Background and objectives: Lanthanum carbonate (FOSRENOL®, Shire Pharmaceuticals) is an effective noncalcium, nonresin phosphate binder for the control of hyperphosphatemia in chronic kidney disease (CKD) stage 5 patients undergoing dialysis.

Design, setting, participants and measurements: A Phase 2, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of lanthanum carbonate in CKD stage 3 and 4 patients. Of 281 patients screened, 121 were randomized (2:1) to lanthanum carbonate or placebo (80 versus 41). The modified intent-to-treat population included 90 patients (56 versus 34); 71 (43 versus 28) completed the study. After run-in, when any current phosphate binders were discontinued and dietary counseling reinforced, patients with serum phosphorus >4.6 mg/dl received lanthanum carbonate (titrated up to 3000 mg/d) or matching placebo for 8 wk.

Results: At the end of treatment, 25 (44.6%) versus nine (26.5%) patients had serum phosphorus <4.6 mg/dl (difference 18.1%, $P_{<0.12}$) in the lanthanum carbonate and placebo groups, respectively. Statistically significant differences were observed between groups in change from baseline to end of treatment for serum phosphorus ($P_{<0.02}$), intact parathyroid hormone ($P_{<0.02}$), and urinary phosphorus excretion ($P_{<0.04}$). The safety profile and tolerability of lanthanum carbonate were similar to that of placebo.

Conclusions: Because <1% of phosphorus is in the extracellular fluid, serum measurements may not accurately reflect total body burden in patients with CKD stages 3 and 4. However, lanthanum carbonate is an effective phosphate binder in this patient population, with a safety profile and tolerability similar to that of placebo.

therapy and entered a 3- to 4-wk run-in period (treatment-naïve patients were also included), during which dietary phosphorus counseling was reinforced and serum phosphorus concentrations were assessed.

Patients with serum phosphorus concentrations >4.6 mg/dL (1.49 mmol/L) after 2 to 3 wk of run-in were randomized 1 wk later to receive lanthanum carbonate or matching placebo (2:1 ratio). Patients with serum calcium concentrations <8.0 mg/dL (2.0 mmol/L) at the baseline visit were withdrawn from the study and excluded from the modified intent-to-treat (ITT) population. Serum Pi, serum phosphorus. To convert mg/dL to mmol/L, multiply by 0.25. eGFR, estimated glomerular filtration rate.

Assessments
The safety population comprised all patients who received at least one dose of lanthanum carbonate or placebo and had at least one safety measurement. The modified intent-to-treat (mITT) population comprised all patients who received at least one dose of the study drug and had at least one postdose serum phosphorus measurement.

The study’s primary endpoint was the percentage of patients who had serum phosphorus concentrations ≤4.6 mg/dL after 8 wk of lanthanum carbonate or placebo treatment. Eighty-four patients (2:1 randomization) were required to complete the study to give 80% power (at α = 0.05) for a χ² (two-sided) test for proportions, given the assumptions of 23% for placebo and 57% for lanthanum carbonate (34% difference).

Secondary endpoints included changes in serum phosphorus, intact parathyroid hormone (iPTH) and calcium–phosphorus product (Ca × P product) from baseline, and safety and tolerability, compared with placebo.

Biochemical and hematologic parameters were measured. Serum iPTH was measured using the Immulite 2000 immunooassay (Diagnostic Products Corporation, Los Angeles, CA). Urine specimens were collected at baseline, week 4, and week 8. Adverse events (AEs) and serious adverse events (SAEs) were recorded.

Statistics
For the primary efficacy analysis, the percentages of patients in each treatment group (mITT population) with phosphorus concentrations ≤4.6 mg/dL were compared using Fisher’s exact test. For patients who discontinued treatment before the end of the study, the last available (i.e., at end of treatment) serum phosphorus value was used in the analysis. Observed-case data with 95% confidence intervals (CI) are presented along with end of treatment data in Figure 2.

Absolute changes in serum phosphorus concentrations from baseline to each visit were analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline assessment as a covariate. Again, for patients who discontinued treatment before the end of the study, the last available serum phosphorus value was used in the analyses. Data are reported as mean ± standard error of the mean (SEM), although where statistical comparisons between groups are presented, data refer to the least squares mean ± SEM. Similar analyses were undertaken for other serum and urinary parameters. Observed-case data are presented along with end of treatment data in Figures 3–5.
Patient Demographics

After screening, 121 patients met the entry criteria and were randomized (80 lanthanum carbonate, 41 placebo, Figure 1). The baseline characteristics of the safety population (N = 119) are shown in Table 1. Treatment groups were well matched. Twenty-nine patients were excluded from the mITT population because they did not have a postbaseline serum phosphorus value. The baseline characteristics of the mITT population (N = 90; 56 lanthanum carbonate, 34 placebo) were similar to those of the safety population. Seventy-one patients (58.7%) completed the study.

Mean eGFR values for the mITT population are shown in Table 2. When categorized by CKD stage, 75.0% and 79.4% of patients in the lanthanum carbonate and placebo groups, respectively, were classified as CKD stage 4 at screening. The difference between groups in the decrease in mean eGFR from screening to the end of treatment was not significantly different (P = 0.93). The percentage of patients who were naïve to phosphate-binder therapy was similar across groups (78.6% lanthanum carbonate, 79.4% placebo).

Before entering the study, a greater proportion of patients were receiving supplemental calcium carbonate in the lanthanum carbonate group than in the placebo group (10.7% versus 2.9%; Table 2). During the study, 9/56 patients (16.1%) received concomitant calcium treatment in the lanthanum carbonate group. Of these, seven received calcium carbonate as a supplement, and three took calcium-based phosphate binders. In the placebo group, 3/34 patients (8.8%) received concomitant calcium treatment. Two patients took supplemental calcium carbonate, and one received calcium as a phosphate binder.

Before entering the study, a smaller proportion of patients were receiving vitamin D compounds in the lanthanum carbonate group than in the placebo group (30.4% versus 47.1%; Table 2). One patient in each group discontinued vitamin D use before the first dose of study drug, whereas in the placebo group, one patient increased their daily dose during the study.

At week 4, the majority of patients were receiving 2250 mg/d of lanthanum carbonate or matching placebo (62.8% and 71.9%, respectively); mean doses were 1930.2 ± 71.4 mg/d and 2085.9 ± 82.7 mg/d, respectively. At week 8, the majority of patients were receiving the maximum 3000 mg/d of lanthanum carbonate or matching placebo (74.4% and 85.7%, respectively); mean doses were 2645.3 ± 96.9 mg/d and 2785.7 ± 120.1 mg/d, respectively. Mean length of drug exposure was similar across groups (45.1 ± 2.6 d for lanthanum carbonate, 50.1 ± 2.2 d for...
placebo); at least 75% of patients in each group completed 6 wk of treatment. Compliance to treatment was 80% in both groups.

Efficacy

At baseline, mean serum phosphorus concentrations (mITT population) were similar in the lanthanum carbonate and placebo groups (5.28 ± 0.09 mg/dl [1.71 ± 0.03 mmol/L] versus 5.38 ± 0.12 mg/dl [1.74 ± 0.04 mmol/L]). At the end of treatment, 44.6% of patients in the lanthanum carbonate group and 26.5% in the placebo group had serum phosphorus concentrations ≤ 4.6 mg/dl; the difference between groups (18.1%) was not statistically significant (P = 0.12). The percentage of patients with serum phosphorus ≤ 4.6 mg/dl is shown by week in Figure 2. At the end of treatment, serum phosphorus concentrations had decreased from baseline by 0.55 ± 0.10 mg/dl (0.18 ± 0.03 mmol/L) and 0.18 ± 0.13 mg/dl (0.06 ± 0.04 mmol/L) in the lanthanum carbonate and placebo groups, respectively (P = 0.02 for difference between groups).

At baseline, mean serum iPTH concentrations were similar in the lanthanum carbonate and placebo groups (183.5 ± 19.5 pg/ml versus 179.3 ± 24.4 pg/ml). Changes from baseline are shown in Figure 4. At the end of treatment, mean serum iPTH level had decreased by 23.8 ± 8.6 pg/ml in the lanthanum carbonate group and had increased by 8.8 ± 11.0 pg/ml in the placebo group (P = 0.02 for difference between groups). At baseline, mean serum calcium concentrations were similar in the lanthanum carbonate and placebo groups (8.86 ± 0.07 mg/dl [2.22 ± 0.02 mmol/L] versus 8.97 ± 0.09 mg/dl [2.24 ± 0.02 mmol/L]). From baseline to the end of treatment, there was a slight increase in mean serum calcium in the lanthanum carbonate group (0.12 ± 0.05 mg/dl [0.03 ± 0.01 mmol/L]), and a slight decrease in the placebo group (−0.09 ± 0.07 mg/dl [−0.02 ± 0.02 mmol/L]; P = 0.02 for difference between groups).

Mean Ca × P product decreased slightly from baseline in both the lanthanum carbonate and placebo groups. At the end of treatment, the difference in reduction from baseline between groups was not statistically significant.

At baseline, mean 24-h urinary excretion of phosphorus was similar in the lanthanum carbonate and placebo groups (836.35 ± 60.19 mg/d [26.98 ± 1.94 mmol/d] versus 783.58 ± 68.48 mg/d [25.28 ± 2.21 mmol/d]), and concentrations decreased only slightly in the placebo group during the study (Figure 5). In contrast, at the end of treatment, urinary phosphorus excretion had decreased by 247.70 ± 48.46 mg/d (7.99 ± 1.56 mmol/d) in the lanthanum carbonate group; the difference compared with the placebo group was statistically significant (P = 0.04).

Safety and Tolerability

AEs were experienced by 47.4% of patients in the lanthanum carbonate group compared with 61.0% in the placebo group.

\[\text{Figure 4.} \text{ Change from baseline in intact parathyroid hormone (iPTH) concentrations during 8 wk of lanthanum carbonate (LC) or placebo treatment. Data are least squares mean ± SEM. Observed-case and end-of-treatment (EOT) data are shown.} ^*P < 0.05 \text{ between treatments, analysis of covariance (ANCOVA) model. To convert pg/ml to ng/L, multiply by 1.0.}\]

\[\text{Figure 5.} \text{ Change from baseline in urinary phosphorus excretion during 8 wk of lanthanum carbonate (LC) or placebo treatment. Data are least squares mean ± SEM. Observed-case and end-of-treatment (EOT) data are shown.} ^*P < 0.05 \text{ between treatments, analysis of covariance (ANCOVA) model. To convert mg/d to mmol/d, divide by 31.}\]
These were mainly gastrointestinal in nature, with nausea (lanthanum carbonate and placebo: 9.0% and 9.8%, respectively) and vomiting (6.4% and 2.4%, respectively) being the most common. In total, 19.3% of AEs experienced in the lanthanum carbonate group were considered related to treatment, compared with 16.7% in the placebo group.
Twelve treatment-emergent SAEs were experienced by seven patients in the lanthanum carbonate group. Acute pulmonary edema, exacerbated dyspnea, and myocardial infarction were experienced by one patient; anemia, congestive cardiac failure, and catheter-site pain were experienced by another. An additional patient experienced anemia and exacerbation of congestive cardiac failure, and the other four patients experienced single SAEs (bacterial arthritis, impaired gastric emptying, pneumothorax, and perinephric abscess). None of the SAEs were suspected to be related to treatment. In the placebo group, three SAEs were experienced by two patients (respiratory failure following chronic obstructive pulmonary disease in one patient, pneumonia in the other).

Two patients treated with lanthanum carbonate and four patients treated with placebo experienced AEs resulting in discontinuation of study participation. In the lanthanum carbonate group, nausea, loss of appetite, low-grade fever, and increased urinary frequency were experienced by one patient and were not suspected to be associated with treatment, whereas mild abdominal itching was suspected to be related to treatment in the other patient.

No clinically important differences were observed between groups with respect to mean concentrations of 1,25-dihydroxy vitamin D3 and 25-hydroxy vitamin D, or other laboratory parameters and vital signs, either at baseline or during treatment. At the end of treatment, the mean plasma lanthanum concentration of the lanthanum carbonate group (0.37 ± 0.05 ng/ml) was within the range observed in previous trials of similar duration involving patients with CKD stage 5 (20).

### Discussion

In patients with CKD stages 3 and 4, lanthanum carbonate treatment resulted in a reduction in the mean serum phosphorus level (a difference of 0.37 mg/dl [0.12 mmol/L] compared with placebo, \( P = 0.02 \)). A greater percentage of patients achieved the target serum phosphorus level of ≤4.6 mg/dl in the lanthanum carbonate group compared with placebo (44.6% versus 26.5%); however, this difference was not statistically significant.

The primary pharmacologic effect of lanthanum carbonate is to form insoluble complexes with dietary phosphorus within the GI tract (21). Therefore, the ability of lanthanum carbonate to bind dietary phosphorus is independent of CKD stage and dialysis status. In patients not on dialysis, serum phosphorus concentrations are influenced by residual renal function, dietary phosphorus burden, blood pH, vitamin D status, degree of hyperparathyroidism, the responsiveness of the skeleton to parathyroid hormone (PTH) (22), and the time after consumption at which phosphorus concentrations are assessed.

A 70-kg man has a total body phosphorus content of approximately 700 g. Approximately 85% is in the skeleton, and approximately 15% can be found in soft tissues (23). Only about 1% is present in the extracellular fluid. Patients with CKD stages 3 and 4 have a positive phosphorus balance; it is not known to what extent serum phosphorus concentrations accurately reflect total body phosphorus burden in this population. Dietary phosphorus restriction has been shown to prevent secondary hyperparathyroidism in patients with renal failure; experimental studies have demonstrated that this effect is independent of serum calcium and 1,25-dihydroxy vitamin D3 (24). The biologic effects of a reduction in phosphorus burden should also be considered in patients with CKD stages 3 and 4.

Unlike patients with CKD stage 5 undergoing dialysis, patients with CKD stages 3 and 4 maintain urine output and the ability to excrete a proportion of any phosphorus that is absorbed. In the “steady-state” condition, the amount excreted in the urine is proportional to the amount absorbed. As a result, measurement of urinary phosphorus excretion can be used as a marker of intestinal phosphorus absorption, and thus as an indicator of phosphorus-binding efficacy (19,25). Lanthanum carbonate treatment resulted in a substantial decrease in intestinal phosphorus absorption as demonstrated by the reduction in urinary phosphorus excretion compared with placebo (\( P = 0.04 \)). Studies in healthy volunteers and patients with CKD stages 3 and 4 (with known dietary phosphorus intake) indicate that up to 75% of dietary phosphorus is absorbed (19,25). Thus with a daily phosphorus intake of 1200 mg, intestinal absorption may approach 900 mg (25). The decrease in urinary phosphorus excretion (approximately 300 mg) observed with <3000 mg/d lanthanum carbonate is equivalent to about a third of daily phosphorus absorption. This result confirms that lanthanum carbonate is an effective dietary phosphate binder in patients with CKD stages 3 and 4. Future studies should include estimates of dietary phosphorus intake and fasting serum phosphorus concentrations in addition to urinary phosphorus excretion.

Although there were differences in prior use of calcium and vitamin D compounds between treatment groups at the start of the study, these were controlled during the study and were not considered to be clinically significant. The decrease from baseline in mean iPTH observed in the lanthanum carbonate group was statistically significant (\( P = 0.02 \)) compared with placebo. The slight increase in serum calcium observed with lanthanum carbonate treatment may be due to phosphorus reduction raising calcium levels via an increase in the calcemic action of PTH. In future studies designed to investigate the efficacy of phosphate binders, measurement and interpretation of these multiple markers of mineral metabolism, along with serum phosphorus and urinary phosphorus excretion, may be a more appropriate main efficacy variable than evaluation of serum phosphorus in isolation.

Analysis of 1,25-dihydroxy vitamin D3 and 25-hydroxy vitamin D concentrations revealed no differences between lanthanum carbonate and placebo groups. A further post hoc analysis in patients who received prior vitamin D therapy (data not shown) revealed that lanthanum carbonate did not reduce vitamin D concentrations in these patients, suggesting that it does not interfere with absorption of vitamin D. This is consistent with results from studies in patients with CKD stage 5 undergoing dialysis (21).

A study including patients with CKD and stable serum phosphorus concentrations treated with a low-phosphorus diet (<800 mg/d) and calcium carbonate (2000 mg/d) or sevelamer hydrochloride (1600 mg/d) showed that despite small but
significant decreases in urinary phosphorus excretion (approximately 80 mg/d), neither binder had reduced serum phosphorus concentrations after an average of 2 yr of treatment (19). Notably, the decrease in phosphorus burden by a combination of dietary phosphorus restriction and reduced intestinal absorption was associated with a reduction in the progression of coronary artery calcification.

In this short-term study, the safety profile and tolerability of lanthanum carbonate was similar to that of placebo. When considering earlier intervention in patients with CKD stages 3 and 4, the long-term safety profile of a phosphate binder should also be considered. Data from animal studies (26,27) have demonstrated lanthanum deposition in bone and increased levels in the liver; the latter is consistent with its hepatic route of excretion (28,29). In patients with CKD stage 5 undergoing dialysis, data on the safety of lanthanum carbonate are published for up to 6 yr of treatment (18). In this long-term follow-up study, lanthanum carbonate was not associated with organ-specific toxicity in liver or bone. In addition, a detailed assessment over 2 yr showed no difference in changes in cognitive function between patients receiving lanthanum carbonate or alternative phosphate binders (30), providing clinical confirmation of animal experiments demonstrating that lanthanum does not cross the blood–brain barrier (31).

Results from this study also suggest that achieving target serum phosphorus concentrations may not accurately reflect changes in phosphorus load produced by phosphate-binder therapy in predialysis patients with CKD. Serum phosphorus levels should not be considered in isolation, but with other markers of disordered mineral metabolism. This study further demonstrates the utility of measuring urinary phosphorus excretion (19).

Overall, this study demonstrated that lanthanum carbonate is an effective phosphate binder in patients with CKD stages 3 and 4, with a safety profile and tolerability similar to that of placebo. It offers a potential treatment option for preventing phosphorus accumulation in this patient population. Further studies are required to assess the potential long-term benefits of earlier intervention with phosphate binders in patients with CKD.

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