Author's response to reviews

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

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Author's response to reviews: see over
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Timothy Shipley
Executive Editor
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Dear Dr. Shipley,

On behalf of my coauthors, I am resubmitting the revised original manuscript “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” (MS: 1664002735989438) for consideration for publication in BMC Endocrine Disorders. We appreciate the reviewers’ time and feedback and have revised the manuscript accordingly. Please find below our responses to the individual reviewer comments.

Reviewer 1
Comment 1a: Can you please explain why the question that you are trying to answer is relevant to a clinician?

Progressive beta-cell dysfunction drives type 2 diabetes mellitus progression (DeFronzo. Diabetes. 2009;58:773-795), and most patients ultimately require combination therapy to adequately maintain glycemic control, as discussed in the Background section (paragraph 1). Because many patients have comorbidities, polypharmacy is common, and the pill burden is high (Blonde and San Juan. Adv Ther. 2012;29(1):1-13), which may undermine adherence (Donnan et al. Diabet Med. 2002;19:279-284). As noted in the Background section, the current recommended dose of saxagliptin in the European Union and other markets is 5 mg, once daily. Previous controlled trials have demonstrated the effectiveness of this dose as add-on therapy to metformin or initial combination therapy with metformin in decreasing HbA1c in patients with type 2 diabetes mellitus (Background, paragraphs 3 and 4). The current study evaluates saxagliptin taken as a divided dose of 2.5 mg twice daily in combination with metformin immediate release (IR) twice daily. The effectiveness and safety of this regimen is relevant to the clinician in that it provides data in support of a fixed-dose combination of saxagliptin with metformin IR (Background, last paragraph).

Comment 1b: 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?

The effectiveness and safety of this new regimen of saxagliptin administration require careful evaluation. The purpose of the placebo control is to evaluate the potential bias of participating in a clinical trial. Thus, it is not accurate to equate the placebo control with “doing nothing.”

Comment 1c: What are your thoughts on giving placebo to inadequately controlled diabetic patients from an ethical standpoint?

With regard to the ethics of the placebo-controlled design, we share your concern and feel that in patients with inadequate glycemic control, time on placebo should be limited and/or rescue therapy should be provided. In that regard, please note that this trial was 12 weeks in duration. In addition, patients were discontinued from treatment and withdrawn from the study if they had lack of glycemic control during the double-blind treatment period at weeks 4 and 8. In studies of longer duration, it is standard practice to use rescue therapy.
Comment 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?

Cardiovascular risk management is an important component of diabetes treatment, as recognized by the American Diabetes Association, European Association for the Study of Diabetes, and International Diabetes Federation. However, macrovascular risk reduction was not an end point in the current study, and the inconsistent evidence regarding macrovascular risk reduction with antihyperglycemic therapy cannot be considered a study limitation. The ongoing Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes-mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 study (NCT01107886) will provide information about the long-term cardiovascular as well as general safety and efficacy of saxagliptin versus placebo in patients with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors (Mosenzon et al. Diabetes Metab Res Rev. 2013. Epub ahead of print). It should not be forgotten that the primary rationale for glucose-lowering therapy in diabetes is to reduce microvascular complications, for which HbA1c is considered an appropriate surrogate marker.

Comment 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?

Guidelines recommend a personalized approach to selecting diabetes medication, taking into account patient features, including propensity for side effects, and disease features (Raz et al. Diabetes Care. 2013;36:1779-1788). A modest reduction in HbA1c with a low risk of hypoglycemia and neutral weight effects would be considered advantageous in some patients.

We have attempted to provide more context for the change in HbA1c in the Discussion (paragraph 2). At week 12, the adjusted mean reduction in HbA1c with saxagliptin + metformin was 0.56%, which is consistent with the known glucose-lowering effectiveness of the DPP-4 inhibitors (Inzucchi et al. Diabetes Care 2012;35:1364-1379) and in the range of that reported in previous studies of saxagliptin once daily in combination with metformin, although the placebo-subtracted difference (~0.34%) was smaller than that reported in a previous 24-week study of saxagliptin versus placebo as add-on to metformin (~0.83%). It was not possible to statistically determine if this translated to a significant increase in the proportion of patients achieving a therapeutic glycemic response (HbA1c <7%), as the reduction in FPG did not reach statistical significance, precluding statistical testing of subsequent end points per study protocol and analysis plan. As acknowledged in the Discussion (paragraph 6), the short study duration and small sample size are important limitations to the current study that may limit interpretation of the findings.

As noted in our response to comment 2, macrovascular outcomes were not evaluated in this trial, and it would not be appropriate for us to speculate as to macrovascular risk reduction.

Comment 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.

We have reworded this sentence. As noted in the Background (paragraph 2), saxagliptin and metformin have complementary mechanisms of action, but the mechanisms of action underlying the observed improvements in HbA1c were not assessed in the current study.
Comment 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, second, “improves glycemic control” implies that it is clinically relevant which I am not sure that you have shown.

We have revised this sentence as suggested.

Comment 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.

Descriptive analyses of reduction in HbA1c ≥0.5% and ≥0.7%, and FPG <110 mg/dL and <126 mg/dL were specified in the clinical protocol. As already noted in the Methods (Data Analysis/Statistics, paragraph 2), body weight was analyzed post hoc. We have revised the Assessments section (paragraph 1) to further clarify that body weight was analyzed post hoc.

Comment 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?

Amylase levels were not assessed in this study. However, there were no AEs of pancreatitis in this study, as noted in the last paragraph of the Results.

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

The study protocol required enrollment with full consent for screening of inclusion and exclusion criteria, leading to a large group of enrolled patients (n=117) not meeting criteria for lead-in. These patients had provided written informed consent to participate in the study but did not satisfy the required inclusion and exclusion criteria. We have added this detail to Figure 1.

Comment 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?

It is typical for phase 3 studies not to be powered for safety. The title is appropriately descriptive of the study design, as safety was a specified outcome, which was assessed using adverse events, electrocardiograms, vital signs, physical exams, and clinical laboratory tests. For this same reason, we consider it appropriate to include safety in the abstract. In fact, not including safety could be considered an omission. The title does not make a conclusive statement about the safety of the drug and does not imply that the results of this trial are sufficient to demonstrate safety. In the Discussion (paragraph 6), the relatively small sample size and 12-week timeframe of the study are acknowledged as study limitations that affect the interpretation of findings.

Per comment #18, we have also replaced statements in the Abstract and Discussion that the intervention “was well tolerated” with more specific language (ie, saxagliptin 2.5 mg BID added to metformin therapy had an adverse events profile similar to placebo and no unexpected safety findings).

Comment 10) In your abstract you are writing “At week 12, adjusted mean changes (95%
The adjusted mean change is the least-squares mean change adjusted for baseline HbA1c value. We have clarified this in the Abstract and Methods (Data Analysis/Statistics, paragraph 1).

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

We have made this clarification in the Abstract and Conclusions.

Comment 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?

There was no comparison of saxagliptin once daily to saxagliptin twice daily in this study; therefore, no conclusions are made regarding the comparative efficacy of these regimens. In the Discussion, we report adjusted mean changes from baseline HbA1c from 3 previous trials of saxagliptin 5 mg QD as add-on therapy in patients with inadequate glycemic control in metformin IR monotherapy, including the DeFronzo study. Adjusted mean changes from baseline HbA1c were −0.52% (18-week trial), −0.69% (24-week trial), and −0.74% (52-week trial). We have also added between-group differences from these studies as well as reiterated results for the current study. The adjusted mean change from baseline HbA1c value of −0.56% in the 12-week trial is within the range reported in previous studies, although the between-group difference is in fact smaller than in the DeFronzo et al study. We elected not to make direct comparisons between studies because of differences in sample size and study duration.

Comment 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.

We have removed this sentence.

Comment 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.

We have added between-group differences in adjusted mean change from baseline HbA1c for the 3 previous trials and the current trial (Discussion, paragraph 2). Since some of these trials included active comparison groups, we feel it is important to report the within-group adjusted mean changes from baseline as well.

Comment 15) Please use “inadequate glycemic control” throughout manuscript instead of “uncontrolled”.

We have made this change.
Comment 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)

Patients were enrolled at each study site, and at the screening visit each patient was assigned a unique sequential subject number by an Interactive Voice Response System (IVRS), which was used for identification throughout the study. Patients were randomly assigned in a 1:1 ratio to saxagliptin or placebo using a blocked randomization schedule. The computer-generated randomization scheme was developed and kept by the study sponsor. Randomization was performed by calling the IVRS. Placebo tablets were identical in appearance to the saxagliptin tablets, and medication was dispensed using bottle numbers assigned by the IVRS. We have added this information to the Methods (Treatment section).

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

We have added study start and end dates, as well as the recruitment period (Methods, Study Design).

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

We have revised the conclusory statement to incorporate more specific language.

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

We have added a sentence specifying that all authors had access to case report form data upon request.

Comment 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.

The patient, who had a history of chronic low back pain and degenerative disc disease, had severe back pain requiring hospitalization. She was determined to have a lumbar strain.

Discretionary Revisions

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

We have included a completed CONSORT checklist in our revised submission.

Comment 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.

We have clarified this point in the abstract (Methods and Results).
Reviewer 2
No comments to address.

Editorial Requests
Please provide the name of the ethics committee that approved your study.

The protocol, amendments, and subject informed consent received appropriate approval by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to initiation of the study at the site. Each IRB/IEC was composed of a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in the clinical investigation and was adequately constituted to provide assurance of that protection.

We hope that the reviewers are satisfied with our responses and revisions and find our manuscript suitable for publication in Clinical Drug Intervention.

Sincerely,

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