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 uncontrolled on metformin monotherapy

Version: 1 Date: 22 May 2013

Reviewer: Jeppe Schroll

Reviewer's report:

This is a well conducted and well reported randomized trial but an identical, larger and longer trial has already been conducted. The only difference is that in this trial saxagliptin is divided into two daily doses instead of one. It is hard to imagine that this would lead to much difference in efficacy and safety.

1. Is the question posed by the authors well defined?
   Yes

2. Are the methods appropriate and well described?
   Yes

3. Are the data sound?
   Yes

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   It was registered on Clinical trials.gov but I did not see CONSORT checklist.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Not entirely. See my comments

6. Are limitations of the work clearly stated?
   Yes but there is lacking a few.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   Yes

8. Do the title and abstract accurately convey what has been found?
   Not completely see comments.

9. Is the writing acceptable?
   Yes.
Reviewer's report

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Major Compulsory Revisions

1) Can you please explain why the question that you are trying to answer is relevant to a clinician? If a patient is inadequately controlled on metformin is the clinician really interested in knowing whether it’s better to do nothing or giving an extra drug?

What are your thoughts on giving placebo to inadequately controlled diabetic patients from an ethical standpoint?

2) Since a reduction in HbA1C in the case of rosiglitazone was not a predictor for patient relevant macrovascular events could this not be a limitation in your study?

3) Could you discuss whether the reduction due to saxagliptin of 0.34% at week 12 is clinically relevant? For instance how big a reduction in macrovascular events does that equal?

4) In your conclusion you write that “improved glycemic control by a complementary mechanism of action.”. Can you please specify how you have shown this as I can’t find any support for this in your paper.

5) I suggest that you, in your conclusion, write that saxagliptin “lowers HbA1C” instead of writing that it improves glycemic control. First, FPG was not significantly reduced and, and second, “improves glycemic control” implies that it is clinically relevant which I am not sure that you have shown.

6) The 0.5% and 0.7% HbA1C reduction threshold was not specified in the protocol (clinicaltrials.gov). Neither were the FPG<110 or FPG<126 nor body weight. It should be clear that these outcomes were defined post hoc.

7) There is suspicion that the drug class can cause pancreatitis and since abnormal amylase values were not present on clinicaltrials.gov could you please specify whether you encountered any abnormal values?

8) 283 were enrolled but 117 did not enter the lead in. Why was that?

9) In your title and as a purpose in your abstract you are writing “safety”. Can you discuss whether you can be sure that the drug is safe given your small sample and considering it was not a part of the power calculation?

10) In your abstract you are writing “At week 12, adjusted mean changes (95% CI) from baseline HbA1c”. Perhaps I don’t get it but isn’t it just posttreatment value – baseline value? Isn’t that just simply called mean change (without the adjustment) or is it adjusted for something else?.

11) Abstract – conclusion: I think you should specify that a reduction in HbA1C by saxagliptin is compared to placebo.

12) The question that you are actually answering is that two times a day is comparable in effect and safety to once a day. But is it just as good? In DeFronzo the difference between placebo and saxagliptin for 5mg was actually 0.83% vs only 0.34% in this study. Perhaps that needs to be commented?
13) Under limitations you write that more effect could be expected due to the downward slope of HbA1C at 12-weeks. However, in your 24-week study (DeFronzo) this was not the case. Actually the reduction became smaller after 12-weeks so I would downplay this speculation a bit.

14) In the discussion you are reporting the following “adjusted mean changes from baseline HbA1c were #0.52% (18-week trial), #0.69% (24-week trial), and #0.74% (52-week trial),”

For the 24-week trial this is only the results of the treatment arm. It is more appropriate to report the difference between the treatment arm and the placebo arm. I would also urge you to do this with your own results even though the effect will seem smaller.

Minor Essential Revisions
15) Please use “inadequate glycemic control” throughout manuscript instead of “uncontrolled”.

16) Please describe how randomization was done in practice (From CONSORT: Method used to generate the random allocation sequence, Type of randomisation; details of any restriction (such as blocking and block size), Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned, Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions)

17) Dates defining the periods of recruitment should be stated.

18) In your conclusion you write that saxagliptin was “well tolerated” which is unspecific and not recommended by CONSORT.

19) Could you please specify under acknowledgements whether all authors had access to raw data.

20) Why was ‘back pain’ considered a serious adverse event? Since it is normally trivial I think you should mention the reason for this categorization in the text.

Discretionary Revisions
21) A completed CONSORT checklist would be a great amendment to your work.

22) In your abstract you are writing that all randomized patients were analyzed for safety and efficacy. In the methods section you are defining populations (“Randomized Patients Population”) who received the drug and attended at least one postbaseline assessment. I missed that all these populations were the same so perhaps you should specify it.

Level of interest: An article of limited interest

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 interests