1. The proposal was vague in its methodological intent and would be strengthened with minor revisions to be sure pre-specified plans are clear.

Answer: We are currently working on developing a principled approach to (1) estimate individualized treatment rules (or policies) based on patient covariates and (2) to evaluate the associated benefit. Since this is part of our research, we did not detail the specific method we are developing, but more the context and issues related to our project. We understand that this may therefore seem vague. We had also chosen to describe the whole research program aims, adding for instance the extension of the methods to observational data, which is irrelevant for this specific data request.

To be more intelligible and more precise, we have therefore revised the description of the project to make it more focused, and more detailed into pre-specified analyses.

2. I appreciate the authors' intent with this innovative proposal but found some of the language to be a bit too vague. I think the proposal could be clearer to other scientists, and thus allow better understanding of the objectives and methods, with revision. For instance, the specific aims of the project are quite broadly stated. Could the investigators be more specific with the explicit intent of these analyses?

Answer: As stated above, we understand this concern and have decided to describe in a more detailed way how data will be analyzed, rather than why we are trying to develop new methods in the field.

3. The authors' proposed statistical analysis could be better defined:

"This can be performed either in one step using a regression model with suitable interaction terms between the X's and the treatment arm Z, or separately for each treatment arm, thus being non-parametric on the form of these interactions. There is no need for the model to be correctly specified to determine an ITR. However, model misspecification may influence the properties of the resulting ITR at two levels. First, a parametric model may put too many constraints on the relationship between predictors and treatment effect, and therefore miss regions of the parameter space where one treatment in superior to the other, or conversely, wrongly identify regions where a treatment would seem beneficial, thus decreasing the benefit of the ITR overall. Second, the model for E(Y(1)|X) and E(Y(0)|X)—and therefore the ITR—and the benefit of this ITR are usually estimated using the same set of data, which leads to over-fitting and over-optimism."

The authors should consider writing the statistical analysis section to mirror the explicit research objective statement and to be clear in which is the primary analysis and how it will be performed, which is the secondary analysis and how it will be performed.

Answer: The statistical analysis section has been revised in-depth to describe more precisely how data will be analyzed. However, since this implied describing concisely and for a wide audience a method that is still under development and for which details are currently being summarized in a complex methodological article (still not finished), the explanations may be
hard to follow. Nonetheless, we tried our best to give a precise though not too technical overview of which analyses will be performed, in a constrained limit of 4000 characters.

4. The authors explain that they will write two articles: one for a statistical audience and a second for a clinical audience. I was confused by this. Will the statistical article report a method that will be developed using the CANTATA-SU data? Or will it report a method developed prior to beginning work with this data? I'd imagine that the clinical article will be a report of the application of the method to this data. Please clarify.

Answer: Sorry if this was unclear. Actually, we are writing an article for a statistical audience describing the method we are currently developing, and we would like to use the CANTATA-SU data as an illustration of our approach in this paper. This is commonly done in the biostatistical field, in order to show what a new method can produce. Usually, the analysis is not as thorough as it would be in a clinical article, because it only serves the purpose of illustration. For instance only one comparison (canagliflozin 300 mg + metformin versus glimepiride + metformin or canagliflozin 100 mg + metformin versus glimepiride + metformin) and only one outcome (changes in HbA1c or proportion of patients with HbA1c < 7%) would be presented.

Then, we plan to write a more clinical paper reporting the application of the method to the data, but with a more in-depth analysis, including for instance sensitivity analyses, checking of model assumptions, proper handling on missing data. The reporting is also different, because for a different audience.

5. I think this proposal will enhance the debate around this approach to personalizing medicine. However, the particular example is unfortunate because type 2 diabetes is a risk state where the effect of lowering blood glucose is often unconnected to any long term benefit or harm, especially at this low target HbA1c. Identifying individuals who show a glucose response over a limited period is not the same as identifying individuals who would get long-term benefit or harm. For this, there is no surrogate measure which can be depended on.

Answer: Thank you for raising this important point. We understand that achieving lower blood glucose may not translate into longer-term clinical benefit. But we see more our proposal the other way around. By identifying patients for whom canagliflozin does not achieve glycemic control, we may spare this line of treatment that would unlikely provide a clinical benefit. In that respect, the question of personalizing treatment remains important.

6. If the study database includes information on patient adherence, it would be advisable to conduct this analysis in an "on-treatment" cohort.

Answer: Thank you for this suggestion. Up to now, the methods we are developing rely on randomization, and extension to observational data has not been considered yet. If we only analyzed the on-treatment cohort, we would loose the benefit of randomization—at least from a theoretical point-of-view. On the contrary, relying on intent-to-treat analyses maintains the
benefit of randomization. While being agnostic on the mechanism by which a group may not benefit from the treatment (it may be because biologically the treatment is less effective than the control, but also because the patients have more side effects with the experimental treatment and therefore less compliance), we may still derive pragmatic individualized treatment rules.

7. Please note: analysis of change in A1c from baseline to Week 52 as well as analyses of the proportion of patients reaching A1c < 7% have been conducted by Janssen and reported in the CSR summary (attached). If individual participant-level data is still requested, please clarify how the proposed analyses differ from those already conducted.

Answer: We acknowledge that changes in HbA1c from baseline to week 52 as well as the proportion of patients achieving HbA1C <7.0% have already been analyzed by the trial sponsor. In this project, the analysis will however be different since it aims at using a method we have developed in order to define individualized treatment rules after identifying patients for whom the treatment effect is negative.

8. There were several typos throughout the proposal. A close read to correct these errors would be helpful.

Answer: Sorry for this. We have tried to correct typos.