Response to “Letter to the Editor Regarding: Patient Preferences for Glucagon-like Peptide-1 (GLP-1) Receptor Agonist Treatment of Type 2 Diabetes Mellitus in Japan: A Discrete Choice Experiment”

Anne B. Brooks · Jakob Langer · Tommi Tervonen · Mads Peter Hemmingsen · Kosei Eguchi · Elizabeth D. Bacci

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Dear Editor,

We would like to thank you for the opportunity to respond to the issues raised in the letter related to our publication [1] and to provide details of the methodology to address the concerns. In the letter, the author noted concerns about the cardiovascular (CV) outcome risk reduction value used for the semaglutide 0.50 mg profile. The author also requested clarification and disclosure of the references related to attribute levels.

The author is correct that the CV outcome risk reduction for the semaglutide 0.50 mg profile (26% versus placebo) was based on combined data for the 0.50 and 1.0 mg doses reported in the primary publication of SUSTAIN-6 by Marso et al. [2]. This was in accordance with the primary outcome of the study and to support noninferiority and superiority testing. As presented in the appendix of Marso et al., and noted in the letter, CV risk reduction was not significant for either dose independently (23% \[p = 0.13\] for semaglutide 0.50 mg and 29% \[p = 0.06\] for semaglutide 1.0 mg) [2], which was expected because the study was not powered or intended to assess the doses separately.

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By contrast, providing the uncertainty (95% confidence intervals) around the predicted choice probability for the semaglutide 0.50 mg profile versus the dulaglutide 0.75 mg profile would have strengthened our conclusions and might have alleviated the author’s concern. Uncertainty around estimates from patient preference studies should be provided to help interpret results and inform patient-centered benefit–risk assessments [3]. The confidence interval around the predicted choice probability was small (78% [95% confidence interval, 74–82%]), supporting the conclusion that the large majority of participants preferred the semaglutide 0.50 mg profile.

### Table 1 Attributes, levels, and sources for the discrete choice experiment

| Attribute                     | Level                                                                 | Represents            | Reference                                      |
|-------------------------------|-----------------------------------------------------------------------|-----------------------|------------------------------------------------|
| Method of administration      | Multi-dose prefilled pen, used with disposable injection needles, with dose adjustment possible | Semaglutide 0.50 mg   | Ozempic® prescribing information at the time of study conduct |
|                               | Single-dose, disposable prefilled pen, with no dose adjustment possible | Dulaglutide 0.75 mg   | Trulicity® prescribing information at the time of study conduct |
| HbA1c change                  | On average, patients achieve a 1.9% reduction in HbA1c level          | Semaglutide 0.50 mg   | Seino et al. [6]                                |
|                               | On average, patients achieve a 1.6% reduction in HbA1c level          | Intermediate level    | Not applicable                                  |
| CV risk reduction             | 26% reduction of risk in cardiovascular diseases (heart attack, stroke, death due to cardiovascular diseases) | Semaglutide 0.50 mg   | Marso et al. [2]                                |
|                               | No data for the benefit or risk in cardiovascular diseases (heart attack, stroke, death due to cardiovascular diseases) | Dulaglutide 0.75 mg   | None available                                  |
| Weight change                 | On average, patients have a 2.2 kg weight loss                       | Semaglutide 0.50 mg   | Seino et al. [6]                                |
|                               | On average, patients have a 1.1 kg weight loss                       | Intermediate level    | Not applicable                                  |
|                               | On average, patients do not have any weight loss                     | Dulaglutide 0.75 mg   | Miyagawa et al. [7]                             |
| Common side effects           | On average, 1 out of 9 patients will experience transient nausea     | Semaglutide 0.50 mg   | Seino et al. [6]                                |
|                               | On average, 1 out of 12 patients will experience transient nausea    | Intermediate level    | Not applicable                                  |
|                               | On average, 1 out of 19 patients will experience transient nausea    | Dulaglutide 0.75 mg   | Miyagawa et al. [7]                             |
To address the concern of the author about using a 26% CV risk reduction for the semaglutide 0.50 mg profile, we conducted an additional sensitivity analysis for the predicted choice probability. Using a 23% CV risk reduction, the predicted choice probability was 76% (95% confidence interval, 71–80%) in favor of the semaglutide 0.50 mg profile, which is close to the original value and supports the robustness and validity of our original conclusion.

Additional relevant data have been published since the discrete choice experiment was performed. SUSTAIN-7, a head-to-head randomized clinical trial, showed that hemoglobin A1c (HbA1c) and body weight were reduced significantly more with semaglutide 0.50 mg than with dulaglutide 0.75 mg [4]. This was confirmed in a network meta-analysis among patients with type 2 diabetes mellitus in Japan [5]. The REWIND study showed that dulaglutide 1.5 mg reduces cardiovascular risk compared to placebo, although this dosage is still not currently approved in Japan.

Finally, to address the request for clarification and disclosure of the references related to attribute levels, we provide them as Table 1.

Respectfully,
Anne Brooks, BS
Jakob Langer, MS
Tommi Tervonen, PhD
Mads Peter Hemmingsen, MD
Kosei Eguchi, MD, PhD
Elizabeth Dansie Bacci, PhD

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