Author's response to reviews

Title: Understanding of Chest Pain in Microvascular Disease Proved by Cardiac Magnetic Resonance Image (UMPIRE): Study Protocol for a Randomized Controlled Trial

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Dear Editors-in-Chief of Trials

Thank you very much for your letter and for the very helpful comments from the reviewers. We appreciate the opportunity to resubmit our revised manuscript entitled “Understanding of Chest Pain in Microvascular Disease Proved by Cardiac Magnetic Resonance Image (UMPIRE): Study Protocol for a Randomized Controlled Trial”

Revisions have been made to the manuscript according to the reviewers’ suggestions. By responding fully to their concerns, the manuscript has been significantly strengthened. Please find below our detailed responses to the reviewer’s comments. We have also attached the revised manuscript, with the changes highlighted.

We hope that the revised manuscript is now suitable for publication in Trials.

We look forward to your review of the revised manuscript
Sincerely,

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Response to reviewer’s comment

[Comment #1]

This RCT currently conducted in Korea is a multi-center, prospective, randomized, placebo controlled trial, designed to evaluate the effect of udenafil on myocardial ischemia and symptoms in female patients with MVA. Evaluation in the design and statistical consideration are listed as below:

Sample size calculation is based on the dichotomous endpoint approach using 2 sample proportional test. The primary endpoint is the improvement in perfusion defect size >25% in adenosine-stress CMR from baseline to 3 months udenafil treatment. The calculation is based on the 25% in treatment group versus 2% in placebo group. But the evaluation in deriving the primary endpoint is from the PI’s evaluation from CMR analysis.

1. What is the definition of improvement of perfusing defect size?

Response: We thank you for this valuable comment. Since UMPIRE-study is the first clinical study to evaluate whether udenafil offers benefits in treatment of MVA in female patients women with MVA, there exist no clinical data on definition of the “positive response” or expected “response rate”.

CMR imaging with gadolinium supported the presence of coronary microvascular dysfunction in cardiac syndrome X (CAS) patients by showing an impairment of myocardial perfusion in subendocardial layers in response to adenosine [Pang et al. N Engl J Med 2002;346:1948 –53]. Lanza et al. provide novel evidence of coronary microvascular dysfunction in CSX patients [J Am Coll Cardiol 2008;51:466–72]. Perfusion defects were localized in subendocardial layers in CMR in study population. There were strict relation between the DST-induced reversible perfusion defects on CMR and the reduced CFR to
adenosine, as assessed by transthoracic Doppler coronary flow recording, in the LAD territory, thus confirming by an independent method the microvascular origin of the CMR perfusion defects. Therefore, adenosine-perfusion defect in CMR might represent a very helpful method for a complete characterization of coronary microcirculatory dysfunction in CSX patients.

An impairment of endothelium-dependent vasodilation due to reduced nitric oxide (NO) release is mainly accounted for the proposed mechanisms of MVA. NO availability plays a critical role in the regulation of microvascular, endothelial functions and the arterial structure. Phosphodiesterase-5-inhibitor (PDEi) has been reported to improve the endothelial function in animal and clinical studies such as heart failure, ischemia/reperfusion injury and coronary artery occlusion. In our study, we test the hypothesis whether udenafil offers benefits in treatment of female MVA-patients, who have documented perfusion defect in CMR. We evaluate the benefit of udenafil in MVA patient using the improvement of CMR perfusion defect. The primary endpoint is arbitrarily defined as “the improvement in perfusion defect size >25% in adenosine-stress CMR from baseline to 3 months udenafil treatment”. The response rate of PDE-5 inhibitors in erectile dysfunction ranges between 80%-90%, and in PAH between 40%-50% [Leuchte et al, CHEST 2004; 125:580–586]. Hence, we believe that a 25% response rate or the assumed difference between udenafil and placebo groups is reasonable. Since follow-up duration is only 3 month, and udenafil is a well-tolerated drug, we believe that a drop-out rate of 15%, as proposed in this study, is reasonable.

We thank you for this sharp and constructive comment.

1. *Meanwhile, it is evaluated by 2 CMR specialists, how does one differentiate the difference between these two specialists if there is?*

Response: We are very sorry to give you confusion related to CMR analysis. Visual analysis of myocardial perfusion will be performed off-line by consensus of 2 CMR specialists. When the
discrepancy will be developed between 2 CMR specialists, we will not include that patient to study candidate. For example, one CMR specialist will analyze 25% -50% adenosine-perfusion defect. Other CMR specialist will analyze 15-25% adenosine-perfusion defect. We will not include that patient to study population. We thank you for this sharp and constructive comment.

1. **I did not see any approval of IRB document.**

Response: We are very sorry to give you confusion related to approval of IRB document.

We already included all ethical bodies that approved UMPIRE study in the various centers involved in the methods section ‘10.5. Ethical approval’ as below:

Page 12, line 1:

**10.5. Ethical approval**

The study was approved by the institutional review board of each center (Samsung Medical Center Institutional Review Board (2011-07-048-001), Seoul National University Bundang Hospital Institutional Review Board (B-1106-129-016)) and will be carried out in compliance with the Helsinki Declaration.

[Comment #2]

1. **The statistics section is very brief, consisting of two sentences. The first states only that t-test will be used for continuous variables and chi squared for categorical, which says little more than that “when we run our statistical analyses, the tests we use won’t be grossly erroneous based on the type of data”. The second sentences states that the main analysis will be by logistic regression adjusting for “confounding variables”. This is a randomized trial, so there are not any**
Confounding variables. Moreover, the likely event rates will be far too small for multiple regression and I suggest that Fisher’s exact test is used instead.

Response: We thank you for this sharp and insightful comment. We totally agree with your opinion. As the reviewer pointed, we changed the manuscript as below:

Page 10, line 16:

To evaluate improvement of perfusion defect size >25% between udenafil treatment and control group, we would analyze using Fisher’s exact test. The difference in the continuous outcome between experimental and control group will be assessed using generalized linear models. Frequency differences will be tested using \(\chi^2\)-test or Fisher’s exact test. We will be analyzing this data using an intention-to-treat analysis. All randomized patients will be included in the analysis. A P value of less than 0.05 will be considered statistically significant.
Editorial requests

1) Please include the date your study was registered with your trial registration number at the end of your Abstract.

Response: We included the date this study was registered with this study’s trial registration number at the end of the abstract as below:

Page 2:

**Trial registration:** ClinicalTrials.gov: NCT 01769482 (Nov 20, 2012)

2) Please include the IRB reference numbers with your ethics statement in your Methods section.

Response:

We included all ethical bodies that approved UMPIRE study in the various centers involved in the methods section as below:

Page 12, line 14:

10.5. Ethical approval

The study was approved by the institutional review board of each center (Samsung Medical Center Institutional Review Board (2011-07-048-001), Seoul National University Bundang Hospital Institutional Review Board (B-1106-129-016)) and will be carried out in compliance with the Helsinki Declaration.

3) Please include a list of abbreviations used and their meanings after your Trial Status.

Response:

We included a list of abbreviations used and their meanings after Trial Status as below:

Page 16, line 19;

**Abbreviations**

- CCTA, coronary CT angiography
- CEAC, Clinical Events Adjudication Committee
- cGMP, 3’5’-guanosine monophosphate
- CMR, cardiac magnetic resonance image
- DSMB, Data and Safety Monitoring Board
- ECG, electrocardiography
- MR, magnetic resonance image
- MVA, microvascular angina
- NO, nitric oxide
- PDE,
phosphodiesterase; PDEi, Phosphodiesterase-5-inhibitor; 2-D, two-dimensional; TTE, transthoracic echocardiography; SAEs, serious adverse events; SS-SSFP, saturation-recovery steady-state free precession; UADEs, unanticipated device effects; QoL, quality of life