Letter Regarding "Dose-Response of Tenapanor in Patients With Hyperphosphatemia Undergoing Hemodialysis in Japan—A Phase 2 Randomized Trial"

To the Editor: We read the study on the efficacy and safety of tenapanor in Japan with interest.[1] We present a few concerns.

Our first concern is about the reason for the withdrawal of patients from the study in the 60 mg per day titration group. In the discussion, the stated reason for these withdrawals was diarrhea. In the 60 mg per day dose-titration group, the dose was adjusted according to the gastrointestinal symptoms. Therefore, we think that a factor other than diarrhea may have caused the withdrawals in the 60 mg per day dose-titration group. We believe that further clarification and investigation into the reason for these withdrawals could help to reduce the number of withdrawals in clinical practice.

Our second concern is about the appropriateness of the minimum dose. In a previous study conducted in the United States, the efficacy was confirmed in the 6 mg per day group.[2] This would suggest that perhaps a lower dose than the minimum dose used in this study[1] would have been a better choice.

Finally, our third concern is about a typographical error. In Table 1, the number of people taking vitamin D in the placebo group ought to be 33, and not 3.

1. Inaba M, Une Y, Ikejiri K, Kanda H, Fukagawa M, Akizawa T. Dose-response of Tenapanor in patients with hyperphosphatemia undergoing hemodialysis in Japan—a phase 2 randomized trial. *Kidney Int Rep*. 2021;7:177–188. https://doi.org/10.1016/j.ekir.2021.11.008
2. Block GA, Rosenbaum DP, Yan A, Chertow GM. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: a randomized phase 3 trial. *J Am Soc Nephrol*. 2019;30:641–652. https://doi.org/10.1681/ASN.2018080832

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The Authors Reply: We are extremely grateful to Drs. Aoki and Kataoka for their thoughtful review of our article. Regarding their first point, 1 of the 7 discontinuations in the 30 mg titration group was due to diarrhea as an adverse event, and 4 were withdrawals owing to patient request. The other 2 discontinuations were a patient with serum phosphorus concentration <2.5 mg/dl and a patient who was lost to follow-up. Although the detailed data of discontinuations due to withdrawals by patient request in all groups were not obtained, it can be inferred that this includes patients who discontinued due to diarrhea. We confirmed that the patient who discontinued due to diarrhea as an adverse event was receiving a study drug dose of 60 mg at the time of discontinuation, and the study drug was discontinued before any dose reduction was implemented. This suggests that even if a dose reduction was possible, some patients may have discontinued before dose reduction, depending on the severity of diarrhea. This is only one possibility, because there are no detailed data on the reasons for discontinuation. We will continue to evaluate possible ways to reduce the number of discontinuations in clinical practice. In Japanese phase 3 studies (ClinicalTrials.gov identifiers: NCT04771780,