Author’s response to reviews

Title: ULTIMATE- SHF trial [UdenafiiL Therapy to Improve symptoMAtology, exercise Tolerance and hEmodynamics in Patients with chronic Systolic Heart Failure]: study protocol for a randomized, placebo-controlled, double-blind trial

Authors:

Kyung-Hee Kim Dr (learnbyliving9@gmail.com)
Hyung-Kwan Kim Dr (cardiman73@gmail.com)
In-Chang Hwang Dr (inchang.hwang@gmail.com)
Seung-Pyo Lee Dr (splee0624@gmail.com)
Hyun-Jai Cho Dr (hyunjaicho@snu.ac.kr)
Hyun-Jae Kang Dr (nowkang@snu.ac.kr)
Yong-Jin Kim Dr (kimdamas@snu.ac.kr)
Goo-Yeong Cho Dr (cardioch@medimail.co.kr)
Dae-Won Sohn Dr (dwsohn@snu.ac.kr)

Version: 2 Date: 3 June 2013

Author’s response to reviews: see over
Dear Editor:

I, on behalf of all the authors, would like to thank you and the reviewers of Trials for taking time and effort to review our manuscript. The comments were thoughtful and provided valuable insights into our study. After going over all comments carefully, we have revised the manuscript for reconsideration. Below are the responses to the reviewer comments, with the revised portions of the text highlighted by yellow color in the revised manuscript.

As you can see, we tried our best to abide by the recommendations and comments of the reviewers. We believe that these revisions improve our manuscript significantly and hope that this better meets the requirements of your journal.

We would like to thank you again for your comprehensive review and positive initial decision, and will be waiting for good news in the near future.

Sincerely yours,

Hyung Kwan Kim, MD, PhD
Division of Cardiology, Department of Internal Medicine
Seoul National University College of Medicine
28 Yongon-dong, Chongno-gu,
Seoul, 110-744, Korea
Tel: 82-2-2072-0243, Fax : 82-2-2072-3757
Email: cardiman73@gmail.com or hkkim73@snu.ac.kr
Response to Reviewers

Reviewer 1 Comments for the Author:

We sincerely thank the reviewer 1 for his positive comment on our manuscript.

Comment 1.
I read the paper from Dr. Kyung-Hee Kim et al. “A randomized, placebo-controlled, double-blind trial of UdenafiL Therapy to Improve symptomatology, exercise Tolerance and hEmodynamics in Patients with chronic Systolic Heart Failure [ULTIMATE- SHF trial]: Rationale and Design” and I think it is suitable for publication in Trials. But before recommending publication, I would like authors to address the 2 following suggestions.

You specify an intention to treat analysis, that requires including in the analysis all randomized patients (see CONSORT 2010, E&E). Also, in order to protect patient rights, you allow dropping out in several parts of your manuscript ("will be dropped from the trial", P8L24; "patients will be permitted to request withdrawal", P9L18; and “allowing a loss of 10%”, P10L24). Please note that patients may drop out of the treatment but still continue in the trial in order to obtain their final outcome value. You will find useful advice in the NEJM recommendations to prevent and treat missing data: (http://www.nejm.org/doi/full/10.1056/NEJMsr1203730).

Response to comment 1
Thank you for your valuable comment. We reviewed all the suggestions in NEJM as you commented and discussed the relevant findings with our statistical experts. Based on these, we changed some words which could be misunderstood to more clearly define who will be analyzed in the final data management. Data which are missing completely at random will be omitted without analysis. The followings are the changes we made in the revised manuscript;

“Patients will be permitted to request withdrawal from treatment at any time without providing reasons. The primary investigator and the attending physician will also have authority
to drop out patients from the trial treatment, if it is considered that further participation in the
trial would be detrimental to the patient's well-being. Such treatment withdrawals will be
documented using a case report form and in patient's medical records. In addition, we have a plan
to evaluate the results of this trial in the middle of this study and based on the interim results, the
trial can be prematurely terminated if the drug effect would be highly suggested to be beneficial
or harmful. “

“Thus, allowing for a loss of 10% (data are missing completely at random, which
implies that the missing data are unrelated to the study variables), maximum 52 patients would
be required or 26 patients per group.”

“However data which are missing completely at random will be omitted without
analysis.”

**Comment 2.**
To avoid reporting bias, it is usually preferred to fully specify the statistical analysis without any
ambiguity. As treatment effects are expected to change the mean but not the outcome shape, you
may already choose a concrete statistical analysis. Please, also note that a t-test would fully agree
with your sample size formula. You may also consider improving your efficiency and power by
adjusting for baselines in the final analysis (see, for example, chapter 7 in “Statistical Issues in
Drug Development”, by Stephen Senn, Ed Wiley). If so, please consider changing P11L2-3 to the
following:

“The differences between the treatment groups in the main outcome will be assessed using an
unpaired t-test adjusted by baseline values (ANCOVA).”

**Response to comment 2**
We definitely agree with your comment. We changed the sentences you recommended
to the same you commented as it is follows,
The differences between the treatment groups in the main outcome will be assessed using an unpaired t-test adjusted by baseline values (ANCOVA). Binary end points will be compared using Fisher exact probability test.

**Editorial requests:**

1) Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ___________: study protocol for a randomized controlled trial.

; We changed the title as follows,

ULTIMATE- SHF trial [UdenafiL Therapy to Improve symptoMAtology, exercise Tolerance and hEmodynamics in Patients with chronic Systolic Heart Failure]: study protocol for a randomized, placebo-controlled, double-blind trial

2) Please remove the conclusion from the abstract. This is not required for a protocol.

; We deleted the conclusion from the abstract.

3) Please include an Authors Contributions section at the end of the manuscript, before the reference list. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

; We added an Authors Contributions section at the end of the manuscript, as follows

K-H Kim, H-K Kim and I-C Hwan contributed to the study design, and performed the analysis. H-J Cho, H-K Kim, S-P Lee, Y-J Kim, and D-W Sohn recruited patients and interpreted data. K-
H Kim and H-K Kim wrote the manuscript. All authors have read and approved the final manuscript.

4) If applicable, please include an acknowledgement section at the end of the manuscript before the reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for all authors. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.

We added an Acknowledgements at the end of the manuscript, as follows,

The ULTIMATE-SHF trial is funded by the Korea Healthcare Technology Research and Development Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (A102169)