PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does glucagon-like peptide-1 (GLP-1) receptor agonist stimulation reduce alcohol intake in patients with alcohol dependence? Study protocol of a randomized, double-blinded, placebo-controlled clinical trial
AUTHORS	Antonsen, Kerstin; Klausen, Mette; Brunchmann, Amanda; le Dous, Nina; Jensen, Mathias; Miskowiak, Kamilla; Fisher, Patrick; Thomsen, Gerda; Rindom, Henrik; Fahmy, Thomas; Vollstaedt-Klein, Sabine; Benveniste, Helene; Volkow, Nora; Becker, Ulrik; Ekstrøm, Claus; Knudsen, Gitte; Vilsbøll, Tina; Fink-Jensen, Anders

VERSION 1 – REVIEW

REVIEWER	MATTEO MONAMI AOU CAREGGI FLORENCE ITALY
REVIEW RETURNED	04-Dec-2017

GENERAL COMMENTS	The rationale of this trial protocol is convincing and the paper is generally well-written. I have only few minor comments: 1) Consort guideline is not mentioned. 2) I suggest to better specify whether HbA1c or glycemia are tested during follow-up. 3) In the par.: GLP-1RA: A potential new treatment for alcohol use disorder, please add other possible indirect mechanisms: e.g.body weight reduction possibly induced by exenatide LAR could theoretically have an influence on depressive symptoms (if present) and therefore on alcohol intake.

REVIEWER	Diego Garza, MD. MPH Gillings School of Global Public Health The University of North Carolina at Chapel Hill Public Health Leadership Program.
REVIEW RETURNED	14-Dec-2017

GENERAL COMMENTS	-Table 1: Baseline Characteristics of the included population- Not present. We need one to be able to check for several things like Quality of the randomization process, differences, and similarities between arms of the study. Need this to be able to address confounding and selection bias. -Protocol for enrollment not very clear -Randomization process not clearly stated? Type of randomization? Elaborate more. Background too extensive, we could use more information on the actual study less on the reasons you are doing it, some strong statements on the background should be enough. Describe statistics more clearly, too much wording without actual

	numbers. How was confounding adjusted for, was it at all, have sources of confounding been identified? Measurement bias could be a concern as well. Since the sample size is small, maybe subgroup analysis will give us more information on the matter.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

The rationale of this trial protocol is convincing and the paper is generally well-written.
I have only few minor comments:

-Consort guideline is not mentioned.
Answer: The CONSORT guidelines will be fully implemented when reporting the results. This has been specified along with the description of the randomization process cf. the guidelines item 8-10.

-I suggest to better specify whether HbA1c or glycemia are tested during follow-up.
Answer: HbA1c is only tested at inclusion (week 0) and at the end of the trial (week 26). This has been specified in the text.

-In the par.: GLP-1RA: A potential new treatment for alcohol use disorder, please add other possible indirect mechanisms: e.g.body weight reduction possibly induced by exenatide LAR could theoretically have an influence on depressive symptoms (if present) and therefore on alcohol intake.
Answer: Thank you very much for your interesting reflections. However, we find that these issues are complicated in nature and difficult to confine. We will therefore suggest not to elaborate further on this in the present manuscript.

Reviewer 2:

-Table 1: Baseline Characteristics of the included population- Not present. We need one to be able to check for several things like Quality of the randomization process, differences, and similarities between arms of the study. Need this to be able to address confounding and selection bias.
Answer: table 1 is not present in the manuscript as it is a protocol article, and we are in the process of including patients. When the study has been finalized and data has to be published, a table 1 will be included in accordance with your suggestion.

-Protocol for enrollment not very clear
Answer: Thanks for your comment. It has been somewhat difficult for us to improve on this issue.

-Randomization process not clearly stated? Type of randomization? Elaborate more.
Answer: Thanks for this valuable comment. We have elaborated on the randomization process.

-Background too extensive, we could use more information on the actual study less on the reasons you are doing it, some strong statements on the background should be enough.
Answer: Thanks for your valuable comment. The background information has been shortened.

-Describe statistics more clearly, too much wording without actual numbers. How was confounding adjusted for, was it at all, have sources of confounding been identified? Measurement bias could be a concern as well.
Answer: Since the study is a RCT we have – by construction – ensured that potential confounders and selection bias will be minimized/eliminated. It can be advantageous to include additional

predictors that are associated with the outcome to reduce the residual variation and increase the power to detect the treatment effect. The RCT gives unbiased estimates of the treatment effect regardless of whether we correct for additional covariates. To reduce variance we will correct for the variables using as block randomization in the stratification process.

-Since the sample size is small, maybe subgroup analysis will give us more information on the matter.
Answer: The sample size was computed to obtain a 90% power to detect a difference in 10% between treatments so while the number appears small it is sufficient to obtain the desired power. Subgroup analysis will result in a substantial loss in power simply because the sample size will be diminished and because the subgroups essentially should be similar across treatments because of the RCT.

VERSION 2 – REVIEW

REVIEWER	Diego Garza, MD, MPH. Gillings School of Global Public Health at the University of North Carolina at Chapel Hill.
REVIEW RETURNED	08-Apr-2018

GENERAL COMMENTS	Great job addressing previous comments from both reviewers.