PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of liraglutide on body weight and pain in patients with overweight and knee osteoarthritis: Protocol for a randomised, double blind, placebo-controlled, parallel group, single-centre trial
AUTHORS	Gudbergsen, Henrik; Henriksen, Marius; Wæhrens, Eva; Overgaard, Anders; Bliddal, Henning; Christensen, Robin; Boesen, Mikael; Knop, Filip K; Astrup, Arne; Rasmussen, Marianne; Bartholdy, Cecilie; Daugaard, Cecilie; Bartels, Else; Ellegaard, Karen; Heitmann, Berit; Kristensen, Lars Erik

VERSION 1 – REVIEW

REVIEWER	Reviewer name: David Hunter Institution and Country: University of Sydney, Australia Competing interests: None declared
REVIEW RETURNED	26-Jun-2018

GENERAL COMMENTS	This is an important area of research given the prevalence of both obesity and osteoarthritis. Taking a drug to assist in its management, has appeal. In general, the manuscript is well written and clear. This said, there are a number of important areas that warrant further clarification by the authors. The investigators propose to conduct a lot of visits. Just wondering about the necessity for these and how generalisable this will be for subsequent clinical implementation? As I look at table 1 I would be very worried for participants about the burden involved as well as its practicality. I notice for the active drug that there appears to be a commencement dose of 0.6 mg followed by dose escalation. Are there any rules by which that dose would not be escalated (or not)? For the inclusion criteria the lower age bound and upper age bound are somewhat unusual-can you please justify? How will you assess whether a person is motivated for weight loss? There are a lot of exclusion criteria. Again when thinking about the generalisability of this study given such a substantial proportion of patients with osteoarthritis have concomitant depression and/or diabetes, please consider as to whether all these are absolutely necessary. For the treatment related impact measure weight outcome measure can you please incorporate the seven thematic domains into the description on page 12. One of the more immediate concerns in instituting an intervention like this would be related to adverse effects. I note that these will be captured frequently in table 1 but have little idea from an outcome perspective what are the likely major adverse effects that you will be looking for.

	It would be important to anticipate some common side-effects and to include adverse effects as an outcome (albeit secondary) in this trial. For participants who are unfamiliar with injecting themselves what provision will be made for training them, or directly administering the agent? There is no mention of a formal cost effectiveness analysis? Given the number of visits, the options for alternative means of pursuing weight loss and the intervention cost it would be valuable to incorporate a plan for this.

REVIEWER	Reviewer name: Gurjit Bhogal Institution and Country: Consultant in Musculoskeletal and Sports Medicine. Royal Orthopaedic Hospital. Bristol Road South. Northfield. Birmingham. B31 2AP. England Competing interests: No
REVIEW RETURNED	28-Sep-2018

GENERAL COMMENTS	Robust protocol

REVIEWER	Reviewer name: Greg Atkinson Institution and Country: School of Health and Social Care, Teesside University, UK Competing interests: None declared
REVIEW RETURNED	12-Oct-2018

GENERAL COMMENTS	I have only minor comments on this otherwise robust and clearly-communicated trial protocol: 1. Page 11, line 9 onwards. Amongst the inclusion criteria, I cannot seem to see the earlier stated criterion that only those participants who initially lose >5% body mass will be recruited? 2. Page 13, line 9 onwards. I'm sorry but I cannot quite follow the multiple outcome criteria presented here. Are the percentage improvements and absolute changes actually linked in some way? When it says "at least two of the following……..", I cannot quite follow things because an "improvement of 20%" is then mentioned three times. Also, do the % changes correspond to changes in body mass specifically? Can this be said explicitly if so please. 3. Page 19. Can you confirm that the sample size estimation is based on differences in baseline-to-follow-up change scores? Or is it differences in body mass specifically at the follow-up timepoint? 4. Whatever the sample size is based on, can you please justify the selection of 10 kg for the SD? Is this the SD for general body mass at baseline/follow-up? Or is it the SD of the change scores? Please say where you have got this SD value from. 5. What is a "a simple non-responder imputation technique"?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

6) The investigators propose to conduct a lot of visits. Just wondering about the necessity for these and how generalizable this will be for subsequent clinical implementation? As I look at table 1 I would be very worried for participants about the burden involved as well as its practicality.

Response:
The number and timing of visits has been outlined to ensure observation of any safety issues as well as thorough management of medication hand-out and usage throughout the study.
Based on involvement of patients as well as the existing experience within the field of weight loss and knee OA management the study design is considered to be acceptable for patients as well as feasible to implement. Nevertheless, this study will deliver comprehensive insights into the practicality and acceptability of the interventions studied in this specific context, and provide valuable information regarding the generalizability of the interventions in question.
This description has been included in the revised manuscript.

7) I notice for the active drug that there appears to be a commencement dose of 0.6 mg followed by dose escalation. Are there any rules by which that dose would not be escalated (or not)?

Response: The main protocol, version 6, states that “Dose escalation will be based on safety as well as tolerability and if dose escalation is not feasible, then delayed increments are allowed. Subjects will be maintained at the highest tolerated dose level. Reduction of the achieved maintenance dose will lead to patient discontinuation.”
This information has been included in the revised manuscript.

8) For the inclusion criteria the lower age bound and upper age bound are somewhat unusual-can you please justify?

Response: The bounds were set to reflect the age limits in which the experience with liraglutide has been thoroughly documented, and to include all adult patients with a clinical diagnosis of knee OA.

9) How will you assess whether a person is motivated for weight loss?

Response: Potential study participants will initially partake in a motivational assessment including an interview in which the nature of the initial IDI is explained together with a description of the overall study, a thorough outline of the interventions and visits, and a session in which the investigator addresses any questions the potential participant may have. The study will not use any standardised scoring system to assess motivation, but during the interview the investigator will assess the individual’s motivation for weight loss through both the IDI period and the subsequent participation in the randomised part of the study.
This information has been included in the revised manuscript.

10) There are a lot of exclusion criteria. Again when thinking about the generalizability of this study given such a substantial proportion of patients with osteoarthritis have concomitant depression and/or diabetes, please consider as to whether all these are absolutely necessary.
Response: This is indeed a highly relevant aspect. The exclusion criteria have been selected to ensure alignment with the European label for liraglutide 3 mg (Saxenda) and to incorporate the existing knowledge regarding clinical studies within the domains of weight loss and knee OA (incl. exclusion of patients receiving specific treatment for OA and to ensure monitoring of potential AEs). As such, the authors do consider all of the listed criteria to be highly relevant and needed.

11) For the treatment related impact measure weight outcome measure can you please incorporate the seven thematic domains into the description on page 12.

Response: Thank you for the comment. The description of the TRIM-weight questionnaire has been updated to include a description of the seven thematic domains.

12) One of the more immediate concerns in instituting an intervention like this would be related to adverse effects. I note that these will be captured frequently in table 1 but have little idea from an outcome perspective what are the likely major adverse effects that you will be looking for. It would be important to anticipate some common side-effects and to include adverse effects as an outcome (albeit secondary) in this trial.
Response: Thank you for the comment. The outcomes section has been updated to include a description of the prespecified safety outcomes.

13) For participants who are unfamiliar with injecting themselves what provision will be made for training them, or directly administering the agent?
Response: Research nurses with experience in trials involving self-administered injections will instruct participants in the use of pens, and the materials used to support the verbal instructions will be the publicly available materials produced by Novo Nordisk for Liraglutide.
The trial conduct section has been updated to include this description.

14) There is no mention of a formal cost effectiveness analysis? Given the number of visits, the options
for alternative means of pursuing weight loss and the intervention cost it would be valuable to incorporate a plan for this.
Response: That is a highly relevant comment. The current protocol does not contain any plan for such analysis and any such investigations will therefore be part of a secondary analysis of the study results and be reported in a separate manuscript.

Reviewer 2
15) Robust protocol
Response: Thank you for the feedback.

Reviewer 3
16) I have only minor comments on this otherwise robust and clearly-communicated trial protocol:
Response: Thank you for the feedback.

17) Page 11, line 9 onwards. Amongst the inclusion criteria, I cannot seem to see the earlier stated criterion that only those participants who initially lose >5% body mass will be recruited?
Response: Thank you for the comment. The requirement of > 5 % weight loss during the initial 8-week weight loss period has only to do with the randomisation of patients.
The ‘trial population’ and ‘trial design’ sections have been updated to include more specific descriptions of this aspect.

18) Page 13, line 9 onwards. I’m sorry but I cannot quite follow the multiple outcome criteria presented
here. Are the percentage improvements and absolute changes actually linked in some way? When it says “at least two of the following……..”, I cannot quite follow things because an "improvement of 20%" is then mentioned three times. Also, do the % changes correspond to changes in body mass specifically? Can this be said explicitly if so please.
Response: Thank you for the comment. The paragraph has been updated in order to provide a clearer description of the OMERACT-OARSI tool.

19) Page 19. Can you confirm that the sample size estimation is based on differences in baseline-tofollow-
up change scores? Or is it differences in body mass specifically at the follow-up time point?
Response: The sample size and power calculations are based on the changes from baseline for the ITT population.

20) Whatever the sample size is based on, can you please justify the selection of 10 kg for the SD? Is this the SD for general body mass at baseline/follow-up? Or is it the SD of the change scores? Please say where you have got this SD value from.
Response: The selection of 10 kg for the SD is based on our previous weight loss trial in knee OA patients (Christensen R, Arthritis Care Res (Hoboken). 2015 May;67(5):640-50), where the SD was approximately 8 kg. Thus we conservatively estimated the SD in the current trial to 10 kg.
We have added a note and reference to the manuscript

21) What is a “a simple non-responder imputation technique”?
Response: This paragraph has been updated in order to clarify that the authors intend to carry forward observations from enrolment in case of missing data in the ITT population.
FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:

22) Kindly re-upload each figure under ‘Image’ file designation with at least 300 dpi resolution and at least 90mm x 90mm of width.
Response: The figure has been uploaded as separate files as described in your comment.

23) We have implemented an additional requirement to all articles to include 'Patient and Public Involvement’ statement within the main text of your main document. Please refer below for more information regarding this new instruction.
Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions:
a) How was the development of the research question and outcome measures informed by patients’ priorities, experience, and preferences?
Response: Via a formal review process, the authors retrieved input from an appointed knee OA patient advisor in a discussion focusing on the development of hypotheses, interventions and outcomes related to this study.
This description is a part of the section 'Patient and Public Involvement' in the manuscript.
b) How did you involve patients in the design of this study?
Response: The design of the study was not discussed with patients.
This description is a part of the section 'Patient and Public Involvement' in the manuscript.
c) Were patients involved in the recruitment to and conduct of the study?
Response: The patient board and our knee OA advisor were involved in proposing potential routes for communication regarding recruitment of patients, including websites and patient associations.
This description is a part of the section 'Patient and Public Involvement' in the manuscript.
d) How will the results be disseminated to study participants?
Response: “Patients will be informed, via dialogue and a briefing document, that they may access results on an individual basis throughout the trial and that the study personnel will engage in presenting the overall results for each individual patient once the trial is complete. Upon trial completion, patients will also be invited to a meeting where the project results are presented in a manner that is understandable by laymen.”
This description is a part of the section 'Patient and Public Involvement' in the manuscript.
e) For randomised controlled trials, was the burden of the intervention assessed by patients themselves?
Response: The burden of the study was assessed by all patients via an initial appraisal of their motivation to participate in the study and via a thorough description of the study in relation to signing the informed consent.
This description is a part of the section 'Patient and Public Involvement' in the manuscript
f) Patient advisers should also be thanked in the contributorship statement/acknowledgements.
Response: The study protocol specifically thanks the Parker Institutes patient board as well as the Parker Institutes knee OA patient advisor.

This description is a part of the section 'Acknowledgements' in the manuscript
g) If patients and or public were not involved please state this.
Response: Our patient board as well as a specific knee OA advisor were involved, please see the updated description in the manuscript.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: David Hunter Institution and Country: University of Sydney, Australia Competing interests: No competing interests
REVIEW RETURNED	15-Nov-2018

GENERAL COMMENTS	The authors have adequately addressed the concerns that I raised

REVIEWER	Reviewer name: Atkinson, Greg Institution and Country: Teesside University, UK Competing interests: None declared
REVIEW RETURNED	20-Nov-2018

GENERAL COMMENTS	Thank you for considering my comments

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: David Hunter
Institution and Country: University of Sydney, Australia
Please state any competing interests or state ‘None declared’: No competing interests
Please leave your comments for the authors below
The authors have adequately addressed the concerns that I raised
Response: Thanks for your feedback

Reviewer: 3
Reviewer Name: Greg Atkinson
Institution and Country: Teesside University, UK
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
Thank you for considering my comments
Response: Thanks for your feedback