Effects of etelcalcetide on fibroblast growth factor 23 in patients with secondary hyperparathyroidism receiving hemodialysis

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ABSTRACT

Background. Etelcalcetide is an intravenous calcimimetic approved for treatment of secondary hyperparathyroidism (sHPT) in patients receiving hemodialysis. Besides lowering parathyroid hormone (PTH), etelcalcetide also significantly reduces fibroblast growth factor 23 (FGF23), but the mechanisms are unknown.

Methods. To investigate potential mediators of etelcalcetide-induced FGF23 reduction, we performed secondary analyses of the 26-week randomized trials that compared the effects on PTH of etelcalcetide (n = 509) versus placebo (n = 514) and etelcalcetide (n = 340) versus cinacalcet (n = 343) in adults with sHPT receiving hemodialysis. We analyzed changes in FGF23 in relation to changes in PTH, calcium, phosphate and bone turnover markers. We also investigated how concomitant treatments aimed at mitigating hypocalcemia altered the FGF23-lowering effects of etelcalcetide.

Results. Etelcalcetide reduced FGF23 [median % change (quartile 1–quartile 3)] from baseline to the end of the trial significantly more than placebo [–56% (–85 to –7) versus +2% (–40 to +65); P < 0.001] and cinacalcet [–68% (–87 to –26) versus –41% (–76 to +25); P < 0.001]. Reductions in FGF23 correlated strongly with reductions in calcium and phosphate, but not with PTH; correlations with bone turnover markers were inconsistent and of borderline significance. Increases in concomitant vitamin D administration partially attenuated the FGF23-lowering effect of etelcalcetide, but increased dialysate calcium concentration versus no increase and increased dose of calcium supplementation versus no increase did not attenuate the FGF23-lowering effects of etelcalcetide.
**Conclusion.** These data suggest that etelcalcetide potently lowers FGF23 in patients with shHPT receiving hemodialysis and that the effect remains detectable among patients who receive concomitant treatments aimed at mitigating treatment-associated decreases in serum calcium.

**Keywords:** calcimimetics, FGF23, hemodialysis, PTH, secondary hyperparathyroidism

**INTRODUCTION**

Circulating concentrations of fibroblast growth factor 23 (FGF23) are markedly elevated in patients with advanced chronic kidney disease (CKD) [1]. Increased FGF23 helps to maintain phosphate homeostasis in progressive CKD by stimulating renal phosphate excretion and suppressing circulating vitamin D levels, the latter of which promotes secondary hyperparathyroidism (shHPT) [2–8]. Although these effects of FGF23 mitigate hyperphosphatemia [1, 2, 9], elevated FGF23 is independently associated with increased risks of cardiovascular disease, infection, anemia and mortality [10–14].

Current guidelines for management of disordered mineral metabolism in patients receiving hemodialysis focus on achieving target concentrations of parathyroid hormone (PTH), calcium and phosphate [15]. Multiple combinations of therapeutic strategies are utilized, including dietary phosphate restriction, calcium-based and noncalcium-based phosphate binders, vitamin D preparations and calcimimetics [13, 16–22]. Different therapeutic approaches to shHPT have differential effects on FGF23. Cinacalcet tends to lower FGF23, vitamin D tends to increase or no increase in these interventions.

MATERIALS AND METHODS

**Study population**

We assessed the effects of etelcalcetide and cinacalcet on circulating concentrations of FGF23 in a post hoc pooled analysis of Phase 3 trials that were designed to evaluate the efficacy of etelcalcetide to achieve PTH ≤ 300 pg/mL [24, 25]. The trials were approved by institutional review boards at participating trial sites and were conducted in accordance with the Declaration of Helsinki. Adult patients with shHPT receiving hemodialysis were randomized 1:1 to 26 weeks of treatment with etelcalcetide (n = 509) versus placebo (n = 514) or etelcalcetide (n = 340) versus cinacalcet (n = 343) added to the standard of care. All participants provided written informed consent. Etelcalcetide was administered intravenously at a starting dose of 5 mg three times weekly after hemodialysis and cinacalcet was taken orally at a starting dose of 30 mg/day. Etelcalcetide (and the corresponding intravenous placebo) could be titrated in increments of 2.5 or 5 mg and cinacalcet in increments of 30 mg (dose range 30–180 mg) at Weeks 5, 9, 13 and 17. With investigators blinded to PTH concentrations throughout the trial, calcimimetics were titrated by protocol using an interactive voice or web response system up to a maximum of 15 mg of etelcalcetide per dialysis session or 180 mg of cinacalcet per day to achieve target PTH levels between 100 and 300 pg/mL. The median average weekly calcimimetic doses during the efficacy assessment phase at Weeks 20–26 was 15.0 mg for etelcalcetide and the median average daily cinacalcet dose was 51.4 mg [interquartile range (IQR) 26.4–80.4] [25]. Dialysate calcium concentrations and specific types and doses of phosphate binders, calcium supplements and vitamin D preparations could be adjusted by individual investigators at their discretion. Due to difficulty in standardizing individual participants’ total calcium dose across the wide range of binders and supplements prescribed by investigators, we chose to dichotomize calcium supplementation into groups that either received any increase or no increase based on a comparison of their average doses during the efficacy assessment phase and their baseline doses. We used a similar strategy to dichotomize changes in vitamin D dose and dialysate calcium concentration according to whether individuals received an increase or no increase in these interventions.

**Assays**

Central laboratories (Covance Central Laboratory Services, Indianapolis, IN, USA; Meyrin, Switzerland; and Singapore) measured intact PTH (immunometric assay; ADVIA Centaur PTH Assay, Siemens Healthcare, Erlangen, Germany), calcium and phosphate in real time throughout the trials and stored and analyzed samples for measurements of intact FGF23 (Kainos ELISA kit, Kainos Labs, Tokyo, Japan), bone-specific alkaline phosphatase (BSAP) and C-telopeptide (CTX) at baseline and at the beginning of Week 27. Note that while treatment in both trials was 26 weeks, the final laboratory values were obtained at the beginning of Week 27. Albumin-corrected serum calcium is presented in all analyses.

**Statistical analysis**

Within the placebo-controlled trials, we stratified participants into three groups of shHPT severity according to baseline PTH (<600, 600–1000 and >1000 pg/mL) and investigated the effects of etelcalcetide versus placebo on the change in PTH from baseline to Week 27 within these groups. Within each PTH stratum we determined the mean baseline calcium, phosphate, calcium × phosphate product and FGF23 and the percent change from baseline following treatment with etelcalcetide or placebo during the efficacy assessment phase, which was Weeks 20–27.
We compared the percent change in FGF23 from baseline to Week 27 between etelcalcetide and placebo and etelcalcetide and cinacalcet using Wilcoxon rank sum tests. We calculated Pearson correlation coefficients for percent changes in FGF23, BSAP and CTX from the baseline to Week 27 measurements; for PTH, calcium, phosphate and calcium x phosphate, we calculated percent changes from baseline using the mean of all values during the efficacy assessment phase (Weeks 20–27). We analyzed the effects of an increase versus no increase in vitamin D dose, calcium supplementation and dialysate calcium concentration on randomized treatment-associated changes in FGF23 levels at Week 27 by testing the Spearman correlations of the within-group changes in FGF23 among participants in whom concomitant treatments were or were not increased. We analyzed all available data without imputation. Statistical significance was defined as P < 0.05 without adjusting for multiple comparisons. All analyses were performed using SAS software (SAS Institute, Cary, NC, USA).

Data-sharing agreement
There is a plan to share data. This may include deidentified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form and/or clinical study report. Data-sharing requests relating to data in this article will be considered after the publication date and (i) this product and indication (or other new use) have been granted marketing authorization in both the USA and Europe or (ii) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data-sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of reevaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests. If not approved, then requests may be further arbitrated by a Data Sharing Independent Review Panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen’s sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data-sharing agreement. This may include anonymized individual patient data and/or available supporting documents containing fragments of analysis code where provided in analysis specifications. Further details are available at https://www.amgen.com/science/clinical-trials/clincial-data-transparency-practices/

RESULTS
Baseline data
Characteristics of the study population from the placebo-controlled trial of etelcalcetide are presented in Table 1 overall and according to baseline severity of sHPT, expressed in ascending strata of pretreatment PTH (≤600, 600–1000 and >1000 pg/mL). Participants in the highest PTH stratum had the highest baseline serum concentrations of calcium, phosphate and FGF23 while the dose of calcitriol or vitamin D analogs at baseline was similar across strata (Table 1).

Postrandomization data
The mean percent reduction in PTH with etelcalcetide treatment was similar regardless of baseline sHPT severity, ranging from –54% (95% confidence interval [CI] –59 to –50), to –58% (95% CI –62 to –54), to –55% (95% CI –62 to –49) from the lowest to the highest baseline PTH strata, despite the progressive increase in delivered dose of etelcalcetide across the ascending PTH strata (Table 2). In the full study populations, etelcalcetide decreased FGF23 from baseline to Week 27 significantly more than placebo [–56% (95% CI –85 to –7) versus –2% (–40 to –65); P = 0.001; Figure 1A] and significantly more than cinacalcet [–68% (95% CI –87 to –26) versus –41% (–76 to –25); P < 0.001; Figure 1B]. Although patients in the highest baseline PTH stratum in the placebo-controlled trial had the largest relative reduction in calcium, phosphate and FGF23 induced by etelcalcetide (Table 2), etelcalcetide (and cinacalcet)-induced reductions in FGF23 correlated strongly with concomitant reductions in calcium, phosphate and calcium x phosphate product, but not with changes in PTH (Table 3); changes in bone markers were less strongly correlated with change in FGF23.

Effects of concomitant treatments
Etelcalcetide significantly decreased FGF23 compared with placebo, irrespective of whether the dose of vitamin D was increased (between-group comparisons; Figure 2A), but within the etelcalcetide group, the effect on FGF23 was partially attenuated among participants who received an increase versus no increase in their dose of calcitriol or vitamin D analog (median change –48% versus –62%; P = 0.045). In the active-controlled trials (Figure 2B), etelcalcetide decreased FGF23 significantly more than cinacalcet among participants whose calcitriol or vitamin D analog dose was not increased (–71% versus –41%; P < 0.001), but there was no significant difference among those in whom the calcitriol or vitamin D analog dose was increased (–60% versus –42%; P = 0.07); similar to the placebo-controlled trials, the etelcalcetide effect on FGF23 was partially attenuated among participants who received an increase versus no increase in their dose of calcitriol or vitamin D analog (–60% versus –71%; P = 0.004; Figure 2B). Etelcalcetide decreased FGF23 significantly more than placebo or cinacalcet regardless of whether dialysate calcium or calcium supplementation was increased (between-group comparisons; Figures 3 and 4). Compared with no increase, an increase in dialysate calcium concentration did not attenuate the FGF23-lowering effects of etelcalcetide in the placebo-controlled trials (–55% versus –57%; P = 0.68; Figure 3A) and was associated with significantly more FGF23 reduction in the active-controlled trials (–82% versus –66%; P = 0.02; Figure 3B). Likewise, compared with no increase, an increase in dose of calcium supplementation did not attenuate the FGF23-lowering effects of etelcalcetide in the placebo-controlled trials (–59% versus –53%; P = 0.24; Figure 4A) and was associated with significantly more FGF23 reduction in the active-controlled trials (–76% versus –64%; P = 0.03; Figure 4B).

DISCUSSION
This secondary analysis of etelcalcetide clinical trials offers new evidence relevant to our understanding of the pathogenesis and management of sHPT in patients receiving hemodialysis. Etelcalcetide markedly reduced FGF23 concentrations compared with placebo and also more than cinacalcet. The magnitude of the FGF23-lowering effect was largest among patients with the
Table 1. Baseline demographics and laboratory values by baseline PTH strata for etelcalcetide- or placebo-treated subjects

|                          | Entire cohort | PTH <600 pg/mL | PTH 600–1000 pg/mL | PTH >1000 pg/mL |
|--------------------------|--------------|----------------|-------------------|----------------|
|                          | ETL (n = 509) | Placebo (n = 514) | ETL (n = 172) | Placebo (n = 169) | ETL (n = 225) | Placebo (n = 233) | ETL (n = 112) | Placebo (n = 112) |
| Age (years)              | 58.4 ± 14.6 | 58.1 ± 14.3 | 60.5 ± 13.8 | 59.4 ± 14.2 | 58.1 ± 14.4 | 58.2 ± 14.3 | 55.6 ± 15.8 | 55.8 ± 14.1 |
| Sex (female), n (%)      | 196 (38.5) | 209 (40.7) | 68 (39.5) | 63 (37.3) | 83 (36.9) | 88 (37.8) | 45 (40.2) | 58 (51.8) |
| Race, n (%)              |              |                |                |                |                |                |                |                |
| White                    | 336 (66.0) | 344 (66.9) | 114 (66.3) | 101 (59.8) | 147 (65.3) | 160 (68.7) | 75 (67.0) | 83 (74.1) |
| Black                    | 136 (26.7) | 149 (29.0) | 48 (27.9) | 58 (34.3) | 59 (26.2) | 67 (28.8) | 29 (25.9) | 24 (21.4) |
| Asian                    | 18 (3.5) | 9 (1.8) | 2 (1.2) | 4 (2.4) | 11 (4.9) | 4 (1.7) | 5 (4.5) | 1 (0.9) |
| Other                    | 10 (2.0) | 6 (1.2) | 3 (1.7) | 3 (1.8) | 4 (1.8) | 0 (0.0) | 3 (2.7) | 3 (2.7) |
| Dialysis vintage (years), n (%) |        |                |                |                |                |                |                |                |
| 0–1                      | 60 (11.8) | 67 (13.0) | 27 (15.7) | 23 (13.6) | 29 (12.9) | 30 (12.9) | 4 (3.6) | 14 (12.5) |
| 1–5                      | 247 (48.5) | 245 (47.7) | 92 (53.5) | 95 (56.2) | 105 (46.7) | 108 (46.4) | 50 (44.6) | 42 (37.5) |
| >5                       | 202 (39.7) | 202 (39.3) | 53 (30.8) | 51 (30.2) | 91 (40.4) | 95 (40.8) | 58 (51.8) | 56 (50.0) |
| PTH (pg/mL)              | 724 (552–949) | 716 (557–982) | 505 (459–552) | 500 (453–557) | 771 (671–877) | 759 (682–878) | 1281 (1113–1587) | 1244 (1094–1545) |
| Ca (mg/dL)               | 9.6 ± 0.7 | 9.7 ± 0.7 | 9.6 ± 0.6 | 9.6 ± 0.5 | 9.6 ± 0.7 | 9.7 ± 0.7 | 9.7 ± 0.6 | 9.7 ± 0.7 |
| P (mg/dL)                | 5.9 ± 1.6 | 5.8 ± 1.5 | 5.5 ± 1.4 | 5.4 ± 1.4 | 5.9 ± 1.7 | 5.9 ± 1.5 | 6.2 ± 1.7 | 6.3 ± 1.6 |
| Ca × P (mg·g/L²)         | 56.3 ± 15.4 | 56.0 ± 15.2 | 52.7 ± 13.2 | 51.0 ± 13.7 | 57.2 ± 16.0 | 57.3 ± 14.5 | 60.2 ± 16.3 | 60.9 ± 16.6 |
| Vitamin D dose (µg/week) | 16.2 ± 13.7 | 15.3 ± 14.4 | 15.4 ± 13.0 | 15.7 ± 17.5 | 16.2 ± 13.6 | 15.2 ± 12.9 | 17.6 ± 15.4 | 14.8 ± 11.5 |
| BSAP (µg/L)              | 30.4 ± 26.8 | 33.1 ± 33.6 | 20.3 ± 11.0 | 22.9 ± 11.8 | 28.6 ± 20.2 | 30.0 ± 17.1 | 48.7 ± 41.5 | 54.5 ± 60.9 |
| FGF23 (pg/mL)            | 4206 (1070–15 061) | 3312 (816–12 431) | 2677 (744–10 711) | 1483 (616–6186) | 5437 (1101–18 301) | 3819 (1189–12 586) | 5844 (1842–21 061) | 5509 (1222–21 431) |

Values are reported as mean ± standard deviation or median (quartile 1, quartile 3) unless stated otherwise. Conversion factors for units: Ca in mg/dL to mmol/L × 0.2495; P in mg/dL to mmol/L × 0.3229.

PTH, parathyroid hormone; ETL, etelcalcetide; Ca, calcium; P, phosphate; BSAP, bone-specific alkaline phosphatase; FGF23, fibroblast growth factor-23.
Table 2. Effects of etelcalcetide versus placebo on mineral metabolites overall and by baseline PTH strata

| Mineral metabolites | Entire cohort | PTH <600 pg/mL | PTH 600–1000 pg/mL | PTH 1000 pg/mL |
|---------------------|--------------|----------------|-------------------|---------------|
| ETL                 | Placebo      | ETL Placebo    | ETL Placebo       | ETL Placebo   |
| (n = 514)           | (n = 172)    | (n = 225)      | (n = 112)          | (n = 112)     |
| PTH (% change) a    | 56.3 ± 6     | 54.2 ± 6       | 51.8 ± 6          | 55.5 ± 6     |
| Ca (% change) a     | 7.0 ± 0.4    | 6.0 ± 0.6      | 7.5 ± 0.6         | 6.7 ± 0.6    |
| P (% change) a      | 8.7 ± 1.4    | 7.5 ± 1.0      | 8.6 ± 1.0         | 8.7 ± 1.0    |
| Ca × P (% change) b| 15.1 ± 1.3   | 15.7 ± 1.3     | 16.2 ± 1.3        | 15.1 ± 1.3   |
| FGF23 (% change) b  | 56.1 (7.1)   | 42.8 (17.0)    | 44.3 (7.9, 68.3)  | 35.9 (68.3)  |
| ETL dose (mg/week) c| 21.5 ± 13.4  | 21.5 ± 13.4    | 21.5 ± 13.4       | 21.5 ± 13.4  |

Mean ± SE of change from baseline during the efficacy assessment period of Weeks 20–27. Percent change in baseline FGF23 and ETL dose values <0.5 were rounded to zero.

**Mean (±SE)**

**ETL dose (mg/week)**

ETL, etelcalcetide; Ca, calcium; P, phosphate; SE, standard error; FGF23, fibroblast growth factor-23.

aMean ± SE of change from baseline during the efficacy assessment period of Weeks 20–27.

bMean ± SE of change from baseline during the efficacy assessment period of Weeks 20–27.

cPotential mediators through which calcimimetics reduce FGF23. The candidate factors we examined included PTH, calcium, phosphate and bone turnover markers. While PTH, calcium and phosphate were associated with baseline FGF23, etelcalcetide-mediated reductions in FGF23 were associated with reductions of calcium, phosphate and calcium × phosphate product, but, remarkably, not with changes in PTH; associations of FGF23 reduction with markers of bone turnover were of borderline and inconsistent significance. The significant relations among changes in FGF23 with changes in calcium, phosphate and calcium × phosphate could be interpreted as suggesting that osteocytes may respond to total mineral ion load. This is supported by synergistic stimulation of FGF23 by calcium and phosphate in a double knockout mouse lacking both PTH and the calcium-sensing receptor [39–41]. The lack of association between PTH reduction and changes in FGF23 in the current analysis is also consistent with prior studies of cinacalcet in which reductions in FGF23 were unrelated to changes in PTH, but instead correlated with changes in calcium and phosphate [20, 22]. Furthermore, in patients receiving dialysis who underwent subtotal parathyroidectomy, which acutely and drastically reduces PTH, postoperative decreases in FGF23 were most closely related to changes in calcium × phosphate product [42]. In another study of total parathyroidectomy, FGF23 changed minimally in patients who were treated postoperatively with calcitriol and calcium to maintain serum calcium [43].

In aggregate, these data suggest that calcium and phosphate are more important drivers of calcimimetic-induced FGF23 reduction than PTH or bone turnover markers. However, alternative interpretations are also possible. For example, more biological variability in PTH versus calcium and phosphate and more laboratory imprecision in PTH assays relative to calcium and phosphate assays might have obscured a relation between the magnitude of PTH and FGF23 reduction. In support of this hypothesis, the highest PTH stratum did experience the greatest
magnitude of FGF23 reduction (although this group also had the largest variations in serum calcium and phosphate). While it is presumed that PTH reduction is the mediator of etelcalcetide-induced reductions in calcium and phosphate, varying degrees of PTH resistance at the level of bone might also blur the relation between changes in PTH and changes in FGF23 [10, 27].

There also remains the possibility that calcimimetics might influence calcium and phosphate homeostasis (or FGF23 directly) via PTH-independent mechanisms mediated by direct effects on bone cells and bone turnover. Although the association with bone turnover markers was weak, this mechanism is plausible given that an investigational calcimimetic (AMG641) affected bone turnover in a uremic thyro-parathyroidectomized rat model in which PTH levels were maintained at a constant level by PTH infusion [44]. Finally, it is possible that while PTH is an important basal regulator of FGF23 [6, 26–29], its effects might be overwhelmed by concomitant changes in calcium and phosphate in the presence of a potent calcimimetic.

The second major aim of this study was to investigate the extent to which treatments that mitigate etelcalcetide-induced hypocalcemia might also lessen its efficacy to reduce FGF23 levels. In the trials, investigators were blinded to treatment and PTH levels but were able to monitor serial serum calcium levels for safety reasons. Treatment of calcium reduction was allowable but not mandated unless calcium decreased to <7.5 mg/dL or the patient developed symptomatic hypocalcemia. Potential interventions could include starting or increasing doses of calcitriol or vitamin D analogs, calcium supplements and calcium-based binders or increasing the dialysate calcium concentration. Overall, etelcalcetide reduced FGF23 by a median of at least 52% and as high as 82%. This might have occurred because patients who required calcium-raising interventions were likely those who had the largest reductions in serum calcium, and thus FGF23, in response to etelcalcetide. These results have potentially important clinical implications. They suggest that if FGF23 reduction is advanced as a therapeutic goal in the future, use of etelcalcetide could be a potent therapeutic. While etelcalcetide is associated with high rates of hypocalcemia by virtue of its known mechanism of action to suppress PTH, our data suggest that ancillary treatments to abrogate symptomatic hypocalcemia will not fully offset the FGF23-lowering effects of etelcalcetide.

Table 3. Pearson correlation coefficients between percent changes in FGF23 and other bone mineral markers

| Bone mineral markers                      | Placebo-controlled | Head-to-head |
|-------------------------------------------|---------------------|--------------|
|                                           | Etelcalcetide       | Placebo      | Etelcalcetide | Cinacalcet |
| PTH                                       | -0.08               | 0.01         | -0.02        | 0.13       |
| Calcium                                   | 0.52                | 0.06         | 0.46         | 0.34       |
| Phosphate                                 | 0.34                | 0.48         | 0.56         | 0.51       |
| Calcium × phosphate                       | 0.61                | 0.50         | 0.66         | 0.60       |
| Bone-specific alkaline phosphatase        | -0.23               | -0.27        | -0.17        | -0.15      |
| Collagen type I cross-linked C-telopeptide| -0.11               | 0.00         | -0.02        | 0.02       |

Bold numbers connote statistical significance of P < 0.01.

FGF23 = fibroblast growth factor-23; PTH, parathyroid hormone.
The strengths of this study include its large and diverse clinical trial populations, frequent central measurements of PTH, calcium, phosphate and markers of bone turnover and protocol-directed titration of the interventions. In addition to these strengths, certain limitations may influence our interpretation of the data. Although PTH, calcium and phosphate were assessed at several points throughout the trials, we only measured FGF23 at baseline and at Week 27. It is also unclear how the results would have differed had we included a population with shorter dialysis vintage and less severe sHPT at baseline. Due to the complexity of standardizing individual patients’ total calcium dose across the multiple different preparations they could have received, we chose to dichotomize calcium supplementation and the other concomitant medications into two groups defined by whether their dose was or was not increased. Results below the figure panels summarize between-group comparisons stratified by the change in vitamin D dosing.
enabled our hypothesis-generating analyses that otherwise would have been limited had these strategies been tightly regulated by protocol rather than at the discretion of investigators.

The evaluation of changes in FGF23 was a prespecified exploratory analysis of the placebo-controlled and active-controlled etelcalcetide clinical trials, but the studies were not primarily designed to explore the effect of etelcalcetide on FGF23. We speculate that etelcalcetide could induce even more pronounced reductions in FGF23 if drug titration were motivated by FGF23 rather than PTH targets. Since our results focused only on biochemical endpoints, additional studies are also needed to determine the effect on clinical outcomes of etelcalcetide-induced reduction in FGF23.

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AUTHORS’ CONTRIBUTIONS

M.W., G.A.B., G.M.C., K.C., B.F., S.M.M., Y.S., H.T., M.V. and R.O. were involved in conception and study design. G.A.B., G.M.C., S.M.M. and R.O. acquired the data. G.A.B., G.M.C., K.C., B.F., S.M.M., Y.S., H.T. and R.O. analysed and interpreted the data. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

M.W. has received consultancy fees from Akebia, AMAG Pharmaceuticals, Amgen, Diasorin and Sanofi and grants from Shire. G.B. has received consultancy fees from Akebia, Amgen, AstraZeneca, Daiichi-Sankyo, Keryx, Kirin, Omeros, Ono and OPKO; participated in the speakers bureau for OPKO and received research grants from Keryx. G.C. is on the Board of Directors of Satellite Healthcare; owns stock/stock options in Ardelyx, Cricket Health, DirecT, DxNow, Eliaz Therapeutics, Outset Medical, Physiowave and Puracath Medical; has received an institutional grant from Amgen and Janssen; has received consulting fees from AMAG Pharmaceuticals, Gilead and Sanaft; has Data and Safety Monitoring Board membership for Bayer, Bristol-Myers Squibb and ReCor and is on the Trial Steering Committee for Akebia and AstraZeneca. S.M.M. reports grants from Chugai, the National Institutes of Health and Department of Veterans Affairs and personal fees from Sanofi/Genzyme and Amgen. H.T. was an employee and stockholder of Amgen at the time the study was conducted and during initial drafting of the manuscript. M.V. has received grants from Amgen, AbbVie, FMC and Sanofi and personal fees from Amgen, Baxter, FMC and Otsuka. R.O. has received grants from Amgen, Chiesi, Fresenius and Sanoﬁ and participated in speakers bureaus for Amgen, Astellas,
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