

May 10, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 2966-review.doc).

Title: Vildagliptin-insulin combination improves glycemic control in Asians with type 2 diabetes

Author: Plamen Kozlovski, James Foley, Qing Shao, Valentina Lukashevich, Wolfgang Kothny

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 2966

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 00505919

(1) p7 results section: 87 patients to vildagliptin and 86 patients to placebo. p8: the corresponding numbers are 85 and 84, respectively. The statistical analysis plan states that LOCF was used for missing data in the efficacy analysis. The authors should clarify the discrepancy in the numbers, were these patients lost?

RESPONSE: We appreciate the reviewer's comment. There were 87 Asian patients randomized in vildagliptin and 86 in placebo. The baseline demographic and background characteristics were summarized in the randomized set. Among the randomized patients, there were four patients (two in each treatment) who withdrew their consent at the beginning of the study. No post-randomization efficacy measurements were available for these four patients. The LOCF is applicable only when a patient had at least one post-randomization assessment (i.e. only post-baseline measurements were eligible to be carried forward as study endpoint) so these four patients were excluded from the full analysis set (FAS), which resulted in efficacy data reported on 85 and 84 patients as stated on p. 8. Note that these four patients were included in the safety set for safety data analysis since they had taken at least one dose of study medication.

(2) p9: blurred vision: do the authors know whether these were hidden cases of hypoglycaemia? There seems to be quite a difference between the groups - the authors should comment on that.

RESPONSE: We thank the reviewer for pointing out this difference between the treatment groups. Blurred vision was reported by 8 patients (9.2%). For three of them, blurred vision was identified as hypoglycemia and included in the hypoglycemic events summary since they had accompanying glucose measurements < 3.1 mmol/L. Of the

remaining five, four reported, together with the blurred vision, one or more symptoms suggestive of hypoglycemia (dizziness, weakness, palpitations, tremor or hyperhidrosis), however no blood glucose measurement had been performed to confirm a hypoglycemic event. Six of the eight patients experienced considerable reduction in HbA1c of 1.4% or more during the study; another one had a smaller HbA1c reduction, but reached HbA1c of 6.5%. These events of blurred vision could be symptoms of hypoglycemia, or in some cases a reflection of rapidly improving glucose levels.

We have now modified the text of the manuscript to explain this difference in blurred vision.

(3) HbA1c should be also given as mmol/mol

RESPONSE: We have now addressed this issue in the revised manuscript.

Reviewer 00674619

(1) The authors should highlight along of the revised text more about the novelty and importance of their paper.

RESPONSE: We thank the reviewer for this comment. The novelty and importance of the paper lies in the fact that double-blind randomized studies in Asian patients with type 2 diabetes investigating the effect of DPP-4 inhibitors as add-on to insulin have not been reported to date. 40% of the patients in our study were from Asia. We have made an effort to discuss all these factors in the 'Introduction'.

(2) At 'Abstract', Results section, the first sentence should be removed at Methods section

RESPONSE: We have now addressed this issue in the revised manuscript.

(3) At 'Introduction', the authors could add the articles regarding metformin's effects in patients with type 2 diabetes mellitus (T2DM).

Also, the aim of the study from the last part of 'Introduction' should be reformulated.

RESPONSE: We thank the reviewer for this comment. However, we wished to highlight the insulin-vildagliptin combination in our manuscript and any references regarding the effects of metformin did not seem appropriate. The manuscript does refer to a study of vildagliptin in combination with metformin (Ref #10) in 'Introduction'.

We have revised the statement describing the aim of the study in the last part of the 'Introduction' as requested.

(4) At 'Materials and Methods, 'Study design and patients' section, should be mentioned the number of patients both men and women.

RESPONSE: We have now addressed this issue in the revised manuscript.


(5) The authors should avoid the minus sign (for example - 0.82%) and to find another formulation.

RESPONSE: We have now addressed this issue in the revised manuscript.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,

Signature 

Plamen Kozlovski, MD

Novartis Pharma AG

Postfach

CH-4002 Basel

Switzerland

Phone: +41-61-6964697

Fax: +41-61-3247921

E-mail: plamen.kozlovski@novartis.com