiabetic therapy on cardiovascular outcomes is particularly important, because more than 65% of deaths in patients with diabetes are from cardiovascular causes.[4] Therefore, we performed a meta-analysis of trials comparing rosiglitazone with placebo or active comparators to assess the effect of this agent on cardiovascular outcomes. The source material for this analysis consisted of publicly available data from the original registration package submitted to the Food and Drug Administration (FDA), another series of trials performed by the sponsor after approval, and two large, prospective, randomized trials designed to study additional indications for the drug.

METHODS

ANALYZED STUDIES

Table 1 lists the 42 trials included in this meta-analysis. We screened 116 phase 2, 3, and 4 trials for inclusion. Of these, 48 trials met the predefined inclusion criteria of having a randomized comparator group, a similar duration of treatment in all groups, and more than 24 weeks of drug exposure. Six of the 48 trials did not report any myocardial infarctions or deaths from cardiovascular causes and therefore were not included in the analysis because the effect measure could not be calculated. Of the remaining 42 studies, 38 reported at least one myocardial infarction, and 23 reported at least one death from cardiovascular causes. In these trials, 15,565 patients were randomly assigned to regimens that included rosiglitazone, and 12,282 were assigned to comparator groups with regimens that did not include rosiglitazone.

Multiple groups of patients who received rosiglitazone within a single trial were pooled together, when applicable. The control group was defined as patients receiving any drug regimen other than rosiglitazone. The trials fall into three categories. One group includes five of the studies submitted to the FDA for the March 22, 1999, advisory board hearing that recommended approval of rosiglitazone. Group-level data from these five studies are available in publicly disclosed briefing documents archived on the FDA Web site.[6] Data from these same trials are also reported in a summary fashion on a clinical-trial registry Web site maintained by the drug manufacturer, GlaxoSmithKline.[5] Reports of four of these five trials were also published in peer-reviewed journals.[7-9] In these five trials, 1967 patients were randomly assigned to receive rosiglitazone, and 793 patients were assigned to receive various comparator drugs (Table 1).

Other studies that we included in the meta-analysis were initially identified in the GlaxoSmithKline clinical-trial registry.[5] As noted in Table 1, we included 35 studies in this category, 9 of which were published in peer-reviewed journals and 26 of which remain unpublished.[10-18] Whenever possible, the results obtained on the GlaxoSmithKline Web site were cross-checked with the publication. In cases of disagreement between published and unpublished data, data derived from the manufacturer's Web site were used. In this group of 35 trials, 9507 patients were randomly assigned to receive rosiglitazone, and 5960 patients were assigned to receive various comparator drugs.

A third data source consisted of two large, recently published trials, the Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication (DREAM) NCT00095654 trial[20] and the A Diabetes Outcome Prevention Trial (ADOPT)

(ClinicalTrials.gov number, NCT00279045).[21] In the DREAM study, 2635 patients were randomly assigned to receive rosiglitazone and 2634 patients were assigned to receive placebo. The DREAM study was designed to determine whether rosiglitazone could prevent the development of type 2 diabetes in patients at high risk for this disorder. In the ADOPT trial, 1456 patients were randomly assigned to receive rosiglitazone and 2895 patients were assigned to receive either metformin or glyburide. The ADOPT study was designed to assess the durability of glycemic control with rosiglitazone therapy, as compared with therapy with metformin or glyburide.

OUTCOME MEASURES

We reviewed data summaries provided in the FDA review documents, the GlaxoSmithKline clinical-trial registry Web site, and published trial results and then abstracted from the adverse-event tabulations information on myocardial infarction and death from cardiovascular causes. With the exception of the DREAM study, the included trials did not describe adjudication of myocardial infarction or death from cardiovascular causes. Time-to-event data for cardiovascular events were not available in any of these trials, which precluded the calculation of hazard ratios. Because only summary data were available, it was not possible to discern whether the same patient had both events. Therefore, an outcome measure based on the composite of death or myocardial infarction could not be constructed. Accordingly, these two outcomes are reported separately.

STATISTICAL ANALYSIS

Many trials had few cardiovascular events, so the odds ratios and 95% confidence intervals were calculated with the use of the Peto method.[22-24] Because all trials had similar durations of follow-up for all treatment groups, the use of odds ratios represents a valid approach to assessing the risk associated with the use of rosiglitazone. Trials in which patients had no adverse cardiovascular events in either group were excluded from analyses. All reported P values are two-sided. Statistical heterogeneity across the various trials was tested with the use of Cochran's Q statistic. A P value of more than the nominal level of 0.10 for the Q statistic indicated a lack of heterogeneity across trials, allowing for the use of a fixed-effects model. For additional analyses, the active comparator control groups were subgrouped into the following four classes for comparison with rosiglitazone: metformin, sulfonylurea, insulin, and placebo. Odds ratios and 95% confidence intervals were calculated for each subgroup with the use of methods similar to those used in the pooled analyses. Data were analyzed with the use of Comprehensive Meta-Analysis software, version 2.2 (Biostat).

RESULTS

BASELINE CHARACTERISTICS

Table 2 reports the doses of rosiglitazone and comparator drugs, baseline demographic characteristics, study periods, and glycated hemoglobin levels or fasting blood glucose levels for patients enrolled in the trials. The patients were relatively young, averaging less than 57 years of age for both the rosiglitazone group and the control group. Overall, there was a moderate predominance of men. Diabetes control was relatively poor, with a mean baseline glycated hemoglobin level of approximately 8.2% for both study groups.

MYOCARDIAL INFARCTION AND DEATH

Table 3 reports the myocardial infarction events and deaths from cardiovascular causes that were reported in the 42 clinical trials we reviewed. There were 86 myocardial infarctions in the rosiglitazone group and 72 in the control group. There were 39 deaths from cardiovascular causes in the rosiglitazone group and 22 in the control group. Table 4 lists the odds ratios, 95% confidence intervals, and P values for myocardial infarction and death from cardiovascular causes for the rosiglitazone group and the control group. The summary odds ratio for myocardial infarction was 1.43 in the rosiglitazone group (95% confidence interval [CI], 1.03 to 1.98; P=0.03). The odds ratio for death from cardiovascular causes in the rosiglitazone group, as compared with the control group, was 1.64 (95% CI, 0.98 to 2.74; P=0.06). Table 4 also lists odds ratios and 95% confidence intervals for the pooled group of trials that were smaller and of shorter duration; results for the DREAM and ADOPT studies are shown separately.

Table 5 lists odds ratios for myocardial in-

Table 1. Clinical Trials of Rosiglitazone in the Meta-Analysis.*

Study and Reference	Registry Number	Phase	Duration	Rosiglitazone Group		Control Group	
				Drug	No. of Patients	Drug	No. of Patients
			wk				
Trials included in original registration package							
49653/011[5-7]		3	24	Rosiglitazone	357	Placebo	176
49653/020[5,6]		3	52	Rosiglitazone	391	Glyburide	207
49653/024[5,8]		3	26	Rosiglitazone	774	Placebo	185
49653/093[5,6,9]		3	26	Rosiglitazone with or without metformin	213	Metformin	109
49653/094[5,6,9,10]		3	26	Rosiglitazone and metformin	232	Metformin	116
Subtotal					1,967		793
Additional phase 2, 3, and 4 efficacy trials							
100684[5]		4	52	Rosiglitazone and glyburide	43	Glyburide	47
49653/143[5]		4	24	Rosiglitazone and glyburide	121	Glyburide	124
49653/211[5]		4	52	Rosiglitazone and usual care	110	Usual care	114
49653/284[5,11]		4	24	Rosiglitazone and metformin	382	Metformin	384
712753/008[5]		4	48	Rosiglitazone and metformin	284	Metformin	135
AVM100264[5]	NCT00359112	4	52	Rosiglitazone and metformin	294	Metformin and sulfonylurea†	302
BRL 49653C/185[5]		4	32	Rosiglitazone with or without metformin	563	Usual care with or without metformin	142
BRL 49653/334[5]		4	52	Rosiglitazone	278	Placebo	279
BRL 49653/347[5]	NCT00054782	4	24	Rosiglitazone and insulin	418	Insulin	212
49653/015[5,12]		3	24	Rosiglitazone and sulfonylurea‡	395	Sulfonylurea‡	198
49653/079[5]		3	26	Rosiglitazone with or without glyburide	203	Glyburide	106
49653/080[5,13]		3	156	Rosiglitazone	104	Glyburide	99
49653/082[5,14]		3	26	Rosiglitazone and insulin	212	Insulin	107
49653/085[5]		3	26	Rosiglitazone and insulin	138	Insulin	139
49653/095[5]		3	26	Rosiglitazone and insulin	196	Insulin	96
49653/097[5]		3	156	Rosiglitazone	122	Glyburide	120

49653/125[5,13]	3	26	Rosiglitazone and sulfonylurea§	175	Sulfonylurea§	173
49653/127[5]	3	26	Rosiglitazone and glyburide	56	Glyburide	58
49653/128[5]	3	28	Rosiglitazone	39	Placebo	38
49653/134[5]	3	28	Rosiglitazone	561	Placebo	276
49653/135[5]	3	104	Rosiglitazone and glipizide	116	Glipizide	111
49653/136[5]	3	26	Rosiglitazone	148	Placebo	143
49653/145[5,16]	3	26	Rosiglitazone and gliclazide	231	Gliclazide	242
49653/147[5,17]	3	26	Rosiglitazone and sufonylurea¶	89	Sulfonylurea¶	88
49653/162[5,18]	3	26	Rosiglitazone and glyburide	168	Glyburide	172
49653/234[5]	3	26	Rosiglitazone and glimepiride	116	Glimepiride	61
49653/330[5]	3	52	Rosiglitazone	1,181	Placebo	382
49653/331[5]	3	52	Rosiglitazone	706	Placebo	325
49653/137[5]	3	32	Rosiglitazone and metformin	204	Glyburide and metformin	185
SB-712753/002[5]	3	24	Rosiglitazone and metformin	288	Metformin	280
SB-712753/003[5]	3	32	Rosiglitazone and metformin	254	Metformin	272
SB-712753/007[5]	3	32	Rosiglitazone with or without metformin	314	Metformin	154
SB-712753/009[5]	3	24	Rosiglitazone, metformin, and insulin	162	Insulin	160
49653/132[5,19]	2	24	Rosiglitazone and sulfonylurea‖	442	Sulfonylurea‖	112
AVA100193[5]	2	24	Rosiglitazone	394	Placebo	124
Subtotal				9,507		5,960
Recently published large, prospective, randomized trials						
DREAM[20]	NCT00095654	3	156	Rosiglitazone	2,635	Placebo	2,634
ADOPT[21]	NCT00279045	3	208	Rosiglitazone	1,456	Metformin or glyburide	2,895
Total					15,565		12,282

* Studies are listed according to the number designated by the sponsor, GlaxoSmithKline, and are available on the company's Web site.[5] ClinicalTrials.gov numbers are listed for trials included in that registry. DREAM denotes Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication, and ADOPT A Diabetes Outcome Prevention Trial.
† The administered drug was either glyburide or gliclazide.
‡ The administered drug was glyburide, gliclazide, or glipizide.
§ The administered drug was glyburide, glipizide, gliclazide, chlorpropamide, glimepiride, or tolbutamide.
¶ The type of sulfonylurea was unspecified.
‖ The administered drug was glyburide, glipizide, gliclazide, chlorpropamide, gliquidone, or tolbutamide.

Table 2. Doses, Baseline Demographic Characteristics, Study Periods, and Glycated Hemoglobin Levels.*

Study	Drug	Daily Dose	Population	Study Period	Age	Male Sex	Race†	Baseline Glycated Hemoglobin Level
					yr		percent	
100684	Rsg/Gly	4 or 8 mg	Korean patients with type 2 DM	Dec. 2003–July 2005	55.2	53.5	100 A	NA
	Gly	5–15 mg			54.5	45.6	100 A	NA
49653/143	Rsg/Gly	8 mg	Type 2 DM poorly controlled on glyburide	July 2000–Jan. 2003	52	45.3	44:56 B:H	9.2
	Gly	Usual care			53	48.3	38:62 B:H	9.4
49653/211	Rsg	4 mg	Type 2 DM with CHF	July 2001–Nov. 2003	64.3	84.3	99	7.7
	Plc	—			63.9	79.0	99	7.8
49653/284	Rsg/Met	4 or 8 mg/1 g	Type 2 DM	June 2001–Feb. 2003	55.5	51.1	72	8.1
	Met	1–2 g			55.6	51.0	71	7.9
7127S3/008	Rsg/Met	8 mg/1 g	Type 2 DM poorly controlled on Met	June 2003–Dec. 2005	54.6	63.2	70	NA
	Rsg/Met	4 mg/2 g			56.0	65.2	78	NA
	Met	2g			56.9	53.4	69	NA
AVM100264	Rsg/Met	4 or 8 mg/2 g	Overweight patients with type 2 DM poorly controlled on Met	July 2004–Jan. 2006	58.5	52.7	94	8.0
	Met/Su	2 g/titrated			59.3	52.5	95	8.0
BRL49653C/185	Rsg/ELM/Met	4 mg/1.5 g	Type 2 DM	May 2000–May 2002	58.0	65.2	76	7.5
	Rsg/ELM	4 mg			59.0	60.2	78	7.4
	Met/ELM	1.5 g			60.0	56.4	78	7.5
	ELM	—			57.0	60.9	83	7.4
BRL 49653/334	Rsg	4 or 8 mg	Type 2 DM or insulin resistance syndrome	March 2002–Nov. 2004	67.7	44.8	99	6.3
	Plc	—			67.3	47.7	100	6.3
BRL 49653/347	Rsg/insulin	4 mg	Type 2 DM poorly controlled on insulin	Nov. 2002–April 2004	52.6	48.1	57	9.0
	Rsg/insulin	2 or 4 mg			52.7	60.0	57	8.9
	Insulin/Plc	Usual care			53.8	46.2	57	9.1
49653/011	Rsg	8 mg	Type 2 DM	Sept. 1996–Sept. 1997	60.7	66.9	73	8.8
	Rsg	4 mg			59.6	64.5	75	9.0
	Plc	—			58.8	65.8	74	9.0
49653/015	Rsg/Su	4 mg	Type 2 DM	Aug. 1996–March 1998	60.6	53.2	98	9.2
	Rsg/Su	2 mg			61.0	62.8	86	9.2
	Su				61.9	57.3	97	9.2

49653/020	Rsg	8 mg	Type 2 DM	Oct. 1996–May 1998	60.9	57.6	97	8.2		
	Rsg	4 mg			60.4	68.2	99	8.1		
	Gly	Titrated			60.1	70.4	99	8.2		
49653/024	Rsg	4 mg once daily	Type 2 DM	Jan. 1997–Feb. 1998	57.5	58.6	76	8.9		
	Rsg	2 mg twice daily			56.8	59.1	78	8.9		
	Rsg	8 mg once daily			58.9	65.7	80	8.9		
	Rsg	4 mg twice daily			56.5	59.9	71	9.0		
	Plc	—			57.7	68.8	79	8.9		
49653/079	Rsg	4 mg	Type 2 DM poorly controlled on maximum dose of Gly	April 1997–March 1998	59.1	63.6	70	9.1		
	Rsg/Gly	4 mg/20 mg			57.7	69.4	70	9.2		
	Gly	20 mg			58.5	66.7	69	9.3		
49653/080	Rsg	8 mg	Type 2 DM	Nov. 1996–May 2000	55.1	75.0	73	8.9		
	Gly	2.5–5.0 mg			56.1	70.1	76	9.4		
49653/082	Rsg/insulin	8 mg	Type 2 DM poorly controlled on insulin	July 1997–Aug. 1998	57.7	54.3	71	9.0		
	Rsg/insulin	4 mg			57.1	56.6	72	9.1		
	Insulin	Usual care			55.6	55.8	68	8.9		
49653/085	Rsg/insulin	4 or 8 mg	Type 2 DM	May 2000–June 2001	61.3	54.0	99	NA		
	Insulin	Usual care			61.5	46.8	100	NA		
49653/093	Rsg/Met	8 mg/2.5 g	Type 2 DM poorly controlled on Met	June 1997–April 1998	57.8	60.0	58	8.7		
	Rsg	8 mg			58.8	53.7	59	8.7		
	Met	2.5 g			59.5	67.0	60	8.8		
49653/094	Rsg/Met	8 mg/2.5 g	Type 2 DM poorly controlled on Met	April 1997–March 1998	58.3	68.2	77	8.9		
	Rsg/Met	4 mg/2.5 g			57.5	62.1	80	8.9		
	Met	2.5 g			58.8	74.3	81	8.6		
49653/095	Rsg/insulin	8 mg	Type 2 DM poorly controlled on insulin	Aug. 1997–Dec. 1998	57.4	58.9	73	9.1		
	Rsg/insulin	4 mg			57.8	63.9	68	8.8		
	Insulin	Usual care			58.9	45.3	73	9.1		
49653/097	Rsg	8 mg	Type 2 DM	Aug. 1997–Jan. 2001	55.8	72.1	74	8.9		
	Gly	Titrated			56.0	70.8	84	8.8		
49653/125	Rsg/Su	4 mg	Type 2 DM	May 1999–Aug. 2000	54.6	45.7	56 A	9.1		
	Su	Usual care			57.3	42.4	59 A	8.9		
49653/127	Rsg/Gly	8 mg/<20 mg	Type 2 DM poorly controlled on Gly	Jan. 1999–Dec. 1999	60.0	51.0	75	9.1		
	Gly	<20 mg			59.4	66.0	75	8.9		

Table 2. (Continued.)

Study	Drug	Dose	Population	Study Period	Age	Male Sex	Race†	Baseline Glycated Hemoglobin Level
					yr		*percent*	
49653/128	Rsg/Su	4 mg	Type 2 DM on concurrent Su	May 1999–June 2000	58.3	51.3	100 A	9.6
	Su	Usual care			57.7	42.1	100 A	9.9
49653/134	Rsg/Gly/Met	8 mg	Type 2 DM on Gly and Met	March 1999–Aug. 2000	55.5	62.0	71	8.7
	Rsg/Gly/Met	4 mg			55.6	58.0	68	8.6
	Gly/Met	Usual care			55.8	61.0	71	8.7
49653/135	Rsg/Glip	4 or 8 mg/20–40 mg	Elderly patients with type 2 DM	May 1999–Oct. 2002	68.7	74.1	90	7.6
	Glip	20–40 mg			68.2	71.2	91	7.3
49653/136	Rsg/Su/insulin	4 or 8 mg	Type 2 DM with chronic renal failure on Su, insulin, or both	July 1999–June 2001	64.9	60.7	97	8.2
	Su/insulin	Usual care			66.3	60.8	98	8.3
49653/145	Rsg/Su	8 mg	Type 2 DM	Oct. 1999–Nov. 2000	61.1	57.3	97	8.5
	Su	Usual care			61.9	62.7	98	8.6
49653/147	Rsg/Su	8 mg	Indo-Asian patients with type 2 DM	July 1999–Aug. 2000	54.3	20.2	100 A	9.2
	Su	Usual care			54.1	25.3	100 A	9.1
49653/162	Rsg/Gly	8 mg	Type 2 DM	Nov. 2000–April 2002	60.0	55.1	97	7.9
	Gly	Maximum, 15 mg			59.9	61.8	96	8.0
49653/234	Rsg/Glim	8 mg	Type 2 DM	Jan. 2001–Feb. 2002	62.9	44.0	100	8.1
	Rsg/Glim	4 mg			60.5	57.0	100	8.2
	Glim	Up-titrated			65.0	60.0	100	7.9
49653/330	Rsg	8 mg	Chronic psoriasis	Jan. 2003–Oct. 2004	44.3	65.0	92	NA
	Rsg	4 mg			44.8	66.0	91	NA
	Rsg	2 mg			45.0	63.0	90	NA
	Plc	—			44.5	63.0	93	NA
SB-712753/003	Rsg/Met	4 or 8 mg/1–3 g	Mild type 2 DM	June 2003–Dec. 2004	58.9	54.7	98	7.2
	Met	1–3 g			59.0	55.5	99	7.2

49653/331	Rsg	4 mg	Chronic psoriasis	Jan. 2003–Oct. 2004	44.9	64.1	88	NA
	Rsg	2 mg			45.2	62.0	90	NA
	Plc	—			46.4	58.3	93	NA
49653/137	Rsg/Met	≥2 mg/≥1 g	Type 2 DM	April 2000–March 2004	60.0	63.4	78	NA
	Gly/Met	≥5 mg/≥1 g			58.8	68.9	76	
SB-712753/002	Rsg/Met	4 or 8 mg/2–3 g	Type 2 DM poorly controlled	July 2003–June 2004	58.1	58.3	97	7.4
	Met	2–3 g			57.6	56.8	98	7.5
SB-712753/007	Rsg/Met	2 or 8 mg/0.5–2.0 g	Type 2 DM without previous drug therapy	Oct. 2003–Dec. 2004	50.1	57.4	54	8.9
	Rsg	4 or 8 mg			51.5	56.5	58	8.8
	Met	0.5–2.0 g			50.6	58.5	59	8.8
SB-712753/009	Rsg/Met/insulin	8 mg/2 g	Type 2 DM with insulin	Oct. 2003–Nov. 2004	57.2	51.8	98	8.7
	Insulin	Usual care			56.9	53.1	99	8.8
49653/132	Rsg/Su	4 mg/usual care	Patients in China with type 2 DM	April 1999–Feb. 2000	58.9	47.6	100 A	9.9
	Rsg/Su	8 mg/usual care			59.0	41.4	100 A	9.7
	Su	Usual care			58.8	45.7	100 A	9.6
AVA100193	Rsg	2 mg	Mild-to-moderate Alzheimer's disease	Jan. 2004–May 2005	71.0	44.1	100	NA
	Rsg	4 mg			70.0	43.8	100	NA
	Rsg	8 mg			71.0	34.1	100	NA
	Plc	—			72.0	36.9	100	NA
DREAM	Rsg	4 or 8 mg	Impaired glucose tolerance or fasting glucose	July 2001–Aug. 2003	54.6	41.7	66	104.5‡
	Plc	—			54.8	39.9	66	104.5‡
ADOPT	Rsg	4 mg	Recently diagnosed type 2 DM	April 2000–June 2002	56.3	55.7	87	7.4
	Met	500 mg			57.9	59.4	89	7.4
	Gly	2.5 mg			56.4	58.0	89	7.4
Weighted adjusted means§								
	Rsg				56.1	60.7	84.4	8.2
	Control				56.9	53.3	77.5	8.2

* Rsg denotes rosiglitazone, DM diabetes mellitus, Gly glyburide, Plc placebo, CHF congestive heart failure, Met metformin, ELM enhanced lifestyle management, Su sulfonylurea, Glip glipizide, Glim glimepiride, and NA not available.
† Percentages are the proportion of white patients, unless otherwise specified as black (B), Hispanic (H), or Asian (A).
‡ The fasting plasma glucose level (in milligrams per deciliter) is listed.
§ Weighted adjusted means were calculated for the rosiglitazone and control groups by multiplying individual means by sample sizes, adding them together, and dividing the sum by the total sample size for each treatment group.

Table 3. Myocardial Infarctions and Cardiovascular Deaths in Rosiglitazone Trials.

Study	Rosiglitazone Group			Control Group		
	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause
		number			*number*	
49653/011	357	2	1	176	0	0
49653/020	391	2	0	207	1	0
49653/024	774	1	0	185	1	0
49653/093	213	0	0	109	1	0
49653/094	232	1	1	116	0	0
100684	43	0	0	47	1	0
49653/143	121	1	0	124	0	0
49653/211	110	5	3	114	2	2
49653/284	382	1	0	384	0	0
712753/008	284	1	0	135	0	0
AVM100264	294	0	2	302	1	1
BRL 49653C/185	563	2	0	142	0	0
BRL 49653/334	278	2	0	279	1	1
BRL 49653/347	418	2	0	212	0	0
49653/015	395	2	2	198	1	0
49653/079	203	1	1	106	1	1
49653/080	104	1	0	99	2	0
49653/082	212	2	1	107	0	0
49653/085	138	3	1	139	1	0
49653/095	196	0	1	96	0	0
49653/097	122	0	0	120	1	0
49653/125	175	0	0	173	1	0
49653/127	56	1	0	58	0	0
49653/128	39	1	0	38	0	0
49653/134	561	0	1	276	2	0
49653/135	116	2	2	111	3	1
49653/136	148	1	2	143	0	0
49653/145	231	1	1	242	0	0
49653/147	89	1	0	88	0	0
49653/162	168	1	1	172	0	0
49653/234	116	0	0	61	0	0
49653/330	1172	1	1	377	0	0
49653/331	706	0	1	325	0	0
49653/137	204	1	0	185	2	1
SB-712753/002	288	1	1	280	0	0
SB-712753/003	254	1	0	272	0	0
SB-712753/007	314	1	0	154	0	0
SB-712753/009	162	0	0	160	0	0
49653/132	442	1	1	112	0	0

Table 3. (Continued.)

Study	Rosiglitazone Group			Control Group		
	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause
		number			*number*	
AVA100193	394	1	1	124	0	0
DREAM	2635	15	12	2634	9	10
ADOPT	1456	27	2	2895	41	5
Total		86	39		72	22

farction and death from cardiovascular causes associated with rosiglitazone for subgroups defined according to the comparator drug. Similar results were obtained when the analysis excluded trials with an active comparator group. The heterogeneity P values were 0.53 for myocardial infarction and 0.68 for death from cardiovascular causes across subgroups. As compared with placebo or other antidiabetic regimens, the estimated odds ratios in all cases were greater than 1.0, suggesting that observed adverse effects during rosiglitazone treatment were not unique to any specific comparator regimen.

In an analysis that was not prespecified, we also studied the effects of rosiglitazone on death from any cause. The odds ratio for death from any cause was 1.18 (95% CI, 0.89 to 1.55; P=0.24).

DISCUSSION

Our data show that, as compared with placebo or with other antidiabetic regimens, treatment with rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that was of borderline significance. The similar odds ratio for comparison with placebo suggests that the increased risk associated with rosiglitazone was not a function of the protective effects of active comparator drugs. However, these findings are based on limited access to trial results from publicly available sources, not on patient-level source data. Furthermore, results are based on a relatively small number of events, resulting in odds ratios that could be affected by small changes in the classification of events. Nonetheless, our findings are worrisome because of the high incidence of cardiovascular events in patients with diabetes.[4] Because exposure of such patients to rosiglitazone is widespread, the public health impact of an increase in cardiovascular risk could be substantial if our data are borne out by further analysis and the results of larger controlled trials.

Although we did not have access to the source data to construct a composite outcome that included myocardial infarction or death from cardiovascular causes, the increase in the odds ratios for both of these end points suggests that observed adverse effects associated with rosiglitazone were probably not due to chance alone. This meta-analysis included a group of trials that were of relatively short duration (24 to 52 weeks). The odds ratio for these shorter-term trials was similar to the overall results of the meta-analysis. Thus, in susceptible patients, rosiglitazone therapy may be capable of provoking myocardial infarction or death from cardiovascular causes after relatively short-term exposure. In contrast, long-term therapies that improve cardiovascular outcomes, such as statins and antihypertensive drugs, often take several years to provide benefits. Notably, the estimates for the odds ratios for myocardial infarction and death from cardiovascular causes appear elevated for rosiglitazone in comparison with placebo or other commonly prescribed antidiabetic therapies (Table 5).

The mechanism for the apparent increase in myocardial infarction and death from cardiovascular causes associated with rosiglitazone remains uncertain. One potential contributing factor may be the adverse effect of the drug on serum lipids. The FDA-approved rosiglitazone product label reports a mean increase in low-density lipoprotein (LDL) cholesterol of 18.6% among patients treated for 26 weeks with an 8-mg daily dose, as compared with placebo.[25] In observational studies and lipid-lowering trials, elevated levels of

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

LDL cholesterol were associated with an increase in adverse cardiovascular outcomes. Thus, an increase in LDL cholesterol of the magnitude observed in the rosiglitazone group may have contributed to adverse cardiovascular outcomes, although the rapidity and magnitude of the apparent hazard was not consistent with an effect produced by lipid changes alone.

Several other properties of rosiglitazone may contribute to adverse cardiovascular outcomes. Rosiglitazone and other thiazolidinediones are known to precipitate congestive heart failure in susceptible patients.[26] Congestive heart failure is a physiological state that is associated with an increased intravascular volume. Volume overload increases stress on the left ventricular wall, a factor that determines myocardial oxygen demand. In susceptible patients, an increase in myocardial oxygen demand could theoretically provoke ischemic events. The administration of thiazolidinediones, including rosiglitazone, also produces a modest reduction in the hemoglobin level.[25] In susceptible patients, a reduced hemoglobin level may result in increased physiological stress, thereby provoking myocardial ischemia. A study of rosiglitazone that was conducted in rats reported an increase in the rate of death after experimentally induced myocardial infarction.[27]

Rosiglitazone is not the first PPAR agonist that has been reported to increase adverse cardiovascular events. Muraglitazar, an investigational dual PPAR-α and PPAR-γ agonist, increased adverse cardiovascular events, including myocardial infarction, during phase 2 and 3 testing.[28] After publication of an analysis of cardiovascular outcomes, muraglitazar was not approved by the FDA, and further development was subsequently halted by the manufacturer. Development programs for many other PPAR agonists have been terminated after evidence of toxicity emerged during preclinical studies or initial trials in humans. According to a former FDA official, more than 50 Investigational New Drug applications for novel PPARs have been filed, but no additional drugs have successfully reached the market in more than 6 years.[29] In some cases, these drugs have failed because of evidence of direct myocardial toxicity in studies in animals,[29] but few data on toxicity are available in the public domain because of the common industry practice of not publishing safety findings for failed products.

PPAR agonists such as rosiglitazone have very complex biologic effects, resulting from the activation or suppression of dozens of genes.[30] The patterns of gene activation or suppression differ substantially among various PPAR agonists, even within closely related compounds. The biologic effects of the protein targets for most of the genes influenced by PPAR agonists remain largely unknown. Accordingly, many different and seemingly unrelated toxic effects have emerged during development of other PPAR agents.[29] Some drugs have provoked multispecies, multiorgan system cancers; others have resulted in rhabdomyolysis or nephrotoxicity.[29] Troglitazone was withdrawn from the market for rare, but

sometimes fatal, liver toxicity. Accordingly, it must be assumed that a variety of unexpected toxic effects are possible when PPAR agonists are administered to patients.

The question as to whether the observed risks of rosiglitazone represent a "class effect" of thiazolidinediones must also be considered. Pioglitazone is a related agent also widely used to treat type 2 diabetes mellitus. However, unlike rosiglitazone, pioglitazone has been studied in a prospective, randomized trial of cardiovascular outcomes, called Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE).[31] The primary end point, a broad composite that included coronary and peripheral vascular events, showed a trend toward benefit from pioglitazone (hazard ratio, 0.90; P=0.095). A secondary end point consisting of myocardial infarction, stroke, and death from any cause showed a significant effect favoring pioglitazone (hazard ratio, 0.84; P=0.027). Notably, pioglitazone appears to have more favorable effects on lipids, particularly triglycerides, than does rosiglitazone.[32]

These emerging findings raise an important question about the appropriateness of the current regulatory pathways for the development of drugs to treat diabetes. The FDA considers demonstration of a sustained reduction in blood glucose levels with an acceptable safety profile adequate for approval of antidiabetic agents. However, the ultimate value of antidiabetic therapy is the reduction of the complications of diabetes, not improvement in a laboratory measure of glycemic control. Although reductions in blood glucose levels have been shown to reliably reduce microvascular complications of diabetes, the effect on macrovascular complications has proved to be unpredictable.[33] After the failure of muraglitazar and the apparent increase in adverse cardiovascular outcomes with rosiglitazone, the use of blood glucose measurements as a surrogate end point in regulatory approval must be carefully reexamined.

Our study has important limitations. We pooled the results of a group of trials that were not originally intended to explore cardiovascular outcomes. Most trials did not centrally adjudicate cardiovascular outcomes, and the definitions of myocardial infarction were not available. Many of these trials were small and short-term, resulting in few adverse cardiovascular events or deaths. Accordingly, the confidence intervals for the odds ratios for myocardial infarction and death from cardiovascular causes are wide, resulting in considerable uncertainty about the magnitude of the observed hazard. Furthermore, we did not have access to original source data for any of these trials. Thus, we based the analysis on available data from publicly disclosed summaries of events. The lack of availability of source data did not allow the use of more statistically powerful time-to-event analysis. A meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest. Although such a dedicated trial has not been completed for rosiglitazone, the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial may provide useful insights.[34]

Despite these limitations, our data point to the urgent need for comprehensive evaluations to clarify the cardiovascular risks of rosiglitazone. The manufacturer's public disclosure of summary results for rosiglitazone clinical trials is not sufficient to enable a robust assessment of cardiovascular risks. The manufacturer has all the source data for completed clinical trials and should make these data available to an external academic coordinating center for systematic analysis. The FDA also has access to study reports

Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

Comparator Drug	Odds Ratio (95% CI)	P Value
Myocardial infarction		
Metformin	1.14 (0.70–1.86)	0.59
Sulfonylurea	1.24 (0.78–1.98)	0.36
Insulin	2.78 (0.58–13.3)	0.20
Placebo	1.80 (0.95–3.39)	0.07
Combined comparator drugs	1.43 (1.03–1.98)	0.03
Death from cardiovascular causes		
Metformin	1.13 (0.34–3.71)	0.84
Sulfonylurea	1.42 (0.60–3.33)	0.43
Insulin	5.37 (0.51–56.52)	0.16
Placebo	1.22 (0.64–2.34)	0.55
Combined comparator drugs	1.64 (0.98–2.74)	0.06

and other clinical-trial data not within the public domain. Further analyses of data available to the FDA and the manufacturer would enable a more robust assessment of the risks of this drug. Our data suggest a cardiovascular risk associated with the use of rosiglitazone. 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.

Dr. Nissen reports receiving research support to perform clinical trials through the Cleveland Clinic Cardiovascular Coordinating Center from Pfizer, AstraZeneca, Daiichi Sankyo, Roche, Takeda, Sanofi-Aventis, and Eli Lilly. Dr. Nissen consults for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. No other potential conflict of interest relevant to this article was reported.

We thank Craig Balog for statistical programming support.

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CORRECTION

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes . The fifth and sixth sentences of the first paragraph of the Methods section (page 2458) should have read "Of the remaining 42 studies, 38 reported at least one myocardial infarction, and 23 reported at least one death from cardiovascular causes. In these trials, 15,565 patients were randomly assigned to regimens that included rosiglitazone, and 12,282 were assigned to comparator groups with regimens that did not include rosiglitazone." The last sentence of the third paragraph of the Methods section should have read "In this group of 35 trials, 9507 patients were randomly assigned to receive rosiglitazone, and 5960 patients were assigned to receive various comparator drugs." In Table 1 (page 2461), the subtotal in the rosiglitazone group should have been 9507 rather than 9502, and the subtotal in the control group should have been 5960 rather than 5961, which brings the total number of patients in the rosiglitazone group to 15,565 and the total in the control group to 12,282. In Table 4 (page 2468), the rate of myocardial infarction in the small trials combined should have read "44/10,285" for the rosiglitazone group and "22/6106" for the control group. The rate of myocardial infarction for the ADOPT trial should have read "41/2895 (1.42)" for the control group. Death from cardiovascular causes in the small trials combined should have read "25/6845 (0.36)" for the rosiglitazone group and "7/3980 (0.18)" for the control group, death from cardiovascular causes in the DREAM trial should have read "12/2635 (0.46)" for the rosiglitazone group, and death from cardiovascular causes in the ADOPT trial should have read "5/2895 (0.17)" for the control group. The text and tables have been corrected on the *Journal*'s Web site at www.nejm.org.

FOOTNOTE 12

"John McMurray"
<j.mcmurray@[redacted]
>
29-May-2007 00:34

To Nigel.P.Jones[redacted]
cc hanefeld@[redacted],
henning.beck-nielsen@[redacted],
Philip.Home@[redacted], rgomis@[redacted]
bcc
Subject Re: URGENT. RECORD MS REQUIRING REVIEW WITHIN 24 Hours

Here are my (extensive) comments (as track changes etc) - only on Methods, results and Discussion at moment.

There are several striking issues:

1) The HR ratio (and 95% CI) for MI in RECORD is not inconsistent with Nissen's - and he had more events; what's to stop him adding the events from RECORD to his meta-analysis and re-enforcing his view? Stuart - if we write (as we have done) that we have completed 2/3 of planned follow-up, could the informed reader conclude that the trial will never be able to exclude a significant hazard of rosiglitazone?

2) Same is true for CV death, although the number of events in RECORD and in the meta-analysis are similar and at least in RECORD the HR is in the other direction!

3) Manuscript looks to me to play down 239% INCREASE in HF. I have taken the liberty of doing some rewording.

4) The big discrepancy between the numbers for the primary composite and the CV death/MI/stroke composite is striking - more than twice as many primary outcomes - if I was the reviewer I would want to know what are all those additional events are and whether they are swamping (hiding?) important events. Is the MI signal supported by a similar signal in other acute coronary syndromes? A CV death/MI/stroke/HF composite would also be valuable in giving a better perspective on "hard" CV outcomes - looking at HF alone is not helpful.

5) The BIGGEST thing to me is how little is said about what seems to me to be a really extraordinary step in CV trials - publication of an interim analysis of an ongoing trial - is there any precedent for that? What are the implications for future trials? I can think of a few in the CV community at least who will be very critical (although whether they do this publicly or not is another matter).

6) I didn't think the order of the Discussion was correct

Only my views of course!

John

FOOTNOTE 13, 55

The NEW ENGLAND JOURNAL of MEDICINE

Philip D. Home, M.D.
Newcastle University
NE1 7RU
United Kingdom
Email: philip.home@[redacted]

June 1, 2007

Re manuscript 07-3394

Dear Prof. Home:

On behalf of the editors of the New England Journal of Medicine, I want to thank you for submitting your interesting manuscript titled, "Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) Study: Interim Findings on Cardiovascular Hospitalizations and Deaths." We have completed our review of your manuscript, and I am pleased to inform you that the manuscript has been recommended for publication in the Journal, subject to appropriate revisions. The purpose of this letter is to underscore and prioritize the revisions that the editors believe are necessary if we are to proceed with your manuscript.

The manuscript has been read by many members of the editorial staff and eight reviewers. Below we have summarized the critical points that require changes in the manuscript in response to each reviewer's concerns. We expect your revisions to carefully address all of the points raised below. Please understand that we cannot make a final commitment to publish your manuscript until we have received a revised version that successfully addresses each point in the critiques.

Reviewer A:
Please pay particular attention to paragraphs 3-9 in this review.
The reviewer points out that given the 95% CI around the primary endpoint (0.89 to 1.31 for the adjudicated endpoints, or 0.93 to 1.32 for all endpoints), the data demonstrate neither non-inferiority nor inferiority. That is, the data are inconclusive about the question of increased risk in the rosiglitazone arm. This reviewer, along with other reviewers, asks that you modify the language in multiple locations in the manuscript to tone down your conclusions. This is especially important given that this is an unplanned interim analysis of an ongoing trial, a fact that introduces additional uncertainty. Please note that, in the opinion of all readers, the data that you present are completely compatible with the results of the meta-analysis by Nissen and the meta-analysis for myocardial ischemic events posted on the GSK Web site [http://ctr.gsk.co.uk/Summary/rosiglitazone/studylist.asp].

Reviewer B:
Please note the reviewer's point #4 (Interpretation of Results). The reviewer underscores that your interpretation of a nonsignificant difference as "no evidence of a difference" is not acceptable. The data must be interpreted in the light of the 95% CIs, which are compatible with as much as a 7% reduction in risk of the primary endpoint, or as much as a 32% increase in risk of the primary endpoint. For the MI endpoint, which was a focus of the Nissen meta-analysis, there is considerable overlap of the 95% CIs of the point estimates in the RECORD trial and the Nissen meta-analysis. This reviewer points out that MI relative risks in the two studies do not differ significantly. The editors feel strongly that your data do not support the statement that the RECORD results for MI contradict the Nissen meta-analysis; this statement must be removed or modified.

Reviewer C:
The editors agree with all the points raised by this reviewer, and it is essential that all these thoughtful comments be addressed by making changes in the manuscript. The third paragraph of the review deals with the lack of blinding. The fourth paragraph deals with the weak choice of a primary endpoint, since cardiovascular hospitalizations do not always involve coronary-related events, and therefore noise is introduced (for example, atrial fibrillation or valvular heart disease). The sixth paragraph points out the serious problem of the low event rate, especially for MI events, in this study. Do you have an explanation for the very low event rate? This should be explicitly addressed in the revised manuscript. There is concern that there may have been a failure to ascertain events. The reviewer also reiterates points made by reviewer A and B about the wide 95% CIs for the point estimates, and the need to greatly tone down your language to reflect the substantial level of uncertainty in the data.

Reviewer D:
Please pay particular attention to the first and third paragraphs of this review. The editors agree that you should present alternative analyses including events pending adjudications for all outcomes that you include in this manuscript. Given the very low power of your study at this point, it is sensible to include all endpoints reported by the investigators, not just the adjudicated ones, since this will add power. The editors also agree that an explanation of the rationale for the continued use of rosiglitazone is needed in this manuscript.

Reviewer E:
Please give special attention to points #2, 9, 10, 12, and 14. Some of these points request changes in wording. Point #9 asks for the rationale for the 20% non-inferiority margin. We realized that this was determined long ago, but the reader should not have to refer back to your methods article to understand how this margin was determined.

Reviewer F:
In points #1 through 5, this reviewer effectively underscores points made by other reviewers, thus no new specific response is required here, except with regard to the issues

concerning loss to follow up (Comments #2 and 3). The loss to follow up impacts on the power of the study, and also raises the question of the fate of those lost to follow up.

Reviewer G:
While underscoring many of the points made in other reviews, this reviewer also points out that "the Kaplan-Meier curves, point estimates, and event rates suggest a reasonably high probability that the study will fail to show non-inferiority at trial completion. Note the pattern of separation beginning at 18-24 months with a gradual widening of the differences over time (particularly in the version that includes events pending adjudication)." The editors were also struck that the K-M curves (Figure 1b) appear to be progressing in a direction of cardiovascular harm for rosiglitazone, raising the question of whether the study will fail to establish non-inferiority. Please comment on this trend.

When you send in your revised manuscript, please include a covering letter that lists the reviewers' comments and provides a response to each. You should return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. The revised manuscript should be triple-spaced, including references, tables, and figure legends. Please include a word count for the text. Your revised paper should not exceed 2500 words. The title cannot contain more than 75 letters and spaces. You should submit your revised manuscript using the *Journal*'s online-submission Web site. Please go to **http://authors.nejm.org/** and select "**Submit a Revised Manuscript**."

During the preparation of your revised manuscript, please complete the attached "**Manuscript Checklist**" and return it with your submission. Failure to return the form will delay the processing of your manuscript.

A combined **Disclosure and Authorship Statement** is also attached. Each author must complete and sign a copy. To ensure that it is legible, please fill out the form directly on your computer, print it out, sign it, and return it by fax to 617-739-9864. It is essential that you return the signed forms as soon as possible, because we cannot process your manuscript without them.

Please recall that the *Journal* requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the *Journal*. Copies of any related manuscripts should be submitted along with the revised manuscript, if this has not already been done. If you have any questions about compliance with these policies, please contact the editorial office for clarification.

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. Please ask all authors to sign and fax back the enclosed form as soon as possible. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The editors want to thank you again for allowing us to review your interesting work. We look forward to reading the revised version of your manuscript. Given the high interest in this dataset, we would like to receive your revised manuscript no later than 08:00 hrs Eastern Daylight time (13:00 hours in the UK or GMT-4) in the U.S. on Monday June 4, 2007. If you need to consult with an editor over the weekend, please call Dr. Gregory Curfman on his mobile phone at (978) [redacted]

Sincerely,

Gregory D. Curfman

Gregory D. Curfman M.D.
Executive Editor
gcurfman@nejm.org
Mobile: (978)-[redacted]
Office (but not over the weekend): (781) [redacted]

FOOTNOTE 15

Assessment of the cardiovascular risks and health benefits of rosiglitazone

David J. Graham, MD, MPH

Office of Surveillance and Epidemiology
Food and Drug Administration

July 30, 2007

Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007

The questions of greatest importance to OSE

1° Does RSG increase the risk of CV events, most importantly, cardiac death, AMI, and stroke?

2° Does CV risk with RSG differ from that of PIO?

3° Does CV risk with RSG differ from that of other oral anti-diabetic agents (e.g., Met, SU)?

If answer to any question is "yes"

- Do the documented health benefits of RSG justify its cardiovascular risks?

Randomized clinical trials data and the OSE question they help to address

Study	Comparison group	Of relevance to Question #
ADOPT	Active	3?
BARI 2D	Active	3?
DREAM	PBO	1,2
GLAI	PIO	2
PIO meta	Mixed	2
PROactive	PBO	2
RECORD	Active	3?
RSG meta	PBO	1,2

Does rosiglitazone use increase the risk of cardiac death, AMI and stroke?

RSG meta-analysis
DREAM

Overview of RSG meta-analysis and DREAM

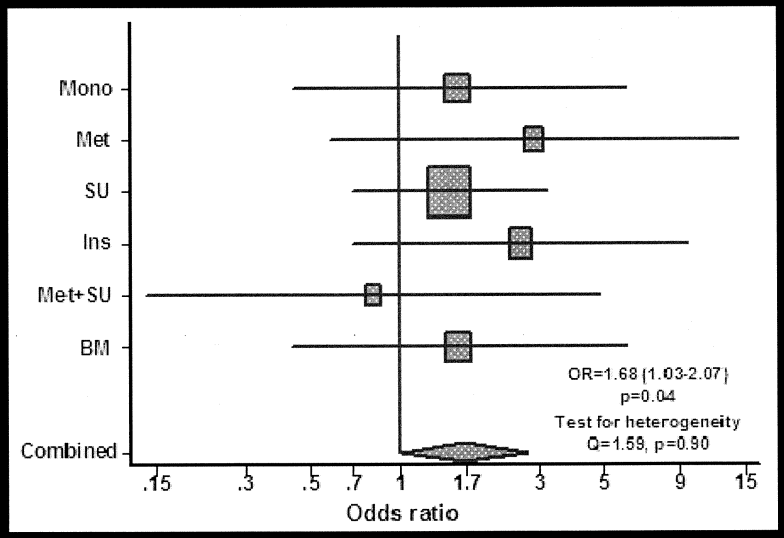
RSG meta-analysis

- 1° outcome: total and "serious" Ischemic Heart Disease
- Mean duration DM 5 yrs
- PBO add-on control accounted for 86% of RSG exposure-time; mean f/u ~6 mos
- *Post hoc* adjudication of routinely reported events

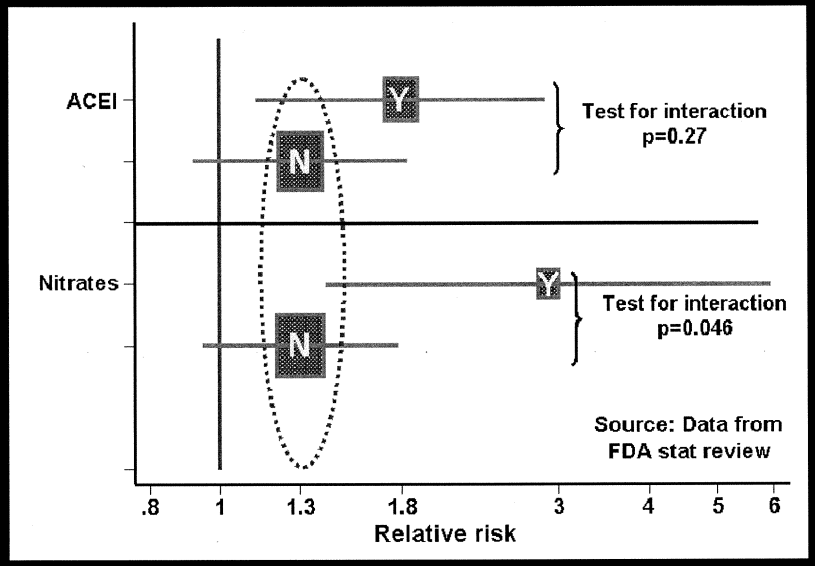
DREAM

- Pre-diabetics; PBO-controlled; f/u ~4.5 years
- Adjudicated CV outcomes

Meta-analysis of "serious" IHD risk with rosiglitazone from placebo-controlled trials only



Potential for interactions from RSG meta-analysis



CV outcomes from DREAM by treatment arm

	RSG + ACEI	ACEI only	RSG only	PBO only
N	1310	1313	1325	1321
CV composite (%)	3.4	1.8	2.4	2.4
AMI (%)	0.8	0.2	0.4	0.5
CHF (%)	0.8	0.1	0.2	0.1

Does RSG increase CV risk?

- Yes
  - FDA meta-analysis shows 20%-68% increased risk with 6-12 months RSG use compared to non-use, especially noticeable in the placebo-controlled analysis
  - DREAM shows ~40% increased risk with RSG
    - Relatively low-risk population; placebo-controlled
    - Uncertainty about what the possible ACEI "interaction" findings mean, but CV risk is increased
    - In 2006, 54% of RSG users took concomitant ACEIs or ARBs, and there is evidence to suggest that all patients with T2DM might benefit from their use

Does rosiglitazone increase CV risk compared to pioglitazone?

PIO meta-analysis

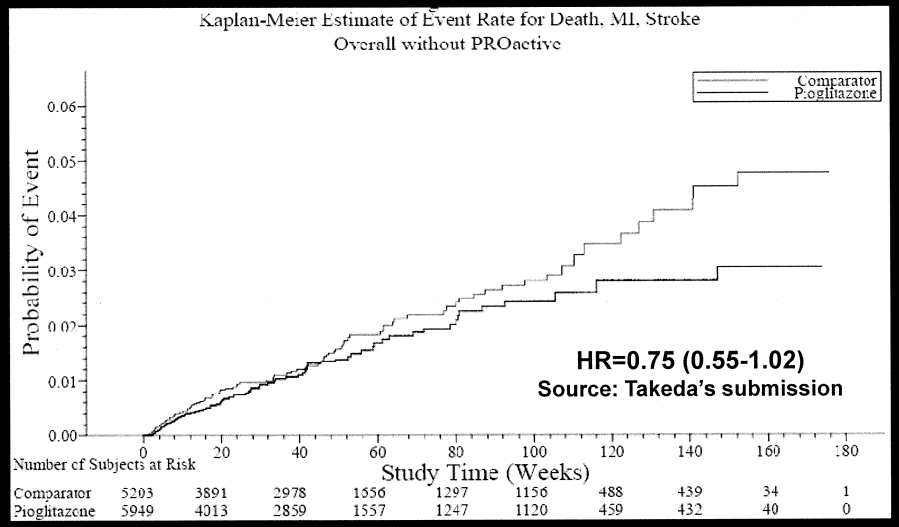
PROactive

GLAI

Pioglitazone meta-analysis of clinical trials

- All randomized, double-blind, controlled trials in Takeda's clinical trials database excluding PROactive
  - 10,199 PIO patients; 11,247 PIO person-years
- Submitted in Oct 2006; FDA review completed Jan 2007; FDA re-analysis not performed
- Pre-specified patient-level, time-to-event analysis, stratified by category of study duration
- 1° outcome: all deaths + nonfatal AMI + nonfatal CVA
  - Identified from standard RCT AE reporting process
  - Not adjudicated

Cardiovascular outcomes from PIO meta-analysis of clinical trials (excludes PROactive)



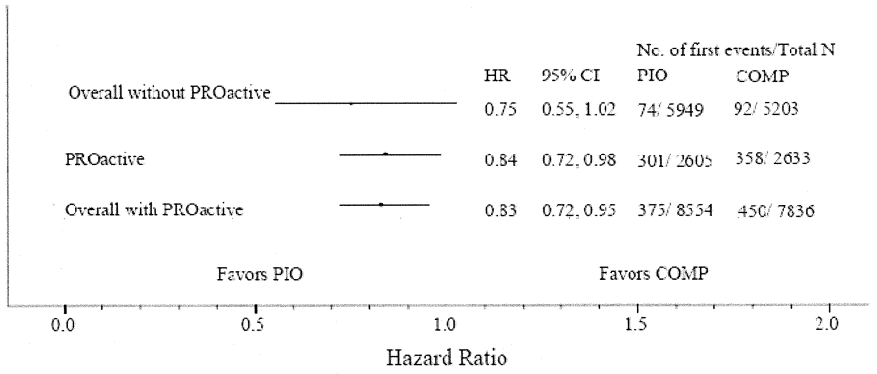
PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive)

- Randomized, double-blind, add-on PBO-controlled
- Mean follow-up: 34.5 months
- 1° outcome:
  - All-cause mortality, nonfatal AMI, nonfatal CVA, coronary revascularization, acute coronary syndrome, leg amputation, leg revascularization
    - HR = 0.90 (0.80-1.02)
- 2° outcome:
  - All-cause mortality, nonfatal AMI, nonfatal CVA
    - HR = 0.84 (0.72-0.98)

Summary of meta-analysis of pioglitazone clinical trials including PROactive

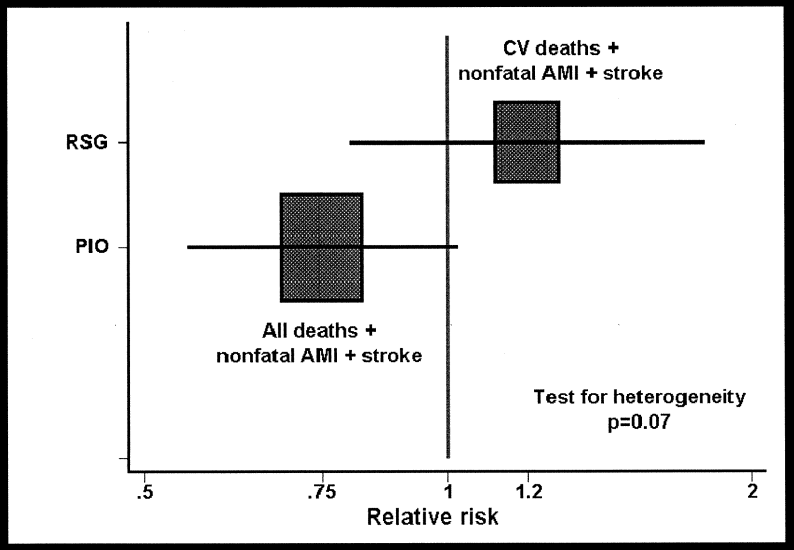
Source: Takeda's submission

Figure 4.a **Time to Composite Endpoint Events of All-cause Death, Nonfatal MI, or Nonfatal Stroke**



N=Number of randomized subjects; PIO=Pioglitazone; COMP=Comparator.

Comparison of CV risk observed in meta-analyses of RSG and PIO



Study H6E-US-GLAI: head-to-head RSG *vs.* Pio

- Study results submitted to FDA Feb 2005 by Takeda
- FDA review completed November 2005
- Randomized, double-blind; 24 wks
- Assessment of lipid effects
- CV events collected; not adjudicated
  - Case report descriptions very convincing
- Balanced with respect to age (56 years), duration of T2DM (4 years), HgbA1c (7.6%); BMI (33)

Cardiovascular risk of RSG *vs.* Pio from GLAI

	RSG	PIO
N	366	369
Person-years	169	170
Cardiac SAEs[1]	7	2
Rate per 100 pyrs	4.1	1.2

RR = 3.52 (0.67-34.7), p=0.11

[1] RSG: sudden death 1, AMI 1, emergency CABG 4, unstable angina 1
PIO: AMI 1, emergency CABG 1

Does CV risk with RSG differ from that with PIO?

- Yes
  - From DREAM, relatively low-risk population:
    RSG increased risk by ~40% c/w PBO
  - From PROactive, high risk population:
    PIO decreased risk by ~15% c/w PBO
  - From RSG meta-analysis:
    RSG increased risk of serious IHD by ~40% c/w all comparators & by ~70% c/w PBO
  - From PIO meta-analysis:
    PIO decreased risk by ~25% c/w all comparators
  - From head-to-head GLAI:
    RSG increased risk 3.5-fold c/w PIO

Does CV risk with rosiglitazone differ from that of metformin and sulfonylurea oral anti-diabetic agents?

ADOPT

RECORD

BARI 2D

A Diabetes Outcome Progression Trial (ADOPT)

- Recently diagnosed T2DM (mean=1.1 yrs)
- All outcomes were efficacy-related
- No pre-specified CV outcomes
- No CV adjudication; *post hoc* arbitration of CHF

Pertinent adverse event data from ADOPT

Source: N Engl J Med 2006; 355:2427-43

	RSG	Met	SU	Met+SU
N	1456	1454	1441	2895
CV disease (%)	3.4	3.2	1.8	2.5
AMI (%)	1.8	1.5	1.2	1.4
CHF (%)	1.5	1.3	0.6	1.0
CVA (%)	1.1	1.3	1.2	1.2
PVD (%)	2.5	1.9	2.2	2.0
Edema (%)	14.1	7.2	8.5	7.8

Limitations of BARI 2D

- BARI 2D not designed to answer questions about specific drugs
- Assignment to RSG or metformin not blinded or random
- BARI 2D will not meaningfully inform the issue of RSG's CV risk *vís a vís* other oral anti-diabetes meds
- Markedly low statistical power for drug-specific CV risk questions
- The finding of increased risk in RSG + insulin meta-group may have implications for BARI 2D

Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD)

- Randomized, non-inferiority, open-label; active-control
- Concerns:
  - Noninferiority design has intrinsic limitations for safety
    - Suboptimal study execution related to AE identification and reporting could mask differences between groups
  - Noninferiority margin too large (20%) & rationale not provided
  - Open-label (increases bias potential)
  - 1° endpoint not focused on most important CV outcomes
  - Very low to absent statistical power

Statistical power of ADOPT, BARI 2D, and RECORD to exclude a 20% increase in risk of cardiovascular death + AMI + stroke for RSG *vs.* Met

	ADOPT	BARI 2D	RECORD
Power to exclude RR=1.2	<10%	<10%	<10%

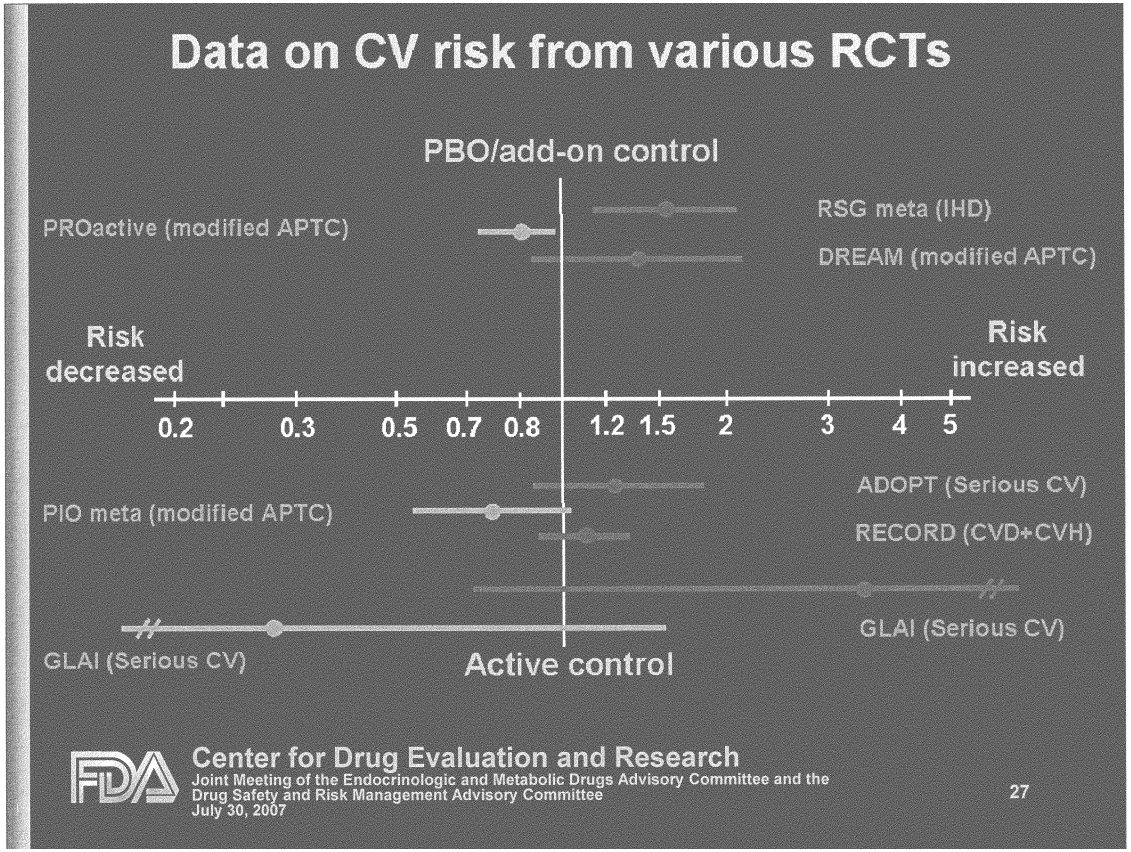
None of these studies will provide meaningful evidence about the comparative cardiovascular risk of rosiglitazone and metformin

The hidden dangers of low statistical power when dealing with a comparative safety issue

- Low power = high “type II” error rate
  - Probability of concluding that treatments are similar when they really differ
- Consequences of low power
  - Falsely concluding that treatments are similar when important differences in risk exist
  - Promotes a false sense of security and complacency
  - Leads to failure to take appropriate measures to protect patients from unnecessary harm
- “Absence of evidence is not evidence of absence”

Does the CV risk of RSG differ from that of metformin or sulfonylurea?

- The data provide inadequate and insufficient evidence to conclude that RSG does not increase CV risk compared to metformin or sulfonylureas
- Neither RECORD nor BARI 2D will provide meaningful answers to this question


Data on CV risk from various RCTs
PBO/add-on control
PROactive (modified APTC)
RSG meta (IHD)
DREAM (modified APTC)
Risk decreased
Risk increased
0.2
0.3
0.5
0.7
0.8
1.2
1.5
2
3
4
5
PIO meta (modified APTC)
ADOPT (Serious CV)
RECORD (CVD+CVH)
GLAI (Serious CV)
GLAI (Serious CV)
Active control
Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007
27

Population impact of cardiovascular risks and benefits of rosiglitazone use

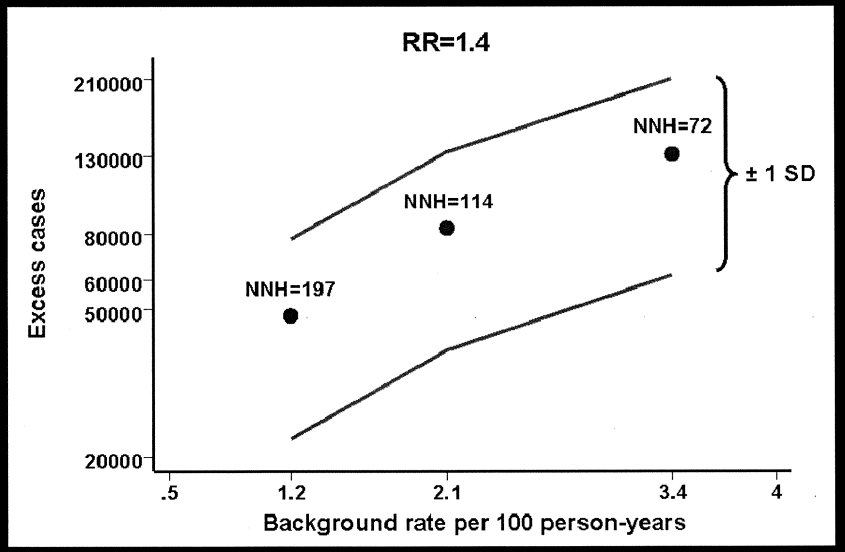
Sources of data for estimation of excess cases of cardiovascular deaths and nonfatal AMI (1)

- Estimates of the relative risk for CV events obtained from RSG meta-analysis & DREAM
- Background rates of CV death + nonfatal AMI, and CV death + nonfatal AMI + nonfatal stroke from published literature
- National prescription data used to estimate person-years of RSG use (time at-risk)

Sources of data for estimation of excess cases of cardiovascular deaths and nonfatal AMI (2)

- Analysis accounted for variability in level of excess risk while focusing on range of most likely risk
  - By using three point estimates of relative risk
    - RR=1.2 (“MACE” RSG meta-analysis)
    - RR=1.4 (RSG meta-analysis; DREAM)
    - RR=1.7 (RSG meta-analysis of PBO-controlled data)
  - ± 1 standard deviation (68% confidence intervals)
  - By using the inter-quartile range for the background event rates in diabetic patients

Excess cases of cardiac death and nonfatal AMI attributable to RSG use over the range of expected background rates in diabetic patients, 1999-2006



Excess cases of serious CV events attributable to RSG use over the range of expected background rates in diabetic patients, 1999-2006[1]

	RR=1.2	RR=1.4	RR=1.7
CV death + nonfatal AMI	41K (20K-67K)	83K (39K-133K)	129K (60K-219K)
CV death + nonfatal AMI + stroke	66K (31K-110K)	131K (62K-210K)	205K (95K-338K)

[1] Point estimate (± 1 SD) estimated at the median background rate

RSG health benefit assessment (1)

- What benefits are we interested in?
  - How does RSG compare to PIO?
  - How does RSG compare to Met or SU?
  - Are there benefits unique to RSG?
- Two systematic reviews provide insight
  - Bolen et al. Ann Intern Med 2007
    Oral anti-diabetes agents
  - Bandeira-Echtler et al. Cochrane Collaboration 2007
    Rosiglitazone

RSG health benefit assessment (2): Major clinical outcomes

	Evidence to support RSG benefit
CV composite	None
CV death	None
Nonfatal AMI	None
Stroke	None
Diabetic complications	None
Retinopathy	None
Nephropathy	None
Neuropathy	None

Source: Cochrane Collaboration 2007

RSG health benefit assessment (3): Intermediate outcomes

	Met	TZD	SU	Repag
HgbA1c	↓	↓	↓	↓
HDL-C		↑		
LDL-C	↓	↑		
Weight		↑	↑	↑
Heart failure		↑		
Hypoglycemia			↑	↑
Bone fractures		↑		

Source: Ann Intern Med 2007

RSG health benefit assessment (4)

- No major clinical health benefits have been demonstrated for RSG
  - No macrovascular benefits
  - No microvascular benefits
- RSG confers no clear advantage over other oral anti-diabetes drugs for a variety of intermediate outcomes
- RSG confers no unique advantage over PIO and appears to be inferior to PIO with respect to some intermediate outcomes (HDL-C, LDL-C, triglycerides)

Risks, benefits, and degree of certainty (1)

- At approval, "definitive proof" of efficacy obtained; health benefit is assumed, not demonstrated or "proven"
  - But efficacy measures often don't translate into long-term benefits
- When postmarketing safety concerns arise, reappraisal of "assumed benefit" is necessary; benefit-risk assessment must be made at the population-level
- "Actionable" threshold of evidence for serious risk is not "definitive proof"
  - Rarely possible due to statistical power (at least 95% power needed to minimize false negative conclusion)
  - Unreasonably high threshold, considering obligation to protect public from serious harm

Risks, benefits, and degree of certainty (2)

- Despite uncertainty, the analysis must take into account the potential consequences of the risk, as well as the magnitude and certainty of health benefits
- Prior measures of efficacy often inadequate to justify serious risk; actual health benefits are essential
- For a health benefit to justify a serious risk, it must be *clinically important and meaningful*, of *comparable or greater health-value*, and of *greater frequency of occurrence* than the risk; and *there must be definitive evidence to support the benefit*.

Decision analysis of RSG risks and benefits

- The cost of a wrong decision is not symmetric
  - First, absolutely no evidence of major clinical health benefits with RSG
  - If RSG increases CV risk, wrong decision will cost thousands of lives
  - If RSG doesn't increase CV risk, wrong decision causes no population harm; other therapies are available
- The data on RSG CV risk, though not definitive, strongly suggest the following:
  - RSG CV risk is increased (3 studies: RSG meta-analysis, DREAM, GLAI)
  - PIO CV risk is not increased, and may be decreased compared to other therapies including RSG (3 studies: PIO meta-analysis, PROactive, GLAI)
  - Other studies such as BARI 2D and RECORD will not provide adequate evidence to refute these findings

Conclusions

- RSG increases cardiovascular risk compared to its non-use
- PIO does not increase cardiovascular risk
- RSG has no unique short-term benefits related to glycemic control
- RSG has no demonstrated long-term health benefits related to cardiovascular disease, diabetic retinopathy, nephropathy, or neuropathy
- Given these conclusions, are there definitively documented population-level health benefits of RSG to justify its continued marketing?
  - No
  - RSG should be removed from the market

Acknowledgments

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FDA library staff

FOOTNOTE 16, 19

ADVISORY BOARD EXECUTIVE SUMMARY REPORT

GSK Diabetes Franchise Cardiology Advisory Board
March 1-2, 2007
Boston, Massachusetts
Date of Report: March 16, 2007

To: Karen Colquitt-Hall
Cc: Shannon Stevens

Meeting Overview (purpose, objectives, and tactics; 2–3 paragraphs MAXIMUM)

The objectives of this meeting were to review and assess 2 post hoc CV safety analyses (CV Integrated Clinical Trials Analyses and CV Safety Epidemiology Study) and data from recent clinical trials (DREAM, ADOPT, PROactive, and Study 211) as they relate to the risk vs benefit of Avandia across the diabetes disease continuum. Particular emphasis was placed on obtaining input on the significance of heart failure and ischemic events associated with Avandia from the advisors, and guidance on cardiovascular questions from the FDA that GSK will need to address upon filing of these data for a change in Avandia labeling.

Agenda

Thursday, March 1, 2007

Afternoon	Arrivals
5:00 PM	Slide review for presenters
7:00 PM	Buffet dinner

Friday, March 2, 2007

7:00 AM	Breakfast
7:45 AM	**General Session**
7:45 AM	GSK Welcome and Introduction of Program Chairman *Eric Dube, PhD*
7:55 AM	Welcome, Advisory Board Objectives, and Meeting Plan *Richard W. Nesto, MD, Chairman*
8:05 AM	Rosiglitazone Cardiovascular Pharmacovigilance: Integrated Clinical Trials Analyses and Epidemiology Study *Alexander R. Cobitz, MD, PhD, and Carol E. Koro, PhD*
8:45 AM	Discussion: Integrated Clinical Trials Analyses *Richard W. Nesto, MD, Moderator*
9:35 AM	Discussion: Epidemiology Study *Richard W. Nesto, MD, Moderator*
10:10 AM	Break
10:30 AM	DREAM: Review of Results *Nikheel S. Kolatkar, MD, MPH*

Friday, March 2, 2007 (continued)

GSK CONFIDENTIAL

10:50 AM Discussion: DREAM
Richard W. Nesto, MD, Moderator

11:20 AM ADOPT: Review of Study Results
Paul Aftring, MD, PhD

11:50 AM Discussion: ADOPT
Lawrence A. Leiter, MD, FRCPC, FACP, Moderator

12:15 PM Working Lunch/ Continuation of ADOPT and DREAM Discussion

1:15 PM Key Findings From PROactive
Richard W. Nesto, MD

1:30 PM Discussion: PROactive
Richard W. Nesto, MD, Moderator

2:00 PM Effects of Rosiglitazone on Cardiovascular Structure and Function in Patients With Type 2 Diabetes and Congestive Heart Failure (Study 211)
Steve McMorn, PhD

2:30 PM Discussion: Cardiovascular Safety Data With Avandia
Richard W. Nesto, MD, Moderator

3:15 PM Summary and Next Steps, Meeting Closure
Richard W. Nesto, MD, Chairman

3:20 PM Departures

Attendees (Earlier Day)

Last Name	First Name	City, State	High	Average	Low
Bakris	George	Chicago, IL	X		
Cannon	Christopher	Boston, MA		X (arrived late)	
Carson	Peter	Washington DC		X	
Deedwania	Prakash	Fresno, CA		X	
Fowler	Michael	Palo Alto, CA	X		
Greenberg	Barry	San Diego, CA		X	
Leiter	Lawrence	Toronto, Canada	X		
Nesto	Richard	Burlington, MA	X		
Plutzky	Jorge	Boston, MA		X (left early)	

Meeting Content

Presentation: Welcome, Objectives, and Meeting Plan
Presenters: Eric Dube, PhD, and Richard W Nesto, MD, Chairman
Presentation Synopsis: Dr Dube welcomed the attendees on behalf of GlaxoSmithKline and thanked them in advance for their helpful perspectives on the new data to be presented at the meeting. Dr Nesto provided an overview of the objectives and meeting plan. He encouraged candid feedback from the advisors, noting that the presentations would address the full spectrum of data, from prediabetes to late-stage diabetes, allowing for discussion of Avandia across the disease continuum. Dr Nesto also reminded the advisors that GSK would be presenting data from Study 211 that had not been published yet.

Presentation: Rosiglitazone Cardiovascular Pharmacovigilance: Integrated Clinical Trials Analyses and Epidemiology Study

Presenters: Alexander R. Cobitz, MD, PhD, and Carol E. Koro, PhD

Presentation Synopsis: Dr Cobitz introduced the rationale for GSK's cardiovascular pharmacovigilance program, and he outlined the methods used in the Integrated Clinical Trials Analyses. These analyses revealed that the use of rosiglitazone in combination with a sulfonylurea (SU) or insulin resulted in an increased incidence of congestive heart failure (CHF). The risk of myocardial ischemia was also higher in rosiglitazone-treated patients (1.99% vs 1.51%; hazard ratio of 1.31) as compared with comparators. Dr Koro presented the CV Safety Epidemiology Study, which was designed to complement the Integrated Clinical Trials analyses. She outlined the design of the study and described the propensity score matching technique. Overall, the epidemiology study showed comparable risk with rosiglitazone and comparators - a finding not consistent with data from the Integrated Clinical Trials. Dr Koro provided a few hypotheses as to why the data were inconsistent, and she led the advisors into a discussion of the differences between the 2 data analyses.

Discussion: Integrated Clinical Trials Analyses

Moderator: Richard W. Nesto, MD

Key Questions	Answers/Findings
▪ What impact does the CV Integrated Clinical Trials Analyses have on the perceived risk/benefit of Avandia?	▪ Before discussing the risk vs benefit of Avandia, the advisors debated at length over the definition of CHF, as used in these trials and in general medical terminology. Dr Carson stated that CV adverse effects (AEs) in rosiglitazone and pioglitazone are characterized by fluid retention and should not be termed CHF. Dr Fowler countered with the argument that fluid retention characterizes CHF. He later made the point that it is important to fully describe the nature of CHF; for instance, physicians should differentiate between fluid retention and worsening angina. ▪ Dr Nesto commented that the CV effect seen in the Integrated Clinical Trials Analyses with rosiglitazone was small but real, and that it is counter to the proposed CV benefits associated with Avandia. Dr Carson agreed, noting that all data pointed to rosiglitazone having a hazard ratio greater than unity. ▪ Dr Plutzky noted that the duration of type 2 diabetes (T2DM) will affect AEs, and that the length of time that a patient is diabetic is as relevant as what medications he or she is taking. Dr Bakris added to this point, stating that patients taking insulin were more likely to be older and to have already failed to reach normoglycemia on metformin or SU. He stressed the importance of stratifying patients by the natural history of their disease, duration of disease, and dose of study medication. It was also suggested that the ischemic changes may be caused by changes in heart rate, resulting from weight gain and related sympathetic activation. ▪ Dr Leiter expressed concern that the Integrated Clinical Trials data raise a "red flag" for Avandamet, because the Avandia + metformin group showed higher myocardial ischemic events than predicted. ▪ Dr Nesto summarized the discussion on the Integrated Clinical Trials data by stating that rosiglitazone causes weight gain and edema, leading to a greater number of events. Further analysis should be stratified by age, weight gain, and duration of diabetes, dose of Avandia, and baseline CVD. ▪ The group suggested that it would be helpful to investigate the baseline characteristics helpful in predicting those patients at risk for heart failure or an ischemic event.

▪ What questions related to review of the CV Integrated Clinical Trials Analyses for product label inclusion can GSK anticipate from regulators?	▪ With regards to the CHF draft labeling changes presented by Dr Cobitz, Dr Cannon suggested making the wording more specific. He proposed the inclusion of the phrase "a higher incidence of fluid retention resulting in hospitalization", instead of "heart failure". There was disagreement among the advisors over how to define these events. Dr Cannon then suggested that GSK leave the phrase "heart failure" in as written, but include a new sentence that more precisely defines heart failure, as it was observed in these studies. ▪ Similarly, for the myocardial ischemia draft labeling changes, Dr Nesto suggested more specific wording that would more accurately characterize the myocardial ischemic events observed.
▪ What additional data analyses or clinical studies are necessary to further define the nature of the relationship between Avandia and a) heart failure events? b) myocardial ischemia?	▪ Dr Bakris asked whether GSK had analyzed the data from the standpoint of which patients were using β-blockers. He advised that sympathetic activation may play a role in some of these patients' CHF. ▪ Dr Fowler added that it is important to differentiate between fatal and nonfatal myocardial ischemia, and that these data should be presented. ▪ The advisors agreed that a safety analysis of these patients, stratified by duration of T2DM, would be a more useful assessment.

Discussion: Epidemiology Study
Moderator: Richard W. Nesto, MD

Key Questions	Answers/Findings
▪ What are your overall interpretations of the CV Safety Epidemiology Study and the CV Integrated Clinical Trials Analyses, taken together?	▪ The advisors had many questions for Dr Koro regarding the propensity score matching technique that was used in the Epidemiology Study. One important point that came from the questions was that those rosiglitazone patients who could not be matched were eliminated from the data set. Dr Heise acknowledged that the rosiglitazone patients who could not be matched were probably further advanced in their T2DM. ▪ Dr Leiter commented that the renally impaired patients were likely taking rosiglitazone and SU. Dr Bakris agreed, stating that those patients taking rosiglitazone and SU probably had higher creatinine levels. Dr Koro responded to their queries by noting that renal function was one of the 70 groups matched during this analysis. ▪ The advisors expressed concern that the results of the Epidemiology Study did not match those of the Integrated Clinical Trials Analyses. ▪ Dr Leiter commented that the epidemiology data were reassuring from a safety standpoint, but not necessarily from the perspective of CV benefit. Dr Fowler agreed, noting that because he had been expecting a CV benefit, mere neutrality in CV events was disappointing. ▪ Dr Greenberg reminded the advisors that the average age in the clinical trials database was 60, compared with 53 in the epidemiology analyses. Dr Bakris furthered the point by stating that there was likely to be a huge difference in AEs with the variation of a decade in average age. ▪ Dr Nesto presented a few slides that showed no signal for higher mortality despite fluid retention with TZD use, matching what is known with COX-2 inhibitors. He concluded by stating that although fluid retention is a real effect of TZDs as a class, it does not contribute to excess mortality. ▪ As a final point, Dr Cannon suggested listing CV deaths, MI, and strokes separately in the label. He commented that GSK should be

	very clear about defining what was observed.
▪ What additional analyses or observational studies would you recommend to further characterize the CV safety of Avandia?	▪ Dr Bakris advised that GSK should develop a rationale for the differences between the 2 analyses before presenting to the FDA. He and other advisors commented that the FDA would be likely to disregard the epidemiology data in favor of the clinical trials data. Nevertheless, he offered that GSK should try to supply a mechanistic link that rationalizes the different results of the 2 analyses. ▪ Dr Carson asked whether there were data in older populations at higher risk for complications. He also mentioned that longer term data (3 year vs 1 year) would be more appropriate. ▪ Dr Fowler commented that Dr Nesto's data were very important and that GSK should highlight the fact that the increased CHF did not increase mortality. ▪ Dr Plutzky suggested publishing these combined analyses in a paper that frames the data. Dr Fowler suggested a summary of data to be published in a widely read journal, such as *Journal of the American College of Cardiology*. Dr Bakris suggested publication in the *American Journal of Medicine* because it would be more widely read. Dr Plutzky offered that an alternative strategy might be to get the data out as quickly as possible and then to look for a chance to publish reviews in *Diabetes* or *Diabetes Care*. ▪ Dr Bakris suggested finding 3 or 4 academics to interpret the data and then publishing results in a high-level journal.

Presentation: DREAM: Review of Results
Presenter: Nikheel S. Kolatkar, MD, MPH
Presentation Synopsis: Dr Kolatkar provided the advisors with a brief presentation on the primary outcomes and safety results from the ramipril and rosiglitazone arms of DREAM. He presented a slide that showed the distribution of CHF cases within the factorial design, which elicited much debate and discussion from the advisors. Dr Kolatkar concluded his presentation with an overview of the DREAM substudies currently in progress.

Discussion: DREAM
Moderator: Richard W. Nesto, MD

Key Questions	Answers/Findings
▪ How do the findings from DREAM impact the perceived risk/benefit of Avandia as a preventative strategy in patients at risk for developing type 2 diabetes?	▪ The advisors agreed that there was a small but noticeable signal for increased CHF events with rosiglitazone. ▪ In response to the schematic presented by Dr Kolatkar, which outlined CHF within the 2x2 factorial design, the advisors were somewhat doubtful that ramipril + rosiglitazone would increase CHF significantly more than rosiglitazone alone. Dr Deedwania noted that ramipril has not increased CHF in any previous trials, and Dr Bakris added that there was no mechanistic, pharmacokinetic, or pharmacodynamic reason that could potentiate an interaction between the 2 drugs.
	▪ Dr Fowler stated that the diabetes prevention afforded by rosiglitazone was very impressive, but there was no cardioprotective benefit. He asked what the point of diabetes prevention is if there is no cardiovascular benefit. Other advisors commented that preventing hyperglycemia is always important and has beneficial effects on all systems, not just cardiovascular health. ▪ Dr Plutzky suggested that the results of DREAM might have further benefits in the long term (eg, a reduction in the number of diabetes drugs taken by these patients in 10 years). ▪ Patients who do not convert to T2DM will have fewer microvascular complications and delayed β-cell deterioration. ▪ Dr Bakris commented that it is important to view the results of DREAM in the context of the DPP. The DREAM study shows the possibility of altering the natural history of T2DM with pharmacologic therapy. ▪ The advisors discussed whether treatment with rosiglitazone has a "lasting" effect on prediabetes patients. Although glycemic improvement with rosiglitazone lasts longer after washout than does treatment with metformin, there is no sustained "memory effect" with rosiglitazone.
▪ What additional analyses will be required or useful to further characterize the incidence of heart failure in DREAM?	▪ Dr Fowler noted that the results of DREAM-ON would be very important in characterizing the success of DREAM ▪ Dr Carson suggested publishing a paper on the 16 heart failure events in DREAM, in which the natural history of this form of heart failure is described fully. ▪ Dr Leiter stated that with the proper wording, GSK may be successful in filing for delayed onset of T2DM with the results of DREAM. Dr Deedwania urged caution, stating that it will be difficult to garner FDA approval, because no drug has yet been approved for the prevention of T2DM.

Presentation: ADOPT: Review of Study Results
Presenter: Paul Aftring, MD, PhD
Presentation Synopsis: Dr Aftring provided the advisors with a brief presentation on the primary and secondary outcomes and safety results from ADOPT. Rosiglitazone showed very favorable effects on glycemia as compared with metformin and glyburide. Safety issues were similar with rosiglitazone and metformin and higher than those seen in the glyburide group. Dr Aftring reminded the advisors that like DREAM, ADOPT was not powered to be a cardiovascular outcomes trial.

Discussion: ADOPT
Moderator: Lawrence A. Leiter, MD, FRCPC, FACP

Key Questions	Answers/Findings
▪ In light of the CV Integrated Clinical Trials Analyses and the CV Safety Epidemiology Study, what is the overall impact of the findings from ADOPT?	▪ Dr Fowler remarked that the CHF event rate was surprisingly low in the 3 groups. This may be because of the high dropout rates in each group. ▪ Dr Nesto commented that he is particularly surprised at the low event rates with glyburide; he questioned whether there was a protective effect. ▪ Dr Cannon summarized by stating that rosiglitazone is a potent drug with confirmed, albeit small, CHF risk.
▪ What is the impact of ADOPT with regards to the risk of CV ischemia vs metformin and glyburide?	▪ Dr Cannon was enthusiastic about the filing of ADOPT, stating that the glycemic data were spectacular. ▪ The advisors agreed that there was nothing surprising about the cardiovascular data with rosiglitazone in this trial. ▪ Some advisors commented that the lower incidence of CV events with glyburide could be indicative of a flawed data set. ▪ If GSK approaches the FDA with these data, it must be prepared to answer questions regarding the differences in CV events in the rosiglitazone and glyburide groups.
▪ What cardiovascular questions will GSK need to answer to prepare for the filing of ADOPT?	▪ The advisors suggested additional lipid analyses (eg, measurement of triglycerides) and a modeling analysis to project the impact of rosiglitazone on small-vessel disease. ▪ Additional suggestions for publication topics included: an article countering the Nathan editorial in *NEJM*, an analysis of outcomes in patients who had weight gain, a detailed characterization of heart failures associated with TZDs compared with heart failures seen with metformin. ▪ The advisors did not know what to conclude from the fracture data presented and suggested that further analyses would be needed. ▪ The advisors concluded that overall, the efficacy data presented for Avandia in these studies was excellent, but the safety results were disquieting. Avandia provides good glycemic control over the long term at the expense of weight gain coupled with a low incidence of heart failure and bone fractures. The data in ADOPT and DREAM as well as the CV Clinical Trials analyses are consistent in indicating a signal for heart failure and ischemic events.
▪ What additional analyses and publications of ADOPT would be helpful to further characterize the risk/benefit of Avandia in patients with T2DM?	▪ Analyses of collagen or other bone density markers regarding bone fractures. ▪ An analysis of what happens to the patients with edema and weight gain from ADOPT (and DREAM) over time. ▪ A better characterization of the heart failure seen in the metformin and glyburide groups will be needed.
▪ What CV surrogate markers or biomarkers will provide useful information if obtained from available ADOPT blood samples?	▪ The advisors suggested analyzing the following markers, if available from blood samples: ▪ Collagen or other bone density markers ▪ Adiponectin & adiponectin relationship to PAI 1 ▪ DPH oxidase ▪ Angiotensin II

Presentation: Key Findings From PROactive
Presenter: Richard W. Nesto, MD
Presentation Synopsis: Dr Nesto presented a brief overview of the key results from the PROactive trial. He reviewed

the primary composite end point and safety data and concluded by offering a balanced view of the risks vs benefits of using TZDs in patients with advanced T2DM.

Discussion: PROactive
Moderator: Richard W. Nesto, MD

Key Questions	Answers/Findings
▪ How do the findings from PROactive affect the perceived risk/benefit profile of TZDs in patients with advanced T2DM?	▪ Dr Fowler stated that the data from PROactive were very positive. ▪ Dr Leiter agreed, stating that the data from PROactive would have a positive outcome on how rosiglitazone is viewed.
▪ What additional data analyses or publications could help to further characterize and inform physicians of the risk/benefit profile of TZDs?	▪ Dr Greenberg suggested that it would be valuable to put together data on the natural history of patients with heart failure with TZDs, and to analyze these patients as compared with other patients without background heart failure.

Presentation: Effects of Rosiglitazone on Cardiovascular Structure and Function in Patients With Type 2 Diabetes and Congestive Heart Failure (Study 211)
Presenter: Steve McMorn, PhD (by phone)
Presentation Synopsis: Dr McMorn presented the results of Study 211, which will be published in *JACC* on April 24, 2007. He assessed the efficacy of rosiglitazone in meeting the primary and secondary objectives and reviewed the safety results. Rosiglitazone showed significant improvements in all glycemia-related end points with respect to control. Consistent with previous studies, there were a higher number of fluid-related events in the rosiglitazone group.

Discussion: Study 211
Moderator: Richard W. Nesto, MD

Key Questions	Answers/Findings
▪ In light of the CV Event Analysis and the CV Safety Epidemiology Study, how do the findings from Study 211 impact the overall risk/benefit of Avandia?	▪ Dr McMorn opened the discussion by informing the advisors that the patients in Study 211 were the highest-risk population that had been observed in trials with rosiglitazone. ▪ Dr Fowler followed by stating that the event rate was quite high, but that the data were not adjudicated. He also commented that it was reassuring that there were no AEs on cardiac end points. ▪ A recurring theme in the discussion was the weight gain associated with use of rosiglitazone. Dr Dube noted that patients taking Avandamet gain less weight than those taking Avandia. ▪ The advisors made a final recommendation to the GSK team, proposing an educational program targeted at practicing physicians on how to delay or manage T2DM in patients with heart failure
▪ Is there a better way to characterize heart failure associated with TZDs? If not, why not?	▪ A recommendation was made to adjudicate the ischemia-related AEs from this study. ▪ Dr Carson suggested an MRI study to better assess ventricular function. ▪ Dr Cannon followed up with a suggestion to look at the secondary objectives in a subgroup of patients treated with diuretics.

Meeting Conclusion (2-3 paragraphs MAXIMUM)

Dr Nesto concluded the meeting by reiterating the main points from the day's discussion. Dr Dube very briefly addressed the advisors, thanking them for their attention and valuable insight on the large volume of data presented. He assured them that their comments would be very helpful in analyzing new data on the efficacy and safety of Avandia, and interpreting it in context with older studies, which continue to garner considerable interest.

Strategic Recommendations

Medical Education Supplier to Complete ↓	*Product Manager to Complete* ↓		
	Agree	Implementation Date (Q1...Q4/Yr)	Disagree
▪ In future safety analyses, stratify patients by the duration of T2DM	☐	See note #1	✓
▪ Provide more specific wording in the product label that more clearly characterizes the events of CHF and myocardial ischemia that were observed	✓	If FDA is in agreement	☐
▪ Consider separate listings for CV deaths, myocardial infarction, and strokes in the label	☐	Only upon FDA request	✓

▪ Supply a mechanistic link to rationalize the differences between the Integrated Clinical Trials data and the results from the Epidemiology Study	✓	Ongoing process	☐
▪ Publish a summary of combined safety data analyses in a widely read journal such as *JACC* or *AJM*; also consider publishing reviews in *Diabetes* or *Diabetes Care*	✓	See note #2	☐
▪ Publish a paper on the 16 heart failure events in DREAM, in which the natural history of this form of heart failure is fully described	✓	Will encourage McMaster to publish.	☐
▪ Prepare to answer questions from the FDA regarding differences in CV events with rosiglitazone and glyburide in ADOPT	✓	Q4/07	☐
▪ Conduct additional lipid analyses (eg, measurement of trigiycerides) and a modeling analysis to project the impact of rosiglitazone on small-vessel disease	✓	Already underway	☐
▪ Obtain the following markers, if available from ADOPT blood samples: ▪ Collagen or other bone density markers ▪ Adiponectin ▪ DPH oxidase ▪ Angiotensin II	✓	TBD with ADOPT steering cmte	☐
▪ Collect data on the natural history of patients who experience heart failure with TZDs, and analyze these patients as compared with other patients without background heart failure	☐	See note #3	✓
▪ Adjudicate the ischemia-related AEs from Study 211	☐	See note #4	✓
▪ Consider using an MRI study to more accurately assess ventricular function	☐	See note #5	✓
▪ Follow up on Study 211 with an assessment of secondary objectives in a group of patients treated with diuretics	✓	Nik Kolatkar will follow-up with Drs. Bakris & Pratley	☐
▪ Utilize educational programs to provide practicing physicians with strategies to delay or manage T2DM in patients with heart failure	✓	Not enough data now, provide after proposed diuretic study above	☐

Product Manager Comments

1) Duration of diabetes has been evaluated as a factor in previous analyses and has failed to be predictive once covariates are considered.
2) Each piece of the CV analysis (integrated clinical trials analysis, epidemiologic study and the recursive partitioning analysis) will be published and then a review article will be planned including a comprehensive look at recent trials.
3) The recommendation to evaluate the natural history of heart failure with TZDs is interesting but not feasible.
4) Since study 211 is already completed, it is no longer possible to perform a true adjudication of ischemic-related AEs. A post-hoc review given the small number of cases would not provide additional insights.
5) Study 211 was initially proposed as an MRI study. It was determined at that time an MRI study with few patients would not be as valuable as an ECHO study with more patients.

FOOTNOTE 21

DREAM

Diabetes REduction Assessment with ramipril and rosiglitazone Medication

DREAM

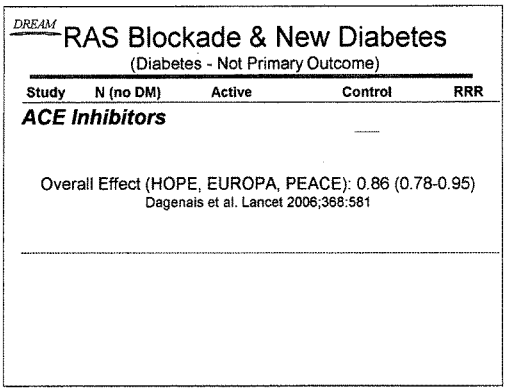
Prevention of Type 2 Diabetes

- Clinical trials have shown that diet & exercise can prevent diabetes by > 50% in people with impaired glucose tolerance (IGT)
- Clinical trials have also shown that drugs (e.g. metformin, acarbose) can prevent diabetes to a lesser extent in people with IGT
- Growing evidence suggests that
  - ACE inhibitors may prevent diabetes
  - Thiazolidinediones may prevent diabetes

DREAM

Properties of ACE-Inhibitors

- Inhibition of the Renin-Angiotensin system with ACE inhibitors:
  - Lowers BP
  - Reduces mortality, MI & strokes in people with
    - Heart failure
    - Previous CV events without heart failure
    - Diabetes plus other CV risk factors
- The HOPE trial suggested that the ACE-I ramipril may also reduce DM



If pooled the results for ACE-Is what would be effect

Effect of small size for DSOLVD

Do ACE-Inhibitors Prevent Diabetes?

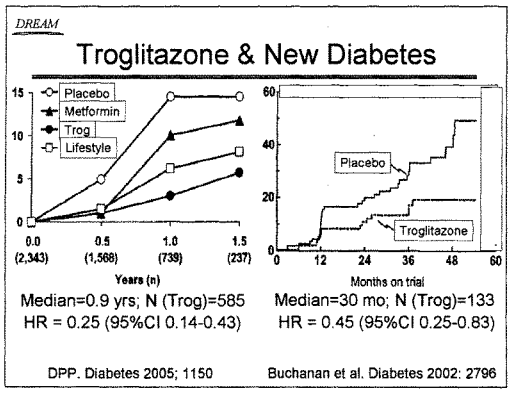
Limitations of Previous Reports

- Glucose tolerance tests **not** done at baseline or end.
  - →may have missed prevalent diabetes at baseline & new DM on follow-up
  - → no ability to detect regression
- Different definitions of new DM were used
- Participants were of high cardiovascular risk & intermediate diabetes risk (e.g. DM rate ~ 2%/year)
- DM prevention was not the primary outcome

DREAM

Properties of Thiazolidinediones (TZDs)

- Binds to PPAR gamma receptors
  - Increases insulin sensitivity
  - Reduces lipolysis
  - Increases preadipocytes→adipocytes (SC fat)
- Possible beta cell protection
- Reduces glucose levels if elevated



Trog is better than lifestyle - -Go through ILS meaning

DREAM

The *DREAM* Trial

Aims:	Does ramipril 15 mg/d prevent diabetes?
	Does rosiglitazone 8 mg/d prevent diabetes?
Design:	2 X 2 factorial, double-blind RCT
Sample:	Age 30+; IGT (FPG <7 & 2 hr 7.8-11) &/or IFG (FPG 6.1-6.9)
Pts:	5269 in 191 sites, 21 countries, & F/U 3 yrs
Outcome:	Incident DM (confirmed FPG ≥ 7 or 2 hr ≥ 11.1; or MD diagnosis) or death*

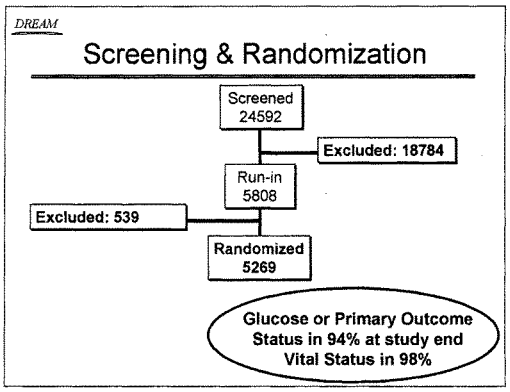
*because undiagnosed diabetes may be more frequent in those who die than in those who do not

DREAM

The *DREAM* Trial

Independent Coordination, Data Management & Analysis
Population Health Research Institute
McMaster University & Hamilton Health Sciences
Hamilton, Ontario, Canada

Funding Canadian Institutes of Health Research
Sanofi-Aventis
King Pharmaceuticals
GlaxoSmithKline



UPDATED SEPT

DREAM

Baseline Characteristics

	Overall	Rami	Plac	Rosi	Plac
N	5269	2623	2646	2635	2634
Age	54.7	54.7	54.7	54.6	54.8
Females	59.2%	59.7	58.7	58.3	60.1
IIGT (%)	57.5%	57.7	57.3	57.1	57.9
IIFG (%)	14.0%	14.0	14.1	14.0	14.0
IGT + IFG (%)	28.5%	28.4	28.6	28.9	28.1
Hypertension	43.5%	43.3	43.7	44.0	43.0
Smoking	44.6%	44.2	45.1	43.9	45.3
Sedentary	26.8%	27.1	26.5	26.4	27.2

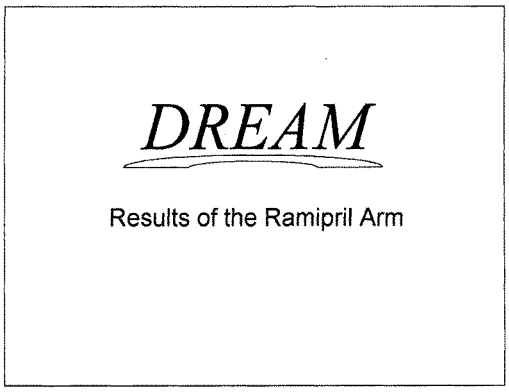
Updated Sept 6/06

DREAM

Baseline Characteristics (Mean)

	Overall	Rami	Plac	Rosi	Plac
N	5269	2623	2646	2635	2634
SBP/DBP (mm Hg)	136/83	136/83	136/83	136/83	136/84
BMI (kg/m^2)	30.9	30.9	30.9	30.8	31.0
Weight (kg)	84.9	84.8	85.0	84.8	85.0
Waist/Hip (M)	0.96	0.96	0.96	0.96	0.96
Waist/Hip (F)	0.87	0.86	0.87	0.86	0.87
FPG (mM)	5.8	5.83	5.84	5.84	5.83
2 Hr PG (mM)	8.7	8.66	8.71	8.68	8.67

Updated Sept 6/06



DREAM

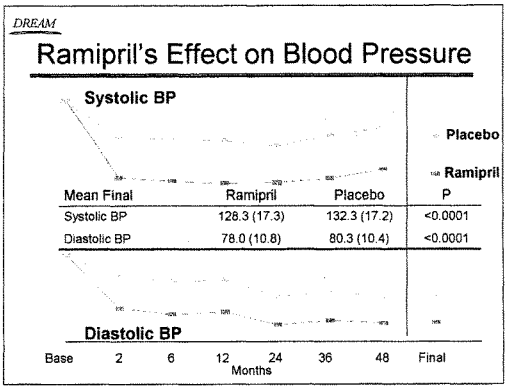
Adherence/Adverse Effects

		Ramipril	Placebo
On Study Drug	**at 1 year**	**86.6%**	**89.9%**
	at 2 years	**81.3%**	**84.8%**
	at 3 years	**75.4%**	**80.9%**
Reasons for Stopping Study Drug			
Participant Refusal		17.4%	17.7%
MD advice		2.3%	2.5%
Cough		9.7%	1.8%
Hypotension		0.8 %	0.4%

UPDATED SEPT

Note – Ps/JP given groupings for compliance as individual list indicates categories are not grouped.

Updated Sept 6/06



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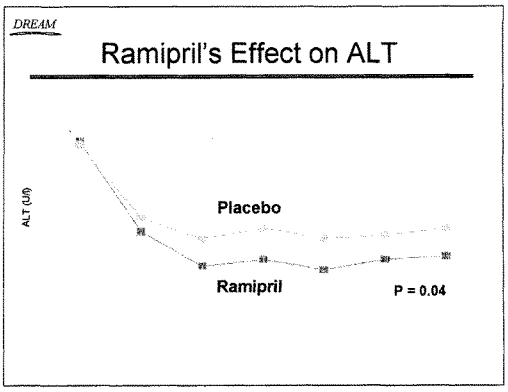

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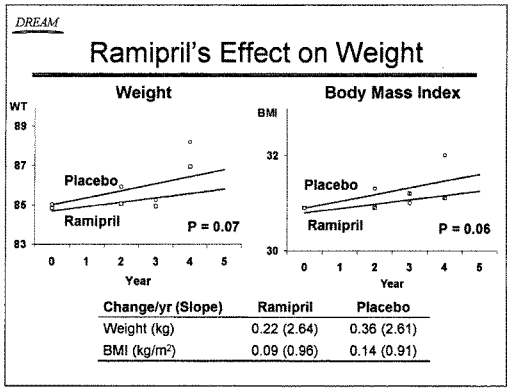


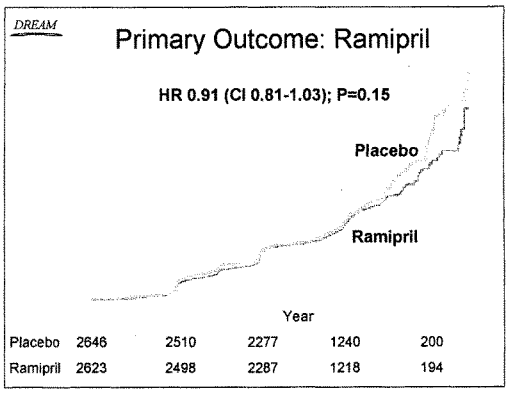
Updated Sept 6/06

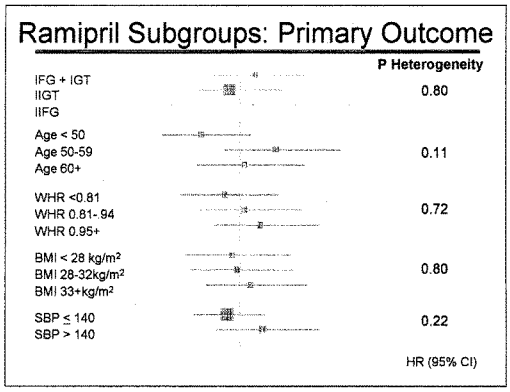
DREAM

Ramipril: Primary Outcome

	Ramipril N=2623	Placebo N=2646	HR (95% CI)	P
Primary Composite	**475 (18.1)**	**517 (19.5)**	**0.91 (0.81-1.03)**	**0.15**
Diabetes	449 (17.1)	489 (18.5)	0.91 (0.80-1.03)	0.15
Dx by FPG/OGTT	375 (14.3)	411 (15.5)	0.91 (0.79-1.04)	0.17
MD Diagnosed	74 (2.8)	78 (3.0)	0.95 (0.69-1.30)	0.75
Death	31 (1.2)	32 (1.2)	0.98 (0.60-1.60)	0.93

UPDATED SEPT





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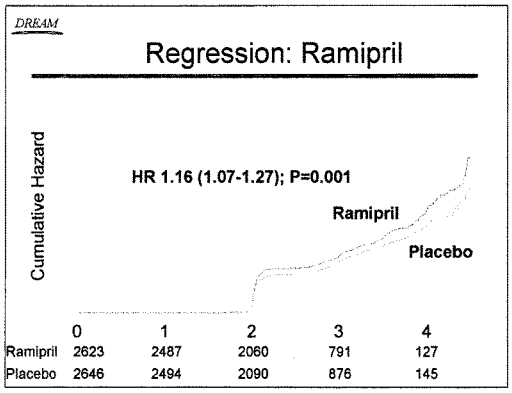

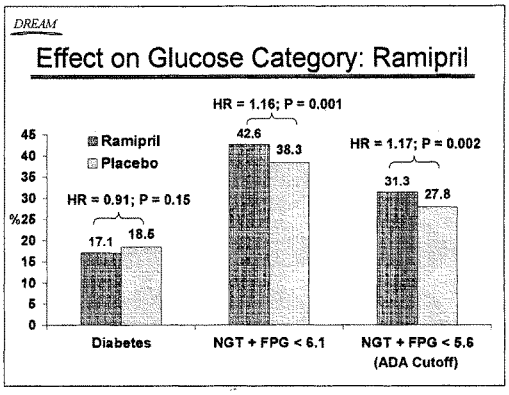

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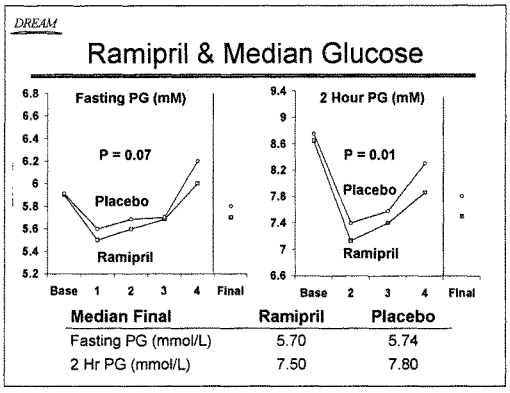

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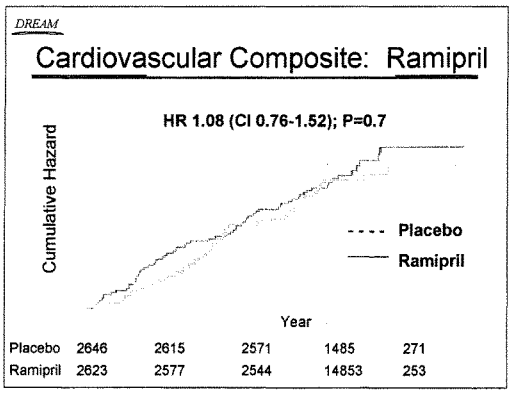


DREAM

Summary & Conclusions: Ramipril

- Modestly improves glycemic status in IFG/IGT
  - A nonsignificant 9% DM reduction
  - Significant 16% increase in regression to normal glucose levels by at least 2 yrs
  - Reduced 2 hr glucose by 0.3 mM by study end
- Significantly reduces BP in IGT / IFG
- Small, favourable effect on liver function

DREAM

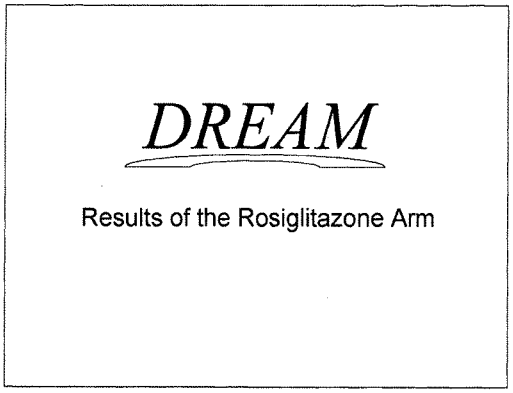
DREAM vs. Previous Trials

- Diabetes was the primary outcome in DREAM
- People with undiagnosed diabetes were excluded
- Regression was a predefined secondary outcome
- People were low vs. high CV risk so:
  a) may have had a less activated RAS
  b) controls were less likely on drugs that raise glucose
  c) there was low power to detect differences in CVD events (short duration, low risk participants)

DREAM

Summary & Conclusions: Ramipril

- The DREAM results provide the best estimate of the effect of ACE-Is on diabetes prevention in people with IFG / IGT & no previous CV disease
- Ramipril cannot currently be recommended for DM prevention
- However, in people in whom there is an indication for ACE inhibitors (high BP, CHF, vascular disease, high risk DM) the favourable effects on glucose may be of added benefit



DREAM

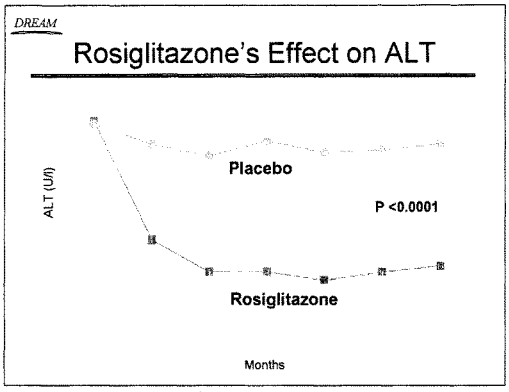
Adherence/Adverse Effects

		Rosiglitazone	Placebo
On Study Drug	**at 1 year**	**88.4%**	**91.3%**
	at 2 years	**83.7%**	**87.7%**
	at 3 years	**79.5%**	**84.0%**
Reasons for Stopping Study Drug			
Participant Refusal		19.1%	16.7%
Edema		4.8%	1.6%
MD advice		1.9%	1.5%
Weight Gain		1.9%	0.6%

UPDATED SEPT

Note – Ps/JP given groupings for compliance as individual list indicates categories are not grouped.

Updated Sept 6/06



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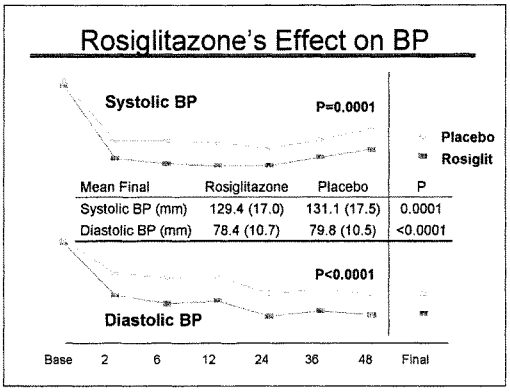
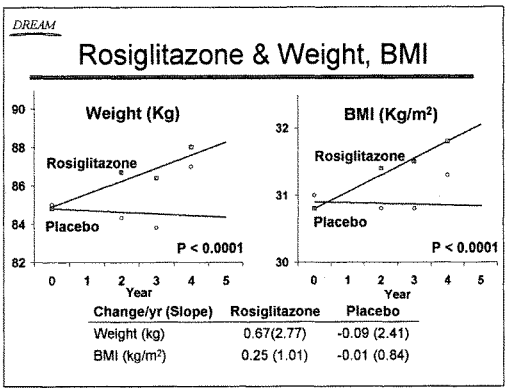


Needs to be updated with JPs revisions



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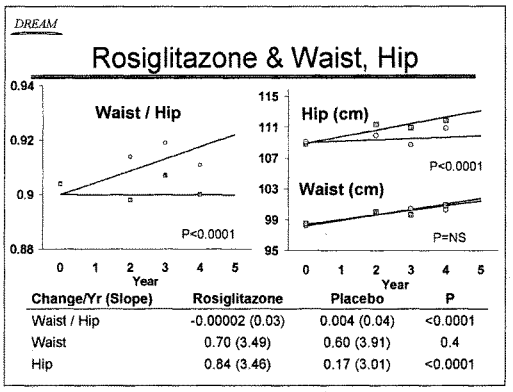


Change/Yr (Slope)	Rosiglitazone	Placebo	P
Waist / Hip	-0.00002 (0.03)	0.004 (0.04)	<0.0001
Waist	0.70 (3.49)	0.60 (3.91)	0.4
Hip	0.84 (3.46)	0.17 (3.01)	<0.0001

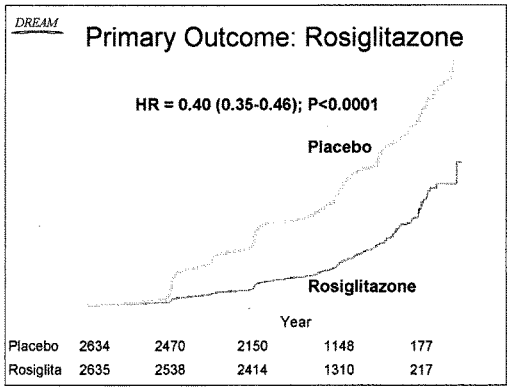
UPDATED Sept 6/06

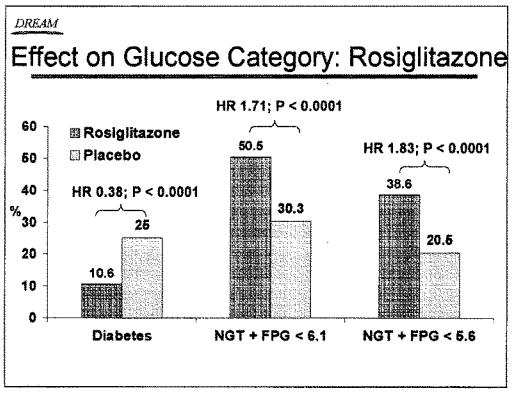
DREAM

Rosiglitazone & Primary Outcome

	Rosi N=2635	Placebo N=2634	HR (95% CI)	P
Primary Composite	306 (11.6)	686 (26.0)	0.40 (0.35-0.46)	<0.0001
Diabetes	280 (10.6)	658 (25.0)	0.38 (0.33-0.44)	<0.0001
Dx by FPG/OGTT	231 (8.8)	555 (21.1)	0.38 (0.33-0.44)	<0.0001
MD Diagnosed	49 (1.9)	103 (3.9)	0.47 (0.33-0.66)	<0.0001
Death	30 (1.1)	33 (1.3)	0.91 (0.55-1.49)	0.70

UPDATED SEPT

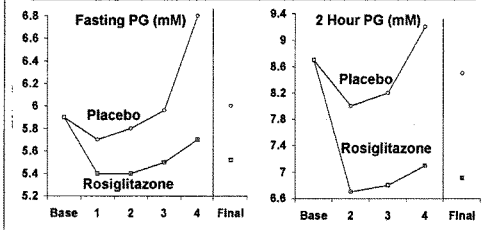




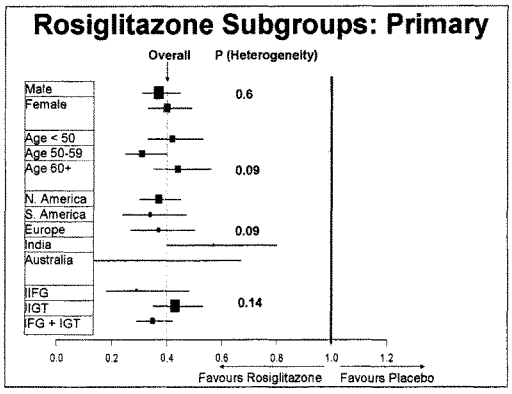
UPDATED SEPT
Updated Sept 6/06

DREAM

Rosiglitazone & Median Glucose

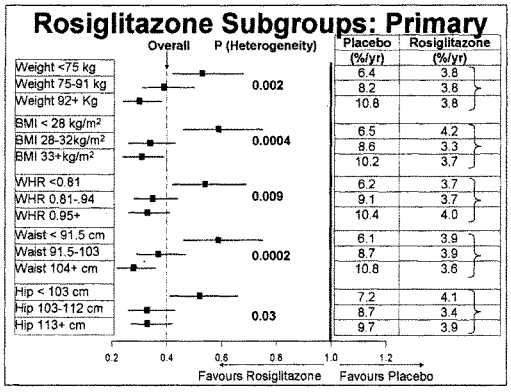


Median Final	Rosiglitazone	Placebo	P
Fasting PG (mmol/L)	5.5	6.0	<0.0001
2 Hr PG (mmol/L)	6.9	8.5	<0.0001

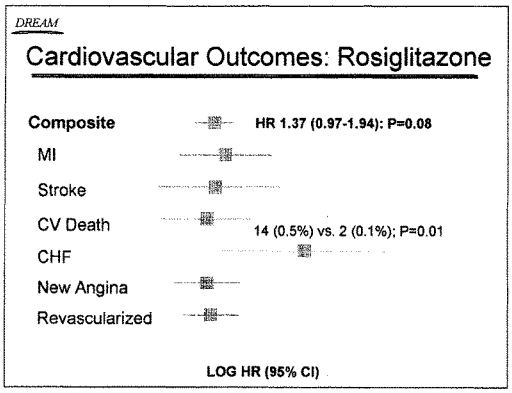


UPDATED SEPT

Updated Sept 6/06



UPDATED SEPT



DREAM

Summary & Conclusions: Rosiglitazone

- A dose of 8 mg/day reduces new DM by > 60% in people with IGT or IFG
- Promotes regression to normal FPG & 2 hr PG by >70%
- Effective in all regions of the world
- Eliminates the gradient of DM risk with increasing weight
- ~ 3% increase in body weight, but a favourable effect on waist/hip ratio
- Reduces ALT

Too short to look at events……

DREAM

Summary & Conclusions: Rosiglitazone

- Modestly lowers systolic BP & diastolic BP
- Increases the risk of CHF
- Too few events to draw any conclusions re the effect on other CV events or death

For every 1000 people treated with rosiglitazone for ~ 3 years, 144 cases of DM will be prevented with an excess of ~ 4 cases of CHF

DREAM

Conclusions of the DREAM Trial

- Rosiglitazone has a substantial benefit on prevention of diabetes & regression to normoglycaemia
- Ramipril has a modest benefit on regression to normoglycaemia
- The durability of the glycaemic effect of these drugs is being assessed in a washout phase

DREAM Slides:	**www.phri.ca/dream**
2 DREAM Papers:	**NEJM & Lancet - online**

DREAM TEAM

International Leaders

H.C. Gerstein **S. Yusuf**
R. Holman **J. Bosch**

S. Anand	M. Davis	M. Hanefeld	F. Lanas	V. Pirags
A. Avezum	R. Diaz	T. Hedner	E. Lonn	J. Probstfield
A. Budaj	N. Dinccag	B. Hoogwerf	M. McQueen	I. Schmid
J. Chiasson	M. Enjalbert	K. Jolly	V.Mohan	J. Shaw
I. Conget	A. Escalante	M. Keltai	A. Phillips	K. Teo
G. Dagenais	G. Fodor	M. Laakso	L. Piegas	P. Zimmet
				B. Zinman

Statisticians: P. Sheridan, J. Pogue

TMC: D. Sackett; D. Altman; C. Clark; P. Bennett; R. Hamman; L. Ryden

FOOTNOTE 22

From: Nevine Zariffa/PharmRD/GSK

To: Lawson 2 Macartney/PharmRD/GSK@GSK

CC: Anne M Phillips/PharmRD/GSK@GSK;
Frank W Rockhold/DEV/PHRD/SB_PLC@GSK

Subject: Re: I would appreciate a conversation

Date: 05/03/2007 07:31:09 (GMT-05:00)

happy to discuss tomorrow. I am in avandia meetings all day and will step out for this.

N vine Zariffa
Therapy Area Director, Cardiovascular and Metabolism
Biomedical Data Sciences
GlaxoSmithKline Pharmaceuticals
TEL: (610)-[redacted]
2301 Renaissance Blvd, Building #510
King of Prussia, PA, 19406

Lawson 2 Macartney/PharmRD
03-May-2007 06:50

To
Frank W Rockhold/DEV/PHRD/SB_PLC@GSK, Nevine Zariffa/PharmRD/GSK@GSK
cc
Anne M Phillips/PharmRD/GSK@GSK
Subject
I would appreciate a conversation

Frank and Nevine,

I would appreiate your advice on the proposal below interms of analyses. I have made oit clear in my letter of Feb 26 that analyses should be conducted by GSK personnel pursuant to a prespectively agreed analyses plan. I shall take the liberty of setting up a telecon tomorrow to discuss.

Thanks,

Lawson

Dr. Lawson Macartney,
Senior Vice-President, WW Development
GlaxoSmithKline,
RN 0315
tel 610[redacted]
Fax 610[redacted]
assistant ([redacted]) 610[redacted]
—— Forwarded by Lawson 2 Macartney/PharmRD/GSK on 05/03/2007 11:47 AM ——

"Steven E. Nissen" <nissens@[redacted]>
02-May-2007 19:28

To
Anne.M.Phillips@gsk.com
cc
Lawson.2.Macartney@gsk.com, ronald.l.krall@gsk.com
Subject
Re: Re; Avandia

Dear Anne et al,

Thank you for sending the attached letter. I ,m eager to conduct this formal meta-analysis and hope you can secure the permission of other parties to allow the Cleveland Clinic Cardiovascular Coordinating Center access to the necessary patient-level data.

Because of the public health importance of this issue, a timely approach to this study is critically important. As I mentioned on the phone with Ron Krall, because of the delay in receiving a response from GSK to my initial request for data in January, I have pursued an independent study-level analysis. As we negotiate patient-level access to all of the rosiglitazone cardiovascular safety data, I must reserve the right to proceed with completion of our current analyses and to publish the findings.

Regardless of the results of our study-level analyses, the full patient-level analysis must be performed very quickly. I believe it is imperative for this study to be performed by an independent academic coordinating center through unrestricted access to the study databases. The analysis must be done very promptly and by individuals without real or perceived conflicts of interest.

We stand ready to help complete these analyses once you secure full data access.

Steve

Steven E. Nissen MD MACC
Chairman, Department of Cardiovascular Medicine
Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland, Ohio 44195

Immediate Past-President
American College of Cardiology

Phone: 216-[redacted]
fax: 216-[redacted]
Blackberry cell 216-[redacted]

—

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On 5/2/07 2:06 PM, "Anne.M.Phillips@gsk.com" <Anne.M.Phillips@gsk.com> wrote:

Hi Steve, attached is the letter Ron spoke with you about earlier in your telephone conversation.

Please let me know how you would like to move forward on this or if you have questions .

Kind regards,

Anne

Anne M Phillips MD FRCPC
Vice President, Clinical, CV-Metabolic MDC.
GlaxoSmithKline
Renaissance, PA
Phone (610) [redacted]

==========

FOOTNOTE 26, 30

FAX

GlaxoSmithKline

Upper Providence
FAX: 10-917-7494

To Bob Schmitz

Company

Fax

From VAL Fedoso

Tel

E-mail

Date Pages including cover

Subject

8-456-7777

053048

Frank -
I'm at UP site today (Mon).
Thought you'd like a copy of
RSU assessment of AVANDIA
meta-analysis —
Bob

8275 7004
Bob Schriver

CONFIDENTIAL DRAFT 4 May 2007

(3)

Report on the article by SE Nissen & K Wolski "Effect of rosiglitazone on the risk of myocardial infarction and cardiovascular death"

[redacted] *MA DipMathStat CStat*
Research Statistics Unit, GSK, Harlow

4 May 2007

I use "N&W" to refer to the authors of the article and the results they report.

Section 5 was contributed by my colleague:

[redacted] *PhD*
Research Statistics Unit, GSK, Greenford

Homogeneity of trials is a very strong assumption. GSK analyses with covariates included may help to understand the vulnerability of this assumption

1. Selection of studies

One of the main potential sources of bias in meta-analysis is the selection of studies. N&W reported searching published literature, the FDA website and the GSK Trials Registry and finding 116 studies. From these, they selected the 42 that had duration at least 24 weeks, randomized control group not receiving rosi, and reported outcome of MI and CV death. This compares to the internal GSK investigation, which also found 42 studies, but did not include the ADOPT and DREAM results as far as I am aware, as they had not reported by the cut-off date of August 2005. The selection criteria were different for the internal investigation; in particular, I don't think that reported outcomes of CV death were necessary for inclusion, though I doubt if an outcome this important would be missing in many trials. I don't have the list of GSK studies available to check against N&W's list.

The selection of trials therefore appears to be thorough, though others familiar with the trials can comment more knowledgeably. One possible issue is that trials for which only MI events were reported were not included in the analysis of CV deaths, and vice versa. But I expect there would be few, if any, such trials, and the omission would be unlikely to be important.

One important issue, though, is that several studies involving insulin treatment were included (347, 082, 085, 095 and 009). There are known and notified issues with CV events for patients taking insulin and rosi, as found also in the GSK internal study, and N&W's subgroup analyses shown in Table 6 indicate that the insulin subgroup has a much higher odds ratio than the other subgroups. There is a strong argument that the insulin studies should not be included in the meta-analysis, because this mixes known effects with the effects being investigated. I follow this up below.

2. Reported results

I am unable to check the reported numbers of MI and CV deaths reported in the paper. However, I note an inconsistency between Table 3 and 5: the first lists two CV deaths

for comparators in Study 211, while the second lists four. I refer to these alternatives as "CVD (2)" and "CVD (4)".

I have checked the results using Peto's method reported in Tables 4 and 5. For MI, I get the same results. If I omit the insulin studies, however, the odds ratio decreases:

	OR	95% CI		p-value
MI all	1.43	1.03	1.98	0.032
MI no insulin	1.36	0.97	1.90	0.072

For CV Deaths, my results match those given in all rows of Table 5 (except for some final digit changes) except that I get a different combined estimate.

	OR	95% CI		p-value
published	1.72	1.04	2.86	0.035
CVD (2) all	1.74	1.06	2.87	0.030
CVD (2) no insulin	1.65	0.99	2.75	0.055
CVD (4)	1.61	0.98	2.63	0.058
CVD (4) no insulin	1.52	0.92	2.52	0.102

Personally I am very suspicious of Peto's method for small rates. However no time to programme 'exact' methods

3. Method of analysis

N&W use the Peto odds-ratio method to combine the observed incidence of MI and CV death across studies. This method is recommended, e.g. by the Cochran Collaboration, for use in investigations with binary response and small treatment effects. The method is not recommended when there is imbalance between treatments (Greenland S, Salvan A, Stats in Med 1990, 9:247-252; Sweeting MJ, Sutton AJ, Lambert PC, Stats in Med 2004, 23:1351–1375). In N&W's study, there are many trials with imbalance: of the 38 used in the MI analysis, 21 (including the large DREAM study) have approximately 1:1 randomization ratios (Treatment:Control), 11 have 2:1, two have 3:1, three (including the large Study 330) have 4:1, and one (the large ADOPT study) has 1:2. The results of Sweeting et al's simulation study (Figure 4b) indicate that the Peto method has an average bias of about +0.1 on the log-odds scale for a 1:2 ratio; they used a control event rate of 0.01, odds ratio (treatment:control) of 0.5, and 10 trials in the meta-analysis. I am not sure how this would change with an average 2:1 ratio, an odds ratio of 1.43, and 38 trials; but if it reverses it would give a log-odds bias of −0.1, corresponding to an odds bias of −10%, i.e. an odds ratio of 1.29 rather than 1.43 for the MI analysis. This needs further investigation.

VF

It may change variance if they are pooled with similar studies having events See page (7) for some our results

Note that N&W correctly exclude studies from each analysis if they have no events in either treatment group. This is counter-intuitive if we are interested in estimating the actual incidence rates of events; but the Peto method is intended simply to compare the rates in terms of odds ratios. For that purpose, there is no evidence to contribute to the comparison from trials with no events.

The meta-analysis effectively summarizes the evidence using stratification by study, to compare groups of patients with similar characteristics (i.e. within study), and then forms a weighted combination of the comparisons. This is intended to avoid a misleading combined statistic, as seen in Simpson's Paradox, when other

characteristics that may affect incidence rate vary within treatment groups. It is interesting to note that the naïve analysis, ignoring the potential bias of Simpson's Paradox, shows much smaller effects that the stratified analysis using Peto's method.:

	Rosi	Comp	OR
MI	86/15,556 = 0.0055	72/12,277 = 0.0059	0.94
CVD (4)	42/15,556 = 0.0027	25/12,277 = 0.0020	1.33
CVD (2)	42/15,556 = 0.0027	23/12,277 = 0.0019	1.44

This prompts the question as to whether the stratification used, by trial only, is sufficient to handle the differences between patient characteristics. There is certainly a strong argument to stratify also by comparator (metformin, sulfonylurea, placebo), as was done in the GSK investigation. The difference seen between the naïve analysis and the trial-stratified analysis suggests that a similar difference, potentially in either direction, may be seen with further stratification.

4. Comparison to GSK investigation

N&W make no reference to the GSK investigation, which has been published on the GSK Clinical Trials Register, or to previous meta-analyses.

The GSK investigation used the actual data rather than summary statistics, and adjusted for covariates. It also stratified by comparator treatment, and reported seven separate meta-analyses for each stratum rather than trying to combine all in one.

5. Other methods of meta-analysis

(See pages ④-⑤ for more "other methods". Pay attention page 5 & 6. VF

A logistic regression was fitted to the observed number of events in each trial by randomization group (RG) for both MI and CV. In both cases an exact p-value was derived. There was no evidence for heterogeneity of RG effect across the studies for either MI or CV, so a random-effects model was not fitted. The random effect would have had a very small variance estimate and the conclusions about the odds ratios would have been very similar.

For MI the RG effect had an odds ratio of 1.43 (95% CI 1.03 to 1.98, exact P=0.037). For CV the effect had an odds ratio of 1.77 (95% CI, 1.05 to 2.98, exact P=0.031). These results are very similar to the conclusions from the paper using the Peto method. As such there is no statistical reason for disregarding the findings as presented.

Results in fa (GSK favor)

6. Interpretation of results

Good remark!

N&W do not report the actual incidence rates of events at any point, restricting themselves to odds ratios. It is essential in the reporting of risks to give absolute values so that reported differences are put into context. In addition, the rates reported in these studies should be compared with the rates experienced by the general population of patients with this disease.

The language used by N&W is unnecessarily extreme and scare-mongering.

(4)

Frank Maninno's analyses

Pooled data

If we assume no differences between the studies, we can consider all data as coming from a single large study. Under this assumption, the data reduces to the following table.

# of patients on Avandia	15556
# of MI events	86
# of Cardiovascular events	72
# of patients on Comaprator	12277
# of MI events	42
# of Cardiovascular events	23

Using these numbers we can calculate an estimate of the odds ratio for each type of event. For MI, the odds ratio is 0.9423 with a 95% confidence interval of (0.688, 1.290). For CV, the odds ratio estimate is 1.44 with a 95% confidence interval of (0.867, 2.40).

Pooling by number of weeks

The number of events that will occur in any trial will depend heavily upon the length of the trial. For this reason, we consider pooling the data from studies of equal length. There were 9 different study lengths, and the data set now becomes

	Avandia			Comparator			
Weeks	Patients	MI	CV	Patients	MI	CV	# of studies
24	2959	11	6	1770	1	0	9
26	2951	13	9	1795	5	1	14
28	600	1	1	314	2	0	2
32	1335	5	0	753	2	1	4
48	284	1	0	135	0	0	1
52	2994	10	9	1651	6	4	7
104	116	2	2	111	3	1	1
156	2861	16	12	2853	12	10	3
208	1456	27	3	2895	41	6	1

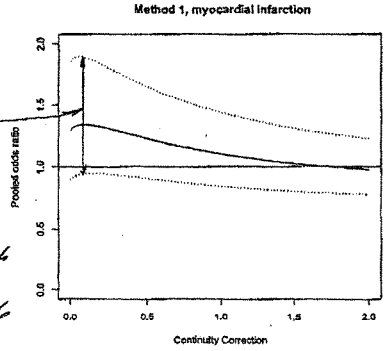
Using this data we can repeat the Peto method as described in Sweeting et al. (2004, section 2.3) and unlike the previously described Peto method, here we utilize all 42 studies, including those with no events. For MI we obtain an odds ratio of 1.34 with a 95% confidence interval of (0.966, 1.85). For CV we

(5)

obtain an odds ratio of 1.55 with a 95% confidence interval of (0.943, 2.56).

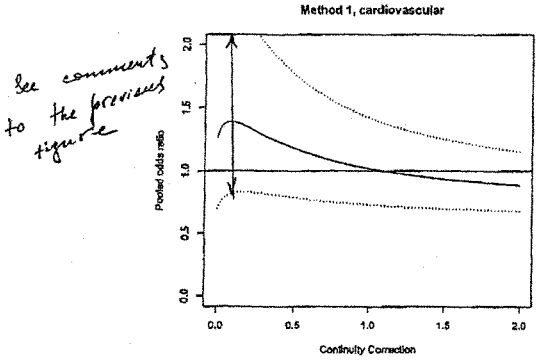
Inverse variance weighted method

We can combine our the odds ratios from our studies using the inverse variance-weighted method as described in as described in Sweeting et al. (2004, section 2.1). To do this we must first obtain an odds ratio estimate for each study, requiring the use of a continuity correction. The choice of continuity correction can obviously have a large effect on the result, so we have tested various values. The odds ratio (solid line) and corresponding confidence intervals (dashed line) for both MI and CV can be seen in figures 1 and 2. This method makes use of data from all 42 studies.



Worst case scenario. We do not have enough evidence to reject H_0

(6)



see comments to the previous figure

Mantel-Haenszel method

Using the Mantel-Haenszel method (see Sweeting et al. 2004, section 2.2) requires us to use only those data sets that have at least one event, similarly to the Peto method. This leads to the loss of 1180 Avandia patients (7.6%) and 642 comparator patients (5.2%) in looking at MI events. When looking at CV events we lose information from 4898 (31.4%) and 3047 (24.8%), respectively. The odds ratio estimate for MI is 1.43 with a 95% confidence interval of (1.03, 1.98). For CV we obtain an odds ratio of 1.81 with a 95% confidence interval of (1.06, 3.07).

Additional studies

The paper mentions that 48 studies were available, yet only 42 are presented in table 3, with the other 6 have no events for MI or CV. While we do not know how many patients are in these studies, we can consider the effect of the

(57)

inclusion of these studies. The median numbers of patients for a study are 231.5 for Avandia and 148.5 for the comparator. If consider this to be a likely number of patients in a single trial, 6 trials leads to an additional 1389 and 891 patients, respectively. Repeating the pooled data approach, we obtain an estimate of the odds ratio for MI of 0.928 with a 95% confidence interval of (0.678, 1.27). For CV, the odds ratio estimate is 1.42 with a 95% confidence interval of (0.854, 2.36). We cannot repeat the method of pooling by weeks, as the number of weeks is unknown. For the inverse variance-weighted estimate, we present a comparison when we use a continuity correction of 0.25 between the currently known data, the currently known data augmented with one study of size 1389 and 891, and the currently known data augmented with 6 data sets each of size 231 and 148.

	MI odds ratio (95% CI)	CV odds ratio (95% CI)
Using known data (42 studies)	1.30 (.943, 1.80)	1.32 (.827, 2.10)
Using 43 studies	1.30 (.941, 1.79)	1.31 (.824, 2.09)
Using 48 studies	1.30 (.942, 1.79)	1.31 (.825, 2.07)

FOOTNOTE 31, 36

From: Lawson 2 Macartney
Date Sent: 5/8/2007 9:27:42 PM
To: Nevine Zariffa
CC:
Subject: Fw: Avandia pls mull this over tonight

I think we have good data on all of these questions but pls give some thought tonight.
Thx

Dr. Lawson Macartney,
Senior Vice-President, WW Development
GlaxoSmithKline,
RN 0315
tel 610 [redacted]
Fax 610 [redacted]
assistant ([redacted]) 610 [redacted]
----- Forwarded by Lawson 2 Macartney/PharmRD/GSK on 05/08/2007 11:27 PM -----

Moncef M Slaoui/MGMT/PHRD
08-May-2007 21:17

To
Lawson 2 Macartney/PharmRD/GSK@GSK
cc
Patrick 5 Vallance/PharmRD/GSK@GSK, Allan 2 Baxter/PharmRD/GSK@GSK, Ronald L Krall/MGMT/PHRD/SB_PLC@GSK, Colin Dollery-1/MGMT/PHRD/SB_PLC@GSK
Subject
Avandia

Lawson

In analyzing the data from the integrated analysis, ADOPT and from the Ingenix Epi study, the following take home messages come to mind

1- Integrated study:
-FDA, Nissen and GSK all come to a comparable conclusion regarding increased risk for ischemic events, ranging from 30% to 43%!
-FDA and Nissen (but no final data from GSK date) reach the conclusion of an HR for death (CHF+ IHD) of 1.72 or 1.75!
-highest ischemic events risk associated with Rosi+Met, or Rosi +Insulin.

2- ADOPT
The team did a good work, the analyzes all show that HR are never statistically significantly different comparing Avandia vs Met or SU for either Ischemic events and/or CV related deaths.The one numerical difference we may want to probe is the % SAE Myoc Isch: 1.17% for Rosi vs 0.83% for SU....

3- Ingenix/Epi study
-All comparisons for the composite end point (MI+CR) show no statistically significant difference between Rosi and the comparators either as mon, dual or combo with insulin.

Based on the above, and on the outcome of the ProActive study testing Pioglitazone in high risk CV disease patients where a potentially "beneficial

effect was observed (6 to 16%) on the combined all cause mortality+MI+stroke end point, the following questions appear critical, and I would like to team to have answers for our meeting tomorrow(or start to)

a- see question above on Adopt (SU vs Rosi)

b- In the integrated study, do we confirm the various sub-analyses done by the FDA? ie: for instance, Rosi monotherapy vs Placebo or vs active control mono? this would confirm ADOPT...and then of course we have to deal with the fact that this is an early diabetes population, not really representative of the real world. How much do we know of the real use of Avandia? what can we build here?

c-how can we reinforce the value of the Epi study. The FDA criticizes the fact that we excluded cases of Sudden cardic death. Did we? why? what would the data look like if we included them?

d- one of the recurring questions of the FDA given the contrasted outcome of the Proactive trial vs our data is: how much more data on Rosi before it is obsolete compared to Actos. This is potentially a one sided narrow view. What "comparative" efficacy data do we have vs Actos?
Hba1c, renal, ocular, limb....? did we ever run a comparative study?

e- What studies could we offer the FDA to further assess the contradictory data between the integrated study and the two others? can we expand Record? propose something else (very high risk patients? ok? ethical?), compare to Actos for superiority on some end points?

There are of course many more questions, but I would like us to spend some time on these please.
Please have the team prepared

Thank you for your commitment
Moncef

FOOTNOTE 38

From: Nancy J Pekarek(CN=Nancy J Pekarek/OU=FPL/OU=Corp/O=SB_PLC)
Date Sent: 5/9/2007 6:43:25 PM
To: CN=Mary A Rhyne/OU=CORP/O=GSK@GSK
CC:
Subject: messages

Key messages
Safety of Avandia:
Avandia is an important medicine to help people with Type 2 diabetes manage their disease long-term. CHF is a well known and well described risk associated with medicines in the same class as Avandia. Because of this, GSK has undertaken a large program of clinical studies and analyses to further understand the cardiovascular safety of Avandia.
Avandia,s record of safety and effectiveness is backed by one of the largest clinical trial programs (52,000) ever undertaken for ANY medicine, and THE LARGEST for ANY oral anti-diabetic medicine to date.
We have posted those data online, shared them with regulators worldwide, and updated the drug label to ensure physicians know how to appropriately care for patients.
The Nissen analysis is one way of looking at the data, but it doesn,t reflect all we know about the safety of this medicine. According to a similar analysis by GSK, the rate of ischemia (obstructed blood flow) in the study population is very low, and we saw no consistent trends indicating that Avandia causes these events. The GSK analysis of cardiovascular events showed [4] deaths among 8,000 patients; the NEJM analysis shows [17] additional deaths out of 28,000. This is a small numerical increase; but when we look at a larger set of data from real world use and large clinical trials) the gold standard for evaluating patient experience) we are not seeing a proven link between Avandia and increased cardiovascular deaths, alone or in combination with other anti-diabetics treatments.
However, we are closely evaluating this analysis and continue to actively talk to regulatory authorities about the safety and benefit of Avandia.
Balance of Risk/Benefit:
Diabetes is a relentlessly progressive and potentially life threatening disease. Diabetic patients are at significant risk of complications, especially if their diabetes is not under control. A significant number of diabetic patients also suffer from cardiovascular problems. A recent study has shown that Avandia is better than older medicines in controlling the disease. A physician needs to consider both the benefits and the potential risks of these medicines when choosing the best treatment for a particular patient.

Nancy Pekarek
VP Corporate Media Relations US
GlaxoSmithKline
215 [redacted] (office)
215 [redacted] (mobile)

FOOTNOTE 40

Lawson 2 Macartney/PharmRD/GSK
05/09/2007 11:13 AM

To Robert P Aftring/PharmRD/GSK@GSK, Murray W Stewart/PharmRD/GSK@GSK

cc Anne M Phillips/PharmRD/GSK@GSK, Nevine Zariffa/PharmRD/GSK@GSK, Joanna M Balcarek/PharmRD/GSK@GSK, Robin 2 Saltzman/DEV/PHRD/SB_PLC@GSK

bcc

Subject Fw: Avandia

Colin makes some salient points here about the benefit in diabetes. I don;t know that we can conduct all of the analyses which he is looking for but I do think some of the arguments could be woven credibly into a r/b picture.

Dr. Lawson Macartney,
Senior Vice-President, WW Development
GlaxoSmithKline,
RN 0315
tel 610 [redacted]
Fax 610 [redacted]
assistant ([redacted]) 610 [redacted]

----- Forwarded by Lawson 2 Macartney/PharmRD/GSK on 05/09/2007 11:11 AM -----

Colin Dollery-1/MGMT/PHRD
09-May-2007 08:20

To Moncef M Slaoui/MGMT/PHRD/SB_PLC@GSK

cc Allan 2 Baxter/PharmRD/GSK@GSK, Lawson 2 Macartney/PharmRD/GSK@GSK, Patrick 5 Vallance/PharmRD/GSK@GSK, Ronald L Krall/MGMT/PHRD/SB_PLC@GSK

Subject Re: Avandia

Dear Moncef,

Avandia Issues

I have approached the problem from a different perspective. To a great extent the numbers are the numbers, the Cleveland analysis is very similar to our own. The ADOPT team have done a good job with their recent analysis but I should like to use these for a different aspect of the argument (see below). We cannot undermine the numbers but I think that they can be explained so we must concentrate on effective risk management. My approach is to look at possible mechanisms and how these might different for rosiglitazone and pioglitazone. I will go through this discussion with numbered points.

1. **Off target effects?**
These seem very unlikely as the dose of rosiglitazone (2 to 8 mg) makes this implausible and the dose of pioglitazone is only slightly higher.
2. **Adverse effects on atheroma amount or stability**.
The main argument here lies in that pioglitazone causes a small reduction of LDL and rosiglitazone causes a small elevation. We should run a calculation based on Framingham coefficients to show what effect this would have over the time period (patient years of exposure) in the trials analysed.
We should then use the data just generated in the "Avandastat" trial to show that use of statins is just as effective in loweringl LDL in the combination as is the statin alone and the positive effect this would have on CV risk in diabetics.
Finally we should search for evidence that the use of statins in diabetics generally and with rosilglitazone in particular has risen steeply over the time the thiazolidenediones have been on the market. We can then argue that any problem that existed with LDL is now controlled or controllable. It would also be worth obtaining the evidence that the use of antihypertensives in diabetics has also been increasing rapidly.
The weak anti-inflammatory effect (fall in CRP in atheroma patients on rosiglitazone) is an additional indirect argument against adverse effects on plaque stability.
My aim here is to show rosiglitazone as a valuable part of a package in diabetes management along with statins and antihypertensives and to support it with calculations to show the magnitude of such a policy.
3. **Adverse effects of fluid retention and cardiac dilatation**.
Fluid retention is a reality with all PPAR gamma agonists. If substantial in patients with an impaired myocardium it can lead to CHF and to cardiac ischemia by decreasing myocardial efficiency in the face existing of coronary disease. If there is a criticism of GSK it might be that we were a bit slow off the market in making firm recommendations about use of diuretics and recognising that the sodium retention is mediated via distal renal tubular ENaC. Bearing in mind this mechanism the best diuretics might be amiloride or spironolactone. Spironolactone (and recent analogues such as eplerenone) also have a cardioprotective effect. (see Circulation. 115(13):1754-61, 2007 Apr 3). This article is also provides a useful but indirect argument about effects of fluid retention. The relative decline in medical concern about thiazolidenedione edema suggest that the physicians have learnt to avoid use of PPAR gamma agonists in the patients at highest risk and are probably making effect use of diuretics in the remainder, if they retain visible fluid.
Can we produce data showing an increasing use of diuretics over time in patients on rosiglitazone to buttress this point? Also compare the inclusion – exclusion criteria in ADOPT with those used in the earlier trial and argue that these are an important reason for the difference. Aim to show that the problem can be/is being managed clinically.

4. Avandia **as part of a package of risks management in diabetes.**

Basically this is the case I think we have to make. Avandia is a valuable part of the glucose control combined with an active LDL and blood pressure strategy in diabetes. All supported by calculations . It will not be easy but I think it is valid and a clear statement of the arguments around risk management and the time trends in events between early trials and ADOPT support it. Just trying to explain the numbers without a mechanistic argument and a management strategy will cut no ice.

Colin T Dollery May 8-9th 2007

FOOTNOTE 44

Press Release

GlaxoSmithKline

GlaxoSmithKline Responds to NEJM Article on Avandia

Philadelphia, PA (May 21, 2007) – GlaxoSmithKline [NYSE:GSK] today issued the following response to an article in the New England Journal of Medicine (NEJM) on Avandia® (rosiglitazone maleate), a widely used and highly effective treatment for type 2 diabetes:

GSK strongly disagrees with the conclusions reached in the NEJM article, which are based on incomplete evidence and a methodology that the author admits has significant limitations.

The NEJM paper is based on an analysis of summary information that combines a number of studies – a meta-analysis - which is not the most rigorous way to reach definite conclusions about adverse events. Each study is designed differently and looks at unique questions: for example, individual studies vary in size and length, in the type of patients who participated, and in the outcomes they investigate. The data compiled from these varied studies is complex and can be conflicting.

Importantly, the editorial in the NEJM states: "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 were due to chance cannot be excluded. In their discussion, the authors properly emphasize the fragility of their findings."

In contrast to a meta-analysis, the most scientifically rigorous way to examine the safety and benefits of a medicine is to conduct large scale, long-term clinical trials in patients with the disease. Several trials of this type have been ongoing for many years. To date concerns regarding patient safety have not been identified by the independent Safety Monitoring Boards for these trials. Several trials have completed and the results published. For example, GSK's long-term, landmark study 'ADOPT' (A Diabetes Outcome Progression Trial) - one of the longest clinical trials in people with type 2 diabetes to date - directly compared both the safety and effectiveness of Avandia with other oral anti-diabetic medicines in over 4,300 patients studied for up to 6 years.

Data from ADOPT showed that the overall risk of serious, cardiovascular events (CV death, myocardial infarction, and stroke, or MACE endpoint) for patients on Avandia was comparable to metformin and sulfonylurea (glyburide) – two of the most commonly used medicines to treat type 2 diabetes. ADOPT showed comparable rates of cardiovascular deaths: Avandia – 5 reports out of 1,456 patients, or 0.34%; metformin – 4 out of 1,454, or 0.28%; and glyburide – 8 out of 1,441 or 0.56%. The ADOPT clinical trial did show a small increase in reports of myocardial infarction among the Avandia-treated group (Avandia: 24 out of 1,456 or 1.65%) vs metformin (20 out of 1,454 or 1.38%) vs glyburide (14 out of 1,441 or 0.97%); however, the number of events is too small to reach a reliable conclusion about the role any of the medicines may have played in this finding. Importantly, ADOPT also demonstrated that Avandia was superior to metformin and sulfonylurea regarding long-term control of blood sugar over five years, which is a key goal in managing diabetes to avoid the long-term complications of the disease.

In another long-term study, DREAM – which followed over 5,200 patients at high risk of developing of type 2 diabetes for a period of three to five years - Avandia monotherapy showed no increase in cardiovascular risk when compared to placebo.

Furthermore, in 2000, GSK initiated RECORD - a large, long-term clinical trial in people with diabetes- which has been prospectively designed to look at cardiovascular outcomes. The independent Safety Monitoring Boards responsible for overseeing the safety of this trial monitors patients closely, and in its

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929

www.gsk.com

regular operations has not found any safety risk that would interrupt continuation of the study.

In addition, in a comprehensive analysis of patients in a US managed care database of more than 33,000 people with diabetes -- performed by independent investigators - there was no difference in ischemic cardiovascular events (including myocardial infarction) among patients taking Avandia-containing regimens versus other oral anti-diabetic medicines.

The totality of the data show that Avandia has a comparable cardiovascular profile to other oral anti-diabetic medicines. GSK stands firmly behind the safety of Avandia when used appropriately, and we believe its significant benefits continue to outweigh any treatment risks.

Because Avandia has been shown to control blood sugar for longer than other standard oral anti-diabetic medicines, it is an important treatment option for physicians who often need to prescribe two or three medicines to help their patients maintain their blood sugar levels. Type 2 diabetes is chronic, relentlessly progressive and life threatening; yet, two-thirds of diabetic patients suffer with uncontrolled disease. If left uncontrolled, diabetes can lead to heart disease, and is the leading cause of blindness, kidney disease and non-traumatic amputations in the US.

GSK has consistently shared its data on Avandia from meta-analyses and controlled studies with the FDA and other regulatory agencies. Data is also posted publicly on the company's Clinical Trial Register. We continue to work closely with regulatory authorities and physicians to keep them fully informed so they can make the best decisions for patients based on both the safety and benefit of the medicine.

GlaxoSmithKline - one of the world's leading research-based pharmaceutical and healthcare companies - is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For company information, visit GlaxoSmithKline on the World Wide Web at www.gsk.com.

Inquiries

US Media inquiries:	Nancy Pekarek	(215) 751 7709
	Mary Anne Rhyne	(919) 483 2839
	Alice Hunt	(215) 751 7709
UK Media inquiries:	Phil Thomson	(020) 8047 5502
	Joss Mathieson	(020) 8047 5502
	Gwenan White	(020) 8047 5502
US Analyst/ Investor inquiries:	Frank Murdolo	(215) 751 7002
	Tom Curry	(215) 751 5419
European Analyst/Investor inquiries:	Anita Kidgell	(020) 8047 5542
	David Mawdsley	(020) 8047 5564
	Sally Ferguson	(020) 8047 5543

FOOTNOTE 46

HIV Articles

Back ▶

GSK Defends Rosiglitazone in Letter to The Lancet: "Cardiovascular safety of rosiglitazone"

Letter to The Lancet
Ronald L Krall, MD
Chief Medical Officer, GlaxoSmithKline, King of Prussia, PA 19406, USA

Published Online, May 30, 2007DOI:10.1016/S0140-6736(07)60824-1

In response to your Editorial (published online May 23)1 regarding the study in the New England Journal of Medicine by Steve Nissen and Kathy Wolski,2 I would like to provide further perspective. Nissen and Wolski estimate a 43% increase in myocardial infarction associated with rosiglitazone. In an associated Editorial, Bruce Psaty and Curt Furberg3 allege that if their estimate is valid there has been a failure of drug use and approval.

GlaxoSmithKline did similar meta-analyses in 2005 and 20064 and found hazard ratios in the same direction as Nissen and Wolski. However, all these results are highly dependent on the methods used and the studies included, given the small number of events reported. For example, the actual number of myocardial infarctions in the Nissen and Wolski meta-analysis yields a very low frequency of events (0.6%), and the absolute difference in rates of myocardial infarctions between rosiglitazone and controls is less than 0.1%.

These observations support a view expressed by Nissen and Wolski them-selves: "a meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest." There are three such trials on which we can rely, two of which have completed, and one, which although still ongoing, has undergone an informative interim analysis.

The first trial, ADOPT (A Diabetes Outcome Progression Trial),5 was a 4-6 year study of glycaemic durability in 4360 people recently diagnosed with type 2 diabetes. Patients were randomly assigned to monotherapy with rosiglitazone, metformin, or glibenclamide for a median of 4a0 years. Since publication of the primary paper, GlaxoSmithKline has further analysed the ADOPT database, examining all major adverse cardio-vascular events (table 1, see below). Our analysis, which adjusted for medication exposure, found that such events were rare in this population and that all treatments were comparable. Hazard ratios for the comparisons between rosiglitazone and the other standard oral antidiabetic agents, metformin and glibenclamide, varied from 0.58 to 1.52 and 95% CIs for all comparisons included unity.

Data from the DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication)6 trial provide a similar picture of the cardiovascular profile for rosiglitazone. Briefly, DREAM assessed whether long-term treatment with rosiglitazone (or ramipril) can reduce the risk of type 2 diabetes in 5269 patients with impaired glucose tolerance or impaired fasting glucose. The trial had a randomised, double-blind, 2x2 factorial design, in which patients were randomised to rosiglitazone or placebo and to ramipril or placebo. In their initial publication, the DREAM study investigators reported no significant difference between the rosiglitazone-containing groups (rosiglitazone plus placebo and rosiglitazone plus ramipril) and the placebo groups (ramipril plus placebo and placebo plus placebo) in their secondary composite endpoint of cardiovascular events (myocardial infarction, stroke, cardiovascular deaths, confirmed heart failure, new angina, and revascularisation procedures). A cell-level intention-to-treat analysis of the final DREAM database by GlaxoSmithKline found that similar numbers of patients on rosiglitazone, ramipril, and placebo had cardiovascular events (table 2). The increased numbers of events in the rosiglitazone plus ramipril group of the study is currently unexplained.

The most compelling evidence comes from RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes),7 an open-label, 6-year cardiovascular outcomes trial (with prospectively

defined cardiovascular endpoints) in 4458 patients that started in 2000. The independent data safety monitoring board for RECORD recently reviewed an interim analysis of unblinded cardiovascular endpoints and confirmed that the trial should continue (manuscript in preparation).

Other cardiovascular outcomes trials, such as the 2368-patient Bypass Angio-plasty Revascularisation Investigation Type 2 Diabetes trial (BARI 2D)8 and the 10 251-patient ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, will further inform the cardiovascular safety profile of rosiglitazone. Their data safety monitoring boards have also confirmed that those studies should continue.

Finally, confirmation of the observations made in ADOPT, DREAM, RECORD, and the other cardiovascular outcome trials can be found by examining the usual care of patients with type 2 diabetes. In 2006, Glaxo-SmithKline commissioned a balanced-cohort observational study in a managed-care database of 33,363 patients who began oral antidiabetic treatment between 2000 and 2004. The study, which assessed a composite cardiovascular endpoint of hospital admissions for myocardial infarction, coronary revascularisation, or both, compared rosiglitazone, metformin, or sulfonylurea as mono-therapy, dual-therapy combinations, and insulin combinations. The incidence of the composite cardiovascular endpoint was 1.75 events per 100 patient-years for the rosiglitazone-containing regimen and 1.76 events per 100 patient-years for the non-rosiglitazone-containing regimen (hazard ratio 0.93, 95% CI 0.80-1.10).

We believe that these studies provide clear evidence of the cardiovascular safety of rosiglitazone and that the estimates of cardiovascular morbidity from the meta-analyses completed to date are not robust. The drug use and approval system is working. We should stay the course and allow ongoing trials to provide their definitive answers.

FOOTNOTE 47

From: Trevor G Gibbs
Date Sent: 5/23/2007 10:12:36 PM
To: Frank W Rockhold
CC:
Subject: Fw: Discussion points with the SC for RECORD

Frank here are the call details , plus speaking points for SC

Simon A Guiver/PharmRD
23-May-2007 10:35

To
rgomis@[redacted], Philip.Home@[redacted], hanefeld[redacted],
michel.komajda@[redacted], Stuart.Pocock@[redacted],
henning.beck-nielsen@ouh.[redacted], ABOSCH@[redacted],
j.mcmurray@[redacted], Murray W Stewart/PharmRD/GSK@GSK, Anne M
Phillips/PharmRD/GSK@GSK, Jill X Donaldson/PharmRD/GSK@GSK, Nigel P
Jones/PharmRD/GSK@GSK, Nevine Zariffa/PharmRD/GSK@GSK, Salim G
Janmohamed/TRAC/PHRD/SB_PLC@GSK, Adam X Crisp/PharmRD/GSK@GSK, Jacqueline C
Richards/PharmRD/GSK@GSK, Alexander R Cobitz/PharmRD/GSK@GSK, Jason
Gubb/PharmRD/GSK@GSK
cc

Subject
URGENT - Important meeting of RECORD Steering Committee

Dear Members of the RECORD STEERING COMMITTEE,

It has been decided that a formal RECORD STEERING COMMITTEE meeting should be held via telephone on Thursday 24 May at 4pm UK time.

Please use the dial in details below

Conference Code: 205777#
GSK VPN: 454 [redacted] (To use from your office, your mobile if you have VPN set-up or from a GSK office abroad)
Freephone Dial-In Number: 0800 [redacted] (To use within the UK from a non-GSK landline)
International Dial-In Number: +44 (0) [redacted] (To use from anywhere outside of the GSK network abroad)

The discussions that will take place at the meeting on Thursday will be of great importance.

Please do not hesitate to contact me should you require any other information or if you are UNABLE to attend this call.

Best regards

Simon Guiver
+44 (0)[redacted]

Regards

Trevor Gibbs

----- Forwarded by Trevor G Gibbs/PharmRD/GSK on 24/05/2007 00:11 -----

Nevine Zariffa/PharmRD
23-May-2007 19:54 Biomedical Data Sciences REN Floor 4 TEL: 8-275-3863
(610-787-3863) FAX: 7006 MAILCODE REN4020

To
Murray W Stewart/PharmRD/GSK@GSK
cc
Anne M Phillips/PharmRD/GSK@GSK, Ian Laws/PharmRD/GSK@GSK, Jill X Donaldson/PharmRD/GSK@GSK, Lawson 2 Macartney/PharmRD/GSK@GSK, Trevor G Gibbs/PharmRD/GSK@GSK, Adam X Crisp/PharmRD/GSK@GSK
Subject
Re: Discussion points with the SC for RECORD

Murray -

Looks fine to me. Thanks for taking this forward; it should be a good discussion tomorrow (can I have TC details please?).

My personal view is that short pub on the planned safety interim is warranted (as is) followed in short order by what might be coined as an orderly close out of the main phase of the trial and that accompanying full publication. We would then initiate the follow up phase of the trial with Fracture & oncology assessments along with blinded adjudicated MACE endpoint and its components (glycemic control endpoints not as critical in my view). We should consider presentation at ADA and/or EASD.

Assuming we end up in this neighborhood following the SC/DSMB discussions tomorrow....

We will need to finalise key elements of the RAP before the results become public. Ian, if Rapporteur becomes aware of numerical results from safety interim before he can review the RAP we may need to forgo formal buy-in to the final analysis plan unless he can delegate to another individual? Seems like a detail but we have yet to get endorsement on some key issues. The one thing I can guarantee is that the final results of the main phase of the trial will differ from the interim results (!).

All for now.

N,vine Zariffa
Therapy Area Director, Cardiovascular and Metabolism
Biomedical Data Sciences
GlaxoSmithKline Pharmaceuticals
TEL: (610)-[redacted]
2301 Renaissance Blvd, Building #510
King of Prussia, PA, 19406

Murray W Stewart/PharmRD
23-May-2007 14:26 ADP UW2290 276 6848

To

Jill X Donaldson/PharmRD/GSK@GSK, Trevor G Gibbs/PharmRD/GSK@GSK, Lawson 2 Macartney/PharmRD/GSK@GSK
cc
Nevine Zariffa/PharmRD/GSK@GSK, Ian Laws/PharmRD/GSK@GSK, Anne M Phillips/PharmRD/GSK@GSK
Subject
Discussion points with the SC for RECORD

Dear All

Here is an outline for the discussion with the steering committee of RECORD

1) Remind them that we discussed the ICT for ischaemia and ADOPT data at steering committee at heathrow 3rd May

2) Asked Philip and Stuart to endorse safety interim for RECORD on 14th May (as well as DSMB) to help dialogue with FDA on overall risk/benfit for patient safety.

3) Firewalled safety analysis performed and shared with DSMB and FDA (also firewalled)

4) 21st May Online publication of Meta-analysis of Avandia by S Nissen
a) Response by FDA - "Other published and unpublished data from long-term clinical trials of Avandia provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking Avandia"
b) Response of GSK
i) Press release - disagree with conclusions of Nissen limitations of analysis results of ADOPT, DREAM supportive and RECORD is ongoing
ii) Letter to patients in all studies sent out
iii) Letter to NEJM/Lancet in response to Nissen article

5) Concern re patient safety on Avandia in media and US government Congress Hearing with GSK and FDA on June 6th. High probability the data on RECORD interim safety will be disclosed.

6) Risk to RECORD -
a) safety concern of patients in study due to publication by Nissen and comments in the Media - patients may drop out, bias in reporting by patients/investigators -study compromised
b) RECORD compromised by comments from FDA
c) RECORD compromised by further disclosure

Questions for the SC
a) Do the SC want endorsement from the DSMB in light of data to continue the study
b) Would the SC consider publishing formally the data on safety interim if the data is going to be disclosed.
c) Would the SC consider to continue the study even if the safety interim data is known.

Jill and I have set up a pre call at 3.30 UK time (10.30 US time) for GSK staff only prior to discussions with SC at 4.00pm UK Time

Murray

FOOTNOTE 48 - 50

REDACTED - Attorney-Client Privileged

Trevor G Gibbs/PharmRD
24-May-2007 04:22 Medical Governance and Pharmacovigilance Greenford Bld 60, room 218 711 2575

To
Lawson 2 Macartney/PharmRD/GSK@GSK
cc
Allan 2 Baxter/PharmRD/GSK@GSK, Frank W Rockhold/DEV/PHRD/SB_PLC@GSK, Moncef M Slaoui/MGMT/PHRD/SB_PLC@GSK, Nancy J Pekarek/FPL/Corp/SB_PLC@GSK, Paul D Huckle/PharmRD/GSK@GSK, Ronald L Krall/MGMT/PHRD/SB_PLC@GSK
Subject
Re: Fw: Endocrine Society Statement to Providers on Avandia

Lawson very balanced, I note the 4th paragraph.

We would urge that the RECORD study be continued until its planned completion date in 2009 unless its Data Safety Monitoring Committee finds specific cause to stop it. Premature termination of this important study would leave the medical community without a definitive answer to the key question of the safety of rosiglitazone and would leave a cloud over other members of the thiazolidinedione class, a vital part of the current armamentarium in the treatment of diabetes.

I refer to Frank's question contained in the e mail below. Would help to have an answer before 4pm GMT. Further, if the Steering Committee are reluctant to publish- Frank and I will argue the case that there is a balance to be drawn

between very negative external press coverage and specific reaassurance for the patients in the study. However if the SC believe that publishing interim data will fatally damage their abilty to bring the study to a completion- Frank and I will bring that opinion with reasons back to GSK , before pursuing the line- that a decision has been made- live with it.

Frank W Rockhold/DEV/PHRD
24-May-2007 00:29 SVP, Drug Development Sciences Renaissance Center 610 787 3890, Internet: Frank.W.Rockhold@gsk.com

To
Ronald L Krall/MGMT/PHRD/SB_PLC@GSK
cc
Lawson 2 Macartney/PharmRD/GSK@GSK, Trevor G Gibbs/PharmRD/GSK@GSK
Subject
Re: RECORD

Anyone willing to share why and how that decision was made? Trevor and I are meeting with the SC tomorrow and it will be awkward if we do not know that

Frank

Ronald L Krall/MGMT/PHRD
23-May-2007 08:00 Office of the Chief Medical Officer Upper Merion 610-270-6107

To
Lawson 2 Macartney/PharmRD/GSK@GSK
cc
Frank W Rockhold/DEV/PHRD/SB_PLC@GSK, Trevor G Gibbs/PharmRD/GSK@GSK
Subject
Re: RECORD

Now that we've decided we will disclose the results, I agree a small additional group should join the firewalled team and help prepare the presentation materials. They should consider posting on our clinical trial register, and submission of a short scientific paper or report.

Please send me the names so I can formally record the people and date they entered the firewall.

Ron

Lawson 2 Macartney/PharmRD
24-May-2007 08:26

To
Nancy J Pekarek/FPL/Corp/SB_PLC@GSK, Moncef M Slaoui/MGMT/PHRD/SB_PLC@GSK, Ronald L Krall/MGMT/PHRD/SB_PLC@GSK, Allan 2 Baxter/PharmRD/GSK@GSK, Trevor G Gibbs/PharmRD/GSK@GSK, Frank W Rockhold/DEV/PHRD/SB_PLC@GSK, Paul D Huckle/PharmRD/GSK@GSK
cc

Subject
Fw: Endocrine Society Statement to Providers on Avandia

This is a measured and balanced response to the immediate issue and is one which has good points for us to endorse in our communications.

Dr. Lawson Macartney,
Senior Vice-President, WW Development
GlaxoSmithKline,
RN 0315
tel 610 [redacted]
Fax 610 [redacted]
assistant ([redacted]) 610[redacted]
----- Forwarded by Lawson 2 Macartney/PharmRD/GSK on 05/24/2007 08:24 AM -----

Lorraine A Fitzpatrick/PharmRD
23-May-2007 23:50

To
R&D_Avandia Bone Working Group Ad Hoc, R&D_Avandia Bone Working Group Core
cc
Anne M Phillips/PharmRD/GSK@GSK, Lawson 2 Macartney/PharmRD/GSK@GSK, Sandy Macrae-1/DEV/PHRD/SB_PLC@GSK
Subject
Fw: Endocrine Society Statement to Providers on Avandia

Thought this would be of interest- please forward as appropriate.

best, Lorie

----- Forwarded by Lorraine A Fitzpatrick/PharmRD/GSK on 05/23/2007 06:48 PM -----

"The Endocrine Society" <societyservices@endo-society.org>
23-May-2007 16:09

To
lorraine.a.fitzpatrick@gsk.com
cc

Subject
Endocrine Society Statement to Providers on Avandia

May 23, 2007

The Endocrine Society Statement to Providers on the Report Published in the New England Journal of Medicine on Avandia

On May 21, 2007, the New England Journal of Medicine released a meta-analysis by Steven Nissen, M.D., and Kathy Wolski, M.P.H., examining the effects of rosiglitazone (Avandia) on cardiovascular morbidity and mortality. Since it was approved in 1999, rosiglitazone has been used by almost 6 million patients in the US for the treatment of type 2 diabetes. The findings of the NEJM article are based on 42 studies that met the inclusion criteria: duration of more than 24 weeks; use of a randomized control group not receiving rosiglitazone; and availability of outcome data for myocardial infarction and death from cardiovascular causes. The data analysis indicated that the use of rosiglitazone put patients at a statistically significant 43 percent higher risk of experiencing a heart attack (p=0.03) and a borderline significant 64 percent higher risk of cardiovascular death (p=0.06) compared to patients who took other drugs or a placebo. All-cause mortality was not different between the rosiglitazone and control groups.

The Endocrine Society shares the concerns of the article's authors and the FDA about the potential risk to patients using this drug. However, we also feel that no precipitous action should be taken by the FDA or the medical community based on this meta-analysis, given the study's substantial limitations as pointed out by both the article's authors and by those writing the accompanying editorial (Bruce Psaty, M.D., Ph.D. and Curt Furberg, M.D., Ph.D.). We agree that a circumspect interpretation of the data is warranted given that the vast majority of the adverse events were not pre-defined nor subsequently validated/adjudicated; reclassification of such events could lead to substantial changes in the calculated odds ratios and consequently in the study's conclusions. Further hampering a definitive interpretation of the findings is the authors' lack of access to source data, thereby precluding critical time-to-event and dose-response analysis. Other points of concern include the extensive use of unpublished data (only 11 of 42 studies used in the meta-analysis were peer-reviewed); the small size of the studies (none were powered to evaluate the cardiovascular risks); and the similarity of the crude incidence rates of myocardial infarction in the two groups (5.5 per 1000 patients for rosiglitazone vs 5.9 per 1000 patients for control).

The FDA has stated that an interim report from the RECORD study - a long-term trial of rosiglitazone begun four years ago that is powered to assess cardiovascular risks (4500 patients randomized) - did not note such adverse effects. Of relevance, a 2005 report of an adequately powered, prospective study of another drug in this thiazolidinedione class also did not suggest an increase in cardiovascular events.

We would urge that the RECORD study be continued until its planned completion date in 2009 unless its Data Safety Monitoring Committee finds specific cause to stop it. Premature termination of this important study would leave the medical community without a definitive answer to the key question of the safety of rosiglitazone and would leave a cloud over other members of the thiazolidinedione class, a vital part of the current armamentarium in the treatment of diabetes.

What should providers do at this juncture? Given our concerns about the current study, as noted above, we feel that providers should react in a measured way. The firestorm of publicity surrounding this article, and the ensuing barrage of phone calls from patients, may well require a response from providers. Switching patients from rosiglitazone to another drug in the same class is not risk-free, both because the NEJM study's findings might represent a class effect and because the impact of any drug substitution can be unpredictable. Fortunately, numerous drugs in several different classes have become available over the past decade for providers' use in the treatment of diabetes; such options may be helpful in dealing with this situation. Providers with the ability to identify patients currently taking rosiglitazone from an electronic medical record or other data base may wish to take a pro-active stance by contacting them. Whether by proactive contact or in response to a patient's inquiry, the provider should counsel each person about the findings of the study, discussing the study's implications on an individual basis, and reviewing the risks and benefits of remaining on rosiglitazone versus changing therapy. It would also seem prudent, given the very high baseline risk of cardiovascular events in patients with diabetes, to redouble efforts to reduce other cardiovascular risk factors by aggressive treatment of the co-morbidities of hyperlipidemia and hypertension in those diabetic patients taking medications with postulated cardiovascular side effects.

Finally, this NEJM study highlights the need for strict and transparent post-marketing surveillance of all new drugs. Such an approach would complement the existing use of surrogate markers to gauge effectiveness when new drugs for the treatment of chronic illnesses are evaluated by the FDA and would facilitate continued innovation in pharmaceutical research.

For further information, please contact Stephanie Kutler, Associate Director, Government & Professional Affairs, at skutler@endo-society.org.

Founded in 1916, The Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones, and the clinical practice of endocrinology. Today, The Endocrine Society's membership consists of over 14,000 scientists, physicians, educators, nurses and students in more than 80 countries. Together, these members represent all basic, applied, and clinical interests in endocrinology. The Endocrine Society is based in Chevy Chase, Maryland. To learn more about the Society, and the field of endocrinology, visit our web site at www.endo-society.org

8401 Connecticut Avenue, Suite 900 Chevy Chase, Maryland 20815-5817 Tel. 301.941.0200 Fax 301.941.0257 www.endo-society.org

FOOTNOTE 51, 52

From: Frank W Rockhold/DEV/PHRD/SB_PLC

To: Ronald L Krall;Trevor G Gibbs/PharmRD/GSK

Subject: Fw: RECORD brief report to NEJM

Date: 05/24/2007 16:18:16 (GMT-05:00)

----- Forwarded by Frank W Rockhold/DEV/PHRD/SB_PLC on 05/24/2007 16:18 -----

"Stuart Pocock" <Stuart.Pocock@[redacted]>
24-May-2007 15:53

To
nigel.P.Jones@gsk.com
cc
Frank.W.Rockhold@gsk.com
Subject
Fwd: RE: RECORD brief report to NEJM

emailconfirmation

Stuart Pocock
Medical Statistics Unit
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT

Tel +44 (0)2[redacted]

Fax +44 (0)[redacted]
----- Message from "Drazen, M.D., Jeff" <jdrazen@[redacted]> on Thu, 24 May 2007 15:49:04 -0400 -----
To: "Stuart Pocock" <Stuart.Pocock@[redacted]>
Subject: RE: RECORD brief report to NEJM
Stuart,
As we discussed the NEJM is interested in seeing and reviewing the RECORD study. In order to expedite the review process we would be most grateful if you could forward to us the list of involved investigators.
Thank you for considering the NEJM as a venue for publishing your research.
Best,
jmd

Jeffrey M. Drazen, M.D.
Editor-in-Chief, New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine, Harvard Medical School

Editorial Office
10 Shattuck Street
Boston, MA 02115 USA

Phone: 617-[redacted]
Fax: 617-[redacted]
Email: jdrazen@[redacted]

Publication Office
Massachusetts Medical Society
860 Winter Street
Waltham, MA 02451 USA

Assistant:
Caryn Sandrew
Phone: 781-[redacted]
Email: csandrew@[redacted]

No trees were killed in the sending of
this message. However, a large number
of electrons were terribly inconvenienced.

-----Original Message-----
From: Stuart Pocock [mailto:Stuart.Pocock@[redacted]]
Sent: Thursday, May 24, 2007 2:53 PM
To: Drazen, M.D., Jeff
Subject: RECORD brief report to NEJM

Dear Dr Drazen

We the Steering Committee of the RECORD Study would like to submit a brief report of the current interim findings in this ongoing trial concerning the key cardiovascular outcomes.

Since this issue is very topical, we would be grateful if this report could be considere for publication in the same issue as the meta-analysis by Nissen and Wolski. We realize the tight timeline and accordingly could submit this brief report within a week, ie by end of May.
I t would contain just one Table of results.

RECORD comprises 4447 patients with median follow-up over 4 years, and hence is the largest body of evidence concerning the cardiovascular effects of rosiglitazone. Under other circumstances we would not have published interim results, but it seems important now to reveal these current findings, which were just recently sent to FDA.

Jim Ware, NEJM statistical consultant, suggested I approach you right away. We would be grateful for your rapid response on how we might best proceed. If discussion would help please phone my cell +44 [redacted]

We look forward to hearing from you shortly.

Yours sincerely

Stuart Pocock
Acting chair of RECORD Steering committee

Stuart Pocock
Medical Statistics Unit
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT

Tel +44 (0)[redacted]

Fax +44 (0)[redacted]

From: Frank W Rockhold/DEV/PHRD/SB_PLC

To: Trevor G Gibbs/PharmRD/GSK

CC: Nigel P Jones/PharmRD/GSK@GSK;Ronald L Krall

Subject: Fw: RECORD brief report to NEJM

Date: 05/24/2007 15:36:10 (GMT-05:00)

I just had a long discussion with Stuart and he updated me on this. Will try to update Ron later today, but call me tonight or tomorrow if you want details.

Good news but has to be an original article so more work involved than we thought.

Frank
----- Forwarded by Frank W Rockhold/DEV/PHRD/SB_PLC on 05/24/2007 15:34 -----

"Stuart Pocock" <Stuart.Pocock@[redacted]
24-May-2007 15:17

To
Frank.W.Rockhold@gsk.com
cc

Subject
Fwd: RECORD brief report to NEJM

See attached. Jeff Drazen just phoned to say YES. I'll phone now to explain details.

Stuart

Stuart Pocock
Medical Statistics Unit
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT

Tel +44 (0)[redacted]

Fax +44 (0)[redacted]
----- Message from "Stuart Pocock" <Stuart.Pocock@[redacted] on Thu, 24 May 2007 19:53:03 +0100 -----
To: jdrazen@[redacted]
Subject: RECORD brief report to NEJM
Dear Dr Drazen

We the Steering Committee of the RECORD Study would like to submit a brief report of the current interim findings in this ongoing trial concerning the key cardiovascular outcomes.

Since this issue is very topical, we would be grateful if this report could be considere for publication in the same issue as the meta-analysis by Nissen and Wolski. We realize the tight timeline and accordingly could submit this brief report within a week, ie by end of May.

I t would contain just one Table of results.

RECORD comprises 4447 patients with median follow-up over 4 years, and hence is the largest body of evidence concerning the cardiovascular effects of rosiglitazone. Under other circumstances we would not have published interim results, but it seems important now to reveal these current findings, which were just recently sent to FDA.

Jim Ware, NEJM statistical consultant, suggested I approach you right away. We would be grateful for your rapid response on how we might best proceed. If discussion would help please phone my cell +44 [redacted].

We look forward to hearing from you shortly.

Yours sincerely

Stuart Pocock
Acting chair of RECORD Steering committee

Stuart Pocock
Medical Statistics Unit
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT

Tel +44 (0)[redacted]

Fax +44 (0)[redacted]

FOOTNOTE 53

"Henning Beck-Nielsen" <Henning.Beck-Nielsen@[redacted]>

29-May-2007 08:53

To j.mcmurray@[redacted], ABOSCH@[redacted], rgomis@[redacted], j.gavigan@[redacted], Nigel.P.Jones@gsk.com, hanefeld@[redacted],
cc Murray.W.Stewart@gsk.com, stuart.pocock@[redacted]
bcc
Subject Svar: URGENT. RECORD MS REQUIRING REVIEW WITHIN 24 Hours

Comments to the Rosiglitazone paper

Dear all

First of all, I want to congratulate Stuart and Nigel for an excellent paper. I am happy to see that the data are so convincing.

Then, I have the following comments:

First of all, I think it is important to stress as much as acceptable that cardiovascular death and overall death are not increased with rosiglitazone treatment. In fact, the numbers tend to be lower with rosiglitazone.

This is the key finding!

We do not find more myocardial infarctions with rosiglitazone treatment, but again there is a tendency supporting the Nissen argument. It is important to stress that it does not affect cardiovascular death. The small difference in numbers between the two groups may be explained by other variables, such as e.g. statin treatment. Could we give any data on statin treatment and is that a good idea? We may remember that the results in the PROACTIVE study were different in statin and non-statin treated subjects. At least I think that it should be mentioned in the discussion.

Of course, heart failure should be mentioned and not hidden. It is important to show that the numbers are very low; in fact the frequency is 1.5 % in the rosiglitazone group and 0.6 % in controls, which is a much lower number than shown in previous reports and this indicates that these problems can be avoided by labelling the drug and taking the patients out of treatment in case of oedema.

Should we create a figure of the classical type with hazard ratio around a vertical line through hazard ratio = 1.0? That could be informative.

I have no comments to the order of authors.

Best regards

Henning

>>> <Nigel.P.Jones@gsk.com> 05/28/07 12:57 >>>

Here is the draft MS for review.

The editor of the New England Journal of Medicine, Jeff Drazen, has been very helpful and is expecting the MS to be submitted by Thursday 31st May.

FOOTNOTE 54

"Dr. Hanefeld"
<hanefeld@[redacted]>

29-May-2007 17:05

To "John McMurray" <j.mcmurray@[redacted]>, Nigel.P.Jones@gsk.com
cc hanefeld@[redacted], henning.beck-nielsen@[redacted], Philip.Home@[redacted], rgomis@[redacted],
bcc
Subject AW: URGENT. RECORD MS REQUIRING REVIEW WITHIN 24 Hours

Dear all, dear Dr. Donaldson!
Sorry, I just left the plane from Japan when I got the last version (Mc Murray, May 29) of the MS to the NEJM. I think this is now a well balanced article taking into account most of the proposals for amendment. There are still two points to be emphasized
(1) Tab. 2 contains predefined, already published endpoints most adjusticated. Nissen's paper by contrast reports non-adjudicated adverse events of a selected number of short term trials
(2) The critical issue is heart failure which is consistent with DREAM, PROACTIVE and ADOPT. It is essential to add the numbers of fatal HF. I very hope that most cases represent overload HF without serious consequences as it was the case in the above mentioned studies.
Best regards
Markolf

useful → to know (maybe at the revision + request)

-----Ursprüngliche Nachricht-----
Von: John McMurray [mailto:j.mcmurray@[redacted]]
Gesendet: Dienstag, 29. Mai 2007 01:35
An: Nigel.P.Jones@gsk.com
Cc: hanefeld@[redacted]; henning.beck-nielsen@[redacted]; Philip.Home@[redacted]; rgomis@[redacted]; michel.komajda@[redacted]; ABOSCH@[redacted]; j.gavigan@[redacted]; Murray.W.Stewart@gsk.com; stuart.pocock@[redacted]; John J V McMurray
Betreff: Re: URGENT. RECORD MS REQUIRING REVIEW WITHIN 24 Hours

Here are my (extensive) comments (as track changes etc) - only on Methods, results and Discussion at moment.

There are several striking issues:

1) The HR ratio (and 95% CI) for MI in RECORD is not inconsistent with Nissen's - and he had more events; what's to stop him adding the events from RECORD to his meta-analysis and re-enforcing his view? Stuart - if we write (as we have done) that we have completed 2/3 of planned follow-up, could the informed reader conclude that the trial will never be able to exclude a significant hazard of rosiglitazone?

2) Same is true for CV death, although the number of events in RECORD and in the meta-analysis are similar and at least in RECORD the HR is in the other direction!

3) Manuscript looks to me to play down 239% INCREASE in HF. I have taken the liberty of doing some rewording.

4) The big discrepancy between the numbers for the primary composite and the CV death/MI/stroke composite is striking - more than twice as many primary outcomes - if I was the reviewer I would want to know what are all those additional events are and whether they are swamping (hiding?) important events. Is the MI signal supported

ABOSCH@[redacted]
28-May-2007 17:03

To Nigel.P.Jones@gsk.com
cc hanefeld@[redacted], henning.beck-nielsen@[redacted], Philip.Home@[redacted], michel.komajda@[redacted],
bcc
Subject RV: URGENT. RECORD MS REQUIRING REVIEW WITHIN 24 Hours

[redacted]

Dear Nigel,

Thank you for providing me the draft of the Record study related to cardiovascular endpoints. First of all, let me apologize my delay on sending my comments, I was outside of Barcelona.

I agree with the content of the paper, and in my personal point of view reflects carefully the motivations of the steering comitee to publish these interim data and it maintain an open window for a full information in the future.

Let me only make a small comment related to the discussion:

3trd paragraph. RECORD is the first large ..... with type 2 diabetes to determine the cardiovascular safety of rosiglitazone. In Diabetologia (2005) 48: 1726-1735 we concluded that "it will investigate the premises that thiazolidinediones, wich improve glycaemic control by decreasing insulin sensitivity, reduce the incidence of macrovascular complications in individuals with type 2 diabetes." So, I suggest RECORD is the first large prospectively designed study....to evaluate the long-term impact impact of rosiglitazones on C outcomes, as well as on long term glycaemic control in subjects suffering type 2 diabetes.....

Then in the same paragraph we comment "This study is therefore importabt in answering some of the safety concerns raised by meta.-analysis"

In my opinion it is relevant to maintain the first concept of record based in previous data suggesting that in addition to blood glucose concentrations rosiglitazine improve some CV risk factors and surrogate markers that are anormal in type 2 diabetes.

Best wishes

Dr. Ramon Gomis

-----Mensaje original-----
De: Nigel.P.Jones@gsk.com [mailto:Nigel.P.Jones@gsk.com]
Enviado el: lunes, 28 de mayo de 2007 12:58
Para: hanefeld@[redacted]; henning.beck-nielsen@[redacted]; Philip.Home@[redacted]; GOMIS, RAMON (DIR.RECERCA); michel.komajda@[redacted]; j.mcmurray@[redacted]; BOSCH, ANA (DIR.RECERCA); j.gavigan@[redacted]
CC: Murray.W.Stewart@gsk.com; stuart.pocock@[redacted]
Asunto: URGENT. RECORD MS REQUIRING REVIEW WITHIN 24 Hours
Importancia: Alta

"Philip Home"
<Philip.Home@[redacted]>

29-May-2007 05:37

To "Stuart Pocock" <stuart.pocock@[redacted]>, Nigel.P.Jones@gsk.com
cc
bcc
Subject RECORD study interim

Stuart

I think you have done a fine job here, and even after reading John M's comments. Ultimately of course a reviewer can attack the CIs, and even the likely CIs at 6 years, but there is not much we can do about that. The point about number of events is well taken - we discussed the problem of the primary on 03 May, but I am tempted just to let the matter stand (it is explained in effect by anyone reading the Methods carefully). An alternative would be an additional comment in the Discussion about the numbers inevitably being low at this stage (under 2/3 complete), but I read this as obvious.

I do have some minor editorial and formatting commments - these are tracked on the attached..

I did think about authorship order even before getting this - my attitude would I think be different for a brief report, but this is not that by a long way. I ended up with the order you have - except HBN who on ABC grounds should I think be further forward.

I will try to ring you in the morning - about 0730 h Mountain Daylight Saving Time - 7 h behind BST. 14 30

Nigel: has everyone seen the report; I do not think they can endorse the paper without having done so!

Philip

PHILIP HOME
> Professor of Diabetes Medicine, Newcastle University, UK
> http://www.staff.ncl.ac.uk/philip.home/
> Tel +44 [redacted]; Fax +44[redacted]

On Mon, 28 May 2007 Nigel.P.Jones@gsk.com wrote:

> Philip,
>
> If you are at all able to telephone Stuart then I know he would very much
> appreciate reassurance that you are happy with all that is happening with
> the manuscript. He is hoping that it's a case of you really wanting to
be
> with your family. As he put it "we haven't forgotten that you are the
> chairman".
>
> To save looking it up, Stuart's mobile number is [redacted].
>
> My message from me: seeing as we are currently plaguing your holiday, it
> may seem incongruous to hope you are having a fine time... but I hope you
> are!
>
> kind regards
>
> Nigel
>
> P.S. I asked Stuart if it would help for me to drop you a line on this -

FOOTNOTE 55, 61

The NEW ENGLAND JOURNAL of MEDICINE

Philip D. Home, M.D.
Newcastle University
NE1 7RU
United Kingdom
Email: philip.home@[redacted]

June 1, 2007

Re manuscript 07-3394

Dear Prof. Home:

On behalf of the editors of the New England Journal of Medicine, I want to thank you for submitting your interesting manuscript titled, "Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) Study: Interim Findings on Cardiovascular Hospitalizations and Deaths." We have completed our review of your manuscript, and I am pleased to inform you that the manuscript has been recommended for publication in the Journal, subject to appropriate revisions. The purpose of this letter is to underscore and prioritize the revisions that the editors believe are necessary if we are to proceed with your manuscript.

The manuscript has been read by many members of the editorial staff and eight reviewers. Below we have summarized the critical points that require changes in the manuscript in response to each reviewer's concerns. We expect your revisions to carefully address all of the points raised below. Please understand that we cannot make a final commitment to publish your manuscript until we have received a revised version that successfully addresses each point in the critiques.

Reviewer A:
Please pay particular attention to paragraphs 3-9 in this review.
The reviewer points out that given the 95% CI around the primary endpoint (0.89 to 1.31 for the adjudicated endpoints, or 0.93 to 1.32 for all endpoints), the data demonstrate neither non-inferiority nor inferiority. That is, the data are inconclusive about the question of increased risk in the rosiglitazone arm. This reviewer, along with other reviewers, asks that you modify the language in multiple locations in the manuscript to tone down your conclusions. This is especially important given that this is an unplanned interim analysis of an ongoing trial, a fact that introduces additional uncertainty. Please note that, in the opinion of all readers, the data that you present are completely compatible with the results of the meta-analysis by Nissen and the meta-analysis for myocardial ischemic events posted on the GSK Web site [http://ctr.gsk.co.uk/Summary/rosiglitazone/studylist.asp].

find the multiple locations

Reviewer B:
Please note the reviewer's point #4 (Interpretation of Results). The reviewer underscores that your interpretation of a nonsignificant difference as "no evidence of a difference" is not acceptable. The data must be interpreted in the light of the 95% CIs, which are compatible with as much as a 7% reduction in risk of the primary endpoint, or as much as a 32% increase in risk of the primary endpoint. For the MI endpoint, which was a focus of the Nissen meta-analysis, there is considerable overlap of the 95% CIs of the point estimates in the RECORD trial and the Nissen meta-analysis. This reviewer points out that MI relative risks in the two studies do not differ significantly. The editors feel strongly that your data do not support the statement that the RECORD results for MI contradict the Nissen meta-analysis; this statement must be removed or modified.

Reviewer C:
The editors agree with all the points raised by this reviewer, and it is essential that all these thoughtful comments be addressed by making changes in the manuscript. The third paragraph of the review deals with the lack of blinding. The fourth paragraph deals with the weak choice of a primary endpoint, since cardiovascular hospitalizations do not always involve coronary-related events, and therefore noise is introduced (for example, atrial fibrillation or valvular heart disease). The sixth paragraph points out the serious problem of the low event rate, especially for MI events, in this study. Do you have an explanation for the very low event rate? This should be explicitly addressed in the revised manuscript. There is concern that there may have been a failure to ascertain events. The reviewer also reiterates points made by reviewer A and B about the wide 95% CIs for the point estimates, and the need to greatly tone down your language to reflect the substantial level of uncertainty in the data.

Reviewer D:
Please pay particular attention to the first and third paragraphs of this review. The editors agree that you should present alternative analyses including events pending adjudications for all outcomes that you include in this manuscript. Given the very low power of your study at this point, it is sensible to include all endpoints reported by the investigators, not just the adjudicated ones, since this will add power. The editors also agree that an explanation of the rationale for the continued use of rosiglitazone is needed in this manuscript.

Reviewer E:
Please give special attention to points #2, 9, 10, 12, and 14. Some of these points request changes in wording. Point #9 asks for the rationale for the 20% non-inferiority margin. We realized that this was determined long ago, but the reader should not have to refer back to your methods article to understand how this margin was determined.

Reviewer F:
In points #1 through 5, this reviewer effectively underscores points made by other reviewers, thus no new specific response is required here, except with regard to the issues

concerning loss to follow up (Comments #2 and 3). The loss to follow up impacts on the power of the study, and also raises the question of the fate of those lost to follow up.

Reviewer G:
While underscoring many of the points made in other reviews, this reviewer also points out that "the Kaplan-Meier curves, point estimates, and event rates suggest a reasonably high probability that the study will fail to show non-inferiority at trial completion. Note the pattern of separation beginning at 18-24 months with a gradual widening of the differences over time (particularly in the version that includes events pending adjudication)." The editors were also struck that the K-M curves (Figure 1b) appear to be progressing in a direction of cardiovascular harm for rosiglitazone, raising the question of whether the study will fail to establish non-inferiority. Please comment on this trend.

When you send in your revised manuscript, please include a covering letter that lists the reviewers' comments and provides a response to each. You should return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. The revised manuscript should be triple-spaced, including references, tables, and figure legends. Please include a word count for the text. Your revised paper should not exceed 2500 words. The title cannot contain more than 75 letters and spaces. You should submit your revised manuscript using the *Journal*'s online-submission Web site. Please go to **http://authors.nejm.org/** and select "**Submit a Revised Manuscript.**"

During the preparation of your revised manuscript, please complete the attached "**Manuscript Checklist**" and return it with your submission. Failure to return the form will delay the processing of your manuscript.

A combined **Disclosure and Authorship Statement** is also attached. Each author must complete and sign a copy. To ensure that it is legible, please fill out the form directly on your computer, print it out, sign it, and return it by fax to 617-739-9864. It is essential that you return the signed forms as soon as possible, because we cannot process your manuscript without them.

Please recall that the *Journal* requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the *Journal*. Copies of any related manuscripts should be submitted along with the revised manuscript, if this has not already been done. If you have any questions about compliance with these policies, please contact the editorial office for clarification.

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. Please ask all authors to sign and fax back the enclosed form as soon as possible. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The editors want to thank you again for allowing us to review your interesting work. We look forward to reading the revised version of your manuscript. Given the high interest in this dataset, we would like to receive your revised manuscript no later than 08:00 hrs Eastern Daylight time (13:00 hours in the UK or GMT-4) in the U.S. on Monday June 4, 2007. If you need to consult with an editor over the weekend, please call Dr. Gregory Curfman on his mobile phone at (978) [redacted]

Sincerely,

Gregory D. Curfman

Gregory D. Curfman M.D.
Executive Editor
gcurfman@[redacted]
Mobile: (978)-[redacted]
Office (but not over the weekend): (781)[redacted]

FOOTNOTE 64

ORIGINAL ARTICLE

Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

Philip D. Home, D.M., D.Phil., Stuart J. Pocock, Ph.D., Henning Beck-Nielsen, D.M.S.C., Ramón Gomis, M.D., Ph.D., Markolf Hanefeld, M.D., Ph.D., Nigel P. Jones, M.A., Michel Komajda, M.D., and John J.V. McMurray, M.D., for the RECORD Study Group*

From Newcastle Diabetes Centre and Newcastle University, Newcastle upon Tyne, United Kingdom (P.D.H.); the Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London (S.J.P.); the Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark (H.B.-N.); Hospital Clinic, University of Barcelona, Barcelona (R.G.); Zentrum für Klinische Studien Forschungsbereich Endokrinologie und Stoffwechsel, Dresden, Germany (M.H.); GlaxoSmithKline Pharmaceuticals, Harlow, United Kingdom (N.P.J.); Université Pierre et Marie Curie Paris 6 and Hôpital Pitié–Salpêtrière, Paris (M.K.); and the Department of Cardiology, University of Glasgow, Western Infirmary, Glasgow (J.J.V.M.). Address reprint requests to Dr. Home at SCMS-Diabetes, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, United Kingdom, or at philip.home@newcastle.ac.uk.

*Investigators for the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study group are listed in the Appendix.

This article (10.1056/NEJMoa073394) was published at www.nejm.org on June 5, 2007.

N Engl J Med 2007;357:28-38.

ABSTRACT

BACKGROUND

A recent meta-analysis raised concern regarding an increased risk of myocardial infarction and death from cardiovascular causes associated with rosiglitazone treatment of type 2 diabetes.

METHODS

We conducted an unplanned interim analysis of a randomized, multicenter, open-label, noninferiority trial involving 4447 patients with type 2 diabetes who had inadequate glycemic control while receiving metformin or sulfonylurea, in which 2220 patients were assigned to receive add-on rosiglitazone (rosiglitazone group), and 2227 to receive a combination of metformin plus sulfonylurea (control group). The primary end point was hospitalization or death from cardiovascular causes.

RESULTS

Because the mean follow-up was only 3.75 years, our interim analysis had limited statistical power to detect treatment differences. A total of 217 patients in the rosiglitazone group and 202 patients in the control group had the adjudicated primary end point (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of end points pending adjudication, the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There were no statistically significant differences between the rosiglitazone group and the control group regarding myocardial infarction and death from cardiovascular causes or any cause. There were more patients with heart failure in the rosiglitazone group than in the control group (hazard ratio, 2.15; 95% CI, 1.30 to 3.57).

CONCLUSIONS

Our interim findings from this ongoing study were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes. There was no evidence of any increase in death from either cardiovascular causes or all causes. Rosiglitazone was associated with an increased risk of heart failure. The data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction. (ClinicalTrials.gov number, NCT00379769.)

FOR PATIENTS WITH TYPE 2 DIABETES, CARdiovascular disease is the leading cause of death and the major cause of morbidity.[1] In such patients, cardiovascular risk is considerably elevated,[2] although recent reports have moderated this concern.[3,4] Factors that are implicated in the development of atherosclerosis include dyslipidemia, obesity, hypertension, hyperglycemia, and hyperinsulinemia.[5]

Type 2 diabetes is a progressive disease and its prevalence in the population is increasing. Since there is greater attention to glycemic targets, more patients are receiving combination therapies. Clinical trials comparing monotherapies are common, but comparisons of new dual-agent combinations with the standard of metformin plus sulfonylurea are rare. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial is a long-term, multicenter, randomized, open-label study[6] that compares cardiovascular outcomes in patients with type 2 diabetes treated with rosiglitazone (Avandia) plus metformin or sulfonylurea (rosiglitazone group) with outcomes in patients treated with metformin plus sulfonylurea (control group). The results of the United Kingdom Prospective Diabetes Study (UKPDS) suggest that the comparators metformin and sulfonylurea used in the RECORD trial reduce myocardial infarction by 39% and 16%, respectively, as compared with conventional treatment and diet.[7,8]

After a recent meta-analysis by Nissen and Wolski[9] raised concern about the cardiovascular safety of rosiglitazone, the current totality of evidence needs to be made available. Accordingly, this interim report presents the outcomes and deaths from cardiovascular causes so far in the RECORD study.

METHODS

PATIENTS

The RECORD study has been described in detail previously.[6] We recruited patients for the study from April 2001 through April 2003. Eligible patients had type 2 diabetes, as defined by criteria of the World Health Organization[10]; were between the ages of 40 and 75 years; had a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 25.0; and had a glycated hemoglobin level of more than 7.0% and less than or equal to 9.0% while receiving maximum doses of metformin or a sulfonylurea. Exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension. The study protocol was approved by ethics review committees or institutional review boards in accordance with the laws and customs of each country participating in the study.[6] Written informed consent was obtained from all patients.

STUDY DESIGN

The study is being conducted at 338 centers in 23 countries in Europe and Australasia. After a 4-week run-in period, patients who were already taking a sulfonylurea were randomly assigned to receive either additional rosiglitazone or metformin; those taking metformin were assigned to receive either additional rosiglitazone or a sulfonylurea (glyburide, gliclazide, or glimepiride, according to local practice). Random allocation was performed by telephone, with random permuted blocks stratified according to background medication.

Throughout the study, the target glycated hemoglobin level was 7.0% or less. The starting dose of rosiglitazone (Avandia, GlaxoSmithKline) was 4 mg per day. The starting doses of metformin and sulfonylurea were determined according to local practice. If the glycated hemoglobin level exceeded 7.0% after 8 weeks of treatment, the doses of study drugs were increased to a maximum daily dose of 8 mg of rosiglitazone, 2550 mg of metformin, 15 mg of glyburide, 240 mg of gliclazide, and 4 mg of glimepiride. If the glycated hemoglobin level exceeded 8.5% while patients were receiving the maximum tolerated dose, a third agent was added for patients in the rosiglitazone group or insulin was initiated for patients in the control group. If patients receiving triple therapy in the rosiglitazone group had glycated hemoglobin levels of more than 8.5%, the study protocol recommended that rosiglitazone be stopped and insulin therapy started.

OUTCOME MEASURES

The primary end point was hospitalization (for acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or any

other definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute myocardial infarction, sudden death, and death caused by acute vascular events including stroke); the outcome was analyzed as the time to first occurrence. Members of an independent committee evaluating clinical end points (five cardiologists, a neurologist, and a diabetologist) were unaware of study-group assignments and used prespecified criteria to adjudicate all potential outcomes reported by investigators. Evaluators in the trial's contract organization (Quintiles) were unaware of study-group assignments in screening all serious adverse events for potential end points.

This interim report evaluated data that were available as of March 30, 2007. Secondary end points were death from cardiovascular causes and from any cause, myocardial infarction (resulting in either hospitalization or death), congestive heart failure (hospitalization or death), and the composite of death from cardiovascular causes, myocardial infarction, and stroke. Some events were pending adjudication while this report was being written. Analyses are reported both for adjudicated events only and for adjudicated events plus events pending adjudication. For 19 cardiovascular deaths pending adjudication, we cannot determine yet whether any were due to acute myocardial infarction or congestive heart failure.

STUDY OVERSIGHT

An independent data and safety monitoring board meets twice annually to review unblinded safety data for the ongoing study; the most recent meeting took place on May 24, 2007. Members of the steering committee (seven academic investigators and one representative of the sponsor) developed the study design, had full access to the interim data, were responsible for the decision to publish the results, and wrote the manuscript. The committee members vouch for the accuracy and completeness of the data reported. Study committees and investigators are listed in the Appendix.

STATISTICAL ANALYSIS

The RECORD study was designed as a noninferiority trial. The rosiglitazone group was defined as noninferior to the control group if the upper limit of the two-sided 95% confidence interval for the hazard ratio for the primary end point comparing the rosiglitazone group with the control group was below 1.20 on completion of the study. A total of 4000 patients to be followed for a median of 6 years would give a power of 99% to detect such noninferiority when the control group had an event rate of 11% per year (3% with deaths from cardiovascular causes and 8% with hospitalizations), allowing for a 2% annual loss to follow-up.

This interim report follows a prespecified plan for statistical analysis. All analyses were performed according to the intention-to-treat principle, with the exclusion of 11 patients who received no study medication. The time from randomization to the event was derived for each end point, with follow-up censored at the cutoff date of March 30, 2007, for patients who did not have an event. Cumulative incidence was estimated with the use of the Kaplan–Meier method. The relative risk comparing the rosiglitazone group with the control group was estimated as a hazard ratio and 95% confidence interval on the basis of Cox proportional-hazards regression stratified according to background medication. Two-sided P values were calculated with the use of log-rank tests, unadjusted for multiple testing.

RESULTS

PATIENTS

Of 7428 patients who underwent screening, 4458 were randomly assigned to study groups (Fig. 1). No study medication was received by 11 patients (6 in the rosiglitazone group and 5 in the control group), who were excluded from the analysis. At baseline, 2222 patients who were receiving metformin monotherapy were assigned to receive either rosiglitazone plus metformin (1117 patients) or metformin plus sulfonylurea (1105 patients); 2225 patients receiving sulfonylurea monotherapy were assigned to receive rosiglitazone plus sulfonylurea (1103) or metformin plus sulfonylurea (1122). Results presented here are for all patients who were randomly assigned to receive rosiglitazone combinations (2220), as compared with all patients assigned to receive metformin plus sulfonylurea (2227).

Approximately 10% of patients (218 in the rosiglitazone group and 223 in the control group) were lost to follow-up. This fact, along with the much lower overall event rate than we had predicted, substantially lowered the statistical power of our analysis. A total of 140 patients in the rosiglitazone group and 244 patients in the control group began to receive insulin. At the latest visit, 1626 patients in the rosiglitazone group and 1476 patients in the control group were receiving their

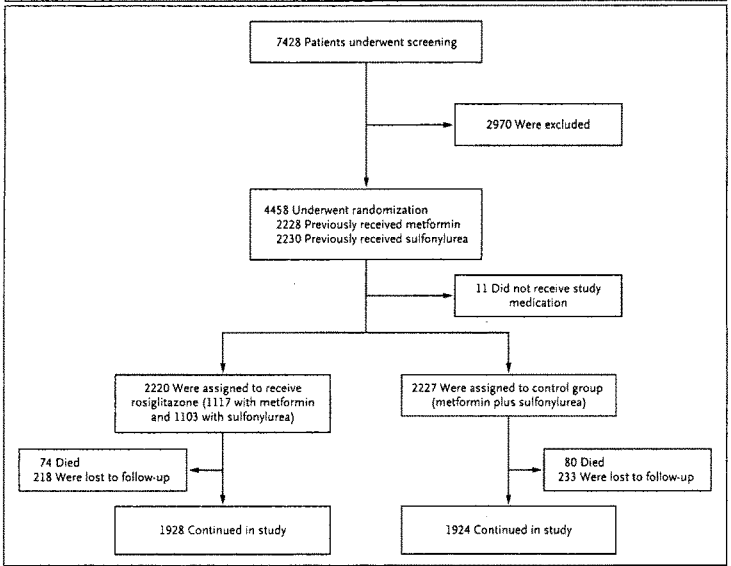


Figure 1. Enrollment and Outcomes.

The numbers of participants who were assessed for safety were 2220 in the rosiglitazone group and 2227 in the control group.

allocated treatment. In total, 675 patients (263 in the rosiglitazone group and 412 in the control group) withdrew from receiving study drugs but were still in follow-up.

Baseline characteristics were well balanced between the groups (Table 1). Table 2 shows by group the numbers of patients with the primary end point (hospitalization or death from cardiovascular causes) and several secondary end points over a mean follow-up of 3.75 years (3.77 years for the rosiglitazone group and 3.73 years for the control group). Results are reported for adjudicated events and for events adjudicated plus those pending adjudication. Kaplan–Meier plots are shown in Figures 2 and 3.

For adjudicated primary end points (217 in the rosiglitazone group and 202 in the control group), the hazard ratio was 1.08 (95% confidence interval [CI], 0.89 to 1.31). An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication. The inclusion of these events resulted in a hazard ratio of 1.11 (95% CI, 0.93 to 1.32). A subgroup analysis of patients who were classified according to previous monotherapy with metformin or sulfonylurea revealed no evidence of a treatment-by-stratum interaction (interaction test, P=0.41). The time-to-event curves in Figure 2 may suggest possible divergence between groups, with more events in the rosiglitazone group after 2.5 years of follow-up. However, data after 4 years involve small numbers of patients, and further follow-up will be necessary.

There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: acute myocardial infarction, death from cardiovascular causes or any cause, or the composite of cardiovascular death, myocardial infarction, and stroke (both for adjudicated events and adjudicated plus pending events). However, the power to detect

Table 1. Baseline Characteristics of the Patients.*

Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)
Previous medication — no. (%)		
Metformin only	1117 (50.3)	1105 (49.6)
Sulfonylurea only	1103 (49.7)	1122 (50.4)
Age — yr	58.4±8.3	58.5±8.3
Male sex — no. (%)	1142 (51.4)	1152 (51.7)
White race — no. (%)†	2200 (99.1)	2199 (98.7)
Time since diagnosis — yr	7.0±5.0	7.1±4.9
Body-mass index	31.6±4.7	31.5±4.9
Glycated hemoglobin — %	7.9±0.7	7.9±0.7
Fasting plasma glucose — mg/dl	177±43	177±40
Hypertension — no. (%)‡	1754 (79.0)	1774 (79.7)
Ischemic heart disease — no. (%)		
Any disease	359 (16.2)	374 (16.8)
Stable angina	222 (10.0)	228 (10.2)
Myocardial infarction	102 (4.6)	114 (5.1)
Unstable angina	20 (0.9)	30 (1.3)
Cerebrovascular disease — no. (%)		
Any disease	100 (4.5)	97 (4.4)
Stroke	54 (2.4)	54 (2.4)
Transient ischemic attack	50 (2.3)	47 (2.1)
Peripheral arterial disease — no. (%)	124 (5.6)	131 (5.9)
Congestive heart failure — no. (%)	12 (0.5)	6 (0.3)
Lipid disorder — no. (%)§	2123 (95.6)	2100 (94.3)
Smoking history — no. (%)		
Current smoker	363 (16.4)	343 (15.4)
Former smoker	565 (25.5)	539 (24.2)

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was determined by the investigators.
‡ Hypertension was defined as a systolic blood pressure of more than 130 mm Hg or a diastolic blood pressure of more than 80 mm Hg.
§ A lipid disorder was defined by investigator-reported diagnosis or as a low-density lipoprotein cholesterol level of 100 mg per deciliter or more, a triglyceride level of 200 mg per deciliter or more, or a high-density lipoprotein cholesterol level of less than 40 mg per deciliter for men or less than 50 mg per deciliter for women.

significant differences was low, as reflected by the wide 95% confidence intervals (Table 2). The hazard ratio for death from cardiovascular causes for adjudicated plus pending events was 0.80 (95% CI, 0.52 to 1.24). For myocardial infarction, the hazard ratio for adjudicated plus pending events was 1.23 (95% CI, 0.81 to 1.86).

Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI, 1.27 to 3.97). The inclusion of events pending adjudication increased the number of events to 47 and 22, respectively (hazard ratio, 2.15; 95% CI, 1.30 to 3.57), resulting in an excess risk of heart failure in the rosiglitazone group of 3.0 (95% CI, 1.0 to 5.0) per 1000 patient-years of follow-up.

DISCUSSION

Since patients with type 2 diabetes have a high risk of cardiovascular disease, any hypoglycemic agent the patient receives should not worsen that risk and preferably should lower it. Although the RECORD study is ongoing, we believe the exceptional circumstances surrounding a recent safety concern regarding rosiglitazone make it important to publish interim data.

A recent meta-analysis by Nissen and Wolski raised concern that rosiglitazone was associated with an increased risk of myocardial infarction and death from cardiovascular causes.[9] The limitations of the meta-analysis have been pointed out by its authors and by others.[11] Many contributing studies were small-scale and short-term, were designed to evaluate glycemic control, had no event adjudication, and had an imbalance in follow-up (with more patients in the control group withdrawing owing to hyperglycemia). Trials with no myocardial infarctions and no deaths from cardiovascular causes were excluded, and rates of myocardial infarction were low.[12]

The RECORD trial is a large, randomized, long-term study involving patients with type 2 diabetes that was designed to assess the cardiovascular safety of rosiglitazone combined with metformin or sulfonylurea, as compared with the combination of metformin and sulfonylurea, medications with previous evidence of a reduction in cardiovascular risk.[7,8] All cardiovascular end points that are reported by investigators in the trial undergo independent blinded adjudication to enhance the quality of the data. A wide variety of patients with type 2 diabetes, with and without previous cardiovascular disease, are included in the study.

This interim report is based on data for 4447 participants with a mean follow-up of 3.75 years, representing 16,675 patient-years of follow-up — almost two thirds of the follow-up that was in-

Table 2. Hospitalization or Death from Cardiovascular Causes.*

Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)	Hazard Ratio (95% CI)	P Value
	no. of patients			
Adjudicated events				
Primary end point	217	202	1.08 (0.89–1.31)	0.43
Death				
From cardiovascular causes†	29	35	0.83 (0.51–1.36)	0.46
From any cause	74	80	0.93 (0.67–1.27)	0.63
Acute myocardial infarction‡	43	37	1.16 (0.75–1.81)	0.50
Congestive heart failure‡	38	17	2.24 (1.27–3.97)	0.006
Death from cardiovascular causes, myocardial infarction, and stroke	93	96	0.97 (0.73–1.29)	0.83
Events adjudicated and pending adjudication				
Primary end point	267	243	1.11 (0.93–1.32)	0.26
Death				
From cardiovascular causes†	37	46	0.80 (0.52–1.24)	0.32
Acute myocardial infarction‡	49	40	1.23 (0.81–1.86)	0.34
Congestive heart failure‡	47	22	2.15 (1.30–3.57)	0.003
Death from cardiovascular causes, myocardial infarction, and stroke	109	114	0.96 (0.74–1.24)	0.74

* Each patient was counted only once for each category. The primary end point was the first occurrence of a hospitalization or death from cardiovascular causes.

† Of the adjudicated deaths from cardiovascular causes, 38 (16 in the rosiglitazone group and 22 in the control group) were primary end points. The remainder occurred after the patient had already been hospitalized for a cardiovascular event. For deaths from cardiovascular causes that were adjudicated or pending adjudication, 47 (20 in the rosiglitazone group and 27 in the control group) were primary end points.

‡ This category included both hospitalizations and deaths. Some of the 19 deaths from cardiovascular causes (8 patients in the rosiglitazone group and 11 in the control group) that were pending adjudication may have been due to acute myocardial infarction or congestive heart failure, but these data were not available at the time of the study cutoff.

tended by the end of the study. The study design calls for targeting similar glycemic control in the rosiglitazone group and the control group to assess cardiovascular safety independent of glycemia. Patients and investigators are encouraged to follow a carefully planned treatment algorithm. A recent report on the first 1122 patients showed that patients in the rosiglitazone group and the control group had similar glycemic control after 18 months of treatment.[13]

Overall, the rate of primary end points (hospitalization or death from cardiovascular causes) was low: 3.1% per year for adjudicated plus pending events. The protocol excluded some high-risk patients (e.g., those with heart failure, hospitalization for cardiovascular causes during the previous 3 months, and pending cardiovascular intervention). Targeting treatment toward current management guidelines for dyslipidemia, hypertension, and improved glucose control may also contribute to the low event rate. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD, ISRCTN number 64783481) study reported an increase from 0 to 36% in the use of lipid-lowering therapy in its control group during 1998–2005.[14] This finding reflects guidelines that patients should be actively treated to reduce cardiovascular risk, notably with glucose-lowering drugs, statins, aspirin, and more intensive use of blood-pressure–lowering agents.[15] Moreover, event rates in recent similar trials involving patients with diabetes — the Collaborative Atorvastatin Diabetes Study (CARDS,[4] NCT00327418), Heart Protection Study (HPS,[3] ISRCTN 48489393), and FIELD[14] — are similar to those in the RECORD trial.

The interim results for the primary end point were inconclusive, with a hazard ratio of 1.08 (95% CI, 0.89 to 1.31) on the basis of events ad-

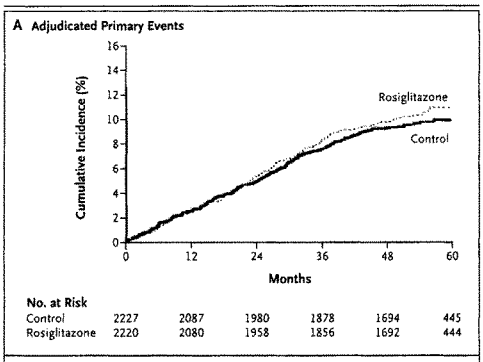


Figure 2. Kaplan–Meier Analysis of the Primary End Point of Hospitalization or Death from Cardiovascular Causes.

The graph shows the adjudicated events in the study (Panel A) and the adjudicated events plus events that were pending adjudication at the time of the study cutoff (Panel B).

judicated by the committee reviewing clinical end points. In any interim trial report, there are inevitably some potential primary events pending adjudication. Adding in these pending events increased the hazard ratio to 1.11 (95% CI, 0.93 to 1.32). Thus, the data for the primary end point are compatible with as much as a 7% improvement, or as much as a 32% worsening, in cardiovascular risk. The study lost statistical power because of the withdrawal of patients from their assigned treatment and losses to follow-up, although patients in the rosiglitazone group fared better in these respects than did patients in the control group. We cannot determine whether some consequent bias in end-point ascertainment occurred. All serious adverse events were screened for possible end points.

The low rate of the primary end point, along with the notable loss to follow-up, meant that the study has less statistical power than was originally planned. Assuming a continued primary-event rate of 3.1% per year, we project that 750 patients will have a primary end point by study completion. Under the hypothesis of no true treatment difference, this estimate would provide a power of 70% to claim noninferiority relative to a noninferiority margin of 1.20 for the hazard ratio. However, we already have 510 patients with a primary event (adjudicated plus pending events) and an observed hazard ratio of 1.11, which means that the conditional power to claim noninferiority on study completion is somewhat less.

As compared with the control group, the rosiglitazone group had no evidence of an increased risk of death, either from any cause (hazard ratio, 0.93; 95% CI, 0.67 to 1.27) or from cardiovascular causes (hazard ratio, 0.80, 95% CI, 0.52 to 1.24). The primary end point included all first hospitalizations or deaths from cardiovascular causes and as such included myocardial infarction and congestive heart failure. Our study showed that the risk of heart failure in the rosiglitazone group was more than twice that in the control group. This finding is consistent with previous evidence regarding heart failure and the thiazolidinediones.[16,17] Although the absolute excess risk was relatively small, this finding is of concern and reinforces advice that patients should be warned of the risk and that thiazolidinediones should not be started or continued in patients with heart failure.

For acute myocardial infarction, the difference between the rosiglitazone group and the control group was not statistically significant (hazard ratio for adjudicated events, 1.16; 95% CI, 0.75 to 1.81; hazard ratio for adjudicated plus pending events, 1.23; 95% CI, 0.81 to 1.86). These estimates are somewhat lower than those reported in the meta-analysis by Nissen and Wolski.[9] They are consistent with as much as a 19% improvement, and as much as an 86% worsening, in risk. For the composite end point of death from cardiovascular causes, myocardial infarction, and stroke, the rosiglitazone group did not differ significantly from the control group.

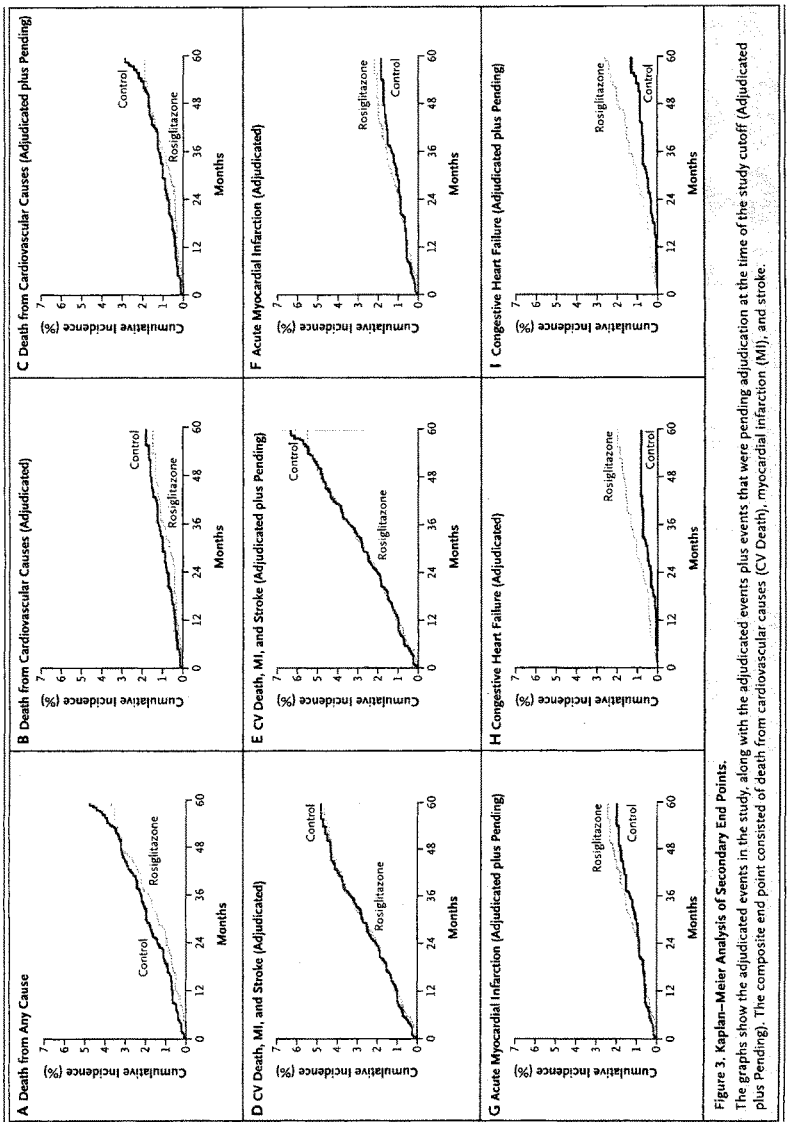


Figure 3. **Kaplan–Meier Analysis of Secondary End Points.**
The graphs show the adjudicated events in the study, along with the adjudicated events plus events that were pending adjudication at the time of the study cutoff (Adjudicated plus Pending). The composite end point consisted of death from cardiovascular causes (CV Death), myocardial infarction (MI), and stroke.

A significant limitation of our study was that it was an open-label trial. The allocation of drugs was nonblinded owing to the number of preparations and dosing schedules and because the time for the introduction of insulin therapy differed between groups. Monitoring staff checked site records for missing events, and all serious adverse events underwent blinded screening for potential cardiovascular end points; in addition, the adjudication of events was blinded. These procedures and the choice of end points reduce, but do not remove, the risk of ascertainment bias.

The primary composite end point reflects the study objective — an assessment of overall cardiovascular safety — but therefore includes some hospitalizations (e.g., for valvular disease) that no observer would consider potentially related to treatment. The inclusion of such events tends to favor the achievement of noninferiority. Hence, sensitivity analyses will be performed at the end of the study that include only events related to atherosclerotic arterial disease.

We made the decision to publish our interim findings because in their absence, concern raised by the meta-analysis by Nissen and Wolski could well compromise the study's integrity through an increase in the dropout rate and potential biases in reporting events. At present, every effort is being made to maintain follow-up until study completion in 2 years. Extra inquiries to investigators, to identify any end points previously missed,[18] are expected to reduce substantially the extent of loss to follow-up by the end of the study.

This interim analysis is restricted to a limited amount of information. The statistical plan was predefined. The intent was primarily to estimate treatment differences, with no planned action regarding study continuation, so the significance level of the final analysis was not affected. The final report will be more extensive, with data presented for different background medications and other subgroups and examining possible imbalances across treatment groups for concomitant medications and other possible confounders.

In conclusion, our interim findings from a large, prospective trial are inconclusive with respect to the primary end point of hospitalization or death from cardiovascular causes and are as yet insufficient to claim noninferiority. There is no evidence of any increased mortality, either from any cause or from cardiovascular causes. There is a significant increase in the risk of heart failure. The data do not allow a conclusion as to whether treatment with rosiglitazone results in a higher rate of myocardial infarction than does therapy with metformin or a sulfonylurea. The study's data and safety monitoring board, which is charged with safeguarding the study patients, has recommended continuation of the trial. Study completion will enable a clearer determination of the long-term cardiovascular effects of treatment with rosiglitazone and thus help determine the most appropriate combination therapies for patients with type 2 diabetes.

Supported by GlaxoSmithKline.

Dr. Home reports being involved in research, consulting, health care development, and teaching activities for all major pharmaceutical companies active in diabetes research (including GlaxoSmithKline), but all consulting and lecture fees he receives are donated to the institutions with which he is associated (Newcastle University, Worldwide Initiative for Diabetes Education, and the International Diabetes Federation); Dr. Pocock, receiving consulting fees and grant support from GlaxoSmithKline; Dr. Beck-Nielsen, receiving consulting fees from GlaxoSmithKline, Merck, and Novartis and grant support and lecture fees from GlaxoSmithKline and Novo Nordisk; Dr. Gomis, receiving consulting and lecture fees from GlaxoSmithKline, Novartis, Pfizer, Merck, and Sanofi-Aventis; Dr. Hanefeld, receiving consulting fees from GlaxoSmithKline, Novo Nordisk, and Sanofi-Aventis and lecture fees from Bayer-AG, Sanofi-Aventis, Hoffmann–La Roche, Takeda, and Eli Lilly; Mr. Jones, being an employee of and holding stock in GlaxoSmithKline; Dr. Komajda, receiving consulting fees from GlaxoSmithKline and Servier and lecture fees from GlaxoSmithKline and Takeda; and Dr. McMurray, receiving consulting fees from GlaxoSmithKline and Amgen and grant support from GlaxoSmithKline, Novartis, and Amgen. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The following were participants in the RECORD study: **Steering Committee:** P.D. Home (chair), H. Beck-Nielsen, R. Gomis, M. Hanefeld, N.P. Jones, M. Komajda, J.J.V. McMurray, S.J. Pocock. **Data and Safety Monitoring Board:** I. Campbell (chair), I. Ford, P. Hildebrandt, R. Landgraf, F. Verheugt. **Clinical End Point Committee:** M. Komajda (chair), M. Böhm, A. Gavazzi, K. Lees, M. Marre, P. Ponikowski, M. Syvänne. **Investigators (numbers in parentheses after country indicate number of randomized patients):** *Australia (51)* — G. Jerums, Heidelberg West; A. Lang, Malvern; R. Watts, Port Lincoln; F. De Looze, Sherwood; S. Colagiuri, Randwick; R. Moses, Wollongong; V. Heazlewood, Kippa Ring; M. McKeirnan, Carina Heights; A. Lowy, Miranda; T. Roberts, Keswick. *Belgium (104)* — B. Weber, Arlon; F. Coucke, Sint-Gillis-Waas; J. Tits, Genk; B. Keymeulen, Brussels; M. Giri, Gent; J. Mortelmans, Oostham; A. Hutsebaut, Moerkerke; W. Denier, Genk. *Bulgaria (204)* — A. Borissova, N. Ovcharova, V. Hristov, N. Veleva, Sofia; L. Koeva, Varna; M. Mitkov,

Plovdiv; T. Rusev, Pleven; I. Daskalova, Sofia. *Croatia (274)* — Z. Metelko, V. Rotvik, V. Goldoni, Zagreb; M. Jandric, Slavonski Brod; J. Rubes, Krapinske Toplice; Z. Beer, Varazdin; I. Aganovic, Zagreb; M. Persic, Rijeka. *Czech Republic (145)* — J. Janousek, Trutnov; F. Saudek, E. Valentova, Praha; M. Honka, Ostrava Poruba; V. Sobeslavská, Tábor; E. Mandakova, Rakovník; J. Belobradkova, Brno; P. Skala, Holice v Cechách; P. Weiner, Jindrichuv Hradec; M. Komrskova, Pisek; L. Dohnalova, Ceske Budejovice. *Denmark (57)* — H. Juhl, Slagelse; K. Kolendorf, Koge; S. Larsen, Glostrup; H. Lervang, Aalborg; A. Prange, Kolding; L. Ørskov, Silkeborg; O. Snorgaard, Hillerød; T. Storm, Næstved; H. Perrild, København. *Estonia (220)* — A. Kork, Tallinn; H. Tupits, Tallinn; M. Kunder, Tallinn; L. Viitas, Pärnu; T. Toomsoo, Tallinn; H. Vides, Viljandi; B. Adojaan, Tartu; I. Last, Paide; K. Veidrik, Rakvere; R. Lanno, Tallinn; K. Arbeiter, Tallinn; M. Stern, Saku. *Finland (193)* — J. Eriksson, Helsinki; J. Hopsu, Espoo; R. Siren, Helsinki; S. Sulosaari, Kerava; T. Piippo, Tampere, J. Saltevo, Jyväskylä; A. Latva-Nevala, Seinäjoki; T. Kaitila, Lappeenranta, P. Jarvinen, Hyvinkaa; A. Piiroinen, Rovaniemi; H. Pirttiaho, Oulun Kaupunki; P. Himanen, Turku; V. Ilvesmaki, Lahti; L. Juurinen, Riihimäki; R. Siren, Helsinki; M. Pietilä, Turku; S. Ruotsalainen, Kuopio. *France (86)* — O. Verier-Mine, Valenciennes; J. Brun, Dijon; G. Charpentier, Corbeil Essonne; C. Le Devehat, Nevers; M. Rieu, Paris; E. Verlet, Dunkerque; P. Triot, Arras; R. Fonteny, Chartres; J. Quadrelli, Nogent le Phaye; P. Poisson, Voves; P. Fournier, Chartres; J. Vogel, Husseren Wesserling; O. Decloux, Cernay; L. Goepfert, Mulhouse; M. Ruetsch, Dessenheim; J. Huberschwiller, Colmar; M. Gissler, Wittenheim; B. Michalak, Marseille; D. Obadia, Aubagne; M. Bourgoin, Gemenos; D. Cadinot, Broglie; C. Jouin, Saint Leger sur Yvelines; D. Sacareau, M. Bismuth, Labarthe-sur-Leze; T. Coeure, Champhol; C. Fabie, Calmont; J. Reinard, Toulouse; P. Poinot, Carbonne; P. Galy, Pinsaguel; H. Vilarem, Castelnaudary; G. Binet, Salles sur l'Hers; B. Gay, Badens; P. Munck, Trebbes. *Germany (178)* — P. Ott, Dresden; M. Nauck, Bad Lauterberg; R. Paschke, Leipzig; H. Frick, Rhaunen; A. Sammler, Friedrichsthal; M. Moreos, Heidelberg; W. Stuermer, Wuerzburg; T. Segiet, Speyer; W. Schaffstein, Kronberg; U. Berek, Wetzlar; A. Schaffert, Stuttgart, C. Raddatz, Gau-Algesheim; D. Ayasse, Kallstadt; R. Naumann, Chemnitz; G. Scholz, Offenbach; P. Kirrbach, Burgstaedt; O. Mueller, Lambrecht. *Greece (139)* — S. Raptis, Athens; E. Pagkalos, Thessaloniki; S. Pappas, Piraeus; E. Giannoulaki, Patra; N. Katsilambros, A. Melidonis, G. Piaditis, C. Zoupas, Athens; K. Soulis, Thessaloniki; A. Vagenakis, Patra; D. Makriyannis, Ioannina; P. Kaldrimidis, I. Migdalis, Athens. *Hungary (400)* — M. Baranyai, Szombathely; P. Faludi, Budapest; I. Foldesi, Szentes; B. Gachalyi, Budapest; M. Dudas, Gyula; T. Hidvegi, Gyor; E. Juhasz, Eger; Z. Kerenyi, Budapest; G. Neuwirth, Debrecen; T. Oroszlan, Zalaegerszeg; J. Patkay, Dunaujvaros; K. Simon, Siófok; J. Szegedi, Nyiregyhaza; G. Tamas, Budapest; B. Valenta, Nyiregyhaza; G. Vandorfi, Veszprem; P. Voros, Budapest; G. Kurta, Berettyoujfalu. *Italy (116)* — C. Fossati, Milan; L. Uccioli, Rome; R. Pasquali, N. Melchionda, Bologna; M. Parenti, Rimini; A. Galluzzo, Palermo; L. Carboni, Cagliari; O. Giampietro, Pisa; M. Calderini, Parma; R. Giorgino, Bari; B. Ambrosi, San Donato Milanese; A. Arcangeli, Prato; A. Aiello, Campobasso; G. Ghirlanda, Rome; R. Carleo, Naples; U. Valentini, Brescia; P. Pozzilli, Rome; F. Orio, Salerno. *Latvia (173)* — I. Rezgale, Riga; L. Kokare, Riga; I. Andersone, Tukums; B. Vizina, Limbazi; D. Teterovska, Ogre; A. Eglite, Jekabpils; V. Pirags, Riga; L. Kudule, I. Sturis, Riga; I. Lagzdina, Liepaja. *Lithuania (134)* — J. Lasiene, Kaunas; J. Pliuskys, Vilnius; N. Jakuboniene, E. Varanauskiene, Kaunas; B. Urbonaite, Klaipeda; J. Butkus, Vilnius; G. Gumbrevicius, Kaunas. *The Netherlands (76)* — W. de Backer, Rijswijk; V. van de Walle, Geleen; J. Jonker, Groningen; M. Janssen, Ridderkerk; F. Gulzar, Zwijndrecht; I. Ong, Hoogvliet; H. Ferguson, Rotterdam; W. Feis, Oude Pekela; H. Fransen, Musselkanaal; J. Snijders, Landgraaf; M. Osinga-Meek, 's-Hertogenbosch. *New Zealand (36)* — R. Cutfield, Auckland; R. Scott, Christchurch; J. Mann, Dunedin; B. Smith, Wellington; A. Dissanayake, Auckland; M. Khant, Tauranga; R. Leikis, Hastings; P. Dixon, Palmerston North. *Poland (363)* — I. Kinalska, Bialystok; B. Wierusz-Wysocka, Poznan; E. Semetkowska-Jurkiewicz, Gdansk; A. Stankiewicz, Cracow; D. Zytkiewicz-Jaruga, Wroclaw; M. Polaszewska-Muszynska, Bydgoszcz; K. Jedynasty, Warsaw; Z. Szybinski, Cracow; K. Jusiak, Warsaw; A. Mikolajczyk-Swatko, Lodz; E. Bandurska-Stankiewicz, Olsztyn; M. Bojarska-Los, Lublin; E. Krzyzagorska, Poznan; A. Bochenek, Warsaw; J. Lopatynski, Lublin; H. Szczecinska, Warsaw; P. Kubalski, Grudziadz. *Romania (157)* — C. Ionescu-Tirgoviste, Bucharest; N. Hancu, Cluj-Napoca; V. Serban, Timisoara; M. Graur, Iasi; M. Mota, Craiova; A. Barnea, Bucharest; C. Dobjanschi, Bucharest. *Russia (149)* — A. Ametov, Moscow; A. Dreval, Moscow; L. Vedeneeva, St. Petersburg; I. Demidova, Moscow; N. Vorokhobina, St. Petersburg; L. Subaeva, Moscow. *Slovakia (325)* — M. Macko, Presov; J. Fabry, Bratislava; I. Buganova, Zilina; L. Fabryova, Bratislava; L. Kalinova, Bratislava; J. Dzuponova, Prievidza; B. Krahulec, E. Toserova, Z. Nemethyova, Bratislava; J. Vozar, Samorin; A. Gabrisova, Trencin; I. Tkac, Kosice; J. Okapcova, Banska Bystrica; T. Kupcova, Lucenec; E. Nehajova; Kysucke Nove Mesto; P. Farkas, Sahy; E. Martinka, Lubochna. *Spain (64)* — M Muñoz Torres, Granada; L. Escobar Jimenez, Cadiz; I. Conget, Barcelona; J Herrera Pombo, Madrid; S. Gaztambide, Bilbao; J. Manzanares, Reus; A. Serrano, Vizcaya; C. Vazquez, Barcelona. *Sweden (469)* — M Schönander, Göteborg; A. Norrby, Göteborg; R. Tengel, Skene; A. Nilsson, Helsingborg; I. Lager, Kristianstad; U. Mathiessen, Oskarshamn; P Andersson, Eksjö; U. Adamsson, Danderyd; F. Sjöberg. Linköping; E. Forbes, Nacka; L. Nicol, Köping; S. Lindmark, Umeå; D. Aronsson, Mora; M. Dahl, Kungälv; M. Landin-Olsson, Lund; B. Polhem, Uddevalla; P. Hellke, Göteborg; J. Waller, Vadstena; B. Zethelius, Uppsala. *Ukraine (103)* — M. Tronko, P. Bodnar, O. Larin, Kiev; Y. Karachentsev, Kharkov; T. Pertseva, Dnepropetrovsk; A. Serhiyenko, Lvov; P. Prudius, Vinnitsa. *United Kingdom (242)* — P. O'Hare, Warwickshire; P. Allamby, Dronfield; M. Blagden, Derbyshire; M. Gumbley, Westbury, I. Grandison, Wiltshire; D. Keating, Sheffield; P. Maksimczyk, Somerset; M. Pimm, Weston-Super-Mare; I. Strawford, Somerset; T. Wall, Woking; A. Matthews, Chesterfield; M. Sampson, Colney; A. Adler, Cambridge; T. Cahill, Frome; C. Fox, Northampton; J. Ham, Rugby; A. Harrower, Airdrie; J. Hole, S. Rowlands, Wiltshire; P. Husselbee, Leigh on Sea; A. Boyd, Dumbarton; I. Brown, Thornhill; J. McIntyre, Airdrie; J. Hannah, Hamilton; N. Davda, Kirkintilloch; D. MacNeill, Glasgow; A. Duddy, Motherwell; G. Murphy, Uddingston; S. Murray, Wishaw; A. Mishra, Motherwell; D. Brandon, Paisley; D. Brydie, J. Simpson, Glasgow; T. Dunlop, Renfrewshire; A. Baksi, Newport; A. Cowie, Corsham; A. Middleton, Fowey; J. Ryan, Penzance; A. Seaman, Falmouth; T. Leong Lee, Watford; L. Adler, Harrow; W Jones, Chesterfield; N. Leech, Newcastle upon Tyne.

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FOOTNOTE 65

The Record on Rosiglitazone and the Risk of Myocardial Infarction

Bruce M. Psaty, M.D., Ph.D., and Curt D. Furberg, M.D., Ph.D.

In this issue of the *Journal*,[1] Home and colleagues report interim results from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes, or RECORD, study (NCT00379769). The RECORD study is a 6-year, open-label, noninferiority trial in which patients with type 2 diabetes who had inadequate glucose control with metformin or sulfonylurea alone were randomly assigned to receive rosiglitazone (Avandia) or the combination of metformin and sulfonylurea. The primary outcome was a composite of hospitalization and death from cardiovascular causes. As of March 2007, data were available on the 4447 patients randomly assigned to receive one of these treatments and followed for a mean of 3.75 years. Rosiglitazone was associated with a small, nonsignificant increase in the risk of the primary outcome (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). For the fatal or nonfatal myocardial infarction outcome, the hazard ratio was 1.16 (95% CI, 0.75 to 1.81). According to the authors, "the findings are important in answering some of the safety concerns raised by the recent meta-analysis by Nissen and Wolski."[2]

The RECORD trial has several strengths. Among the most important are interim sensitivity analyses that include events pending adjudication and a design that compares dual-agent combination therapies in a long-term trial among high-risk patients with diabetes.

The trial also has several weaknesses in design and conduct. Although outcomes were reviewed in a blinded fashion, the randomization was not concealed.[3] The primary outcome, which was a composite of all hospitalizations and deaths from cardiovascular causes, is a weak choice for a noninferiority design.[4,5] A preferred cardiovascular outcome would have been, for instance, myocardial infarction or death from coronary heart disease.[6] Including all cardiovascular hospitalizations, some of which are not likely to be related to the randomized treatments, in a composite outcome will tend to drive the relative risk toward the null and enhance the chances of a finding of noninferiority. Finally, the use of a composite outcome to design the trial will generally yield few data and low power for any composite-outcome elements that might be of special interest.

The primary weakness in the conduct of the trial is the exceptionally low event rate in a high-risk population of patients with diabetes. For the myocardial infarction outcome, for instance, the event rate in the RECORD control group was 4.5 per 1000 person-years. With a mean age near 60 years, the patients in the RECORD trial had had diabetes for an average of 7 years, about 25% had preexisting clinical cardiovascular disease, and almost 80% had hypertension. The myocardial infarction rate of 4.5 per 1000 person-years in the RECORD study is about 40% of the incidence rate in a population-based study of patients with diabetes 56 to 60 years of age[7] and is close to rates seen in the general population 55 to 59 years of age.[8] Incomplete ascertainment of events is perhaps the most likely explanation for this difference. Loss to follow-up was high (about 10%). Another explanation may be the large number of eastern European countries involved in the study. Medical care, including criteria for cardiovascular hospitalization, may differ between eastern and western Europe.

The "exceptional circumstances" cited by the authors in their decision to report interim findings from this long-term trial were the result of publication of the meta-analysis by Nissen and Wolski.[2] The primary finding of the meta-analysis was an increase in the risk of myocardial infarction associated with treatment with rosiglitazone (odds ratio, 1.43; 95% CI, 1.03 to 1.98). Although the limitations in design and conduct of the RECORD trial argue for a cautious interpretation of its findings, the results for risk of myocardial infarction (hazard ratio, 1.16; 95% CI, 0.75 to 1.81) are nonetheless compatible with those of the meta-analysis. The overlap between the 95% confidence intervals for the trial and the meta-analysis is substantial.

Combining the findings about the risk of myocardial infarction from the RECORD trial and the meta-analysis provides a cumulative summary of the clinical-trial evidence. A variance-weighted fixed-effects meta-analysis that includes the

RECORD trial, ADOPT (A Diabetes Outcome Prevention Trial, NCT00279045),[9] the DREAM trial (Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication, NCT00095654),[10] and the stratum of small trials in the meta-analysis by Nissen and Wolski still suggests that rosiglitazone is associated with an increased risk of myocardial infarction (odds ratio, 1.33; 95% CI, 1.02 to 1.72). Use of the updated myocardial event rates provided by Krall[11] yields an odds ratio of 1.36 (95% CI, 1.04 to 1.78). Thus, even with the findings from the RECORD trial included, the possibility of a benefit in terms of the risk of myocardial infarction remains remote, and there is still significant evidence of harm. The level of risk, a hazard ratio of 1.33, is substantial and approximately equivalent in magnitude, but in the opposite direction, to the health benefits of lipid-lowering statin drugs.

The main limitations of the meta-analysis are the quantity and quality of the available data.[12] The responsibility for the limited availability of high-quality data resides primarily with the manufacturer (GlaxoSmithKline) and also perhaps with the Food and Drug Administration (FDA). Insofar as the findings of the meta-analysis represent a valid estimate of the risk of myocardial infarction, the "exceptional circumstances" seem to us to be the history of missed opportunities in the scientific and regulatory evaluation of rosiglitazone, which was first approved in 1999.

As we indicated recently,[12] rosiglitazone was approved on the basis of its ability to improve glycemic control, a surrogate end point. Because high glucose levels increase the risk of vascular disease, a glucose-lowering drug is presumed to reduce the risk of major adverse health outcomes such as myocardial infarction. Rosiglitazone, however, appears to be associated with an increase rather than a decrease in the risk of myocardial infarction.

The manufacturer did not make a serious effort to verify the presumed health benefits of rosiglitazone in a timely fashion. In ADOPT,[9] which compared rosiglitazone with metformin and glyburide in terms of the duration of glycemic control, cardiovascular events were not identified or recorded in a systematic fashion, and heart failure was the only outcome that was reviewed and adjudicated at the end of the trial.[9] Nonetheless, even though misclassification and incomplete ascertainment of events effectively reduce the ability of a study to detect a difference in event rates, rosiglitazone in ADOPT was associated with a higher risk of cardiovascular events, including heart failure, than glyburide.[9]

The DREAM trial,[10] which included an adjudication of cardiovascular events, recruited a low-risk population of prediabetic patients to evaluate whether rosiglitazone, as compared with placebo, could prevent the chemical onset of diabetes. In the DREAM trial, rosiglitazone was associated with a lower risk of diabetes (hazard ratio, 0.38; 95% CI, 0.33 to 0.44) and with a higher though nonsignificant risk of myocardial infarction (hazard ratio, 1.66; 95% CI, 0.73 to 3.80). In the absence of evidence of actual health benefits, the public health rationale for the use of a drug to treat a precondition and thereby to prevent the onset of a related condition that would, normally and simply, mark the beginning of drug treatment is not clear. The DREAM study represents an effort to medicalize a predisease state.[13]

The DREAM trial and ADOPT focused largely on marketing questions and failed to address questions of myocardial infarction–related risk or benefit directly. These industry-sponsored trials do not represent compelling science.[14]

When drugs that have been approved on the basis of surrogate end points will be used by millions of people for many years, it is essential to document their health risks and benefits.[15] Laboratory measures such as glycemic control must be converted into clinically meaningful outcomes.[16] If manufacturers do not voluntarily initiate large, long-term trials that are of public health importance, then the FDA needs the authority to insist that they do so in a timely fashion.[17,18]

In August 2006, the manufacturer of rosiglitazone provided the FDA and the European Medicines Agency with the results of several studies, including a meta-analysis[19] similar to that by Nissen and Wolski.[2] In the manufacturer's meta-analysis, rosiglitazone was associated with an increased risk of myocardial ischemic events (hazard ratio, 1.31; 95% CI, 1.01 to 1.70). By October 2006, the product labels in Europe were revised to include this information.[20] The U.S. product label still does not identify ischemic cardiovascular disease as an adverse reaction in the general population of patients with diabetes. Why did the FDA not make this information public in a timely fashion?

The natural history of new drugs in the post-marketing setting includes major black-box warn-

ings for about 7.5% and withdrawal for about 2.7%.[21] The primary measure of regulatory success is the timeliness of information, warnings, and withdrawals. With rosiglitazone, the FDA failed to warn or inform in a timely fashion.

The history of rosiglitazone highlights the importance of several recommendations made by the Institute of Medicine Committee on the Assessment of the US Drug Safety System.[17,18] The FDA needs the leadership and the authority to require manufacturers to conduct high-quality postmarketing trials of selected drugs in a timely fashion. The House of Representatives, which is about to take up drug-safety legislation, has a unique opportunity to reinvigorate an essential regulatory agency that has many outstanding and dedicated scientists.

Patients and physicians will need to weigh the benefits and risks of treatment with rosiglitazone. Glycemic control and durability appear to be the major benefits.[9,10] Rosiglitazone is also associated with significant weight gain, an adverse effect on low-density lipoprotein cholesterol, an increased risk of heart failure, an increased risk of fractures in women, and an apparent increase in the risk of myocardial infarction.[1,2,9,10] Patients should not stop treatment on their own, but if they have concerns, they should consult their physicians. Together, patients and physicians can decide whether they wish to suspend the use of rosiglitazone.

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From the Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, and the Center for Health Studies, Group Health, Seattle (B.M.P.); and the Division of Public Health Sciences, Wake Forest University, Winston-Salem, NC (C.D.F.).

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FOOTNOTE 66

diabetic patients who are at risk of many major complications. They were cited: kidney failure, limb amputation, nerve injury, blindness, cardiovascular events, deaths. Unfortunately, the world-wide epidemic of type 2 diabetes shows no signs of abating.

All medicines have risks. But the benefits of oral anti-diabetic medicines like Avandia help millions of patients control their diabetes and live healthier, more productive lives.

I will say that we found the RECORD data which we published yesterday in the New England Journal of Medicine very reassuring, recognizing that it is interim and therefore not fully conclusive. We are extremely disappointed by the editorials published yesterday in the New England Journal of Medicines that cherry-picked data points when the data taken as a whole supports the safety profile of Avandia.

I thank you very much for your attention, and I would be happy to take your questions.

[Prepared statement of Mr. Slaoui follows:]

********** INSERT **********

FOOTNOTE 67

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RECORD FAQ's – For Sales Force

RECORD Study Questions

Why an interim analysis? Why not wait for the study to finish before announcing the findings?

Because of the widespread media coverage of the NEJM meta-analysis and the confusion it has created, the RECORD Steering Committee decided it was important to publish the interim analysis in the interests of patient safety. It wanted to make the information available to physicians and patients immediately so that treatment decisions may be based on the overall totality of the evidence.

Why were these results published in the NEJM?

The Steering Committee recommended publication in the NEJM. The objective for publication of the interim analysis was to make the data available as quickly and as far reaching as possible.

What is the difference between a prospective, randomized, controlled clinical trial and a meta analysis?

A prospective, randomized controlled clinical trial is designed specifically to compare the effect of two different treatments on an event of interest.

A meta analysis is a statistical retrospective analysis based on the combined results of several studies to test for a specific hypothesis.

What is the primary goal of RECORD?

The study was designed to evaluate the non-inferiority of *Avandia*-containing regimens vs. control group with respect to cardiovascular hospitalization and death. This means the study was designed to show that *Avandia*-containing regimens are no worse than the control group. The study design and protocol was published in *Diabetologia* in April 2005.

Was RECORD a monotherapy or a combination therapy study?

RECORD compares *Avandia* combination therapy (*Avandia* plus either metformin or sulfonylurea) with metformin-sulfonylurea combination in patients who did not attain glycemic control while receiving maximum doses of metformin or SU alone. These patients had a mean HbA1c of 7.9% and the mean duration of diagnosis of T2DM was 7.1 years. Please refer to the publication for the full study design.

How many patients were evaluated in this interim analysis and how long were they evaluated for?

There were 4,447 patients evaluated in this analysis and followed for an average of 3.75 years.

What were the key results from this interim analysis?

The interim analysis found a low number of events overall, and a similar number of events in each group.

Like all interim analyses, these data do not offer final conclusions. Based on the interim analysis, key findings include:

- The interim results suggest that the *Avandia* group was not significantly different from the control group in the primary endpoint of cardiovascular hospitalization or death. Due to the limited power of the interim analysis, a conclusion on the primary endpoint must await the completion of the study.
- The interim results showed no evidence of any increase in the secondary endpoints of mortality, either from any cause or from cardiovascular causes, with the *Avandia* group compared to the control group.
- There was no statistically significant difference between the *Avandia* group and the control group on the secondary endpoint of composite events of cardiovascular death, myocardial infarction, and stroke.
- There was no statistically significant difference between the *Avandia* group and the control group on the secondary endpoint of myocardial infarction. At this point, the data do not allow a conclusion on the relative risks of myocardial infarction among the drugs studied.
- A difference between the *Avandia* and control groups was seen only in the secondary outcome of congestive heart failure (CHF), where significantly more cases were seen in *Avandia* patients. This finding is consistent with the well known association between fluid retention and TZDs. Fluid retention can worsen or lead to CHF.
- Importantly, despite the increase in CHF, the primary outcome of cardiovascular hospitalizations and death showed the *Avandia* group was not significantly different from the control group.
- The RECORD study has not yet been completed, and the safety monitoring board has recommended that the trial should continue. The final results as well as results from other ongoing long-term trials, such as BARI-2D and ACCORD, will provide further information about the cardiovascular safety profile of *Avandia*.

Why was RECORD designed as an open-label study?

For many patients, it would be necessary to add insulin to keep their blood sugar under control. Because insulin would be added at different times for a patient in the *Avandia* group vs the control groups, the study would have unblinded itself.

Is the dropout rate in RECORD different from similar type studies?

No. The dropout rates in RECORD are consistent with other long-term studies of this length in time.

Why are the event rates in RECORD so low?

The protocol excluded some high-risk patients and treatment is targeted toward current management guidelines for dyslipidemia, hypertension and improved glucose control. These may contribute to the low event rate.

When will RECORD be completed?

The study is due to finish in late 2008, with results expected in early 2009.

How many patients in RECORD were on insulin?

This information is not available at this time. The final analysis of RECORD will provide more in-depth analysis and data than what is available at this time.

Has the interim analysis from RECORD been shared with the FDA? How will the study impact future labeling?

Yes. FDA is aware of the findings from the interim analysis. We expect it will contribute to the scientific evidence on which FDA bases decisions on labeling.

Where can I get more details on the interim analysis study results?

RECORD NEJM Reprint
RECORD Study Overview Document
Representative Key Messages Document
Updated GSK Letter to HCPs

How do we respond to NEJM editorials regarding RECORD?

GSK will provide a response to the editorials. Please urge your physicians to read the original RECORD interim analysis published in the NEJM. The editorials are 3 different opinions of the interim analysis. The RECORD data safety monitoring board reviewed the interim analysis and recommended that the study should continue. If your customer requires more information, please contact the GSK Response Center.

Does the European label for *Avandia* contain a contraindication for all classes of heart failure?

Yes.

How do we respond to questions about Takeda's study, Proactive?

Please do not discuss Actos or the Proactive study with your physicians. For questions regarding Actos or the Proactive study, healthcare providers should contact Takeda. GSK's focus is on *Avandia*. Communicate the key points from the interim analysis of RECORD to your physicians.

RECORD Communications Questions

Should I proactively communicate the results of the interim analysis to HCPs?

Yes, use approved promotional materials only, such as the updated GSK letter to healthcare professionals.

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What should I be communicating to HCPs?

You should refer to the Representative Key Messages Document for the speaking points to be used with your customers.

What materials will I have to communicate this information with HCPS?

Updated GSK Letter to HCPs
Postcard that will direct HCPs to Avandia.com

Will there be any changes to the sales aid?

No, not yet. There have been no changes to the label and therefore no changes to your selling materials. Please continue to use the current sales aid and approved selling materials as directed.

Can we use the GSK press release from GSK.com with my physicians?

Please direct physicians to Avandia.com where they can access all the current information regarding *Avandia*.

What is GSK doing to communicate this information to current *Avandia* patients?

The patient ad running in newspapers will continue to run through Friday, June 8. In addition, we have updated the patient Q&A.

What is GSK doing to communicate this information to speakers and advisors?

- National speakers and advisors contacted by the brand team to inform them of the interim analysis of the RECORD data being published
- Coordinated effort at regional level to contact regional and local speakers regarding publication of interim analysis
- Planning near-term training for national, regional and local speakers

What is GSK doing to communicate this information to medical associations such as ADA and AACE?

Marketing will be contacting ADA, AACE, ENDO, AHA, and ACC.

What is GSK doing to communicate this information to pharmacies?

The trade account managers are being trained on the information. They will be attempting to contact all of their accounts.
We will also be sending a mailing to all pharmacies informing them of the results.

What is GSK doing to communicate this information to managed care providers?

The managed markets managers are being trained on the information. They will be attempting to contact all of their accounts.

If my customers have additional questions, what resources are available to address them?

Representatives can forward questions in one of three ways:

- Representatives can call the GRC directly.
- Submit a question via Passport system that will be forwarded to MI
- Request a Regional Medical Scientist (RMS)

RECORD Training Questions

What additional training will be available for representatives?

Diabetes University is being updated with a module that will provide additional training on the publication.

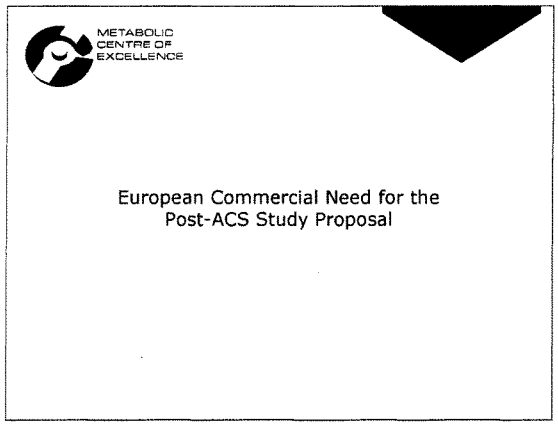
Have the RMS, MI and GRC teams been updated on the RECORD interim analysis data?

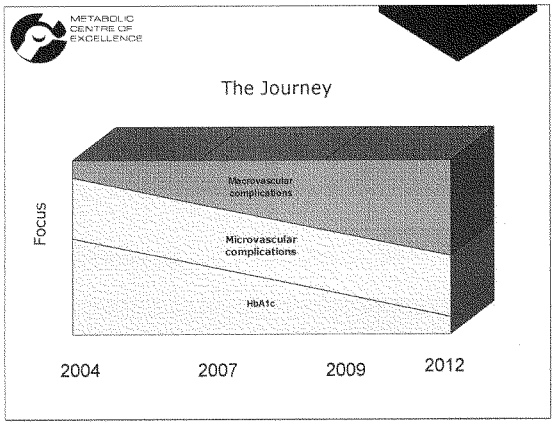
Yes.

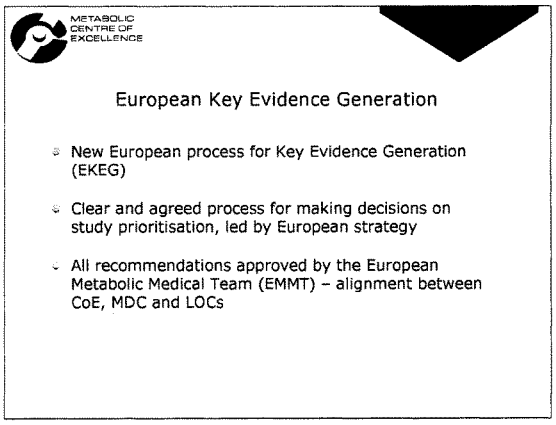
Will an updated speaker deck containing this information be available and when?

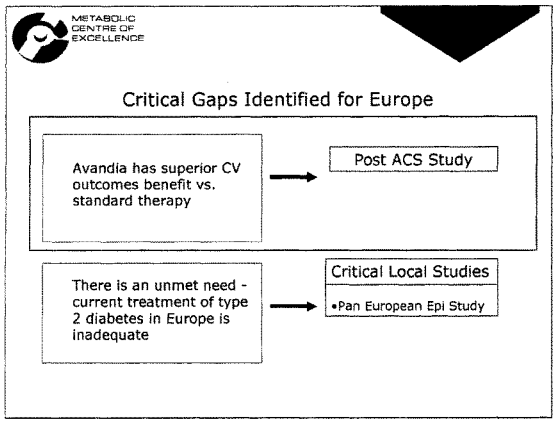
Yes. An updated speaker deck is in development and will be distributed on Monday, June 11, 2007. We plan to train the new deck on web-ex speaker training.

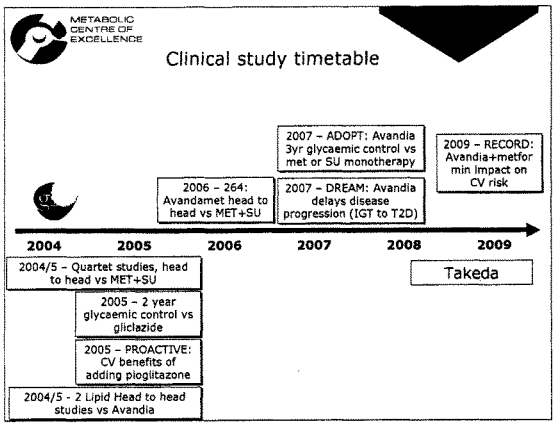
FOOTNOTE 69

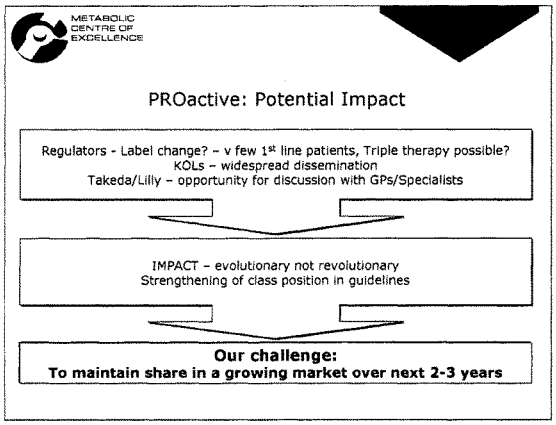


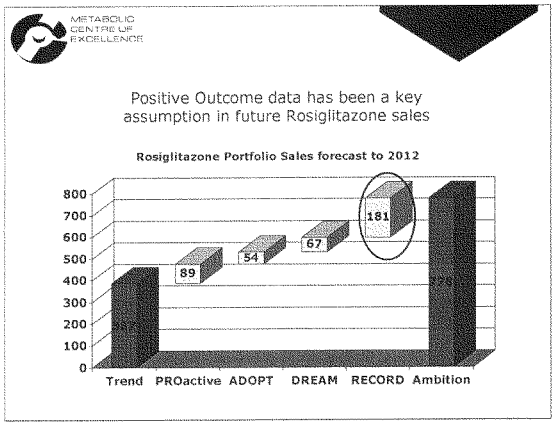


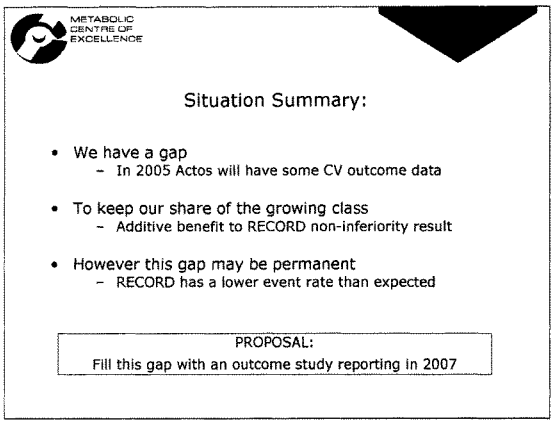


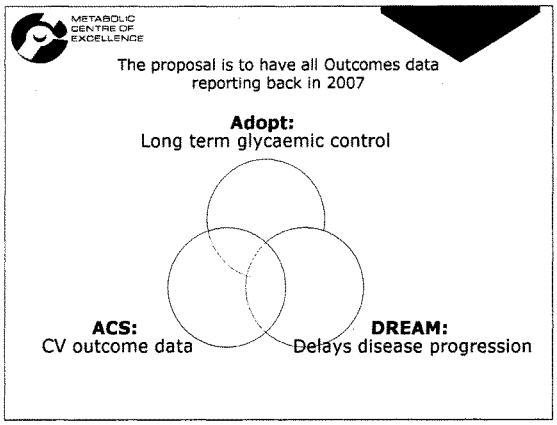


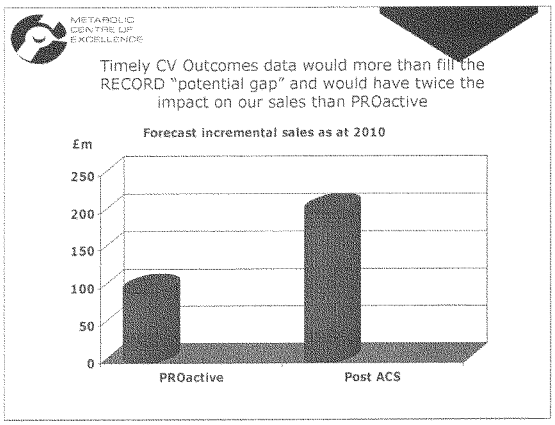

METABOLIC CENTRE OF EXCELLENCE
Clinical study timetable
2007 – ADOPT: Avandia 3yr glycaemic control vs met or SU monotherapy
2009 – RECORD: Avandia+metfor min impact on CV risk
2006 – 264: Avandamet head to head vs MET+SU
2007 – DREAM: Avandia delays disease progression (IGT to T2D)
2004
2005
2006
2007
2008
2009
2004/5 – Quartet studies, head to head vs MET+SU
Takeda
2005 – 2 year glycaemic control vs gliclazide
2005 – PROACTIVE: CV benefits of adding pioglitazone
2004/5 - 2 Lipid Head to head studies vs Avandia

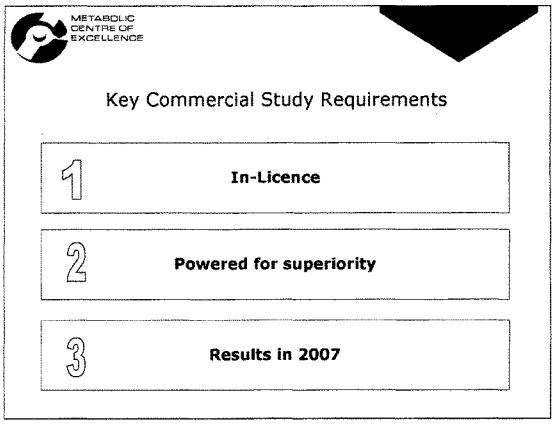


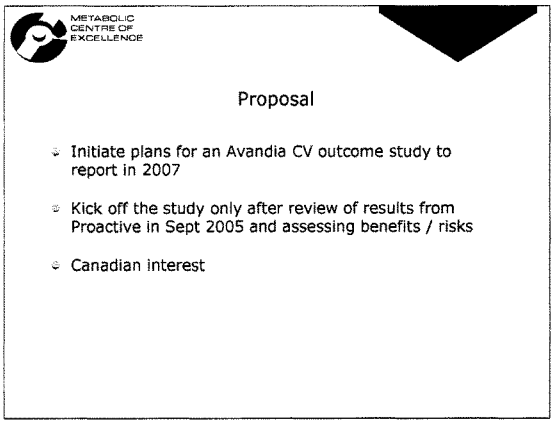

METABOLIC CENTRE OF EXCELLENCE
Positive Outcome data has been a key assumption in future Rosiglitazone sales
Rosiglitazone Portfolio Sales forecast to 2012
800
700
600
500
400
300
200
100
0
89
54
67
181
Trend
PROactive
ADOPT
DREAM
RECORD
Ambition











FOOTNOTE 74

From: Alexander R Cobitz
Date Sent: 6/16/2005 4:18:47 PM
To: Andrew 2 Zambanini
CC: Alexander R Cobitz; Joanna M Balcarek; Lawson 2 Macartney; Margaret 2 Sowell; Murray W Stewart; Nevine Zariffa; Robin 2 Saltzman; Hubert S Chou
Subject: Re: European Post-ACS Study: AVD104821

Andy,

I understand the need to start putting together something at risk.

As we bring this forward and as we have discussed, we will need to ensure that the history of the last peri-MI study proposed is clear (including the preclinical background, as you had mentioned to Trevor).

Alex

Alexander R Cobitz, MD, PhD
Senior Director Metabolism
Clinical Development and Medical Affairs
GlaxoSmithKline
(610) [redacted]

Andrew 2 Zambanini/PharmRD
16-Jun-2005 12:06 MDC CVM Europe, Greenford Building 20E, Ground Floor, 09 C #711 3241, +44 (0[redacted], Mobile: +44 (0)[redacted]

To
Alexander R Cobitz/DEV/PHRD/SB_PLC, Joanna M Balcarek/PharmRD/GSK@GSK
cc
Robin 2 Saltzman/DEV/PHRD/SB_PLC@GSK, Margaret 2 Sowell/PharmRD/GSK@GSK, Nevine Zariffa/PharmRD/GSK@GSK, Murray W Stewart/DEV/PHRD/SB_PLC@GSK, Lawson 2 Macartney/DEV/PHRD/SB_PLC@GSK
Subject
European Post-ACS Study: AVD104821

Dear Alex and Joanna,
I hope I didn't surprise you too much with my question to Trevor post GSB!

Last week EMED agreed funding for the proposed European Avandia in Post-ACS patients study and the plan is to get much of the study organised at risk pending the results of PROactive due on Tuesday September 13th. Although the study proposal has been evaluated at the ClinMT, CommMT, Project team and at the US-EU MDC review forum, I am aware that both Robin and Nevine have probably not heard much about this study and the plan is to bring it to the

MDM in July for discussion. Statistical support has been provided by Norbert Banik in Germany as originally this was to be a Germany only study.

In terms of timelines, I'd like to take the protocol to PRF after the MDM discussion, and if possible take the protocol to GSB in August so that we can finalise the protocol in anticipation of the PROactive data. Clearly no patients will be recruited until will have made a decision based on the go-no go criteria from the PROactive data. However there is a great deal of EU commercial push to initiate this study in 2005.

I have attached copies of the latest draft of the concept protocol and slides that provide a summary of the study. I'd welcome comments from everyone and in particular Nevine and Robin, and if necessary I will organise some time with both of you in advance of the MDM in July to go over any issues that you may have.

Kind regards,

Andy Z

<<...>> <<...>>

FOOTNOTE 75

[Alex] On December 2, 2004, the Avandia Cardiovascular Event Modeling Team **(or whatever we decide to call ourselves for the purpose of this document)** reviewed with the Global Safety Board (GSB) plans for a statistical analysis of cardiac adverse events drawn from the integrated clinical trials data for rosiglitazone (RSG). Endorsement to conduct the proposed analysis was not granted due to a number of GSB concerns., The purpose of this briefing document is to address these concerns, as mandated, and complete the situational analysis begun at the previous meeting. Thereby, the team hopes to gain GSB endorsement to conduct the previously proposed RSG cardiovascular analysis.

[Missy] Background:

- Why we initiated this activity (see old briefing document)

In integrated clinical trials safety data for rosiglitazone used in combination with insulin, the incidence of CHF and events typically associated with myocardial ischemia were higher in patients treated with a combination of RSG plus insulin than with insulin alone. Small numerical differences in the incidence of CHF and other cardiac events have been noted in some other rosiglitazone studies although the actual number of events was very low.

Request from GSB to provide est of relative risk and confidence interval for non-CHF CV events for the RSG+Insulin combination vs. Insulin monotherapy.

From GSB minutes, 30-Jun-2004, at which data from study 211 (RSG in Class I & II CHF and T2DM) was discussed, the following was noted: "The cardiac disorders statements in the clinical trial data subsection of the Adverse Reactions section of the GDS were discussed and it was agreed that meta-analyses of the relative risk of CHF and ischaemic events for RSG versus control are required. The team was asked to provide an analysis plan for the meta-analyses to GSB within the next 1-2 months.

GSB was assured that the DSMB are closely monitoring all cardiovascular events associated with RSG and data from all ongoing cardiovascular studies are due 2008/9. Also, the team is intending to update the slide that was presented to GSB in March 2002 showing CHF incidence rates."

In addition, the World Health Organization's (WHO) Uppsula Drug Monitoring Center (UMC) has notified GSK of a review of postmarketing safety with regard to "Thiazolidinediones and cardiac disease" that appeared in the WHO newsletter SIGNAL. This review was undertaken in response to elevated reporting ratios for a variety of cardiac events (e.g. cardiac failure, cardiomegaly, myocardial ischemia, myocardial infarction, and angina pectoris) for patients receiving thiazolidinediones including rosiglitazone. With regard to the post-marketing reports of cardiac adverse events including heart failure and ischaemic events, external cardiologists have concurred that in some cases fluid retention sufficient to exacerbate heart failure may be attributed to rosiglitazone. However, , in the absence of

appropriately powered controlled trials or of large epidemiological surveys with appropriately defined controls, the role of other risk factors and prior vascular events must be taken into account in assigning causality.

No other cardiovascular problems have been clearly related to rosiglitazone."

Other events, such as renal failure, acute coronary syndrome (including myocardial infarction, occasionally fatal),stroke, and sudden death occurred in patients receiving rosiglitazone; but the temporal pattern of their occurrence and the associated findings provide no basis for an inference that the events resulted from use of the drug. Notably, such events are not uncommon in patients with type 2 diabetes mellitus; thus, in the absence of appropriately powered controlled trials or of large epidemiological surveys with appropriately defined controls, the role of other risk factors and prior vascular events must be taken into account in assigning causality.

Current Environment:

1. In light of recent publicity regarding the safety of a variety of medications, the pharmaceutical industry has fallen under ever increasing public scrutiny. This has resulted in the expectation that all clinical trial results be made public. GSK has responded by establishing a Clinical Trials Registry (CTR). The availability of the CTR enables investigators to conduct their own post-hoc analyses, as exemplified by a recent report published by *Prescrire*, alleging that rosiglitazone treatment is associated with increased mortality over that of control. Because the studies in the CTR vary in duration, design, and patient population, such post hoc analyses is generally inappropriate. Indeed, prospective outcomes studies, as well as analyses of clinical trials utilizing models which address the specific limitations of heterogeneously pooled data, offer more reliable conclusions. With respect to the former, GSK has undertaken a number of prospective cardiovascular outcomes trials **(transition to Andy below)**
2. [Andy] Summary of GSK prospective studies: what they will and won't tell us [table from external reviewer documentation]
3. [Andy] RECORD: what will it provide, what will it not provide (no mono, no insulin; excludes patients w/ previous events; low event rates)
4. [Andy] PROACTIVE results to be coming soon—need to be able to respond to a variety of different outcomes
    - Communications plan in place for various possible outcomes of PROACTIVE

[Missy] Need for Analysis

1. It is the right thing to do: appropriate medical governance by monitoring integrated safety database. This analysis is the next logical step in the ongoing monitoring of cardiac safety with RSG. To be able to best describe to prescribers and regulators ... for best patient care-- appropriately communicate findings

2. More appropriate and informative analysis than either incidence rates or a simple relative risk calculated for insulin+RSG regimen
3. Provides the most robust quantitative assessment of cardiovascular risk across all currently licensed indications for rosiglitazone: monotherapy, in combination with Met, SU or Met+SU, in combination with insulin

[Mark] Proposed Analysis

Actions Requested by GSB at Dec 2, 2005

- [Mark] External Review—internal GSK cardiologists review; 2 external cardiologist and 1 external statistician review; are implementing input from them
  - Has influenced proposed analysis described above
  - Reviewers agreed with basic approach
  - Modified statistical approach
  - Review of individual verbatim terms and narratives where available to determine assignment to CHF or myocardial ischaemia
- [Andy] Mechanism
- [Andy] Communications plan—MDM endorsement

[Later] Team requests endorsement to initiate plan ASAP

- May need to prospectively inform EU regulators of our plan to conduct analysis

FOOTNOTE 76

Briefing Document for 27 June 2005 PMB
Avandia Cardiovascular Modeling Plan

The objective of this briefing is to inform PMB regarding a GSB endorsed analysis of cardiovascular event data from the AVANDIA clinical trials.

Background

In integrated clinical trials safety data for AVANDIA (rosiglitazone, RSG), the incidence of heart failure (CHF) and events typically associated with myocardial ischemia were higher in patients treated with a combination of AVANDIA plus insulin than with insulin alone. Small numerical differences in the incidence of CHF and other cardiac events have been noted in some other AVANDIA studies and in some integrated datasets although the actual number of events was very low.

During discussions of a proposal to add text to the AVANDIA GDS regarding the incidence of ischemic type cardiac events in RSG+Insulin clinical trials, GSB requested an estimation of the relative risk for pooled ischemic (non-CHF) cardiac events. Following review of this information GSB and subsequently Global Labeling Committee (GLC) approved the amendment to the AVANDIA GDS.

In January 2004, the World Health Organization's (WHO) Uppsula Drug Monitoring Center (UMC) notified GSK of a review of postmarketing safety with regard to "Thiazolidinediones and cardiac disease" that appeared in the WHO newsletter SIGNAL. This review was undertaken in response to elevated reporting ratios (i.e. greater than expected by chance) for a variety of cardiac events (e.g. cardiac failure, cardiomegaly, myocardial ischemia, myocardial infarction, and angina pectoris) for patients receiving thiazolidinediones including AVANDIA.

GSK has closely monitored postmarketing reports of cardiac adverse events since the launch of AVANDIA. Shortly after the US launch of AVANDIA, an external board of cardiologists[1] was established to review reported post-marketing adverse cardiovascular events. Based on their review they have concluded *"that in some cases fluid retention sufficient to exacerbate heart failure may be attributed to rosiglitazone."* For reports of other cardiac events, the external consultants have stated that *"the temporal pattern of their occurrence and the associated findings provide no basis for an inference that the events resulted from use of the drug. Notably, such events are not uncommon in patients with type 2 diabetes mellitus; thus, in the absence of appropriately powered controlled trials or of large epidemiological surveys with appropriately defined controls, the role of other risk factors and prior vascular events must be taken into account in assigning causality."*

Following on from the above, and after *ad hoc* discussions with GSB members, GCSP and Clinical agreed that a similar but more refined statistical approach to that requested by GSB for the RSG+Insulin non-CHF events would be helpful in evaluating cardiac safety in the larger AVANDIA clinical trial experience. Specifically, such an analysis would better characterize the association, if any, between AVANDIA and heart failure or ischemic type cardiac events.

[1] In 1Q2004, GSK and the external cardiologists agreed that with the benefit of nearly five years of marketed experience, in the future the opinion of these cardiologists would be solicited on an ad hoc basis.

Importantly, such an analysis would provide insights on cardiac safety while awaiting data from ongoing studies (see Appendix for additional details) and might also provide important insights regarding treatment regimens not specifically addressed in these studies.

Planned Analysis

To characterize the degree of association, if any, between AVANDIA and events of congestive heart failure (CHF) or myocardial ischemia, a detailed plan for statistical analysis of the AVANDIA clinical trials program has been developed.

Key features of the analysis include:

- Data from controlled, randomized, double-blind clinical trials.
- Events to be analyzed include CHF and myocardial ischemia, where individual verbatim terms or serious adverse event narratives were reviewed in a blinded fashion to define event assignment.
- Statistical modeling methods (logistic regression) will adjust for important patient risk factors and baseline characteristics, plus duration of treatment with double-blind study medication.
- Primary analysis will be based on serious adverse events (SAEs) of CHF and myocardial ischemia, with a supplemental analysis of all adverse events of CHF and myocardial ischemia.
- Primary output of analysis will consist of estimates of relative risk (point estimates and confidence intervals) for AVANDIA vs. active control and placebo.
- Separate estimates will be provided for the various AVANDIA treatment regimens: as monotherapy, in combination with metformin, in combination with an SU, in triple therapy (RSG + metformin + SU) or in combination with insulin.

Development, Review, and Endorsement of Analysis Plan

The analysis plan was developed by a group of physicians (clinical and GCSP) in conjunction with statisticians from BDS. Additional review and input was provided by senior leadership within the CVM MDC as well as the GSK Internal Cardiology Board. External input was solicited from both cardiologists and an external statistician.

The analysis has received endorsement from the AVANDIA Project Team, AVANDIA ClinMT, ComMT, CST, CVM MDC and CVM MDM, and Global Safety Board.

Scenario Planning and Communications Plan

Results of the analysis will be communicated to regulatory authorities and will be made public. A detailed scenario plan has been developed and endorsed by the MDC and GSB. A detailed plan for internal and external communication of the outcomes of this analysis has been prepared in conjunction with the AVANDIA Global Issues Management Team.

Appendix

Prospective Cardiovascular (CV) studies with AVANDIA

GSK has invested in a number of studies examining the potential benefits of AVANDIA for the modification of the atherosclerotic process (Table 1). The majority of these studies are examining changes in arterial wall structure or plaque morphology in patients with established coronary heart disease (CHD). Standard safety monitoring has been incorporated into all these studies and in addition, conduct of study 521 will include an Independent Data Monitoring Committee (IDMC).

Outcome Studies using AVANDIA

There are also a number of outcomes studies utilizing AVANDIA that evaluate the development and progression of T2DM and also the development of cardiovascular events (Table 2).

The non-GSK collaborative studies are utilizing AVANDIA as part of a treatment strategy that includes a number of different anti-diabetic agents and these studies are not designed to assess the CV profile of AVANDIA compared to other agents. Studies such as DREAM and ADOPT (GSK study 048), although not primarily designed as CV outcome studies, are collecting data in patients with impaired glucose tolerance and early T2DM.

RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) **is the only study** primarily designed to assess cardiovascular outcomes with AVANDIA. The anticipated average treatment duration is 6 years and the study is due to complete in 2009. This is an open label, randomised study in patients with T2DM, comparing the combination of AVANDIA and either metformin or sulphonylurea (SU) versus metformin + SU on cardiovascular endpoints and glycaemia. The primary objective of this study is to compare the time to reach the combined cardiovascular (CV) endpoint of CV death and/or CV hospitalisation between those patients treated with AVANDIA combination (AVANDIA group) and those treated with SU+metformin combination in patients with T2DM who are inadequately controlled on either metformin or SU alone. The study is powered to test the hypothesis that the AVANDIA group is **non-inferior** to the non-AVANDIA group when comparing the hazard of observing the combined primary endpoint of CV death and/or CV hospitalisation. If non-inferiority holds true, a test for superiority will be performed.

Important limitations of RECORD include:

- RECORD does not utilise AVANDIA either as monotherapy or in combination with insulin and therefore this study will not provide any information regarding the cardiovascular profile of AVANDIA when used in either of these regimens.
    - Current labelling for the combination of insulin and AVANDIA suggests that there may be an increased risk of CHF and other cardiovascular events with this combination, and there are no ongoing prospective studies that will provide clarification on this issue.
- This study recruited 'typical' patients with T2DM that required dual combination therapy with oral anti-diabetic drugs. Therefore a small proportion of patients were 'high risk' as defined by the presence of a history of established CV disease (see PROACTIVE below).
- Results from the study will not be available until 2009.

- The current observed event rate for the primary endpoint is very much lower (approximately 3.5% per annum) than that anticipated in the original protocol (11% per annum). A number of activities are ongoing to address this situation.

CV Studies with Other Marketed TZDs

Two studies are ongoing evaluating the effects of pioglitazone (*Actos*) on vascular structure (CHICAGO - IMT and coronary calcium score, and PERISCOPE - IVUS) and are due to complete in 2007.

The PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study completed in 2004 and is due to be reported at the European Association for the Study of Diabetes (EASD) Annual Meeting in September 2005. This study evaluated the cardiovascular effects of pioglitazone in over 5000 high-risk patients (established coronary heart disease or peripheral vascular disease) with T2DM. The combined primary endpoint for this study included all cause mortality, nonfatal MI, acute coronary syndrome, cardiac intervention (PCI or CABG), stroke, leg amputation or revascularisation. The secondary endpoints include CV mortality and the individual components of the primary endpoint.

A communications package has been developed by GSK to address possible scenarios that may arise from the presentation/publication of the PROACTIVE data.

Table 1: Ongoing mechanistic cardiovascular studies utilizing AVANDIA

Study	Status	Established CHD?	Duration and Subject Numbers	Data available
49653/334 Carotid IMT	Completed	Some	12 months, 200 T2DM, 356 non-T2DM	Q2 2005
49653/278 Carotid IMT	Completed	Yes	12 months, 200 non-T2DM	Q2 2005
49653/351 Carotid MRI	Ongoing	Some	60-week pilot, 60 T2DM	Q4 2005
49653/405 Coronary IVUS	Ongoing	Yes	6-month pilot, 60 T2DM	Q3 2006
102268 ETT in CHD	Ongoing	Yes	12 weeks ETT, 80 T2DM	Q3 2006
49653/416 Vein Graft IVUS	Ongoing	Yes	12 months, 280 T2DM	Q1 2007
104490 ETT in CHD	Ongoing	Yes	12 weeks ETT, 80 non-T2DM	Q1 2007
49653/521 Coronary IVUS	Ongoing	Yes	18 months, 634 T2DM	2007

Table 2: Ongoing large studies utilizing AVANDIA where CV event data will be available

Ongoing studies	Completion date	Number of patients
Non-GSK Collaborative Studies-ongoing:		
Primary CV Outcome		
• 297 (BARI-2D)	(2009)	n = 2600
• 294 (ACCORD)	(2009)	n = 10000
• 244-(VADT)	(2008)	n = 1700
CV Safety in Long-term Diabetes Prevention Study: 281(DREAM)	(2007)	n = 4000
GSK sponsored Studies:		
CV Safety in Long term Glycemic Outcome Study:048 (ADOPT)	(2006)	n > 4200
RECORD (Study 231) EMEA commitment	(2008)	n > 4000

FOOTNOTE 78

From: Andrew 2 Zambanini
Date Sent 7/26/2005 12:56:05 PM
To: Sanjay 2 Jariwala; Nikki M Yates
CC: Joanna M Balcarek
Subject: Fw: URGENT ACTION NEEDED TODAY - brief David Stout on RECORD

Dear Sanjay and Nikki,
Ron Krall has asked Lawson to provide anurgent update to David Stout regarding RECORD. In particular he has asked for 'our intent to manage information flow in Europe to manage the competitive situation'. Clearly we can provide a summary of the communications around PROactive but I wonder if you could put a few sentences together regarding the communications piece around RECORD. I have attached below a draft of what we hope to provide to Lawson but this will be reduced in size. We need to provide this to Lawson by eob today. Please give me a call if we need to discuss further.

Apologies for the short time-line.

Kind regards,

Andy Z

----- Forwarded by Andrew 2 Zambanini/PharmRD/GSK on 26-Jul-2005 02:51 PM -----

Andrew 2 Zambanini/PharmRD
26-Jul-2005 13:51 MDC CVM Europe, Greenford Building 20E, Ground Floor, 09 C #711 3241, +44 (0)[redacted], Mobile: +44 (0)[redacted]

To
Joanna Balcarek, Alex Cobitz, Jill Donaldson
cc

Subject
Fw: URGENT ACTION NEEDED TODAY - brief David Stout on RECORD

Dear All,
I have attached a brief summary of the RECORD and CV programme for RSG. It is probably still too long so we will need to cut back further. On key thing that is missing is the "intent to manage information flow in Europe to manage the competitive situation". Nikki is in Philly at the moment so I wonder whether we need to ask her for her input on this?

Please tweak/add comments as necessary.

Kind regards,

Andy Z

----- Forwarded by Andrew 2 Zambanini/PharmRD/GSK on 26-Jul-2005 01:46 PM

Nadine Ryder-1/DEV/PHRD
26-Jul-2005 11:29 CVM MDC H83/L3, NFSP(S) Tel: [redacted] Fax: [redacted]
External Tel: (0)[redacted]

To
Jill X Donaldson/PharmRD/GSK@GSK, Andrew 2 Zambanini/PharmRD/GSK@GSK
cc
Lawson 2 Macartney/DEV/PHRD/SB_PLC@GSK, Murray W Stewart/DEV/PHRD/SB_PLC@GSK
Subject
Fw: URGENT ACTION NEEDED TODAY - brief David Stout on RECORD

Jill/Andy - Please can you respond to Lawson in Murray's absence.

----- Forwarded by Nadine Ryder-1/DEV/PHRD/SB_PLC on 26-Jul-2005 11:24 AM

Lawson 2 Macartney/DEV/PHRD
26-Jul-2005 10:35

To
Joanna M Balcarek/PharmRD/GSK@GSK, Alexander R Cobitz/PharmRD/GSK@GSK, Murray W Stewart/DEV/PHRD/SB_PLC@GSK
cc

Subject
Fw: URGENT ACTION NEEDED TODAY - brief David Stout on RECORD

can you guys put this together today and let me have it ASAP include the additional CV studies we are proposing..the ACS study and the MRI imaging.

Dr. Lawson Macartney,
Senior Vice-President, WW Development
GlaxoSmithKline,
RN 0315
tel 610[redacted]
Fax 610[redacted]
assistant ([redacted]) 610[redacted]
----- Forwarded by Lawson 2 Macartney/DEV/PHRD/SB_PLC on 26-Jul-2005 05:33 AM

Ronald L Krall/MGMT/PHRD
26-Jul-2005 05:12 Worldwide Development Upper Merion 610-270-6107

To
Lawson 2 Macartney/DEV/PHRD/SB_PLC@GSK
cc

Subject
URGENT - brief David Stout on RECORD

Lawson, David Stout needs a 2 paragraph written brief on the event rate in RECORD and our intent to manage information flow in Europe to manage the competitive situation. He also would appreciate a phone call on Wednesday to talk him through it. all in preparation for results meeting Thursday, in case he gets questions. He is in CET on Wed in London GSK house, but try him anytime. phone number 215-[redacted]

thanks
Ron

Ronald Krall, MD
GlaxoSmithKline Pharmaceuticals
709 Swedeland Road
King of Prussia, PA 19406
Office:610-[redacted]
Cell: 484-[redacted]
Fax #: 610-[redacted]

<<...>>

FOOTNOTE 79

MDC Briefing Document

Ad-hoc meeting 18th July 2005

AVD104821: rOSIGLITAZONE IN post-acs patients

A double-blind, placebo controlled study examining the role of rosiglitazone for the prevention of cardiovascular events in patients with Type 2 diabetes mellitus immediately following high risk acute coronary syndromes.

Aims

1. Provide MDC executive members with a clear rationale for the European need for this proposed study
2. Provide an overview of the study design and outcomes
3. Provide an update on timelines and key milestones

European Commercial Need

A recently completed evidence gap analysis completed by the Metabolic Centre of Excellence, has identified the need for the rapid generation of clinical endpoint data to support the superiority of rosiglitazone (RSG) for the prevention of future cardiovascular clinical events in patients with T2DM. Publication of the PROactive data may result in important commercial disadvantages in Europe. We therefore have the opportunity to start a CV outcomes study with the aim of getting superiority data in 2007.

Although a number of large studies evaluating the potential cardiovascular benefits of RSG are ongoing (Table 1), there are important limitations. The primary endpoint in RECORD is powered for non-inferiority and taking into account the low observed event rate, it is unlikely that this study will demonstrate any potential for RSG combination to be superior in terms of the primary endpoint compared to SU+MET combination therapy. DREAM and ADOPT are collecting CV safety data, but these are low CV risk populations and it is unlikely that RSG will be superior to controls for the prevention of CV events. The non-GSK collaborative studies are utilizing RSG as part of a treatment strategy that includes a number of different antidiabetic agents and these studies are not designed to assess specifically the CV benefits of RSG compared to other agents.

Table 1: Ongoing large studies utilizing RSG where CV event data available

Ongoing studies	Completion date	Number of patients
RECORD (Study 231) EMEA commitment	(2008)	n>4000
Non-GSK Collaborative Studies-ongoing		
• Primary CV Outcome		
• 297 (BARI-2D)	(2009)	n=2600
• 294 (ACCORD)	(2009)	n=10000
• 244-(VADT)	(2008)	n=1700
CV Safety in Long-term Diabetes Prevention Study: 281(DREAM)	(2007)	n=4000
CV Safety in Long term Glycemic Outcome Study: 048 (ADOPT)	(2006)	n>4300

Background to study design and evaluation

Following the presentation of the DIGAMI-2 data at the EASD in Munich in September 2004, Dr. Nico Marx approached colleagues in GSK Germany with a proposal to evaluate the potential cardiovascular benefits of RSG in T2DM patients who had recently suffered a myocardial infarction. The original proposal was for a multicentre study to recruit 900 German patients, but it soon became clear on further evaluation of the proposed study that a much larger number of patients would be required to power the study appropriately.

In parallel with these discussions, GSK Canada held an advisory board with local cardiologists to discuss the potential benefits and further development of RSG for cardiovascular disease. There was great interest in evaluating the CV benefits of RSG in a high risk population of patients with acute coronary syndrome (ACS). Following the advisory board, GSK Canada approached the MDC in Europe and suggested a potential collaboration on this project with European LOCs.

The proposed study has undergone extensive internal and external evaluation. These groups include the AVANDIA Clinical and Commercial Matrix Teams, AVANDIA Project Team, European Metabolic Medical Team, Joint US/European Metabolic MDC Clinical review group and EMED. Furthermore comments and feedback have been sought and incorporated from GSK physicians and scientists who are working in the ACS therapy area. The concept protocol was also reviewed and rewritten following discussions with an expert panel of cardiologists and diabetologists (Appendix 1).

Potential issues regarding study design

The rationale for evaluating the potential role of RSG in high risk ACS patients is provided in the concept protocol (see additional documents). However potential issues regarding study design are listed below:

1. **Why choose high risk patients with ACS?**
The DIGAMI-2 study clearly demonstrates an unmet medical need for T2DM patients with high risk ACS. CV morbidity and mortality remains high in this population despite the use of insulin both acutely and chronically and improvements in glycaemic control. Alternative strategies that influence vascular and ventricular remodelling should be evaluated.

This high risk group of patients has a very high CV event rate (20% MACE per annum) and both clinically and statistically significant benefits will be observed within the proposed median 16.5 months treatment period.

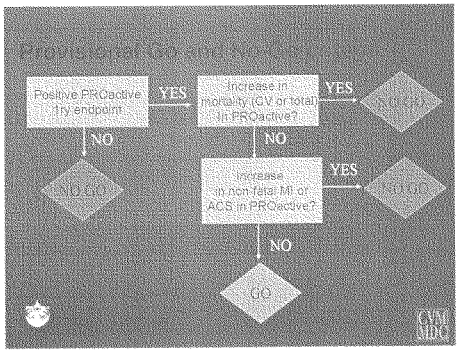
2. **Are there potentially detrimental effects associated with RSG when given to this population?**
Patients with ACS may have evidence of acute left ventricular dysfunction. The protocol therefore proposes that all patients should be cardiovascularly stable at the time of randomisation, that all coronary interventions have been completed and there be no clinical evidence of symptomatic heart failure. A time window of 7 days following hospitalisation has been provided for patients to be randomised. Furthermore patients will initially receive RSG 2mg od. This dose has been evaluated in patients concomitantly treated with insulin, and there was no evidence of significant fluid retention (no clinically or statistically significant differences in haematocrit were observed compared to placebo and fewer AEs of oedema were seen in those treated with RSG 2mg compared to placebo). These findings have been confirmed in a large cohort of non-diabetic patients with psoriasis.

The dose of RSG will only be increased to 4mg following 1 month of treatment with RSG 2mg od, in patients where there no evidence of clinically relevant fluid retention and where there is no severe LV systolic dysfunction.

3. **What is the optimal treatment duration?**
Previous studies of similar design have treated patients for a total of 2 years. However as described above there is a need to obtain data in 2007. The proposed ACS patient population has been 'enriched' by focusing on troponin positive T2DM patients and furthermore although the minimum duration of treatment will be 1 year, the estimated median duration will be 16.5 months. The IDSM and steering committees will receive periodic updates during the recruitment period and randomised treatment periods of the blinded event rates.

Timelines and Milestones

The key milestone for the team is the presentation of the PROactive data in September at EASD. The results of this study will determine whether the proposed study initiates. Key Go-No Go criteria are as follows:



The team would welcome the MDC's guidance on quantifying the specified increases in mortality and non-fatal MI described above.

Both operational and MDC activities relating to study start-up are to be performed at risk; when a GO decision is made in mid-September, this will permit a FPFV date of 2nd December 2005.

ADD GANTT chart timings

Potential risks:

1. 'grey' data from PROactive requiring further evaluation impacts on initiation of study. As the eCRF and protocol need to be finalised in parallel, any changes to these as a result of PROactive data will impact on study initiation date.

2. Lower event rate than anticipated. Event rate will be evaluated during course of study and in particular during the 9 month recruitment window. If necessary

recruitment period can be extended or overall study duration can be increased. Time and budgetary impact for both scenarios.

Appendix 1

External contributors to the concept protocol:

N. Marx, Germany (C)
H.-U- Häring, Germany (D)
C. Hamm, Germany (C)
J.-C. Tardif, Canada (C)
J. Mancini, Canada (C)
M. Laakso, Finland (D)
P. Valensi, France (D)

FOOTNOTE 82

AUTODATE

Avandia 211 CHF study

Senior Review of Additional Analysis

AUTODATE

Meeting #1

- Share sensitive data from 211 study which may have global implications
- Echo data - positive
- Safety profile - 'as expected'
- Many outstanding questions

Aims of meeting #2

- Presentation of 'Post hoc' data
- Feedback from senior review team

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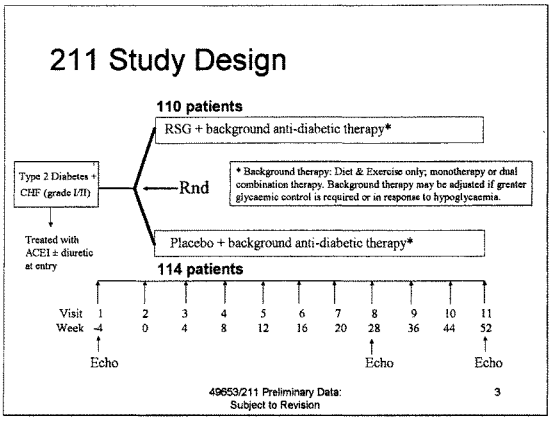


I would now like to discuss the study design in more detail.

As discussed earlier, 200 patients with T2D and NYHA Grade I/II CHF, who are treated with at least an ACEI, will enter a 4-week single-blind placebo run-in. Within 7 days of Visit 1, patients will undergo a screening echo to assess EF.

If at Visit 2, 4 weeks later, the patient meets all inclusion criteria and none of the exclusion criteria, they will be randomised into the study to receive RSG or placebo in addition to background anti-diabetic therapy in a 1 : 1 ratio.

Throughout the study patients should be treated to an FPG of 7.0 m Molar. Background therapy may consist of D & E only or with oral monotherapy or dual therapy. Background therapy may be adjusted if greater glycaemic control is required or in response to hypoglycaemia.

Throughout the 1 year study, there are a total of 11 visits. For visits 2 – 7, the visit interval is 4 weeks ± 7 days and then 8 weeks ± 14 days from visit 8 to 11.

The next section of this presentation will look at the main Inclusion and exclusion criteria.

AUTODATE

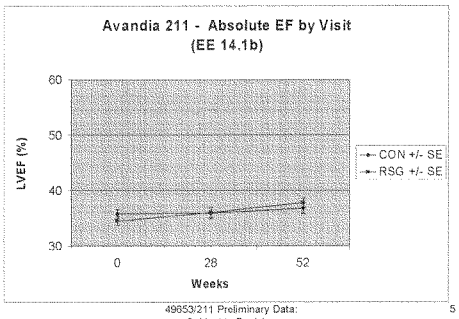
Primary Objective

- To compare the change from baseline of EF following 52 weeks of treatment in the Efficacy Evaluable population.
- The hypothesis to be tested is that rosiglitazone is non-inferior to control in the change from baseline to week 52 for EF in the EE population
- If rosiglitazone was non-inferior, test for superiority for EF in the ITT with LOCF population

49653/211 Preliminary Data: Subject to Revision 4

AUTODATE

211 - Absolute EF by visit (EE)



49653/211 Preliminary Data:
Subject to Revision

5

AUTODATE

Secondary Objectives (ITT+LOCF)

- *Cardiac Structure & Function*
  - EF — No Change - Not superior
  - LVEDVI — No change
  - LVESVI — No change
  - LVMI — No change
  - Cardiac Index — No change

BMI – no effect

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6

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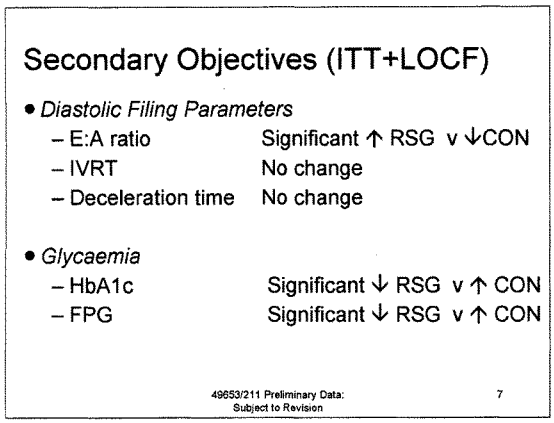

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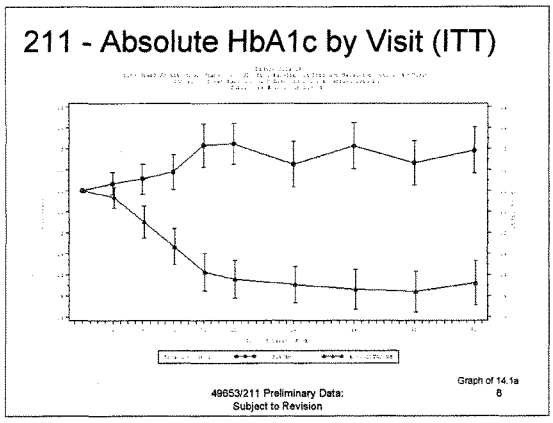
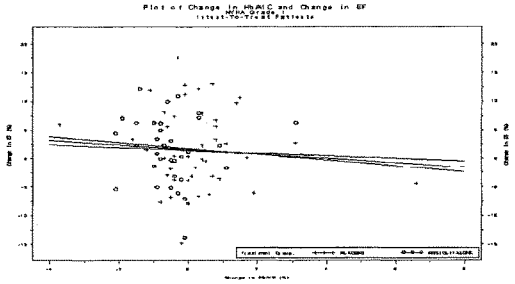


AUTODATE

Post hoc - HbA1c v EF - NYHA I



	Overall	Placebo	Rosiglitazone
Correlation:	-0.08096	-0.10510	-0.04121
p-value:	0.4781	0.4870	0.8199
N:	79	46	33

49653/211 Preliminary Data:
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9

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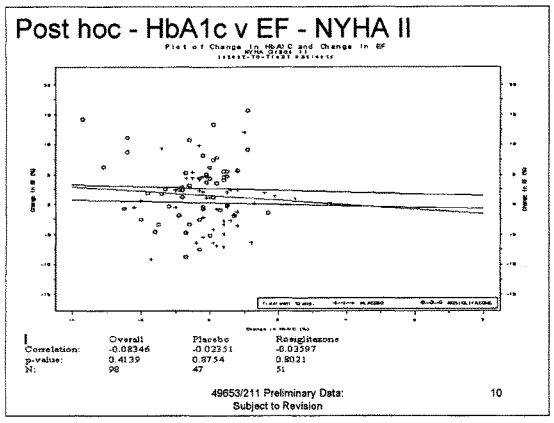
Post hoc - HbA1c v EF - NYHA II
Overall
Placebo
Reng1Reseve
Correlation:
-0.08346
-0.02251
-0.03597
p-value:
0.4139
0.8754
0.8021
N:
96
47
51
49653/211 Preliminary Data:
Subject to Revision
10

AUTODATE

Adjud. M&M - Incidence

Data Source Table 15.9.2
Summary of Cardiovascular Morbidity and Mortality Events
All Randomized Patients

Endpoint	PLACEBO (N=114)	Treatment ROSIGLITAZONE (N=110)	Total (N=224)
TOTAL	29 (25.4%)	45 (40.9%)	74 (33.0%)
All Cause Mortality or Worsening of CHF	8 (7.0%)	11 (10.0%)	19 (8.5%)
All Cause Mortality *1	5 (4.4%)	8 (7.3%)	13 (5.8%)
Cardiovascular Death	4 (3.5%)	5 (4.5%)	9 (4.0%)
CV Hospitalization*	15 (13.2%)	21 (19.1%)	36 (16.1%)
Worsening of CHF or Possible Worsening of CHF	4 (3.5%)	7 (6.4%)	11 (4.9%)
Worsening of CHF	4 (3.5%)	5 (4.5%)	9 (4.0%)

***1- NB - 5/5** LTFU still living so no effect on this data*

49653/211 Preliminary Data:
Subject to Revision

11

AUTODATE

Adjud. M&M - Incidence

Endpoint	Treatment PLACEBO (N=114)	Treatment ROSIGLITAZONE (N=110)	Total (N=224)
New or Worsening Oedema	10 (8.8%)	28 (25.5%)	38 (17.0%)
New or Worsening Oedema Without Worsening of CHF or Possible Worsening CHF	8 (7.0%)	25 (22.7%)	33 (14.7%)
New or Worsening Oedema Without Confounding Factors	7 (6.1%)	13 (11.8%)	20 (8.9%)
New or Worsening Dyspnoea	19 (16.7%)	29 (26.4%)	48 (21.4%)
New or Worsening Dyspnoea Without Worsening of CHF or Possible Worsening CHF	17 (14.9%)	25 (22.7%)	42 (18.8%)
New or Worsening Dyspnoea Without Confounding Factors	13 (11.4%)	12 (10.9%)	25 (11.2%)
Increase in CHF Medication	20 (17.5%)	36 (32.7%)	56 (25.0%)

49653/211 Preliminary Data:
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12

AUTODATE

Post Hoc - Breakdown of CV hosp

On-therapy events (not PIDs)

		RSG	CON
Non-CV	Non-CV	16	7
		appendicitis, haematemesis, pancreatitis, GI bleed, 2 x fracture, renal failure, oes ca, gall stones, hypocal abdo pain, rectal blood loss, pneumonia x2, pyelonephritis prostate Ca	acromioplasty, ovarian cyst, salivary gland Ca, hernia, gastroent, prostate Ca
CV	MI	3	0
	W. CHF	9	8
	Stroke / TIA	2	2
	Atrial Arr	0	0
	Vent Arr	1	1
	Unstable angina	1	2
	Op/prod/invest	0	0
	Other	4	2
		Angina x 2 Unstable ang Palps	poss angina dyspnoea

49653/211 Preliminary Data:
Subject to Revision

13

AUTODATE

Post Hoc - Breakdown of CV hosp

Post-therapy events (not PIDs) - EWD patients

		RSG	CON
Non-CV	*Non-CV*	*6*	*2*
		Oesph ca, pleural eff, weight loss, herpes, acute cholecystitis, kidney failure	Lung Ca, aortic aneurysm
CV	*MI*	*1*	*0*
	W. CHF	*3*	*1*
	Stroke / TIA	*0*	*3*
	Atrial Arr	*0*	*0*
	Vent Arr	*0*	*0*
	Unstable angina	*0*	*0*
	Op/prod/invest	*0*	*0*
	Other	*0*	*0*

49653/211 Preliminary Data: Subject to Revision

14

AUTODATE

Post hoc - Incidence of M&M by NYHA

Priority Analysis 4
Summary of Cardiovascular Morbidity and Mortality Events by NYHA
All Randomized Patients

Response	PLACEBO NYHA I (N=54)	PLACEBO NYHA II (N=60)	ROSIGLITAZONE NYHA I (N=43)	ROSIGLITAZONE NYHA II (N=67)
All Cause Mortality or Worsening of CHF	3 (5.6%)	6 (8.3%)	2 (4.7%)	9 (13.4%)
All Cause Mortality	2 (3.7%)	3 (5.0%)	1 (2.3%)	7 (10.4%)
Cardiovascular Death	2 (3.7%)	2 (3.3%)	0	5 (7.5%)
CV Hospitalization	2 (3.7%)	12 (20.0%)	6 (14.0%)	15 (22.4%)
Worsening of CHF or Possible Worsening of CHF	1 (1.9%)	3 (5.0%)	3 (7.0%)	4 (6.0%)
Worsening of CHF	1 (1.9%)	3 (5.0%)	1 (2.3%)	4 (6.0%)
New or Worsening Oedema	3 (5.6%)	7 (11.7%)	6 (14.0%)	22 (32.8%)
New or Worsening Oedema Without Worsening of CHF or Possible Worsening CHF	2 (3.7%)	6 (10.0%)	4 (9.3%)	21 (31.3%)
New or Worsening Oedema Without Confounding Factors	2 (3.7%)	5 (8.3%)	2 (4.7%)	11 (16.4%)
New or Worsening Dyspnoea	6 (11.1%)	13 (21.7%)	7 (16.3%)	22 (32.8%)
New or Worsening Dyspnoea Without Worsening of CHF or Possible Worsening CHF	6 (11.1%)	11 (18.3%)	5 (11.6%)	20 (29.9%)
New or Worsening Dyspnoea Without Confounding Factors	2 (3.7%)	11 (18.3%)	2 (4.7%)	10 (14.9%)
Increase in CHF Medication	6 (11.1%)	14 (23.3%)	8 (18.6%)	28 (41.8%)

49653/211 Preliminary Data:
Subject to Revision

15

AUTODATE

Post hoc - Incidence of M&M by NYHA

Priority Analysis 4
Summary of Cardiovascular Morbidity and Mortality Events by NYHA
All Randomised Patients

Endpoint	PLACEBO NYHA I (N=54)	PLACEBO NYHA II (N=60)
All Cause Mortality or Worsening of CHF	3 (5.6%)	5 (8.3%)
All Cause Mortality	2 (3.7%)	3 (5.0%)
Cardiovascular Death	2 (3.7%)	2 (3.3%)
CV Hospitalisation	3 (5.6%)	12 (20.0%)
Worsening of CHF or Possible Worsening of CHF	1 (1.9%)	3 (5.0%)
Worsening of CHF	1 (1.9%)	3 (5.0%)
New or Worsening Oedema	3 (5.6%)	7 (11.7%)
New or Worsening Oedema Without Worsening of CHF or Possible Worsening CHF	2 (3.7%)	6 (10.0%)
New or Worsening Oedema Without Confounding Factors	2 (3.7%)	5 (8.3%)
New or Worsening Dyspnoea	6 (11.1%)	13 (21.7%)
New or Worsening Dyspnoea Without Worsening of CHF or Possible Worsening CHF	6 (11.1%)	11 (18.3%)
New or Worsening Dyspnoea Without Confounding Factors	2 (3.7%)	11 (18.3%)
Increase in CHF Medication	6 (11.1%)	14 (23.3%)

49653/211 Preliminary Data:
Subject to Revision

16

AUTODATE

Post hoc - Incidence of M&M by NYHA

Priority Analysis 4
Summary of Cardiovascular Morbidity and Mortality Events by NYHA
All Randomized Patients

Endpoint	PLACEBO NYHA I (N=54)	ROSIGLITAZONE NYHA I N=43)
All Cause Mortality or Worsening of CHF	3 (5.6%)	2 (4.7%)
All Cause Mortality	2 (3.7%)	1 (2.3%)
Cardiovascular Death	2 (3.7%)	0
CV Hospitalization	3 (5.6%)	6 (14.0%)
Worsening of CHF or Possible Worsening of CHF	1 (1.9%)	3 (7.0%)
Worsening of CHF	1 (1.9%)	1 (2.3%)

49653/211 Preliminary Data:
Subject to Revision

17

AUTODATE

Post hoc - Incidence of M&M by NYHA

Priority Analysis 4
Summary of Cardiovascular Morbidity and Mortality Events by NYHA
All Randomized Patients

Endpoint	PLACEBO NYHA I (N=54)	ROSIGLITAZONE NYHA I N=43)
New or Worsening Oedema	3 (5.6%)	6 (14.0%)
New or Worsening Oedema Without Worsening of CHF or Possible Worsening CHF	2 (3.7%)	4 (9.3%)
New or Worsening Oedema Without Confounding Factors	2 (3.7%)	2 (4.7%)
New or Worsening Dyspnoea	6 (11.1%)	7 (16.3%)
New or Worsening Dyspnoea Without Worsening of CHF or Possible Worsening CHF	6 (11.1%)	5 (11.6%)
New or Worsening Dyspnoea Without Confounding Factors	2 (3.7%)	2 (4.7%)
Increase in CHF Medication	6 (11.1%)	8 (18.6%)

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18

AUTODATE

Post hoc - Incidence of M&M by NYHA

Priority Analysis 4
Summary of Cardiovascular Morbidity and Mortality Events by NYHA
All Randomized Patients

Endpoint	PLACEBO NYHA II N=60)	ROSIGLITAZONE NYHA II (N=67)
All Cause Mortality or Worsening of CHF	5 (8.3%)	9 (13.4%)
All Cause Mortality	3 (5.0%)	7 (10.4%)
Cardiovascular Death	2 (3.3%)	5 (7.5%)
CV Hospitalization	12 (20.0%)	15 (22.4%)
Worsening of CHF or Possible Worsening of CHF	3 (5.0%)	4 (6.0%)
Worsening of CHF	3 (5.0%)	4 (6.0%)

49653/211 Preliminary Data:
Subject to Revision

19

AUTODATE

Post hoc - Incidence of M&M by NYHA

Priority Analysis 4
Summary of Cardiovascular Morbidity and Mortality Events by NYHA
All Randomized Patients

Endpoint	PLACEBO NYHA II N=60)	ROSIGLITAZONE NYHA II (N=67)
New or Worsening Oedema	7 (11.7%)	22 (32.8%)
New or Worsening Oedema Without Worsening of CHF or Possible Worsening CHF	6 (10.0%)	21 (31.3%)
New or Worsening Oedema Without Confounding Factors	5 (8.3%)	11 (16.4%)
New or Worsening Dyspnoea	13 (21.7%)	22 (32.8%)
New or Worsening Dyspnoea Without Worsening of CHF or Possible Worsening CHF	11 (18.3%)	20 (29.9%)
New or Worsening Dyspnoea Without Confounding Factors	11 (18.3%)	10 (14.9%)
Increase in CHF Medication	14 (23.3%)	28 (41.8%)

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20

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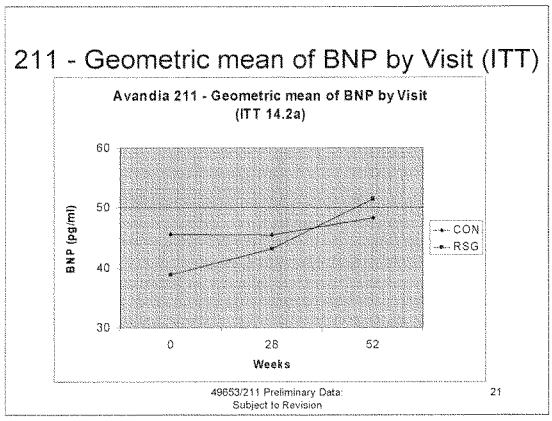

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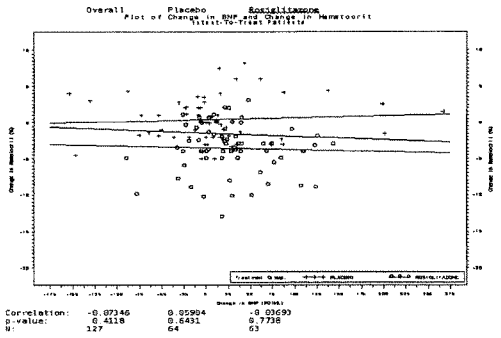
Post hoc - BNP v Haematocrit



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22

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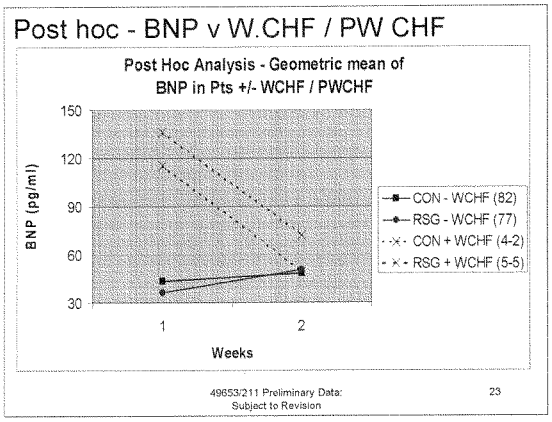

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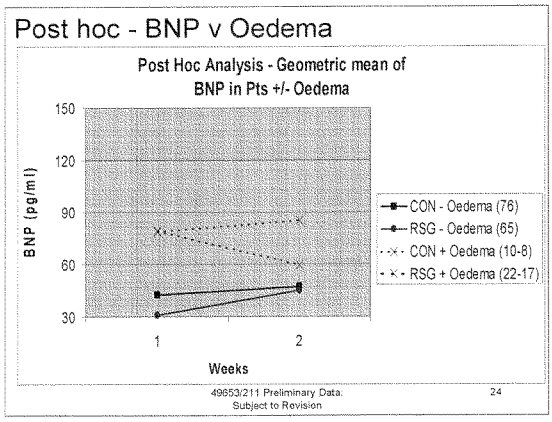
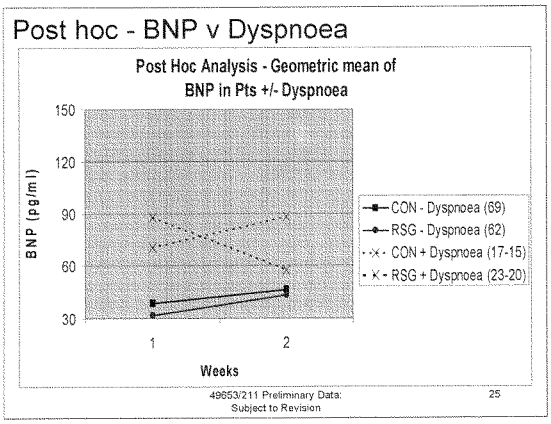

Post hoc - BNP v Oedema
Post Hoc Analysis - Geometric mean of BNP in Pts +/- Oedema
BNP (pg/ml)
150
120
90
60
30
1
2
Weeks
CON - Oedema (76)
RSG - Oedema (65)
CON + Oedema (10-8)
RSG + Oedema (22-17)
49653/211 Preliminary Data. Subject to Revision
24

AUTODATE



AUTODATE

211 - All AEs - Slide I - >4%

Data Source Table X15.2.4
Summary of On-Therapy Adverse Experiences by Preferred Term
All Randomized Patients

Any Adverse Event Preferred Term	PLACEBO (N=114)	ROSIGLITAZONE (N=110)	TOTAL (N=224)
TOTAL	74 (64.9%)	77 (70.0%)	151 (67.4%)
CARDIAC FAILURE	10 (8.8%)	19 (17.3%)	29 (12.9%)
HYPERGLYCEMIA	16 (14.0%)	2 (1.8%)	18 (8.0%)
BACK PAIN	2 (1.8%)	10 (9.1%)	12 (5.4%)
BRONCHITIS	0 (0.0%)	8 (7.3%)	8 (3.6%)
ANEMIA	0 (0.0%)	7 (6.4%)	7 (3.1%)
HYPERCHOLESTEROLEMIA	2 (1.8%)	7 (6.4%)	9 (4.0%)
PNEUMONIA	2 (1.8%)	6 (5.5%)	8 (3.6%)
DIARRHEA	6 (5.3%)	3 (2.7%)	9 (4.0%)
INJURY	6 (5.3%)	4 (3.6%)	10 (4.5%)
RESPIRATORY DISORDER	6 (5.3%)	6 (5.5%)	12 (5.4%)
UPPER RESP TRACT INFECTION	5 (4.4%)	6 (5.5%)	11 (4.9%)
COUGHING	1 (0.9%)	5 (4.5%)	6 (2.7%)
EDEMA	5 (4.4%)	5 (4.5%)	10 (4.5%)
INFECTION VIRAL	5 (4.4%)	2 (1.8%)	7 (3.1%)
DIABETES MELLITUS AGGRAVATED	5 (4.4%)	1 (0.9%)	6 (2.7%)
MYOCARDIAL INFARCTION	2 (1.8%)	5 (4.5%)	7 (3.1%)

Note - no oedema >4%

49653/211 Preliminary Data:
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26

AUTODATE

211 - SAEs (>1)

Data Source Table X15.2.3
Summary of On-Therapy Serious Non-Fatal Adverse Experiences by Preferred Term
All Randomized Patients

Any Adverse Event Preferred Term	PLACEBO (N=114)	ROSIGLITAZONE (N=110)	TOTAL (N=224)
TOTAL	17 (14.9%)	34 (30.9%)	51 (22.8%)
CARDIAC FAILURE	4 (3.5%)	6 (5.5%)	10 (4.5%)
MYOCARDIAL INFARCTION	1 (0.9%)	4 (3.6%)	5 (2.2%)
PNEUMONIA	0 (0.0%)	4 (3.6%)	4 (1.8%)
ANGINA PECTORIS AGGRAVATED	1 (0.9%)	3 (2.7%)	4 (1.8%)
CEREBROVASCULAR DISORDER	3 (2.6%)	3 (2.7%)	6 (2.7%)
CHOLECYSTITIS	0 (0.0%)	2 (1.8%)	2 (0.9%)
INJURY	1 (0.9%)	2 (1.8%)	3 (1.3%)
PULMONARY EDEMA	2 (1.8%)	1 (0.9%)	3 (1.3%)

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27

AUTODATE

211 - Comparison of AEs v Endpoints in RSG treatment group

	AEs	Endpoints
• **Cardiac failure**	19 (17.3%)	7 (6.4%)[1]
• **Oedema**	5 (4.5%)[2]	28 (25.5%)
• **Dyspnoea**	5 (4.5%)	29 (26.4%)

[1] Adjudicated "Worsening of CHF or possible worsening of CHF"
[2] oedema, oedema legs, oedema dependent, face oedema, generalised oedema and peripheral oedema

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28

AUTODATE

Post hoc - Investigate differences in numbers of AEs versus Endpoints

Two approaches

(1) JR - programmatically (but technically difficult)

(2) SM - manually (but long winded)

with the aim of compare & contrast against one another to validate both methods

49653/211 Preliminary Data: Subject to Revision 29

AUTODATE

Post hoc - differences in SAEs v Endpoints Method 2 - SM - manually

Endpoint (I) - RSG - Worsening of CHF or Possible Worsening of CHF

		Adverse Events			
	Endpoint	Cardiac failure	Oedema	Dyspnoea	Other
211.203.92971	Possible worsening of CHF	1	0	0	0
211.713.92684	Worsening of CHF	1	0	0	0
211.811.92787	Worsening of CHF	2	1	0	0
211.910.92653	Possible worsening of CHF	1	0	0	0
211.911.92578	Worsening of CHF (post-tx)	0	0	0	0
211.924.93084	Worsening of CHF	0	0	0	Pneumonia
211.950.93133	Worsening of CHF	1	0	0	0
Total	7 PIDs	5(6)	1(1)	0(0)	1(1)

# of individual pts (# of AEs)

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30

AUTODATE

Post hoc - differences in SAEs v Endpoints Method 2 - manually - Summary

Endpoint	Adverse Events			
Worsening or PW CHF	Cardiac failure	Oedema	Dyspnoea	Other
7	5(6)	1(1)	0(0)	1(1)
New or worsening oedema	Cardiac failure	Oedema	Dyspnoea	Other
28 (1post-tx)	15(18)	6(6)	4(4)	8(10)
New or worsening dyspnoea	Cardiac failure	Oedema	Dyspnoea	Other
29 (1post-tx)	17(20)	6(6)	6(6)	5(5)

49653/211 Preliminary Data: Subject to Revision

31

AUTODATE

Ischaemia -related AEs

Data Source Table X15.2.4
Summary of On-Therapy Adverse Experiences by Preferred Term - CV Terms
All Randomized Patients

Any Adverse Event Preferred Term	PLACEBO (N=114)	ROSIGLITAZONE (N=110)	TOTAL (N=224)
TOTAL	74 (64.9%)	77 (70.0%)	151 (67.4%)
MYOCARDIAL INFARCTION	2 (1.8%)	5 (4.5%)	7 (3.1%)
ANGINA PECTORIS AGGRAVATED	1 (0.9%)	4 (3.6%)	5 (2.2%)
ANGINA PECTORIS	2 (1.8%)	3 (2.7%)	5 (2.2%)
THROMBOSIS CORONARY	0 (0.0%)	1 (0.9%)	1 (0.4%)
Myocardial ischaemia	**0**	**0**	**0**
Coronary artery disorder	**0**	**0**	**0**
Cardiac arrest	**0**	**0**	**0**
	5	**13**	**18**

49653/211 Preliminary Data:
Subject to Revision

32

AUTODATE

Ischaemia -related SAEs

Data Source Table X15.2.3

Summary of On-Therapy Serious Non-Fatal Adverse Experiences by Preferred Term - CV TERMS

Any Adverse Event	PLACEBO (N=114)	ROSIGLITAZONE (N=110)	TOTAL (N=224)
TOTAL	17 (14.9%)	34 (30.9%)	51 (22.8%)
MYOCARDIAL INFARCTION	1 (0.9%)	4 (3.6%)	5 (2.2%)
ANGINA PECTORIS AGGRAVATED	1 (0.9%)	3 (2.7%)	4 (1.8%)
ANGINA PECTORIS	0 (0.0%)	1 (0.9%)	1 (0.4%)
THROMBOSIS CORONARY	0 (0.0%)	1 (0.9%)	1 (0.4%)

49653/211 Preliminary Data: Subject to Revision

33

AUTODATE

Post hoc - baseline factors for Isch AEs

MYOCARDIAL INFARCTION		Medical history
PLACEBO	**2**	
211.810.92710	MYOCARDIAL INFARCTION*	Prev MI, Artery disease (legs)
211.954.93212	ACUTE MYOCARDIAL INFARCTION	Prev MI, Angina, IHD, Hypertension
ROSIGLITAZONE	**5**	
211.403.92605	MYOCARDIAL INFARCTION	Prev MI, IHD, Hypertension, ongoing Q waves
211.652.92664	MYOCARDIAL INFARCTION	5 x prev MI, CABG, intermittent claudification
211.758.93024	MYOCARDIAL INFARCTION	Prev MI, Angina
211.972.93207	NON ST ELEVATION MI	Prev MI, Hypertension, Hyperlipidaemia, CABG
211.972.93210	ECG: OLD MYOCARDIAL INFARCTION	Prev MI, Hypertension, CABG

Summary	Prev MI	IHD/ angina	Other CV	ECG	Lipids	Other
MI - CON (2)	**2**	**1**	**2**	**0**	**0**	**0**
MI - RSG (5)	**5**	**2**	**3**	**1**	**1**	**?int claud**

* listed on fatal AES

AUTODATE

Post hoc - baseline factors for Isch AEs

Summary	Prev MI	IHD/ angina	Other CV	ECG	Lipids	Other
MI - CON (2)	2	1	2	0	0	0
MI - RSG (5)	5	2	3	1	1	?int claud
Angina Pectoris Ag - CON (1)	1	0	1	0	0	0
Angina Pectoris Ag - RSG (4)	3	4	3	0	2	0
Angina Pectoris - CON (2)	2	0	1	0	1	?endarterectomy
Angina Pectoris - RSG (3)	2	3	2	1	1	AF
Thrombo Coronary - RSG (1)	1	1	1	1	1	?pacemaker

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35

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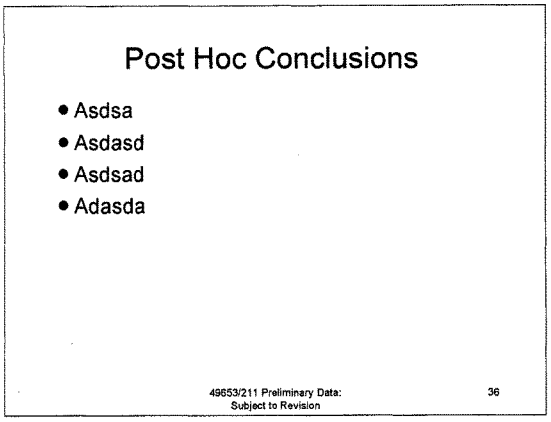
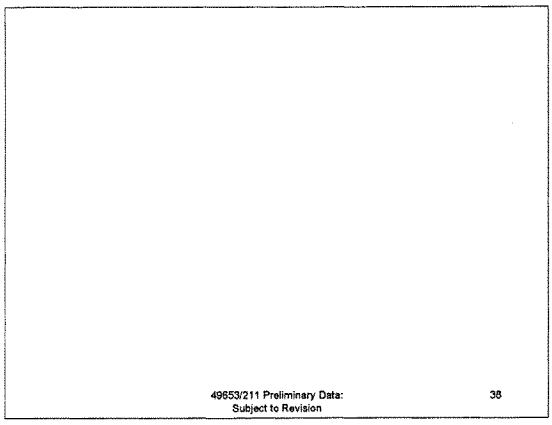


AUTODATE

Questions

- Does group agree with conclusions drawn?
- What impact does post hoc data have on the company position and Avandia label?
- Do we need to present data to Global Safety Board

AUTODATE



AUTODATE

211 - Change in NYHA grade

Data Source Table 14.10A

Summary of NYHA Grading

Intent-to-Treat Patients with LOCF

		PLACEBO	ROSIGLITAZONE
CHANGE FROM SCREENING TO WEEK 52	N	103	95
	Worsening	18 (17.5%)	16 (16.8%)
	No change	81 (78.6%)	74 (77.9%)
	Improvement	4 (3.9%)	5 (5.3%)

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39

AUTODATE

Post hoc - NYHA transitions

NYHA Transition from Screening to Week 52
ITT with LOCF

Screening	Week 52	PLACEBO	ROSIGLITAZONE
1	.	2	6
1	1	33	24
	2	13	8
	3	0	0
	4	0	0
2	.	5	7
2	1	4	5
	2	48	50
	3	4	8
	4	1	0

49653/211 Preliminary Data:
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40

FOOTNOTE 83

Avandia 211 CHF study – Review of Study Results

Feedback from Professor John McMurray
Chairman of independent 211 CEC

Thursday 3rd June 2004

Overview
On 3rd June, Steve McMorn (SM), study leader of the 211 study was scheduled to meet with Professor John McMurray (JMcM), chairman of the independent clinical endpoint committee, to present the result of the Avandia 211 CHF study. However, due to air traffic control computer problems, SM was unable to travel to Glasgow and the results were reviewed and discussed over the telephone.

Feedback from JMcM
Overall, JMcM was disappointed with the results from the 211 study. JMcM was expecting some 'benign' fluid-retention but he was not expecting increased BNP or dyspnoea which concerned him in light of increased CV medications. JMcM said there was more worsening of CHF in the RSG group compared to control 'whichever way the results were presented,' although the RSG group were disadvantaged by worse cardiac function at baseline.

With regard to CV mortality and morbidity data, JMcM said that the results were 'almost identical' to the results he had seen from a previous glitazone study as a member of their DSMB with increased CV events, hospitalisations and ischaemic events. JMcM said he felt this was a class effect as a result of reduced oxygen carrying capacity as a result of haemodilution due to fluid-retention.

Whilst discussing the impact of fluid-retention on the function of the heart, JMcM said there was no starling mechanism in this population and increased pre-load due to fluid-retention would not result in increased cardiac output in these patients.

JMcM was interested in the interaction between EF and NYHA grade due to the highly significant P value. JMcM thought interaction analyses were 'weak' tests and, as such, it was usual to use a P value of less 0.1. Therefore, with a P value of less than 0.01 for the interaction between EF and NYHA grade, JMcM felt this may be a real effect.

When asked how these results would influence his prescribing habits in the future, JMcM replied these data would not stop him prescribing RSG in this population as 211 was only a small study and it was important not to over-interpret the data. JMcM would continue to use RSG as a second or third line therapy whilst taking appropriate cautions.

JMcM felt the 211 study was too small with too many worrying trends to be used by GSK to lift the CHF contraindication in the current European license. JMcM thought the results were positive in patients with NYHA class 1 CHF but the data was not sufficient to change the current indication as regulators are generally very cautious.

With regard to publications, JMcM felt GSK should target 'mid-range' journals.

FOOTNOTE 86

Summary of the feedback from the Advisory Board Meeting held on June 23rd, 2004 the Philadelphia Airport Marriott to discuss Study Protocol 211

The advisors were:

Chris O'Connor, M.D.
Professor of Medicine
Director of Heart Failure
Duke University

Marc Semigran, M.D.
Associate Professor of Medicine
Harvard Medical School
Director of Heart Failure
Massachusetts General Hospital

Richard Shannon, M.D.
Professor and Chairman Department of Medicine
Allegheny General Hospital in Pittsburgh

In attendance from GSK were:

Jim Carr, US Marketing for Avandia
Alexander Cobitz, M.D., Ph.D., Sr. Director, Clinical Development and Medical Affairs
Martin Freed, M.D., VP, Clinical Development and Medical Affairs
Shamik Parikh, M.D., Clinical Development and Medical Affairs
Andrew Zambanini, M.D., European Clinical Development
Steve McMorn, M.D., Lead Study Manager, European Clinical Development
Stuart Magargee, Senior Counsel, GSK US Legal Operations
Sean Roberts, Asst. General Counsel, GSK R&D Legal Operations
Shannon Stevens, GSK Professional Meetings Planner

The consultants related that the echo data does appear to show that there is no adverse effect on the structure of the heart. They also agreed that the increase in ejection fraction (EF) is probably not clinica significant. Concern was raised that an increase in EF could turn out to be negative if it reflects a positiv inotropic effect on the heart. One of the advisors alluded to a pre-clinical study by Faruse showing that t TZD class may have a calcium sensitizing effect. If this is true in humans, the increase in EF would probably be a negative finding. This concern seemed to fade when the LV volume data was reviewed a showed that there was no increase in LV volumes over the 52 week study. An increase in volumes may have predicted a negative myocardial effect. Overall, the advisors seemed to feel that there was no evidence of an adverse effect on the structure of the heart. There was speculation that the increase in t E:A ratio may have been caused by an increase in preload (fluid retention).

There was disappointment verbalized about the morbidity and mortality table that showed there were ter ischemia-related adverse events in the rosiglitazone group versus five events in the placebo group. On advisor pointed out that he would have expected the rosiglitazone group to have fewer events based on antiinflammatory effects of TZDs on the vasculature.

There was considerable discussion about the incidence of edema observed in the trial. Dr. Shannon expressed concern over the incidence because patients on insulin therapy or who are renally insufficien were excluded from the study. Therefore, the edema incidence seems to contradict the belief that eden typically occurs predominantly in high risk patients, i.e. in patients that possess the aforementioned risk factors. Some of the concern was dispelled with the realization that the 52-week trial involved a longer duration of follow up than has ever been reported previously. That is, the longer the duration of follow u likely led to a higher accrual of complications related to fluid retention. All three advisors felt that the ver aggressive follow up and management of edema likely prevented the patients from "tipping over" into cardiac failure. However, the patients were seen monthly, which is far more frequent than is typical in h failure trials. In routine clinical practice, this type of follow up is not realistic so there was some discussi about the ability of physicians to detect signs of edema and manage it before it led to worsening heart failure. There was also concern expressed about the incidence of dyspnea in the rosiglitazone group as this is a symptom that may reflect a worsening of pulmonary congestion.

There was considerable optimism about the potential ability to predict which patients might develop ede by the use of brain natriuretic peptide (BNP) assessments. The BNP data revealed that the patients tha were most likely to develop edema had high BNP levels at baseline, likely reflective of the fact that they were already fluid overloaded before starting on therapy. This was also observed in the patients that received placebo. However, there was disappointment raised about the lack of BNP assessments at the time the event was reported. Dr. O'Connor suggested that we do a multivariate analysis to look for predictors of worsening heart failure. His belief is that BNP will be quite predictive of edema. There wa also a recommendation to interrogate the data to determine if patients that developed edema were receiving a higher dose of rosiglitazone. The advisors speculated that patients that developed edemato complications were probably receiving the 8mg dose.

Dr. Shannon found unusual that there was an increase in edema and cardiac events despite the fact tha there was a significant improvement in glycemic control in the rosiglitazone arm of the trial. He thought the glycemic control and pleiotrophic effects of rosiglitazone would have predicted a different outcome th what was observed. The advisors agreed that the trial was just too small and that there were too few endpoints to speculate as to the ability of rosiglitazone to improve M&M in this population.

There was a general discussion about the implication of these findings which resulted in a minor debate about the management of these patients. Dr. O'Connor pointed out that management likely includes the aggressive use of diuretics to manage fluid retention and this may produce unfavorable outcomes in patients. He alluded to the finding in the SOLVD trial that showed that higher doses of diuretics led to increased mortality. Dr. Shannon believes that the trial will help to define the boundaries that should not crossed when using TZDs in the setting of heart failure. There was agreement that the trial showed resu that seem consistent with the statement that was made by the ADA/AHA last year. However, the advisc don't agree with the recommendation that patients should only be monitored closely for the first 3 month as the 211 trial showed that edema occurred throughout the course of the trial.

FOOTNOTE 88

Rosiglitazone

Further Interim Results from Retrospective Analysis of Cardiovascular Events in Clinical Trials

DRAFT

Date:

TABLE OF CONTENTS

1. Executive Summary

Will be completed in a later draft

2. introduction

As part of GSK's ongoing monitoring and assessment of the safety of rosiglitazone, an analysis was undertaken to evaluate the association (if any) between rosiglitazone and events of CHF and myocardial ischemia across the clinical trial program using statistical methodology which accounts for some of the important patient characteristics and pre-existing conditions that have been shown to impact overall risk for these cardiac events. An initial analysis was conducted on the cohort of type 2 diabetic patients enrolled in the GSK-sponsored double-blind, controlled studies that utilized total daily doses of 4 mg or 8 mg of rosiglitazone and had statistical analyses finalized on or before September 30, 2004. This preliminary analysis and preliminary conclusions were submitted on October 13, 2005, and subsequently on December 15, 2005, a CBE supplement was submitted which provided additional language in the US prescribing information regarding cardiac failure in patients receiving rosiglitazone in sulfonylurea combinations.

Subsequent to the submission of preliminary results, GSK has performed additional exploratory work in an effort to more fully understand the events related to myocardial ischemia. These further analyses included

- Analysis of an expanded cohort of patients, i.e inclusion of patients from clinical trials that completed after September 30, 2004. The expanded cohort included approximately 2800 additional patients from 5 additional studies. Exact logistic analyses for both CHF and events related to myocardial ischemia were conducted on the expanded datatset.
- A recursive partitioning method was utilized for an exploratory risk factor analysis to identify factors which may identify high-risk subgroups of patients. The analysis was first conducted on the original cohort of patients. For the expanded cohort, the incidence of events related to myocardial ischemia were summarized for the subgroups identified by the recursive partitioning method on the original dataset Hazard ratios for RSG vs non-RSG were also evaluated.

The summary results of these additional analyses are provided in this document.

3. Exact Logistic Analyses on the expanded dataset

The expanded dataset included 5 studies that completed prior to xxxx approximately an additional 2,800 patients to the 11,600 in the original cohort including approximately 1,200 newly diagnosed type 2 diabetes patients. These studies were double-blind, controlled studies of 24-32 weeks duration.

3.1. CHF

The output of the original analyses using the expanded dataset is consistent with that from the original dataset. Tables 1 and 2 below show the odds ratio point estimate and 95% confidence interval for both datasets, as well as the number of events and total number of patients for each treatment regimen using the updated integrated dataset.

Table 1 CHF SAEs – Results from Exact Logistic Regression Analysis

		Exact Logistic Analysis—Odds Ratio Point Est. (95% CI)		Updated Integrated Dataset: Events / Patients (%)	
RSG Treatment Regimen	Control Group	Original Integrated Data	Updated Integrated Data	RSG	Control
RSG mono	Placebo	0.24 (<0.01, 4.70)	0.25 (<0.01, 4.75)	1 / 1737 (0.06%)	2 / 792 (0.25%)
RSG mono	SU or Met mono	0.17 (0.00, 1.32)	0.23 (<0.01, 2.14)	1 / 1127 (0.09%)	5 / 1001 (0.50%)
RSG + Met	Met mono	0.93 (0.00, 36.46)	0.95 (0.01, 75.20)	1 / 1608 (0.06%)	1 / 1419 (0.07%)
RSG + Met	Met + SU	0.60 (0.00, 8.28)	0.60 (0.00, 8.28)	0 / 285 (0.00%)	2 / 294 (0.68%)
RSG + SU	SU mono	1.08 (0.40, 2.95)	1.04 (0.39, 2.86)	11 / 2505 (0.44%)	9 / 1926 (0.47%)
RSG + Met + SU	Met + SU	3.15 (0.35, 150.52)	3.15 (0.35, 150.52)	5 / 597 (0.84%)	1 / 310 (0.32%)
RSG + Insulin	Insulin mono	1.54 (0.49, 5.68)	1.63 (0.52, 6.01)	11 / 867 (1.27%)	5 / 663 (0.75%)

Table 2 CHF all AEs (serious and non-serious) – Results from Exact Logistic Regression Analysis

		Exact Logistic Analysis—Odds Ratio Point Est. (95% CI)		Updated Integrated Dataset: Events / Patients (%)	
RSG Treatment Regimen	Control Group	Original Integrated Data	Updated Integrated Data	RSG	Control
RSG mono	Placebo	0.45 (0.03, 6.22)	0.46 (0.03, 6.40)	2 / 1737 (0.12%)	2 / 792 (0.25%)
RSG mono	SU or Met mono	0.26 (0.03, 1.25)	0.38 (0.07, 1.48)	3 / 1127 (0.27%)	11 / 1001 (1.10%)
RSG + Met	Met mono	0.55 (0.05, 4.90)	0.70 (0.10, 4.12)	3 / 1608 (0.19%)	4 / 1419 (0.28%)
RSG + Met	Met + SU	0.95 (0.08, 6.97)	0.95 (0.08, 6.97)	2 / 285 (0.70%)	4 / 294 (1.36%)
RSG + SU	SU mono	1.53 (0.78, 3.12)	1.54 (0.79, 3.12)	27 / 2505 (1.08%)	15 / 1926 (0.78%)

RSG + Met + SU	Met + SU	4.36 (0.98, 40.00)	4.36 (0.98, 40.00)	13 / 597 (2.18%)	2 / 310 (0.65%)
RSG + Insulin	Insulin mono	2.16 (0.88, 6.03)	2.26 (0.92, 6.29)	21 / 867 (2.42%)	7 / 663 (1.06%)

3.2. Myocardial Ischemia

The output of the original analyses using the expanded dataset is consistent with that from the original dataset. Tables 3 and 4 below show the odds ratio point estimate and 95% confidence interval for both datasets, as well as the number of events and total number of patients for each treatment regimen using the updated integrated dataset.

Table 3 Myocardial Ischemia SAEs – Results from Exact Logistic Regression Analysis

		Exact Logistic Analysis—Odds Ratio Point Est. (95% CI)		Updated Integrated Dataset: Events / Patients (%)	
RSG Treatment Regimen	Control Group	Original Integrated Data	Updated Integrated Data	RSG	Control
RSG mono	Placebo	1.79 (0.59, 7.31)	2.03 (0.67, 8.24)	19 / 1737 (1.09%)	4 / 792 (0.51%)
RSG mono	SU or Met mono	1.63 (0.50, 5.78)	1.20 (0.46, 3.21)	11 / 1127 (0.98%)	10 / 1001 (1.00%)
RSG + Met	Met mono	3.58 (0.71, 34.88)	3.33 (0.88, 18.63)	11 / 1608 (0.68%)	3 / 1419 (0.21%)
RSG + Met	Met + SU	1.03 (0.21, 4.48)	1.03 (0.21, 4.48)	4 / 285 (1.40%)	6 / 294 (2.04%)
RSG + SU	SU mono	1.31 (0.67, 2.62)	1.08 (0.57, 2.07)	25 / 2505 (1.00%)	19 / 1926 (0.99%)
RSG + Met + SU	Met + SU	1.26 (0.29, 7.61)	1.26 (0.29, 7.61)	7 / 597 (1.17%)	3 / 310 (0.97%)
RSG + Insulin	Insulin mono	2.23 (0.68, 9.52)	2.29 (0.69, 9.77)	12 / 867 (1.38%)	4 / 663 (0.60%)

Table 4 Myocardial Ischemia all AEs (serious and non-serious) – Results from Exact Logistic Regression Analysis

		Exact Logistic Analysis—Odds Ratio Point Est. (95% CI)		Updated Integrated Dataset: Events / Patients (%)	
RSG Treatment Regimen	Control Group	Original Integrated Data	Updated Integrated Data	RSG	Control

RSG mono	Placebo	1.05 (0.52, 2.25)	1.15 (0.58, 2.46)	32 / 1737 (1.84%)	12 / 792 (1.52%)
RSG mono	SU or Met mono	1.21 (0.59, 2.53)	1.13 (0.60, 2.11)	25 / 1127 (2.22%)	22 / 1001 (2.20%)
RSG + Met	Met mono	1.89 (0.67, 6.10)	2.72 (1.17, 7.03)	23 / 1608 (1.43%)	8 / 1419 (0.56%)
RSG + Met	Met + SU	1.25 (0.34, 4.47)	1.25 (0.34, 4.47)	6 / 285 (2.11%)	7 / 294 (2.38%)
RSG + SU	SU mono	1.23 (0.80, 1.88)*	1.09 (0.72, 1.65)*	53 / 2505 (2.12%)	39 / 1926 (2.02%)
RSG + Met + SU	Met + SU	1.80 (0.55, 7.63)	1.80 (0.55, 7.63)	13 / 597 (2.18%)	4 / 310 (1.29%)
RSG + Insulin	Insulin mono	2.02 (0.90, 4.94)	2.07 (0.93, 5.07)	24 / 867 (2.77%)	9 / 663 (1.36%)

4. Exploratory risk factor analysis for myocardial ischemia events

4.1. Exploratory Analyses Using Recursive Partitioning Method

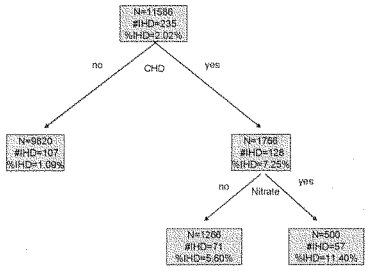
In order to assess whether there is any subgroup(s) of patients at particular risk for a myocardial ischemic event, an exploratory analysis using Recursive Partitioning methodology was conducted on the original dataset. This newer methodology is generally most useful for hypothesis generation and also uses all available data; however, after the initial identification of subgroups of interest, a single comparison between all RSG and all control was performed in each subgroup as opposed to the previous analyses which provided comparison relative to each control group(s).

The endpoint used for the Recursive Partitioning analysis was the time to myocardial ischemia events (both AEs and SAEs). Based on important baseline patient characteristics, this method identifies patient subgroups with different levels of risk. The candidate baseline characteristics included major cardiovascular risk conditions, other cardiovascular risk conditions for myocardial ischemia, use of cardiovascular medications, prior therapy for diabetes, duration of diabetes, study timing, baseline laboratory measures (Hematocrit, Fasting Glucose, HbA1c, HDL, LDL, Triglycerides, total Cholesterol/ HDL ratio), blood pressure, BMI, age and gender. Within each subgroup identified by the Recursive Partitioning analysis, a Cox proportional hazard model was performed to obtain the hazard ratio for myocardial ischemia events for RSG-treated patients relative to non-RSG treated patients.

The results of the first stage of this exploratory analysis are shown in Figure 1. The best single predictor of on-therapy events of myocardial ischemia was the presence of pre-existing coronary heart disease (CHD). Within patients who had pre-existing CHD, the best predictor of ischemic events was whether a patient was taking concomitant nitrates at screening. Note that subgroup identification was performed without consideration of

whether a patient was treated with RSG.

Figure 1 Subgroup Identification from Recursive Partitioning Analysis



N = Number of Patients in Subgroup

#IHD = Number of Patients with On-therapy Ischaemic Event

%IHD = (#IHD / N) x 100%

Table 5 displays the results of the second stage of the exploratory analysis. Within each of the three subgroups identified above, a Cox proportional hazards regression was performed to compare the risk of ischemic events for RSG vs. control. For the first two sub-groups, those identifying low and middle risk subgroups, the hazard ratio is close to one and the confidence interval overlaps 1. However, the hazard ratio for the high risk subgroup, patients with pre-existing CHD who were taking nitrates at screening, was elevated, with a point estimate of 2.45 and 95% confidence interval of (1.34, 4.49). This suggests that patients within this subgroup who received RSG may have an elevated risk of ischemic events relative to patients within this subgroup who did not take RSG.

Table 5 **Ischemia All AEs (serious and non-serious) – Results from Cox Proportional Hazards Regression Analysis**

Recursive Partitioning Subgroup	Hazard Ratio Point Estimate (95% CI)	RSG Events / Patients (%)	Control Events / Patients (%)
No pre-existing CHD	1.25 (0.84, 1.87)	71 / 5933 (1.20%)	36 / 3887 (0.93%)
Pre-existing CHD, no nitrates	1.08 (0.67, 1.74)	42 / 745 (5.64%)	29 / 521 (5.57%)
Pre-existing CHD, with nitrates	2.45 (1.34, 4.49)	43 / 298 (14.43%)	14 / 202 (6.93%)
Overall	1.29 (0.99, 1.69)	156 / 6976 (2.24%)	79 / 4610 (1.71%)

The observations from the expanded integrated dataset are consistent with the original integrated dataset which identify patients with pre-existing CHD who are taking nitrates at study baseline as a potential group at risk of ischemic events.

Table 6 Ischemia all AEs (serious and non-serious) – Results from Proportional Hazards Regression in Recursive Partitioning Subgroups

	Proportional Hazards Regression—Hazard Ratio Point Est. (95% CI)		Updated Integrated Dataset: Events / Patients (%)	
Recursive Partitioning Subgroup	Original Integrated Data	Updated Integrated Data	RSG	Control
No pre-existing CHD	1.25 (0.84, 1.87)	1.42 (0.96, 2.11)	81 / 7395 (1.10%)	36 / 4788 (0.75%)
Pre-existing CHD, no nitrates	1.08 (0.67, 1.74)	1.06 (0.68, 1.65)	47 / 886 (5.30%)	33 / 622 (5.31%)
Pre-existing CHD, with nitrates	2.45 (1.34, 4.49)	2.14 (1.20, 3.81)	43 / 323 (13.31%)	16 / 223 (7.17%)
Overall	1.29 (0.99, 1.69)	1.31 (1.01, 1.70)	171 / 8604 (1.99%)	85 / 5633 (1.51%)

4.2. Exploration of Types of Events

It is important to note that none of the events were adjudicated prospectively by an expert panel and that the aim of retrospective review of study narratives was to group these events under a general category of myocardial ischemia. Any attempt to adjudicate whether the reported preferred term was indeed correct would have been flawed by the lack of key clinical data (ECGs, cardiac enzyme changes, etc.) available to the reviewers, since such data was not collected during all clinical trials. Thus Table 7, Table 9 and Table 10 represent a list of unadjudicated events.

The number of myocardial ischemic events with fatal outcome was low, with no appreciable difference between overall incidence in RSG-treated patients and control patients (Table 7). Of the serious AEs relating to myocardial ischemia in the subgroup with a history of CHD and taking nitrates at baseline, there were small numerical differences between the treatment groups in the incidence of events such as angina pectoris aggravated and myocardial infarction (Table 8). No individual preferred term contributed the majority of serious AEs in either the RSG or control group.

Table 7 Reports of fatal events of myocardial ischemia by recursive

partitioning subgroup

	RSG		Control	
Subgroup	Events/patients	%	Events/patients	%
No CHD	9 / 7395	0.12	1 / 4788	0.02
CHD without nitrates	1 / 886	0.11	2 / 622	0.32
CHD with nitrates	2 / 323	0.62	3 / 223	1.35
All Patients	12 / 8604	0.14	6 / 5633	0.11

Table 8 Myocardial ischemia serious AEs by preferred term: subjects with CHD taking nitrates (original dataset)

Preferred Term	All RSG (N = 298)		All Control (N = 202)	
	n	%	n	%
Patients with event	20	6.7	8	4.0
Angina pectoris	5	1.7	2	1.0
Angina pectoris aggravated	5	1.7	0	
Angina unstable	1	0.3	0	
Cardiac arrest	0		1	0.5
Chest pain	0		1	0.5
Coronary artery disease	0		1	0.5
Coronary artery occlusion	1	0.3	0	
Myocardial infarction	8	2.7	3	1.5
Myocardial ischemia	1	0.3	0	
Thrombosis coronary	1	0.3	0	

Table 9 includes all (both serious and non-serious) AEs of myocardial ischemia in the subgroup with CHD and taking nitrates. There were generally more non-serious AEs of angina and ischemic chest pain in the group treated with RSG. No individual preferred term contributed the majority of non-serious AEs in either the RSG or control group.

Table 9 Myocardial ischemia serious and non-serious AEs by preferred term: subjects with CHD taking nitrates (original dataset)

Preferred Term	All RSG (N = 298)		All Control (N = 202)	
	n	%	n	%
Patients with event	43	14.4	14	6.9

Angina pectoris	18	6.0	5	2.5
Angina pectoris aggravated	14	4.7	2	1.0
Angina unstable	1	0.3	0	
Cardiac arrest	0		1	0.5
Chest pain	5	1.7	2	1.0
Coronary artery disease	1	0.3	1	0.5
Coronary artery disorder	2	0.7	0	
Coronary artery occlusion	1	0.3	0	
Dyspnoea	1	0.3	0	
Myocardial infarction	8	2.7	3	1.5
Myocardial ischemia	2	0.7	0	
Thrombosis coronary	1	0.3	0	

4.3. Baseline characteristics of CHD patients who were using nitrates at study start

The baseline characteristics of patients from the updated dataset with a history of CHD who were taking nitrates at baseline are shown in Table 10. This patient population is representative of a high risk population with severe CHD being generally male, elderly, with a long history of diabetes, using multiple CV medications, and with evidence of cardiovascular disease other than CHD. Importantly, while treated according to standard practice in place at the time, this population was sub-optimally treated for their CV disease according to current guidelines since approximately 30% of patients were not taking an antiplatelet agent and more than 50% were not receiving statin therapy. Furthermore, while appropriate at the time, the use of beta-blockers was sub-optimal according to current practice as these agents are now recommended as first line medical therapy in patients with symptomatic myocardial ischemia. Of interest is the relatively high rate of background CHF in this population particularly in the RSG group, which is mirrored by a similar frequency of use of loop diuretics.

Table 10 Baseline characteristics of CHD patients taking nitrates (expanded dataset)

	RSG Patients	Control Patients
	N=223	N=323
Age (yr; mean±SD)	65.2±8.06	64.4±7.81
Males (%)	72	68
Taking 3 or more CV meds n(%)	195 (87%)	285 (88%)
ACEI or ARB	115 (51.6%)	157 (48.6%)
CCB	67 (30.0%)	141 (43.7%)
Beta-blocker	113 (50.7%)	140 (43.3%)
Loop diuretic	49 (22.0%)	72 (22.3%)
Antiplatelet agent	146 (65.5%)	227 (70.3%)
Statin	105 (47.1%)	150 (46.4%)

Median duration of diabetes (yrs)	6	7
Serum creatinine (mg/dL; mean±SD)	90.8±33.27	90.5±33.98
Additional major CV risk (% with at least one)		
Cerebrovascular disease (%)	22 (9.9%)	23 (7.7%)
CHF (%)	52 (23.3%)	54 (16.7%)
Peripheral Vascular Disease (%)	40 (17.9%)	62 (19.2%)

4.4. Exploration of Relationship Between Type of Nitrate and the Occurrence of Future Myocardial Ischemic Events

In clinical practice, patients with CHD and intermittent angina may typically be prescribed a short-acting nitrate such as glyceryl trinitrate for PRN use. However, patients with more severe and frequent symptoms are likely to be prescribed a longer acting agent, such as isosorbide dinitrate, which should be used daily in order to prevent the onset of anginal symptoms. Table 11 shows an approximate two-fold higher incidence of myocardial ischemic events in the RSG-treated patients compared to the control group irrespective of whether nitrates were used intermittently or regularly, or in combination. The frequency of events in the RSG group was similar irrespective of whether nitrates were used intermittently or regularly.

Table 11 Myocardial ischemia serious and non-serious AEs by type of nitrate: subjects with CHD taking nitrates (original dataset)

Nitrate	Treatment group	N	Patients with events	
			n	%
PRN nitrates	control	67	6	9.0
REG nitrates		105	5	4.8
Both PRN and REG nitrates		30	3	10.0
PRN nitrates	RSG	84	11	13.1
REG nitrates		165	20	12.1
Both PRN and REG nitrates		49	12	24.5

5. Exploration of Potential On-Therapy Predictors of Events Related to Myocardial ischemia

Evaluation of potential on-therapy predictors for myocardial ischemic events included review of AEs of edema, laboratory values for haematocrit, weight, and blood pressure. To summarize, there were small differences in the mean changes from baseline in both weight and hematocrit between patients who developed myocardial ischemic events and those who did not, suggesting that small differences identified in the degree of fluid retention could potentially be contributing to the development of myocardial ischemic events in patients with severe coronary heart disease. However, none of these markers of

fluid retention were robust enough to guide changes in the clinical management of individual patients.

For numeric variables (hematocrit, weight, SBP, DBP), summary statistics by visit for change from baseline were produced for RSG vs. control patients further subdivided according to whether patients had an on-therapy event of myocardial ischemia. To partially account for different sets of patients contributing data at each of the visits, summary statistics based on a multivariate linear (i.e., repeated measures) model were produced. Adjusted means at each visit were obtained from a model which includes data from all on-therapy visits and was conducted using PROC MIXED in SAS. Correlations among repeated measurements within subjects were modeled. Group, visit, group*visit interaction and baseline*visit were treated as fixed effects in the model, where visit was treated as the repeated variable within a patient; patient, group and visit were treated as class variables.

Adjusted mean changes from baseline for hematocrit, weight, SBP, and DBP are presented in Figure 2 to Figure 4. For RSG patients with on-therapy events of myocardial ischemia vs. RSG patients without on-therapy myocardial ischemia, a small directional trend was noted for weight and hematocrit. No differences were observed for SBP or DBP

Figure 2 **Response Profile for mean change from baseline in weight; all patients (standard error bars shown)**

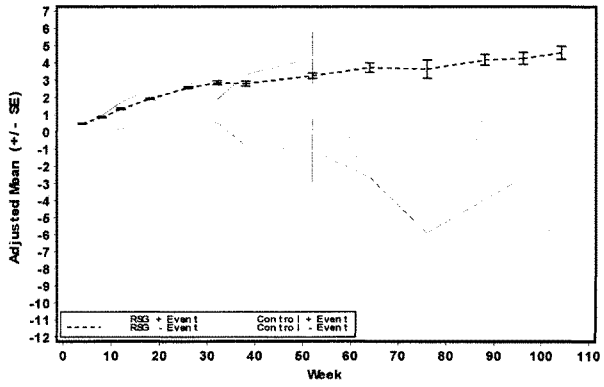


Figure 3 **Response profile for change from baseline in hematocrit; all patients (standard error bars shown)**

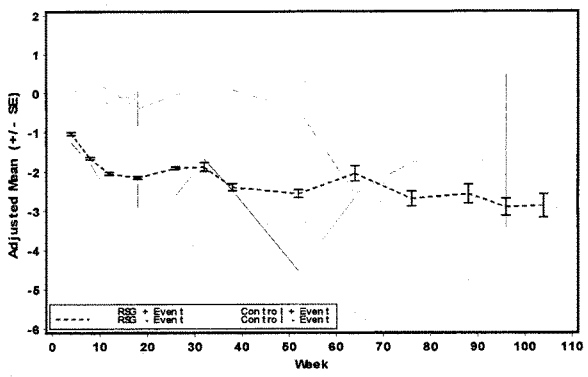


Figure 4 Response profile for change from baseline in diastolic blood pressure; all patients (standard error bars shown)

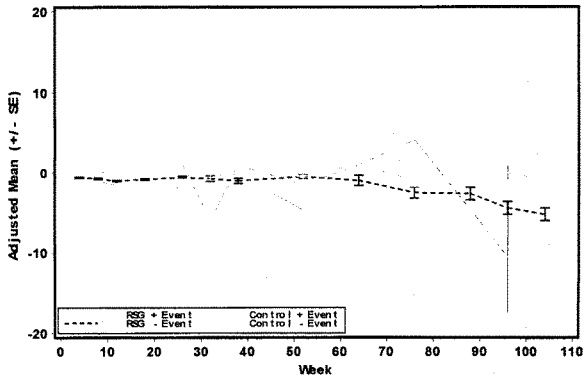
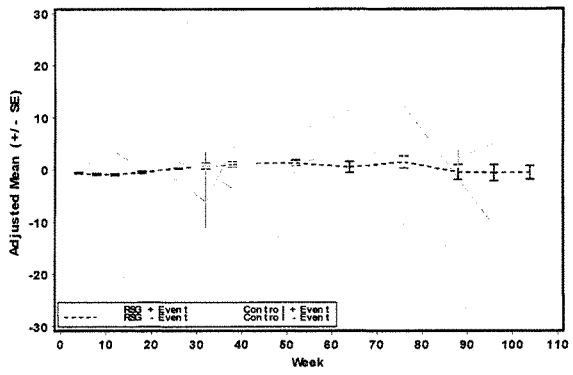
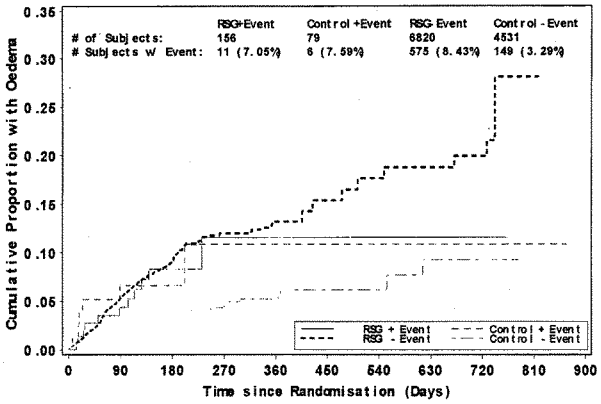


Figure 5 **Response profile for change from baseline in systolic blood pressure; all patients (standard error bars shown)**



Cumulative incidence plots for on-therapy AEs of edema within the subgroups of patients described above were also produced (Figure 6). The incidence of edema for RSG patients with on-therapy events of myocardial ischemia was very similar to incidence for RSG patients without on-therapy events of myocardial ischemia. However, incidence of edema was higher for control patients who subsequently experienced on-therapy events of myocardial ischemia than for control patients who did not.

Figure 6 **Cumulative incidence plot of edema; all patients**



While the outputs shown above allow for a qualitative assessment of potential on-therapy predictors, proportional hazards regression with time-dependent covariates allows for a more formal statistical assessment. This regression model allows the risk of an event to depend on covariates which assume different values over time. The covariates considered were change from baseline in hematocrit, change from baseline in weight, change from baseline in SBP, change from baseline in DPB, and AEs of edema. A stepwise variable selection algorithm using the proportional hazards regression model was performed to indicate which, if any, of these five on-therapy candidate variables has potential predictive value. The statistical analysis forced a term for treatment (RSG vs. control) into the model, and then performed stepwise variable selection on the five on-therapy candidate variables.

The stepwise variable selection procedure based on all patients selected three variables: AEs of edema (p=0.0094), hematocrit reduction from baseline (p=0.0314) and DBP increase from baseline (p=0.0367). Note that inclusion of AEs of edema in the model was driven by control patients. There was a small numerical change in the hazard ratio for RSG vs. control patients in the model adjusting for edema, hematocrit and DBP relative to the model without adjustment and is shown in Table 12. The adjustment for the variables identified by stepwise regression did not appreciable impact the overall results.

Table 12 Hazard Ratios for RSG vs. Control Patients Based on Proportional Hazard Regression

Terms Included in Model	Hazard Ratio Point Estimate (95% Confidence Interval)

Treatment	1.29 (0.99, 1.69)
Treatment, On-therapy edema, Hct, DBP	1.18 (0.89, 1.56)

A final exploratory summary was performed to help assess the potential impact of using incidence of on-therapy edema and various discrete cut-off values for the continuous candidate variables which were selected in the model. Positive predictive value (PPV) was calculated across a range of potential cut-off values. PPV is the proportion of patients with a positive result for a predictor variable who actually go on to have an event of myocardial ischemia. In all cases, PPV was less than 4%, indicating that predictive value of these on-therapy parameters is poor for myocardial ischemia.

The plots of change from baseline over time, plots of cumulative incidence of edema, and stepwise proportional hazards regression were similarly performed within the subset of patients with pre-therapy CHD who were taking nitrates, as well as the other two recursive partitioning subgroups. Results are not provided in this document, since they do not provide any additional insights regarding potentially useful on-therapy predictors of myocardial ischemia.

6. Other data currently available

6.1. Epidemology Data: TZDs and Ischemic Heart Disease

GSK has initiated an epidemiology study to further investigate the observations from the statistical modelling of the integrated clinical trial data. GSK believes this epidemiology study is important as the recursive partitioning is an exploratory exercise which warrants independent confirmation in another dataset to substantiate these observations. Additionally, the integrated clinical trial data are generally of 6 month duration, and epidemiology data will provide longer term outcomes with respect to myocardial ischemia in a broad and representative population with Type 2 diabetes.

There are only a limited number of epidemiological studies (one article and abstracts presented at scientific meetings) examining the relationship between TZDs and the risk of Ischemic Heart Disease (IHD) currently available. Although somewhat conflicting, these published observational studies have generally not demonstrated an increased risk of ischemic events among users of TZDs.

Sauer et al. (2006) conducted a case-control study of first myocardial infarction (MI) in hospitals in 5-counties of the Philadelphia metropolitan area during a 56 month period. After adjustment for confounders (age, gender, angiotensin-converting enzyme inhibitor use, body mass index, and history of hypertension or hypercholesterolemia), the odds ratio for MI for current monotherapy with thiazolinedione (TZD) compared with monotherapy with sulfonylurea was 0.33 (95% confidence interval 0.12 to 0.92, p = 0.03). The odds ratio for MI for current monotherapy with TZD compared with monotherapy with metformin was 0.67 (95% confidence interval 0.22 to 2.06, p = 0.48). The addition of a

TZD, but not metformin, to sulfonylurea monotherapy was associated with a significant reduction in MI risk compared with sulfonylurea therapy alone (odds ratio= 0.35; 95% confidence interval =0.13–0.95; p=0.04). The authors concluded that the use of insulin-sensitizing drugs is associated with a significantly reduced risk of MI compared with sulfonylurea use, and the addition of a TZD to sulfonylurea monotherapy is associated with a lower risk of MI.

Koro et al. (2004) conducted a case-control study to determine whether TZDs alter the risk of MI compared to traditional antidiabetic agents using Integrated Healthcare Information Services (IHCIS) managed care database from 1997 and 2002. Two hundred and twenty nine incident cases of MI hospitalizations were matched to 1,374 controls on age, gender and calendar year of MI diagnosis. Compared to insulin monotherapy, TZD use was associated with 49% reduction in the risk of MI (95% CI = 0.27-0.95) after adjusting for age, gender, calendar year of MI diagnosis, nitrate use, ACE inhibitors, beta-blockers, diuretics, hyperlipidemia and hypertension. Similar results were observed for comparisons of sulfonlyurea monotherapy (odds ratio=0.62; 95% CI 0.39-0.98), metformin monotherapy (odds ratio= 0.61; 95% CI 0.34-1.09) and metformin and SU bicombination therapy (odds ratio=0.56; 95% CI 0.33-0.95) compared to insulin monotherapy.

A retrospective balanced cohort study in a large US health care claims database (United Health Care) evaluated the relative risk of acute major CHD events, myocardial infarction (MI) and coronary revascularization (CR), in adults with type 2 diabetes initiating TZDs (N=16,685), sulfonylurea monotherapy (N=19,380), metformin monotherapy (N=25,473), and sulfonylurea-metformin combination during 1999 through 2002 ((Johannes et al. 2005, GSK study report). Analysis of the "as-balanced" cohorts revealed an incidence of any acute cardiac event that was generally similar in TZD initiators compared with metformin initiators: adjusted hazard ratio (HR) of MI= 1.22 (95% CI= 0.93-1.61) and HR of CR =1.26 (95% CI= 1.05-1.52). The incidence of acute cardiac events was similar in TZD and sulfonylurea initiators: HR of MI= 1.16 (95% CI= 0.84-1.61), and HR of CR= 1.14 (95% CI= 0.92-1.41). Comparing TZD initiators with combination therapy initiators, the differences in event rates of MI (HR=1.21, 95% CI= 0.93-1.56) and CR (HR=0.96, 95% CI= 0.81-1.14) were consistent with chance variation. This matched retrospective cohort study found that choice of oral antidiabetic medications had very little effect on the risk of clinical measures of CHD, MI and CR. The results were not consistent with either a protective or deleterious effect of TZDs on short-term cardiovascular risk relative to metformin or sulfonylurea.

6.2. Blinded data from RECORD

Blinded review was performed of adjudicated and pending endpoint data from the RECORD study relating to myocardial ischemic events, up to and including 12th September 2005. These events correspond to an average duration of treatment of approximately 2 years. Review of the investigator allocated endpoints with those obtained following formal adjudication, suggests that in the majority of cases events of myocardial ischemia are confirmed although the exact diagnosis (i.e. myocardial infarction or unstable angina pectoris) may change. Few events described by investigators as related to

myocardial ischemia were reclassified by the endpoint committee as non-myocardial ischemic events.

Adjudicated endpoints that were included in the analysis were hospitalizations for acute myocardial infarction or unstable angina pectoris, sudden death, and death following myocardial infarction. For the 4447 patients in the study, a total of 57 cardiovascular events (1.3%) require final adjudication, and of these 21 (0.5%) have been reported by investigators as hospitalizations for myocardial infarction, and 14 (0.3%) are reported as hospitalizations for unstable angina. A total of 14 deaths (0.3%) remain to be fully adjudicated (provisionally these have been reported by investigators as cardiovascular (n=3), non-cardiovascular (n=10), and unknown (n=1)). Adjudicated myocardial ischemic events are summarized in Table 13. The incidence of adjudicated and pending events of myocardial ischemia in the RECORD study, taking into account the longer treatment duration, is therefore lower than the incidence of unadjudicated serious adverse events shown for the integrated analysis of RSG studies.

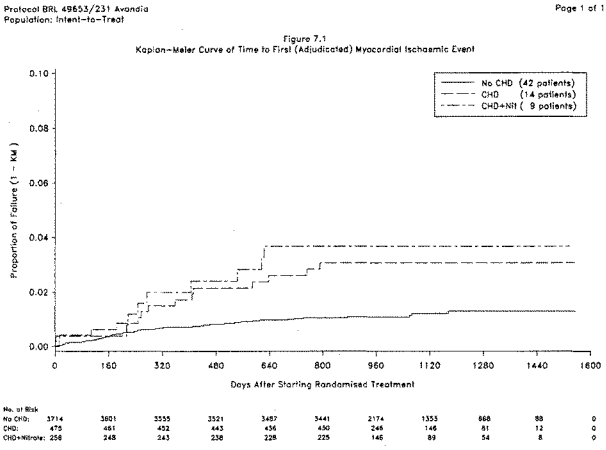
Table 13 Adjudicated myocardial ischemic events reported in the RECORD study (up to 12 September 2005)

N(%)	N=4447
Adjudicated events	65 (1.4%)
Non-fatal MI	34 (0.8%)
Unstable angina pectoris	20 (0.5%)
Fatal MI	3 (0.07%)
Sudden death	9 (0.2%)

Kaplan-Meier curves for time to first event of myocardial ischemia were generated for the population of patients studied, according to whether there was no history of CHD at baseline, a history of CHD without concomitant use of nitrate therapy, and a history of CHD with concomitant use of nitrate therapy (Figure 6). The overall number and incidence of events event rate was very low across all three subgroups of patients, and at six months treatment duration, there was no identifiable difference between the curves. However the curves began diverging thereafter, with the highest incidence of events occurring in the CHD group using nitrate therapy (n=9, 3.5%), followed by the CHD group not using nitrates (n=14, 2.9%), and the no CHD group (n=42, 1.1%).

In summary, these data suggest that the overall event rate for myocardial ischemic events in RECORD is lower than that observed in historical RSG studies, even in higher risk patients with a history of CHD who utilize nitrate therapy. Furthermore as the data for RECORD remain blinded, there is a need to evaluate further the initial findings from the exploratory analysis in the integrated dataset described above in patients with CHD treated

with nitrates and RSG as proposed in the epidemiology trial.



7. Discussion and conclusion

CHF

The observations from the expanded datatset are consistent with the observations from the preliminary analyses of an increased incidence of fluid-related events, including CHF when rosiglitazone is added to pre-existing insulin, to sulfonylurea alone or to sulfonylurea in combination with metformin compared to these regimens alone.

Myocardial ischemia

The odds ratio point estimates for events relating to myocardial ischemia were generally slightly greater than 1 for all treatment combinations, with broad confidence intervals identified. The treatment regimen associated with the highest incidence of myocardial ischemia events was RSG in combination with insulin. These data are consistent with the interpretation of the data from the 6 month placebo-controlled insulin add-on studies as reflected in the US Prescribing Information. However, another high risk group (i.e. CHD patients using nitrates) was identified using recursive partitioning, an exploratory data analysis methodology. This group overall had the highest incidence of myocardial ischemia events, and the elevated risk estimate for RSG vs. control is similar in magnitude

to that observed in insulin-treated patients.

The use of nitrate therapy in the patients with CHD in this updated dataset is likely to signify that patients had anginal symptoms. However, standards of care and clinical practice vary between different centers and countries, and the baseline characteristics of this patient population suggest that, according to today's standards, they were sub-optimally managed from a CHD perspective. Nevertheless, these patients appear to represent a high risk population with severe CHD.

Although the evaluation of potential on-therapy predictors for myocardial ischemia events was inconclusive, there was a suggestion that slightly greater reductions in hematocrit and slightly greater weight gain, may have occurred within the first 3 months of initiating RSG in patients who subsequently reported ischemic events. These data lend credence to the hypothesis that small degrees of fluid retention may be an important contributor to the development of worsening myocardial ischemia in high risk patients.

The importance of fluid retention leading to potential exacerbation of ischemic symptoms in high risk patients with severe CHD should not be underestimated. For example, a number of mechanisms contributing to nitrate tolerance in patients with coronary artery disease have been identified and include not only abnormalities in organic nitrate biotransformation, abnormalities in nitric oxide signal transduction, but also plasma volume expansion (Gori 2002). A small study evaluating the effect of 1 week of diuretic therapy on the time to onset of angina during exercise testing in patients treated with isosorbide dinitrate suggested that exercise capacity could be maintained and weight reduced significantly, whereas exercise time was progressively reduced following use of isosorbide dinitrate alone (Sussex 1994). These data suggest that patients with severe coronary artery disease may be acutely sensitive to changes in fluid status, and that fluid retention could contribute to a reduction in functional capacity and to the development of ischemic symptoms.

GSK believes that the exploratory nature of the findings in the subgroup of patients with CHD treated with nitrates at study start warrants independent confirmation in another dataset. Notwithstanding the somewhat conflicting results from previous epidemiological studies and those discussed above suggesting a low overall incidence of blinded myocardial ischemic events in RECORD, epidemiological data specific to RSG is also considered necessary. Furthermore, both the short term (6 month) and longer term outcomes with respect to myocardial ischemia require evaluation in a broad and representative population with Type 2 diabetes. These issues are currently being explored in an epidemiology study (Ingenix United Healthcare), and results will be available in May/June 2006. Long term data relating to events of myocardial ischemia will be available in Q4 2006. The ADOPT study, conducted in drug naïve patients, will permit the comparison of RSG monotherapy with metformin and SU monotherapy over an average treatment period of 4 years

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