Author's response to reviews

Title: Efficacy of Alogliptin in Type 2 Diabetes Treatment: A Meta-analysis on Randomized Double Blind Controlled Studies

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Authors’ response to 2nd time reviewers’ comments

Efficacy of Alogliptin in Type 2 Diabetes Treatment: A Meta-analysis of Randomized Double-Blind Controlled Studies

Reviewer # 1 (Apostolos Tsapas):

General:
We would like to say thank you for taking again your time to review our revised manuscript. We still find your comments very constructive and we hope we have accommodated or explained as described below point by point.

Specific:

Major Compulsory Revisions

Comment 1: “Results, paragraphs 3 and 4: were subgroup analyses, sensitivity analyses, meta-regression etc predefined, or were they decided post-hoc? How did the authors correct for all these exploratory analyses? Mentioned in initial comments as well.”

Response: These comments come for the second time. We realized that we have misunderstood it and replied wrongly in our previous reply. Now, as described in detail in the methods section (DATA SYNTHESIS & STATISTICAL ANALYSIS –paragraph 3) and partly in the results section (3rd paragraph), it is well addressed. To minimize the false positive, we have limited the number of covariates to one.

Comment 2: “Page 7, paragraph 3: Please explain rule utilised to assess OVERALL risk of bias when applying Cochrane risk of bias tool (which were your predefined key domains?? When was overall risk of bias deemed low, when unclear and when high?).”

Response: To accommodate this comment, the statement on Risk of bias of individual studies is further elaborated with the following statements in the methods section (DATA SYNTHESIS & STATISTICAL ANALYSIS –paragraph 4). “Risk of bias of individual studies was assessed with the Cochrane risk of bias tool. The predefined key domains include: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. A bias that is unlikely to affect the result was considered as “low risk of bias”, while bias that raises doubt about the results was considered as “unclear risk of bias” and bias that seriously affect the results was considered as “high risk of bias”.
Comment 3: “Page 8, paragraph 1: "...In subgroup analysis, use of both doses of alogliptin as add-on or alone (alogliptin alone vs alogliptin plus other antidiabetic drug) and patients difference in experience to antidiabetic drug (antidiabetic drug naïve vs antidiabetic drug experienced) did not explain the observed heterogeneity. ..." Please rephrase - not clear what you mean. How did you check that? What do you mean with experience?”.

Response: Now, we have elaborated the statement and operationalized what antidiabetic drug naïve and and antidiabetic drug experienced means in the method section (Under subtitle – OPERATIONAL DEFINITION). The variation among the subgroups was checked by the test for the subgroup differences.

Comment 4: “Page 8, paragraph 1: "... But subgroup analysis depending on study location (study in a single country vs study in multiple countries) showed significant reduction in HbA1c in single country studies than studies in multiple countries. ...". If you want to check for effect of study location why are you comparing single site vs multi-centre studies? This is not the same question.”.

Response: Yes, we do also found it being a little bit confusing. The intension of this subgroup analysis was to evaluate the difference in treatment outcome of multinational studies (conducted in multiple countries) from one nation studies (conducted in a single country at multiple sites) but was not to check the effect of study location on the treatment outcome. Now, we have attempted to make it more lucid and informative.

Comment 5: “Page 9, paragraph 2: the results of meta-regression analysis should be analysed more in the discussion. What is the potential clinical relevance of this finding? Could alogliptin be not-useful if used for > 12 weeks (the real clinical life...)? What is the implication of your finding for clinical life and for research??

Response: Now, it is well explained in the Discussion section (paragraph 3)

Comment 6: “Discussion: In initial comments the authors were asked to comment on the following point: What is the clinical relevance of outcomes assessed? Please comment. Why use both HbA1c and FBG? CVD mortality is more patient important. Did the authors extract data for it? If not, why?".”.

Response: Now, we have included comments on HbA1c and FPG in the first paragraph of the discussion section. Regarding CVD, we have conducted additional meta-analyses on the adverse events of alogliptin including hypertension, hypoglycemia etc and its effects on the serum lipid level (Table 1). Since the number of studies that addressed this issue were very few, it may be too early to make strong conclusions.
Minor essential revisions:

Comment  7-9:  
Response: Thank you for your in-depth review. All comments are well taken and accommodated.

Comment 10: “Data synthesis and statistical analysis: Is funnel plot / visual inspection good enough for assessment of publication bias? See relevant articles in BMJ and consider using formal assessment (Egger test).”

Response: No, it was not good enough. But, from the journal that you rightly recommended, the tests for funnel plot asymmetry were not recommended in meta-analyses of randomized controlled trials with fewer than 10 studies, which is true in our meta-analysis (the maximum number of studies analyzed at a time was only nine). Thus, we have not used the tests for funnel plot asymmetry in this study. Since we find this description so important, we have included in the methods section (last paragraph). For your information, the Egger’s test and Begg’s test of the funnel plot asymmetry showed the existence of significant publication bias (It is attached in the resubmission as additional file). However, we didn’t report these findings in our results section. This is because our reference article (Ref 14) recommends not to be used unless the included articles are above 10 and above. In Box 2, it says, “As a rule of thumb, tests for funnel plot asymmetry should not be used when there are fewer than 10 studies in the meta-analysis because test power is usually too low to distinguish chance from real asymmetry.”
Reviewer # 2 (Marc Rendell):

General:
We would like to say thank you for taking again your time to review our revised manuscript. We still find your comments very constructive and we hope we have accommodated or explained as described below point by point.

Specific:

Major Compulsory Revisions

Comment 1: “The authors must explain the clear differences between the Japanese studies and the American and European studies. They need to account for the obvious heterogeneity. They must explain why the HbA1c lowering meta results were much more weighted by the Japanese studies”.

Response: To our understanding, as described in detail in the discussion section (paragraph 4), the major differences between the Japanese studies and the American and European studies:
1. The duration of therapy in Japanese studies were only 12 weeks,
2. The sample sizes of Japanese studies were relatively smaller
3. May be difference in ethnicity and cultural background.

Comment 2: “There has to be a metanalysis of adverse events including the skin effects which are well documented with alogliptin and the incidence of pancreatitis”.

Response: Thank you for your recommendation. As we replied in the previous comment, the major reason was lack of adequate number of studies that reported specific adverse events. Though the included number of studies is small, now, we have conducted 14 meta-analyses on adverse events and incidence of infection/infestation; 4 meta-analyses on serum lipids profile. Since the number of additional Figures (Forest plots) become 4 and relatively lengthy, we summarized all in Table 2 and Table 3. Still for your information, we have attached all additional Forest plots as additional material. But, it should be noted that the incidence of pancreatitis was not found being reported in the included studies. We find several cases of pancreatitis with other DPP-4 inhibitors like Sitagliptin.
Reviewer # 3 (Abd Tahrani):

General:
We would like to say thank you for taking again your time to review our revised manuscript. We still find your comments very constructive and we hope we have accommodated or explained as described below point by point.

Specific:

Major comments
Comment 1: “The subgroup and sensitivity analysis performed by the authors is useful and interesting. Nonetheless, the authors need to discuss the findings of these analysis in the discussion section of the paper”.

Response: Now, it is well addressed in the Discussion section (paragraph 2 and 3).

Comment 2: “In addition, I think the authors need to "water down" their statements about the efficacy of Alogliptin 12.5mg as removing single studies resulted in the HbA1c change becoming non-signficant, depending on which study is removed. This needs to be explained/discussed.

Response: The overall odds ratios and SMDs were stable when single study was withdrawn from the analysis. Therefore, the overall efficacy of Alogliptin 12.5mg on HbA1c was not affected significantly when single study was withdrawn from the analysis.

Comment 3: The limitations sections need to include a comment about the excessive heterogeneity.”

Response: Well taken comment. It is accommodated.