Effects of Phosphate Binders in Moderate CKD

Geoffrey A. Block,* David C. Wheeler,† Martha S. Persky,* Bryan Kestenbaum,‡ Markus Ketteler,§ David M. Spiegel,‖ Matthew A. Allison,¶ John Asplin,** Gerard Smits,* Andrew N. Hoofnagle,‡ Laura Kooyenga,* Ravi Thadhani,†† Michael Mannstadt,‖ Myles Wolf,‡‡ and Glenn M. Chertow§§

*Denver Nephrology, Denver, Colorado; †Centre for Nephrology, Royal Free Campus, University College London Medical School, London, United Kingdom; ‡University of Washington, Seattle, Washington; §Nephrologische Klinik, Klinikum Coburg, Coburg, Germany; ‖University of Colorado, Denver, Colorado; ¶University of California, San Diego, California; **Litholink Corp, Chicago, Illinois; ††Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; ‡‡University of Miami, Miami, Florida; and §§Stanford University School of Medicine, Palo Alto, California

ABSTRACT
Some propose using phosphate binders in the CKD population given the association between higher levels of phosphorus and mortality, but their safety and efficacy in this population are not well understood. Here, we aimed to determine the effects of phosphate binders on parameters of mineral metabolism and vascular calcification among patients with moderate to advanced CKD. We randomly assigned 148 patients with estimated GFR=20–45 ml/min per 1.73 m² to calcium acetate, lanthanum carbonate, sevelamer carbonate, or placebo. The primary endpoint was change in mean serum phosphorus from baseline to the average of months 3, 6, and 9. Serum phosphorus decreased from a baseline mean of 4.2 mg/dl in both active and placebo arms to 3.9 mg/dl with active therapy and 4.1 mg/dl with placebo (P=0.03). Phosphate binders, but not placebo, decreased mean 24-hour urine phosphorus by 22%. Median serum intact parathyroid hormone remained stable with active therapy and increased with placebo (P=0.002). Active therapy did not significantly affect plasma C-terminal fibroblast growth factor 23 levels. Active therapy did, however, significantly increase calcification of the coronary arteries and abdominal aorta (coronary: median increases of 18.1% versus 0.6%, P=0.05; abdominal aorta: median increases of 15.4% versus 3.4%, P=0.03). In conclusion, phosphate binders significantly lower serum and urinary phosphorus and attenuate progression of secondary hyperparathyroidism among patients with CKD who have normal or near-normal levels of serum phosphorus; however, they also promote the progression of vascular calcification. The safety and efficacy of phosphate binders in CKD remain uncertain.


CKD is a significant public health concern; roughly 13% of the US population has an estimated GFR (eGFR) below 60 ml/min per 1.73 m² or albuminuria.¹ The risks of death and cardiovascular disease in CKD are not fully explained by associated diabetes, hypertension, and other conventional risk factors.² With declining kidney function, serum phosphorus concentration increases but generally remains within the normal range until late in stage 4 or 5 CKD. A normal or near-normal serum phosphorus concentration is maintained at the expense of elevated levels of the phosphaturic hormones parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23).³⁴ Serum concentrations of phosphorus and hormones responsible for its regulation have been implicated as putative cardiovascular risk factors.⁵⁻⁹

Received March 2, 2012. Accepted May 10, 2012.
Published online ahead of print. Publication date available at www.jasn.org.
Correspondence: Dr. Geoffrey A. Block, Denver Nephrology, 130 Rampart Way, Suite 300b, Denver, CO 80230. Email: gablock@denverneph.net
Copyright © 2012 by the American Society of Nephrology
Three intestinal phosphate binders are approved for the treatment of hyperphosphatemia in patients with ESRD in the United States—calcium acetate (Phoslo; Fresenius), lanthanum carbonate (Fosrenol; Shire), and sevelamer carbonate (Renvela; Genzyme)—but none are approved for use in patients with CKD not on dialysis.10 Because higher serum phosphorus concentrations—even within the population reference range—are associated with mortality, some have proposed the use of phosphate binders to lower serum phosphorus in this population.11 We undertook this pilot clinical trial to determine the safety and efficacy of phosphate binders in patients with moderate CKD and normal or near-normal serum phosphorus concentrations.

RESULTS

Enrollment, Baseline Characteristics, and Study Conduct

Figure 1 shows patient disposition. Baseline characteristics (Table 1) were similar across treatment groups. Mean doses of study medication were 5.9 g/d calcium acetate (1.5 g elemental calcium), 2.7 g/d lanthanum carbonate, and 6.3 g/d sevelamer carbonate. Average adherence was >85% in each of the treatment arms. The median duration of follow-up was 249 days. Changes in selected on-study biochemical parameters are shown in Supplemental Table 1. Table 2 shows adverse effects. Gastrointestinal side effects were more common with lanthanum but were generally mild and of limited duration. Only one related serious adverse event (hypothyroidism in placebo group) was observed during the study.

Primary Endpoint

Change in mean serum phosphorus was significantly different between active- and placebo-treated groups (P=0.03). Mean serum phosphorus declined from 4.2 to 3.9 mg/dl in patients treated with phosphate binders and was unchanged in placebo-treated patients (Figure 2A). Results in the individual active treatment arms show statistically significant reductions versus placebo only in the lanthanum carbonate arm (P=0.04), and they are shown in Supplemental Figure 1A.

Secondary Endpoints

Urine Phosphorus

Change in mean urine phosphorus excretion was significantly different between active- and placebo-treated groups (P=0.002) (Figure 2B). Daily urine phosphorus excretion was reduced by 22% with active therapy and unchanged with placebo. Similar results were observed for the mean fractional excretion of phosphorus, which decreased (32%–26%) with active treatment and was unchanged (31%–32%) with placebo (P<0.0001). All active treatment arms showed similar reductions in phosphorus excretion (Supplemental Figure 1B).

PTH and 1,25 Dihydroxy Vitamin D

Change in PTH was significantly different between active- and placebo-treated groups (P=0.002). PTH concentrations remained stable with active therapy and increased by 21% in patients on placebo (P=0.002) (Figure 2C). 1,25 dihydroxy vitamin D concentration was significantly reduced with active therapy (P=0.004) (Supplemental Table 1). Effects on PTH and 1,25 dihydroxy vitamin D seemed to differ by binder type; patients treated with calcium acetate experienced a larger relative decline, whereas the effects of lanthanum and sevelamer relative to placebo were less pronounced (Supplemental Figure 1C and Supplemental Table 1).

FGF23

Plasma C-terminal FGF23 concentrations were markedly elevated in both treatment arms at baseline relative to population norms. There was no significant difference in the change between active and placebo in plasma C-terminal FGF23 (P=0.67) (Figure 2D). Findings using the intact FGF23 assay measured at baseline and end of study similarly showed no difference between all active and all placebo (P=0.42). The effects on intact FGF23 seemed to differ by binder type; patients treated with sevelamer carbonate experienced a significant decrease in intact FGF23 (median decrease=24 pg/ml, P=0.002 versus placebo), whereas those patients treated with calcium acetate had a significant increase (median increase=28 pg/ml,
P=0.03 versus placebo) and those patients treated with lanthana-
um carbonate were no different compared with placebo ($P=0.30$) (Supplemental Figure 2, D and E).

**Vascular Calcification and Bone Mineral Density**

Assessment of change in vascular calcification was available in a subset of 96 patients (60 active and 36 placebo). No patient with a zero calcium score at baseline developed a positive score during follow-up. Among patients with nonzero calcium scores at baseline ($n=81$), active therapy resulted in significant increases in median annualized percent change of coronary artery ($P=0.05$) (Figure 3A) and abdominal aorta ($P=0.03$) (Figure 3B) calcium volume scores. Using the Hokanson square-root follow-up criterion, 20 of 52 (38%) phosphate

---

**Table 1. Baseline characteristics of study participants**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Active ($n=88$)</th>
<th>All Placebo ($n=57$)</th>
<th>Lanthanum ($n=28$)</th>
<th>Sevelamer ($n=30$)</th>
<th>Calcium ($n=30$)</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50%</td>
<td>49%</td>
<td>54%</td>
<td>50%</td>
<td>47%</td>
<td>1.00</td>
</tr>
<tr>
<td>Caucasian</td>
<td>81%</td>
<td>79%</td>
<td>82%</td>
<td>80%</td>
<td>80%</td>
<td>1.00</td>
</tr>
<tr>
<td>African-American</td>
<td>10%</td>
<td>11%</td>
<td>7%</td>
<td>7%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>age (years ± SD)</td>
<td>68±11</td>
<td>65±12</td>
<td>70±10</td>
<td>66±12</td>
<td>68±12</td>
<td>0.72</td>
</tr>
<tr>
<td>body mass index (kg/m² ± SD)</td>
<td>31±9</td>
<td>32±9</td>
<td>30±7</td>
<td>33±8</td>
<td>30±5</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**Comorbidity**

| diabetes                      | 56%                | 58%                  | 57%                | 53%                | 57%              | 0.86 |
| CHF                           | 27%                | 11%                  | 25%                | 23%                | 33%              | 0.02 |
| CAD                           | 26%                | 14%                  | 21%                | 27%                | 30%              | 0.10 |
| HTN                           | 98%                | 100%                 | 100%               | 97%                | 97%              | 0.52 |
| MI                            | 12%                | 5%                   | 4%                 | 3%                 | 10%              | 0.25 |
| PVD                           | 24%                | 19%                  | 21%                | 20%                | 30%              | 0.55 |
| CVA                           | 8%                 | 4%                   | 14%                | 3%                 | 7%               | 0.48 |
| secondary                     | 72%                | 72%                  | 79%                | 60%                | 77%              | 1.00 |
| hyperparathyroidism           |                    |                      |                    |                    |                  |      |
| nontraumatic fracture         |                    |                      |                    |                    |                  |      |

**Laboratory characteristics**

| serum phosphorus (mg/dl ± SD)  | 4.2±0.4            | 4.2±0.4              | 4.2±0.4            | 4.2±0.4            | 4.2±0.4          | 0.47 |
| eGFR (ml/min ± SD)            | 32±8.1             | 30±8.5               | 33±7.9             | 32±9.1             | 30±7.1           | 0.32 |
| intact PTH (pg/ml ± SD)       | 78±56              | 91±52                | 87±54              | 70±56              | 76±58            | 0.05 |
| C-terminal FGF23 (RU/ml ± IQR) | 227 (135–322)      | 211 (140–278)        | 230 (126–368)      | 230 (143–362)      | 219 (157–287)    | 0.59 |
| intact FGF23 (pg/mL ± IQR)    | 120 (88–176)       | 119 (95–169)         | 111 (65–194)       | 147 (95–202)       | 114 (90–152)     | 0.79 |
| 1,25 dihydroxy vitamin D³      | 25.7±9.4           | 27.2±10.3            | 26.9±10.0          | 24.7±10.3          | 25.5±8.1         | 0.69 |
| coronary artery calcium volume score | 262 (87–863) | 225 (18–737) | 216.5 (102–1694) | 362.5 (113–940.5) | 130 (13–645) | 0.33 |
| thoracic aorta calcium volume score | 583 (165–2282) | 496 (58–1539) | 1609 (98–5030) | 536 (351–2147) | 511 (50–2145) | 0.52 |
| abdominal aorta calcium volume score | 1551 (326–5377) | 1693 (212–6861) | 4035 (200–8578) | 1367 (519–3234) | 1468 (16–4328) | 0.70 |
| L2 to L4 bone mineral density (g/cm²) | 111±34 | 108±45 | 99±22 | 111±29 | 120±42 | 0.45 |
| total urinary excretion of phosphorus (mg ± SD)³,d | 757±444 | 805±359 | 747±606 | 769±350 | 727±354 | 0.20 |
| fractional excretion of phosphorus (% ± SD)³ | 0.32±0.12 | 0.31±0.10 | 0.30±0.13 | 0.33±0.12 | 0.33±0.11 | 0.48 |
| total urinary excretion of calcium (mg ± SD)³,d | 55±42 | 61±47 | 53±40 | 56±43 | 58±43 | 0.69 |

CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebro-vascular disease; HTN, hypertension; MI, myocardial infarction; PVD, peripheral vascular disease.

*Significance. Fisher exact test for all active versus all placebo for binary measures and Wilcoxon rank sum tests for continuous measures.

Mean.

Median (IQR).

Twenty-four hour urine measurements were adjusted for adequacy of collection using the mean of each individual urinary creatinine excretion.

---

www.jasn.org | CLINICAL RESEARCH


1409
binder-treated patients experienced progression of coronary artery calcification compared with 5 of 29 (17%) placebo-treated patients \((P=0.03)\). There was no significant difference in the thoracic aorta calcium score by treatment status (Figure 3C). Phosphate binder-treated patients showed significant improvement \((P=0.03)\) in annualized change in bone mineral density (BMD) (Figure 3D).

The apparent adverse effects on vascular calcification and salutary effects on BMD were most pronounced among patients randomized to calcium acetate (Supplemental Figures 1 and 2).

**DISCUSSION**

This randomized placebo-controlled pilot clinical trial shows that the use of phosphate binders in patients with nondialysis-requiring CKD reduces urinary phosphorus excretion (a surrogate of intestinal phosphate absorption) and attenuates progressive secondary hyperparathyroidism. The effect on serum phosphorus, although statistically significant, was modest, despite relatively high-dose therapy and a significant effect on urinary phosphorus excretion. Active therapy resulted in progression of vascular calcification, particularly among patients randomized to calcium acetate.

Higher serum phosphorus concentrations within the normal range are associated with cardiovascular events and mortality in persons with CKD as well as persons with normal or near-normal kidney function.\(^{12-14}\) For example, among 3368 participants in the Framingham Offspring Study who were free of cardiovascular or kidney disease followed for 16.1 years, a serum phosphorus \(>3.5\) mg/dl was associated with a 55% higher risk for a first cardiovascular event.\(^{12}\) In the Atherosclerosis Risk in Communities Study \((n=15,732)\), the corresponding multivariable-adjusted relative risk of death was increased by 14% \((P<0.001)\).\(^{15}\) More recently, a reanalysis of the Ramipril in Nondiabetic Renal Disease study showed that patients with serum phosphorus \(>3.5\) mg/dl were more than two times as likely to experience progression to ESRD or a doubling of serum creatinine. Moreover, higher serum phosphorus attenuated the renoprotective benefit of ramipril.\(^{16}\)

The lack of a larger change in measured serum phosphorus is surprising given the relatively large reduction in urine phosphorus excretion, although similar findings have been reported in the work by Oliveira et al.\(^{17}\) A single determination of serum phosphorus may not accurately reflect the time-averaged value. In normal, healthy men given phosphorus-supplemented diets, single, fasting morning serum phosphorus concentrations grossly underestimate 24-hour exposure to phosphorus and fail to distinguish between low and high dietary phosphorus intake.\(^{18}\) Our results suggest that, in moderate to advanced CKD, the serum phosphorus concentration may be a relatively poor marker of phosphate binder efficacy or adherence.

Intestinal absorption of phosphate is highly dependent on the nature and absolute amount of ingested phosphorus and the expression of the intestinal sodium–phosphorus cotransporter type 2b (NPT2b). Heterozygous NPT2b knockout mice show a 50% reduction in receptor expression but have identical serum phosphorus concentrations compared with wild-type mice.\(^{19}\) Mice with an inducible conditional knockout of NPT2b also maintain serum phosphate concentrations, possibly the result of compensatory increases in paracellular intestinal phosphate absorption and renal expression of NPT2a and NPT2c.\(^{4,20}\) If phosphate binders were to upregulate expression of intestinal NPT2b and enhance paracellular transport, the efficacy of binders could be limited, particularly after missed doses. Clinical trials of niacin and niacin derivatives, which are known to inhibit the expression of intestinal NPT2b and kidney NPT2a, have shown significant reductions in serum phosphorus in patients with mild to moderate CKD.\(^{21}\)

FGF23 seems to be a sensitive marker of impaired kidney function, with elevations preceding detectable increases in serum creatinine.\(^{22}\) Circulating FGF23 concentrations are strongly associated with progression to ESRD and mortality, and higher concentrations of FGF23 have recently been shown to cause left ventricular hypertrophy in rats.\(^9\) It had been assumed that reduction in intestinal phosphate absorption
would decrease FGF23, although shorter-term phosphate binder intervention failed to show any reduction in FGF23, despite yielding significant reductions in urinary phosphorus excretion. Whether our disparate findings with C-terminal and intact FGF23 reflect better precision with the intact assay or true differential effects on both molecules is unknown. A similarly discrepant result between the C-terminal and intact FGF23 assays was described in 66 subjects with normal kidney function, in whom dietary phosphate restriction reduced intact FGF23 but had no effect on C-terminal FGF2. Our results confirm the results in the works by Olivieri et al. and Yilmaz et al. Despite what seems to represent similar efficacy in terms of intestinal phosphate binding, intestinal phosphate binders seem to exert disparate effects on serum concentrations of FGF23. Treatment with phosphate binders resulted in significant progression of vascular calcification in coronary arteries and the abdominal aorta. Assessment of coronary artery calcification (CAC) progression using the square-root follow-up method in the work by Hokanson et al. has been shown to be the best method to predict mortality in a large cohort of asymptomatic patients. These results support the conceptual risk of inducing positive calcium balance in patients with CKD,
where disordered mineral metabolism results in dystrophic calcification. Short-term calcium balance studies suggest that the provision of 2000 mg/d elemental calcium in patients with CKD stage 3 results in substantial net positive calcium balance. However, progression of vascular calcification was evident not only in patients receiving calcium acetate, suggesting that use of other phosphate binders in CKD might also have unexpected and potentially, adverse consequences. It is possible that noncalcium-containing phosphate binders also enhance the availability of free intestinal calcium and result in a positive calcium balance. Although our primary analyses compared all actively treated groups with placebo, subgroup analyses suggested that calcium- and noncalcium-containing phosphate binders exert differential effects on PTH, FGF23, and mineralization of the bone and vasculature. In contrast, the work by Russo et al. studied 2-year

Figure 3. Vascular calcification and bone mineral density changes on study by treatment arm. Percent change in (A) median (IQR) annualized total coronary artery, (B) abdominal aorta, and (C) thoracic aorta calcium volume scores among active- and placebo-treated patients. (D) Median (IQR) percent change in annualized BMD among active- and placebo-treated patients. A trained reader examined each region of interest with exclusion of vertebral abnormalities.
progression of calcification in 90 patients with CKD stage 3/4 randomized to a low phosphate diet, sevelamer carbonate, or calcium carbonate. Patients receiving calcium carbonate experienced marked progression of CAC; however, in their analysis, subjects given a low phosphate diet alone had rates of CAC progression similar to those subjects receiving calcium, whereas our placebo-treated subjects experienced little or no progression in CAC.

This study has several strengths, including the relatively long study duration, blinding of participants and investigators, and excellent overall adherence. This study also has several important limitations. This study was a single-center study, which served to diminish any impact of regional or cultural differences of diet on serum phosphorus concentrations but may have limited the generalizability of our findings to other geographic regions. We may have observed larger or less variable effects of phosphate binder therapy on serum phosphorus had we standardized the time of day at which serum phosphorus was measured. We made no attempts to standardize intake of phosphorus, calcium, or other dietary components, and we made no attempt to standardize sun exposure or limit or match enrollment by season.

In summary, treatment with phosphate binders in patients with moderate to advanced CKD and normal or near-normal serum phosphorus concentrations significantly lowered serum and urinary phosphorus and attenuated progression of secondary hyperparathyroidism, but it resulted in progression of coronary artery and abdominal aortic calcification. The safety and efficacy of phosphate binders in patients with CKD and normal serum phosphorus remain uncertain.

CONCISE METHODS

Study Setting
This trial was a randomized, double blind, placebo-controlled trial of phosphate binders in patients with moderate to advanced CKD. Recruitment at a single study center (Denver Nephrologists, Denver, CO) began in February of 2009 and continued until September of 2010. Active drug and matching placebo were supplied by the three manufacturers. The protocol was developed by an independent steering committee with full authority over study design and conduct. A four-member independent data and safety monitoring board reviewed safety data. The study was approved by the Schulman Institutional Review Board (Cincinnati, OH) and registered at ClinicalTrials.gov (NCT 00785629).

Study Population
We obtained written informed consent from all patients. Patients were identified using an electronic medical record to capture all consecutive patients seen in the study center clinic offices who met preliminary study criteria. Patients were required to have an eGFR using the Modification of Diet in Renal Disease study equation between 20 and 45 ml/min per 1.73 m², a serum phosphorus ≥3.5 and <6.0 mg/dl, and willingness to avoid any intentional change in diet. Key exclusion criteria included use of any medication for the purpose of binding intestinal phosphate, use of any active vitamin D or the calcimimetic cinacalcet, intact PTH ≥500 pg/ml, or uncontrolled hyperlipidemia.

Study Design
An independent statistician performed randomization using SAS version 9.1. A random seed was set, and data were generated using a Data Step with a sequence of uniform random deviates. Patients were block-randomized into one of three treatment arms, calcium acetate, lanthanum carbonate, and sevelamer carbonate, in a 1:1:1 fashion. We then randomly assigned patients within each treatment arm to receive either active medication or matching placebo (3:2). Statistical comparisons were made between the two treatment groups—all active versus all placebo. We stratified randomization by diabetic status. Sealed envelopes were opened at the study center by a staff member not involved in the conduct of the trial. All study medication was released by a single unblinded staff member in bottles identified by a unique identification number. All clinical personnel, data analysts, and participants remained blinded to study treatment assignment. We administered 1 or 2 units per meal of study medication (calcium acetate=667 mg, lanthanum carbonate=500 mg, and sevelamer carbonate=800 mg) based on screening serum phosphorus below or above 4.5 mg/dl. We increased study medication at each visit if the serum phosphorus remained >3.5 mg/dl to a maximum dose of 4 calcium acetate per meal (2668 mg), 3 lanthanum carbonate per meal (1500 mg), or 4 sevelamer carbonate per meal (3200 mg). We gave all patients cholecalciferol (1000 IU daily). Patients underwent laboratory testing and event assessment at week 2 and months 1, 2, 3, 6, and 9. We assessed adherence with pill counts at each study visit.

Study Assessments

Laboratory Assessments
All clinical chemistry analyses were performed by Quest Diagnostics (Denver, CO). We obtained samples in a nonfasting state but generally at the same time of day. Timed and spot urine chemistry measurements were performed by Litholink Corp. (Chicago, IL). Protein intake was estimated using the equation 6.25×(urine urea nitrogen in grams+30 mg/kg)+1 g/g proteinuria×5 g.29 Phosphorus intake was estimated using the equation 11.8×protein intake in grams+78.30

1,25-Dihydroxy vitamin D assays were performed using a commercially available radioimmunoassay (DiaSorin Inc., Stillwater, MN). We measured FGF23 in plasma using the second generation C-terminal ELISA assay (Immutopics, San Clemente, CA); we also measured intact FGF23 at baseline and month 9 using a sandwich immunoassay (Kainos, Japan).

Imaging Assessments
We used the GE-Imatron C150 scanner at baseline and month 9 using a standard protocol as previously described.31 We defined atherosclerotic calcium as a plaque area≥1 mm² with a density of ≥130 Hounsfield units. Total calcium volume score was derived by the sum of all lesion volumes in cubic millimeters.32 The thoracic aorta was defined as the segment from the aortic root to the diaphragm, whereas
the abdominal aorta was the segment from the diaphragm to the iliac bifurcation. A single experienced investigator, blinded to treatment assignment, performed all image assessments.

Lumbar BMD was determined using abdominal computed tomography scans with a calibrated phantom of known density (Image Analysis QCT 3D PLUS, Columbia, KY). Measurements of BMD were performed in a 5-mm-thick slice of trabecular bone from each vertebra (L2 to L4) at baseline and month 9.

Endpoints
The primary endpoint was change in serum phosphorus from baseline (the average of the last two measures in screening) to the mean of months 3, 6, and 9 among all active- versus all placebo-treated patients. Secondary laboratory endpoints included changes in serum PTH, FGF23, 1,25 dihydroxy vitamin D, urine phosphorus, and fractional excretion of phosphorus. Secondary clinical endpoints included change in coronary artery, thoracic and abdominal aorta calcium volume scores, and change in lumbar BMD. Comparisons of individual treatment arms versus placebo were considered exploratory.

Sample Size Determination
We estimated that a sample size of 150 (90 active versus 60 placebo) would provide >80% power to detect a change in serum phosphorus $\geq 0.4$ mg/dl between groups, with a two-sided $\alpha = 0.05$ and an anticipated dropout rate of 25%.

Statistical Analyses
We analyzed all data in accordance with the intent-to-treat principle comparing all actively treated patients with all placebo-treated patients. We imputed missing data using last observation carried forward. We used analysis of covariance to examine change in endpoints incorporating age, sex, race/ethnicity, diabetes, eGFR, and baseline values as covariates. Because of the association of race with PTH concentration, race/ethnicity was self-reported by subjects from a prespecified list including Caucasian, African-American, Hispanic or Latino, Asian, and American Indian, Alaskan Native, or Native Hawaiian/Pacific Islander, or Other. We used a Dunnett correction when comparing individual active arms with placebo. For the analysis of change in calcification, we included only patients with nonzero calcification at baseline. In companion analyses, we used the Hokanson criterion to gauge progression of vascular calcification.26 For the analysis of change in BMD, we additionally considered Quetelet's (body mass) index and history of nontraumatic fracture as covariates. We performed statistical analyses using SAS software version 9.2 (SAS Institute Inc., Cary, NC).

ACKNOWLEDGMENTS
The authors would like to acknowledge Stephanie Brillhart, MSCI, and Linda Loftin, NP, for their assistance in the conduct of the trial as the designated unblinded study representatives for study drug storage and assignment. The authors would also like to acknowledge the important contribution of our Data Safety and Monitoring Committee, led by the Chairman, Colin Baigent, FRCP. Members of this committee donated their time and expertise in providing oversight of the trial conduct. In addition to Dr. Baigent, committee members included Grahame Elder, Alistair Hutchison, FRCP, Jonathan Emberson, PhD, and Edmund Ng.

G.A.B., D.C.W., M.S.P., B.K., M.K., D.M.S., J.A., R.T., M.W., and G.M.C. participated in the design, analysis, interpretation, and manuscript preparation. G.S., M.A.A., A.N.H., and M.M. participated in data acquisition, analysis, interpretation, and manuscript preparation. L.K. participated in the design and data acquisition. G.A.B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding for this investigator-initiated study was provided by Shire, Inc., Fresenius NA, Genzyme, Inc., Denver Nephrologists, PC, Novartis, Inc., and Davita, Inc.

Funding entities had no role in the design, conduct, analysis, interpretation, or preparation of the manuscript. Each funding entity was permitted to review the manuscript for verification that no proprietary or confidential information was included.

DISCLOSURES
G.A.B. has received research grants from Amgen, Roche, Cytochroma, and CMD; received honoraria from Genzyme; has been on advisory boards or a consultant for Amgen, Genzyme, KAI, Ardevlyx, and Mitsubishi; and was a Medical Director for Davita. D.C.W. received research grants from Genzyme and Abbott and honoraria from Amgen, Fresenius, and Shire; and has been on the advisory board for KAI. M.S.P. has consulted for KAI. B.K. has received a research grant from Amgen. M.K. has received research grants from Amgen and Abbott; honoraria from Amgen, Abbott, Genzyme, FMC, Medice, and Shire; and payment for development of educational presentations from Amgen and Abbott; and has been a consultant for Amgen, Abbott, Genzyme, FMC, Medice, and Shire. D.M.S. has received research grants from Amgen and Keryx and honoraria from Amgen and Sanofi; has been on advisory boards for Affymax, Amgen, and Sanofi; and has been a consultant for Amgen. J.A. has been an employee of LabCorp and a consultant for Oxthera Corp. N.H. has received research grants from Waters and has been a consultant for Onconome. R.T. has received a research grant from Abbott; has been a consultant for Fresenius North America and Mitsubishi Tanabe; and has received honoraria from Shire. M.W. has received research grants from National Institutes of Health, Shire, Amgen, and Genzyme; has received honoraria from Abbott, Genzyme, and Shire; and has been a consultant for Abbott, Genzyme, Luftpold, Mitsubishi, Cytochroma, Biotrends, Ardevlyx, and Astellas. G.M.C. has received a research grant from National Institute of Diabetes and Digestive and Kidney Diseases, Amgen, and Reata; and has been an advisor for Ardevlyx. M.A.A., G.S., L.K., and M.M. have nothing to disclose.

REFERENCES


This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2012030223/-/DSSupplemental.