Author's response to reviews

Title: Effect of additional treatment with EXenatide in patients with an Acute Myocardial Infarction: rationale and design of the EXAMI trial

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Author's response to reviews: see over
Dear Editor,

Please find attached our revised manuscript entitled: “Effect of additional treatment with EXenatide in patients with an Acute Myocardial Infarction: rationale and design of the EXAMI trial.”

We would like to thank the editors and expert reviewer for the valuable comments. Here, we provide our answers to the questions and comments of the expert reviewer. For your convenience, the comments of the reviewers are printed in bold, followed by our answers in normal print. The changes that were made to the manuscript are printed in italics. As requested, the “track changes” option was used in the manuscript itself to highlight all changes made.

Reviewers comment: This is an interesting and well done report. I have one major request and several small clarifications/comments. I list them in order of appearance.

1. INTRODUCTION - The notion of using exenatide for cardioprotection is new to this reader. I would ask the authors to expand on the evidence that such is the case. Realizing that the purpose of the article is to present the trial, I still believe 2-3 sentences on the impact of exenatide on the heart would be of interest to the reader.

Answer: The following text was added to the introduction of the manuscript:

“DPP-4 resistant GLP-1 receptor agonists, such as exendin-4 and its synthetic variant exenatide, have a longer half-life, making them more attractive for clinical application[17]. Exenatide is currently used as blood-glucose lowering-therapy in patients with type 2 diabetes. In a porcine model of ischemia and reperfusion injury, exenatide reduced myocardial apoptosis and oxidative stress. This resulted in reduced infarct size and preserved cardiac performance[18]. Also, in an isolated rat heart model, exendin-4 provided cardioprotection. This effect was abolished by using a GLP-1 receptor antagonist[19]. These data suggest that exenatide exerts a direct cardioprotective effect via the GLP-1 receptor, rather than an indirect effect via increased insulin levels.”

2. METHODS - Did one IRB cover both universities or did each university have its own IRB? It sounds like there was one IRB.

Currently there is one IRB for the VU university medical center in Amsterdam. The interim analysis for the first 40 patients is currently ongoing. When considered safe, the study will be continued in both Amsterdam and Utrecht.

Please remove mention of the NCT number in the middle of the first paragraph. It makes it sound as if the first 40 participants will be a separate study from the overall trial.

Done

Define CAG.

CAG was replaced by coronary angiogram
What does "the study will be put on hold" if the medication is deemed unsafe? Is that a nice way of saying "terminated"?

If significant negative side effects are observed or if any of the endpoints significantly differ in the disadvantage of exenatide, the inclusion of patients will be temporarily halted. A panel of experts will analyze the nature of the side effects and its potential relationship to the administration of exenatide. Depending on the outcome of the analysis, the study can be continued (if it is concluded that this will be safe) or terminated (if continuing the study is considered unsafe). Our interim analysis thus far revealed no significant side effects of exenatide treatment.

Please explain an aspect of the trial that is unclear to me [my major comment]: people are randomized prior to the angiogram. They receive either the placebo or the medicine IV. Yet if the angiogram shows them not to "qualify" for the study (e.g., multi-vessel CAD) are the IV drips then stopped? Thus even if "disqualified" the participant may have already received a bolus of exenatide and a drip. Is this logical? is this ethical? Will you follow these participants? Perhaps I have mis-understood the protocol. Please comment.

The reviewer understands the protocol correctly. The fist minutes of reperfusion are believed to contribute most to cardiac injury and a therapeutic plasma concentration of the cardioprotective compound is to be achieved as quickly as possible, preferably before PCI. Since patients can meet exclusion criteria after coronary angiogram/PCI, i.e. after the initiation of study medication, also participants that are disqualified for study participation during angiogram/PCI received the initial bolus of study medication. These patients will be followed for safety aspects. This protocol is commonly used in conditioning studies.

3. EXENATIDE TREATMENT PROTOCOL - remove "notorious."

Done

4. MRI - "extend" should be "extent".... At the onset of the section please mention that a baseline and a follow up MRI will be done to assess infarct size. This way the reader has a sense of what is being sought rather than reading a dry technical statement. "extend" is replaced by “extent”.

The following text was added to the paragraph:
“The first MRI is performed to visualize myocardial edema, i.e. the area at risk. The second MRI is performed to measure myocardial fibrosis, i.e. infarct area. Doing so, infarct size can be measured as a percentage of the area at risk.”

5. ECHOCARDIOGRAPHY - please explain at the beginning of the section why an echo is being done. Ony after looking at Table 3 is it clear why it is being done

The following text was added:
“Two to 7 days and 4 months after primary PCI, transthoracic echocardiography will be performed to measure global and regional cardiac function.”

6. Table 1 - it would seem that you are excluding multivessel coronary disease and prefer only univessel disease. Is this impression correct or am I mis-interpreting this?
The reviewer is correct. For this phase IIa trial we focus on patients with univessel disease. Infarct size is highly variable among patients and depends on many clinical parameters, such as the area at risk, time between onset of symptoms and reperfusion, total vs subtotal occlusion, etc. Inclusion of patients with multivessel disease would entail more variation in outcome variables and would require a larger sample size. Furthermore, it is conceivable that in patients with multivessel disease a repeated PCI has to be performed during follow up for the non treated significant stenosis and therefore this might interfere with the follow-up results. This study is to demonstrate the proof of principle, if exenatide is safe and feasible for infarct patients and might reduce infarct size in patients. If successful, larger randomized studies, also including patients with multivessel disease, are warranted.

7. Table 2 - "fasten" is "fasting"....what is "BSE"?
“BSE” was replaced by “ESR”, erythrocyte sedimentation rate.

8. Table 3 - "Secundary" is "Secondary".
corrected