Author’s response to reviews

Title: A randomized, placebo-controlled clinical trial evaluating the safety and efficacy of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus inadequately controlled by glimepiride and metformin

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Author’s response to reviews:

Dear Doctor Tahrani,

Thank you for facilitating the review of our manuscript (BEND-D-17-00095) entitled “A randomized, placebo-controlled clinical trial evaluating the safety and efficacy of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus inadequately controlled by glimepiride and metformin.” We very much appreciate the time and effort that Professors Nakamura and Saisho have taken to review our manuscript. Below is our point-by-point reply to the reviewers. We hope that with these responses and the revisions to the manuscript, you will find the manuscript suitable for publication in your journal.
Yoshifumi Saisho (Reviewer 1):

1. Definition of hypoglycemia is not clear. Was hypoglycemia confirmed by SMBG?

The definitions of hypoglycemia used in the trial are presented as footnotes in Table 3. Symptomatic hypoglycemia was defined as episodes with clinical symptoms attributed to hypoglycemia, without regard to glucose level. Asymptomatic hypoglycemia was defined as fingerstick glucose (SMBG) values ≤3.9 mmol/L (70 mg/dL) without symptoms.

2. Was the dose of glimepiride reduced if hypoglycemia occurred? The titration of glimepiride during the study and the final dose of glimepiride at week 24 should be described in the manuscript.

Thank you for pointing out our omission of this design feature. Per the protocol, patients were to remain on a stable dose of glimepiride (≥4 mg/day) throughout the trial. However, the dose of glimepiride could be down-titrated for hypoglycemia to a minimum dose of 1 mg/day. In addition, patients were to remain on a stable dose of metformin (≥1500 mg/day) throughout the trial. Up-or down-titration (including discontinuation) of metformin was not permitted. We have added these facts to the Study Design section of the revised manuscript.

We did not record the mean dose of glimepiride at the beginning or end of the trial. Down-titration of glimepiride, if it occurred, would have most likely occurred in the omarigliptin group more often than in the placebo group, thus, if anything, biasing against the efficacy of omarigliptin.

3. Was adherence to medication assessed? This information should be described.

Compliance with double-blind study medication (omarigliptin or matching placebo) was assessed by site pill count at each visit during the treatment period. Per your comment we have added this information into the manuscript.

4. It may be better to understand if the ethnicity and race are combined in Table 1.

The United States Food and Drug Administration (US FDA) recommends the collection and reporting of the ethnicity data (Hispanic-Latino/not Hispanic-Latino). The US FDA defines “Hispanic” not as a race but as an ethnicity. Therefore, “Not Hispanic or Latino” and “Hispanic or Latino” are reported as ethnicities and cannot be combined with race.
Akinobu Nakamura (Reviewer 2):

Criticism 1: (Results) "At Week 24, the change from baseline in body weight (LS mean [95% CI]) was -0.1 kg [-0.7, 0.4] in the omarigliptin group and -0.9 [-1.4, -0.4] in the placebo group; between-group difference = 0.8 kg (0.1, 1.5)." This result indicated that a significant increase in body weight in the omarigliptin group compared with that in the placebo group was observed. Authors should discuss this result in more detail.

Response:

Per your request, we have added discussion of this point in the Discussion section. In the present trial, there was a slight decrease from baseline in body weight in the omarigliptin group, however, relative to placebo a modest increase in body weight was observed. The between-group difference relative to placebo may be due to the improvement in glycemic control and better metabolic status of the patients treated with omarigliptin compared with placebo.

Criticism 2: (Statistical Analyses) Line 27: "Each patient was categorized as a responder (satisfying the HbA1c specific goal of <7.0% or <6.5% or non-responder at Week 24." There is no ending parenthesis.

Thank you for identifying this typographical error, which we have corrected.

Criticism 3: Please add the word "AHA" into the Abbreviation list.

We have removed “AHA” and replaced it with “antihyperglycemic agent”.