



Efficacy and Safety of Evocalcet Evaluated by Dialysate Calcium Concentration in Patients with Secondary Hyperparathyroidism Undergoing Hemodialysis


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Purpose: Evocalcet is a novel oral calcimimetic drug that has demonstrated similar efficacy to cinacalcet in regulating serum parathyroid hormone (PTH), calcium, and phosphate levels, with fewer upper gastrointestinal tract-related adverse drug reactions (ADRs) in patients with secondary hyperparathyroidism undergoing hemodialysis in Japan. We investigated the efficacy and safety of once-daily oral evocalcet under different dialysate calcium concentrations.

Patients and Methods: A post hoc analysis by dialysate calcium concentration (2.5, 2.75, and 3.0 mEq/L) was performed using data from a previous Phase 3 study that included cinacalcet as an active control. Efficacy endpoints were the proportion of patients who achieved the target intact PTH levels of ≥ 60 and ≤ 240 pg/mL between Week 28 and Week 30; time-course changes in serum intact PTH; calcium and phosphorus levels, bone turnover markers, and fibroblast growth factor 23 (FGF23) over the 30-week study period. Safety endpoints were overall ADRs and hypocalcemia- and upper gastrointestinal tract-related ADRs.

Results: A total of 634 patients were included in the analysis. Levels of intact PTH, calcium, phosphate, bone turnover markers, and FGF23 showed improvement in all sub-groups, irrespective of dialysate calcium concentration. The incidence of upper gastrointestinal tract-related ADRs was significantly lower in the evocalcet group than the cinacalcet group with dialysate calcium concentrations of 2.75 and 3.0 mEq/L ($p < 0.05$ for both concentrations).

Conclusion: Evocalcet was effective and safe in regulating the levels of serum intact PTH, calcium, and phosphate in patients with secondary hyperparathyroidism undergoing hemodialysis, irrespective of dialysate calcium concentration.

Keywords: hypocalcemia, intact parathyroid hormone, oral calcimimetic, post hoc analysis, upper gastrointestinal tract

Introduction

Secondary hyperparathyroidism frequently develops in patients with severe chronic kidney disease (CKD) undergoing hemodialysis, and is characterized by the increased synthesis and secretion of parathyroid hormone (PTH)¹⁻⁴ that can lead to mineral and bone disorders (MBDs), and the development of bone lesions and life-long effects through the calcification of soft tissues such as blood vessels.⁵ It is therefore clear that maintaining a balance in the levels of phosphate, calcium, and PTH is critical in patients with secondary hyperparathyroidism.⁶ The Japanese Society for Dialysis Therapy recommends target ranges for serum PTH, calcium,

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and phosphate levels in its clinical practice guideline for the management of CKD-MBDs, including secondary hyperparathyroidism.⁷

Calcium-sensing receptors detect extracellular calcium concentrations. Upon binding to these receptors, calcium-sensing receptor positive allosteric modulators suppress PTH secretion and are therefore widely used as therapeutic agents for secondary hyperparathyroidism. Cinacalcet, the first calcium-sensing receptor positive allosteric modulator, demonstrated a strong inhibitory effect on PTH secretion without elevating the serum calcium level and increased the proportion of patients achieving the target PTH, calcium, and phosphate concentrations.⁸

Similar to cinacalcet, the novel positive allosteric modulator evocalcet decreases serum PTH and calcium levels.^{9–14} Furthermore, a previous phase 3 study showed that the incidence of adverse drug reactions (ADRs) of upper gastrointestinal disorders was less frequent with evocalcet compared with cinacalcet.¹⁵ Therefore, evocalcet may be beneficial for patients receiving cinacalcet when the occurrence of gastrointestinal ADRs causes lower adherence and insufficient dosages.

Another factor to be considered in the regulation of serum calcium concentration is the dialysate calcium concentration used for maintenance dialysis. Dialysate calcium concentration at 3.5 mEq/L was associated with increased all-cause mortality and cardiovascular-related hospitalization in patients undergoing hemodialysis.^{16,17} Therefore, the Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group recommends a calcium concentration in dialysate of between 2.5 and 3.0 mEq/L.¹⁸ Although one dialysate calcium concentration of 2.75 mEq/L became available in 1993 in Japan,¹⁹ any dialysate calcium concentrations below 3.0 mEq/L were unlikely to have a clinically significant effect on patient prognosis.²⁰ Unlike in other countries, where single-patient dialysis fluid delivery systems have been used based on each patient's condition, a central dialysis fluid delivery system has been adopted for the past 45 years in Japan with the dialysate calcium concentration determined based on the policy of the medical facility.²¹ Because evocalcet and cinacalcet both lower the serum calcium concentration, their efficacy and safety may be affected by the concentration of dialysate calcium.

This study therefore investigated the efficacy and safety of treatment with once-daily oral evocalcet for 30 weeks in patients with secondary hyperparathyroidism receiving hemodialysis by stratifying the previous phase 3 results by dialysate calcium concentration.

Materials and Methods

Study Design

This study (ClinicalTrials.gov, NCT02549391 and JAPIC, JapicCTI-153013) was a post hoc analysis of the previous phase 3, randomized, double-blind, intra-subject dose-adjustment, parallel-group study of evocalcet with cinacalcet as an active control.¹⁵ In brief, the previous study consisted of a 28-week dose-adjustment period followed by a 2-week evaluation period. All patients received daily evocalcet (starting dose of 1 mg for patients with intact PTH <500 pg/mL or 2 mg for ≥ 500 pg/mL, up to 8 mg from Week 3 to Week 28, and a fixed dose until the end of the study period) or cinacalcet (starting dose of 25 mg, up to 100 mg from Week 3 to Week 28, and a fixed dose until the end of the study period) for 30 weeks to achieve an intact PTH level ≥ 60 and ≤ 240 pg/mL. Changes in prescribed dialysis conditions, including dialysate calcium concentration, dialyzer, dialysis time, and number of dialysis sessions per week, as well as initiation of or changes in preparation, dose, and dosing regimen of vitamin D receptor activator (VDRA) medications or derivatives were prohibited from 2 weeks prior to screening to the end of the study. Any changes in preparation, dose, and dosing regimen of phosphate binder and calcium preparation were prohibited from 2 weeks prior to screening until Week 0.

The dose was increased on the day of dialysis after the longest interval between dialysis sessions if all of the following dose increase criteria were met: current dose had been maintained for ≥ 3 weeks and intact PTH level > 240 pg/mL at the last scheduled visit prior to a dose change. However, even where the intact PTH level was ≤ 240 pg/mL, the investigator determined the dose increase to ensure an intact PTH level of approximately 150 pg/mL; serum corrected calcium level at the last scheduled visit before the dose change was ≥ 8.4 mg/dL; and the investigator determined that a dose increase would not interfere with the safety of the patient. The dose was reduced if intact PTH level decreased to < 60 pg/mL or the investigator determined that the dose should be reduced because of an adverse event. The dose of evocalcet was increased or reduced in 1-mg increments, while cinacalcet was increased in 25-mg and decreased in 25-mg or 12.5-mg increments.

Patient Population

Patients with secondary hyperparathyroidism who were receiving hemodialysis 3 times a week, were ≥ 20 years of age, and had a mean intact PTH > 240 pg/mL and corrected serum calcium ≥ 9.0 mg/dL were included in

the study. Major exclusion criteria included treatment with cinacalcet ≤ 2 weeks before screening; change in dose or dosing regimen of VDRA or its derivatives, phosphate binder or calcium preparation, or initiation of treatment with such drugs ≤ 2 weeks before screening; change in dialysate calcium concentration, dialyzer, dialysis time, or number of dialysis sessions per week ≤ 2 weeks before screening; treatment with bisphosphonates, denosumab, teriparatide, and parathyroidectomy and/or parathyroid intervention ≤ 24 weeks before screening.

Stratified Analysis

The previous phase 3 data were stratified by dialysate calcium concentration (2.5: <2.625 mEq/L, 2.75: ≥ 2.625 and <2.875 mEq/L, and 3.0: ≥ 2.875 mEq/L) in the evocalcet and cinacalcet treatment arms. Efficacy endpoints were mean intact PTH level over the study period and mean percent change in intact PTH level from baseline throughout the study period; number and percentage of patients with mean intact PTH level ≥ 60 and ≤ 240 pg/mL in Week 28 to Week 30 of the evaluation period; and change in the level of corrected serum calcium; serum phosphate; bone turnover markers as bone-specific alkaline phosphatase (BAP), tartrate-resistant acid phosphatase-5b (TRACP-5b), and procollagen type I N-terminal pro-peptide (PINP); intact fibroblast growth factor 23 (FGF23); mean daily dose for each study drug; and the conversion ratio between evocalcet and cinacalcet from baseline to the end of the study period. Safety was evaluated by ADRs, including hypocalcemia- and upper gastrointestinal tract-related ADRs.

Statistical Analysis

Efficacy was evaluated in the per protocol set, which included enrolled patients who received at least one dose of any study treatment and had at least one intact PTH measurement after the study began but excluded those who did not meet any of the inclusion criteria or fell under any exclusion criterion; had drug compliance $<70\%$ out of 28 weeks of dispensed drug; received prohibited concomitant medications or therapy such as cinacalcet, bisphosphonates, denosumab, teriparatide, parathyroidectomy, and/or parathyroid intervention or peritoneal dialysis; missed intact PTH measurement at ≥ 2 of 3 time points between Week 28 and Week 30; or had a protocol deviation that might have affected the efficacy evaluation. Safety was evaluated in the safety analysis set, which included patients who enrolled in the study and received at least one dose of any study treatment.

Unless otherwise specified, categorical data were summarized using frequencies and percentages, and continuous data were summarized using descriptive statistics consisting of the number of patients, mean, standard deviation, median, and interquartile range. For the categorical, the Chi-square test was used, and for continuous data, the Kruskal–Wallis test and analysis of variance were used based on the data distribution.

The proportion of patients who achieved the recommended mean intact PTH level of ≥ 60 and ≤ 240 pg/mL⁷ between Week 28 and Week 30 were calculated for each sub-group, and difference in achievement ratio and 95% confidence interval (CI) were analyzed by analysis of variance.

All ADRs that occurred after the start of study treatment were summarized according to the MedDRA version 19.0 and the incidence rate was calculated by sub-groups and treatment arms. For hypocalcemia-related ADRs, corrected calcium decreased, blood calcium decreased, and hypocalcemia by preferred term, as well as a combination of all three were summarized and incidence rates were obtained by sub-group and treatment arm. The same analysis was used for upper gastrointestinal tract-related ADRs that included nausea, vomiting, abdominal discomfort, abdominal distension, and decreased appetite.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and two-tailed p -values of <0.05 were considered statistically significant.

Results

The previous phase 3 study was conducted at 89 sites in Japan from October 2015 to November 2016. The present analysis included 519 patients in the per protocol set and 634 patients in the safety analysis set. A similar number of patients were included in each sub-group between the evocalcet and cinacalcet arms, there were no significant differences in baseline characteristics between the two arms, except in cinacalcet use prior to screening and VDRA use at baseline among the sub-groups in the cinacalcet arm (Table 1).

Efficacy

Mean intact PTH levels gradually decreased over the 28-week dose-adjustment period and 2-week evaluation period in all sub-groups of both arms (Figure 1A). Similarly, the mean percent changes in the intact PTH

Table I Patient Baseline Characteristics by Dialysate Calcium Level

Parameter	Evocalcet (n=253)			p-value*	Cinacalcet (n=266)			p-value*
	Dialysate Calcium Level				Dialysate Calcium Level			
	2.5 mEq/L	2.75 mEq/L	3.0 mEq/L		2.5 mEq/L	2.75 mEq/L	3.0 mEq/L	
	n=71	n=86	n=96		n=70	n=92	n=104	
Female, n (%)	18 (25.4)	24 (27.9)	34 (35.4)	0.3247	19 (27.1)	16 (17.4)	36 (34.6)	0.0245
Age, mean (SD), years	62.2 (11.1)	61.1 (11.1)	59.9 (11.8)	0.4264	61.2 (9.3)	60.2 (11.2)	60.8 (12.1)	0.8386
Body mass index, mean (SD), kg/m ²	24.43 (3.88)	24.75 (4.46)	24.53 (5.12)	0.8969	23.45 (3.34)	24.57 (4.80)	23.63 (4.20)	0.1695
Primary disease, n (%)								
Diabetic nephropathy	19 (26.8)	23 (26.7)	24 (25.0)	0.8283	14 (20.0)	22 (23.9)	27 (26.0)	0.6337
Chronic glomerulonephritis	24 (33.8)	37 (43.0)	43 (44.8)		28 (40.0)	34 (37.0)	47 (45.2)	
Nephrosclerosis	11 (15.5)	9 (10.5)	11 (11.5)		9 (12.9)	12 (13.0)	7 (6.7)	
Other	17 (23.9)	17 (19.8)	18 (18.8)		19 (27.1)	24 (26.1)	23 (22.1)	
Duration of dialysis, mean (SD), months	126.3 (81.7)	126.2 (85.0)	126.9 (91.2)	0.9980	160.1 (91.7)	135.9 (121.6)	151.8 (103.3)	0.3382
Dry weight, mean (SD), kg	61.83 (12.17)	62.72 (13.81)	62.07 (15.23)	0.9155	60.08 (11.33)	63.66 (15.61)	59.17 (14.36)	0.0720
Dialysis efficiency, mean (SD), spKt/V	1.507 (0.290)	1.495 (0.279)	1.488 (0.293)	0.9121	1.592 (0.293)	1.492 (0.305)	1.544 (0.332)	0.1288
Cinacalcet use (prior to screening), n (%)	47 (66.2)	54 (62.8)	54 (56.3)	0.4006	54 (77.1)	54 (58.7)	71 (68.3)	0.0445
VDRA use at baseline, n (%)								
Oral only	62 (87.3)	74 (86.0)	81 (84.4)	0.8611	68 (97.1)	84 (91.3)	85 (81.7)	0.0042
Parenteral	18 (25.4)	29 (33.7)	34 (35.4)	0.2616	16 (22.9)	38 (41.3)	37 (35.6)	0.0113
Parenteral	44 (62.0)	45 (52.3)	47 (49.0)		52 (74.3)	46 (50.0)	48 (46.2)	
Laboratory data (baseline), mean (SD)								
Intact PTH, pg/mL	408.8 (143.8)	411.0 (197.3)	431.8 (180.7)	0.4929	395.5 (137.4)	438.5 (232.9)	437.5 (191.8)	0.6622
Corrected calcium, mg/dL	9.5 (0.6)	9.5 (0.5)	9.5 (0.6)	0.8901	9.6 (0.5)	9.6 (0.6)	9.6 (0.7)	0.7531
Phosphate, mg/dL	5.82 (1.41)	5.54 (1.24)	5.89 (1.28)	0.1647	5.57 (1.05)	5.50 (1.22)	5.56 (1.09)	0.8950
BAP, µg/L	18.50 (9.42)	17.87 (12.55)	16.64 (7.22)	0.1546	17.07 (5.89)	16.79 (10.16)	18.11 (11.63)	0.3495
TRACP-5b, mU/dL	812.35 (369.07)	759.45 (374.98)	782.85 (430.76)	0.3807	917.90 (427.99)	819.57 (348.06)	854.97 (490.99)	0.3374
FGF23, pg/mL	19,386.18 (21,356.01)	20,761.41 (21,101.79)	23,159.40 (22,139.88)	0.3123	19,488.39 (22,153.09)	19,767.96 (20,321.43)	19,180.45 (19,687.39)	0.7452

Notes: *Chi-square test (categorical), Kruskal–Wallis test, or analysis of variance (continuous).

Abbreviations: BAP, bone alkaline phosphatase; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; SD, standard deviation; TRACP-5b, tartrate-resistant acid phosphatase 5b; VDRA, vitamin D receptor activator.

levels from the baseline showed approximately a 50% reduction by the evaluation period ([Figure 1B](#)).

During the evaluation period, no significant difference was found among the sub-groups of both treatment arms in the number and percentage of patients who achieved the mean intact PTH level of ≥ 60 pg/mL and ≤ 240 pg/mL (71.8% to 79.3%), irrespective of dialysate calcium concentration ([Supplementary Table S1](#)).

The daily doses of evocalcet and cinacalcet started to increase from Week 3. Although the daily evocalcet dose continued to increase until Week 20, the daily cinacalcet dose stabilized by Week 12. The ratio subsequently

decreased, approaching an equal conversion dose of 12.5 by Week 20 ([Supplementary Figure S1](#)).

The mean level of corrected serum calcium decreased to a similar extent in the 3 sub-groups of each arm ([Figure 2A](#)). In the cinacalcet arm, the level increased slightly up to Week 30. The mean level of serum phosphorus decreased slightly over the 30 weeks in all sub-groups of both arms ([Figure 2B](#)).

The levels of bone metabolic markers showed similar trends in both arms irrespective of dialysate calcium concentration. The mean BAP level increased slightly after the start of the treatment, subsequently decreased, and returned to the

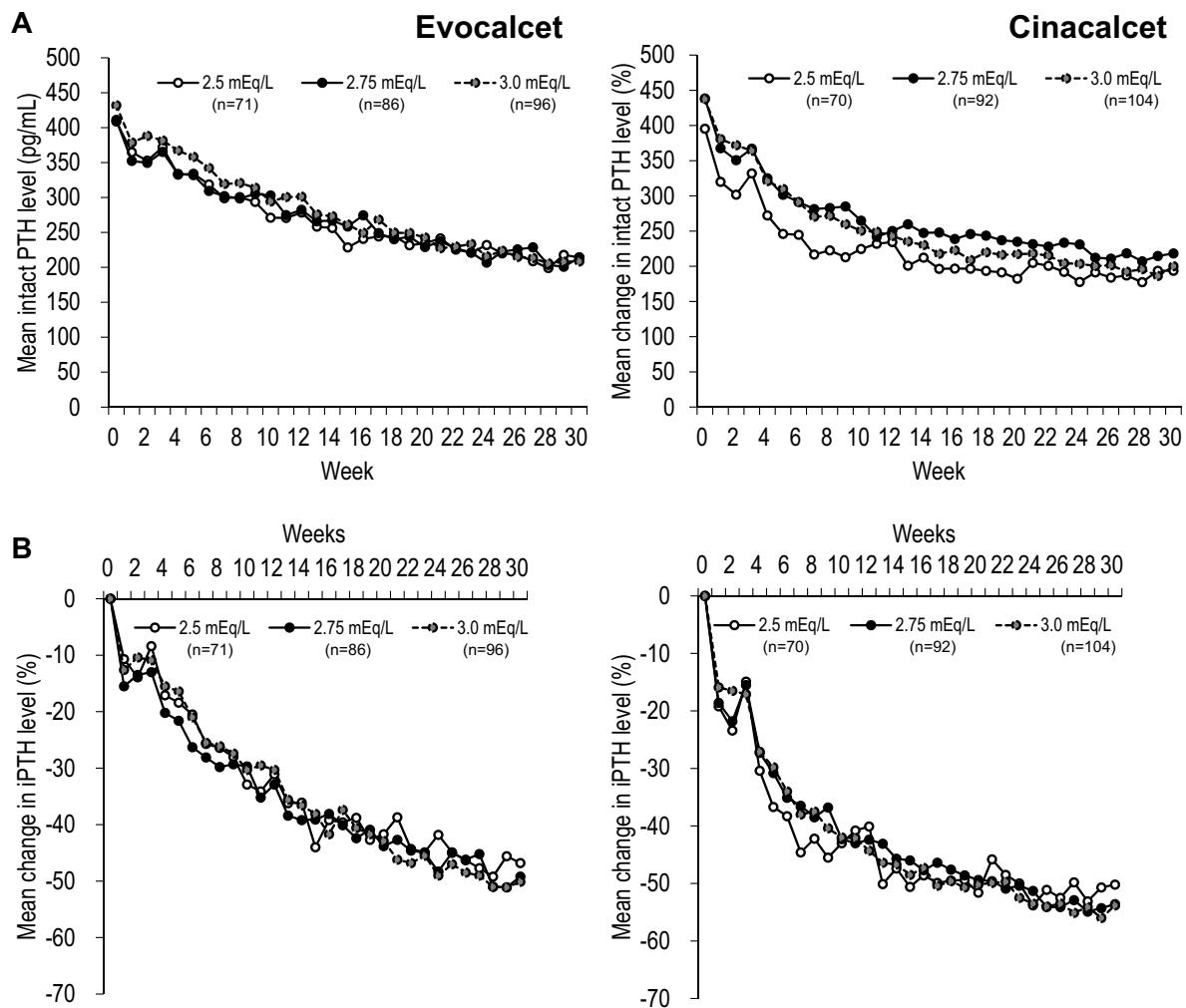


Figure 1 Trends in mean intact PTH level (A) and mean percent change in intact PTH level (B) by dialysate calcium concentration in patients treated with evocalcet and cinacalcet. **Abbreviation:** PTH, parathyroid hormone.

baseline level by Week 30 in all sub-groups of both arms ([Supplementary Figure S2A](#) and [Supplementary Table S2](#)). The mean TRACP-5b and PINP levels in all sub-groups of both arms were similarly decreased throughout the study period after the initiation of treatment ([Supplementary Figure S2B](#) and [Supplementary Table S2](#)).

The median level of intact FGF23 decreased over the study period with some variability among the sub-groups of both treatment arms although the differences were not significant ([Supplementary Figure S2C](#) and [Supplementary Table S2](#)).

Safety

The incidence of ADRs in the sub-groups of the evocalcet arm was slightly lower than that in the cinacalcet arm ([Supplementary Table S3](#)), but was similar among the sub-groups in each arm. Hypocalcemia-related

ADRs such as corrected calcium decreased and blood calcium decreased were marginally less frequent in the evocalcet arm than in the cinacalcet arm, but no clear difference was observed among the sub-groups within each arm ([Figure 3A](#)). The upper gastrointestinal tract-related ADRs occurred at similar frequencies among the sub-groups in each arm, irrespective of dialysate calcium concentration. However, a significantly lower incidence rate was observed in the evocalcet arm compared with the cinacalcet arm under dialysate calcium concentrations of 2.75 mEq/L ($p=0.0053$) and 3.0 mEq/L ($p=0.0429$) ([Figure 3B](#)).

Discussion

Dialysate calcium concentration is a contributing factor to the levels of serum PTH, calcium, and phosphate in

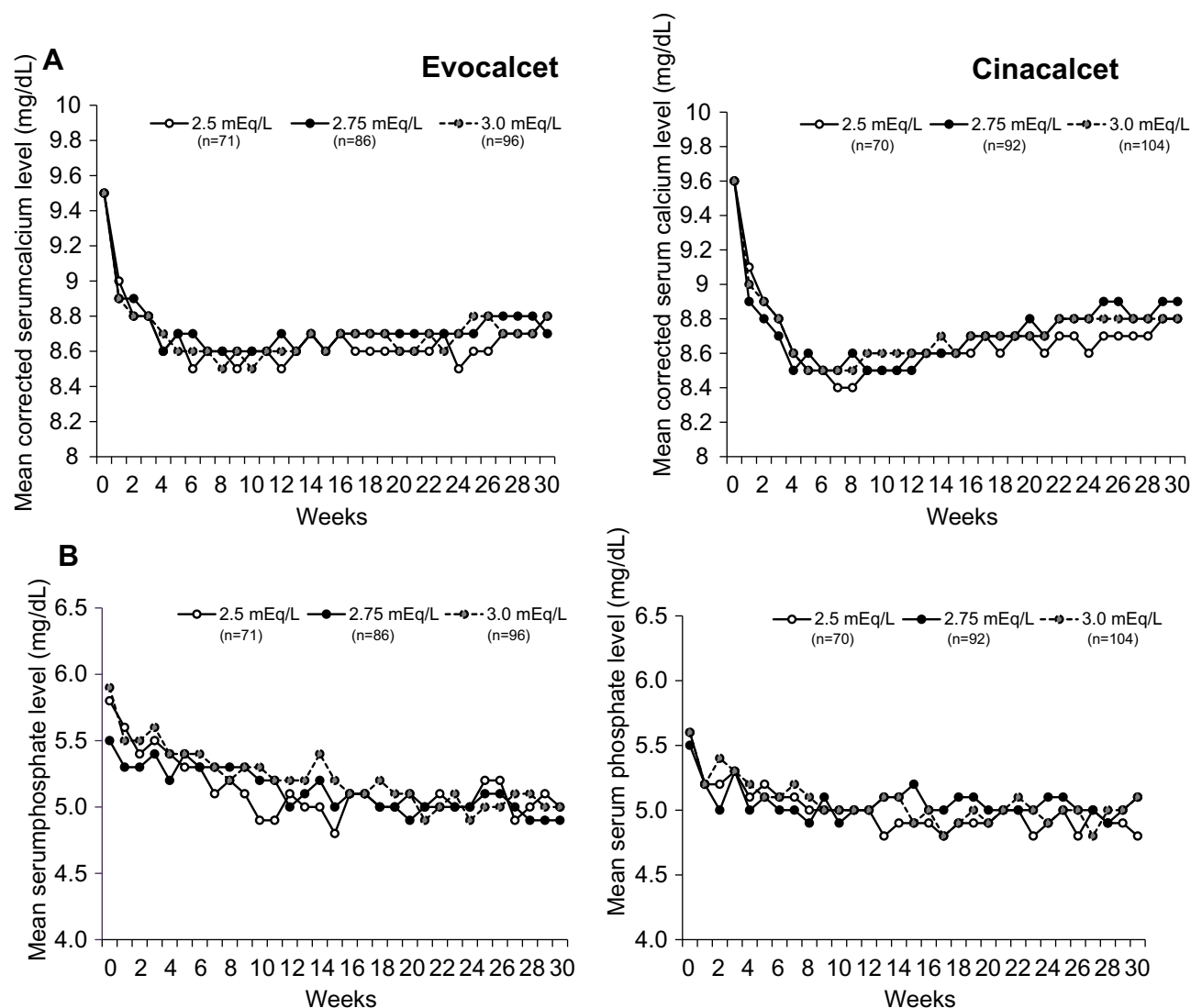


Figure 2 Trends in mean serum corrected calcium (A) and phosphate (B) level by dialysate calcium concentration in patients treated with evocalcet and cinacalcet.

patients undergoing hemodialysis.^{22,23} Despite concerns that dialysate calcium concentration can affect the efficacy of calcimimetics, the present results showed that evocalcet and cinacalcet are effective and safe, irrespective of dialysate calcium concentration.

The efficacy and safety of treatment with once-daily oral evocalcet for 30 weeks¹⁵ and 52 weeks²⁴ were investigated in the previous phase 3 studies in patients with secondary hyperparathyroidism receiving hemodialysis. The results of those studies demonstrated the noninferiority of evocalcet to cinacalcet in suppressing intact PTH levels, with a lower incidence of gastrointestinal tract-related ADRs. The results of the present post hoc analysis are consistent with those of the previous results, indicating that similar efficacy and

safety can be expected for evocalcet with dialysate calcium concentrations ranging from 2.5 to 3.0 mEq/L for up to 30 weeks.

A potential negative impact of dialysate calcium concentration on disease control has been addressed in a previous study, in which a decrease in dialysate calcium concentration from 3.0 mEq/L to 2.5 mEq/L had a negative impact on MBD parameters and increased PTH concentration.²⁵ In contrast, our present results showed that evocalcet and cinacalcet were effective in achieving the target intact PTH levels in 70% of patients for all dialysate calcium concentrations, suggesting that although serum calcium concentration can affect the PTH level, dialysate calcium concentrations in the range of 2.5

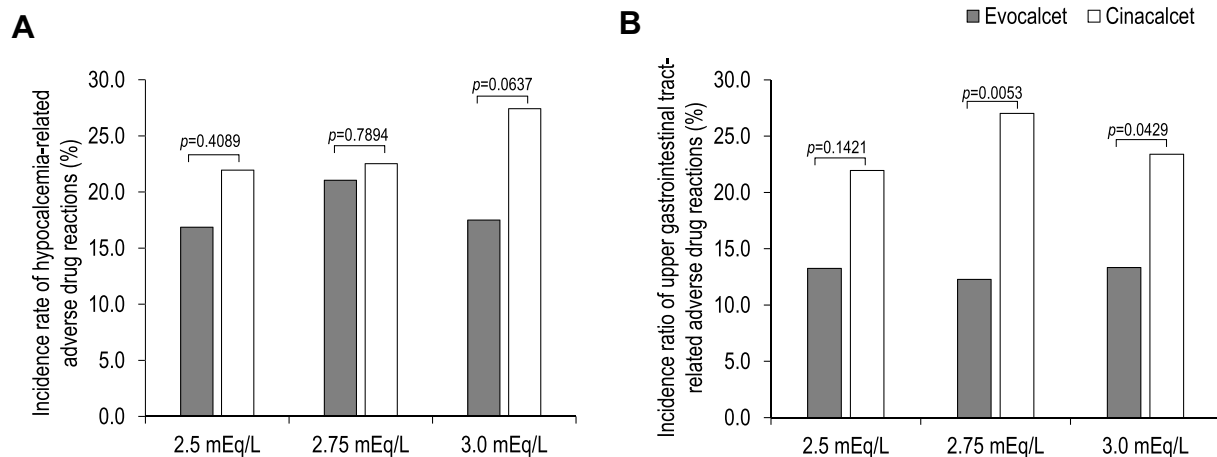


Figure 3 Incidence of hypocalcemia- (A) and upper gastrointestinal tract-related (B) adverse drug reactions by dialysate calcium concentration in patients treated with evocalcet and cinacalcet. Chi-square test.

to 3.0 mEq/L are unlikely to affect the efficacy of evocalcet or cinacalcet.

In this study, the level of BAP increased transiently but returned to the baseline level by Week 30, while the level of TRACP-5b gradually decreased over the 30-week study period. These findings are consistent with those observed following treatment with other calcimimetics.^{26,27} Although further studies are needed, evocalcet and cinacalcet appear to improve bone metabolism with dialysate calcium concentrations of 2.5 to 3.0 mEq/L.

The present results showed that the FGF23 level decreased to approximately 50% in all sub-groups of each arm, which is consistent with the EVOLVE study of cinacalcet.²⁸ However, the FGF23 levels were somewhat variable, which is consistent with previous studies,^{24,26,27} indicating that other factors, likely uncontrolled for in the present analysis and in previous studies, may be involved in the regulation of serum intact FGF23 level. Given the accumulating evidence to suggest a significant association between elevated FGF23 and cardiovascular disease,^{28–30} the decreasing trend in FGF23 level observed after treatment with evocalcet and cinacalcet may be a beneficial effect.

Given the known association between secondary hyperparathyroidism in patients receiving hemodialysis and MBDs, all of which contribute to cardiovascular disease and mortality, calcimimetics, especially evocalcet, which exerts its efficacy at lower doses than cinacalcet with a lower incidence of developing upper digestive tract-related ADRs, may confer a clinical benefit as well as optimal control of mineral and bone metabolism.

A limitation of this study is that the efficacy and safety of evocalcet and cinacalcet by dialysate calcium concentration were assessed only for 30 weeks. Given that patients with severe CKD undergo hemodialysis for longer than 30 weeks, and that their prognosis with respect to cardiovascular disease and MBDs is dependent on the calcium balance,⁶ further studies are required to understand how different dialysate calcium concentrations affect the outcome of long-term treatment with evocalcet and cinacalcet. Another limitation of this study is the inclusion of a specific patient population in Japan. Because evocalcet was developed and first approved in Japan, the present analysis may represent the first validation of the efficacy and safety of evocalcet irrespective of dialysate calcium concentration. However, it should be noted that the PTH level in Japan is controlled at a lower range than that recommended by the KDIGO guidelines¹⁸ and, therefore, the PTH levels in patients in Japan are controlled lower than those in other regions.³¹

A further limitation is that patient characteristics were not controlled among the sub-groups. In addition, because of the small sample size in each sub-group of both arms, the study might have insufficient power to compare efficacy or safety among the sub-groups. However, since the present results were consistent with those of the previous phase 3 study, evocalcet and cinacalcet appear to be effective and safe when used alongside all dialysate calcium concentrations evaluated in this study.

Finally, patients in this study were not permitted to change the dialysate calcium concentration and dose or

dosing regimen of any VDRA or its derivative during the evaluation period. However, changes in the administration of calcium-based/non-calcium-based phosphate binders were allowed; therefore, any effects related to these medications cannot be ruled out.

Conclusion

In summary, evocalcet and cinacalcet were effective in controlling the levels of serum intact PTH, corrected calcium and phosphate, irrespective of dialysate calcium concentration. Overall, no important safety concerns were raised, and the incidence of upper gastrointestinal tract-related ADRs was lower in the evocalcet arm compared with the cinacalcet arm. These findings demonstrate that evocalcet and cinacalcet are effective and safe when used alongside dialysate calcium concentrations of 2.5 to 3.0 mEq/L in patients with secondary hyperparathyroidism undergoing hemodialysis.

Abbreviations

ADR, adverse drug reaction; BAP, bone-specific alkaline phosphatase; CI, confidence interval; CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; KDIGO, Kidney Disease: Improving Global Outcomes; MBD, mineral bone disorder; PINP, procollagen type I N-terminal pro-peptide; PTH, parathyroid hormone; TRACP-5b, tartrate-resistant acid phosphatase-5b; VDRA, vitamin D receptor activator.

Data Sharing Statement

Data sharing is not available as all the relevant data are included in the manuscript and its [Supplementary materials](#).

Ethics and Consent Statements

The study was approved by the ethics committee at each study site, and was carried out in accordance with the principles of the Declaration of Helsinki and in compliance with the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act, Good Clinical Practice (Ministry of Health and Welfare Ordinance No. 28 dated March 27, 1997), and the partial revision of the Ordinance. Signed informed consent was obtained from all patients before the study.

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Author Contributions

TS was responsible for writing the manuscript and contributed to the research and data analysis. SA, YE, and TK contributed to the study design, data analysis, and manuscript preparation. MF and TA had overall responsibility for the study, and contributed to the study design, research, analysis, and manuscript preparation. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

TS received consulting fees from KKC, Ono Pharmaceutical, Taisho Toyama Pharmaceutical, Fuji Pharma, and FUSO pharmaceutical industries, and lecture fees from KKC, Chugai Pharmaceutical, Bayer, Kissei Pharmaceutical, Torii Pharmaceutical, Ono Pharmaceutical, and FUSO pharmaceutical industries. SA, YE, and TK are employees of KKC. MF received consulting fees from KKC and Ono Pharmaceutical; lecture fees from KKC, Bayer, Torii Pharmaceutical, and Ono Pharmaceutical; and grants from KKC and Bayer. TA received consulting fees from KKC, Astellas Pharma, Bayer, Fuso Pharmaceutical, Japan Tobacco, Ono Pharmaceutical, Sanwa Chemical, Otsuka, GSK, and NIPRO, and lecture fees from KKC, Chugai Pharmaceutical, Bayer, Kissei Pharmaceutical, Torii Pharmaceutical, and Ono Pharmaceutical. The authors report no other conflicts of interest in this work.

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