Author's response to reviews

Title: Safety and tolerability of sitagliptin in clinical studies: A pooled analysis of data from 10,246 patients with type 2 diabetes

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Rachel Neilan, MSc.
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Dear Ms. Neilan:

On behalf of my co-authors, I am submitting the revised manuscript entitled, "Safety and tolerability of sitagliptin in clinical studies: A pooled analysis of data from 10,246 patients with type 2 diabetes," to be considered for publication in BMC Endocrine Disorders. We appreciate the efforts and comments from the reviewers. Below we provide responses to the comments from the reviewers and editor. In addition, sections in the manuscripts that have revised are highlighted. We feel that the revisions have improved the clarity and content of the manuscript and look forward to receiving the journal's decision.

Please let me know if you require any additional information.

Sincerely,

Debora Williams-Herman, MD
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Reviewer 1's report:
The authors report a pooled safety and tolerability analysis of 10,000+ persons randomized to sitagliptin vs. control treatment for 12-104 weeks (mean 282 vs. 259 days of treatment, total 4700+ sitagliptin vs. 3900+ comparator patient-years of follow-up).

The analyses were based upon the time to the first (incident) event, calculated as follows: incident event rate = 100 * (total number of patients with >1 event during eligible exposure period per total patient-years of exposure). Question: was there also capture of individual events, in case some persons had >1 event?

Authors' response: Yes, if patients had multiple occurrences of the same event, they were all collected in the database. The primary statistical analysis followed the common convention of counting the number of patients with events, and only considered the time to the first event.

The observations “included data after initiation of glycemic rescue therapy” – Question: was the sitagliptin (or comparator) always continued after such treatment was initiated?

Authors' response: Yes, patients continued taking the blinded treatment to which they had been assigned at randomization even if they initiated glycemic rescue therapy during the study. This information has been added to the Methods section (p. 7).

The noteworthy findings, such as they are, are in table 4:

Blood and Lymphatic System Disorders 1.1 vs. 0.6 mean diff 0.4 (0.0, 0.8) – the authors explain this is because of increased likelihood of anemia with sitagliptin.

Metabolism And Nutrition Disorders 9.3% of sitagliptin vs. 16.3% of comparator mean diff 6.8 (-8.5, -5.2) – the authors explain this is because of increased likelihood of hypoglycemia with sulfonylurea comparators to sitagliptin

Skin and Subcutaneous Tissue Disorders 8. 6% of sitagliptin vs. 7.3 mean diff 1.3 (0.1, 2.5) – the authors state that this appears to reflect several different skin conditions, none occurring with high frequency.

Also somewhat noteworthy are the gastrointestinal conditions in table 5, more diarrhea and abdominal pain occurring with comparators, and related to effects of metformin, while more constipation occurred with sitagliptin, and although the
authors do not comment on it this likely reflects what is in effect a “therapeutic” effect of metformin for persons who would without such treatment have constipation.

Authors' note: An interesting observation. The data could also suggest that sitagliptin has a "therapeutic effect" on the diarrhea and nausea associated with metformin.

The cardiovascular analysis is of interest in suggesting no evidence of adverse effect of sitagliptin, with the 95% CI showing an upper bound < 1.3-fold above comparators.

Reviewer 2's report:

Minor Essential Revisions:

1. The question posed by the authors is well defined and methods are appropriate and well described. The information in clearly relevant. Nevertheless, regarding methods, we would need to know more on the characteristics of the included studies: are they all “international multicentric studies”? Are the authors also collecting information from local studies? Are these results collected from all the controlled trials the sponsor carried out during the stated period? (if not, state in a deeper manner the inclusion criteria for the 19 studies entered into analysis). Some of them are published, other presented just as abstract to congresses. Is that correct?

Authors' response: The authors have updated the description (all inclusive) of the data source in the manuscript (Methods section, p. 4-5): The pooled population was drawn from all (n = 19) multicenter, U.S. or multinational, double-blind, parallel-group studies conducted by Merck in which patients were randomized to receive sitagliptin 100 mg per day (or comparator) for at least 12 weeks and up to 2 years (the duration of the longest studies) and for which results were available as of July 2009. Details of studies not included are described in the manuscript (p. 4-5)

Results from the majority of the studies that contributed to this analysis have been published in peer-reviewed journals (Table 1 lists current citations for each study); results from all studies except recently-completed clinical trials (that have yet to be published but have been presented at scientific meetings and are therefore available in abstract form) are available on clinicaltrials.gov or clinicalstudyresults.org. Manuscripts from recently-completed studies are either under review or in development for submission to peer-reviewed journals.

2. Hypoglycemia is an adverse event of main interest. But hypoglycemia definition may vary among different studies. What was the definition of hypoglycemia for the 19 selected studies? (please include in methods). Was this definition homogeneous among studies?

Authors' response: The definition of hypoglycemia was the same in all clinical trials included in this analysis. We have updated the Methods section to include the following information (p. 9): "For all of the trials that were pooled for this
analysis, hypoglycemia was based upon investigator interpretation of clinical symptoms, without the requirement for a concurrent glucose determination."

3. Were the adverse events frequencies (at least for those of main interest) homogeneous among studies? (even when it is a pool analysis, among studies heterogeneity could be of interest, at least for most important events).

Authors' response: As one might expect, given the different background and comparator antihyperglycemic therapies across trials (metformin, TZDs, sulfonylureas, insulin, and placebo), there was some heterogeneity of incidence rates for key adverse events of interest among studies. For example, as discussed in the Results section (p. 15-16), the incidence rates of two adverse events of interest, hypoglycemia and diarrhea, were influenced by the use of a sulfonylurea and metformin, respectively, as comparators in some studies. In sensitivity analyses that removed the confounding influence of these agents, the between-group differences for these adverse events were removed.

Also, as noted in the Methods Section, the present analysis employed stratification by study to account for potential differences among studies.

4. Pancreatitis is another event of importance. Even when authors state: “the analysis of reports of pancreatitis, an additional gastrointestinal event of recent interest, is presented elsewhere”, some data could be of importance. Had the authors access to amylase and / or lipase values to detect their modification? If not, please state this as a limitation.

Authors' response: The authors agree that pancreatitis is another event of importance and have devoted an entire manuscript (currently in press, Engel et al, IJCP) to this topic. Given the length of the current manuscript, the authors prefer to refer readers to the other manuscript which is focused entirely on the analysis and discussion of pancreatitis. Amylase and lipase were not collected in these studies. In the absence of clinical symptoms, these laboratory measurements are neither sensitive nor specific for pancreatitis [Yaday et al. Am J Gastroenterol 2002; Sutton et al. Am R Coll Surg Eng 2009; Lankisch et al. Scan J Gastroenterol 2009; Volzke et al. Pancreas 2008] and the authors do not consider that the absence of routine collection of such laboratory measurements is a limitation.

5. Also studies duration is a limitation for some of the events considered into this analysis: e.g. some neoplasias. As far as we understand, the longer trial lasted for two years. Please state this into “study limitations”.

Authors' response: As suggested, study duration has been added to the list of limitations pertaining to this analysis (p. 29).

Assistant editor's report:
While we understand that this manuscript present an analysis of data from several studies can was ask you to confirm that the trials were carried out with
informed consent and local ethical approval. A brief statement to this effect should be included in the methods section.

Authors’ response: The Methods section has been updated to reflect that patients were to provide informed consent and each protocol was reviewed and approved by the appropriate ethical review committees and authorities for each clinical site (p. 5).

Additional Edits from the Authors:

We updated Appendix I to include information on CV deaths that were included in the MACE analysis. The results for liver function tests were also corrected.