Author's response to reviews

Title: Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials

Authors:

Helen M Colhoun (H.Colhoun@dundee.ac.uk)
Jennifer G Robinson (jennifer-g-robinson@uiowa.edu)
Michel Farnier (michelfarnier@nerim.net)
Bertrand Cariou (bertrand.cariou@univ-nantes.fr)
Dirk Blom (dirk.blom@uct.ac.za)
Dean J Kereiakes (Lindner@thechristhospital.com)
Christelle Lorenzato (christelle.lorenzato@sanofi.com)
Robert Pordy (robert.pordy@regeneron.com)
Umesh Chaudhari (Umesh.Caudhari@sanofi.com)

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

Responses to peer review comments, manuscript #1504930353133268

Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials

We would like to thank you and the reviewers for your careful review of our manuscript. Please find below point-by-point responses to the revisions requested. We hope that upon review of these revisions, you will consider the manuscript to be acceptable for publication in BMC Cardiovascular Disorders.

Thank you very much for your time in reviewing the manuscript. We look forward to your response in due course.

Yours sincerely

Helen M. Colhoun, MD, MFPHM, FRCP Edin

Editorial Comments

Please ensure that your trial registration number is included as the last line of your abstract.

Response:
We have revised the abstract accordingly to include the clinical trial registration numbers for the two studies.

Please revise your methods section to include the name of the ethics committee that approved your study.

Response:
As there are numerous ethics committees that approved these multinational, multi-center studies, we have suggested including these details in the appendix to the manuscript and have added accordingly.

Reviewer #1 (Gilles Lambert) Comments

This paper reports the design of the alirocumab phase 3 trials ODYSSEY COMBO I and COMBO II. The quality of the manuscript is indisputable, but it is too long at times particularly the introduction. The introduction is a long summary of reviews published by some of the co-authors (refs 22, 23, 30, 31). The 2 first pages of the background are extremely verbose.

Response:
We thank the reviewer for their careful appraisal of the manuscript; we have worked to reduce the length of the Introduction as suggested.

Reviewer #2 (Baris Gencer) Comments

This is very well-written manuscript presenting the design of large ODYSSEY COMBO I and II clinical trials assessing the efficacy and safety of PCSK9 antibody inhibitors in high cardiovascular risk patients with poorly controlled hypercholesterolemia. Please find some minor comments that authors
Response: We thank the reviewer for their review of the manuscript and considered comments; our point-by-point responses can be found below.

1-Outcome measurement timing
Could the authors justify why the used as primary endpoint the changes of LDL-C levels at week 24, while the study duration is 48 weeks? Is any interim analysis planned based on the results of the outcome at week 24? If yes, could the authors describe the criteria for premature study cessation?

Response: Although both trials have the LDL-c differences at week 24 as the primary endpoint, the studies extend beyond 24 weeks so as to maximise available safety data and to generate further data on durability of lipid lowering effects. The studies will extend to the planned duration regardless of any efficacy data from the week 24 timepoint.

We have inserted a sentence to explain this at the end of the paragraph on Primary Analysis.

2-Inclusion criteria
At table 1, the use of ezetimibe prior randomization could be specified for COMBO II at the top of table where the statin treatment duration is described.

Response: We think it is very clear on table 1 that recent ezetimibe use is an exclusion criterion and it will confuse if we start to move exclusion criteria into the inclusion part of the table so we prefer to leave as is, but have emphasised it in bold.

The authors should define history of documented CVD in the footnotes of table 1.

Response: CVD is defined as CHD, ischemic stroke or PAD. The footnotes have been updated accordingly. More detail on the criteria for these is also given in the online appendix and we reference that now in the table footnote.

Could the authors justify why the LDL-C inclusion targets (70 mg/dL and 100 mg/dL) were different according to history of CVD, while the entire study population of patients is at high-risk per definition.

Based on supplemental table 1 “CHD risk equivalent” was defined as other CVD (PAD, stroke), chronic kidney disease and diabetes mellitus. Could the authors discuss why they did not include patients at high-risk in primary prevention defined by a risk of CHD > 20% according to ATP-III guidelines.

Response: We have now included a paragraph in the discussion that deals with this issue of high risk and treatment targets in the entry criteria and also addresses the impact of the new 2013 AHA/ACC guidelines - see third last paragraph of discussion.

3-Limited power for clinical outcomes
Could the authors mention in the discussions that the statistical power of COMBO I and II trials are not designed to assess the impact on clinical outcomes.

Response: We have amended the text in the analysis section to note that the COMBO studies are not powered to look at CV outcomes.

4-Insight with new 2013 AHA/ACC guidelines
The concept of targeting LDL-C to a specific cardiovascular risk has been abandoned in the new 2013 AHA/ACC guidelines. Could the authors give some insight of their study in this new context? Especially, the inclusion criteria based on unachieved LDL-C targets would be still appropriate in the future?

Response: We have now included a paragraph in the discussion addressing this issue; please see third last paragraph of discussion.

5-Safety
Could the authors discuss on the potential risk of excessive low LDL-C levels based on data in the literature?

Response: To date, potential harm from low, or lower, LDL-C has focussed on reports of increased incidence of cancer, hemorrhagic stroke, and violent death, but there is currently little evidence from outcome trials to show a relationship with low LDL-C.
Since there is the potential to achieve low LDL-C levels with alirocumab, the COMBO trials will carefully monitor safety in patients who reach LDL-C levels of <25 mg/dL, as detailed in the Discussion. Furthermore, the safety of low LDL-C will be assessed throughout the ODYSSEY clinical trials program, which includes a large, cardiovascular outcomes study.

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<th>Reviewer #3 (Eli Roth) Comments</th>
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<td>This manuscript is a discussion of study design for 2 ongoing phase 3 studies of alirocumab in subjects not achieving pre-specified LDL-C levels despite use of a lipid lowering agent or in subjects unable to tolerate a statin. The manuscript is well written, flows well and contains all of the necessary information. I have no criticism or suggestions for the paper or authors. I feel this paper should be accepted without need for revision.</td>
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**Response:**
We thank the reviewer for their kind appraisal of the manuscript. We have made some minor adjustments to the manuscript to address comments from their fellow peer reviewers and some editorial queries, but have tried to maintain the existing flow and detail of the studies.