

LETTER TO THE EDITOR

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The rise and fall of rosiglitazone: reply

GlaxoSmithKline (GSK) understands and supports the value of academic and scientific critique. However, the editorial by Dr Steven Nissen published online on February 12¹ is neither academic nor scientific. Rather, it is rife with inaccurate representations and speculation that fall well outside the realm of accepted scientific debate. We strongly disagree with several key points within the editorial, most importantly those which imply misconduct on the part of GSK and have identified some of these issues below. On this basis, GSK believes that it is necessary for the journal to withdraw this editorial from the website and refrain from publishing it in hard copy, until the journal has investigated these inaccuracies and unsubstantiated allegations.

The editorial's overarching scientific perspective seems to rest primarily upon a restatement of Dr Nissen's well-publicized 2007 hypothesis inferred from limited meta-analyses of primarily short-term data from glycaemic-control studies. However, this hypothesis has not been confirmed by more recent and considerably more robust evidence from prospective, long-term cardiovascular outcomes studies. We address some of the misconceptions in his scientific argument below.

1. 'The rosiglitazone development programme was small, although typical of diabetes drugs in that era, consisting of five trials involving 2902 patients, mostly short-term (26 week) glycaemic-control studies.'

GSK disagrees with the author's assertions. In fact, the development program was at that time (November 1998) one of the largest New Drug Applications (NDA) submitted to the US Food and Drug Administration (FDA). Although five studies were described in the report by the FDA medical reviewer, the complete NDA submitted by GSK to FDA in November 1998 contained 21 clinical trials, including 11 randomized controlled trials (studies 006, 011, 015, 020, 024, 079, 090, 093, 094, 096, and 098) and 10 open-label studies. The NDA provided safety data on 4598 patients treated with rosiglitazone

with over 1000 patients having received rosiglitazone for 1 year or longer.^{2,3}

2. 'The effect on LDL-C was largely dismissed.'

GSK disagrees. Data regarding the effect of rosiglitazone on LDL-C have not been dismissed. LDL-C changes from baseline similar to those cited in the editorial have been included in rosiglitazone product labelling from the very first approved label at launch.

3. 'However, one prominent diabetes expert was... persuaded to sign an agreement barring him from publicly expressing concerns about the safety of the drug.'

The diabetes expert referred to in the editorial is Dr John Buse. The document that Dr Buse signed was not an agreement barring him from speaking but was a factual correction regarding data, which did not bar him from speaking at all. In fact, Dr Buse subsequently communicated his views regarding the safety of rosiglitazone to FDA.

4. 'Although the ADOPT study was actually performed, it was not powered to assess cardiovascular outcomes and did not adjudicate cardiovascular events.'

ADOPT was a Phase 4 commitment to FDA. It was a long-term study to include assessment of rosiglitazone on maintenance/restoration of insulin secretion by the pancreatic beta-cell and examination of the overall safety profile of rosiglitazone, including incidence of ALT elevations, cardiovascular and haematological events, and changes in body weight and lipids. The design of the ADOPT study was discussed with and approved by FDA. The agency did not require adjudication of cardiovascular events in ADOPT. Nevertheless, such a trial, which involved the adjudication of cardiovascular events, was designed and initiated as part of the European regulatory commitment, i.e. RECORD.

5. 'In January 2007, concerned about the cardiovascular safety of the TZD class, we requested access to patient-level data from the manufacturers of both rosiglitazone, GSK, and pioglitazone, Takeda. The makers of pioglitazone agreed, but the manufacturer of rosiglitazone declined.'

GSK did not decline the request but was in fact in active discussions with Dr Nissen about a potential collaboration to perform

another patient-level meta-analysis. GlaxoSmithKline explained to Dr Nissen that GSK had already performed a meta-analysis which was publicly posted to its clinical trial register.

6. 'Both GSK analyses revealed an increased risk of ischaemic myocardial events and were quietly posted on the company's clinical trials register and actually shared with the FDA. However, throughout this period, neither the company nor the FDA revealed these findings to the medical community nor to the public.'

GSK disagrees with the author's characterizations. Upon completing its updated analysis in 2006, GSK published the results on its publicly-available clinical trial register,⁴ informed data safety monitoring boards of ongoing rosiglitazone clinical trials, and submitted the data to global regulatory agencies, including FDA. Of note, rosiglitazone labelling in Europe was updated in 2006 to include the results of the GSK meta-analysis, and updated US labelling was pending FDA review.

7. 'When a meta-analysis of rosiglitazone was eventually submitted for publication, the company subverted the editorial review process by stealing a copy of the manuscript and used this advance knowledge inappropriately to unblind an ongoing randomized trial.'

This is simply not true. GlaxoSmithKline acknowledges receiving a faxed copy of the manuscript unsolicited from one of the reviewers, a fact that the reviewer has publicly acknowledged.⁵ At no time did GSK act in any way to subvert the editorial review process, let alone 'steal' a manuscript. The false allegation that GSK and/or its employees were guilty of criminal conduct in stealing the manuscript is defamatory and damaging.

8. 'The FDA finally added a "black box warning" about the risk of ischaemic myocardial events to the label of rosiglitazone in October 2007.'

GSK submitted data from its meta-analysis to FDA in 2006 with suggested labelling. The FDA performed its own meta-analysis and included precautionary wording in the boxed warning of the labelling for rosiglitazone regarding its meta-analysis as well regarding data from the ADOPT and DREAM trials and interim results of

RECORD. The overall conclusion by FDA, as stated in the boxed warning, is 'in their entirety, the available data on the risk of myocardial ischaemia are inconclusive.'

9. 'This study postulated an 11% annual event rate, but observed only a 2.5% rate.'

GSK disagrees with the implication that it intentionally underpowered the RECORD study. The statistical design was agreed with the EMEA before the study began. The observed event rate for cardiovascular events in RECORD was less than originally postulated when the study was designed (as has been seen in many other recently reported cardiovascular outcomes trials), in part due to advances in standard of care for cardiovascular disease. The RECORD study did, however, achieve its primary endpoint according to its pre-specified non-inferiority margin,⁶ a margin which is more stringent than what is suggested in the 2008 FDA guidance.

10. 'The HR for myocardial infarction was 1.14, but upper 95% CI reached 1.63.'

In RECORD, there was no statistically significant difference for myocardial infarction in patients on rosiglitazone vs. comparator. Additionally, Dr Nissen does not provide results for other secondary endpoints, including arguably the most clinically important parameter of mortality. Hazard ratios from RECORD for cardiovascular mortality (HR 0.84, 95% CI 0.59–1.18) and for total mortality (HR 0.86, 95% CI 0.68–1.08) were both numerically less than unity, with confidence intervals within the pre-specified non-inferiority margin.

11. 'About 40% of patients were no longer taking rosiglitazone by the end of the trial, further diluting any safety signals.'

GlaxoSmithKline disagrees with the author's characterization. In studies evaluating cardiovascular safety, the proportion of follow-up time to which patients were exposed to randomized study medication is more relevant than the proportion that were on the medication at the final visit. As stated in the publication of the final results from RECORD in *The Lancet*, patients in the rosiglitazone arm received rosiglitazone for 88% of total person-years follow-up, and patients in the control arm received control for 83% of total person-years follow-up.

12. 'A consensus treatment algorithm issued by the American Diabetes Association and European Association for the Study of Diabetes "unanimously advised against using rosiglitazone".'

The consensus statement issued by the ADA/EASD does not represent the official position of the ADA as noted in the document which states 'An American Diabetes Association consensus statement represents the authors' collective analysis, evaluation, and opinion at the time of publication and does not represent official association position.' Furthermore, the document states 'that the data are less than conclusive for a CVD risk with rosiglitazone.' Finally, neither the ADA 2010 Standards of Medical Care in Diabetes (which are reviewed and approved by the Executive Committee of ADA's Board of Directors), nor the AACE/ACE Consensus Panel algorithm (Sept/Oct 2009), distinguish between pioglitazone and rosiglitazone or recommend against the use of rosiglitazone.

13. 'In December 2008, the FDA issued a new guidance for the development of drugs to treat diabetes, requiring cardiovascular outcomes trials, sufficient to rule out an upper 95% CI for the HR of 1.8 prior to approval and 1.3 in a Phase IV trial.'

Although not required to meet the new guidance, RECORD satisfies the new standard. The results for the primary outcome of RECORD (cardiovascular hospitalization or cardiovascular death) were HR 0.99, 95% CI 0.85–1.16. Additionally, the hazard ratio in RECORD for MACE (major adverse cardiovascular events; composite of cardiovascular death, myocardial infarction, or stroke), which is a commonly accepted measure of ischaemic morbidity and mortality, was 0.93, 95% CI 0.74–1.15. The MACE endpoint has been suggested by FDA as the preferred measure for the evaluation of overall cardiovascular risk.

14. 'Although early warnings were issued for the risk of heart failure, these warnings went largely unheeded in the face of aggressive marketing and promotion suggesting cardiovascular benefits.'

Heart failure is a well-known class effect of the thiazolidinedione class, and the original US labelling for rosiglitazone contained a Precaution for 'Use in Patients with Heart Failure' describing preclinical effects and echocardiographic studies. As additional data on heart failure have become available, the labelling has been updated. Currently, the labelling for both marketed thiazolidinediones, rosiglitazone and pioglitazone, contains a boxed warning regarding heart failure as well as a contraindication to initiate TZD use in patients with class III–IV CHF. GlaxoSmithKline standard practice is to include full fair balance information, including cardiovascular risks, on all marketing and promotional

materials, and to disseminate the labelling on every sales call with healthcare professionals.

15. 'FDA rushed to approve rosiglitazone because of hepatotoxicity concerns about troglitazone, resulting in failure to consider the "signals" suggesting cardiovascular toxicity.'

US Food and Drug Administration approval of rosiglitazone occurred after a public advisory committee meeting, which entailed a full review of the available safety data. US Food and Drug Administration was clearly cognizant of areas of product safety that needed further study, as illustrated by the agency's placement of a post-marketing commitment for GSK to conduct the ADOPT study. The safety parameters required by FDA within ADOPT included the investigation of the incidence of cardiovascular events as well as ALT elevations, haematological events, and changes in body weight and lipids. And, on 30 July 2007, the FDA convened an Advisory Committee meeting to review the ischaemic cardiovascular safety of rosiglitazone and that Committee voted nearly unanimously to recommend rosiglitazone's continued availability to patients in the USA.

The final results of RECORD showed that rosiglitazone met the pre-defined statistical criteria for demonstrating no excess cardiovascular risk relative to other standard diabetes medications. These clinical trial data are consistent with data from other large, independent, cardiovascular outcomes trials containing significant exposure to rosiglitazone that have reported since 2007, including the Veterans' Administration-sponsored VADT trial and the NIH-sponsored ACCORD and BARI-2D trials.

GlaxoSmithKline is reassured by the evidence from these large prospective, randomized trials, which provide a much more reliable assessment of cardiovascular safety than hypotheses-generating meta-analyses. If fair and appropriate weight is given to the evidence from larger interventional studies that were prospectively designed and included an adjudication process for cardiovascular events, the data on rosiglitazone compel a different conclusion than that reached by the editorialist.

GlaxoSmithKline looks forward to a response from the journal and to an opportunity to promptly rectify the public record.

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