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

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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

Please find below point-by-point responses to the revisions requested before editorial assessment.

1. Ethical and Funding Approval Documentation: Before we can proceed with your submission, can you please forward copies of all ethical approval and funding approval for our records. These documents should be sent as email attachments to the following email address, BMCSeriesEditorial@biomedcentral.com. Please DO NOT upload these documents as additional files in the submission system. If your documents are not in English, please could you provide translated versions of the relevant parts? These should be endorsed and signed by a contactable person at the institution. Please also include the original documents. Can you please confirm in your cover letter that you have forwarded the requested documentation to BMCSeriesEditorial@biomedcentral.com

Response: The manuscript covers the design and rationale for two large multicentre studies (one based in the USA, the other a multinational study), with over 200 sites across the two studies in total. As such, there is a considerable amount of ethical approval documentation.

We have provided a copy of the ethical approval for the US as an example (sent via email); we are happy to supply the remaining approvals for the trial, if required, when we have completed the necessary back translation. We have sent a query via email to clarify exactly which documentation you require and this has been passed on to an Executive Editor via Gilbert Tacbobo.

2. Funding: A study is considered to be externally funded if the authors have been awarded a grant for the study by a major funding body (e.g. governmental funding/ award from a charitable foundation). If a study has not received external funding, then the study protocol will be sent for peer-review with a member of our Editorial Board. If a study has received funding/assistance from a commercial organization, this should be clearly stated in the 'competing interests' section of your manuscript, and the study protocol will be sent for peer-review by a member of our Editorial Board. Can you please confirm whether your study protocol has undergone peer-review by the funding body?

Response: The ODYSSEY COMBO studies were funded by commercial organizations, namely Sanofi and Regeneron Pharmaceuticals. This information is detailed in the ‘Acknowledgments’ section of the manuscript, but is now also stated in the ‘Competing Interests’ section as well for completeness. The study protocols were prepared in consultation between Sanofi, Regeneron, and a Steering Committee composed of university-based scientists and doctors (experts in lipids field, and/or cardiology) with clinical and methodological expertise, working in collaboration with Sponsor-based scientists as disclosed in the appendix.
3. **Study status:** The protocol must be for a study that is ongoing. An ‘ongoing’ study is defined as one where the investigators are still collecting, or analyzing data. Can you please confirm what stage your study is currently at?

**Response:** We can confirm that both studies meet the definition of “ongoing”. Data collection for the COMBO I study is now complete and the investigators are in the process of analyzing data. Data collection for COMBO II is ongoing and is currently expected to complete in July 2015; data for the primary efficacy endpoint are anticipated to be available in June 2014. We have also made minor amendments on p9 of the manuscript to clarify this information.

4. **Related Articles:** Can you please clarify whether any publications containing the results of this study have already been published or submitted to any journal. If so, can you please provide a list of the related articles?

**Response:** The results from the COMBO studies are yet to be submitted to any journal. However, abstracts from the two studies have been submitted to two major meetings (one is currently under review: the other has been accepted for presentation). Details can be found below:

- **COMBO I:** An abstract concerning this study has been submitted to the American Heart Association Scientific Sessions to take place in Chicago, IL, from Nov 15-19, 2014. If accepted, results from this study will be presented here.
- **COMBO II:** Has been accepted for Hot Line presentation at the European Society of Cardiology Annual Meeting, to be held in Barcelona, Spain, from August 30-September 3. The primary efficacy results and safety data up to a cut-off corresponding to the last patient visit at Week 52 will be presented in this session (Sunday, 31 Aug 2014, 16:30 - 18:00: Hot Line: Coronary artery disease and lipids)

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

Yours sincerely

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