Influence of dialysate Ca concentrations on the therapeutic effects of etelcalcetide with concomitant drugs in patients with secondary hyperparathyroidism

Takashi Shigematsu1 | Masafumi Fukagawa2 | Keitaro Yokoyama3 | Takashi Akiba4 | Akifumi Fujii5 | Atsushi Shinoda6 | Tadao Akizawa7

1Department of Nephrology, Wakayama Medical University, Wakayama-city, Japan
2Division of Nephrology, Endocrinology and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, Isehara-shi, Japan
3Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan
4Tokyo Next Nephrology & Dialysis Clinic, Tokyo, Japan
5Clinical Development Planning, Ono Pharmaceutical Co., Ltd., Osaka-shi, Japan
6Medical Affairs, Ono Pharmaceutical Co., Ltd., Osaka-shi, Japan
7Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Correspondence
Dr Takashi Shigematsu, Department of Nephrology, Wakayama Medical University, 811-1 Kimiidera, Wakayama-city, Wakayama 641-8509, Japan.
Email: taki@wakayama-med.ac.jp

Abstract

Aim: Secondary hyperparathyroidism (SHPT), a complication of haemodialysis, is commonly treated with calcimimetics. The impact of dialysates containing different calcium (Ca) concentrations on clinical efficacy of calcimimetics are unclear. We examined whether dialysate Ca concentrations influence the efficacy and dosing of etelcalcetide with concomitant drugs.

Methods: We performed post hoc analyses of a 52-week, open-label, multicentre study of etelcalcetide in Japanese SHPT patients to determine whether dialysate Ca influences the therapeutic effects of etelcalcetide with concomitant drugs. We evaluated the differences in serum intact parathyroid hormone (iPTH), corrected Ca (cCa) and phosphate levels among three dialysate Ca concentration groups (2.5, 2.75 or 3.0 mEq/L Ca). Tartrate-resistant acid phosphatase 5b (TRACP-5b) and bone alkaline phosphatase (BAP) levels were also compared. Since the dialysate Ca concentration may influence dose adjustment, we assessed the etelcalcetide and concomitant drug doses.

Results: There were no clinically meaningful differences in iPTH, cCa and phosphate levels among the 2.5, 2.75 and 3.0 mEq/L groups (n = 34, 64 and 35, respectively) over 52 weeks. At Week 52, more than 82%, 71% and 67% of patients had iPTH, cCa and phosphate levels within target ranges (60-240 pg/mL, 8.4-10.0 mg/dL and 3.5-6.0 mg/dL, respectively) across the three groups. TRACP-5b and BAP levels decreased by Week 52 regardless of dialysate Ca. Changes in etelcalcetide and concomitant drug doses were generally similar in each group.
Conclusion: The efficacy and dosing of etelcalcetide with concomitant drugs were essentially unaffected by the dialysate Ca concentration. Patients showed improvements in bone hypermetabolism during treatment.

SUMMARY AT A GLANCE
This is a small observational study of the effect of dialysate calcium concentrations on etelcalcetide with concomitant drugs in secondary hyperparathyroidism. No statistically significant differences were found between the different dialysate calcium groups suggesting that calcium concentrations in the dialysate do not modulate the effect of etelcalcetide.

KEYWORDS
bone metabolism, calcimimetics, calcium dialysate, etelcalcetide, secondary hyperparathyroidism

Secondary hyperparathyroidism (SHPT) is a potentially serious complication of haemodialysis in patients with chronic kidney disease (CKD). SHPT is generally characterised by progressive parathyroid hyperplasia and excessive release of parathyroid hormone (PTH). Elevated PTH increases bone resorption and disrupts calcium (Ca)-phosphate (P) homeostasis, leading to other complications like vascular calcification, and increased risk of death. Therefore, it is important to maintain serum PTH levels within an appropriate range in patients with SHPT.

Ca homeostasis and PTH secretion are regulated via extracellular Ca acting on calcium-sensing receptors expressed on parathyroid cells, representing a key therapeutic target for controlling PTH secretion. Several calcimimetics have been developed to lower PTH levels and are recommended for the treatment of SHPT in the kidney disease improving global outcomes (KDIGO) and Japan Society for Dialysis Therapy guidelines. The first calcimimetic to be approved for the treatment of SHPT was cinacalcet, which lowered serum PTH levels and improved Ca-P homeostasis in clinical trials. In 2016 and 2017, etelcalcetide, a second-generation calcimimetic, was approved. Etelcalcetide is an intravenous peptide calcimimetic that can be administered at the end of each haemodialysis session with good adherence. However, calcimimetics may increase the risk of hypocalcaemia, so increasing the dose of vitamin D and/or calcium carbonate, decreasing the dose of calcimimetics, and changing the dialysate Ca concentration may be necessary.

Ca is an essential component of the dialysis solution, and dialysate Ca concentrations range from 2.5 to 3.0 mEq/L. It has been reported that the dialysate Ca concentration may influence PTH levels. Moreover, the dialysate Ca concentration may have potential short- and long-term consequences, in that lower concentrations may increase the risk of hypocalcaemia and higher concentrations may contribute to vascular pathology. Therefore, it is important to investigate whether the dialysate Ca concentration influences the clinical efficacy of calcimimetics, which may cause excessive reductions in serum Ca when using a dialysate with a low Ca concentration, and hence increase the severity of SHPT with compensatory increases in the doses of concomitant drugs used to control Ca in SHPT patients.

We performed post hoc analyses of a 52-week multicentre study in Japanese patients with SHPT in order to investigate whether the dialysate Ca concentration influences the therapeutic efficacy of comprehensive treatment comprising etelcalcetide with concomitant drugs. A single-patient dialysate delivery system (SPDDS) is widely used in countries other than Japan and is considered the global standard for dialysis treatment. This makes it possible to change dialysate types and use different Ca concentrations for individual patients. By contrast, almost all facilities in Japan use a central dialysate delivery system and the type of dialysate is seldom changed in individual patients. Therefore, patients generally receive the same dialysate for the life of treatment. Accordingly, this allowed us to compare the therapeutic efficacy and dosing of etelcalcetide with concomitant drugs among three groups of patients according to the dialysate Ca concentration used. Finally, we assessed whether the dialysate Ca concentration had an impact on the safety of etelcalcetide in terms of the frequency of patients with low serum Ca concentrations.

METHODS
The design of this 52-week, multicentre, open-label study is described in more detail in previous reports. Here, we report post hoc analyses, which were performed to investigate whether the dialysate Ca concentration influences the therapeutic efficacy of etelcalcetide.

1.1 Ethics
The study was performed in accordance with the Declaration of Helsinki and International Council on Harmonization-Good Clinical Practice guidelines, and was approved by institutional review boards at all participating centres. The study was registered on the Japan Pharmaceutical Information Center database (JapicCTI-142665).
1.2 | Patients

As previously described,14 Japanese CKD patients with SHPT aged ≥20 years on three-times-weekly haemodialysis for ≥90 days if their serum iPTH was >240 pg/mL were eligible for this study. Although patients receiving acetate-free citrate dialysate (Carbostar; Ajinomoto Pharmaceuticals Co., Ltd., Tokyo, Japan) were enrolled in the study, these patients were excluded from the present analysis because of the Ca chelating effects of citric acid contained in this dialysate.

1.3 | Dosing of etelcalcetide and concomitant drugs

Patients treated with cinacalcet entered a washout period of ≥28 days prior to starting treatment with etelcalcetide. Patients were treated with etelcalcetide three-times-weekly for 52 weeks at an initial dose was 5 mg, which was adjusted within the range of 2.5-15 mg to achieve serum iPTH of 60-240 pg/mL. This PTH target range was set according to the Japanese Society for Dialysis Therapy guidelines for CKD-mineral and bone disease, which is lower than that suggested in the KDIGO guidelines (2-9 × the upper limit of normal).5 The etelcalcetide dose was increased if the patient met all of the dose escalation criteria and the investigator believed there was no problem with safety or tolerability (Table S1). Administration of etelcalcetide was discontinued in patients with serum cCa <7.5 mg/dL, serum cCa >11.5 mg/dL or serum P P >7.0 mg/dL, at two consecutive timepoints with an interval of ≥1 week between measurements (discontinuation criteria). Administration of etelcalcetide was interrupted in patients with serum cCa <7.5 mg/dL before dialysis (interruption criterion). Active vitamin D preparations, Ca preparations and Ca-containing or Ca-free P-binders were permitted, and their doses could be adjusted as appropriate (Table S1). All patients received dialysates with Ca concentrations of 2.5, 2.75 or 3.0 mEq/L for the entire study period. The type of dialysate could be switched during the study providing the Ca concentration was unchanged.

1.4 | Assays and endpoints

Endpoints assessed in this analysis included clinical efficacy markers (iPTH, corrected Ca [cCa] and P), bone biomarkers (tartrate-resistant acid phosphatase 5b [TRACP-5b] and bone alkaline phosphatase [BAP]) and the doses of therapeutic agents (etelcalcetide, vitamin D preparations and P-binders).

The clinical efficacy markers and bone biomarkers were analysed by standard laboratory tests. Serum iPTH was measured using an electrochemiluminescence enzyme immunoassay (Access Ostart; Beckman Coulter, Tokyo, Japan) (normal range, male 3.7-20.9 lg/L, female before menopause 2.9-14.5 lg/L, female after menopause 3.8-22.6 lg/L). Ca and P were measured using standard laboratory tests.

As an index of safety, we determined whether the dialysate Ca concentration had an impact on the proportion of patients with low cCa concentrations (<8.4 or <7.5 mg/mL) at any time during treatment.

1.5 | Statistical analyses

The patients were divided into three groups according to the dialysate Ca concentration (2.5, 2.75 or 3.0 mEq/L). All statistical analyses were performed using global tests for comparisons among the three dialysate Ca concentration groups. Baseline characteristics were compared among the three groups by analysis of variance (ANOVA) or Fisher's exact test. Mixed-model repeated measures (MMRM) analysis was performed to compare the changes in clinical efficacy markers (iPTH, cCa and P), bone biomarkers (TRACP-5b and BAP) and doses of etelcalcetide, vitamin D preparations and P-binders among the three groups. For each analysis, the following explanatory variables were included in the model: baseline value as a covariate, treatment group and time as fixed effects, and an interaction term between treatment group and time. The residual maximum likelihood estimation method was used with an unstructured covariance structure or the Toeplitz method if the model does not converge. The Kenward-Roger method was used to calculate the degrees of freedom. P values for the fixed effect of treatment group were determined by the MMRM analyses. In all analyses, a value of P < .05 was considered statistically significant. Data analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

2 | RESULTS

2.1 | Patients

Of 191 patients enrolled in the study, 133 were included in the present analyses. Overall, 34, 64 and 35 patients received dialysates with Ca concentrations of 2.5, 2.75 and 3.0 mEq/L, respectively, throughout the study period. The other 58 patients were excluded from this analysis because they received acetate-free citrate dialysate at least once. One patient dropped out without receiving etelcalcetide; this patient was in the 2.75 mEq/L group and all results are presented for 63 patients, except for the patient demographics, which includes all 64 patients. Baseline characteristics of the three groups are presented in Table 1. There were no significant differences in baseline characteristics, except for the maximum dose of cinacalcet used prior to enrollment and a slight albeit non-significant imbalance in proportions of males and females among the three groups. The baseline characteristics of patients who received acetate-free citrate dialysate are shown in Table S2; their characteristics were similar to those of the three analysed groups.
2.2 Efficacy markers

Figure 1 shows the changes in iPTH, cCa and P levels in each group over the 52-week study period. Although the serum iPTH levels tended to track lower in the 3.0 mEq/L group than in the other two groups (Figure 1A) due to lower baseline levels, there were no significant differences among the three groups during the study. The percentage of patients with serum iPTH levels within the target level (60-240 pg/mL) increased progressively during the study; at Week 52, the target was met by 82.1%, 82.8% and 93.5% of patients in the 2.5, 2.75 and 3.0 mEq/L groups, respectively (Figure 1A, D).

The cCa and P levels (Figure 1B, C) decreased in all three groups over time and were not significantly different among the three groups at any time-point. The mean cCa and P levels were consistently below the baseline levels throughout the 52-week treatment period, and were within their respective control targets of 8.4-10.0 mg/dL (for cCa) and 3.5-6.0 mg/dL (for P). The percentages of subjects with cCa and P levels within the target at Week 52 were 71.4%, 75.9% and 93.5% for cCa, and 78.6%, 67.2% and 67.7% for P, in the 2.5, 2.75 and 3.0 mEq/L groups, respectively (Figure 1E, F).

The frequency of hypocalcaemia, defined as either <8.4 or <7.4 mg/mL, was comparable in each group and was not increased in patients in the lowest dialysate Ca concentration group (Table 2).

2.3 Bone biomarkers

Figure 2 shows the levels of TRACP-5b as a biomarker of bone resorption and BAP as a biomarker of bone formation at each time-point. As indicated in Figure 2A, TRACP-5b levels decreased rapidly in each group. BAP levels showed a transient increase followed by a
Abbreviation: Ca, calcium; cCa, corrected calcium.

Note (Figure 3A-C) and the distribution of etelcalcetide doses (Figure 3D-F) throughout the study in consideration of target iPTH levels and the dose discontinuation and interruption criteria. There were no clear patterns in the distribution of etelcalcetide doses among the three groups (Figure 3A-C), although dosing varied among the three groups (Figure 3D-F), although dosing varied throughout the study in consideration of target iPTH levels and the dose discontinuation and interruption criteria.

2.4 | Changes in therapeutic regimens

2.4.1 | Etelcalcetide dosing

We also determined the changes in etelcalcetide doses over time (Figure 3A-C) and the distribution of etelcalcetide doses (Figure 3D-F) according to the dialysate Ca concentration. Although the etelcalcetide dose tended to be lower in the 3.0 mEq/L group than in the other two groups, there were no statistically significant differences in etelcalcetide doses among the three groups (Figure 3A-C). There were no clear patterns in the distribution of etelcalcetide doses among the three groups (Figure 3D-F), although dosing varied throughout the study in consideration of target iPTH levels and the dose discontinuation and interruption criteria.

2.4.2 | Doses of concomitant drugs

Figure 4 shows the changes in doses of vitamin D preparations (maxacalcitol and calcitriol [injectable only]) and Figure 5 shows the changes in doses of P binders (calcium carbonate, lanthanum carbonate and sevelamer hydrochloride). The maxacalcitol and calcitriol doses tended to increase from baseline over the first approximately 85 days and then declined thereafter in each of the groups. The dose of maxacalcitol tended to be higher in the 2.5 mEq/L group than in the other groups, although this was not statistically significant (Figure 4A-C). Likewise, there were transient increases in the calcitriol doses in each group. However, the number of patients treated with calcitriol was small and there were no clear differences in calcitriol doses among the three groups (Figure 4D-F).
As shown in Figure 5A-C, there were no significant differences in the doses of calcium carbonate, a Ca-containing P binder, among the three groups, except at baseline, when the dose was higher in the 2.5 mEq/L group (Figure 5A). For lanthanum carbonate, a non-Ca-containing P binder, no significant differences were found among the three groups, although the dose tended to be greater in...
the 2.5 mEq/L group than in the other groups at baseline and day 29 (Figure 5D-F).

Regarding non-Ca-containing P binders, we found no significant differences in sevelamer carbonate doses among the three groups, although its dose tended to be higher in the 2.5 mEq/L group than in the other groups at baseline (Figure 5G-I). Ferric citrate was used by a small number of patients and no clear differences in doses could be seen among the three groups (Figure 5J-L).

The doses of other vitamin D agents and P binders were not assessed owing to the small numbers of patients using these drugs.

3 | DISCUSSION

Calcimimetics are increasingly being used to regulate PTH levels in patients with SHPT. It is well established that the dialysate Ca concentration may influence PTH levels, such that low Ca concentrations may increase the risk of hypocalcaemia while high Ca concentrations may exacerbate vascular pathologies as a consequence of inappropriate PTH levels. Therefore, it is important to assess whether calcimimetics may exacerbate these effects of the dialysate Ca concentration on PTH levels and other clinically relevant endpoints in patients with SHPT. Reassuringly, the present analyses revealed no clinically meaningful differences in iPTH, cCa or P levels among the three groups of Japanese CKD patients who received dialysates containing different Ca concentrations (2.5, 2.75 or 3.0 mEq/L) over a period of 52 weeks. Serum iPTH levels were only slightly lower in patients who received dialysates with higher Ca concentrations (ie, 3.0 mEq/L) than in the lower Ca concentration group (2.5 and 2.75 mEq/L) and were accompanied by slightly lower etelcalcetide doses in the 3.0 mEq/L group. This was due to lower baseline iPTH levels in 3.0 mEq/L group. Nevertheless, these were not statistically significant, suggesting the dialysate Ca concentration has a negligible influence on the efficacy of etelcalcetide. It is also notable that the frequency of hypocalcaemia, defined as serum Ca <7.4 or <8.4 mg/mL, was comparable among the three dialysate Ca concentrations, suggesting that the risk of hypocalcaemia was not related to the dialysate Ca concentration in these patients treated with etelcalcetide. The doses of concomitant vitamin D and P-binders tended to be higher in the 2.5 mEq/L group than in the other groups. Considering that their doses were already high at baseline in this group and the patterns of changes in their doses after baseline were similar in each group, the trends towards higher doses of these drugs in the 2.5 mEq/L group are unlikely to have been due to etelcalcetide. Given that the mean serum cCa and P levels changed similarly over time and their levels were within the target ranges at Week 52 in all three groups, it may...
Boxplots showing the changes in doses of the phosphate binders precipitated calcium carbonate (A–C), lanthanum carbonate hydrate (D–F), sevelamer hydrochloride (G–I) and ferric citrate (J–L) according to the dialysate calcium concentration. A, D, G, J 2.5 mEq/L; B, E, H, K 2.75 mEq/L; C, F, I, L 3.0 mEq/L. Boxes represent the first and third quartiles, thick horizontal lines represent the median, and the thin vertical lines represent the minimum and maximum values. †Excludes acetate-free citrate dialysate.
have been necessary to use higher doses of these drugs in the 2.5 mEq/L group than in other groups in order to control cCa and P levels. In the event that iPTH, cCa or P levels move out of the target range, it is possible to adjust the doses of etelcalcetide and/or concomitant drugs, as necessary. Indeed, changes in doses were done and helped maintain serum iPTH, cCa and P levels within their appropriate ranges. Taken together, these results suggest that the dialysate Ca concentration has a negligible impact on the clinical efficacy of etelcalcetide with concomitant drugs, but slight adjustments of the doses of etelcalcetide and/or concomitant drugs might be required to maintain efficacy markers within appropriate ranges.

This is the first study to examine the impact of the dialysate Ca concentration on the efficacy of comprehensive therapy comprising etelcalcetide with concomitant drugs in patients with SHPT. In terms of other calcimetics, the evaluation of cinacalcet hydrochloride therapy to lower cardiovascular events (EVOLVE) trial revealed that the baseline dialysate Ca concentration and the serum-dialysate Ca concentration on the efficacy of comprehensive therapy comprising etelcalcetide with concomitant drugs among the three dialysate Ca concentration groups. Furthermore, the patients showed improvements in biomarkers of bone resorption and formation, with similar trends in the three dialysate Ca concentration groups, which may lead to favourable effects on quality of life and patient morbidity through improved bone metabolism.

ACKNOWLEDGEMENTS

The investigators were as follows: K. Kukita, Sapporo Hokuyu Hospital; K. Sunaoshi, Teine Urological Clinic; T. Sato, Japan Community Health Care Organization, Sendai Hospital; Y. Fukaya, Southern Tohoku General Hospital; M. Kobayashi, Tokyo Medical University Ibaraki Medical Center; K. Takemura, Takemura Medical Nephro Clinic; K. Ito, Heisei Hidaka Clinic; J. Miroyka, Ora Hospital; J. Oshima, Kubojima Clinic; F. Takeda, Bousei Anesaki Clinic; T. Fujii, Seirei Sakura Citizen Hospital; K. Takao, Kisorazau Clinic; N. Murotani, Japan Community Health Care Organization, Chiba Hospital; A. Suda, Suda Clinic; Y. Komatsu, St. Luke’s International Hospital; H. Emoto, Tokai Hospital; T. Suzuki, Asagaya Suzuki Clinic; T. Ozawa, Kodaira-kitaguchi Clinic; S. Aruga, Monnaka-Jin Clinic; Y. Yamaguchi, Adachi Iriya Toneri Clinic; M. Nishihara, Toushin Clinic; K. Shibata, Yokohama Minami Clinic; T. Kuji, Yokodai Central Clinic; T. Mitsuhashi, Mitsuhashi Clinic; S. Kageyama, Kageyama Clinic; M. Tsuboi, Anjo Kyoritsu Clinic; H. Kasuga, Kaikoukai Central Clinic; T. Onogi, Hekikai Kyoritsu Clinic; T. Sato, Meiko Kyoritsu Clinic; Y. Tsujimoto, Inoue Hospital; Y. Akagaki, Akagaki Clinic; N. Kodama, Kodama Hospital; Y. Matsuoka, Shinsumba Hospital; K. Arimoto, Shigei Hospital; M. Omoto, Saiseikai Imabari Hospital; K. Yusa and K. Ota, Kochi Takasu Hospital; T. Hazama, Kurume University Hospital; H. Hirai, St. Mary’s Hospital; K. Mitsuaki, Japanese Red Cross Fukuoka Hospital; T. Otsubo, Kousiekai Hospital, Japan.

This study was funded and conducted by Ono Pharmaceutical Co., Ltd. The authors thank the Clinical Development Department, Ono Pharmaceutical Co., Ltd., for their assistance in preparing and writing this report, and Nicholas D. Smith (EMC K.K.) for medical writing support, which was funded by Ono Pharmaceutical Co. Ltd.

CONFLICT OF INTEREST

T.S. has received consulting and lecture fees from Ono Pharmaceutical Co., Ltd.; research funding and consulting fees from Kyowa Hakko Kirin Co., Ltd.; consulting fees from Taisho Pharmaceutical Co., Ltd., and Fuji Yakuhin Co., Ltd.; and research funding from Astellas Pharma Inc.
M.F. has received consulting and lecture fees from Ono Pharmaceutical Co., Ltd., and research funding and consulting fees from Kyowa Hakko Kirin Co., Ltd.

K.Y. has received consulting and lecture fees from Ono Pharmaceutical Co., Ltd., Torii Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Kissei Pharmaceutical Co., Ltd.

T.A. has received consulting and lecture fees from Ono Pharmaceutical Co., Ltd., research funding from Torii Pharmaceutical Co., Ltd., and consulting fees from Bristol-Myers Squibb Co.

A.F. and A.S. are employees of Ono Pharmaceutical Co., Ltd.

A.F. organized the study. All authors contributed to design of the study and interpretation of data. T.S., M.F., K.Y., T.A. and T.A. played advisory roles in this study.

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

AUTHOR CONTRIBUTIONS
T.S., M.F., K.Y., T.A. and T.A. played advisory roles in this study. A.F. organized the study. All authors contributed to conception and design of the study and interpretation of data. A.S. contributed to analysis of data and interpretation of data. All authors contributed to manuscript writing/critical revision, and approved the final manuscript.

ORCID
Takashi Shigematsu https://orcid.org/0000-0002-6330-3784

REFERENCES
1. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol. 2011;6:913-921.

2. Silver J, Kilav R, Naveh-Manyy T. Mechanisms of secondary hyperparathyroidism. Am J Physiol Renal Physiol. 2002;283:F367-F376.

3. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15:2208-2218.

4. Kleeman CR, Bernstein D. Chronic renal failure. Its effect on calcium, phosphorus and osseous metabolism unified approach. Calif Med. 1961;94:335-338.

5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7:1-59.

6. Fukagawa M, Yokoyama K, Koiva F, et al. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. Ther Apher Dial. 2013;17:247-288.

7. Block GA, Bushinsky DA, Cheng S, et al. Effect of etelcalcetide vs cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: a randomized clinical trial. JAMA. 2017;317:156-164.

8. Block GA, Bushinsky DA, Cunningham J, et al. Effect of etelcalcetide vs placebo on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: two randomized clinical trials. JAMA. 2017;317:146-155.

9. Cozzolino M, Galassi A, Conte F, Mangano M, Di Lullo L, Bellasi A. Treatment of secondary hyperparathyroidism: the clinical utility of etelcalcetide. Ther Clin Risk Manag. 2017;13:679-689.

10. Hamano N, Komaba H, Fukagawa M. Etelcalcetide for the treatment of secondary hyperparathyroidism. Expert Opin Pharmacother. 2017;18:529-534.

11. Yokoyama K, Kagami S, Ohkido I, et al. The negative Ca(2+) balance is involved in the stimulation of PTH secretion. Nephron. 2002;92:86-90.

12. van der Sande FM, Ter Meulen KJA, Kotanko P, Kooman JP. Dialysate calcium levels: do they matter? Blood Purif. 2019;47:230-235.

13. Hamano T. Mineral and bone disorders in conventional hemodialysis: challenges and solutions. Semin Dial. 2018;31:592-598.

14. Shigematsu T, Fukagawa M, Yokoyama K, et al. Long-term effects of etelcalcetide as intravenous calcimimetic therapy in hemodialysis patients with secondary hyperparathyroidism. Clin Exp Nephrol. 2018;22:426-436.

15. Shigematsu T, Fukagawa M, Yokoyama K, et al. Effects of the intravenous calcimimetic etelcalcetide on bone turnover and serum fibroblast growth factor 23: post hoc analysis of an open-label study. Clin Ther. 2018;40:2099-2111.

16. Pun PH, Abdalla S, Block GA, et al. Cinacalcet, dialysate calcium concentration, and cardiovascular events in the EVOLVE trial. Hemodial Int. 2016;20:421-431.

17. Halleen JM, Ylipahkala H, Alatalo SL, et al. Serum tartrate-resistant acid phosphatase 5b, but not 5a, correlates with other markers of bone turnover and bone mineral density. Calcif Tissue Int. 2002;71:20-25.

18. Ueda M, Inaba M, Okuno S, et al. Serum BAP as the clinically useful marker for predicting BMD reduction in diabetic hemodialysis patients with low PTH. Life Sci. 2005;77:1130-1139.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.