

# Lanthanum carbonate for the control of hyperphosphatemia in chronic renal failure patients: a new oral powder formulation – safety, efficacy, and patient adherence

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**Abstract:** Chronic kidney disease (CKD) is associated with very high mortality rates, mainly of cardiovascular origin. The retention of phosphate (P) and increased fibroblast growth factor-23 levels are common, even at early stages of CKD, due to disturbances in normal P homeostasis. Later, hyperphosphatemia appears, which has also been strongly associated with high mortality rates linked to P-mediated cardiovascular and procalcifying effects. Treatment guidelines for these patients continue to be poorly implemented, at least partially due to the lack of adherence to a P-restricted diet and P-binder therapy. Calcium-free P binders, such as lanthanum carbonate, have been associated with a decreased progression of vascular calcification, rendering them an important therapeutic alternative for these high cardiovascular risk CKD patients. Lanthanum carbonate has typically been available as chewable tablets, and the new presentation as an oral powder may provide a useful alternative in the therapeutic armamentarium. This powder is a tasteless, odorless, and colorless semisolid compound miscible with food. In a recent study in healthy individuals, the safety and efficacy of this novel form were evaluated, and it was concluded that it is well tolerated and pharmacodynamically equivalent to the chewable form. In the long run, individualization of preferences and treatments seems an achievable goal prior to final demonstration of improvements in hard outcomes in wide clinical trials in CKD patients.

**Keywords:** chronic kidney disease, phosphate, phosphate binder

## Introduction

Chronic kidney disease (CKD) is associated with high mortality rates, the main cause of death being cardiovascular disorders. The increased mortality risk of these patients cannot be attributed only to traditional risk factors; rather, many nonclassical risk factors, including disturbances of bone mineral metabolism, are probably involved. Hyperphosphatemia and, particularly, increased fibroblast growth factor-23 (FGF-23, a phosphaturic hormone) together with vitamin D status are the parameters most strongly associated with mortality, ie, those that bear the highest relative risk,<sup>1,2</sup> higher even than the relative risk associated with parathyroid hormone (PTH), plasma calcium or alkaline phosphatase.<sup>1,3</sup>

Phosphate (P) regulation is primarily handled in the kidney by transporters located in the proximal tubule, which regulate P excretion/reabsorption in response to many metabolic factors and various hormones/phosphatonins such as PTH and the aforementioned FGF-23. When the kidney becomes dysfunctional, it is unable to maintain adequate P homeostasis; the consequence is progressive P retention and an early

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increase in FGF-23 levels, even before hyperphosphatemia becomes evident. Since P is a direct inducer of PTH synthesis, secretion, and parathyroid growth and, on the other hand, blocks all potential counter-regulatory mechanisms,<sup>4,6</sup> excessive P not only induces the most severe form of secondary hyperparathyroidism but is also associated with other extrasosseous effects that ultimately seem to be related to increased mortality.<sup>7</sup> These effects include direct and indirect cardiovascular effects, its association with kidney disease progression, inflammation, oxidative stress, and a central role in coronary, vascular, valvular, and myocardial calcification via the upregulation of RUNX2 (Cbf $\alpha$ 1), an “osteoblast” transcription factor.

Due to the increasing importance given to P control, in this article we will briefly summarize the evolution of different clinical guidelines and current recommendations, and provide an overview of treatment options and adherence problems inherently associated with P binders. We will then describe the main general characteristics of lanthanum carbonate and present the available data on the recently released new oral powder formulation.

## P retention versus hyperphosphatemia: clinical guidelines

In 2003, the American National Kidney Foundation issued the K/DOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guidelines, which became the universal reference. These guidelines recommended target serum P levels between 2.7 and 4.6 mg/dL for stages 3–4, and between 3.5 and 5.5 mg/dL for stage 5 (including dialysis).<sup>8</sup> Approximately 11%–15% of the American population suffer from CKD,<sup>9,10</sup> and 60% of American patients on hemodialysis have P levels higher than those recommended by these guidelines. In the international DOPPS (Dialysis Outcomes and Practice Patterns Study) II, serum P levels were >5.5 mg/dL in 47% of patients with CKD undergoing dialysis from all over the world.<sup>11</sup> In a Spanish study including 1,836 patients, Craver et al<sup>12</sup> reported that the target P levels proposed by the K/DOQI were met for pre-dialysis stages 3, 4, and 5 CKD in 90.9%, 77.1%, and 70.3% of cases, respectively. These figures clearly reflect both progressive P retention and undertreatment. However, the greatest matter of concern was that control of all four classic parameters (Ca, P, PTH, and Ca  $\times$  P) was achieved in only 34.9%, 18.4%, and 21.6% of patients with stage 3, 4, and 5 CKD, respectively, the low rates being primarily due to lack of control of PTH. These results drew attention to the difficulty of compliance

with clinical practice guidelines on bone mineral metabolism, even in stages of CKD prior to end-stage renal disease.

In 2008, the OSERCE I study (Epidemiología de la Enfermedad Ósea en la Enfermedad Renal Crónica en España, Epidemiology of Bone Disease in Chronic Kidney Disease in Spain) highlighted the poor implementation of guidelines after surveying 32 Spanish centers. In that study, we observed that the objectives for P were incorrectly reported in 50% of cases in stages 3 and 4, and in 60% of cases in nondialysis stage 5. We suspected that this was probably due not only to the limited availability of approved therapeutic agents for use in CKD before dialysis but also to the difficulty in achieving the suggested goals or a real lack of knowledge or belief in current recommendations.<sup>13</sup>

A second, multicenter part of the OSERCE I trial reevaluated the degree of compliance with guidelines. A total of 634 patients were analyzed, of whom 15% (only 1.8% using centralized analysis out of 409 patients) satisfied all four K/DOQI objectives. Regarding P, 22% had inadequate P levels (3% below and 19% above K/DOQI recommendations), a percentage that agrees with data previously reported by other authors.<sup>12</sup> In a recent Spanish observational cohort study, MERENA (Morbimortalidad en Enfermedad RENal en pacieNtes diAbéticos y no diabéticos), 1129 patients with CKD stage 3 or 4 were analyzed, revealing that 85.1% of the patients had P levels within the K/DOQI target. The objectives for all four parameters as per the K/DOQI guidelines were met in only 10.5% of the total cohort and 12.2% and 9% of those with stage 3 and 4 disease, respectively.<sup>14</sup>

Compared with the K/DOQI guidelines, the K/DIGO (Kidney Disease: Improving Global Outcomes) international guidelines, published in 2009, are somewhat stricter, proposing maintenance of P in the normal range (2.7–4.6 mg/dL) in patients with stage 3–5 CKD; however, they also suggest lowering elevated phosphorus levels “toward the normal range” in dialysis patients.<sup>15</sup> The ERBP (European Renal Best Practice) endorses the K/DIGO proposal regarding P control, whereas UK guidelines suggest that serum P in CKD 3–5 should be maintained in those mentioned levels, and in dialysis patients a goal between 3.4 and 5.2 mg/dL is suggested.<sup>16,17</sup> More recently, the emerging role of P as an atherogenic and procalcifying factor, and its association with increased mortality, has driven some nephrology societies, among them the Spanish Society of Nephrology,<sup>18</sup> to adopt in their clinical practice guidelines a suggestion favoring even the attainment of strictly normal serum P levels in CKD patients. This is independent of their stage and including also dialysis

patients, provided that the ways of attaining this objective are clinically reasonable.

Hyperphosphatemia is a belated consequence of P retention. In light of our new pathophysiologic knowledge, it is likely that initiation of therapy only after hyperphosphatemia has already occurred may represent an outdated approach. In fact, it appears that the earliest possible intervention may be a simple and beneficial way to mitigate the deleterious systemic effects of P overload. The current restriction of non-calcium-containing P binders, reflected in the technical sheets accepting their use before end-stage renal disease only when P is  $>5.5$  mg/dL ( $>1.78$  mmol/L), represents an additional problem while we await the development of wider clinical indications or new therapeutic targets. It is probably advisable to monitor the fractional excretion of P,<sup>18,19</sup> and it has been suggested that P binders might be considered when PTH increases, fractional excretion of P increases (ie,  $>15\%$ – $20\%$ ), or when P tubular reabsorption is significantly diminished (ie,  $<80\%$ – $85\%$ ).<sup>20</sup> However, even though these suggestions sound reasonable, it has to be admitted that there are no results from prospective trials confirming the usefulness of this practice, and controversial studies have been published recently.<sup>21</sup>

Increasingly ambitious treatment guidelines may be rendered possible by the enrichment of the therapeutic armamentarium, especially with non-calcium-containing P binders and their different presentations. These approaches aim both to improve compliance with biochemical targets and to limit side-effects as much as possible.

## Treatment of hyperphosphatemia: diet, dialysis and P binders

Dietary P restriction is usually prescribed in patients with CKD in the presence of secondary hyperparathyroidism and/or hyperphosphatemia.<sup>15,18</sup> It is biologically plausible<sup>15</sup> that such diets are helpful in early CKD;<sup>15</sup> however, there are insufficient data at present to strongly endorse dietary P restriction as the primary intervention for the management of CKD-mineral and bone disorder (MBD).<sup>15</sup> Furthermore, prescribed dietary P restriction has not been associated with a survival benefit among prevalent hemodialysis patients, and increased level of restriction has even been associated with greater mortality, particularly in some subgroups.<sup>22</sup> Since dietary restrictions to control serum P are usually related to a reduction of protein intake, the risk of unsupervised control of dietary P may outweigh the benefit of P control and may lead to protein-energy wasting and poor survival.<sup>22–25</sup> Restriction of nonprotein sources of P such as additives or highly processed

convenience foods is currently underlined.<sup>26,27</sup> Thus, dietary P restriction should probably be considered as an adjunct to P binders, and nutrition parameters should be closely monitored in this setting.<sup>15,18</sup> Increased dialytic removal should also be considered in dialysis patients; nevertheless, it is not easy to implement.<sup>15,28</sup> Consequently, treatment with oral P binders is still considered an important component of P management, especially for most patients undergoing dialysis,<sup>27,29</sup> and a favorable survival effect of P binders on incident hemodialysis patients has been recently reported.<sup>30,31</sup>

Ideally, a P binder should effectively bind most of dietary P with no side effects, regardless of intestinal pH, have minimal systemic absorption, good palatability, a low pill burden, and be available at a low cost.<sup>27,32,33</sup> As described by the latest K/DIGO and Spanish Society of Nephrology guidelines,<sup>15,18</sup> it is reasonable that the choice of P binder takes into account CKD stage, the presence of other components of CKD-MBD (ie, vascular calcification), concomitant therapies (ie, vitamin D compounds and calcimimetics), and the side-effect profile.<sup>15</sup> Thus, classic calcium-based P binders are inexpensive, but it is recommended restricting the dose in the presence of persistent or recurrent hypercalcemia, and it is suggested restricting the dose in the presence of arterial calcification and/or adynamic bone disease and/or if serum PTH levels are persistently low.<sup>15,18</sup> In Table 1,<sup>15</sup> we present a brief comparison among the most frequently used P binders.

In this context, it seems important to obtain not only better drug tolerability but also greater patient adherence to treatments in order to attain the final objective, ie, to slow or halt the progression of vascular calcification, CKD progression, and ultimately, to improve patient survival (Figure 1).<sup>18,34,35</sup>

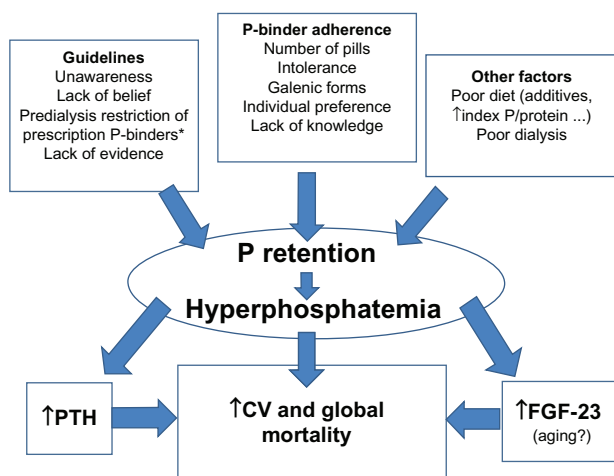
## Lanthanum carbonate

Lanthanum carbonate is a resin-free, non-calcium-based P binder, with a high binding potential, available to date as a chewable tablet (Fosrenol®; Shire US Inc, Wayne, PA, USA). Preclinical trials have shown its efficacy independently of pH variability along the gastrointestinal tract, which represents an advantage over some of its homologues such as calcium carbonate.<sup>36,37</sup> According to some comparative trials, the potency of the different commercially available P binders is essentially comparable, with only small differences among them.<sup>38–41</sup> A recent metabolic trial performed on 18 healthy volunteers, however, observed that with a standard phosphorus diet, 1000 mg of elementary lanthanum reduced P net absorption by 45% as compared with a reduction of only 21% with 2400 mg of sevelamer carbonate ( $P < 0.001$ ).<sup>42</sup>

**Table 1** Comparison among most common phosphate binders

	Advantages	Disadvantages
Aluminum hydroxide	Very effective Variety of forms Cheap	Potential for toxicity (encephalopathy, altered bone mineralization, anemia) Long-term use should be avoided (unanimous K/DIGO vote)
Calcium-based P-binders – Calcium acetate – Calcium carbonate	Effective Long-term experience Readily available Inexpensive	Potential for hypercalcemia and PTH suppression Progression of vascular calcification GI side effects
Magnesium-calcium-based P-binders	Effective Potential for decreased calcium load as compared with calcium-based P-binders	Potential for hypercalcemia and hypermagnesemia Shorter clinical experience GI side effects
Sevelamer – Sevelamer hydrochloride – Sevelamer carbonate	Effective Toxicity free (no calcium/metal) ↓ LDL cholesterol Many other pleiotropic effects (eg, ↓ FGF-23, ↑ Fetuin-A, ↓ CRP) Powder presentation Potential attenuation of the progression of coronary/aortic calcification	High pill burden (sevelamer-HCl) Potential interferences with vitamin D and vitamin K intestinal absorption Potential for decreased bicarbonate levels (sevelamer-HCl) Direct costs (expensive) GI side effects
Lanthanum carbonate	Effective Aluminum and calcium free Reduced pill burden Powder presentation Potential attenuation of the progression of vascular calcification	Difficulties chewing tablets Occasional need for a drug crusher Potential for tissue accumulation. Long-term clinical consequences unknown Direct costs (expensive) GI side effects

**Note:** Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group.<sup>15</sup> Copyright © 2012 by KDIGO. All rights reserved.  
**Abbreviations:** CRP, C-reactive protein; FGF, fibroblast growth factor; GI, gastrointestinal; HCl, hydrochloride; LDL, low-density lipoprotein; P, phosphate; PTH, parathyroid hormone.



**Figure 1** Causes and consequences of P retention and hyperphosphatemia beyond CKD itself. Beyond all the pathophysiological factors leading to P retention and hyperphosphatemia in CKD, we represent their additional causes and potential consequences. Several factors are related to equivocal or unproved guidelines, absence of adherence to prescriptions as well as other circumstances.

**Notes:** \*Technical sheet restriction: non-calcium-based P binders are only indicated for P ≥ 1.78 mmol/L in nondialysis patients. PTH and FGF-23 are also interrelated. Low serum PTH and P levels have also been associated with mortality, maybe related to MIA syndrome. Excess FGF-23 and decreased Klotho have also been associated with the aging processes.

**Abbreviations:** CKD, chronic kidney disease; CV, cardiovascular; FGF-23, fibroblast growth factor-23; MIA, malnutrition-inflammation and atheromatosis; P, phosphate; PTH, parathyroid hormone.

The main advantage of lanthanum carbonate is that it is a calcium-free P binder and so may satisfy the requirements of renal patients, who have a high cardiovascular calcification risk that seems to directly influence survival. As mentioned before, it is reasonable that the choice of P binder takes into account the presence of other components of CKD-MBD and that in the presence of vascular/valvular calcification, calcium restriction is advised. Toussaint et al<sup>43</sup> carried out a randomized controlled trial on 30 patients who underwent hemodialysis and then followed them up for 18 months; this trial showed that lanthanum carbonate significantly diminished progression of aortocoronary calcification when compared with the use of calcium-based P binders. Wilson et al<sup>44</sup> compared the effects of lanthanum carbonate and a calcium P binder on survival in a retrospective study with a 2-year follow-up. In this trial, the best results were seen in the subgroup of patients older than 65, who showed significantly longer survival after using lanthanum carbonate. Importantly, prospective trials have also been performed with other non-calcium-based P binders,<sup>40,45-47</sup> which have proven a reduction of the progression of vascular calcification as compared with calcium-based P binders, with two excep-

tions.<sup>38,48,49</sup> Nevertheless, these trials have not provided definitive evidence; rather they have only reported certain trends in respect of survival benefit, decreased hospitalization days, and reduced institution of dialysis.<sup>15,45,50,51</sup> Only one cross-sectional study in a French hemodialysis population has shown a favorable effect of a calcium-based P binder as compared with sevelamer.<sup>52</sup>

On the other hand, the new, recently commercialized powder galenic form of lanthanum carbonate offers renal patients a therapeutic alternative with the ultimate purpose of improving treatment adherence. The new formulation is an insoluble, odorless, tasteless, and colorless powder that is mixed with soft food as if it were a sort of seasoning (“salt for kidney patients”). It now comes in 750 and 1000 mg sachets, similar to the tablet form. Below, we analyze the main acceptability and adherence problems associated with P binders, as well as the potential advantages offered by the lanthanum carbonate powder in respect of treatment adherence. We shall also review the available data on the safety and efficacy of this new form.

## Acceptability and adherence

Nonadherence to a treatment not only prevents the achievement of control targets but may additionally represent a financial burden to the health system and pose a major obstacle to effective treatment.<sup>27</sup> It has been estimated that the annual costs of therapeutic noncompliance in the USA amount to US\$100 billion, with 10% of hospital admissions and 23% of nursing consultations being attributable to lack of adherence to treatment.<sup>53</sup>

Renal patients are typically chronically ill, have comorbid conditions, are on multiple medications, and are elderly, and several trials have highlighted lack of adherence to different treatments in such patients. In an important analysis, Arenas et al<sup>54</sup> carried out an observational study of 121 hemodialysis patients and detected lack of compliance with the prescribed drugs in up to 40% of patients; in 21% of cases, noncompliance specifically involved P binders, and it was independently associated with higher mean phosphorus levels ( $>5.5$  mg/dL) (odds ratio = 4.7; 95% confidence interval [CI], 1.07–6.5;  $P = 0.03$ ). In a systematic review of 13 trials on nonadherence to P binders, Karamanidou et al<sup>55</sup> reported a prevalence of between 22% and 74%, with a mean of 51%. Such a high prevalence could be explained by the fact that P binders have certain characteristics that make them different from other drugs and may complicate adherence as they necessitate a very strict dosing pattern. For instance, P binders must be taken with meals, and this proves difficult

especially in young people because it interferes with their lifestyles, including their social environment. Such were the conclusions of a Dutch trial that investigated adherence to antiretroviral drugs: the authors observed that the percentage of noncompliant patients increased when the definition of compliance included dietary considerations, eg, when the drug had to be taken together with meals.<sup>56</sup> Moreover, it is obvious and proven that the high number of tablets needed to treat hyperphosphatemia is a limiting factor for adherence. A higher pill number is also associated with lower quality of life and increasing the number of prescribed pills does not seem to improve control of hyperphosphatemia.<sup>57,58</sup> Diagnosing lack of adherence to the treatment is the first step in attempting to solve the problem. Questionnaires are useful, simple, and cheap tools that, together with biochemical results, help identify noncompliant patients. There are no P binder-specific questionnaires, but Arenas et al suggest that the SMAQ (Simplified Medication Adherence Questionnaire) displays adequate levels of sensitivity and specificity and that results are well correlated to P levels. More complex tools that provide some improvement in adherence have also been applied, eg, electronic devices.<sup>59</sup> Lanthanum radio-opacity causes the appearance of a characteristic radiologic abdominal “starry sky” image, which could be exploited in controlling nonadherence to the drug.<sup>60</sup>

Once lack of adherence has been diagnosed, the causative factors should be investigated. A good doctor–patient relationship has recently been identified as a key factor in improving therapeutic compliance. One element of this is fluent communication, which makes patients knowledgeable about the importance of the prescribed drug and enables them to participate in objective attainment and even in choice of their treatment. This is reflected in the current conceptual change that involves a shift from classic terms such as compliance to more modern terminology such as adherence. Compliance is defined as the degree to which patients take their doctor-prescribed medication or follow medical advice. Noncompliance with those instructions would entail disobedience, whereupon the possibility of punishment would be implicit. The term adherence has been suggested as an alternative to compliance, since it seems to reduce the doctor’s power within the doctor–patient relationship and also incorporates wider and more appropriate concepts such as consistency, cooperation, concordance, and partnership. The aim of this conceptual shift is to put aside the paternalistic relationship between doctor and patient and facilitate the development of an empathic attitude, with the focus on patient’s preferences, which permits the customization of treatment.<sup>61</sup>



Arenas et al have also researched patient preferences and their impact on treatment adherence and P control. In the abovementioned study, they observed that of the patients on lanthanum carbonate, 40% considered it their favorite binding agent, 24% considered it their least favorite drug, and 35% had no opinion. When patients were asked why they rejected the prescribed lanthanum carbonate, 17.7% said that the chewable form was not satisfactory; indeed, older patients found it difficult to manage, this being an even stronger reason for discontinuation than gastric intolerance (6.6%).<sup>54</sup> In view of the drawbacks of the chewable form, patients were given drug crushers to facilitate consumption. How et al carried out a small randomized study that included eleven hemodialysis patients to determine the efficacy of the crushed drug versus the standard chewable form.<sup>62</sup> The crushed form reduced P levels significantly, but differences with the chewable form were not significant. Both chewed and crushed lanthanum carbonate were generally well tolerated. They introduced the concept that crushing lanthanum and mixing it with food might be an option for patients who are unable to chew or swallow whole tablets.<sup>62</sup> Due to the insolubility of lanthanum carbonate, the entire pill could migrate along the intestinal tract without adequate P binding. Hence, Yamashita et al<sup>60</sup> targeted subjects who did not chew lanthanum carbonate adequately for the purpose of studying the clinical efficacy of changing to crushed chewable prescriptions. A total of 18 out of 41 patients on maintenance hemodialysis were identified in the “insufficient mastication group” and a progressive significant lowering of P levels from  $5.86 \pm 1.31$  mg/dL before pulverization to  $5.12 \pm 1.34$  mg/dL after 6 weeks ( $P = 0.02$ ) was observed. In this study, the residual images of lanthanum carbonate on the abdominal X-rays disappeared to the point where they could barely be confirmed.

Consequently, a new presentation of lanthanum carbonate powder has recently been approved; this new form could solve some of the problems presented by the classic form of presentation of the drug, especially in patients with reduced ability to chew, whose cognitive functions or medication compliance are poor, but also by decreasing the number of pills and increasing the currently available therapeutic possibilities where patients may choose.

## Safety

The safety of lanthanum carbonate was assessed by Hutchison et al in 2008, following analysis of 93 patients on treatment with lanthanum carbonate as single therapy for the preceding 6 years. Treatment-related side-effects had occurred in

25.8% of the patients, and their nature was primarily gastrointestinal (nausea, diarrhea, and flatulence).<sup>63</sup> More recently, Dellanna et al carried out a study to analyze lanthanum carbonate's safety in 698 dialysis patients over a period of 6 months and with an average dose of  $2,509 \pm 936$  mg/day. A total of 113 adverse events were recorded in 53 patients (7.6%), but only 23 (mostly gastrointestinal disorders: nausea, abdominal discomfort, vomiting, and abdominal distension) in 14 patients (2.4%), were considered to be related to lanthanum carbonate treatment.<sup>64</sup> Despite being a metal, a fact that raises concern over potential toxicity and accumulation in other tissues, the bioavailability of lanthanum carbonate is between 10 and 500 times lower than that of aluminum; in fact it is lower than 0.002%.<sup>65</sup> Plasma monitoring of the drug enabled Hutchison et al to observe that the baseline median level of 0.0 ng/mL increased to 0.3 ng/mL following 6 months of treatment. The maximum value achieved over the 6 years of follow-up was 13.9 ng/mL (in an outlier). However, among a total 574 determinations, the 2 ng/mL level was exceeded by only 15 occasions, and the 4.0 ng/mL level was exceeded by just four.<sup>63</sup>

In 2008, Hutchison et al's study found no evidence of adverse effects in the liver, bones, or central nervous system,<sup>63</sup> although they were described in experimental trials on animals.<sup>66-68</sup> Thus, it has been described that oral administration of lanthanum carbonate to normal and/or uremic rats led to increased tissue lanthanum content in some organs, including lungs, kidneys, femur, and most strikingly in the liver.<sup>66,68</sup> However, no evidence of adverse effects of lanthanum carbonate on the liver in patients who received treatment for up to 6 years was observed in a subset of four Phase III clinical trials and subsequent extension studies.<sup>69</sup> In a recent postmarketing short observational study of efficacy and safety, it was stated that lanthanum carbonate is effective and well tolerated, provided that recipients do not have preexisting liver disease (in 2 out of 112 patients, an increase in transaminases was observed).<sup>70</sup> The technical sheet describes that the effect of hepatic impairment on lanthanum carbonate pharmacokinetics has not been assessed. Due to its mechanism of action and the lack of liver metabolism, doses in hepatic impairment should not be modified, but patients should be monitored carefully. Conditions resulting in a marked reduction of bile flow may be associated with incrementally slower elimination of lanthanum, which may result in higher plasma levels and increased tissue deposition of lanthanum. As the liver is the principal organ of elimination of absorbed lanthanum, monitoring of liver function tests is recommended.<sup>71</sup>

As far as bone is concerned, different studies found no evidence for adverse effects from lanthanum deposition;<sup>70,72,73</sup> furthermore, the incidence of adynamic bone disease and osteomalacia was low as compared with the incidence after calcium carbonate treatment.<sup>72,74</sup> It has even been described that non-calcium-based P binders such as sevelamer may increase the bone formation rate and improve trabecular architecture as compared with calcium carbonate.<sup>75</sup> This highlights the fact that the behavior of lanthanum is quite different from that of aluminum, one of the first P-binding agents used in nephrology.

With regard to the central nervous system, a single case report of lanthanum-related encephalopathy has recently been published. Lanthanum levels in the cerebrospinal fluid were high, suggesting it can cross the blood–brain barrier. High plasma levels were also found, which could be explained by the presence of a portal-systemic shunt secondary to liver disease that could have prevented the drug from being excreted by the bile. Also, the doses administered (3,750 mg/day) were higher than those used in standard clinical practice (1000–3000 mg). Moreover, this patient was undernourished, which could have increased the circulation of the drug-free fraction. The authors suggest that in specific cases in which there is high risk of increased drug plasma levels, lanthanum carbonate treatment should be used with caution.<sup>76</sup>

The safety of lanthanum carbonate powder was evaluated as a secondary objective in a recent study including 72 healthy incident individuals aged 18–55 years who were randomized to receive either chewable tablets or powder. The total study duration was 28 days.<sup>77</sup> The dose administered was 3000 mg/day. With both formulations, 41.7% of the subjects had  $\geq 1$  treatment-emergent adverse event, defined as any adverse event occurring at treatment initiation that was not present at baseline or that was present at the baseline and reemerged or worsened with treatment, to eventually disappear at the end of the treatment. Comparison of the two drug presentations revealed that adverse events appeared following consumption of chewable tablets in 23% of cases and after taking the powder formulation in 32.4%. The sum of individuals reporting adverse events after each treatment (oral powder plus chewable tablets) exceeds the overall number of individuals. This discrepancy is ascribed to individuals reporting separate treatment-emergent adverse events in each treatment period because of the crossover design of the study. The commonest adverse events with the powder were nausea (8.5%), headache (5.6%), and abdominal pain (4.2%). Less frequent adverse events were dyspepsia, gastroenteritis, vertigo, fatigue, and muscular spasms.<sup>65</sup> The overall difference between the

formulations was basically due to gastrointestinal effects, which were observed in 18.3% of patients on the powder formulation and 6.6% of those on tablets. However, this difference in respect of gastrointestinal effects was not considered clinically significant because the frequency of such effects following presentation as tablets was 20% in a Phase I trial, and the percentage of patients who had nausea was similar in both groups (8.5% for oral powder versus 4%–20% for tablets).<sup>78</sup> Thus, the minor difference in respect of treatment-emergent adverse events is mainly due to mild side-effects; these were nonserious in nature and are recognized as common or very common in the European Summary of Product Characteristics.<sup>71</sup> Consequently, it seems that lanthanum carbonate powder was well tolerated, with 67% of patients free of or having nonrelevant adverse events. Since these observations have been evaluated in healthy individuals, it should be emphasized that patients with CKD may differ in terms of gastrointestinal dynamics. Therefore, these initial positive results should be confirmed in regular clinical practice in both predialysis and dialysis patients.

## Efficacy

Pierce and coworkers performed a Phase I, single-center, randomized, open-label, two-period, crossover study designed to assess the pharmacodynamic equivalence of two formulations of lanthanum carbonate (tablets and powder) in 72 healthy subjects.<sup>77</sup> P mean urinary excretion was determined over three treatment days. The urinary excretion of P is a consequence of the intestine's ability to absorb its P content, which has been exploited in many pharmacodynamic studies. The least square mean of daily excreted P was 16.8 mmol for tablet administration and 15.2 mmol for powder formulation. The mean difference was  $-1.6$  mmol (90% CI,  $-2.38$  to  $-0.82$ ), which is within the calculated critical reference range ( $-3.35$  to  $3.35$ ); this enabled the authors to conclude that the two formulations showed pharmacodynamic equivalence. This conclusion was accepted by the European Medicines Agency, and commercialization of the new presentation in the European Union was approved.

This trial also assessed pharmacokinetic parameters as a secondary objective: the systemic exposure of both formulations was within the ranges verified in previous trials with lanthanum carbonate tablets.<sup>78</sup> However, the area under the curve was 34% wider with the powder formulation than with the tablets ( $13.11$  ng · h/mL versus  $9.80$  ng · h/mL; ratio of geometric least square means [90% CI],  $1.34$  [ $1.26$ – $1.42$ ]). The maximal concentration ( $C_{max}$ ) was 26% higher using powder than using tablets, at  $0.60$  and  $0.47$  ng/mL, respectively. The

rate of absorption was also higher after administration of oral powder because the elevated  $C_{max}$  observed after administration of oral powder was reached within the same time as after administration of chewable tablets. On the other hand, the drug half-life was similar for both presentations: 21.9 and 22.3 hours for the powder and the tablets, respectively, with individual values within the 16.2–28.3-hour range. Thus, in this multiple dose study, the oral powder and tablet formulation were well tolerated and met the regulatory criteria for pharmacodynamic equivalence in these healthy volunteers.<sup>77</sup> Although lanthanum route of excretion is biliary and not renal, future studies in CKD patients are guaranteed to definitely assume pharmacodynamic equivalency in these patients.

## Conclusion

A large body of evidence shows a clear association between hyperphosphatemia, P retention, and mortality. Calcium-based P binders have some limitations related to the progression of cardiovascular calcification while non-calcium-based P binders are limited by their technical sheet and cost. However, the poor implementation of guidelines and the multifactorial lack of adherence of patients to treatments remain important factors in the poor P control in CKD patients. Long-term P control using P binders could be improved considering new ways of improving patient adherence, even allowing patients a greater nutritional freedom. The new powder formulation of lanthanum carbonate is the first P binder that can be mixed directly with food, providing a new tasteless form of administration of P binders. It is considered pharmacologically equivalent to the chewable form, but it really remains to be definitely proven in CKD patients. We emphasize that in addition to new formulations, improved adherence will only be achieved when doctors share the clinical importance of P and their treatment goals with their patients. In the long run, individualization of treatments seems an achievable goal prior to final demonstration of improvements in hard outcomes in wide clinical trials.

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## Disclosure

Jordi Bover lectured for SHIRE-sponsored scientific events on the importance of P and FGF-23 in CKD, but he did not lecture on the superiority of lanthanum carbonate as

compared with other P binders. The other authors have no conflicts of interest to declare.

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