Author’s response to reviews

Title: Effects of vildagliptin as compared to glibenclamide on glucose variability after a submaximal exercise test in patients with type 2 diabetes - DIABEX VILDA: study protocol for a randomized controlled trial

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Author’s response to reviews: see over
To
Doug Altman, Editor in Chief
Trials
MS: 2080048603129926

Title: Effects of vildagliptin as compared to glibenclamide on glucose variability after a submaximal exercise test in patients with type 2 diabetes - DIABEX VILDA: study protocol for a randomized controlled trial.

Dear Dr. Doug,

Our thanks to you for critiquing our manuscript entitled “Effects of vildagliptin as compared to glibenclamide on glucose variability after a submaximal exercise test in patients with type 2 diabetes - DIABEX VILDA: study protocol for a randomized controlled trial”. As requested, we have incorporated the suggestions into the text; they are all highlighted in yellow. We believe that the manuscript is now improved. Please find our responses to each comment below.

Thank you for your time and consideration of this manuscript.

Sincerely,
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Editorial requests:
1. Please highlight the ‘Background’ and ‘Methods/Design’ titles in the Abstract. Thank you for the instructions. The alterations were done as required.

2. Please include an additional file title and legend section after the figure legend section. Thank you for the instructions. The alterations were done as required. An additional file is now provided with the manuscript.

Referee 1:
Major compulsory revision:
1.) The authors need to provide the standard deviation used for MAGE in the sample size estimation in order to make the estimation reproducible.
Answer: Thank you for the observation. The standard deviation was added (page 4, line 9).

2.) The section study intervention is not very clear: when will they increase the glibenclamid dose (second week?). In whom will the dose be further increased – the authors mention to aim for an HbA1c of 7.0%, but firstly I think HbA1c will not be of much help given the short treatment period and secondly I have not seen any HbA1c measurements at the 4 or 8 weeks follow up visits.
Answer: You are right, thank you. We added “on the second week” in the appropriate place on text (page 6, line 3). We believe that it is clear now. Moreover, in follow up visits we will have the values of preprandial capillary plasma glucose, so we will be able to adjust the dose, as needed (page 6, line 8).

3.) The authors state that they will evaluate glucose variability after the submaximal exercise test. However, I have not seen a clearly defined time period after the exercise test, which will be used for data analysis for the primary endpoint.
Answer: Thank you for the observation. This information is written in page 7, paragraph 3, and now we highlighted it in yellow.

Minor revision:
4.) The authors mention 10 visits (eligibility, 3 days of assessments, week 4, week 8 and another 3 days of assessment) – did I miss a visit?
Answer: Thank you for the observation. The eligibility assessment will be done in two visits. To clarify this mention, we added “which will last two visits” in the end of first phrase of Eligibility assessment and follow-up visits (page 4, paragraph 5).

5.) P6 “… bring the medicine tablets with them to count the pills” should be rephrased (e.g. Drug accountability will be assessed at each follow up visit.)
Answer: Thank you for the suggestion. This sentence was changed as suggested (page 6, paragraph 2).

Referee 2:

1. Page 3 – The sentence: “The primary outcome will be glucose variability reduction” it should be “The primary outcome will be glucose variability evaluation”
Answer: We changed the sentenced, as suggested (page 4, paragraph 2).

2. Page 4- Sample size calculation section: According to ref 8, in which the authors, however, assessed only one specific aim, this study, that has several aims, will include 20 patients (METV group 10 pts vs METG group 10 pts). Please verify that the samples size calculation provide a valid statistical comparison;
Answer: Thank you for the observation. However, we understand that the primary outcome measure is the pre-specified outcome considered to be of greatest importance to relevant stakeholders (such a patients, policy makers,
clinicians, funders) and is usually the one used in the sample size calculation, as is described in the CONSORT description¹.


3. Page 4 -Exclusion criteria section: no mention of cancer, dysthyroidism, cognitive decline and dementia, recent ischemic cardiovascular and neurological events or the use of antidepressive, insulin, betablockers drugs is done. Please add these informations in the text;

**Answer:** Thank you for the observation. We added the exclusion criteria: current diagnosed cancer, cognitive decline and dementia, no treatment for thyroid dysfunction, neurological events, severe depression, and insulin use (page 4, paragraph 4).

4. Page 5 – Data collection section: in this section does not describe the caloric intake and the meal used before and during the exercise test execution. Again is not clear if glycemic index of the meal is equal in all patients. Will be patients undergoing to a standardized diet during CGM to avoid meal interference? This point should be specified in this section;

**Answer:** Thank you for the observation. Patients will be told to follow their usual diet prescription during all the experiments; they will record their food intake through the same period. The dietary assessment will be performed using a software specific for this end (page 5, paragraph 6).

5. Page 5 – Data collection section: in this section does not describe the heart rate variability analysis. Please specify and add when such data will be recorded (Day 2 ?) and the recording time;

**Answer:** Thank you for the observation. The heart rate variability analysis will be performed on the second day, before and after the submaximal exercise test. We added this information to the data collection section (page 5, paragraph 3 – day 2).

6. Figure 1 – Please add metabolic evaluation (glucose, HbA1c, insulin, glucagon and GLP1 -blood samples) and heart rate variability recording in the flow diagram of the study design.

**Answer:** Thank you for the suggestion. We added the heart rate variability, cardiac output and metabolic evaluation to the figure. The variables: glucose, HbA1c, insulin, glucagon and GLP1 were added in the legend.