ABSTRACT
Patients with CKD often progress to ESRD and develop cardiovascular disease (CVD), yet available therapies only modestly improve clinical outcomes. Observational studies report independent associations between elevated serum phosphate and fibroblast growth factor 23 (FGF23) levels and risks of ESRD, CVD, and death. Phosphate excess induces arterial calcification, and although elevated FGF23 helps maintain serum phosphate levels in the normal range in CKD, it may contribute mechanistically to left ventricular hypertrophy (LVH). Consistent epidemiologic and experimental findings suggest the need to test therapeutic approaches that lower phosphate and FGF23 in CKD. Dietary phosphate absorption is one modifiable determinant of serum phosphate and FGF23 levels. Limited data from pilot studies in patients with CKD stages 3–4 suggest that phosphate binders, low phosphate diets, or vitamin B3 derivatives, such as niacin or nicotinamide, may reduce dietary phosphate absorption and serum phosphate and FGF23 levels. This review summarizes current knowledge regarding the deleterious systemic effects of phosphate and FGF23 excess, identifies questions that must be addressed before advancing to a full-scale clinical outcomes trial, and presents a novel therapeutic approach to lower serum phosphate and FGF23 levels that will be tested in the COMBINE Study: The CKD Optimal Management With Binders and Nicotinamide study.


Reducing the Impact of CKD: Opportunities for Randomized Clinical Trials, phosphate and fibroblast growth factor 23 (FGF23) excess were cited as leading candidates to test in a future full-scale randomized clinical trial aimed at improving outcomes in CKD. However, workshop participants identified major knowledge gaps regarding efficacy assessments, optimal interventions and appropriate outcomes. Scientists called for additional pilot studies to generate high-quality data that could address these gaps before embarking on a long-term, costly outcomes trial targeting phosphate and FGF23 excess in CKD (Figure 1). The purpose of this review is to present data supporting phosphate and FGF23 excess as potential modifiable targets in CKD, provide an overview of prior studies that aimed to lower phosphate and FGF23 levels in CKD,
and outline a development plan that will address critical unanswered questions. Within this context, we briefly describe the justification, hypotheses, and design features of the NIDDK-funded the CKD Optimal Management With Binders and Nicotinamide (COMBINE) Study and how its completion will inform the design of a full-scale trial (Supplemental Material).

CKD AND RISKS OF ADVERSE OUTCOMES

CKD is a strong independent risk factor for ESRD, cardiovascular disease (CVD), fractures, and death.\(^2,7–11\) While progression to ESRD is common in younger CKD patients,\(^7,8\) CVD and death prevail as more likely complications in older individuals and those with diabetes.\(^10,11\) Clinical guidelines acknowledge the interrelationships between CKD and CVD, and recommend that all patients with CKD be viewed as high risk for CVD.\(^12\) At the same time, the guidelines cite the dearth of interventions proven to reduce CVD risk in CKD patients and emphasize the need for novel therapeutic approaches.\(^12\)

ELEVATED PHOSPHATE AND FGF23 AS POTENTIAL THERAPEUTIC TARGETS IN CKD

The typical biochemical phenotype of altered mineral metabolism in CKD stages 2–4 includes early and progressive FGF23 elevation, decline in calcitriol, increase in parathyroid hormone, and gradual rise in phosphate levels within the normal range (Figure 2).\(^13\) Emerging data suggest that phosphate and FGF23 excess in CKD may serve as novel modifiable targets. In addition to epidemiologic studies linking higher serum phosphate and FGF23 levels to ESRD, CVD, and death,\(^14–21\) experimental studies implicate high phosphate in the pathogenesis of vascular calcification and high FGF23 as a potential mechanistic contributor to the development of left ventricular hypertrophy (LVH) in CKD.\(^22,23\) Meta-analyses and pharmaco-epidemiologic studies support the association of phosphate excess with mortality in CKD.\(^24,25\) Thus, multiple lines of evidence (reviewed in detail in Scialla and Wolf\(^26\)) support the need to conduct a randomized controlled trial of therapeutic approaches that lower phosphate and FGF23 to determine their impact on hard outcomes in patients with CKD.

TESTING STRATEGIES TO REDUCE PHOSPHATE AND FGF23 LEVELS IN CKD

Clinical guidelines do not recommend phosphate- or FGF23-lowering treatments for normophosphatemic patients with CKD stages 3–4.\(^27,28\) Therefore, definitive demonstration of the benefits of phosphate and FGF23 reduction in this population, which numbers in the millions in the United States, will have major implications on clinical practice and public health. Only a large randomized controlled clinical outcomes trial can generate such convincing evidence. Although several phosphate- and FGF23-lowering approaches have been tested in small short-term studies,\(^29–32\) additional pilot studies are needed to address major knowledge gaps and to inform the design of the full-scale trial (Figure 1). First, we need to evaluate the phosphate and FGF23 response to interventions aimed at lowering dietary phosphate absorption in long-term interventional studies of patients with CKD. This information is

![Figure 1. Multi-step development of phosphate and FGF23 reduction strategies in CKD. Schematic representation of the multi-step process for testing the utility of phosphate and FGF23 reduction strategies in CKD. The COMBINE (CKD Optimal Management with Binders and Nicotinamide) study and its objectives are represented by the boxes with dashed outlines.](www.jasn.org)
Figure 2. Biochemical phenotype of disordered mineral metabolism in CKD. The graph summarizes evolution of abnormal mineral metabolism along the spectrum of CKD. Depicted values are based on published literature. The x-axis represents glomerular filtration. The y-axis represents circulating levels of individual analytes with temporal changes in and normal ranges of FGF23 shown in red, 1,25 dihydroxyvitamin D (1,25D) shown in purple, parathyroid hormone (PTH) shown in green, and phosphate shown in blue. Elevated FGF23 is the earliest alteration in mineral metabolism in CKD (1). Elevations in FGF23 levels cause the early decline in 1,25D levels (2) that leads to secondary hyperparathyroidism (3). All of these changes occur prior to elevations in serum phosphate levels (4). This figure is reproduced from Wolf, 102 with permission from the American Society of Nephrology. Copyright © [2010] the American Society of Nephrology. All rights reserved.

necessary as the full-scale trial is likely to be long, perhaps up to 5 years. Second, we must define which specific interventions most safely and sustainably lower phosphate and FGF23 levels in patients with CKD, and which interventions provide good long-term tolerability. The most efficacious and well-tolerated approach will be the ideal candidate to advance to the full-scale trial. Third, pilot studies should demonstrate that the chosen phosphate- and FGF23-lowering intervention has beneficial effects on intermediate endpoints of CKD complications. Such subclinical surrogates might include LVH, decline in eGFR, or development of secondary hyperparathyroidism. These proof-of-concept data would strengthen the justification for the definitive trial and would facilitate the choice of hard endpoints for the trial, which would likely include CVD events, ESRD, fractures, mortality, or a composite of several of these. By addressing important unanswered questions related to efficacy assessments, optimal interventions, and appropriate intermediate endpoints, completion of this multi-step development process would support the considerable investment required for a full-scale intervention trial (Figure 1).

TARGETING DIETARY PHOSPHATE ABSORPTION TO MODIFY PHOSPHATE AND FGF23 EXCESS

Dietary phosphate absorption is one modifiable target that may influence serum phosphate and FGF23 levels. In physiologic studies of healthy humans, circulating FGF23 levels rose after 3–5 days of dietary phosphate loading in the absence of a significant increase in serum phosphate. However, when dietary phosphate loading follows a period of dietary phosphate depletion, serum phosphate levels rise modestly. In contrast, several days of exposure to very low phosphate diets combined with dietary phosphate binders lower both fasting levels of serum phosphate and FGF23. Taken together, the data from healthy volunteers demonstrate that aggressively reducing dietary phosphate absorption with multiple modalities can lower serum phosphate and FGF23 levels.

The dual contributions of passive paracellular diffusion and active cell-mediated transport to intestinal phosphate absorption can be leveraged in the design of synergistic serum phosphate- and FGF23-lowering interventions (Figure 3). High luminal phosphate concentration gradient drives passive paracellular diffusion through tight junctions across the intestinal mucosa. Active transport of phosphate occurs via sodium phosphate (NPT2b) co-transporters located on the luminal surface of enterocytes, and is induced by dietary phosphate depletion and calcitriol. Therefore, low dietary phosphate, luminal binding of dietary phosphate by a phosphate binder, and NPT2b blockade in combination may yield maximal reduction of dietary phosphate absorption.

EXPECTED BIOCHEMICAL RESPONSE TO REDUCTION OF DIETARY PHOSPHATE ABSORPTION

Several biochemical parameters can be used to identify which intervention most potently blocks dietary phosphate absorption. The characteristics of each have important implications for study design.

Urinary Phosphate Excretion
Under steady-state conditions, 24-hour urinary phosphate excretion matches daily dietary phosphate absorption, which is estimated to be approximately 70%–80% of daily dietary phosphate intake. Interventions that substantially lower dietary phosphate absorption typically but not always result in reductions in 24-hour urinary phosphate excretion, which may be detected even while serum phosphate levels remain unchanged. Inability to collect
Therefore, measurements in the afternoon may have missed meaningful changes in serum phosphate levels.45 Because nicotinamide reduces NPT2b expression, use of this agent in combination with low phosphate diets and phosphate binders may maximize reductions in dietary phosphate absorption.

**Serum Phosphate**

Because serum phosphate levels typically rise very slowly within the normal range as CKD progresses, overt hyperphosphatemia is uncommon among patients with CKD whose eGFR is >30 ml/min per 1.73 m².13 Given the ability of CKD patients to maintain serum phosphate within the normal range, it is not surprising that single interventions aimed at lowering dietary phosphate absorption, such as use of phosphate binders alone, have minimal, if any, effects on serum phosphate levels.45–47 Furthermore, serum phosphate levels are at their nadir in the morning and peak in the afternoon, when the largest differences in serum phosphate levels across a spectrum of dietary phosphate loads are noted.48,49 Because the normal diurnal rhythm in serum phosphate levels is preserved in CKD,48–51 studies that only measured morning fasting serum phosphate levels may have missed meaningful changes that might have been detected if phosphate was measured later in the day. Therefore, measurements in the afternoon are likely to be more sensitive at detecting changes in serum phosphate levels following interventions targeting dietary phosphate absorption.

**Serum FGF23**

Elevated FGF23 is the earliest and most common manifestation of disordered mineral metabolism in CKD.13 In contrast to serum phosphate, FGF23 levels do not vary substantially within individuals throughout the day, in relation to prandial status or over the course of weeks to months.51–53 Because FGF23 regulates serum phosphate levels through its endocrine effects on the kidney, gut, and parathyroid glands, FGF23 is a promising biomarker to detect responses to interventions aimed at lowering phosphate absorption. Interventional studies in healthy individuals33–35 and patients with CKD29–31,45,49,54–60 and experimental studies in animals39,61,62 treated with phosphate binders, nicotinamide, and low phosphate diets support FGF23 as a useful biomarker of phosphate-targeting interventions. In many, but not all, of these studies, serum phosphate was unchanged in response to interventions, but within days to weeks, FGF23 levels were reduced and found to correlate with lower urinary phosphate excretion. In these settings, FGF23 may have declined because less FGF23 was required to dispose of the reduced phosphate load, while maintaining normal serum phosphate levels.

**Phosphate Binders**

Phosphate binders are the mainstay in the management of hyperphosphatemic patients undergoing dialysis because they effectively reduce dietary phosphate absorption.63,64 In dose-finding studies performed in healthy volunteers, phosphate binders potently reduce urinary phosphate excretion, while maintaining serum phosphate levels within the normal range.65,66 Similar findings have been observed in normophosphatemic patients with CKD stages 3–4 in whom phosphate binders, but not placebo, reduce 24-hour urine phosphate by 20%–50%.30,42,45,67 The effects of phosphate binders on levels of FGF23 in patients with CKD are not consistent. Several studies suggest that non-calcium-based phosphate binders lower FGF23 levels in this population by 30%–40%.30,31,45,54–57 whereas calcium-based binders do not,23,38 likely because calcium is a secondary stimulus for FGF23 production.58,69 Taken together, the effect of phosphate binders on serum phosphate and FGF23 levels is relatively small. Insights from elegant experimental studies described below suggest that the potency of phosphate binders may, in part, be offset by the contribution of active transport to total intestinal phosphate absorption.52,70,71
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean GFR</th>
<th>Duration</th>
<th>Intervention</th>
<th>Summary of biochemical effects</th>
</tr>
</thead>
</table>
| Oliveira et al. | 40 | 35 | 6 weeks | Sevelamer hydrochloride | Compared with calcium acetate, sevelamer carbonate treatment led to:  
- modest reduction in 24-hr urine phosphate  
- no change in serum phosphate levels  
- 40% reduction in FGF23 levels |
| Isakova et al. | 39 | 38 | 12 weeks | 900 mg phosphate diet–lanthanum carbonate | Compared with ad libitum diet–placebo, 900 mg phosphate diet–lanthanum carbonate treatment led to:  
- no change in 24-hr urine phosphate  
- no change in serum phosphate levels  
- 35% reduction in FGF23 levels |
| Block et al. | 145 | 31 | 36 weeks | Phosphate binders | Compared with placebo, phosphate binder treatment led to:  
- 22% reduction in 24-hr urine phosphate  
- reduction in serum phosphate levels from a mean of 4.2–3.9 mg/dl  
- no reduction in C-terminal FGF23 levels  
Intact FGF23 levels reduced with sevelamer carbonate, but not with calcium acetate or with lanthanum carbonate |
| Block et al. | 141 | 24 | 12 weeks | Ferric citrate | Compared with placebo, ferric citrate treatment led to:  
- 39% reduction in 24-hr urine phosphate  
- reduction in serum phosphate levels from a mean of 4.5–3.9 mg/dl  
- reduction in FGF23 levels from a median of 159–105 pg/ml |
| Ix, Rao et al. | 261 | 52 | 24 weeks | Niacin | Compared with placebo, niacin treatment led to:  
- no data on 24-hr urine phosphate  
- reduction in serum phosphate levels  
- 11% reduction in FGF23 levels |
| Chue et al. | 109 | 50 | 36 weeks | Sevelamer carbonate | Compared with placebo, sevelamer carbonate treatment led to:  
- no change in 24-hr urine phosphate  
- no change in serum phosphate levels  
- no change in FGF23 levels  
Reduction in FGF23 levels among individuals compliant with active therapy |
| Seifert et al. | 38 | 46 | 48 weeks | Lanthanum carbonate | Compared with placebo, lanthanum carbonate treatment led to:  
- no change in 24-hr urine phosphate  
- no change in serum phosphate levels  
- no change in FGF23 levels |
| Moe et al. | 9 | 32 | 1 week | Vegetarian diet | Compared with meat diet, vegetarian diet in this crossover study led to:  
- Reduction in 24-hr urine phosphate from a mean of 778–416 mg/day  
- Reduction in serum phosphate levels from a mean of 3.5–3.2 mg/dl  
- Reduction in FGF23 levels from a mean of 84–61 pg/ml |
| Diorio et al. | 32 | 30 | 1 week | Very low protein diet | Compared with low protein diet, very low protein diet in this crossover study led to:  
- 34% reduction in 24-hr urine phosphate  
- 12% reduction in serum phosphate levels  
- 34% reduction in FGF23 levels |

*aActive therapy included calcium acetate, sevelamer hydrochloride, and lanthanum carbonate.*
Nicotinamide

Nicotinamide (vitamin B3, also called niacinamide) reduces intestinal NPT2b expression. This is thought to be one of the mechanisms by which nicotinamide and its derivatives reduce dietary phosphate absorption and lower serum phosphate levels in animals and in patients with ESRD. Comparable data have also emerged from pooled analyses of two trials of dyslipidemic patients with CKD stage 3 treated for 24 weeks with niacin or matched placebo. Active treatment resulted in a significant and sustained decrease in the fasting levels of serum phosphate (between-groups change in phosphate level = –0.42 mg/dl; 95% confidence interval, –0.52 to –0.33). The same intervention also resulted in an approximately 11% decline in FGF23 levels in the niacin-treated group compared with placebo. The efficacy of blocking dietary phosphate absorption on biochemical and even cardiovascular endpoints in CKD is also supported by results from recent experimental studies. When an inhibitor of intestinal sodium-hydrogen exchanger-3 that also blocked dietary phosphate absorption was administered to rats with CKD, it decreased urinary phosphate excretion, reduced serum phosphate and FGF23 levels, attenuated vascular calcification, and reduced heart mass.

Nicotinamide may also promote phosphaturia. Intra-peritoneal delivery of nicotinamide increased urinary phosphate excretion without changing urinary excretion of creatinine, potassium, sodium, calcium, or urinary flow rates in rats. Similar observations were made in parathyroidectomized rats, suggesting a PTH-independent effect. Further evidence in support of nicotinamide’s phosphaturic effect comes from studies of rats with normal kidney function treated for 4 days with nigericin, a nicotinic acid derivative. In the treated animals compared with controls, urinary phosphate excretion was not decreased despite a significant increase in stool phosphate content. This observation suggests that, in addition to blocking active phosphate transport in the gut, nigericin and other nicotinic acid derivatives may induce a renal phosphate leak, perhaps by reducing the levels of renal sodium phosphate co-transporters (NPT2a and NPT2c). These dual actions may explain the sustained hypophosphatemic effects of nicin in patients with CKD stage 3 and were also recently implicated as the causal mechanisms for hepatectomy-related hypophosphatemia, in which renal and intestinal sodium phosphate transport were decreased due to increased levels of nicotinic acid derivatives.

Experimental studies have shown that exposure to phosphate-depleted diets or phosphate binders upregulates NPT2b expression, and leads to enhanced dietary phosphate absorption when dietary phosphate loading is reinstated. This is consistent with the observations from human studies that demonstrate spikes in serum phosphate with dietary phosphate loading only after a period of dietary phosphate depletion, which is presumably due to a compensatory increase in active intestinal phosphate transport in the setting of low luminal dietary phosphate. These data suggest that attempts to reduce dietary phosphate absorption using phosphate binders alone may be limited by NPT2b upregulation and resultant increases in dietary phosphate absorption at times when phosphate binders are not present in the intestinal lumen. By blocking intestinal active transport, addition of nicotinamide to binder regimens may therefore synergistically maximize reduction of dietary phosphate absorption. Furthermore, nicotinamide’s phosphaturic effect may also contribute to greater reduction in serum phosphate and FGF23 levels in CKD when phosphate binders are used in combination with blockade of sodium phosphate transporters in the gut and kidney. Proof-of-concept data in support of this hypothesis come from experimental studies of NPT2b-deficient uremic mice. Compared with wild-type uremic mice, NPT2b-deficient uremic animals had lower phosphate and FGF23 levels, and treatment with sevelamer carbonate further reduced serum phosphate and FGF23 levels. In contrast, the tested sevelamer dose did not induce significant reductions in serum phosphate in the wild-type uremic mice, although there was a trend for a decline in FGF23 levels. Human studies are under way to test the possibility of greater response and adverse effects related to the nicotinic acid moiety, including liver test abnormalities, hyperuricemia, and insulin resistance.

Dietary Phosphate Restriction

Dietary interventions that reduce phosphate intake or modify its dietary sources, and hence bioavailability, can lower serum phosphate and FGF23. Sources of dietary phosphate in order of increasing bioavailability are organic phosphate from plants and legumes, organic phosphate from animal and dairy sources, and inorganic phosphates that are used by the food industry as additives to enhance flavor, appearance, and shelf life of processed meats, cheeses, baked goods, and beverages. Consistent with the bioavailability data, serum and urinary phosphate and FGF23 were significantly lower in uremic rats fed a grain-based versus a meat-based diet. Similar findings were reported in a cross-over study of patients with CKD stages 3–4 who were fed grain-based and meat-based diets that contained identical total phosphate content. Compared with a meat-based diet, a grain-based diet led to a 27% decrease in FGF23 and a 9% reduction in serum phosphate (Table 1).

Another approach to reduce phosphate consumption is to target inorganic phosphate additives. In a randomized trial of hyperphosphatemic ESRD patients, educating patients how to read food labels and to select alternative items from experimental studies of NPT2b-deficient uremic mice. Compared with wild-type uremic mice, NPT2b-deficient uremic animals had lower phosphate and FGF23 levels, and treatment with sevelamer carbonate further reduced serum phosphate and FGF23 levels. In contrast, the tested sevelamer dose did not induce significant reductions in serum phosphate in the wild-type uremic mice, although there was a trend for a decline in FGF23 levels. Human studies are under way to test the possibility of synergistic or additive benefit from phosphate binders combined with nicotinamide in CKD. Importantly, unlike the lipid-lowering drug niacin, which contains both nicotinamide and nicotinic acid, nicotinamide does not cause flushing and is thought to be less likely to cause other adverse effects related to the nicotinic acid moiety, including liver test abnormalities, hyperuricemia, and insulin resistance.
net phosphate absorption. This approach may facilitate the efficacy of other phosphate- and FGF23-lowering interventions, as has been shown in a pilot study that tested the combination of phosphate binder therapy with dietary phosphate reduction in patients with CKD stages 3–4.51

**POSSIBLE INTERMEDIATE ENDPOINTS**

In addition to demonstrating that the chosen interventions aimed at reducing dietary phosphate absorption safely lower phosphate and FGF23, a key step will be to test whether the candidate therapies also have beneficial systemic effects. Prior studies attempted to test the hypothesis that phosphate- and FGF23-lowering interventions would improve intermediate CVD endpoints, including LVH, vascular dysfunction, and vascular calcification.45,47,55,89 However, no pilot study has tested whether the combination of phosphate binders and nicotinamide will have beneficial effects on markers of bone and mineral metabolism and on intermediate endpoints of CVD and CKD progression in patients with CKD stages 3–4. The results from such a study will help identify which of the tested surrogate markers should be advanced as the primary endpoints to a larger randomized study to test the utility of phosphate and FGF23 lowering on intermediate endpoints of CVD, renal, and skeletal risks (Figure 1). Taken together, the findings from these studies will be critical to define appropriate hard endpoints for the phase III trial (Figure 1). These may include some combination of congestive heart failure, other CVD events, CVD hospitalizations, CKD progression, ESRD, fractures, and mortality. Below, we provide justification for some of the intermediate endpoints that will be evaluated in the COMBINE study (Table 2).

**Imaging Biomarkers of CVD Risk**

LVH is a common pattern of CVD in CKD and is an established risk factor for CVD events and cardiovascular mortality.90 High FGF23 and serum phosphate levels are associated with elevated left ventricular mass.23,46 Cardiac magnetic resonance imaging (MRI) provides the most precise measurements of left ventricular mass and chamber geometry,91 and is especially useful for detecting small changes over time given its high resolution, reproducibility, and low variability.92 In addition to structural assessments, cardiac MRI yields important functional measures that can identify diastolic dysfunction, such as left ventricular end diastolic volume and left atrial volume. The latter are critical in relatively shorter-term studies when beneficial changes in cardiac function are likely to antedate architectural changes in cardiac structure.

**Imaging Biomarkers of CKD Progression**

Phosphate and FGF23 excess have been linked to accelerated CKD progression,19 but whether these represent causal effects is unknown. Renal fibrosis is a final common pathway for CKD progression and is a key determinant of disease severity.93,94 Renal hypoxia, an important determinant of acute kidney injury,95 has also been implicated in the pathogenesis of renal fibrosis in CKD.96,97 Gadolinium-free diffusion-weighted MRI may quantify renal fibrosis and blood oxygenation level dependent MRI can evaluate intra-renal oxygenation.98–100 These novel methods have not yet been applied to interventional studies designed to lower phosphate and FGF23 levels in patients with CKD.

**Circulating Biomarkers of Bone and Mineral Metabolism**

Phosphate and FGF23 excess play a central role in the pathogenesis of disordered bone and mineral metabolism in CKD.13,101 However, human interventional data directly implicating phosphate and FGF23 excess in the development of secondary hyperparathyroidism, calcitriol deficiency,
and abnormal bone metabolism are lacking. Given that serum phosphate and FGF23 levels would be expected to rise over time in untreated patients with progressive CKD, a placebo-controlled randomized study aimed at phosphate and FGF23 reduction will permit this important hypothesis to be tested by serial measurement of biochemical markers, including PTH, klotho, calcitriol, and bone turnover markers (Table 2).

BRIEF OVERVIEW OF THE COMBINE STUDY

In order to advance testing of promising therapeutic targets in CKD, the NIDDK convened a consortium of clinical centers and a data coordinating center funded by a cooperative agreement (U01; RFA-DK-12–016) to design and conduct pilot studies that would inform the design of a full-scale randomized clinical trial with hard outcomes in CKD. Within this consortium, the COMBINE Study will test the hypothesis that use of nicotinamide combined with lanthanum carbonate on a background of reduced dietary phosphate intake safely reduces serum phosphate and FGF23 levels over 12 months in 200 patients with stages 3–4 CKD. Tables 2 and 3 and Figure 4 display the main features of the COMBINE study. During the first month following randomization, the dose of nicotinamide will be 750 mg once daily and the dose of lanthanum carbonate will be 500 mg three times daily with meals. After the first month, the dose of nicotinamide will be increased to 750 mg twice daily and the dose of lanthanum carbonate will be increased to 1000 mg three times daily with meals. All participants will receive information on how to reduce dietary phosphate intake. Study visits will take place in the afternoon to ensure that serum phosphate levels are measured at a time when the maximal differences between the intervention arms could be detected. Serial 24-hour urine collections will also be obtained to assess impact on dietary phosphate absorption. Pill counts and questionnaires will be used to assess compliance. Tolerability will be summarized as the percentage of persons who come off study drug, and safety will be defined by the number and percentage of the participants who report at least one adverse event. In addition to testing the primary endpoints of safety and biochemical efficacy, there will be longitudinal assessments of circulating biomarkers of bone and mineral metabolism and circulating and MRI imaging intermediate measures of CVD and renal risks at baseline and at 12 months post-randomization (Table 2). By addressing unanswered questions regarding the biochemical response, optimal interventions and intermediate endpoints, the results of the COMBINE study will provide important information to inform the design of a future full-scale outcomes trial. Enrollment began in March 2015, and results are anticipated by 2018.

ACKNOWLEDGMENTS

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Table 3. The COMBINE Study Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<tr>
<td>Patients with eGFR 20–45 ml/min/1.73 m²</td>
<td>History of allergic reaction to nicotinamide, or lanthanum carbonate</td>
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<tr>
<td>Age 18–85 years</td>
<td>Liver disease</td>
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<tr>
<td>Serum phosphate ≥ 2.8 mg/dl</td>
<td>Elevated creatine kinase concentrations (&gt;2 times the upper limit of normal)</td>
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<tr>
<td>Platelet count ≥ 125,000/mm³</td>
<td>Major hemorrhagic event within the past 6 months requiring in-patient admission</td>
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<td>Blood or platelet transfusion within the past 6 months</td>
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<td>Secondary hyperparathyroidism (parathyroid hormone &gt;5 times the upper limit of normal)</td>
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<td>Malabsorption</td>
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<td>Anemia (hemoglobin &lt; 9.0 g/dl)</td>
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<td></td>
<td>Serum albumin &lt; 2.5 mg/dl</td>
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<td>Anticipated initiation of dialysis or kidney transplantation within 12 months</td>
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<td>Use of immunosuppressive medications</td>
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<td></td>
<td>Recent (within 14 days) initiation or change in dose of active vitamin D or its analogs</td>
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<td>Current participation in another clinical trial or other interventional research</td>
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<td>Recent (within 14 days) initiation or change in dose of active vitamin D or its analogs</td>
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<td>Currently taking investigational drugs</td>
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<td>Institutionalized individuals</td>
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<td>Malignancy requiring therapy within 2 years</td>
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<td></td>
<td>Pregnancy or planning to become pregnant or currently breast-feeding</td>
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<tr>
<td></td>
<td>Life expectancy &lt; 12 months</td>
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</tbody>
</table>

Figure 4. The COMBINE study schema. The COMBINE study is a randomized, double-blind, placebo-controlled, 12-month study of 200 CKD stages 3–4 patients that will test the hypothesis that nicotinamide and lanthanum carbonate will safely lower serum phosphate and FGF23 levels compared with placebo.
BRIEF REVIEW

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DISCLOSURES

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