Memorandum

Date: August 8, 2010

From: Robert Temple

To: Janet Woodcock

Subject: Data on Rosiglitazone

The recent July 13, 14 AC meeting to consider rosiglitazone's cardiovascular risk was in many ways thoughtful but in my view left critical questions unaddressed. In particular, it did not really consider the weight of the various lines of evidence in much detail nor did it focus on the particular findings that were most critical in view of the initial stimulus that led to our concern (the Nissen meta-analysis). The following is an attempt to describe all the data, touch on its limitations, and suggest potential additional efforts (mostly related to RECORD). I am not here attempting to propose a decision; it is perfectly clear that there are grounds for concern about risks of rosiglitazone (as there were in 2007) and the question will be whether that concern exceeds the threshold for action beyond what we have already done in rosiglitazone's labeling. This clearly involves particular attention to what new information we have and how it affects our conclusions. What I am hoping to do is to lay out the data so we can be sure we're all considering the same information, identify and resolve disagreements about the data (as distinct from what to do about it), and, where appropriate, see what further analyses might be useful. In most cases, I am not doing new analyses but will be relying on a good deal of work already done.

There can be no doubt that the available data are not all we might wish for. The potentially important comparisons with pioglitazone are either indirect (known to be treacherous) or based on observational data (with recognized limitations, especially when relative risks are close to one). With respect to the rosiglitazone studies, there are seriously inconsistent findings among the controlled studies (here counting single trials and meta analyses as "controlled").

I will divide this discussion into the following segments:

I. Meta-analyses of rosiglitazone RCTs

II. Larger single RCTs of rosiglitazone (ADOPT, DREAM, RECORD, BARI 2D)

III. Meta-analyses and a single large RCT of pioglitazone

IV. Epidemiologic studies comparing rosi and "others" and studies comparing rosi and pio.

V. Conclusions

Let me note two critical premises: MACE and its components are the endpoints of interest, and lack of adjudication of potential endpoints should not create a false positive safety finding.

The endpoints of interest here are CV death, non-fatal MI (NFMI), and non-fatal stroke (also known, when combined, as MACE, major adverse cardiac events), because it is those endpoints (actually, not including stroke) about which concerns were raised by the Nissen meta-analysis. These endpoints can be reasonably well-assessed in clinical trials, even without an events evaluation/adjudication committee (such committees were not used in the short-term rosiglitazone studies included in the meta-analyses and not used in the current epidemiologic studies). Although the individual components are plainly of interest, and were critical in the Nissan meta-analysis, it is MACE that seems like the most informative endpoint and it is the one regularly used to assess favorable CV effects of drugs and drug risks (e.g., in the diabetes guidance). Thus, although RECORD was designed with CV hospitalizations and CV mortality as its primary endpoint, reflecting an important concern with heart failure, our major interest, given the meta-analysis that raised the issue under discussion, should be MACE and its components, leaving heart failure to other considerations.

The lack of an adjudication process for endpoints in the studies going into the meta-analysis has been noted, and is certainly of some concern, but this should not be over-emphasized. As a general matter, in blinded studies (which the meta-analysis studies were) one would expect imprecise endpoint assessment (a potential consequence of non-adjudication) to create “noise”, and a bias toward the null (finding no difference). The unplanned and generally poorly and variably specified endpoint assessments in the studies going into the meta-analyses and epi studies therefore should not create a finding, so long as the observations are unbiased. Such “noise” will not, I believe, be a major problem for a positive finding. I recognize the irony of this: the not very precise, not well-specified findings in the meta-analysis are held to a lower standard than the later trials that seek to examine the concerns stimulated by the meta-analysis. The studies and data in the meta-analysis have, for example, never been analyzed the way the RECORD findings have been scrutinized by Drs. Marciniak and Unger. Unfortunately, the kind of evidence needed to give a persuasive “no finding,” and to overcome the potential “bias toward the null” in any trial intended to show no effect, forces this approach.

I. Meta-analyses of Rosiglitazone

A. Nissen analysis

Nissen’s meta-analysis results are shown in the table below, taken from his NEJM publication. As can be seen, he pooled 40 relatively small studies, most of them 6 months or shorter, with ADOPT and DREAM, a step with important consequences to the outcome and one that is not fully explained in the paper. Among the 40 studies, 32 were either comparisons with placebo or placebo-controlled “add-on” studies. The remaining 8 were comparisons with other oral hypoglycemics. These design features are described in the publication.

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

As can be seen, the small studies alone showed a nominally significant (p = 0.02), and rather large (OR point estimate 2.4) effect on cardiovascular mortality, with a trend, but not a significant effect, on NFMI (p = 0.15). Stroke is not mentioned at all, a strange omission as almost all CV event trials include it, and in the absence of a prior or mechanistic hypothesis, it would seem almost obvious to include stroke. It is possible Nissen had no access to stroke data (and, apparently, did not seek it), but, as we will see from FDA's analyses, rosiglitazone treatment was in fact associated with fewer strokes. MACE, obviously, was not considered by Nissen, nor was the combined endpoint of CV death and AMI, because (as explained in the paper) Nissen could not tell from available data whether a patient had more than one event. I will focus on FDA's updated analysis of these trials (not including ADOPT and DREAM, discussed in Section II) as the most pertinent analysis, but a few points should be noted as relevant to Nissen's analysis and to meta-analyses in general.

1. The overall analysis was carried out with results clearly knowable before it was done.

The decision to do the analysis was apparently (Nissen AC presentation) provoked by DREAM, with its finding of more AMIs, and the decision to include ADOPT/DREAM, etc. were all made with the consequences largely known. Specifically, the interest in AMI arose, according to Nissen, from the excess of AMI in DREAM (a difference of 6 events) and the results of ADOPT had been published, so that the effect of combining these studies with the smaller ones was clear. That is, of course, not what we expect in designing and evaluating RCTs, where we stress the need to make all analytic plans before results are in hand to avoid bias. It is one of the reasons many trialists have noted the "observational" qualities of meta-analyses and the need to interpret their results cautiously. Peto, for example, has emphasized the need to find critical missing data (strokes, for example, or time of events) and in a DIA talk, at least (I can't find a paper saying this) has suggested that only statistically very strong findings, e.g., p-values in the neighborhood of 0.001, should be interpreted as convincing, although he was not focused on safety, where perhaps a lesser degree of "certainty" might suffice.

The very important decision to include ADOPT and DREAM with the small studies is particularly interesting. It clearly took the mortality finding from nominally significant (p = 0.02 for the small studies) to NS (p = 0.06) overall. This might be taken as evidence of "fairness" and caution in interpretation, but there are other interpretations. Presenting only the small study mortality finding would have made the whole finding promptly rebuttable by the lack of a mortality effect in ADOPT/DREAM, perhaps leading to loss of credibility of the meta-analysis. Focusing on AMIs (which were not significantly more frequent on rosiglitazone in the small studies) avoided that outcome. In any event, speculation aside, this was not a blinded effort and the results were obtained with full knowledge of the effect of various analytic decisions on the outcome by the analysts, a very common situation with meta-analyses. As noted above, in his presentation at the July 2010 AC meeting, Nissen made it clear that it was DREAM, with its adverse trends on AMI as well as other endpoints (especially CHF), that provoked the meta-analysis. In such a case one could ask whether DREAM should have been included in the meta-analysis. In any event, although the history here is of interest, the current meta-analysis, whatever its etiology, is what we must consider.

2. In presenting results, both Nissen, and Psaty and Furburg in the accompanying NEJM editorial, emphasized the need for caution in interpreting the meta-analytic results.

Nissen and Wolski stressed certain limitations of the data.

> "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. . . [and] the public health impact of an increase in cardiovascular risk could be substantial <u>if our data are borne out by further analysis and the results of larger controlled trials</u> (my emphasis).
>
> Although [we could not] construct a composite outcome that included AMI and CV death, the increase in the odds ratios for both of these endpoints suggests that observed effects associated with rosiglitazone were probably not due to chance alone."

The "dual" "finding" (AMI and mortality) was thus considered a critical strength of the meta-analysis, enhancing both its clinical importance and, of particular importance for this discussion, its credibility. That is, with BOTH critical endpoints showing (or strongly suggesting) an adverse effect, chance was an unlikely explanation.

Nissen also noted that the odds ratios for the short-term studies were similar to the overall results, suggesting that the adverse effects might occur rapidly. This is a somewhat odd point, as the short term studies, with a large fraction of the events, would obviously be expected to influence the overall result. Nonetheless, it is true that the finding occurs early. In fact, for CV death, as the above table shows, the striking, nominally significant, finding of increased mortality in the short-term studies (n about 10,000) is not present at all in the longer term studies (n about 9000). As described below, (IB) FDA's meta-analysis shows a similar result.

Nissen, later in the paper, reemphasized the limitations of the analysis, but his concern was mainly about the true magnitude of the risk, not whether or not the risk was present

or absent. He also hoped that ongoing RECORD would provide useful insight into the risks, citing, apparently with approval, the study design and protocol paper of 2005.

Nissen and Wolski also noted results on overall mortality (OR 1.18; 95% CI 0.89-1.55, p = 0.24), pointing out that this endpoint was "not prespecified," unlike, one supposes, all the rest of the analytic decisions.

In commenting on the Nissen meta-analysis, Psaty and Furburg noted that the weaknesses of the study were substantial and that "a few events either way might have changed the findings for myocardial infarction or death from cardiovascular causes. In this setting, the possibility that the findings were due to chance cannot be excluded." They noted with approval that in their discussion, Nissen and Wolski properly emphasized the "fragility" of their findings.

And they are in fact fragile, only marginally statistically significant, even without any correction for multiplicity or a more demanding standard for meta-analyses. A strength, on the other hand, as Nissen pointed out, is the finding on two highly pertinent endpoints.

Whatever the limitations of the original Nissen meta-analysis, FDA was able to conduct a more complete analysis and it seems most useful to focus on it, principally the 52-trial updated analysis presented at the July 2010 AC meeting.

B. FDA's Updated Meta-analysis

FDA's updated meta-analyses, presented to the 2010 Avandia Advisory Committee meeting, should be taken as the best available meta-analytic assessment of the studies of at least 2 months duration (but see below regarding a published meta-analysis with far more studies that has not yet been carefully scrutinized), as we had more data available. I note that we still lack detailed assessment of cases and we have not shown a K-M curve.

The 52-trial analysis, focused on MACE and its components and on all-cause mortality, showed the following results:

Outcome	Rosiglitazone # events (%)	Control # events (%)	Stratified Exact OR (CI)
	n = 10,039	n = 6956	
MACE *	70 (0.7)	39 (0.56)	1.44 (0.95-2.20)
CV Death	17 (0.17)	9 (0.13)	1.46 (0.60-3.77)
NFMI	45 (0.45)	20 (0.29)	1.80 (1.03-3.25)
NF Stroke	18 (0.18)	16 (0.23)	0.86 (0.40-1.83)
All-cause death	29 (0.29)	17 (0.24)	1.38 (0.72-2.72)

* Only one per patient, so that CVD, NFMI, and NF stroke are > MACE

I am displaying the stratified exact analysis, the analysis preferred by Biometrics. The 52- trial results are fairly similar to the 42-trial analysis done by FDA in 2007 (Mele

analysis) for MACE, AMI and stroke, except that the AMI finding is now nominally significant (same OR, however), but the mortality findings (both CV and overall) are much weaker, albeit still troublesome. The OR's had been 1.9 for all cause death and 2 for CV death, using the same analysis as used for the 52-trial analysis.

Note I am not looking at subsets, such as insulin users or NTG users, or analyzing by comparator treatment. I believe these subanalyses are too small to rely on very much, although they perhaps illustrate the variability of the data. In fact, most trials compared rosiglitazone to placebo, either alone (i.e., with no other therapy) or with each added to a common background treatment.

C. Interpreting the Initial and Updated Meta-analyses.

As Nissen and Psaty/Furburg emphasize, the Nissen and Wolski meta-analysis is not definitive, although it is surely grounds for concern and the CI upper bounds are impressive. Nonetheless, it must be recognized that there was potential bias in its development (or at least the analysis was done with knowledge of what would emerge) and the findings are statistically marginal in terms of the specific case and marginal in terms of expectations for a meta-analysis ($p = 0.05$ would generally not be enough). The FDA 52-study analysis generally has similar limitations. A few further observations:

1. The AMI finding (in the 52-study analysis) is now nominally statistically significant, but MACE is not, CV and overall mortality are not close, and stroke trends favorably for rosiglitazone. Any sort of correction for multiplicity leaves the finding well short of nominal statistical significance.

2. The patron saint of meta-analysis, Richard Peto, who helped bring the approach back from what we used to dismiss as "unplanned pooling," stressed approaches that would avoid bias and error, including selection of endpoints before the trials are analyzed and a reasonably high level of statistical significance.

The reason for such concern is that meta-analyses can give strikingly incorrect results (to be fair, so can individual RCTs). There are a few well-recognized examples cited in a letter to Dr. Parks from Dr. Salim Yusuf, such as the apparent survival benefit (statistically quite strong) of post-infarction Mg treatment, never confirmed (indeed, strongly rebutted) in a large trial. Dr. Yusuf notes the particular problem when the number of events is small. Very recently, FDA [Kim, et al. Meta-analysis of a possible signal of increased mortality associated with cefapine use. Clin Infect. Diseases. 2010; 51: 381-389] reported on our own experience with a cefapine meta-analysis after a published analysis found in a 41-trial, trial level analysis, a statistically significant 26% increase in 30-day mortality in patients with a variety of infections treated with cefapine compared to other beta-lactams. Our analyses, including a trial level analysis based on 88 reports, and a patient level analysis based on 35 trials, found no significant effect on survival.

Others, notably LeLorier [LeLorier, et al. Discrepancies between meta-analysis and subsequent large randomized controlled trials. NEJM, 1997;337;536-542] and Bailar, have discussed discrepant results between meta-analyses and large trials, discrepancies often not explained, and sometimes very substantial. They uniformly urge a cautious approach. LeLorier, for example, compared 12 large RCTS with 19 previous meta-analyses addressing the same questions, a total of 40 primary and secondary outcomes. They found that the RCT results were not correctly predicted by the meta-

analyses about 35% of the time, although the direction of the effects was generally similar.

These kinds of concerns have led us to treat meta-analytic findings very cautiously when it comes to an effectiveness conclusion. I cannot think of any novel claim we have accepted based on such analyses, although we certainly use them to calculate margins for NI trials, (where, of course, we believe we already know about effectiveness) and we use the ISS and ISE in NDAs to examine demographic and other subsets in NDAs for both safety and effectiveness. But we do regularly use meta-analyses to assess safety, where low event rates and the substantial delay and difficulty that would result from trying to rely on new large trials leave us little choice.

3. The findings of the 2010 meta-analysis can be compared with the expectations we have put forth for new antidiabetic drugs in our recent guidance. At initial approval, generally presuming a database of several thousand patients, we would expect the 95% CI upper bound for the MACE OR to be < 1.8. This has clearly NOT been achieved in this case. The post-approval OR goal of ≤ 1.3 for MACE with a larger database, is, obviously, also not close to having been met in the 52-trial meta-analysis, despite some 17,000 patients and is probably not met even if the meta-analysis is expanded to include all of the longer trials, including RECORD. Nissen showed an analysis for AMI including RECORD (but I presume this had both fatal and NFMI for RECORD) with the upper bound still 1.63 and for CV death, where the upper bound was still 1.36, although the point estimate is only 1.03). Although MACE was not analyzed, I would expect the AMI rate to push the upper level above 1.3. This means that a new drug with these results would not be approved and an approved drug (with OR < 1.8 at time of approval), having conducted its post-marketing effort with results like the meta-analysis, would, presumably, be considered for withdrawal, assuming that these were the only data available. Of course, these conclusions do not consider consistency. What would we do, for example, if a single large study substantially "rebutted" an initial concern, e.g., by being well within the 1.3 upper bound for MACE on its own, even if total data were not (i.e., what RECORD may well show, depending on results of further re-analysis)?

4. In his presentation at the July 2010 Advisory Committee, Nissen noted the lipid effects of rosiglitazone, an approximately 20% increase in LDL cholesterol, with larger effects in people closer to normal. He did not believe change in cholesterol would have an early effect, and that seems correct, based on a quick inspection of statin trials (4S, WOSCOPS). In these lipid-lowering trials, differences emerged only after at least a year. As will be described below (#5), it is largely trials of ≤ 6 months duration that drive the results here and any effect can probably not be attributed to LDL changes.

Certainly, however, the increased LDL caused by rosiglitazone is a long-term concern. It could, of course, be readily dealt with in most cases, but that could mean an extra drug in some patients. It has been noted that statin use in RECORD was greater in the rosiglitazone group; I would consider that good sense, not a problem.

5. I note the recent publication of a meta-analysis by Mannucci, et al [Mannucci E, et al. Cardiac safety profile of rosiglitazone: A comprehensive meta-analysis of randomized clinical trials. Int J Cardiol 2010; 143:35-140] of 164 short-term (> 4 week) rosiglitazone trials with a total of almost 43,000 patients. It reported an OR for CV and total death of 0.93 and 0.94 and for NFMI of 1.14, results similar to RECORD (below). I had not seen any prior reference to this analysis, and it is certainly not a patient level analysis, but I believe it deserves examination. We have no idea what rosiglitazone's mechanism of effect is (if indeed there is one), and trials of 4-26 weeks appear pertinent. Indeed, I

note, as others have pointed out, that in the 52-study FDA meta-analysis, the shorter trials (2-6 months) largely generate the MACE findings, the AMI findings, and the mortality findings. The following table, from the Biometrics' meta-analysis, grouping trials by duration, shows this:

	2-6 Months			> 6 mos - ≤ 1 yr			> 1 yr		
	Rosi n = 7068	Control N = 4716	OR (CI)	Rosi n = 2524	Control n = 1792	OR (CI)	Rosi n = 447	Control n = 448	OR (CI)
MACE	45 (0.64)	18 (0.38)	1.76 (0.98-3.27)	14 (0.55)	11 (0.61)	1.17 (0.48-2.89)	11 (2.46)	10 (2.23)	1.10 (0.42-2.92)
CV Death	14 (0.2)	2 (0.04)	4.71 (1.05-43.33)	3 (0.12)	3 (0.17)	1.01 (0.13-7.58)	0	4 (0.89)	0
MI	29 (0.41)	8 (0.17)	2.62 (1.15-6.73)	9 (0.36)	6 (0.33)	1.28 (0.4-4.44)	7 (1.57)	6 (1.34)	1.16 (0.33-4.22)
Stroke	12 (0.19)	10 (0.21)	0.78 (0.3-2.07)	2 (0.08)	4 (0.22)	0.50 (0.05-3.54)	4 (0.89)	2 (0.45)	2.02 (0.29-22.46)
All-cause	20 (0.28)	5 (0.11)	2.75 (0.98-9.51)	5 (0.2)	5 (0.28)	1.02 (0.23-4.46)	4 (0.89)	7 (1.56)	0.57 (0.12-2.27)

6. Part of the strength of the Nissen meta-analysis was the strong trend on two distinct, independent, albeit potentially mechanistically related, endpoints, CV death and NFMI. This was specifically emphasized by Nissen and Wolski as a significant reason for believing the statistically borderline individual results, and it is clearly a reasonable point. As quoted above they said: "the increase in the odds ratios for both of these endpoints suggests that observed effects associated with rosiglitazone were probably not due to chance alone." What this says is that, apart from the increased clinical concern that would arise from an effect on mortality, the two findings together greatly enhance the credibility of the finding, i.e., the likelihood that the finding is not the result of chance. That noted, the conclusion is surely weakened by the fact that ADOPT and DREAM, the 2 largest studies available at the time, do not support the dual findings. And, as will be described below, it seems clear, whatever reservations reviewers may have about the study, that RECORD does not support the mortality finding, especially the early finding that is prominent in the meta-analysis. Also, as described below, the BARI 2D study shows no suggestion of a mortality effect.

II. Larger Trials of Rosiglitazone

1. ADOPT/DREAM

The Nissen meta-analysis showed results of ADOPT and DREAM as follows

	Rosi	Control	OR/(CI)
AMI			
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)
ADOPT	27/1,456 (1.85)	41/2895 (1.44)	1.33 (0.80–2.21)
CV Death			
DREAM	12/2,635 (0.51)	10/2634 (0.38)	1.20 (0.52–2.78)
ADOPT	2/1,456 (0.14)	5/2895 (0.18)	0.80 (0.17–3.86)

There have been additional analyses of these trials and DREAM is a complex factorial study, but I have not examined these further. It seems clear, however, that, overall, these trials do not support the CV mortality trend in the meta-analysis, but they are consistent with an effect on AMI; indeed, they heavily influence that outcome. The distinction is critical. Both mortality and AMI matter, of course, but as both Nissen and Furburg noted, the survival data are what are really frightening and the consistency of the effect on the two endpoints enhanced the credibility of the meta-analytic findings.

2. RECORD

I will comment relatively briefly on RECORD, as Drs. Unger and Marciniak, and Drs. Parks and Mahoney have addressed it at length. I want to separate the RECORD mortality results, which I believe are relatively clear, and the AMI results, which need further assessment. First, like ADOPT and DREAM, RECORD is clearly inconsistent with the meta-analysis finding of increased CV and overall mortality, even without further adjudication, and no matter which of the various analyses one prefers. Second, we cannot fully assess effects on AMI without further review, although they seem on face nowhere close to the nearly 80% increase seen in the meta-analysis, nor the smaller, but still troublesome, increases in ADOPT and DREAM.

RECORD was a study in 4447 patients with type 2 diabetes mellitus. It was conducted outside the US, and was a response to an EMA (then EMEA) request. It was an open label comparison of rosiglitazone added to metformin (n=1117) or a sulfonylurea (n=1103), for a total n of 2220, with the combination of metformin plus a sulfonylurea (n=2227). Other drugs could be added to gain adequate HbA1c control. The planned endpoint was time to first occurrence of CV hospitalization or CV death. Deaths and possible events were identified by a CRO, Quintiles, from adverse event reporting or direct questioning of participants, and sent to a blinded adjudication committee. The study was open-label because of different insulin programs that could be used in the event of poor control in each group. Although the events reviewed by the blinded adjudication committee are not the major concern, there is a legitimate concern about

whether the unblinded referral process could have been biased by awareness of treatment assignment. This cannot yet be resolved fully but findings on CV mortality, and particularly all-cause mortality, would not be materially influenced by such biases, especially for the on-therapy population (or on-therapy plus 30-60 days), which I believe is generally the best analysis in a safety setting.

a. Reported results (without further adjudication), using ITT analysis:

First Event	Rosiglitazone	Control	HR (CI)
CV Death or Hosp'n	321 (14.5)	323 (14.5)	0.99 (0.85-1.16)
CV Hosp'n	288 (13)	284 (12.8)	
CV Death	33 (1.5)	39 (1.8)	
Total Events			
CV Death	60 (2.7)	71 (3.2)	0.84 (0.59-1.18)
CV Hosp'n	483 (21.8)	490 (22)	
All cause mortality	136 (6.1%)	157 (7.0)	0.86 (0.68-1.08)

I note the upper bound for the protocol-specified endpoint was 1.16 (i.e., very tight), but given the meta-analysis that stimulated our interest in heart attacks and CV death and the well-established ability of rosiglitazone to cause heart failure and consequent hospitalization, the RECORD planned study endpoint is not our major interest. Rather, we have a major interest in MACE (CV death, NFMI and NF stroke).

In general, use of an ITT analysis with many patients no longer on randomized treatment in a setting where demonstration of no difference is of interest tends to bias toward the desired finding of "no difference," and I believe the preferred analysis is on-treatment, or perhaps on-treatment plus 30-60 days (to capture anyone dropped because he or she was doing badly), but the ITT analysis also needs to be considered.

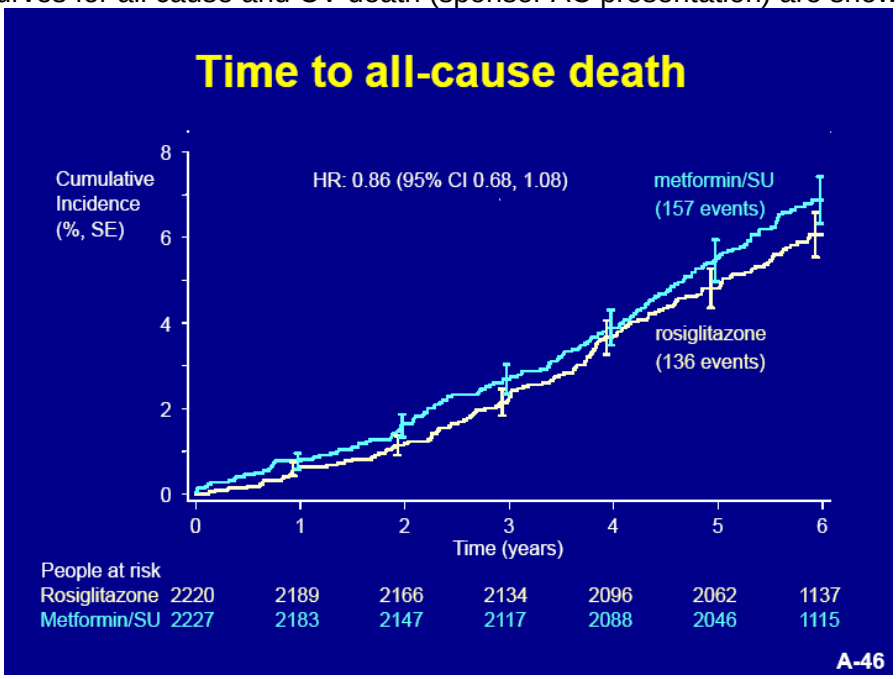
ITT Results for MACE and components, and all cause death

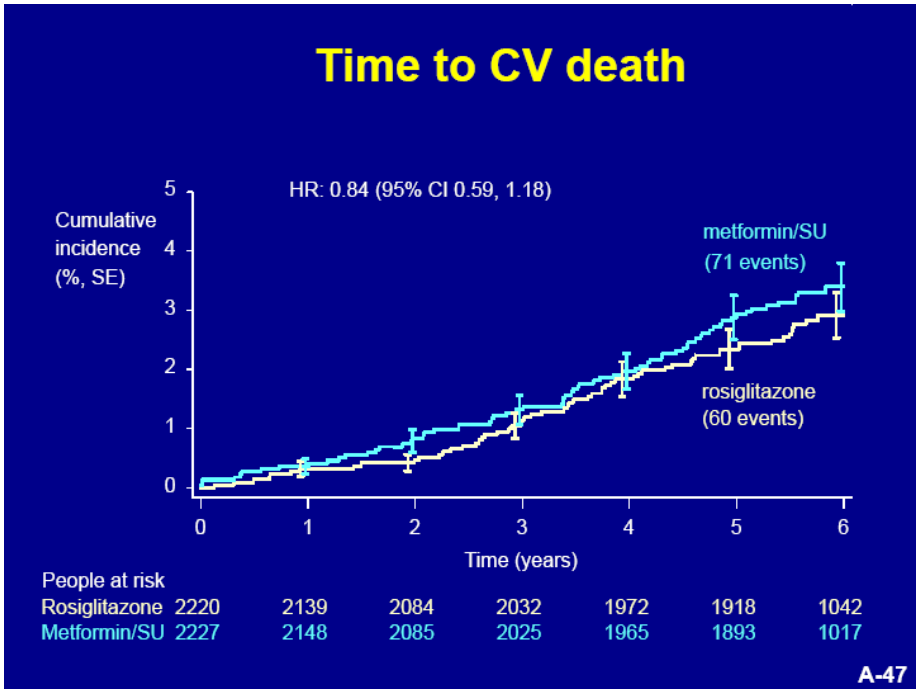
	Rosiglitazone	Control	HR (CI)
All cause death	136	157	0.86 (0.68-1.08)
CV Death	60	71	0.84 (0.59-1.18)
AMI (fatal & NF)	64	56	1.14 (0.8-1.63)
Stroke (fatal & NF)	46	63	0.72 (0.49-1.06)
CV death, MI, Stroke (MACE)	154	165	0.93 (0.74-1.15)

The all cause death, CV death, and MACE results can be examined readily, but assessing NFMI and NF stroke is more difficult because these rates were not presented separately, but were combined with fatal events. The idea of combining fatal and non-fatal MI and stroke is a poor one, in my view, as many CV deaths are not well-characterized with respect to cause (in fact, about half of the CV deaths are "unattributed"). That noted, however, only 7 rosi and 10 control CV deaths are attributed to AMI, so that subtracting them will leave 57 rosi and 46 control NFMI's, not very different from the fatal and NF numbers. All in all, these are very reassuring results with respect to mortality, and they show nothing like the 50% or so increase in AMI reported in the meta-analysis (but see below for concerns about this analysis related to the unblinded nature of the trial). There is, once again, a reduction in stroke. [I also note an additional "finding" that to date has elicited no comment. The published results show a marked reduction in pancreatic cancer, from 13 to 2 (p=0.0074), in rosiglitazone-treated patients. This is of course, either 1) another example of how, if you look at enough endpoints you will surely find something, or 2) a spectacular effect on one of our major tumors. One can only imagine the discussion of this "risk" had it favored the control treatment. At a minimum, these cases deserve a close look.]

(1) Mortality Results - ITT

The K-M curves for all cause and CV death (sponsor AC presentation) are shown below:





It should be noted that over the first 2-3 years, a time when most patients are still in the trial and accounted for (even if no longer taking drug), there is no suggestion of an adverse effect on mortality in the ITT analysis. Any concerns about follow up, especially regarding survival status, as expressed by Dr. Marciniak, should be minimal here.

Moreover, overall follow up for vital status appears to be quite good (Unger review of June 15, 2010), totaling 97.3% for rosiglitazone and 96.9% for control, i.e., all but 127 of the 4447 patients in RECORD, and there is clearly no excessive loss in the rosiglitazone group. As discussed by Dr. Unger, the analysis does depend on the sponsor's determination of the vital status of 394 people said to be alive. Dr. Marciniak has expressed concern about the reliability of these determinations. This can, of course, be checked, and the basis for determination of vital status verified. But I note again that over the first several years of the 5 year trial, the time when problems emerged in the meta-analysis, there was good and equivalent follow up in the two groups, and no suggestion of any excess mortality. I therefore conclude, as Dr. Unger did, that for overall and CV mortality, there is a strong finding of no adverse effect (actually a trend toward a favorable one). The determination by the adjudication committee of whether a death was CV or not has not been challenged in any major way (although one can always find specific cases to debate), so that whether the deaths need to be readjudicated seems open to question. Given the nature of public discussion of RECORD, however, it might be reasonable to do this, even if it is not really necessary, and even though total mortality is itself reassuring and favors rosiglitazone.

(2) Non-fatal event results (particularly AMI) – ITT
The critical question for the non-fatal events is whether there could have been biased referral, i.e., under-referral of the hospitalization events for adjudication in the rosiglitazone group. Dr. Marciniak found 8 rosiglitazone cases he thought should have been referred that were not referred, vs. no such control cases. A possible referral bias is surely a real concern in an open-label study and the 8 vs. 0 finding proved to have a

considerable effect on the advisory committee, which did not give RECORD much weight. In fact, Dr. Unger has now found similar "non-referral cases" in control patients (I note Dr. Marciniak does not think they meet the definition of possible CV events, but DSI did not agree with all of Dr. Marciniak's 8 referable cases. This is a debate for a later time). The question of possible referral bias clearly needs further evaluation. The best protection against such a bias, as Dr. Unger notes in his June 15, 2010 review, would have been a very broad referral requirement, essentially adjudicating any hospitalization. At this stage the only real remedy is a full readjudication.

Discussion of the "referral problem" at the AC meeting also contributed, I believe, to an impression of general sloppiness in the conduct of RECORD, but that impression is not supported by DSI's evaluation, in my view. DSI (helped by Dr. Khin U of the DCaRP) inspected many of the cases of "non-referral" (review of June 11, 2010) at GSK and Quintiles, finding some cases that could have merited transmission to the adjudication committee, but these were few and in most cases Dr. U thought the protocol requirements for transmission had been followed (See Appendix 1 of Dr. U's June 11 review). He did note, however, some very delayed transmissions to the adjudication committee, a troubling finding given the purpose of the study. Dr. Liebenhaut's presentation to the AC of DSI's findings did not identify problems that would suggest that the RECORD data were unreliable, although she noted the limitations of any on- site inspections.

Apart from the referral problem, Dr. Marciniak was not satisfied with the AMI criteria and recalculated the results for AMI based on his assessments, finding a somewhat higher risk than reported (but still not close to the meta-analysis result). I believe we must treat this as a "sensitivity analysis," not a revised result, as he was not blinded and used new AMI criteria, so that this approach can not be considered a valid readjudication. To evaluate the AMI finding properly we will need to adjudicate essentially all hospitalizations. We should do this because, although RECORD (together with ADOPT and DREAM) greatly weakens (really, essentially eliminates) the meta-analysis mortality finding, an increase in non-fatal AMI, even if not accompanied by death, would remain a concern.

b. As treated, on therapy

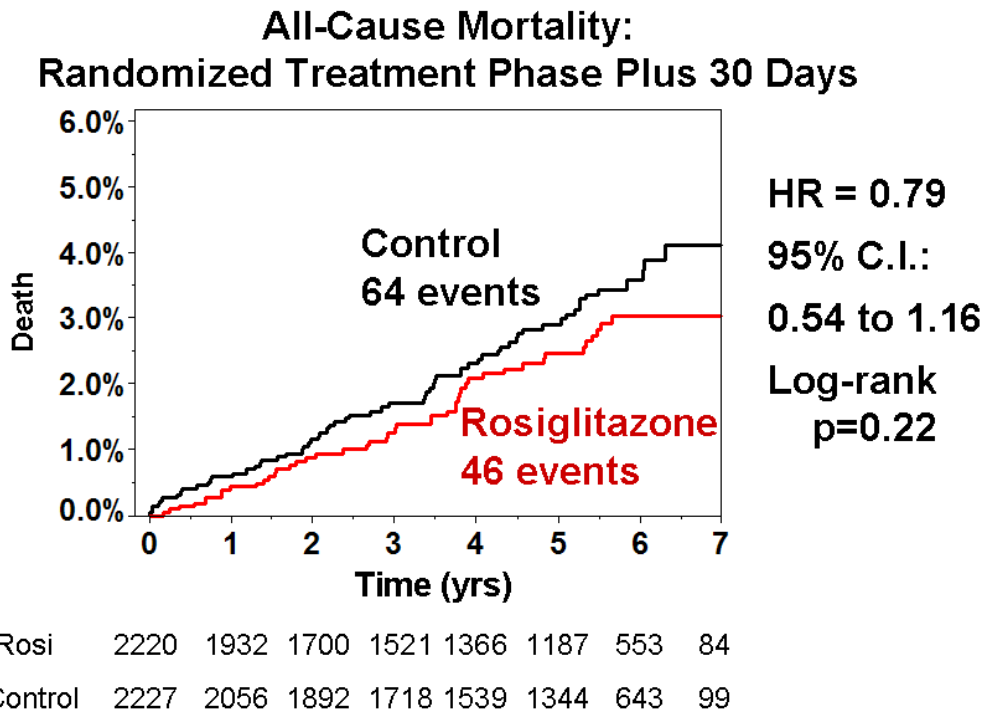
As noted above, in a safety evaluation, there is reason to consider "on therapy" results, as adverse effects should diminish once a drug is stopped. There may be reason to look at ITT as well, notably because of Dr. Marciniak's concern that patients might, especially in an unblinded study, be dropped when doing badly in anticipation of an event. A plausible possibility, e.g., is that exacerbated CHF might lead to discontinuation and that such discontinued patients might be at increased risk of death.

In any case, the sponsor's per protocol analysis, presented in Dr. Mahoney's June 9, 2010 review, p 50, shows:

Endpoint	Rosiglitazone	Control	HR (CI)
All-cause death	29 (1.3)	46 (2.1)	0.69 (0.44, 1.11)
CV death	23 (1.0)	34 (1.5)	0.75 (0.44, 1.27)
CV death, MI or stroke ("MACE")	94 (4.2)	117 (5.3)	0.89 (0.68, 1.17)
Myocardial infarction (fatal or nonfatal)	47 (2.1)	44 (2.0)	1.18 (0.78, 1.78)
Stroke (fatal or nonfatal)	32 (1.4)	51 (2.3)	0.69 (0.45, 1.08)

Note that this is "extreme per protocol," counting only patients still on randomized treatment without any added therapy to gain glucose control. It has many fewer events than other analyses but does address the earlier part of the study. All in all, results are similar to the ITT results shown above.

Another analysis, perhaps preferable because it should capture any patients leaving the study in anticipation of a bad outcome, would be on-therapy plus 30 days. Dr. Unger presented this analysis (confirmed by Dr. David Hoberman) to the AC and his K-M curve is shown below. Again, results are similar to the ITT and per protocol analyses.



RECORD has its limitations, mainly lack of blinding, but its mortality data appear credible and are completely at odds with the meta-analytic results, which show a near 50% increase in CV death. In RECORD, point estimates for OR for total and CV mortality are well below 1.0 and upper bounds for all-cause and CV death, stoke, and MACE are all below 1.2. Only AMI has an OR point estimate >1.0 (1.14), with an upper bound of 1.6.

It is also important to recognize that RECORD had far more overall and CV fatalities (all cause deaths 110 in the randomized plus 30 days analysis, and 293 in the sponsor's ITT analysis) than the meta-analysis (46 all cause fatalities in FDA's meta-analysis), so that these neutral or slightly favorable results are powerful findings against the adverse mortality effect seen in the meta-analysis.

The lack of blinding in RECORD has received extensive comment. We have good and obvious reasons for concern about blinding in any study where endpoints are subjective, and there are less obvious concerns as well, such as differential use of other treatments, different levels of effort to retain patients in the study, etc. ITT analyses may help with the retention issue, but these analyses are not optimal for safety studies or NI studies more generally. As noted earlier, one protection in RECORD would have been to forward essentially all hospitalizations for adjudication any reanalysis should consider all hospitalizations.

It should be appreciated that unblinded studies with MACE endpoints are fairly common, especially in device and surgical trials, but in others as well. The GISSI study of streptokinase and the GUSTO study comparing TPA regimens and SK were open-label (although the primary endpoint in those studies was survival, perhaps less of a problem), but a recent comparison of angioplasty and stenting for carotid stenosis (endpoint MACE) [Brott, et al, stenting vs. endarterectomy for treatment of carotid artery stenosis. NEJM 2010; 363:11-23] was open and used adjudication procedures that sound a lot like RECORD. We know, of course, that many oncologic RCTs are open-label for fairly obvious reasons, even where the endpoint is subjective (PFS), not just mortality. It is possible, of course, that the whole matter needs a re-look, but RECORD is not so exceptional.

4. BARI 2D

BARI 2D was not a randomized comparison of rosiglitazone with other treatments. Rather, it was a comparison of insulin sensitization (IS) approaches (metformin, glitazones) with insulin provision (IP) approaches (insulin, sulfonylureas, or other insulin secretion stimulators). About 55% of patients in the sensitization group got rosiglitazone vs. 3% of patients in the insulin provision group. Assignment to rosiglitazone was not randomized, limiting the interpretability of the study, but two analyses are of interest nonetheless. First, the overall neutral or slightly favorable result of the IS (containing rosiglitazone) group vs. IP is informative, suggesting no adverse effect of rosiglitazone if one assumes a neutral or favorable effect on CV endpoints of the comparators (insulin, sulfonylureas, and secretion stimulators) and no substantial favorable effect of metformin. The IS vs. IP showed (Brooks Presentation before Advisory Committee) the following results:

	K-M Est'd 5 Year Rate		Cox Prop Hazard	
	IS	IP	RR (CI)	P
	n = 1183	n = 1185		
Death	11.8%	12.1%	0.98 (0.79-1.23)	0.89
MI	12.2%	13.6%	0.86 (0.08-1.09)	0.21
Stroke	2.5%	3.7%	0.72 (0.44-1.16)	0.18
Death, MI, Stroke	22.3%	24.6%	0.88 (0.74-1.04)	0.13
CHF (in baseline CHF)	17.7%	13.5%	1.34 (1.07-1.68)	0.011

Obviously, interpretation is complex, but the other IS treatments (about 8% pioglitazone, the rest metformin) are likely, based on existing data, to be more or less neutral, and do not appear beneficial enough to overcome a substantial adverse effect of rosiglitazone. Given that, if the IP treatments are not adverse, it seems clear that rosiglitazone, given to more than half the patients, did not have an adverse effect on endpoints. The credibility of these results is enhanced by the finding of the anticipated adverse effect of rosiglitazone on CHF.

The study was also analyzed as rosiglitazone vs. no TZD, taking patients from both groups (i.e., not a randomized comparison). This analysis found an advantage for rosiglitazone.

	Rate per 100 patient-years			
Outcome	Rosiglitazone	No T2D	RR	P
Death	1.88	2.56	0.77	0.08
MI	2.16	3.16	0.76	0.06
Stroke	0.28	0.77	0.37	0.008
Death, MI, Stroke	3.79	5.81	0.71	0.002

It must be emphasized that this latter analysis needs cautious treatment, as it is not a randomized comparison and pools data from the 2 randomized groups, etc, giving it distinctly epidemiologic qualities, but there is certainly no hint of any adverse direction.

5. Overall Conclusions from Large Studies

We will need to review at least the non-fatal events in RECORD before reaching a complete conclusion, but the overall results of the larger trials are very reassuring with respect to any mortality effect of rosiglitazone – there is in fact no suggestion of such an effect in any of the 4 trials, a result completely at odds with the strong trend seen in the meta-analysis, raising major doubt about the validity of that finding. There is, however, a reason for our focus on MACE and not solely survival. All 3 components are of interest (although one would generally consider death and stroke more important) and an

adverse effect on heart attacks alone would be important. Re-analysis of RECORD therefore seems very much in order, to see whether in fact RECORD is as reassuring as its reported results suggest.

There have been suggestions that the OR > 1 (1.14) for fatal and NFMI seen in RECORD, with the OR upper bound of 1.63, is not "incompatible" with FDA's updated meta-analytic results (NFMI OR point estimate of 1.80, with upper bound of 3.25) but I disagree. Whether they overlap at some CI margin is not really the point. The meta-analytic hypothesis is of a "significant" and substantial (an 80% increase by point estimate) effect on MI, with a very unnerving MACE and mortality "lean." The results of the large studies appear entirely incompatible with any mortality effect, and RECORD, if verified, shows at worst a very modest effect on AMI and a favorable trend on MACE. The results of the meta-analysis and the larger individual studies are a world apart.

III. Meta- analysis and large single trial of pioglitazone.

The meta-analysis of pioglitazone has stimulated a variety of analyses and sub-analyses (trials vs. placebo, trials vs. active, trials of varying duration), but as is usually the case, it is not clear what to make of them. Overall, the pioglitazone meta-analysis raises far fewer "red flags" than the meta-analysis of rosiglitazone.

The results from the A.C. presentation are:

	Pio	***Control***	***Stratified Exact OR***
	N=6132 n(%)	*N=5642 n(%)*	*(95% CI)*
MACE	54 (0.9)	63 (1.1)	0.83 (0.56-1.21)
CV Death	22 (0.4)	18 (0.3)	1.18 (0.60-2.34)
NFMI	31 (0.5)	33 (0.6)	0.91 (0.53-1.53)
NF Stroke	10 (0.2)	16 (0.3)	0.61 (0.24-1.43)
All Cause Death	31 (0.5)	28 (0.5)	1.06 (0.61-1.85)

The rosiglitazone and pioglitazone meta-analyses differed in a number of ways. Unlike the largely short (69% of patients in trials $\leq$ 6 months) trials of rosiglitazone, which is where essentially all of the findings arose, the pioglitazone trials were generally longer (only 47% of patients in trials $\leq$ 6 months). The K-M curve shown by Dr. McEvoy at the AC (slide No 11), however, shows no suggestion of early adverse effect on MACE. There were also differences in control groups (placebo vs. comparator). To our best knowledge, however, none of the control treatments have known MACE effects, so I doubt these differences were important.

The pioglitazone meta-analysis does not, overall, suggest an effect on NFMI or mortality, as the rosiglitazone meta-analysis did. This is not a direct comparison, of course, and if there were some reason (other than that it is a true effect) for the rosiglitazone finding, it might not have been present for pioglitazone. Nonetheless, whatever the explanation, we have an absence of the troublesome rosiglitazone finding in the pioglitazone data. At the same time, and pertinent to the epidemiologic data, there is no real evidence here of any advantage over other treatments. That is, with respect to CV mortality, NFMI, it looks like the other drugs. Only for stroke, with few events, does it lean toward an advantage, and this seems well "rebutted" by the PROacitve trial (below).

The large (n = 5210) 3 year PROactive study compared pioglitazone to placebo, each added to background, and focused on CV risk in patients with a history of microvascular disease. Dr. Parks summarizes the 6 month results in her August 19 memo to Dr. Rosebraugh and Jenkins:

	Pio	***Placebo***	***HR***
Event	*N=2605 n(%)*	*N=2133 n(%)*	
CV Mortality	20 (0.8)	27 (1.0)	0.8
All Cause Mortality	25 (1.0)	30 (1.1)	0.9
NFMI	28 (1.1)	24 (0.9)	1.2
Stroke	20 (0.8)	17 (0.6)	1.3

Dr. Parks notes some suggestions of an adverse direction on NFMI and stroke, and indeed there is a "lean," although CV mortality leans favorably. Later data on Proactive actually border on a favorable result, as shown in slide 13 of the Dr. Parks' AC presentation. PROACTIVE failed to show an effect on its primary endpoint (a composite of all cause mortality, NFMI, NF stroke, ACS, cardiac intervention, major leg amputation, or need for leg bypass), but some of the secondary endpoints looked reasonably good.

Endpoint	***Add on Pio***	***Add on Placebo***	***HR (CI)***
"MACE"(total, not CV, Mortality)	301 (11.0%)	358 (13.6%)	0.84 (0.72-0.98) p=0.0277
CV Mortality	127 (4.9%)	136 (5.2%)	0.94 (0.74-1.20) p=0.6163

I believe any way you look at all of the pioglitazone data they lack any real basis for concern about increased CV risk. It cannot be emphasized too strongly that they do not represent a comparison with rosiglitazone, but they allow one to say that an apparent alternative to rosiglitazone is "concern- free" with respect to MACE. This means that what still remains critical is the strength of the rosiglitazone signal. As noted above, since the first meta-analysis, that signal has weakened, weakened to the point of absence for mortality (and it was never there for stroke) and weakened considerably for NFMI, but the NFMI conclusion will depend on RECORD re-adjudication.

IV. Epidemiologic Data

There seems little doubt that the Advisory Committee was impressed by one particular aspect of what seemed to be epidemiologic consistency: the apparent advantage of pioglitazone over rosiglitazone for important endpoints, notably CV mortality, stroke, and heart failure, in 3 epidemiologic studies, including Dr, Graham's CMS study. A fourth study, the WellPoint study, recently published [Wertz, et al. Qual Cardiovascular Circulation Outcomes. 2010; 3:538-45], was minimally presented at the AC meeting by a presenter who did not know much about the study, and the presentation had little impact. That study has now been published and as presented it clearly does not support any advantage for pioglitazone. Our recent detailed review of it, however, raises important questions about it.

I am in no position to assess the quality of the various epidemiologic studies, but will consider what these studies can tell us about the concerns that have arisen about rosiglitazone. Epidemiologists are well aware of the uncertain meaning of studies reporting very small differences between treatments, i.e. odds ratios of less than 1.5, which is what all of these studies report. Moreover, it is critical to note that the rosiglitazone vs. pioglitazone findings (which have received the most attention) fail to confirm the strongest finding of the meta-analysis, the 80% increase (i.e., OR=1.8) for MFMIs, an effect large enough to allow us to hope that an epidemiologic study might have detected it. The studies did not defect that effect. Instead, they have raised a set of wholly new concerns.

A. What are the epidemiologic findings.

1. Rosiglitazone vs. Other Antidiabetics

Remembering that the hypothesis of interest was generated by a meta-analytic comparison of rosiglitazone with other drugs (drugs not known to have adverse CV effects) and placebo, the most obvious studies of interest are comparisons of rosiglitazone with other drugs (not including pioglitazone for the moment). Dr. Gelperin has analyzed these in great detail and displayed overall results at the AC meeting. In her slides and in her detailed review it is clear that for AMI and all cause mortality, rosiglitazone does not appear worse than other antidiabetic agents (Gelperin AC slides 8,10); that is, the meta-analytic finding is not supported by the epidemiologic studies. Of some interest, however, is that for CHF, rosiglitazone is considerably inferior (slide 9) to other drugs, as we would expect it to be, giving the studies some credibility; i.e., they WERE able to detect a known effect of rosiglitazone. These studies show somewhat more favorable results for pioglitazone, but they are directionally similar. These epidemiologic studies do not support the meta-analytic findings.

2. Rosiglitazone vs. Pioglitazone

It is the epi findings comparing rosiglitazone and pioglitazone (note, no controlled trial data on this) that raised a new issue: whether for critical endpoints pioglitazone was superior to rosiglitazone. Three studies were described: Wickelmayor, Juurlink, and Graham. The results (Graham AC slide 26) were

	Wickelmeyer *n=28,301 2000-2005*	***Juurlink*** *n=39,736 2002-2008*	***Graham*** *n=227,571 2006-2009*
AMI	1.08 (0.93-1.25)	1.05 (0.9-1.23)	1.06 (0.96-1.18)
Stroke	1.07 (0.93-1.23)	------	1.27 (1.12-1.45)
Heart Failure	1.13 (1.01-1.26)	1.30 (1.15-1.45)	1.25 (1.16-1.34)
All Cause Death	1.15 (1.05-1.26)	1.16 (1.02-1.33)	1.14 (1.05-1.24)

Dr. Gelperin described these results (slide 26) as consistent with FDA's meta-analyses of pioglitazone and rosiglitazone, but that does not seem correct. FDA's meta-analysis of rosiglitazone has, as by far its strongest finding, an increase in AMI. But not one of the 3 epidemiologic studies finds a significant excess of AMI for rosiglitazone. That is, to say the least, a failure to support the "going in" hypothesis. The stroke finding, the strongest finding of the Graham study, also does not seem compatible with prior experience, and is not consistently present in the epidemiology studies. Pioglitazone looks good on stroke in its meta-analysis but, as noted above, in PROactive, pioglitazone was not

favored early for stroke. One could say the all cause mortality data for the two meta-analyses are similar to the epi studies but, as noted, the data from RECORD and the other large studies do not show an adverse effect of rosiglitazone on mortality and thus do not suggest that pioglitazone would have an advantage over rosiglitazone for mortality; yet in the Graham and other epi studies they do. This is, I believe, an entirely new observation/hypothesis. For the one endpoint where an advantage for pioglitazone might have been expected based on prior data, NFMI, there is none.

Dr. Graham has suggested that in his trial in the Medicare population, the absence of an effect on AMI can be explained by increased AMI mortality in the elderly Medicare population (average age 74.4) he studied, in effect converting all AMIs to deaths.

This could be examined further, but I looked at rates of fatal and non-fatal MI in 2 studies in elderly populations: STOP (Swedish Trial in Old Patients with Hypertension), with patients aged 70-84 and the Syst-Eur Study of isolated systolic HT in older patients (all > 60, mean age 70). In both studies about 25% of AMI's were fatal.

I. STOP

	Placebo	***Active***
n	*815*	*812*
First Events		
All MI	28	25
Fatal MI	8	6
NFMI	20	19

II. Syst. __

	Placebo	***Active***
n	*2397*	*2398*
All MI	45	33
Fatal MI	14	7
NFMI	31	26

Increased AMI mortality in people over 65 thus did not explain the absence of an AMI finding in Dr. Graham's study. It should be noted also that the rate of non-fatal heart attacks increases with age.

B. How credible would an epidemiologic finding be in this case.

Although there is great enthusiasm these days about the possibility that observational data will enable us to gain comparative data rapidly and relatively inexpensively with no real need to do large, costly, and difficult RCTs, it has long been recognized that when epi studies are looking at OR's < 2 (or less than 1.5 if you're very optimistic) they are of uncertain meaning. This recognition is not confined to clinical trialists but is shared by most epidemiologists as well, although there is a persistent hope that better methods will enhance the ability of the studies to defect small effects. At a conference on Comparative Effectiveness Research some months ago at the U of Pa, Dr. Brian Strom, a well-known epidemiologist, suggested that epi findings of odds ratios < 2 were not credible as comparative evidence (that is not to say they could not generate hypotheses).

One surely hopes that better methods will improve on this, but past history is worrisome:

- One of the very best drug epidemiologists, Hershel Jick, found, in three studies, that reserpine increased the risk of breast cancer by > 2-fold (close to 3-fold), a finding that was later discredited.
- Hormone replacement therapy was repeatedly (although not invariably) shown in epidemiologic studies to reduce CV events in post-menopausal women, a plausible outcome that was well- accepted until the Women's Health Initiative (WHI) study found the opposite to be true.
- A series of epidemiologic studies in the mid 1990's found that calcium channel blockers (CCB's) caused heart attacks, death, GI bleeding, all cancer, breast cancer, and suicide. None of these findings is now considered credible but they had a significant effect on published recommendations for blood pressure treatment, which suggested some reservations about early use of CCBs. It is of interest that a recent trial (ACCOMPLISH) comparing amlodipine (a CCB) 5-10 mg with hydrochlorothiazide 12.5-25 mg, an accepted standard if ever there was one, each added to benazapril, found a marked, highly statistically significant advantage for amlodipine on CV events, reducing them by about 20% compared to hydrochlorothiazide. Amlodipine could well be a drug that needs to be used more, and its use was surely limited by the spurious epidemiologic observations on CCBs.

Epidemiologists are appropriately cautious about small OR's. A 2005 study of the risk of AMI and sudden cardiac death in patients treated with NSAIDs found that the only NSAID with a risk of AMI during current use that was lower than the risk during remote NSAID use was celecoxib. Compared to celecoxib, use of ibuprofen, naproxen, and a mix of other NSAIDs had ORs of 1.26 (ibuprofen), 1.36 (naproxen), or 1.35 (other NSAIDs) for AMI, all statistically significant. The paper was by Graham, et al, including Wayne Ray, and I am quite certain it was well done. It was not, however, apparently believed by its author, who, in another published paper, advised anyone needing an NSAID to use naproxen first. There are, of course, other data to consider, but the advice by the author of what seemed to be a highly credible paper was to ignore it, advice that I am not necessarily disputing, but rather noticing.

V. Conclusions:

Since 2007 we have gained a modest amount of additional information to add to the original meta-analysis that raised the issue of rosiglitazone's cardiovascular toxicity. The expanded meta-analysis, which overlaps considerably with the studies in the Nissen meta-analysis, leaves the observed increase in AMI intact; it weakens the observed increase in mortality, but an adverse trend persists. RECORD, as reported, shows a much smaller effect of rosiglitazone on AMI (but this finding needs further assessment), but shows no effect at all on CV or total mortality. Although RECORD needs further evaluation with respect to AMIs, its mortality findings appear solid and, together with ADOPT, DREAM and BARI 2D, it weakens the evidence of increased CV mortality with rosiglitazone to the point where such an effect does not seem at all credible. Again, as noted above, the RECORD on therapy CV deaths total 57, well more than the 32 in small trials in the Nissen analysis. The as treated and ITT analyses have far more. The sum of the RECORD, ADOPT and DREAM on therapy

CV deaths appears to be almost 3 times the number in the Nissen small trials. There has never been any evidence of an increased stroke rate with rosiglitazone.

New pioglitazone data do not suggest any evidence of an adverse effect of that drug on CV outcomes, leaving us with one drug that might have an adverse effect (increased NFMI but no effect on stroke or mortality) and another member of the same pharmacologic class that does not, certainly an issue to be considered.

The epi data, in my view do not help very much. Apart from the skepticism that should attend reports of ORs in the neighborhood of 1.15, neither comparisons with various anti-diabetic drugs nor comparisons with pioglitazone support the one finding in the meta-analysis that remains potentially real, an increased rate of AMIs. Novel findings, such as increased stroke, are not consistently seen. The mortality observation in the epi studies, with RECORD and other large studies having shown no such effect of rosiglitazone, now seems to represent at best a new hypothesis, unsupported by any other data: superiority of pioglitazone to rosiglitazone on CV mortality and heart failure mortality. This is, in effect, a new effectiveness superiority claim, a claim we would never base on an epidemiologic finding, even a replicated one, but one that could very well deserve examination in a well-controlled study, such as TIDE. The impassioned views presented on TIDE, that the study was unethical, arose from the belief that issue was settled, i.e., that it is already known that pioglitazone is superior with respect to critical CV outcomes, notably mortality and stroke, to rosiglitazone. For the reasons given above, I believe we have no basis for such a conclusion. I should emphasize that as suggested by the IOM presentation at the AC meeting, if we did have clear evidence of a mortality (or even stroke) advantage of pioglitazone over rosiglitazone, I would agree that TIDE could not be conducted. But we do not have that evidence.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
09/10/2010