

Dr Alex Schaefer, PhD
Associate Editor, PLOS ONE

14th April 2023

Re: Revision required [PONE-D-22-25611] - [EMID:10854bcd2088b562] ‘Phase II, double blind, placebo controlled, multi-site study to evaluate the safety, feasibility and desirability of conducting a phase III study of anamorelin for anorexia in people with small cell lung cancer: a study protocol (LUANA trial)’ for publication in the PLOS ONE.

Dear Dr Alex Schaefer,

Thank you to the editorial team for assessing and considering our paper for publication in the PLOS ONE.

We have provided a response to each point raised by the academic editor and reviewers and amended the manuscript accordingly.

We confirm that this work has not been published previously, is not under consideration for publication elsewhere. All the authors have made a substantial contribution to this work and have approved the submitted version.

We look forward to hearing from you again soon.

Sincerely,

Dr Mariana Sousa
(On behalf of the authors)
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Journal requirements:

1. Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming. The PLOS ONE style templates can be found at

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Response: Thank you for the resources. The manuscript meets the journal requirements.

2. Thank you for stating the following financial disclosure:

“This study is sponsored by the University of Technology Sydney and funded by the Helsinn Group including the provision of study medication and matching placebo. Helsinn will not dictate design, conduct, analysis, interpretation nor dissemination of the study’s findings. Helsinn was consulted on study design and will review the manuscript of the primary paper before final submission.”

Please state what role the funders took in the study. If the funders had no role, please state: ""The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.""

If this statement is not correct you must amend it as needed.

Please include this amended Role of Funder statement in your cover letter; we will change the online submission form on your behalf.

Response: We have changed the statement to the following: *The funders were consulted on study design but have no role on data collection and analysis, decision to publish, or preparation of the manuscript.*

3. Thank you for stating the following in the Competing Interests section:

“Prof David Currow is a paid consultant to Helsinn and a member of their Advisory Board. All the other Authors declare that they have no conflict of interest.”

Please confirm that this does not alter your adherence to all PLOS ONE policies on sharing data and materials, by including the following statement: ""This does not alter our adherence to PLOS ONE policies on sharing data and materials." (as detailed online in our guide for authors <http://journals.plos.org/plosone/s/competing-interests>). If there are restrictions on sharing of data and/or materials, please state these. Please note that we cannot proceed with consideration of your article until this information has been declared.

Please include your updated Competing Interests statement in your cover letter; we will change the online submission form on your behalf.

Response: We have changed the statement as follows: *Prof David Currow is a paid consultant to Helsinn and a member of their Advisory Board. This does not alter our adherence to PLOS ONE policies on sharing data and materials. All the other Authors declare that they have no conflict of interest.*

4. We note that the original protocol file you uploaded contains a confidentiality notice indicating that the protocol may not be shared publicly or be published. Please note, however, that the PLOS Editorial Policy requires that the original protocol be published alongside your manuscript in the event of acceptance. Please note that should your paper be accepted, all content including the protocol will be published under the Creative Commons Attribution (CC BY) 4.0 license, which means that it will be freely available online, and any third party is permitted to access, download, copy, distribute, and use these materials in any way, even commercially, with proper attribution.

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Response: We have removed any copyrighted institutional logos, signatures and the confidentiality notice. There are no restrictions on sharing the original protocol file should this work be accepted.

5. We note that the original protocol that you have uploaded as a Supporting Information file contains an institutional logo. As this logo is likely copyrighted, we ask that you please remove it from this file and upload an updated version upon resubmission.

Response: We have removed any copyrighted institutional logos from the file.

Associate Editor Comments:

The reviewers feel that your manuscript does not sufficiently describe the plan for statistical analyses. As such, they recommend that you clearly detail all statistical methods that will be used to analyze the data. In addition, they feel that the manuscript requires additional information regarding the chosen exclusion criteria. Furthermore, they suggest that you should clarify the distinction between your study design and another ongoing clinical trial mentioned in your review (<https://clinicaltrials.gov/ct2/show/NCT03743051>).

Response: Thank you for considering our paper for publication and for the suggestions to improve clarity. We have further described the plan for statistical analyses (please refer to pages 21 and 22 in the revised manuscript). We have also further clarified both the distinction between our design and ongoing trial, as well as about the chosen exclusion criteria (as per response to Reviewer's 1 comments).

Reviewers' Comments to the Author's:

Reviewer #1:

Mariana S. Sousa et al. Presented a Study Protocol LUANA trial, a randomized phase 2 trial with anamorelin for anorexia in people with small cell lung cancer.

My main concern is about the novelty of this trial. I would like to mentioned the fact that a previous trial using the design and the same drug is already ongoing in NSCLC: "NCT03743064 A Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of anamorelin HCl for the treatment of malignancy associated weight loss and anorexia in adult patients with advanced non-small cell lung cancer (NSCLC)." So, the evaluation of the the safety, feasibility and desirability in LUANA trial sounds futile to me. The drugs used in SCLC with platinum-based chemotherapy associated with immunotherapy is also the backbone of NSCLC treatment. Therefore, ANAM 17-21 trail in NSCLC does already address LUANA phase II design presented in this work.

Response:

We acknowledge Reviewer's #1 concerns and wanted to reiterate that this is a feasibility study and this trial is trying to shift the way we analyse data on anamorelin which is primarily an appetite enhancer. Currently, there is no standard of care for cachexia/anorexia and no new drug has been approved by the FDA in the USA, EMA in Europe and TGA in Australia, thus remains an unmet clinical need. While these regulatory agencies have indicated in the past that clinical trials testing new drugs for cachexia/anorexia had to demonstrate meaningful improvements in muscle mass and function as co-primary endpoints, currently this is not necessarily the case due to lack of international consensus on cachexia/anorexia endpoints. Furthermore, promising results for anamorelin as an appetite stimulant in previous clinical trials have been reported which suggests its benefit for anorexia. Therefore, the rationale for the selection of our primary endpoints was based on ongoing developments in the field.

The above mentioned phase 3 trial focuses on people with both NSCLC-associated weight loss (determined as BMI<20kg/m² with involuntary weight loss of >2% within 6 months prior to screening) and anorexia (determined as ongoing problems with appetite/eating associated with the underlying cancer, as determined by having score of ≤ 17 points on the 5-item Anorexia Symptom Scale (5-IASS) and ≤ 37 points on the 12-item FAACT A/CS). The primary outcome measures in this trial are mean change in body weight and mean change in the 5-IASS. Our trial on the other hand, was designed to demonstrate the superiority of anamorelin versus placebo on anorexia symptoms and the ability to complete therapy on time and on dose.

Cont. Reviewer #1:

I am also concern about the fact the list of exclusion criteria:” Pleural effusion requiring thoracentesis. Pericardial effusion requiring drainage. Oedema requiring regular diuretics. Ascites requiring drainage. Oesophagitis, gastritis, Cognitive impairment....” Will exclude most of patient treated in daily routine with advanced SCLC which is a symptomatic disease related to high proportion of metastasis. Only “super Fit” patient with SLCLC and cachexia will be enrolled in the trial. I am quite sure that this kind of patient are highly selected population, consequently the accrual in the trial as well as the clinical application in daily routine practice is questionable.

Response:

Similar to our trial, the exclusion criteria for the NCT03743064 Phase 3 trial also includes pleural effusion requiring thoracentesis, pericardial effusion requiring drainage, oedema requiring regular diuretics, ascites requiring drainage, oesophagitis, gastritis, cognitive impairment, etc. The reason for the selection of such exclusion criteria was based on previously reported data that underlined the development of the Investigator’s Brochure for anamorelin and the fact that any oral and gastrointestinal impairments will impact on the patient’s ability to eat which is the desired effect of anamorelin. While there are very small implications for people experiencing these symptoms, they cannot be ignored within a trial design. For instance, as identified adverse events in clinical trials (HT-ANAM-301, HT-ANAM-302, HT-ANAM-303, RC-1291-203, RC-1291-205, RC-1291-206, ST-ANAM-207), pleural effusion and pericardial effusion were present in 2.6% and 1.6% of participants, respectively.

Cont. Reviewer #1:

Furthermore, this kind of trial should be a pantumor trial, unless if there is strong rational to support a specific tumor histology subtype or specific oncogenic driver.

Response: While we acknowledge your suggestion, the feasibility of including a diverse (pantumoural) population would make it difficult to achieve homogeneity of the sample. We are looking for signals and trends in the data and understand that by adding different variables and confounders would limit our ability to confidently drawn any conclusions. We have for this reason focused on SCLC which is a population largely affected by anorexia. We also acknowledge that NSCLC and pancreatic cancer are the main populations studies with this medication to date.

Reviewer #2:

In this study protocol, a multi-site, randomized-controlled phase II clinical trial aims to assess safety and feasibility, adherence, and completion of study tools to inform the design of a robust Phase III effectiveness trial.

Major revisions:

1- Overall, the current statistical analysis plan is too vague. List and describe all the statistical methods that will be used to analyze the data.

Response: Thank you for your suggestions. We have improved substantially the analysis section of the manuscript and included a detailed statistical plan. Please refer to pages 21 and 22 in the manuscript.

2- Line 355: Provide more details for the following statement. “Comparison between the intervention and control groups will occur using appropriate statistical approaches, depending on the nature of the data.”

Response: We have revised the statistical plan and description in the manuscript. Please refer to pages 21 and 22.

3- Lines 359-362: A repeated measures approach would be superior to repeatedly applying paired t-tests.

Response: Thank you for your suggestions. We have improved substantially the analysis section of the manuscript and included a detailed statistical plan. Please refer to pages 21 and 22 in the manuscript.

Minor revisions:

1- Identify the software that will be used to capture the data as well as the software that will be used for the statistical analysis.

Response: We have included the information about the software that will be used to capture the data and for statistical analysis on page 21, lines 353-354 in the manuscript.

2- Line 355: Replace “analysed” with “summarized” and summarize using both frequencies and percentages.

Response: We have revised this information in the manuscript, please refer to page 21 lines 357- 368.