Author's response to reviews

Title: Effectiveness of combination therapy with nifedipine GITS: a prospective, 12-week observational study (AdADOSE)

Authors:

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Version: 3
Date: 14 January 2015

Author's response to reviews: see over
To: The Editorial Board  
*BMC Cardiovascular Disorders*  

12 January 2015  

Dear Sir or madam  

**Manuscript ID:** 1357637081143185  

**Title:** Effectiveness of combination therapy with nifedipine GITS: a prospective, 12-week observational study (AdADOSE)  

Thank you for the reviewer comments on our manuscript. We are pleased to send you a point-by-point response to the reviewer comments and a resubmitted manuscript with the amendments highlighted that are based on the reviewer comments.  

We confirm that the files have been formatted according to the journal style.  

Please let us know if you have any additional comments or require any additional amendments. We look forward to the journal decision on our revised manuscript version.  

Yours faithfully  

Thomas Petri, PhD  
Medical Advisor, Bayer HealthCare Pharmaceuticals  
Muellerstr. 178, S102, 6.OG, R.172  
13353 Berlin, Germany
From: BMCSeriesEditorial [mailto:BMCSeriesEditorial@biomedcentral.com]
Sent: Montag, 15. Dezember 2014 06:43
To: Thomas Petri
Cc: ‘Bill Wolvey’
Subject: RE: 1357637081143185 - Effectiveness of combination therapy with nifedipine GITS: a prospective, 12-week observational study (AdADOSE)

MS: 1357637081143185
Research article
Effectiveness of combination therapy with nifedipine GITS: a prospective, 12-week observational study (AdADOSE)
Ahmed K Moaweih, Elena Usova, Wajid Hussain, Ziad Dello, Birgit Schmidt and Thomas Petri
BMC Cardiovascular Disorders (Section: Hypertension and Cardiovascular Risk)

Dear Dr. Petri,

I hope this email reaches you well.

I would like to inform you that I have extended the due date on the revision of this manuscript to the 26 January 2015 per your request and I look forward to receiving your manuscript by this date.

If you have any more questions and concerns, please do not hesitate to contact us.

Thank you.

Best wishes,
Gilbert

Gilbert Tacbobo
Journal Editorial Office
BioMed Central
editorial@biomedcentral.com
http://www.biomedcentral.com
Dear Sir,

thank you very much for sending me the reviewers' comments to the submitted above mentioned manuscript. We working already to answer the open issues raised by the reviewers.

However, due to the coming Christmas vacation season, it might be difficult to reach all involved authors and to receive their feedback by Jan 4, 2015 the current deadline for manuscript resubmission. Therefore, I would like to ask you to extend the deadline for the resubmission until Jan 26, 2015 and would be most grateful when you would agree via a short e-mail notice to this request.

Many thanks in advance.

Best regards

Thomas Petri
MS: 1357637081143185
Effectiveness of combination therapy with nifedipine GITS: a prospective, 12-week observational study (AdADOSE)
Ahmed K Moaweh, Elena Usova, Wajid Hussain, Ziad Dello, Birgit Schmidt and Thomas Petri

Dear Dr Petri,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the links below. Do let us know if you have any problems opening the files.

Referee 1:
http://www.biomedcentral.com/imedia/7794137147838878_comment.pdf
Referee 2:
http://www.biomedcentral.com/imedia/7003297861519691_comment.pdf

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals ). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 4 January 2015. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=1357637081143185. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.
With best wishes,
Gilbert

Gilbert Tacbobo
Journal Editorial Office
BioMed Central
on behalf of Dr Iddo Ben-Dov
**Reviewer comments**

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<th>Reviewer #1 (Dr Kragten)</th>
<th>Author response</th>
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<td>In general: It is an interesting question, how anti-hypertensives act in a clinical population, that is a mix of races and a mix of pathophysiological backgrounds. Exactly this happens in the group of patients that was included in this study. As a clinician, every day I decide to start therapy in a multi morbid and – nowadays a multicultural population of patients and it would be a great help, when I could have some predictive value of my intention, a so called prediction on the clinical return on my farmaceutical investment. To say it in a different way: is the farmaceutical approach in this particular patient really paying of in clinical perspective. This study was done in a big group of patients. However, the follow-up was only a short time (12 weeks). The only effect, we can look for is a drop in blood pressure. It is not possible, to pronounce anything on life events or safety, as the observational period is to short. However, this is done in the past, e.g. in the Action study, where people were treated for a longer period. I would advise you to stick to the immediate effect on blood pressure. For safety and effectiveness of Nifedipine GITS you can easily refer to earlier studies. In the study, the effect on treatment is measured in a different way among the population: a single measurement versus a mean of three measurements. This is strange</td>
<td>Thank you for your comments. We agree that the population investigated in the observational AdADOSE study included a wide range of patient types. The consistent efficacy that is demonstrated for nifedipine GITS in AdADOSE across diverse ethnicities and variable pathophysiological backgrounds has relevance to real-world practice, in our view. We agree that blood pressure reduction is a valid measure of efficacy for nifedipine GITS in the 12-week AdADOSE study. It is established in previous studies that reduction in blood pressure contributes to reduced cardiovascular risk. As the reviewer notes, previous studies with a longer follow-up have investigated the impact of nifedipine GITS on cardiovascular events and safety. It is notable that the efficacy of nifedipine GITS is consistent across these studies, and that the safety of nifedipine GITS assessed by AE rate is similar or superior in AdADOSE compared to previous trials, including ACTION (please see the highlighted text on pages 15-16). The techniques for measurement of blood pressure in AdADOSE reflect the national or local variations in clinical practice. Variations such as these are a typical feature of</td>
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and might be conflicting. What would happen, if in the group in Egypt, where three measurements were taken, only the first measurement is taken into account?

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<th>multinational observational studies such as AdADOSE.</th>
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As blood pressure is the main goal in this study, it is important to have a strict definition on that. How is this taken: sitting, after three minutes of rest, done by a doctor by hand, by a machine? It would be helpful, to give some details on this point and add this to the manuscript.

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<th>As noted in the reply above, methods for measurement of blood pressure reflect the current practice that is in place in each country. Details on the proportions of patients measured by each technique are not available.</th>
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In the part on tolerability it would be great, to give information on the way side effects were obtained: Only if the patient mentioned this to his doctor? Was it specifically asked for by the doctor at every visit? This is important, as the number of side effects might differ, depending how these data are established.

<table>
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<th>The methods for eliciting tolerability data reflect the local practices of the investigating physicians. This may, indeed, be considered a valuable contribution of the AdADOSE study, by reflecting the realities of variations in practice in the real world.</th>
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The main part of this manuscript deals with the results and these are written extensively. I do believe, these data are correct, but as a reader, I just miss the clinical perspective of all these data.

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<th>As noted in our manuscript (page 8), all tolerability data obtained were recorded in standardized case report forms.</th>
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My questions are:

- Is there a difference in tolerability depending on the race/background of the patient, or react all patients in a more or less similar way?

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<th>Differences in tolerability or efficacy based on race/background were not specifically investigated in the AdADOSE study. However, we detected no differences in outcome based on race or background. A similar high rate of efficacy was observed across the patients in the study population.</th>
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- Is there a difference in the effect, looking at the co-morbidity/co-medication of a patient? This is important in my decision whether or not I should start therapy or accept side effects. If the additive effect of medication is little, side-effects should be a reason for termination sooner. Of course, this would not be the case,|

<table>
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<th>Over 90% of patients had 1 or more concomitant diseases and 85% of patients had received antihypertensive treatment before the initiation of nifedipine GITS. These high rates of comorbidity / comedication use may be typical of clinical practice.</th>
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<td>if the effect is of great clinical importance.</td>
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<td>- Is it possible, to give a prediction on the effect in blood pressure fall, that might be expected in the individual patient, depending on race, co-morbidity and co-medication. These data are mentioned in the article, but it would certainly help to sum these up.</td>
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<td>My advise would be, to end the manuscript with some clinical advises, in which the points I made are explained. I am sure, most readers would be satisfied with that and those that need more prove have the middle part of the article to get this.</td>
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<td>Reviewer #2 (Dr Sinha)</td>
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<td>The manuscript by Motaweih et. al., is an extensive study on the usefulness of nifedipine with combination therapy. The manuscript has several major issues that must be resolved before the manuscript could be accepted for publication in BMC Cardiovascular Diseases.</td>
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| 1. Major Compulsory Revision:  
Q1: Nifedipine extended release tablets of 30, 60 and 90 mg have been used before and for its anti-hypertensive effect. This anti-hypertensive medication has been used extensively and is routinely used in various countries as anti-hypertensive therapy. That being the issue, what is the novelty of the study that must be explained. | We agree that a number of previous studies have investigated nifedipine GITS in the treatment of hypertension and stable coronary artery disease, including INSIGHT and ACTION.  
As highlighted on page 6, the AdADOSE study is notable for its observational design, large patient population from regions with a high cardiovascular risk burden, and investigation of nifedipine GITS as a component of combination therapy.  
Investigation of combination therapy, as in the AdADOSE study, is topical, as this approach is recommended in recent guidelines, such as those from the ESH/ESC (Mancia 2013). |
| Q 2: The authors claim that the reduction of hypertension reduced the CV events by 60% is controversial. Much lower reduction of CV due to the reduction of hypertension has been reported before. | Highlighted text on page 5 refers to a reduction in risk of CV events by an estimated 50% associated with nifedipine GITS in the INSIGHT study. |
| Q 3: The included portions with "primary hypertension". The primary hypertension is known to be "essential hypertension" for which no diagnostic test is currently available. How did the investigators decided that these patients had "primary hypertension" which is needed to be described in the Methods section. | Thank you. To our knowledge “primary hypertension” and “essential hypertension” are interchangeably used in the medical literature. As suggested by the reviewer “primary hypertension” is now changed to “essential hypertension” (highlighted on page 7).  
The diagnosis of essential hypertension was based on the blood pressure inclusion criteria.
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<th>Q 4: What were the components in the “combination therapy” with nifedipine. The anti-hypertensive effect of these components needed to be included in the “control” experiment. Some of the non-antihypertensive concomitant medication can be anti-hypertensive that has been reported before by several investigators.</th>
<th>The text that describes the study limitations in the Discussion section mentions that an assessment of the impact of concomitant medications was not planned and is not possible in an observational study such as AdADOSE (highlighted on page 15). It should be noted that the majority of patients (85%) were inadequately controlled on their previous antihypertensive therapy (highlighted on page 13). The concomitant antihypertensives used are listed on page 10 (highlighted).</th>
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<td>Q 5: The authors have mentioned “combination therapy in regions with high cardiovascular risk burden”. This statement must be supported by at least appropriate reference, as there are many conditions that are known to increase atherosclerosis, the most important cause of cardiovascular risk.</td>
<td>Please see the references (Guariguata, Whiting et al 2014 and European Society of Cardiology 2006) that are in place on page 6 (highlighted). Guariguata, Whiting et al (2014) cite the high diabetes prevalence in the Middle East. The European Society of Cardiology (2006) reports the high CV mortality in Russia. Additional references are now suggested that support these statements and additionally include CV mortality data for Pakistan: - Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P, Norrving B editors. World Health Organization, Geneva 2011. - OECD/WHO (2012) “Mortality from cardiovascular disease”, in Health at a Glance: Asia/Pacific 2012, OECD Publishing. Available at: <a href="http://dx.doi.org/10.1787/9789264183902-8-en">http://dx.doi.org/10.1787/9789264183902-8-en</a></td>
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<td>2. Minor Essential Revisions: The manuscript needs some language corrections.</td>
<td>The language has been reviewed again by a professional English-language copy-editor.</td>
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<td>Level of interest: An article whose findings are important to those with closely related research interests</td>
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<td>Quality of written English: Needs some language corrections before being published</td>
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<td>The language has been reviewed again by a professional English-language copy-editor.</td>
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<td>Statistical review: No, the manuscript does not need to be seen by a statistician.</td>
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