Author’s response to reviews

Title: Safety and tolerability of sitagliptin in patients with type 2 diabetes: A pooled analysis

Authors:

Debora Williams-Herman (debora_williamsherman@merck.com)
Elizabeth Round (elizabeth_round@merck.com)
Arlene S. Swern (arlene_swern@merck.com)
Bret Musser (bret_musser@merck.com)
Michael J. Davies (michael_davies2@merck.com)
Peter P. Stein (pstein2@comcast.net)
Keith D. Kaufman (keith_kaufman@merck.com)
John M. Amatruda (john_amatruda@merck.com)

Version: 2 Date: 21 September 2008

Author’s response to reviews: see over
September 20, 2008

Melissa Norton, MD
Editor in Chief
BMC Endocrine Disorders

Dear Dr. Norton:

On behalf of all of the authors, I am submitting the revised manuscript entitled, “Safety and tolerability of sitagliptin in patients with type 2 diabetes: A pooled analysis”, to be considered for publication in BMC Endocrine Disorders. We have revised the manuscript based on the feedback from the reviewers. We feel that these revisions have strengthened the manuscript. We have also addressed each concern or question raised by the reviewers. Our responses are included in this letter on the subsequent pages for your review.

In addition to the suggested edits in the manuscript, we include the two appendices that were inadvertently excluded in our initial submission. These appendices list the terms used in some analyses included in the manuscript. Furthermore, as a result of a reviewer's comment, we split Table 7 into 2 tables, which increased the total number of tables from nine to ten.

Please let me know if you require any additional information. We look forward to the final decision on our manuscript.

Sincerely,

John M. Amatruda, MD
Vice President, Clinical Research
Merck Research Laboratories
126 E. Lincoln Ave.
RY34A-212
Rahway, NJ 07065
Phone: 732-594-3632
Fax: 732-594-3750
e-mail: john_amatruda@merck.com
Reviewer #1 report:
The authors have capably described potential adverse outcomes of sitagliptin treatment, comparing these with events in the control population.

* Major Compulsory Revisions

None

* Minor Essential Revisions

None

* Discretionary Revisions

1) In table 5, the most robust adverse effect is hypoglycemia seen in 117 sitagliptin-treated vs 296 control patients. Given the importance of this outcome, the authors might comment on whether the high hypoglycemia group comprised only sulfonylurea-treated patients, and give a bit more information, perhaps in a table, allowing the reader to better understand the treatment regimens compared.

Authors' response: In the manuscript we note that the difference in the incidence rates of hypoglycemia between treatment groups was driven largely by the use a sulfonylurea in the comparator group. We confirmed this by determining the incidence rates of hypoglycemia while patients were using a sulfonylurea. Of the 296 patients in the non-exposed group with at least one episode of hypoglycemia, 239 (81%) had an episode while treated with a sulfonylurea. For the patients not treated with a sulfonylurea, the incidence rates for hypoglycemia were 2.6% (n/N: 87/3298) and 2.3% (50/2428) in the sitagliptin and non-exposed groups, respectively. We've added this information in the Results section (p 13, Lines 2-7).

2) There are two somewhat frequent groups of adverse effects of sitagliptin in table 5, painful symptoms (chest pain, tooth abscess, osteoarthritis) in 94 sitagliptin-treated vs 35 controls. Even if one adds sinus headache from the non-exposed sitagliptin group, this still seems an important finding -- do the authors wish to comment?

Authors' response: Although the adverse experiences cited by the reviewer occurred more frequently in the sitagliptin group, these adverse experiences occurred in different body systems, have different pathophysiology, and are not recorded as "pain". By convention these AEs would not be added together. We prefer to report the data as assessed by the investigator.

3) The second is dermatologic - if one adds acne and contact dermatitis, there were 31 vs. 7 cases, which seems real and about which the authors also might wish to comment. Also, table 6 has 35 vs. 24 patients with rash, quite different numbers -- could the authors explain this discrepancy? The dermatologic question is as the authors state in the introduction very important. Parenthetically, this reader wonders why a dermatologic category is not included in table 7, since it certainly exceeds 0.5% of patients.
Authors' response: In the present analysis, there were increases in the incidence rates of acne and contact dermatitis in the sitagliptin group, although the incidence rates were low (≤0.7%). As we reported, approximately half the cases of contact dermatitis were related to exposure to poison ivy/oak. Although these types of adverse experiences are both dermatologic conditions, they have very different pathophysiology. We prefer to report the data as assessed by the investigator.

Overall the incidence rates of skin- and subcutaneous tissue-related adverse experiences were not different between groups. The reviewer points out that the number of patients with an adverse experience of rash is different in the sitagliptin and non-exposed groups (35 vs. 24, respectively). However, taking into account the difference in the number of patients in each group, the incidence rates were similar between the sitagliptin and non-exposed groups (1.0% and 0.9%, respectively). Lastly, Table 7 comprises specific adverse experiences that were assessed by the investigator as drug-related and are included in this table if they were reported at an incidence rate of ≥0.5%.

4) For table 9, it would be interesting to know the frequency of liver chemistry elevations below the arbitrary 3x ULN level. Similarly, are the uric acid, CPK, Ccreat, etc categories based on arbitrary degrees of change deemed clinically important, or do they refer to any increase or decrease?

Authors' response: The reviewer is correct in noting that in table 9, we report laboratory adverse experiences as assessed by the investigator. These reports are based on the investigator's assessment of laboratory safety reports and do not necessarily reflect specific degrees of change.

Reviewer's report
Title: Safety and tolerability of sitagliptin in patients with type 2 diabetes: A pooled analysis
Version: 1 Date: 28 July 2008
Reviewer: John H Kalbfleisch

Reviewer's report:
MAJOR COMPULSORY REVISIONS
The manuscript seems to require a meta-analysis approach – clarity in the statistical methodology is needed. Elaborate data procurement and analysis in methods.

1) Provide a description of the analysis procedure used to obtain results in the tables. Explain how the “between study” variable (there were 12 studies used) was accounted for in the analysis procedure. If frequency counts of the 12 studies were simply combined (as if in a single large study) then this should be stated. See comment 3).

Authors' response: Because all studies included in the analyses were sufficiently-similar, parallel-arm, randomized, double-blind studies, individual patient-level data from each of the 12 studies were combined and treated as if they were derived from a single, large clinical study. This has been clarified in the manuscript (Methods p. 6, Line 9). Further, we decided not to include a between-study variable in the analyses in order to identify potential imbalances in rare events.
2) “Methods” should identify the inclusion and exclusion criteria used for selecting studies that were used to achieve composite results.

Authors' response: These 12 studies represent the double-blind, randomized, Phase IIB and III studies that included patients treated with the clinical dose of sitagliptin (100 mg/day) for at least 18 weeks up to 2 years and that were available in a single safety database as of November 2007. This information has been added to the abstract (p. 2) and Methods section of the manuscript (p. 5, Lines 12-15).

As reported in the manuscript (p. 5, Lines 5-7), the safety and tolerability of dose-adjusted sitagliptin in a special population of patients with moderate to severe and end-stage renal insufficiency have been reported elsewhere.

MINOR ESSENTIAL REVISIONS
3) Did the 12 studies give the same (similar) group comparison results, or were there conflicting indications between studies for (important) outcomes? How many of the 12 studies showed the reported conclusion in the manuscript (or how many gave a different conclusion).

Authors' response: The results from each of the 12 studies were generally consistent with the conclusions of the pooled analysis. The exception was the incidence rate of hypoglycemia in individual studies, as discussed in the manuscript.

4) In addition to the 95% CI’s the authors could consider showing levels of significance associated with comparing group rates. Because of the number of comparisons presented in the tables via 95% confidence intervals, some Type-I errors are expected.

Authors' response: The 95% CIs were reported rather than p-values because of the number of comparisons that were made and the concern for Type-I error.

5) Major sections of the manuscript have mixed content and a revision is suggested (statements of methodology belong in Methods, results in Results and so on).

Authors' response: In the Methods section describing Potential Mechanism-based Adverse Experiences (pp. 7-9), we provide introductory comments for each grouping of adverse experiences. We felt that it may be easier for the reader to understand the reasons for highlighting these adverse experiences and comparisons if the background information was provided simultaneously. We prefer to keep the format unchanged.

6) Mention unreported outcomes with a rate <1% (as text - unless there are too many). There are some tables that report rates less than 1% - an apparent conflict with statements “that only rates 1% and higher are shown.”

Authors' response: We state in the manuscript (Methods p. 7 Lines 6-8) that "Since drug-related and serious clinical adverse experiences are generally reported less frequently, these events were summarized using lower cut points (i.e., 0.5% and 0.2% of patients, respectively)." We also reported any adverse experience for which the 95% CIs excluded zero for the between-group
difference, regardless of the incidence rate. As expected in this population of patients with type 2 diabetes, numerous adverse experiences were reported in the sitagliptin and non-exposed groups and the table of all adverse experiences would have been too large for publication.

7) Follow the usual table publication format. Omit most horizontal and vertical lines between adjacent rows/columns and remove the horizontal black bar in Table 7.

Authors' response: Per the reviewer's comment, we have split Table 7 into 2 tables (now Tables 7 and 8).

8) Authors could consider 2 decimal places (instead of 1) for reporting 95% CI limits. This is an attempt to be clearer for “0” endpoints of the CIs. Which strategy was used for rounding to report % values (round-down, round-up or round-off)?

Authors' response: Round-off was the strategy used in the analysis. In the footnote of tables, we report that "0.0" and "-0.0" represent rounding for values that are slightly greater and slightly less than zero, respectively.

DISCRETIONARY REVISIONS

9) Incidence is the numerator (count) for an incidence rate. Since the treatment effect is evaluated by comparing group rates, I would suggest using “incidence rate” instead of “incidence” throughout the manuscript.

Authors' response: Per the reviewer's suggestion, we have changed the wording, where applicable, throughout the manuscript.

10) Summary statistics in the tables are N (%). The % is a rate and most of these seem to be incidence rates. Some rates (table 4) might be viewed of as prevalence rates (outcomes that occur before study enrollment and then recur during the study are not “new” recurrences), however, groups are still compared on the reported rate statistics.

Authors' response: The data reported in the manuscript are incidence rates based on adverse experiences with onset dates after randomization that were reported by the investigator.

11) Authors state that rates of drug-related adverse experiences and discontinuations due to drug-related adverse experiences were higher in the non-exposed group, “primarily due to the increased incidence of hypoglycemia in this (non-exposed) group.” However, there is no supporting evidence for this explanatory statement. It seems that the data analysis could show if drug-related adverse events are more frequent in participants reporting hypoglycemic experiences (thus providing supporting evidence) –

Authors' response: In the manuscript we note that the difference in the incidence rates of hypoglycemia between treatment groups was driven largely by the use a sulfonylurea in the comparator group. We confirmed this by determining the incidence rates of hypoglycemia while patients were using a sulfonylurea. Of the 296 patients in the non-exposed group with at least one episode of hypoglycemia, 239 (81%) had an episode while treated with a sulfonylurea. For
the patients not treated with a sulfonylurea, the incidence rates for hypoglycemia were 2.6% (n/N: 87/3298) and 2.3% (50/2428) in the sitagliptin and non-exposed groups, respectively. We've added this information in the Results section (p 13, Lines 2-7).

12) In the “Competing Interests” section, consider a brief statement that addresses the “conflict of interest” outside of employment. I find myself asking if there are studies that were excluded (see inclusion and exclusion in Major Compulsory Revision) because of the result they produced. If all available studies were used, then a statement to that effect should be made. All 12 studies were published, were unpublished studies excluded?

Authors' response: These 12 studies represent the double-blind, randomized, Phase IIB and III studies that included patients treated with the clinical dose of sitagliptin (100 mg/day) for at least 18 weeks up to 2 years and that were available in a single safety database as of November 2007. This information has been added to the abstract (p. 2) and Methods section (p. 5, Lines 12-15).

As reported in the manuscript (p. 5, Lines 5-7), the safety and tolerability of dose-adjusted sitagliptin in a special population of patients with moderate to severe and end-stage renal insufficiency have been reported elsewhere.

13) “Pooling” is mainly a statistical term. An alternative descriptor (combining, composite) might be understandable/informative to more readers. The authors are not clear on the statistical methodology for pooling.

Authors' response: This has been clarified in the manuscript (Methods p. 6, Line 9). Because all studies included in the analyses were sufficiently-similar, parallel-arm, randomized, double-blind studies, individual patient-level data from each of the 12 studies were combined and treated as if they were derived from a single, large clinical study.

14) This is a question or comment I have. Were the groups similar if the study-time is considered for rates? Were some outcomes observed immediately or early in studies and in similar fashion for both study groups? (similar for outcomes occurring across a 2 year) Groups rates could be similar but one group could experience the adverse outcome sooner than the other group (a survival type analysis could detect this).

Authors' response: As noted in the manuscript (p. 11, Lines 11-14), the findings from the primary analysis were generally consistent with those examining the event rates per 100 patient-years.

We appreciate the question of timing as a potential issue in an analysis of this sort. Although we did not conduct time-to-event analyses across these studies of different durations, we did evaluate individual adverse experiences on a case-by-case basis (e.g., nasopharyngitis) for recurrences of events and time of onset during the trials and have seen no notable differences.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare I have no competing interests.