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Comparison of the Oral Calcimimetics Evocalcet and Cinacalcet in East Asian Patients on Hemodialysis with Secondary Hyperparathyroidism

Zhaohui Ni[1], Xinling Liang[2], Chia-Chao Wu[3], Kyubok Jin[4], Yong-Lim Kim[5], Kuo-Cheng Lu[6], Tak Mao Chan[7], Masafumi Fukagawa[8], Jun Kinoshita[9], Chisato Nagai[9], Masahiro Kojima[9], Xueqing Yu[2], and on behalf of the Orchestra Study Group[10]

[1]Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China; [3]Tri-Service General Hospital, Taipei, Taiwan; [4]Keimyung University School of Medicine, Daegu, Republic of Korea; [5]School of Medicine, Kyungpook National University, Daegu, Republic of Korea; [6]Taipei Tzu Chi Hospital, Taipei, Taiwan; [7]The University of Hong Kong, Hong Kong, China; [8]Tokai University School of Medicine, Kanagawa, Japan; and [9]Kyowa Kirin Co., Ltd., Tokyo, Japan

Introduction: Evocalcet is an oral calcimimetic agent with proven efficacy and safety in treating secondary hyperparathyroidism (SHPT) in Japanese patients on dialysis.

Methods: This randomized, double-blind, intrapatient dose-adjustment, parallel-group, international multicenter study compared the efficacy and safety of evocalcet versus cinacalcet for 52 weeks in East Asian hemodialysis patients with SHPT.

Results: In total, 203 and 200 patients were randomized to receive evocalcet or cinacalcet, respectively (overall, 70.1% had baseline intact parathyroid hormone (PTH) levels ≥500 pg/ml, with no between-group difference). Mean percentage changes in intact PTH levels from baseline were −34.7% and −30.2% in the evocalcet and cinacalcet groups at 52 weeks (between-group difference −4.4%, 95% confidence interval [CI] −13.1%, 4.3%, below the predefined 15% noninferiority margin). Overall, 67.3% and 58.7% of patients in the evocalcet and cinacalcet groups, respectively, achieved ≥30% decrease in intact PTH levels from baseline (between-group difference 8.6%; 95% CI −1.8%, 19.1%). No major safety concerns were observed. Gastrointestinal adverse events (AEs) were significantly less frequent with evocalcet compared with cinacalcet (33.5% vs. 50.5%, $P = 0.001$), whereas the incidence of hypocalcemia did not differ.

Conclusion: Evocalcet might be a better alternative to cinacalcet for East Asian patients on hemodialysis with SHPT.

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The number of patients under maintenance dialysis therapy is increasing in East Asian countries, such as China, South Korea, and Japan.[1,2] Mineral and bone disorder due to chronic kidney disease (CKD-MBD) is prevalent in patients on dialysis.[3] SHPT is one of the common complications in CKD-MBD, triggered by hyperphosphatemia, decreased renal production of active vitamin D3, failure in renal calcium (Ca) reabsorption with decreased intestinal Ca absorption, and resulting hypocalcemia. In addition, PTH, which inhibits phosphorus (P) reabsorption from urine and stimulates active vitamin D3 production, is secreted from the parathyroid gland. Therefore, hyperphosphatemia and hypocalcemia further persist, and the chronic stimulation leads to parathyroid hyperplasia and a state of excessive PTH secretion.[4,5]

SHPT leads to a series of pathological conditions including bone fragility, ectopic calcification, and pain,

Correspondence: Xueqing Yu, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, 8F, No.106, Zhongshan 2nd road, Yuexiu District, Guangzhou, Guangdong, China. E-mail: yuxueqing@gdph.org.cn

[10]Members of the Orchestra Study Group are listed in the Appendix.

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in addition to vascular calcifications and atherosclerosis.[5] It is, therefore, necessary to control PTH, P, and Ca levels in patients with SHPT. Treatment goals (i.e., target ranges) have been established in international practice guidelines such as Kidney Disease Outcome Quality Initiative guidelines and The Kidney Disease Improving Global Outcomes.[6,7] Current SHPT treatment options include active vitamin D preparations, phosphate binders, the oral calcimimetic agent cinacalcet hydrochloride (hereafter referred to as cinacalcet), and the intravenous agent etelcalcetide,[8] which has recently become available in East Asia.[9]

Cinacalcet has been shown to reduce intact PTH (iPTH) and concurrently high levels of Ca and P,[10-13] thus improving CKD-MBD management regarding cardiovascular outcomes, fractures, and attenuation of vascular and cardiac valve calcifications.[14,15] In the EVOLVE trial, cinacalcet led to nominally significant decreases in the risk of death or first myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event.[14] Furthermore, in the ADVANCE trial, cinacalcet combined with vitamin D decreased vascular and cardiac valve calcification scores.[15]

Cinacalcet can result in gastrointestinal AEs[16-18] that patients perceive as burdensome and that can interfere with dose adjustments or hinder treatment adherence.[14,19] In addition, cinacalcet strongly inhibits cytochrome P450 (CYP) 2D6 and is metabolized by CYP3A4.[20] Etelcalcetide is an intravenous calcimimetic approved for treating SHPT in patients undergoing hemodialysis.[21] It has become a suitable option, particularly in patients with poor treatment adherence[21]; however, in a head-to-head comparison of etelcalcetide and cinacalcet, no significant difference was observed between the 2 in gastrointestinal AEs, such as self-reported nausea and vomiting.[8] Therefore, there is a need for new-generation drugs with fewer gastrointestinal AEs and a lower risk of drug interactions.

Evocalcet is a new oral calcimimetic agent with long-term efficacy and safety for SHPT demonstrated in clinical studies in Japan.[22-28] Evocalcet has been shown to be noninferior to cinacalcet, and patients treated with evocalcet had a lower incidence of gastrointestinal drug-related AEs than with cinacalcet.[27] Evocalcet does not strongly inhibit major CYP isoforms; therefore, it is considered likely to become an easy-to-use treatment option in terms of drug interactions.[29] Considering that the current evidence on evocalcet safety and efficacy for SHPT is from Japan only, it is necessary to confirm these results in other East Asian populations. Therefore, this study aimed to compare the efficacy and safety of evocalcet orally administered once daily for 52 weeks in East Asian patients with SHPT receiving hemodialysis.

METHODS

Study Design, Setting, and Procedures

This was a randomized, double-blind, intrapatient, dose-adjustment, parallel-group study conducted at 44 sites in East Asia, including mainland China, South Korea, Taiwan, and Hong Kong Special Administrative Region between April 9, 2019 and September 23, 2021. The ethical review boards of the participating sites approved the study protocol. The study was conducted following the principles described in the Declaration of Helsinki, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice Guidelines, and the regulations in each region. All patients provided written informed consent to participate in this study. The study was registered at Clinicaltrials.gov under the identifier NCT03822507.

Cinacalcet was the active control, and the treatment duration was 52 weeks, comprising a 50-week dose adjustment period and a 2-week evaluation period. Screening assessments were conducted 30 days before the initial dose of the study drug (Figure 1).

For randomization, eligible patients were allocated in a 1:1 ratio to the evocalcet or cinacalcet group using a

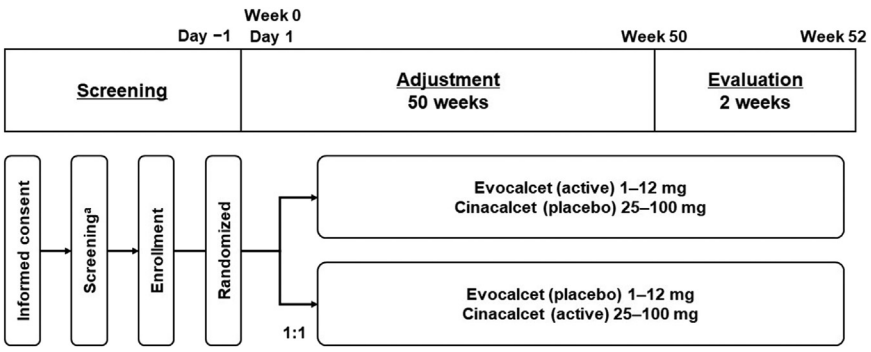

Figure 1. Study design.
[a]The screening assessments were conducted within 30 days prior to the first dose of study drug.

dynamic allocation procedure. iPTH level at screening (<500 pg/ml, ≥500 and <1000 pg/ml, or ≥1000 pg/ml), status of cinacalcet hydrochloride use, country, and investigative site were used as stratification factors. Randomization was performed using an interactive web response system. The blinding method used was a double-dummy, double-blind design. The master randomization list of the study and created code-break were securely stored until unblinding or in case of emergency.

Study treatment was started before the dialysis session on the day of the longest dialysis interval. Patients were administered the study drug orally. The dose-adjustment period was from week 0 to 49 (until the day before the week 50 visit). The starting dose of evocalcet was 1 mg in patients with an iPTH level of <500 pg/ml and 2 mg in those with an iPTH level of ≥500 pg/ml, as measured at screening. The starting dose of cinacalcet hydrochloride was 25 mg for all patients, regardless of the iPTH level at screening. The evaluation period was from week 50 to 52. The dose prescribed at week 49 was maintained without further adjustments throughout the evaluation. However, dose reduction or interruption was allowed.

The dose was adjusted based on the following criteria and was increased (by 1 mg for evocalcet and 25 mg for cinacalcet) if the current dose was maintained for ≥3 weeks and the iPTH level at the last scheduled visit before the dose change was >300 pg/ml; corrected serum Ca level at the last scheduled visit before the dose change was ≥8.4 mg/dl; or the investigator determined that the dose increase would not affect the patient's safety. If the dose of cinacalcet reached 100 mg, only the dose of evocalcet was increased. The dose was reduced (by 1 mg for evocalcet and by 25 mg for cinacalcet) if the iPTH level decreased to <150 pg/ml or the investigator determined that the dose reduction was necessary due to AE onset and to ensure patient safety. The dose was interrupted if the corrected serum Ca level decreased to ≤7.5 mg/dl or the investigator determined that the dose interruption was necessary due to AE onset.

Prohibited medications or procedures were cinacalcet, bisphosphonates, denosumab, teriparatide, parathyroidectomy/parathyroid intervention, and peritoneal dialysis. Active vitamin D preparations and derivatives, phosphate binders, and Ca preparations were permitted but restricted. Detailed criteria for these concomitant medications and therapies are provided in the Supplementary Methods.

Patients

This study targeted patients with SHPT receiving hemodialysis. Patients were included if they were aged ≥18 years at the time of consent (the cut-off age depends on local laws) with stable kidney failure, undergoing hemodialysis 3 times per week for at least 12 weeks before screening, and had centrally measured iPTH of >300 pg/ml and serum-corrected Ca of ≥9.0 mg/dl at screening.

The main exclusion criteria were as follows: treatment with cinacalcet hydrochloride within 2 weeks before screening; change in the dose or dosing regimen of an activated vitamin D drug or its derivative, phosphate binder, or Ca preparation within 2 weeks before screening; or the start of treatment with such drugs within 2 weeks before screening; and change in prescribed conditions of dialysis (dialysate Ca concentration, prescribed dialysis time, and prescribed number of dialysis sessions per week) within 2 weeks before screening. Full eligibility criteria are provided in the Supplementary Methods.

Efficacy End Points

The primary end point was the mean percentage change in iPTH level from baseline. Several secondary end points were evaluated, including the number and percentage of patients achieving a mean percentage decrease in iPTH level of ≥30% (percentage change ≤ −30%) from baseline. The number and percentage of patients achieving a mean iPTH level of ≥150 pg/ml and ≤300 pg/ml and iPTH level, corrected serum Ca level, and serum P level during the evaluation period were also assessed.

Exploratory end points were whole PTH level, intact fibroblast growth factor 23 (FGF23) level, and corrected serum Ca–P product and bone metabolic markers (bone-specific alkaline phosphatase [BAP], tartrate-resistant acid phosphatase 5b [TRACP-5b], and total N-terminal propeptide of type 1 procollagen [P1NP]).

Safety

Safety evaluations included the frequency of AEs, AEs associated with upper gastrointestinal disorders, clinically relevant changes in laboratory values, vital signs, or 12-lead electrocardiogram. MedDRA Version 24.0 was used to code AEs.

Laboratory Measurements

All clinical parameters were measured at a central laboratory. For intact PTH measurements, plasma samples were obtained and analyzed by electrochemiluminescence assay (Cobas e601; Roche Diagnostics GmbH, Mannheim, Germany). For iFGF23, plasma samples were analyzed by enzyme-linked immunosorbent assay (human FGF23 [intact]; Immutopics Inc., San Clemente, CA, USA).

Statistical Analysis

Sample size rationale and calculations are described in the Supplementary Methods. The data sets analyzed were the primary efficacy set (referred to as the full analysis set [FAS]), per-protocol set, and safety analysis set. For the primary end point, descriptive statistics, and corresponding 95% CI were calculated for each treatment group. For the secondary end points, the number and percentage of patients achieving the target for each of the different end points were calculated for categorical data; descriptive statistics were calculated for continuous data.

For the primary analysis, the difference in the mean percentage change in iPTH level from baseline between treatment groups (evocalcet group−cinacalcet group) and the 95% CI for the difference was calculated. When iPTH was missing, missing data were imputed using multiple imputation analysis. Noninferiority was demonstrated when the upper bound of the 2-sided 95% CI for the difference between the treatment groups (evocalcet group−cinacalcet group) was under the noninferiority margin of 15%. Furthermore, if noninferiority was confirmed in the primary end point, the noninferiority of the secondary end point, number, and percentage of patients achieving a mean percentage decrease in iPTH level of ≥30% from baseline, was demonstrated when the lower bound of the 2-sided 95% CI for the difference between the treatment groups was over the noninferiority margin of −15%.

For the incidences of gastrointestinal AEs (i.e., vomiting, abdominal discomfort, abdominal distension, nausea, and decreased appetite) by treatment group, the Clopper–Pearson method was used to calculate the 95% CI for evocalcet and cinacalcet. The 95% CI for between-group differences between evocalcet and cinacalcet was calculated using the Wald test method and the *P*-values using Fisher exact test.

The significance level was 5%, and statistical hypothesis tests were 2-sided. The statistical software used for the analysis was SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Disposition

Of the 531 patients who consented to participate, 404 patients met the study criteria and were randomly assigned to treatment: 203 and 200 patients to the evocalcet and cinacalcet groups, respectively. All randomized patients received the study medication, except 1e in the cinacalcet group, who withdrew at their own decision.

Overall, 83 patients (20.6%) discontinued the study: 40 patients (19.7%) and 43 patients (21.5%) in the evocalcet and cinacalcet groups (SAF), respectively. The most common reason for discontinuation was withdrawal by the patient (20 [9.9%], evocalcet group; 19 [9.5%], cinacalcet group), followed by withdrawal by the investigator due to AE onset (5 [2.5%], evocalcet group; 8 [4.0%], cinacalcet group), withdrawal due to continuous dose interruption for >4 weeks (7 [3.4%], evocalcet group; 5 [2.5%], cinacalcet group), and other reasons (5 [2.5%] in each group) (Figure 2).

Patient Characteristics

In both groups (FAS), most patients were male (62.8% and 64.8% in the evocalcet and cinacalcet groups, respectively) with a mean age (± SD) of 53.0 (12.1) and 52.0 (13.2) years, respectively; in each group, only 20.1% and 17.3%, respectively of patients were aged ≥65 years. In the evocalcet and cinacalcet groups, respectively, most patients were from China (including Hong Kong Special Administrative Region) (69.3% and 69.4%), followed by Taiwan (19.6% and 20.9%) and South Korea (11.1% and 9.7%).

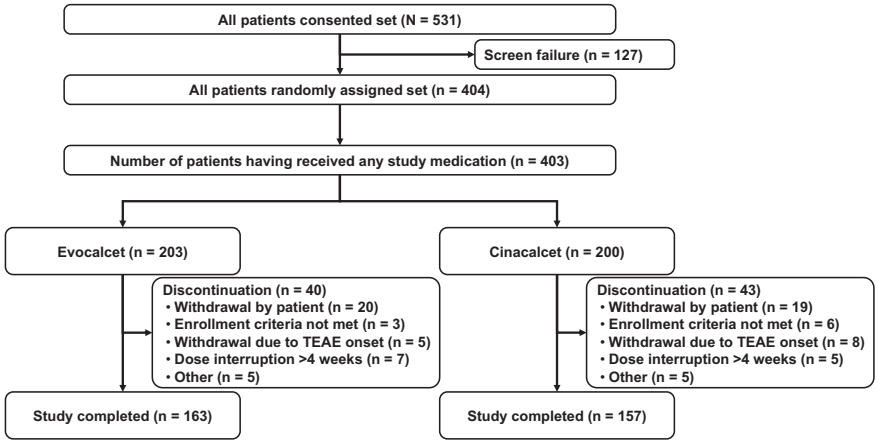

Figure 2. Patient disposition. TEAE, treatment-emergent adverse event.

Table 1. Demographics and other characteristics at baseline (FAS)

Patient characteristics	Evocalcet (n = 199)	Cinacalcet (n = 196)	Total (N = 395)	P-value
Age[a], yrs, mean (SD)	53.0 (12.13)	52.0 (13.16)	52.5 (12.65)	0.449[d]
Median (min, max)	54.0 (26, 79)	53.0 (26, 90)	53.0 (26, 90)	0.425[e]
≥65 yrs, *n* (%)	40 (20.1)	34 (17.3)	74 (18.7)	0.483[f]
Sex, n (%)				
Male	125 (62.8)	127 (64.8)	252 (63.8)	0.681[f]
Female	74 (37.2)	69 (35.2)	143 (36.2)	
Region, *n* (%)				
China (including Hong Kong SAR)	138 (69.3)	136 (69.4)	274 (69.4)	0.877[f]
Taiwan	22 (11.1)	19 (9.7)	41 (10.4)	
South Korea	39 (19.6)	41 (20.9)	80 (20.3)	
Body mass index[b] (kg/m^2), mean ± SD	24.0 ± 4.0	23.9 ± 4.1	24.0 ± 4.0	0.786[d]
Serum iPTH (pg/ml), mean ± SD	778.4 ± 421.24	807.7 ± 517.67	-	0.537[d]
<500	53 (26.6)	65 (33.2)	118 (29.9)	0.182[f]
500–1000	98 (49.2)	79 (40.3)	177 (44.8)	
≥1000	48 (24.1)	52 (26.5)	100 (25.3)	
Corrected serum Ca level (mg/dl)	9.77 ± 0.653	9.73 ± 0.768	-	0.625[d]
Baseline serum P level[c] (mg/dl)	6.35 ± 1.633	6.35 ± 1.931		0.999
<5.5	61 (30.7)	67 (34.2)	128 (32.4)	0.432[f]
≥5.5	138 (69.3)	128 (65.3)	266 (67.3)	
Missing	0	1 (0.5)	1 (0.3)	
Use of cinacalcet hydrochloride				
Yes	111 (55.8)	111 (56.6)	222 (56.2)	0.864[f]
No	88 (44.2)	85 (43.4)	173 (43.8)	
Use of active vitamin D preparations				
Yes	119 (59.8)	122 (62.2)	241 (61.0)	0.618[f]
No	80 (40.2)	74 (37.8)	154 (39.0)	
Presence or absence of underlying diabetic nephropathy				
Yes	17 (8.5)	21 (10.7)	38 (9.6)	0.464[f]
No	182 (91.5)	175 (89.3)	357 (90.4)	
Dialysis history (yrs)				
<10	123 (61.8)	114 (58.2)	237 (60.0)	0.497[f]
≥10	76 (38.2)	81 (41.3)	157 (39.7)	
Missing	0	1 (0.5)	1 (0.3)	
Ca concentration in dialysis solution (mEq/l)				
2.5	49 (24.6)	52 (26.5)	101 (25.6)	0.682[f]
2.75	0	0	0	
3.0	143 (71.9)	138 (70.4)	281 (71.1)	
Other	7 (3.5)	6 (3.1)	13 (3.3)	
Dialysis type				
HD	120 (60.3)	110 (56.1)	230 (58.2)	0.114[f]
HDF	13 (6.5)	6 (3.1)	19 (4.8)	
Other	66 (33.2)	80 (40.8)	146 (37.0)	
Initial dose of study drug				
Evocalcet 1 mg	62 (31.2)	65 (33.2)	127 (32.2)	0.540[f]
Evocalcet 2 mg	137 (68.8)	131 (66.8)	268 (67.8)	

Ca, calcium; FAS, full analysis set; HD, hemodialysis; HDF, hemodiafiltration; P, phosphorus; PTH, parathyroid hormone; SAR, Special Administrative Region.
[a]Calculated relative to informed consent date for non-Koreans. Age was collected on case report forms for South Koreans.
[b]Body mass index (kg/m^2) = weight (kg) / height at baseline (m)^2.
[c]Baseline was defined as the last nonmissing measurement taken prior to the date of first administration of any study medication.
[d]*P*-value based on *t*-test.
[e]*P*-value based on generalized Wilcoxon test.
[f]*P*-value based on chi-squared test.
The percentage of patients in each category was relative to the total number of patients in the relevant analysis set.

In both groups, more than 65% of patients had iPTH level ≥500 pg/ml, more than 60% had ≥9.5 mg/dl corrected serum Ca level, and more than 65% had serum P ≥5.5 mg/dl at baseline. Furthermore, over 50% had used cinacalcet and/or active vitamin D preparations and had continued dialysis for <10 years. Regarding underlying conditions at baseline, most patients in both treatment groups did not have diabetic

nephropathy. In general, no notable differences between the evocalcet and cinacalcet groups were observed regarding demographic and baseline characteristics (Table 1). The mean dosage during the evaluation period (*ad hoc*) was 4.3 ± 3.2 mg in the evocalcet group and 49.4 ± 32.5 mg in the cinacalcet group.

Efficacy

Primary End Point

Mean percentage changes in iPTH levels from baseline during the evaluation period were −34.7% in the evocalcet group and −30.2% in the cinacalcet group, with a between-group difference of −4.4% (95% CI −13.1%, 4.3%) (Table 2). The upper limit of the 2-sided 95% CI of the between-group difference was 4.3%, below the noninferiority margin of 15%; thus, evocalcet was demonstrated to be noninferior to cinacalcet.

Secondary End Points

The percentage of patients achieving a mean percentage decrease in iPTH level of ≥30% (percentage change ≤ −30%) from baseline was 67.3% with evocalcet and 58.7% with cinacalcet (with a between-group difference in the achievement ratio of 8.6% [95% CI −1.8%, 19.1%]; Table 2), indicating evocalcet was noninferior to cinacalcet.

The percentage of patients achieving mean iPTH levels of ≥150 pg/ml and ≤300 pg/ml during the evaluation period were similar in both groups (33.8% and 34.1%), with a between-group difference in the achievement ratio of −0.2% (95% CI −10.2%, 9.8%).

The time courses of iPTH level, corrected serum Ca level, and serum P level are shown in Figure 3a–c. Median baseline iPTH levels were 664.20 and 700.05 pg/ml in the evocalcet and cinacalcet groups and decreased to 325.00 and 361.10 pg/ml at week 52, respectively. Median percentage changes from baseline at week 52 were −48.60% and −43.51% in the evocalcet and cinacalcet groups, respectively. In the evocalcet and cinacalcet groups, median corrected serum Ca levels were comparable at baseline (9.70 and 9.60 mg/dl) and remained similar at week 52 (9.10 and 9.10 mg/dl), with median changes from baseline at week 52 of −0.60 and −0.45 mg/dl, respectively. Median serum P levels were also comparable (6.20 and 5.90 mg/dl) at baseline and decreased slightly at week 52 (5.75 and 5.90 mg/dl) with median changes from baseline of −0.60 and −0.30 mg/dl in the evocalcet and cinacalcet groups, respectively.

Exploratory End Points

Whole PTH (Supplementary Figure S1) over time from baseline and the median (quartile 1 [Q1], Q3) percentage changes in whole PTH level from baseline at week 52 were comparable between the groups (−51.2% [−68.74%, −19.16%] and −46.6% [−67.37%, −15.02%], respectively). Other measures, including corrected serum Ca–P product (Supplementary Figure S2) and the bone metabolic markers BAP levels (Supplementary Figure S3), TRACP-5b (Supplementary Figure S4), total P1NP (Supplementary Figure S5), and intact FGF23 levels (Supplementary Figure S6), generally decreased over time.

In both treatment groups, the higher the iPTH level at baseline, the higher the mean percentage change in iPTH from baseline during the evaluation period (Supplementary Tables S1, S2).

Safety

Summary of AEs

AEs occurred in 197 of 203 patients (97.0%) and 195 of 200 patients (97.5%) in the evocalcet and cinacalcet groups, respectively. Drug-related AEs occurred in 156 of 203 patients (76.8%) in the evocalcet and 168 of 200 patients (84.0%) in the cinacalcet groups. The most common AEs were hypocalcemia (53.2% and 50.5%) (Table 3) in the respective groups.

The proportions of patients who presented Ca decrease-related AEs were similar (125 [61.6%] and 122 [61.0%]) in the evocalcet and cinacalcet groups. Electrocardiogram QT prolonged occurred in 16 patients (7.9%) in the evocalcet group and 20 patients (10.0%)

Table 2. Summary of results of primary and secondary efficacy measures (FAS)

Measures	Evocalcet (n = 199)	Cinacalcet (n = 196)	Difference between groups (evocalcet − cinacalcet), P-value
Mean percentage change in iPTH (95% CI)	−34.7 (−40.8, −28.5)	−30.2 (−36.3, −24.2)	−4.4 (−13.1, 4.3), 0.000
Target iPTH level ≥30% (percentage change ≤ −30%) from baseline (95% CI)	67.3 (60.2, 74.5)	58.7 (51.2, 66.2)	8.6 (−1.8, 19.1), 0.000
Target iPTH level (≥150 pg/ml and ≤300 pg/ml) (95% CI)	33.8 (26.8, 40.8)	34.1 (26.9, 41.2)	−0.2 (−10.2, 9.8), 0.003

CI, confidence interval; FAS, full analysis set, PTH, parathyroid hormone.
95% CI values were derived by t statistic. The noninferiority margin was 15%. P-values were calculated by t-test.

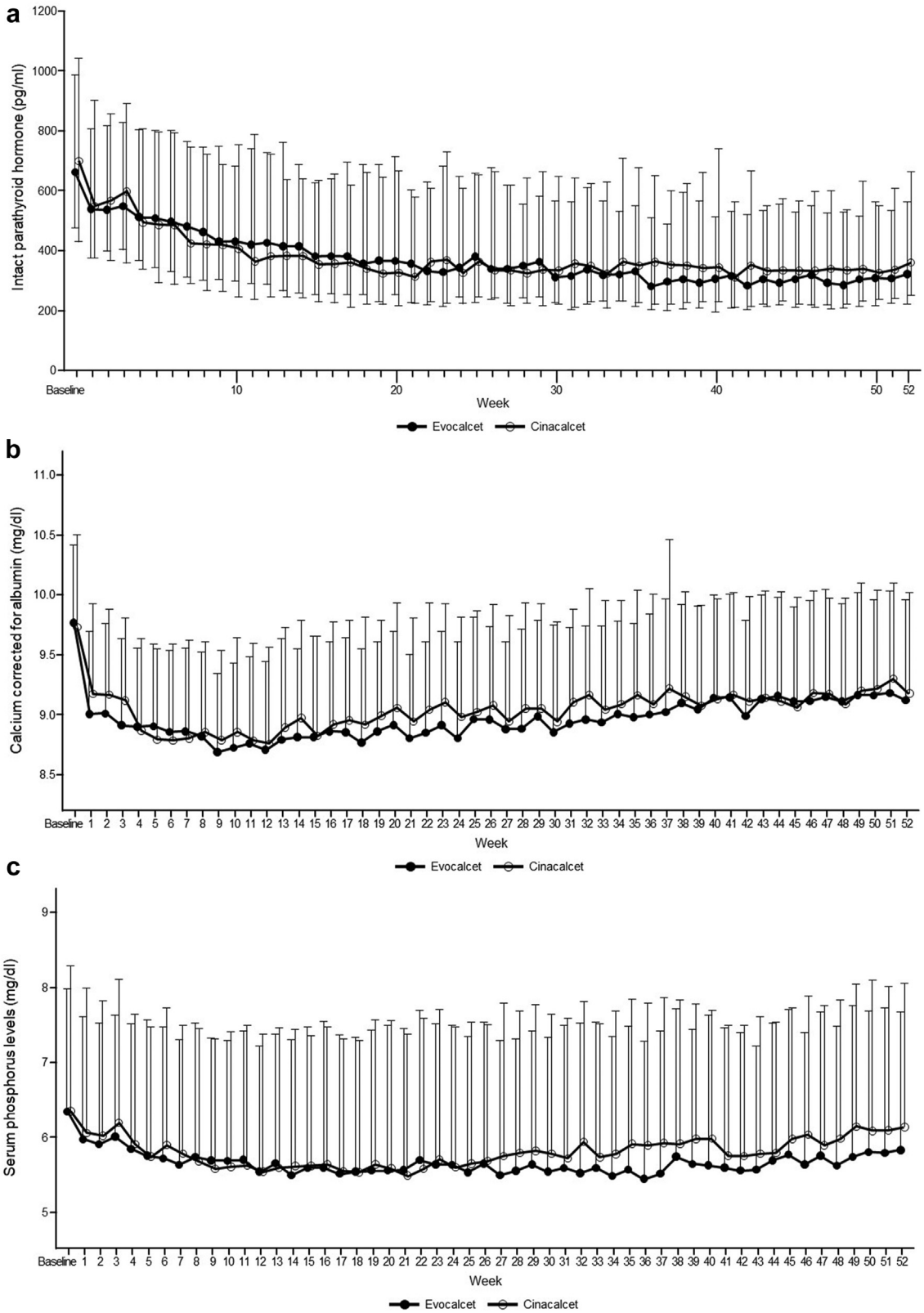

Figure 3. Time course of (a) iPTH (Median [Q1–Q3]), (b) corrected serum Ca (Mean + SD), and (c) serum P levels (Mean + SD) during the study in the FAS. Ca, calcium; FAS, full analysis set; P, phosphorus; PTH, parathyroid hormone; Q, quartile.

in the cinacalcet group. No torsade de pointes AEs occurred during the trial.

Serious AEs occurred in 49 (24.1%) and 40 patients (20.0%) in the evocalcet and cinacalcet groups; these were considered drug-related AEs in 6 (3.0%) and 2 (1.0%) patients in the evocalcet and cinacalcet groups, respectively. Serious AEs that resulted in death occurred in 3 (1.5%) and 2 (1.0%) patients in

Table 3. Drug-related AEs by PT that occurred in ≥3% of patients in any treatment group (SAF)

[SOC] PT	Evocalcet (n = 203) n (%) E	Cinacalcet (n = 200) n (%) E	Total (N = 403) n (%) E	P-value
Number of patients with at least one drug-related AE	156 (76.8) 991	168 (84.0) 1390	324 (80.4) 2381	0.070
[Metabolism and nutrition disorders]	115 (56.7) 559	119 (59.5) 589	234 (58.1) 1148	0.562
Hypocalcemia	108 (53.2) 490	101 (50.5) 448	209 (51.9) 938	0.587
Decreased appetite	14 (6.9) 23	36 (18.0) 97	50 (12.4) 120	0.000
Hypoproteinemia	11 (5.4) 20	9 (4.5) 21	20 (5.0) 4	0.671
[Gastrointestinal disorders]	65 (32.0) 228	95 (47.5) 527	160 (39.7) 755	0.001
Nausea	25 (12.3) 49	49 (24.5) 157	74 (18.4) 206	0.001
Vomiting	19 (9.4) 32	40 (20.0) 127	59 (14.6) 159	0.002
Abdominal discomfort	23 (11.3) 51	35 (17.5) 77	58 (14.4) 128	0.077
Abdominal distension	16 (7.9) 39	31 (15.5) 70	47 (11.7) 109	0.017
Diarrhea	11 (5.4) 22	21 (10.5) 36	32 (7.9) 58	0.059
Abdominal pain upper	5 (2.5) 11	8 (4.0) 11	13 (3.2) 22	0.382
Flatulence	0	8 (4.0) 18	8 (2.0) 18	0.003
Gastroesophageal reflux disease	7 (3.4) 7	1 (0.5) 1	8 (2.0) 8	0.033
[Investigations]	40 (19.7) 133	44 (22.0) 173	84 (20.8) 306	0.570
Blood calcium decreased	16 (7.9) 31	18 (9.0) 50	34 (8.4) 81	0.686
Electrocardiogram QT prolonged	15 (7.4) 29	18 (9.0) 48	33 (8.2) 77	0.555
Calcium ionized decreased	9 (4.4) 65	9 (4.5) 59	18 (4.5) 124	0.974
[Musculoskeletal and connective tissue disorders]	8 (3.9) 12	8 (4.0) 22	16 (4.0) 34	0.975
Muscle spasms	5 (2.5) 9	6 (3.0) 18	11 (2.7) 27	0.740
[Nervous system disorders]	6 (3.0) 7	9 (4.5) 14	15 (3.7) 21	0.412
Dizziness	0	7 (3.5) 10	7 (1.7) 10	0.007

AE, adverse event; PT, preferred term; SAF, safety analysis set; SOC, system organ class.
"n" represents the number of patients, % is the percentage of patients in each category, and E represents the number of drug-related AEs. AEs were defined as AEs that started or worsened in severity on or after the first dose of study medication. MedDRA Version 24.0 was used to code AEs. All P-values were calculated by chi-squared test.

the evocalcet and cinacalcet groups, respectively. One event of cardiorespiratory arrest occurred in a patient with congenital heart disease in the evocalcet group, which was considered related to the study drug.

AEs Associated with Upper Gastrointestinal Disorders

Upper gastrointestinal disorders occurred in 68 (33.5%) and 101 (50.5%) patients in the evocalcet and cinacalcet groups, respectively, with a difference in the incidence of −17.0% (95% CI −26.5%, −7.5%; $P = 0.001$). The most common upper gastrointestinal disorder in both treatment groups was nausea (34 [16.7%], evocalcet group; 55 [27.5%], cinacalcet group). Comparing the evocalcet and cinacalcet groups, the incidences of upper gastrointestinal disorders, including nausea (−10.8 [95% CI −18.8, −2.7]; $P = 0.011$), vomiting (−10.7 [−18.0, −3.4]; $P = 0.005$), decreased appetite (−14.1 [−20.8, −7.4]; $P = 0.000$), and abdominal

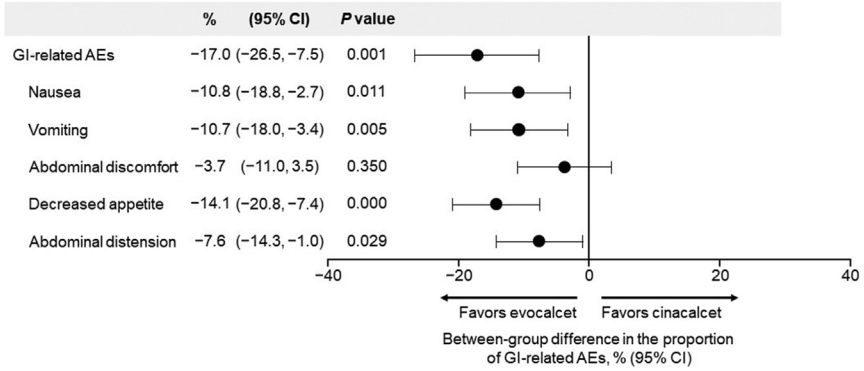

Figure 4. Forest plot quantifying the risk difference of GI-related AEs by treatment group. For the evocalcet group, the 95% CIs were calculated using the Clopper–Pearson method. For the cinacalcet group, 95% CIs were calculated using the Wald test method. The p-value was based on Fisher's exact test. MedDRA Version 24.0 was used to code AEs. A patient was counted only once per AE category and once per unique PT within the AE category. AE, adverse event; CI, confidence interval; GI, gastrointestinal; PT, preferred term; SAF, safety analysis set.

distension (−7.6 [−14.3, −1.0]; $P = 0.029$) were significantly lower in the evocalcet group than in the cinacalcet group (Figure 4). Drug-related AEs involving upper gastrointestinal disorders occurred in 54 patients (26.6%) in the evocalcet group and 87 patients (43.5%) in the cinacalcet group, with a difference in incidence of −16.9% (95% CI −26.1%, −7.7%). The difference in incidences between the 2 groups was consistent for AEs and drug-related AEs.

DISCUSSION

This double-blind, double-dummy, randomized, noninferiority trial of evocalcet and cinacalcet in patients with SHPT receiving hemodialysis demonstrated that evocalcet was noninferior to cinacalcet in reducing iPTH levels. For the secondary end points, the proportion of participants with ≥30% decrease in iPTH from baseline was also noninferior to cinacalcet. In addition, no significant concerns were observed with safety overall in the evocalcet group, and the occurrence of AEs was comparable with cinacalcet. The exception was for upper gastrointestinal disorders, whereby the incidence was significantly lower for patients receiving evocalcet compared with cinacalcet. Furthermore, the incidence of almost all components (i.e., vomiting, nausea, abdominal discomfort, decreased appetite, and abdominal distension) was significantly lower with evocalcet than with cinacalcet, which indicates a clear risk reduction in the incidence of upper gastrointestinal disorders. Therefore, based on these results, evocalcet may improve adherence to SHPT treatment.

Notably, this study enrolled 48 (24.1%) and 52 (26.5%) patients with iPTH ≥1000 pg/ml in the evocalcet and cinacalcet groups. Evocalcet was shown to be effective in such patients, with mean (± SD) percentage changes in iPTH of −46.07 (± 35.081) and −37.13 (± 39.112) pg/ml with evocalcet and cinacalcet, respectively. Such patients (with iPTH ≥1000 pg/ml) generally have severe SHPT. Nodular hyperplasia is also associated with resistance to cinacalcet therapy,[30] and surgical parathyroidectomy is applied to refractory patients.[31] Of note, in the Japanese phase 3 trial, efficacy in patients with such high iPTH remained unknown because of the low number of patients with iPTH ≥1000 pg/ml enrolled in that study.[27] Therefore, according to the present results, evocalcet may provide a therapeutic option for severe SHPT.

The phase 2b study suggested a dose of 2-mg evocalcet elicited an iPTH-lowering effect similar to 25 mg cinacalcet.[23] It is meaningful that the dose of evocalcet can be increased to 12 mg, which is hypothetically equivalent to cinacalcet 150 mg. A higher treatment effect could be achieved with a higher dose. High doses (9–12 mg) were administered to a higher percentage of patients with iPTH baseline level ≥1000 pg/ml than patients with iPTH baseline <1000 pg/ml (data not shown), which could increase the iPTH-lowering effect in a subpopulation with iPTH baseline ≥1000 pg/ml. Conversely, cinacalcet can cause upper gastrointestinal AEs and hypocalcemia, which are major factors affecting patient adherence and dose increases. Importantly, adherence to calcimimetics impacts the clinical outcome. A previous report showed that combining evocalcet with a vitamin D receptor activator, a commonly used SHPT treatment, can suppress PTH levels while reducing hypocalcemia[32]; therefore, concomitant use of a vitamin D receptor activator and evocalcet may provide a more effective and safer treatment for severe SHPT patients with high PTH.

This study had some limitations, such as the 52-week treatment period, and longer-term data on East Asian populations are still needed. Changes in and new initiation of vitamin D preparations and changes to prescribed dialysis conditions were restricted in the study, which does not reflect real-world clinical practice. Furthermore, a surrogate end point (lowering iPTH) was used to evaluate CKD-MBD treatment. Finally, the study only enrolled patients in China, South Korea, Taiwan, and Hong Kong Special Administrative Region; therefore, the results are not necessarily generalizable to other populations.

Conclusion

The mean percentage change from baseline in mean iPTH levels during the evaluation period confirmed that evocalcet was noninferior to cinacalcet. No major safety concerns were observed overall, with a significantly lower incidence of upper gastrointestinal drug-related AEs in the evocalcet group compared with the cinacalcet group. Based on these efficacy and safety findings, evocalcet might be a better alternative to cinacalcet for SHPT in East Asian hemodialysis patients with SHPT.

APPENDIX

List of the Orchestra Study Group

Liang Xinling (Principle Investigator)[1], Liu Shuangxin[1], Li Sijia[1], Xu Lixia[1], Ye Zhiming[1], Feng Zhonglin[1], Huang Renwei[1], Li Zhilian[1], Chen Wei (Principle Investigator)[2], Zheng Xunhua[2], Huang Naya[2], Ai Zhen[2], Wang Xin[2], Zheng Xunhua (former PI)[3], Zhaohui Ni (present PI)[3], Lu Renhua[3], Shen Jianxiao[3], Zhou Yijun[3], Lin Xinghui[3], Xie Yuanyuan[3], Zhang Jiahui[3], Che Miaolin[3], Fang Yan[3], Pang Huihua[3], Su Xinyu[3], Gu Leyi[3], Jin Wei[3], Zhao Peipei[3], Shen Yiwei[3], Zao Liou[3], Lu

Wei (Principle Investigator)[4], Huang Haidong[4], Ji Gang[4], Li Hao (former PI)[5], Wang Deguang (present PI)[5], Wang Deguang[5], Yuan Liang[5], Ding Lihong[5], Wang Xuerong[5], Li Huai[5], Liu Hong (Principle Investigator)[6], Yuan Fang[6], Song Panai[6], Zhou An[6], Chen Xiaojun[6], Li Xiejia[6], He Liyu[6], Tan Xia[6], Chen Jing (Principle Investigator)[7], Zhang Minmin[7], Zhang Qian[7], Qian Jing[7], Kong Yaozhong (Principle Investigator)[88], Chen Youyuan[8], Shen Wei[8], Xiao Guanqing[8], Chen Dezhen[8], Li Dao[8], Hou Aizhen[8], Li Xiaolei[8], He Hanchang[8], Ye Huizhen[8], Sun Zhuxing (Principle Investigator)[9], Zhang Xiran[9], Shan Weiwei[9], Xue Jing[9], Chen Yong[9], Xing Changying (Principle Investigator)[10], Li Li[10], Yu Xiangbao[10], Liu Kang[10], Ge Yifei[10], Xu Yili[10], Huang Zhimin[10], Wu Jingjing[10], Liu Bicheng (Principle Investigator)[11], Tu Yan[11], Pan Mingming[11], Lin Hongli (Principle Investigator)[12], Wang Dapeng[12], Meng Qingyang[12], Luo Renna[12], Ding Guohua (Principle Investigator)[13], Shi Ming[13], Qiu Changjian[13], Lv Xifeng[13], Zhang Guojuan (Principle Investigator)[14], Jiang Liping[14], Ding Ning[14], Zhao Huiying[14], Bao Shumin[14], Chen Wei[14], Chen Shen[14], Liang Qiaojing[14], Zhang Mei[14], Peng Kanfu (Principle Investigator)[15], Xie Pan[15], Yuan Qian[15], Zhuo Yan[15], Li Shaohua[15], Mao Yonghui (Principle Investigator)[16], Zhao Ban[16], Wang Songlan[16], Chen Xianguang[16], Chen Xiaonong (Principle Investigator)[17], Gao Chenni[17], Yu Haijin[17], Weng Qinjie[17], Jin Yuanmeng[17], Ma Xiaobo[17], Luo Ping (Principle Investigator)[18], Gao Dan[18], Wu Man[18], Qi Yonghui[18], Zhang Ping (Principle Investigator)[19], Du Xiaoying[19], Qu Lihui[19], Xu Chunping[19], Sheng Kaixiang[19], Yang Yi[19], Wang Song (Principle Investigator)[20], Tian Xinkui[20], Guo Hongxia[20], Bao Wenhan[20], Lin Weifeng[20], Zhou Sijia[20], Cui Zhuan[20], Yang Wenling[20], Su Kaijie[20], He Lian[20], Zhou Zhihong (Principle Investigator)[21], Zheng Yu[21], Zheng Shubei[21], Jin Lingwei[21], Chen Yan[21], Pan Min[21], Zhang Guojuan (Principle Investigator)[22], Jiang Liping[22], Ding Ning[22], Zhao Huiying[22], Bao Shumin[22], Chen Wei[22], Chen Shen[22], Liang Qiaojing[22], Zhang Mei[22], Chia-Chao Wu (Principle Investigator)[23], Chih-Chien Sung[23], Shuei-Liong Lin (Principle Investigator)[24], Ming-Shiou Wu[24], Jenq-Wen Huang[24], Wen Chih Chiang[24], Chih-Kang Chiang[24], Shao-Yu Yang[24], Vin-Cent Wu[24], Tao-Min Huang[24], Yi-Ting Chen[24], Tai-Shuan Lai[24], Chun-Fu Lai[24], Der-Cherng Tarng (Principle Investigator)[25], Shuo-Ming Ou[25], Chih-Yu Yang[25], Wei-Cheng Tseng[25], Yao-Ping Lin[25], Junne-Ming Sung (Principle Investigator)[26], Te-Hui Kuo[26], Yu-Tzu Chang[26], An-Bang Wu[26], Wei-Hung Lin[26], Hua-Chang Fang (Principle Investigator)[27], Hsin-Yu Chen[27], Chih-Yang Hsu[27], Po-Tsang Lee[27], Chien-Liang Chen[27], Kang-Ju Chou[27], Tzung-Yu Ho[27], Chien-Te Lee (Principle Investigator)[28], Hwee-Yeong Ng[28], Yueh-Ting Lee[28], Yi-Wen Chiu (Principle Investigator)[29], Hung-Tien Kuo[29], Chi-Chih Hung[29], Mei-Chuan Kuo[29], Jia-Jung Lee[29], Jer-Chia Tsai[29], Jer-Ming Chang[29], Lee-Moay, Lim[29], Shang-Jyh Hwang[29], Jyh-Chang Hwang (Principle Investigator)[30], Hsien-Yi Wang[30], Wei-Chih Kan[30], Chia-Chun Wu[30], Ming-Yan Jiang[30], Chih-Chiang Chien[30], Ming-Ju Wu (Principle Investigator)[31], Shang-Feng Tsai[31], Cheng-Hsu Chen[31], Hsi-Hsien Chen (Principle Investigator)[32], Chih-Chin Kao[32], Yen-Chung Lin[32], Yueh-Lin Wu[32], Shu-Ching Yeh[32], Daniel Tak Mao Chan (Principle Investigator)[33], Maggie Ming Yee Mok[33], Lorraine Pui Yuen Kwan[33], Gary Chi Wang Chan[33], Yong-Lim Kim (Principle Investigator)[34], Jang-Hee Cho[34], Jeong-Hoon Lim[34], Hee-Yeon Jung[34], Sun-Hee Park[34], Chan-Duck Kim[34], Kyu Yeun Kim[34], Jung Tak Park (Principle Investigator)[35], Tae-Hyun Yoo[35], Seung Hyeok Han[35], Wookyung Chung (Principle Investigator)[36], Ji Yong Jung[36], Hyun Hee Lee[36], Jae Hyun Chang[36], Han Ro[36], Ae Jin Kim[36], Jong Soo Lee (Principle Investigator)[37], Jongha Park[37], Kyung Sun Park[37], Kyoung Don Yoo[37], Tae Ik Chang (Principle Investigator)[38], Ea Wha Kang[38], Kyoung Sook Park[38], Kyubok Jin (Principle Investigator)[39], Yaerim Kim[39], Jinhyuk Paek[39], Wooyeong Park[39], Seungyeup Han[39], Ohyun Kwon[39], Sung Bae Park[39], Myung-gyu Kim (Principle Investigator)[40], SeWon Oh[40], Jung Pyo Lee (Principle Investigator)[41], Jeonghwan Lee[41], Jihoon Jung[41], Cheol Whee Park (Principle Investigator)[42], Hyung Duk Kim[42], Sunggyun Kim (Principle Investigator)[43], Youngrim Song[43], Narae Joo[43], Hyungsuk Lee[43], Bum-Soon Choi (Principle Investigator)[44], Hoon Suk Park[44], Tae Hyun Ban[44]

[1]Department of Nephrology, Guangdong Provincial People's Hospital, Mainland China

[2]Department of Nephrology, The First Affiliated Hospital of Sun Yat-sen University, Mainland China

[3]Department of Nephrology, Renji Hospital Shanghai Jiaotong University School of Medicine, Mainland China

[4]Department of Nephrology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Mainland China

[5]Department of Nephrology, The Second Hospital of Anhui Medical University, Mainland China

[6]Department of Nephrology, The Second Xiangya Hospital of Central South University, Mainland China

[7]Department of Nephrology, Huashan Hospital, Fudan University, Mainland China

[8]Department of Nephrology, The First People's Hospital of Foshan, Mainland China

[9]Department of Nephrology, Wuxi People's Hospital, Mainland China

[10]Department of Nephrology, Jiangsu Province Hospital, Mainland China

[11]Department of Nephrology, Zhong Da Hospital, Southeast University, Mainland China

[12]Department of Nephrology, The First Affiliated Hospital of Dalian Medical University, Mainland China

[13]Nephrology Department, Renmin Hospital, Wuhan University, Mainland China
[14]Department of Nephrology, Beijing Tongren Hospital, Capital Medical University, Mainland China
[15]Dept.of Nephrology, The First Hospital Affiliated to AMU (Southwest Hospital, Mainland China
[16]Department of Nephrology, Beijing Hospital, Mainland China
[17]Department of Nephrology, Ruijin Hospital of Shanghai Jiaotong University School of Medicine, Mainland China
[18]Nephrology Department, The Second Hospital of Jilin University, Mainland China
[19]Nephrology Department, The First Affiliated Hospital of Zhejiang University school of medicine, Mainland China
[20]Nephrology Department, Peking University Third Hospital, Mainland China
[21]Nephrology Department, The 2nd Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Mainland China
[22]Department of Nephrology, Beijing Tongren Hospital, Capital Medical University, Mainland China
[23]Department of Nephrology, Tri-Service General Hospital, Taiwan
[24]Department of Nephrology, National Taiwan University Hospital, Taiwan
[25]Department of Nephrology, Taipei Veterans General Hospital, Taiwan
[26]Department of Internal Medicine, National Cheng Kung University Hospital, Taiwan
[27]Department of Nephrology, Kaohsiung Veterans General Hospital, Taiwan
[28]Department of Nephrology, Kaohsiung Chang Gung Memorial Hospital, Taiwan
[29]Department of Nephrology, Kaohsiung Medical University Chung-Ho Memorial Hospital, Taiwan
[30]Department of Nephrology, Chi Mei Medical Center, Taiwan
[31]Department of Nephrology, Taichung Veterans General Hospital, Taiwan
[32]Department of Nephrology, Taipei Medical University Hospital, Taiwan
[33]Department of Medicine, Queen Mary Hospital, Taiwan
[34]Department of Nephrology, Kyungpook National University Hospital, Taiwan
[35]Department of Nephrology, Severance Hospital, Yonsei University Health System, Taiwan
[36]Department of Nephrology, Gachon University Gil Medical Center, Taiwan
[37]Department of Nephrology, Ulsan University Hospital, Taiwan
[38]Department of Nephrology, National Health Insurance Service Ilsan Hospital, Taiwan
[39]Department of Nephrology, Keimyung University Dongsan Hospital, Taiwan
[40]Department of Nephrology, Korea University Anam Hospital, Taiwan
[41]Department of Nephrology, Boramae Medical Center, Taiwan
[42]Department of Nephrology, The Catholic University of Korea, Seoul St. Mary's Hospital, Taiwan
[43]Department of Nephrology, Hallym University Sacred Hospital, Korea
[44]Department of Nephrology, The Catholic University of Korea Eunpyeong St.Mary's Hospital, Korea

DISCLOSURE

Y-LK, K-CL, TMC, MF, and XY were advisory board members of this study, and KCL, TMC, MF, and XY have received personal fees from Kyowa Kirin Co., Ltd., during the conduct of the study. MF has received personal fees from Ono pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusyo Co., Ltd., Bayer Yakuhin, Ltd., and Kissei Pharmaceutical Co., Ltd.; and grants and personal fees from Kyowa Kirin Co., Ltd., outside the submitted work. JK, CN, and MK are employees of Kyowa Kirin. ZN, XL, C-CWu, and KJ have no conflicts of interest to disclose in relation to the present work.

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Data Availability

Research data are not shared.

AUTHOR CONTRIBUTIONS

ZN, XL, KJ, and C-CW contributed significantly to patient recruitment, drafted the main manuscript, and provided final approval for submission. Y-LK, K-CL, TMC, MF, and XY contributed to the study design, data interpretation, drafted the main manuscript, and provided final approval for submission. JK, CN, and MK contributed to the study design, data analysis, reviewed the manuscript critically for important intellectual content and provided final approval for submission.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Whole parathyroid hormone levels over time (Median [Q1–Q3]) (FAS).

Figure S2. Corrected serum Ca–P product over time (Mean + SD) (FAS).
Figure S3. BAP levels over time (Mean + SD) (FAS).
Figure S4. TRACP-5b levels over time (Mean + SD) (FAS).
Figure S5. P1NP levels over time (Mean + SD) (FAS).
Figure S6. Intact FGF23 over time (Median [Q1–Q3]).
Table S1. Mean percentage change from baseline in intact PTH during evaluation period by myocardial infarction by subgroup (FAS).
Table S2. Mean dosage at last observation period by baseline iPTH subgroup (FAS).
CONSORT Checklist.

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