Reviewer’s report

Title: A randomized controlled trial of the efficacy and safety of twice-daily saxagliptin plus metformin combination therapy in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy

Version: 2 Date: 26 August 2013

Reviewer: Jeppe Schroll

Reviewer’s report:

1a+b). My concern is that your comparator group (placebo) is not the most relevant to answer a clinical question. The choice for a clinician would probably between saxagliptin or another therapy and not between saxagliptin and nothing. Or perhaps between saxagliptin given twice a day or once.
I believe this is a limitation that should be mentioned.

Only a suggestion, but I think that poor compliance of several drugs could be a good argument to try and combine drugs. It could be worth mentioning in your manuscript with good references.

1c) I encourage you to share these concerns with the readers of the manuscript

2) I encourage you to implement in your manuscript that your assumption is that the reduction in HbA1c will lead to less microvascular events but that the macrovascular outcomes are were not assesed.

3) But when dealing with a continuous outcome you must have a threshold for what you consider clinically relevant? You wouldn't accept a difference of 0.01% even though it was statistically significant, right? Obviously some benefited more than others but to state that it was relevant to some would also apply to a non-working drug (due to an expected random distribution)

4) Ok. But I still don't think that you should write that the mechanism is complementary in the conclusion when this has not been addressed in the current study.

5) Ok.

6) So why were the efficacy outcomes 0.5% and 0.7% HbA1C reduction, FPG<110 and FPG<126 not specified on clinicaltrials.gov? Is it possible to see your protocol?

7) Amylase was not measures or you didn’t do the analysis? If it was not measures can you please specify what laboratory tests you did do? If you didn’t do the analysis I believe it's worth the time given the major public health concern.

8) Ok
9) ok
10) ok
11) ok
12) Ok. I think that the effect sizes written in the discussion provide a fair overview. It does look like the order of references are wrong. 9 relates to the -0.83 reduction right?
13) ok
14) ok thanks.
15) Ok.
16) Thanks
17) Thanks
18) Ok.
19) Thanks
20) Ok
21) Thanks

I suggest that you - under acknowledgements - state who wrote the first draft of the manuscript.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interest