Reviewer’s report

Title: Rationale and design of the CAROLINA® - cognition substudy: a randomised controlled trial on cognitive outcomes of linagliptin versus glimepiride in patients with type 2 diabetes mellitus

Version: 0 Date: 05 Jul 2017

Reviewer: Michael Donohue

Reviewer’s report:

This reviewer's primary interest was the primary analysis approach. The planned approach is to submit dichotomized residualized change on the MMSE, and a composite of trail making and verbal fluency tests, to a logistic regression. The MMSE and composite are first "residualized" to form the Regression Based Index (RBI) which is adjusted, via ANCOVA, for age, language, education, and baseline performance. Cognitive decline will be defined by an MMSE or composite RBI in the lowest 16th percentile (yielding an expect 20-22% of subjects in aggregate with cognitive decline). The are three potential concerns with this approach.

The first concern is that uncertainty in the first stage model is not reflected in the second stage model. This could result in an underestimation of the standard error of the primary estimate of group difference in rate of cognitive decline, and inflation of Type I error. The rationale for this approach appears to be that it "reduces the impact of learning effects." It is unclear what the impact of learning effects would be, and how this approach reduces them compared to, say, a direct MMRM of group difference controlling for the same covariates. Learning effects, if more common in one group, might be an important indication of treatment effect.

The second concern is whether this method meets the standard of being robust to data Missing at Random (MAR). Direct likelihood methods, such as the secondary MMRM analysis is robust to the MAR assumption, but it is unclear that the proposed primary multi-step approach would also be. Multiple imputation might be a useful tool which could be adapted to address both of the above concerns -- incorporating uncertainty in the RBI step and ensuring robustness to MAR. Multiple imputation could be used to supplement the proposed plan for handling missing cognitive data, and impute missing data that remains after the planned review.

Third, dichotomization, while possibly facilitating clinical interpretation, might come at the expense of information loss and power (see, e.g., Cohen, J. (1983) The cost of dichotomization. Applied Psychological Measurement, 7, 249-253.) While this is a fairly large study which is probably adequately powered, why not use the most statistically efficient method? In this case, this might mean analyzing a single continuous outcome, a composite of all three: MMSE, trail making, and verbal fluency.

Awkward: "study treatment stop (referred to as end of follow-up previously)" Why not just use "end of follow-up"?
Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?  
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Yes

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