CLINICAL INVESTIGATION

Clinical rationale of sucroferric oxyhydroxide for controlling hyperphosphatemia in patients with chronic kidney disease

Sucroferric oxyhydroxide (Velphoro®; Vifor Fresenius Medical Care Renal Pharma Ltd) is an iron-based phosphate binder approved for the control of serum phosphorus concentrations in chronic kidney disease patients receiving dialysis. Clinical data indicate that sucroferric oxyhydroxide has similar efficacy to sevelamer carbonate in lowering serum phosphorus levels; however, with a substantially lower pill burden with on average three to four pills/day versus eight to nine pills/day of sevelamer carbonate. Sucroferric oxyhydroxide is associated with discolored feces, as expected for oral iron-based compounds. Some patients reported mild and transient diarrhea, mostly at the start of treatment, which did not require any interventions. There is minimal iron absorption, without risk of iron overload. Overall, sucroferric oxyhydroxide is an effective, well-tolerated new treatment for managing hyperphosphatemia in dialysis patients.

Stuart M Sprague*[,1], Morgan Marcuccilli[2] & Viatcheslav Rakov[3]

[1]NorthShore University Health System, University of Chicago Pritzker School of Medicine, Evanston, IL, USA
[2]University of Colorado School of Medicine, Denver, CO, USA
[3]Vifor Pharma, Glattbrugg, Switzerland
*Author for correspondence: stuartmsprague@gmail.com

Keywords: adherence • chronic kidney disease • dialysis • PA21 • phosphate binder • serum phosphorus • sevelamer • sucroferric oxyhydroxide

Background

Chronic kidney disease (CKD) has an estimated worldwide prevalence of 8–16%; common causes of CKD include hypertension, diabetes, and glomerulonephritis [1]. Hyperphosphatemia is a universal consequence of Stage 5 CKD and, if left untreated, is associated with cardiovascular morbidity, and mortality [2]. Sources of phosphate include dietary protein, polyphosphates that are added to foods as preservatives, and common beverages [3–5]. An association between the consumption of such beverages high in phosphate content and hyperphosphatemia in dialysis patients has been reported [4,6]. Because dietary phosphate restriction and conventional dialysis treatment alone are often insufficient to adequately manage hyperphosphatemia, administration of oral phosphate binders to limit phosphorus absorption from ingested food is necessary in most patients [7]. Several studies have demonstrated that control of hyperphosphatemia, including the use of phosphate binders, is associated with a significant reduction in mortality [2,8,9].

Properties of an ideal phosphate binder include a high phosphate-binding capacity across the wide pH range found in the gastrointestinal (GI) tract, low pill burden, good safety and tolerability profile, and minimal absorption [10]. The presently available phosphate binders include sevelamer, lanthanum carbonate, and compounds containing either aluminum, calcium, magnesium [2,9], iron [11,12], or colestilan [13]. It is challenging to find an established phosphate binder that possesses all the ideal properties. For example, aluminum-based binders are associated with significant hematologic and neurologic toxicity, as well as an increased risk of fractures [9,14,15]. Although oral aluminum-containing phosphate binders may have a direct toxicological effect, it has also been suggested that exposure to aluminum in dialysis fluid was the primary cause of the toxicity [16]. Evidence indicates that calcium-based phosphate binders, such as calcium carbonate

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or calcium acetate, affect the calcium balance [17], and are associated with hypercalcemia [18] and vascular calcification [9,19]. Concerns have also been raised over the mortality rate associated with calcium-containing phosphate binders versus their non-calcium-based counterparts [20]. Although inconclusive results have been obtained from clinical studies (including the RIND study and DCOR study) [21], a meta-analysis indicated that calcium-based phosphate binders were associated with increased risk of all-cause mortality versus non-calcium-based phosphate binders [20]. The use of calcium-based phosphate binders is questionable when there is a positive calcium balance [22]. Finally, the majority of available phosphate binders are associated with a high pill burden, which might compromise a dialysis patient's ability to take the prescribed medication [2,9]. Pill burden is a particularly important consideration, because patients receiving dialysis are often required to take a large number of concomitant tablets each day [23]. Indeed, lower pill burden is associated with increased adherence to phosphate binders, and high levels of medication adherence are associated with increased control of serum phosphorus [24].

Sucroferric oxyhydroxide (Velphoro®, Vifor Fresenius Medical Care Renal Pharma Ltd), previously known as PA21, is a novel, non-calcium-, iron-based phosphate binder, which has received US FDA approval and EU marketing authorization for the control of serum phosphorus levels in CKD patients undergoing dialysis. Sucroferric oxyhydroxide is a stabilized polynuclear iron(III)-oxyhydroxide-based compound, composed of approximately 33% m/m iron(III) oxyhydroxide, 30% m/m sucrose, 28% m/m starch and ≤10% m/m water (Figure 1) [25]. Similar to other phosphate binders, sucroferric oxyhydroxide binds dietary phosphate in the GI tract, preventing its absorption into the blood. The bound phosphate is subsequently eliminated in the feces [26].

In vitro data demonstrate that sucroferric oxyhydroxide has a high phosphate-binding capacity over the entire physiologically relevant pH range found in the GI tract. Assuming 1 mg of iron binds 0.26 mg of phosphate, three sucroferric oxyhydroxide tablets containing a total of 1.5 g of iron are expected to bind 390 mg of phosphate [25]. *In vitro* data also support minimal iron absorption following sucroferric oxyhydroxide administration. Under conditions representative of a full stomach (i.e., in the presence of phosphate) and during passage through the GI tract (i.e., over the pH range of 2.5–8.0), iron release was ≤0.35% [25]. Data from a subsequent Phase I absorption, distribution, metabolism and excretion study demonstrated that iron uptake into the blood following oral administration of ^{59}Fe-labeled sucroferric oxyhydroxide was minimal, particularly in dialysis patients [27]. At 21 days, iron uptake was slightly lower in hemodialysis patients (median: 0.02%; range: 0–0.04%) than in non-dialysis CKD patients (median: 0.06%; range: 0.008–0.44%). Median uptake was approximately tenfold lower across both CKD subgroups, compared with healthy subjects with low iron stores (0.43%; range: 0.16–1.25%). Phase I data in healthy volunteers also showed that there was a low risk of drug–drug interactions, based on systemic exposure, between sucroferric oxyhydroxide and selected drugs commonly taken by dialysis patients, including losartan, furosemide, digoxin, warfarin, and omeprazole [28].

This article provides an overview of the clinical data from Phase II and III trials of sucroferric oxyhydroxide in patients with CKD receiving dialysis.

Efficacy

The efficacy of sucroferric oxyhydroxide in dialysis patients was examined in a Phase II clinical trial (NCT00824460), the purpose of which was to determine the effect of varying doses of the compound on serum phosphorus levels [29]. In this international open-label study, 154 adult patients who had been receiving maintenance hemodialysis three times a week for a minimum of 3 months before screening, with stable calcium content in dialysate for at least 1 month before screening, were included in the study. After a 2-week washout period, patients were randomized in equal proportions to one of five doses of sucroferric oxyhydroxide (low dose: 250 mg iron/day; active doses: 1.0, 1.5, 2.0 and 2.5 g iron/day) or to sevelamer hydrochloride (HCl; 4.8 g/day). A fixed dose of the study treatment was maintained for 6 weeks, with dosing three-times a day with meals (the highest dose was taken with the largest meal[s] of the day). Patients who received 250 mg iron/day took one tablet per day with the largest meal. The primary end point of the study was the change in serum phosphorus concentration from baseline to end of treatment. All patients remained on a phosphate-restricted diet throughout the study. Demographics and baseline characteristics were similar across all five sucroferric oxyhydroxide treatment groups and the sevelamer HCl control group. Mean age of patients was 60.4 years across the five sucroferric oxyhydroxide treatment groups and 61.6 years for the sevelamer HCl control group, and the majority of patients were male (63.5 and 58.3%, respectively). A significant decrease in serum phosphorus concentrations was observed in all four active sucroferric oxyhydroxide dose groups ($p < 0.05$), thus meeting the primary end point. In patients who provided at least one post-baseline efficacy assessment (the efficacy population; n = 150), the mean magnitude

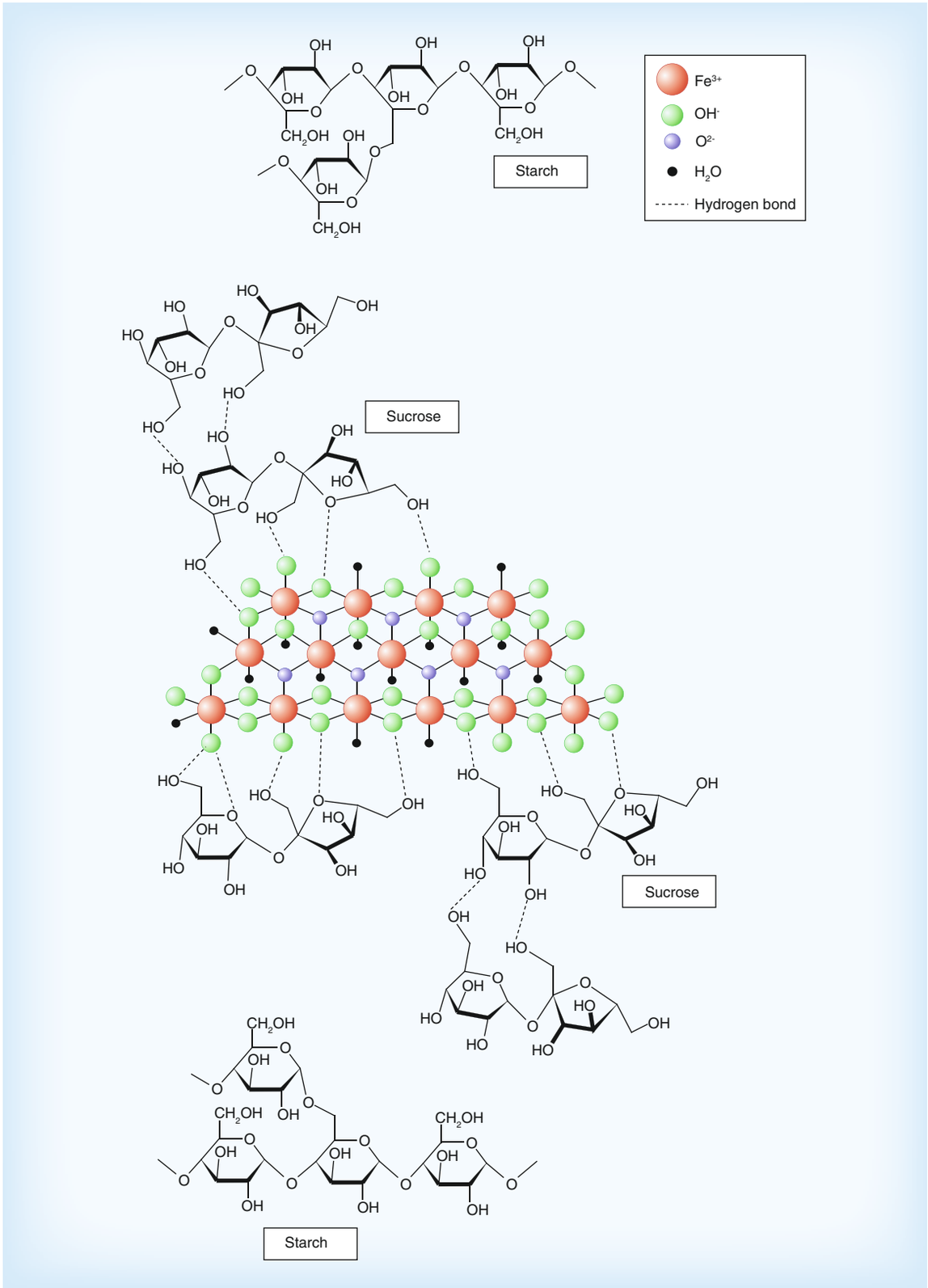

Figure 1. Structure of sucroferric oxyhydroxide.

of the observed reduction tended to increase with increasing doses of sucroferric oxyhydroxide, reaching a maximum for the 2.0 g/day dose (-2.00 mg/dl) and 2.5 g/day dose (-1.69 mg/dl; Figure 2). The observed reductions for the 1.0 g/day dose (-1.08 mg/dl) and the 1.5 g/day dose (-1.25 mg/dl) of sucroferric oxyhydroxide were similar to those observed with 4.6 g/day sevelamer HCl (-1.06 mg/dl). The change in serum phosphorus from baseline to end of treatment was significantly higher in all sucroferric oxyhydroxide dosing groups compared with the 250 mg/day group ($p < 0.05$). A similar pattern was observed in those patients without major protocol violations (per protocol population; Figure 2) [29].

A Phase III program comprising an initial Phase III trial (NCT01324128) [11], followed by an extension study (NCT01464190) was subsequently performed [30]. The purpose of the initial two-stage, randomized, active-controlled, parallel-group, international, multicenter, open-label, Phase III study was to compare the efficacy and safety of sucroferric oxyhydroxide and sevelamer carbonate in managing hyperphosphatemia in patients undergoing hemodialysis or peritoneal dialysis. Patients eligible for the study were aged ≥18 years, and had a history of hyperphosphatemia, for which they had been prescribed stable doses of phosphate binders prior to screening. After a washout period of 2–4 weeks, 1059 patients were randomized in a 2:1 ratio to receive sucroferric oxyhydroxide 1.0–3.0 g/day (two to six tablets/day; twice [at study start] or three-times daily with the largest meals) or sevelamer carbonate 2.4–14.4 g/day (three to 18 tablets/day; three-times daily with meals) [11]. The objective of Stage 1 was to demonstrate the non-inferiority of sucroferric oxyhydroxide compared with sevelamer carbonate at 12 weeks. This stage commenced with an 8-week dose-titration period, during which doses were titrated for efficacy (to achieve serum phosphorus between 0.81 to 1.78 mmol/l [2.5 to 5.5 mg/dl]) or for tolerability. The dose-titration period was followed by a 4-week maintenance period, during which doses could be titrated for tolerability only, and non-inferiority of sucroferric oxyhydroxide against sevelamer carbonate was assessed at the end of the 12-week period. During weeks 13–24 maintenance period, doses could be titrated for efficacy or tolerability. Baseline demographics were similar between the sucroferric oxyhydroxide and sevelamer carbonate treatment groups. Mean age of patients was 56 years across both of the treatment groups, and the majority of patients were male (55.2 and 63.1% in the sucroferric oxyhydroxide and sevelamer carbonate treatment groups, respectively). Across both treatment groups, 92% of patients were undergoing hemodialysis and the remaining 8% were undergoing peritoneal dialysis. No differences in diet were observed between the two treatment groups.

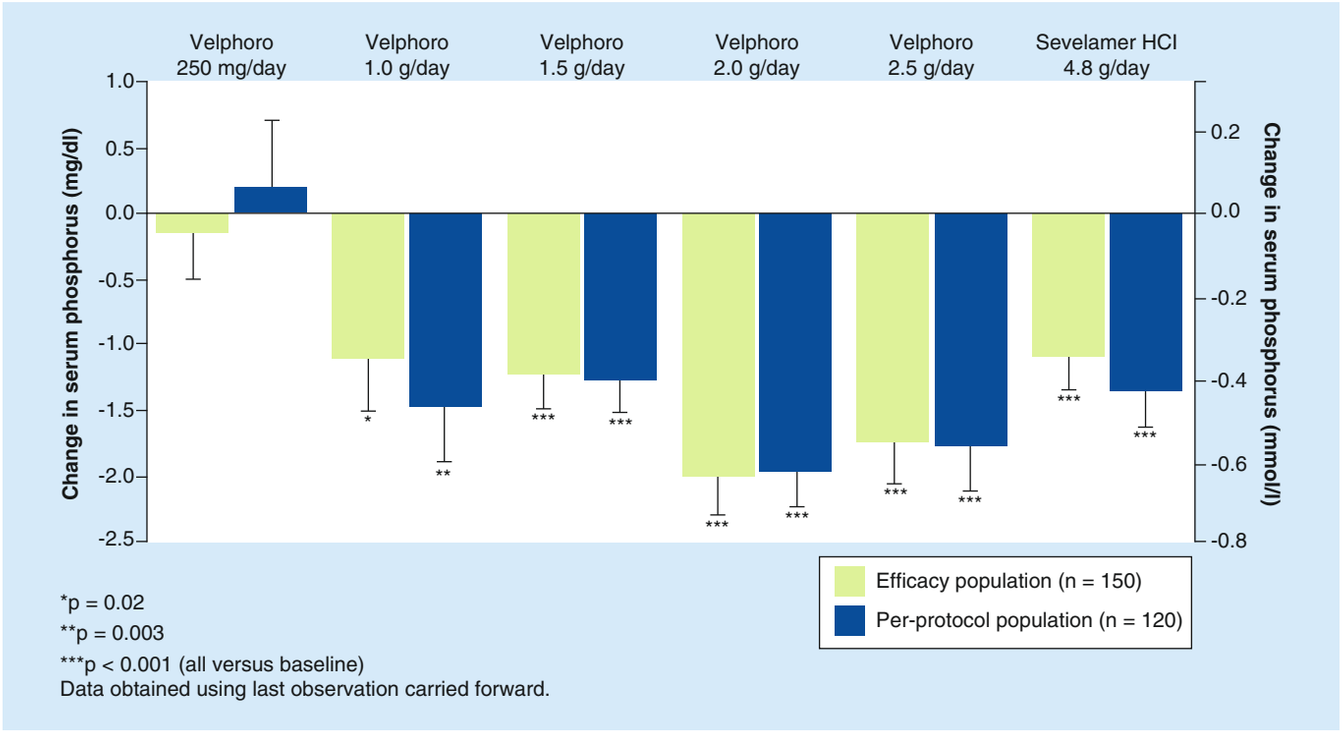

Figure 2. Change in serum phosphorus concentrations from baseline (± standard error of the mean).
Data taken from [29].

Figure 3 shows that, in both treatment groups, rapid reductions in mean serum phosphorus were observed and were maintained to the week 24 end point. At week 12, sucroferric oxyhydroxide was found to be non-inferior to sevelamer carbonate [11]. The serum phosphorus-reducing effect of sucroferric oxyhydroxide was further analyzed across a number of patient subgroups. It was found that sucroferric oxyhydroxide reduced serum phosphorus concentrations in the patient population, irrespective of their geographic region of origin, diabetic status, dialysis type, age, sex, weight, race, ethnicity or prior phosphate binder use [31,32].

The superiority of maintenance-dose sucroferric oxyhydroxide over low-dose sucroferric oxyhydroxide (250 mg/day) was demonstrated in Stage 2 of the trial. In total, 99 hemodialysis patients, who completed the initial 24 weeks of treatment with sucroferric oxyhydroxide, and had a controlled serum phosphorus level between 0.81 to 1.78 mmol/l (2.5 to 5.5 mg/dl), were randomized in a 1:1 ratio to receive either their maintenance dose (dose at week 24) or their regimen was changed to low-dose sucroferric oxyhydroxide during the following 3 weeks. At the start of Stage 2, mean serum phosphorus concentrations were similar in both the maintenance-dose (1.5 mmol/l; 4.7 mg/dl) and low-dose (1.6 mmol/l; 5.0 mg/dl) groups. Whereas mean serum phosphorus concentrations in the maintenance-dose group did not change significantly from week 24 to 27, in the low-dose group serum phosphorus concentrations increased by 0.6 mmol/l (1.8 mg/dl), resulting in a significant difference between the maintenance-dose and low-dose groups ($p < 0.001$), confirming superiority of the maintenance dose [11].

With the exception of patients who were randomized to the low-dose group, those who completed treatment in either Stage 1 or 2 were eligible to enter the 28-week extension study, continuing the same treatment and dosage they were receiving at the end of the initial study. The objectives of the extension study were to evaluate the long-term efficacy and safety of sucroferric oxyhydroxide. In total, 659 patients were enrolled (sucroferric oxyhydroxide, n = 391; sevelamer carbonate, n = 268), and serum phosphorus control was maintained with both sucroferric oxyhydroxide and sevelamer carbonate over 1 year of treatment [30].

Pill burden

Clinical studies performed to date reveal that a major advantage of sucroferric oxyhydroxide is its association with a low pill burden, necessitating fewer tablets per day to attain similar levels of efficacy as the comparator phosphate binder. At week 24 of the initial Phase III trial, similar efficacy results were achieved with a lower number of pills in patients receiving sucroferric oxyhydroxide (mean 3.1 pills/day), compared with patients receiving sevelamer carbonate (mean 8.1 pills/day) [11]. Over 1 year, the mean number of tablets taken per day from baseline to the end of the extension study was 3.3 for patients receiving sucroferric oxyhydroxide compared with 8.7 for those receiving sevelamer carbonate [30]. It is possible that low pill burden may translate to greater adherence for patients prescribed sucroferric oxyhydroxide compared with other phosphate binders. It is noteworthy that adherence to study treatment (defined as taking 70–120% of the expected number of tablets) over the first 24 weeks of the study was 82.6% with sucroferric oxyhydroxide and 77.2% with sevelamer carbonate. Furthermore, non-adherence to study treatment (defined as taking <70% of the expected number of tablets) appeared to be more common in patients receiving sevelamer carbonate compared with those taking sucroferric oxyhydroxide (21.3 vs 15.1%, respectively) [11]. Over the entire 1-year study period, the proportions of patients who were adherent were 83.0 and 79.5% for patients receiving sucroferric oxyhydroxide and sevelamer carbonate, respectively.

Safety & tolerability

As discussed above, an ideal phosphate binder should be well tolerated and provide robust safety data. In the Phase II study, the most frequently reported adverse event (AE) among patients receiving sucroferric oxyhydroxide (across all dose groups) was hypophosphatemia, defined by the study protocol as a serum phosphorus level <1.13 mmol/l (<3.5 mg/dl) (sucroferric oxyhydroxide, 18.0%; sevelamer HCl, 11.5%) [29]. This was least frequent (7.7%) in the 250 mg/day arm and most frequent (29.6%) in the 2.0 g/day arm. GI AEs were reported in 22.7% of sucroferric oxyhydroxide-treated patients and 26.9% of sevelamer HCl-treated patients. There were no clinically significant differences in the occurrence of diarrhea, constipation, or vomiting between the sucroferric oxyhydroxide groups and the sevelamer HCl arm, and no dose-dependence was noted in patients receiving sucroferric oxyhydroxide. As expected for an iron-based product, discolored feces were only reported in participants receiving sucroferric oxyhydroxide (11.7%). No severe or serious treatment-related AEs (TEAEs) were reported. The most frequent causes of discontinuation due to AEs were hypophosphatemia, as cautiously predefined at a serum phosphorus level <3.5 mg/dl (sucroferric oxyhydroxide, 10.2%; sevelamer HCl, 7.7%), hypercalcemia (sucroferric oxyhydroxide, 4.7%; sevelamer HCl, 0%), and hyperphosphatemia (sucroferric oxyhydroxide, 3.9%; sevelamer HCl, 3.8%) [29].

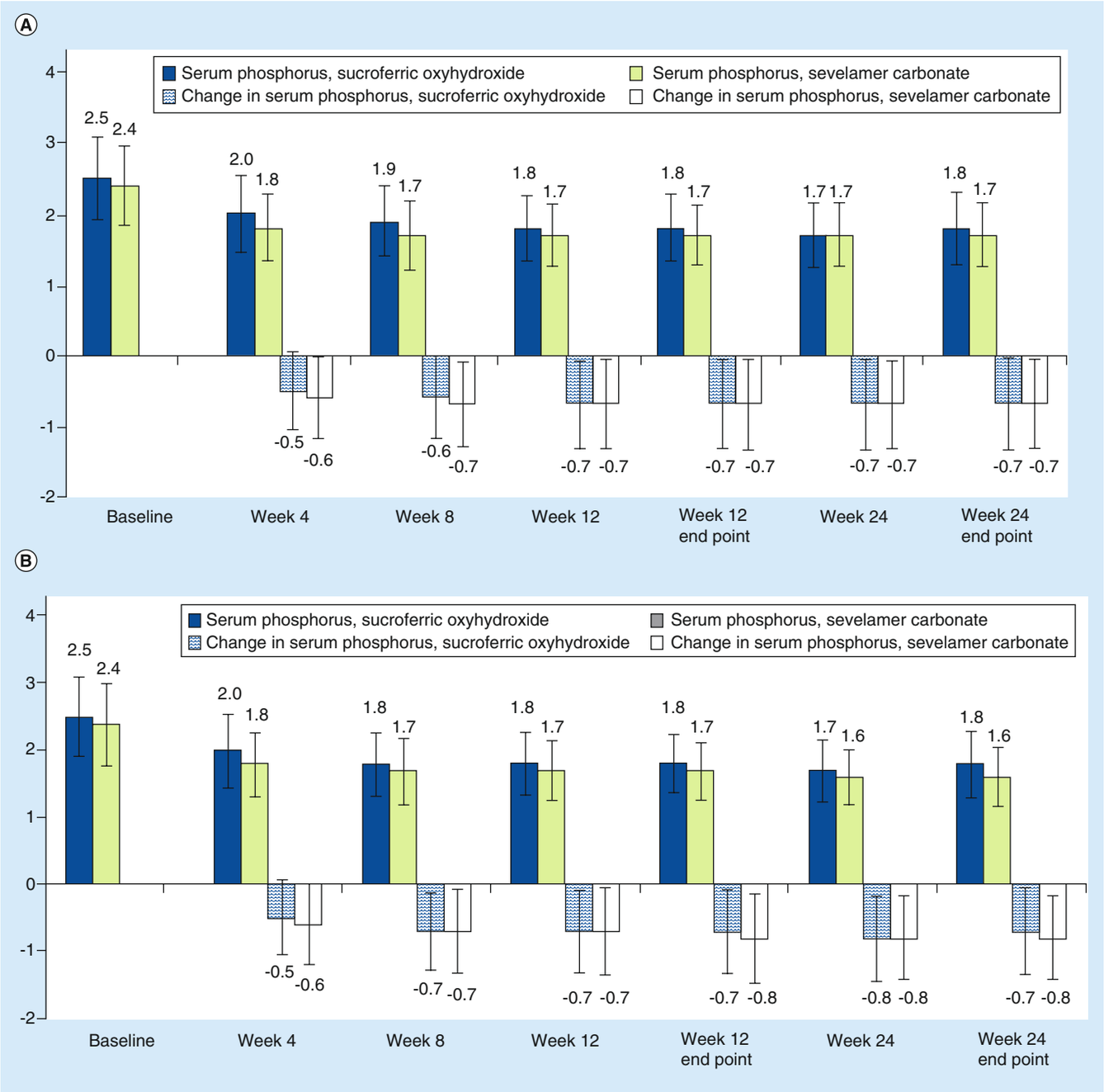

Figure 3. Mean (± standard deviation) serum phosphorus concentrations and mean (± standard deviation) serum phosphorus changes from baseline. (A) Analysis of patients randomized to treatment who received at least one dose of study medication and had at least one post-baseline evaluable efficacy assessment (n = 1041). **(B)** Analysis of patients randomized to treatment who received at least one dose of study medication, had at least one post-baseline evaluable efficacy assessment, had completed from baseline to week 12, had at least one evaluable serum phosphorus result at or after week 12, and had no major protocol deviations (n = 685). Data taken from [11].

Safety and tolerability were investigated further in the Phase III program. In the first 24 weeks there was a higher incidence of TEAEs reported in the sucroferric oxyhydroxide arm compared with the sevelamer carbonate arm (Table 1). AEs reported more frequently with sucroferric oxyhydroxide included diarrhea, discolored stools, and hyperphosphatemia. However, constipation and nausea were reported more frequently in the sevelamer carbonate arm. Incidences of severe and serious TEAEs and deaths were similar between sucroferric oxyhydroxide and sevelamer carbonate treatment groups. Few severe (sucroferric oxyhydroxide,

1.0%; sevelamer carbonate, 1.1%) or serious TEAEs (sucroferric oxyhydroxide, 0.3%; sevelamer carbonate, 0.0%) were related to study treatment, and no study drug-related fatal TEAEs were reported [11].

The most frequent TEAEs in either treatment group were GI related. Overall, the incidence of these TEAEs was higher in the sucroferric oxyhydroxide arm compared with the sevelamer carbonate arm (Table 1). This difference between treatment groups was largely due to higher incidences of discolored feces and diarrhea in the sucroferric oxyhydroxide arm compared with the sevelamer carbonate arm. All cases of discolored feces associated with sucroferric oxyhydroxide were reported during the titration phase of the study and this AE rarely led to withdrawal (0.7%). Stool discoloration is a well-known phenomenon when using oral drugs containing iron and does not impact diagnostic tests for occult blood in stool. Regarding diarrhea, this AE was generally mild in severity in both the sucroferric oxyhydroxide (69%) and sevelamer carbonate (58%) groups, and presented early in treatment. More patients experienced diarrhea during the titration phase compared with the maintenance phase for both sucroferric oxyhydroxide (17.3 vs 5.5%) and sevelamer carbonate (6.0 vs 2.3%). Moreover, cases of diarrhea typically resolved without the need for specific interventions or treatment changes, and led to withdrawal infrequently (sucroferric oxyhydroxide, 2.8%; sevelamer carbonate, 0.6%) [11]. It is important to note that a high proportion – approximately a third – of patients were taking sevelamer prior to their inclusion in the Phase III study. Therefore, the possibility of a selection bias in favor of sevelamer carbonate, which may have influenced the reporting of AEs, cannot be excluded.

Subgroup analysis showed that sucroferric oxyhydroxide was generally safe and well tolerated among patients receiving either hemodialysis or peritoneal dialysis, and that no major differences in the safety profile were observed between these two groups. In terms of laboratory parameters, median serum intact parathyroid hormone (iPTH) levels decreased significantly from baseline to week 24 in both treatment groups, although the decrease was more pronounced in the sucroferric oxyhydroxide group compared with the sevelamer carbonate arm (median values: -4.49 pmol/l [-40.8 pg/ml] vs -1.59 pmol/l [-14.5 pg/ml]; p = 0.040) [11]. As discussed below, this may be explained by the fact that vitamin D receptor agonists (VDRAs) are frequently prescribed to control secondary hyperparathyroidism, and that sevelamer carbonate, but not sucroferric oxyhydroxide, may interfere with their action [33,34].

A further subgroup analysis revealed that treatment with sucroferric oxyhydroxide was well tolerated in patients with diabetes [32]. The proportion of patients experiencing TEAEs appeared to be slightly higher in diabetic (sucroferric oxyhydroxide, 92%; sevelamer carbonate, 94%) versus non-diabetic (sucroferric oxyhydroxide, 87%; sevelamer carbonate, 85%)

Table 1. Treatment-emergent adverse events occurring in ≥5% of patients in either treatment group†.

Adverse event	Sucroferric oxyhydroxide (n = 707), %	Sevelamer (n = 348), %
Any TEAE	83.2	76.1
Any severe TEAE	11.5	10.9
Any serious TEAE	18.2	19.8
Withdrawals due to TEAEs	15.7	6.6
Death	1.8	2.0
Any GI TEAE	45.1	33.6
Any GI TEAE, excluding isolated discolored feces	39.0	33.3
Diarrhea	20.1	7.5
Feces discolored	15.4	0.3
Hyperphosphatemia	11.2	7.8
Nausea	7.2	11.2
Hypertension	6.4	7.5
Vomiting	4.4	5.5
Constipation	3.8	7.2

†Stage 1; n = 1055.
GI: Gastrointestinal; TEAE: Treatment-emergent adverse event.
Data taken from [11].

patients, with no meaningful differences between treatment groups. There was also no clinically significant effect on serum glucose levels [32].

Safety data from the extension study largely affirmed that TEAEs emerged early during treatment [30]. The overall incidences of GI TEAEs during the extension study were 25.6% in the sucroferric oxyhydroxide arm and 19.1% in the sevelamer carbonate arm. In particular, the incidence of diarrhea in the sucroferric oxyhydroxide arm was 8.2% (vs 5.6% in the sevelamer carbonate arm) [30]. A *post-hoc* analysis of pooled safety data over 1 year confirmed that there was a significantly higher relative risk (RR) of mild and moderate diarrhea with sucroferric oxyhydroxide treatment compared with sevelamer carbonate treatment ($p < 0.05$), but that there was no significant difference in the RR of severe diarrhea between treatment groups ($p = 0.221$) [35]. Conversely, patients receiving sucroferric oxyhydroxide had significantly lower RRs for nausea, decreased appetite and constipation compared with those receiving sevelamer carbonate ($p < 0.05$) [35].

A higher incidence of TEAEs leading to withdrawal was observed with sucroferric oxyhydroxide (sucroferric oxyhydroxide, 15.7%; sevelamer carbonate, 6.6%) during the initial 24 weeks [11] and over the entire 1-year treatment period (sucroferric oxyhydroxide, 20.9%; sevelamer carbonate, 10.3%) [30]. Withdrawals due to TEAEs predominantly occurred during the first 24 weeks of treatment. Moreover, GI events (e.g., diarrhea, nausea, constipation, and vomiting) accounted for large proportions of the TEAEs leading to withdrawal in both sucroferric oxyhydroxide and sevelamer groups (54.0 and 43.5%, respectively) [11]. As mentioned above, over a third of the patients enrolled in the Phase III study were previously being treated with sevelamer that may have impacted reporting of TEAEs.

Vitamin D metabolism

A possible undesirable effect of phosphate binders is the adsorption or degradation of nutrients, necessitating supplementation of these dietary components [36]. For example, sevelamer HCl adsorbs copper and zinc ions and a number of vitamins [37]. Therefore, in addition to having high efficacy, a low pill burden, and low risk of side effects, a phosphate binder should also have minimal interaction with other dietary nutrients.

Study data indicate that sucroferric oxyhydroxide does not have a clinically relevant impact on vitamin D metabolism. Levels of the biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]2D) and its prehormone, 25-hydroxyvitamin D (25[OH]D), were assessed in subgroup analyses of the initial Phase III study and its 28-week extension [38,39]. In patients who had received at least one dose of study medication in the initial study (n = 1055), apparent increases in levels of 1,25(OH)D were observed from baseline to week 24 in both the sucroferric oxyhydroxide (3.05 pmol/l; 1.27 pg/ml) and sevelamer carbonate (0.86 pmol/l; 0.36 pg/ml) groups [38]. Conversely, levels of 25(OH)D appeared to decrease from baseline to week 24 in the sucroferric oxyhydroxide (-8.69 nmol/l; -3.48 ng/ml) and sevelamer carbonate (-12.15 nmol/l; -4.86 ng/ml) groups, which may have been a seasonally dependent effect [38]. Among patients completing 1 year of treatment (n = 549), significant increases in mean levels of 1,25(OH)D were observed across both treatment groups (sucroferric oxyhydroxide: 8.08 pmol/l; 3.37 pg/ml [$p = 0.0006$]; sevelamer carbonate: 5.00 pmol/l; 2.08 pg/ml [$p = 0.0112$]) [39]. There were no significant changes from baseline in mean levels of vitamin 25(OH)D [39].

A *post-hoc* analysis of Phase III data was also conducted to evaluate potential effects of sucroferric oxyhydroxide on oral VDRAs at 1 year of treatment, using serum iPTH concentrations as a surrogate marker (n = 525) [40]. In patients with CKD, VDRAs are an important means of controlling secondary hyperparathyroidism [33]. As expected, in patients taking no VDRAs, mean levels of iPTH increased in both the sucroferric oxyhydroxide (5.7 pmol/l; 51.8 pg/ml) and sevelamer carbonate (6.2 pmol/l; 56.4 pg/ml) groups. However, in patients taking oral VDRAs, there was a decrease in iPTH levels in the sucroferric oxyhydroxide group (-2.7 pmol/l; -24.5 pg/ml), indicating no interaction between VDRAs and sucroferric oxyhydroxide. By contrast, an increase in iPTH levels was observed in the sevelamer carbonate group (9.5 pmol/l; 86.4 pg/ml), consistent with a known interaction between sevelamer carbonate and oral calcitriol [34]. This difference between treatment groups was statistically significant ($p = 0.023$) [40].

Iron-related parameters

A further key requirement of an ideal phosphate binder is that it exhibits minimal systemic absorption. In this context, iron-related parameters have been extensively studied in clinical studies of sucroferric oxyhydroxide, and data suggest that there is minimal iron absorption and no iron accumulation in dialysis patients [11,27]. In the initial Phase III study, increases in some iron-related parameters were observed, for example, median serum ferritin concentrations increased in both treatment groups, whereas increases in transferrin saturation (TSAT) were only seen with sucroferric oxyhydroxide [11]. There were no significant changes in hemoglobin parameters [11]. Increases in iron-related parameters observed in the sucroferric oxyhydroxide group occurred early and plateaued with continuing treatment, indicat-

ing no accumulation of iron. There is also evidence that the observed changes in iron parameters were driven by concomitant use of intravenous iron products [41].

The impact of another iron-based phosphate binder, ferric citrate, on iron indices has been investigated. In a Phase II study (n = 55), administration of ferric citrate 4.5–11.25 g/day over 4 weeks to dialysis patients was associated with significant increases in iron, ferritin and TSAT serum levels from baseline ($p < 0.05$), which the authors linked to iron absorption [42]. A subsequent Phase III study (n = 90) also showed that significant increases in iron, ferritin and TSAT serum levels from baseline ($p \leq 0.01$) occurred following administration of ferric citrate 1.5–6.0 g/day for 12 weeks to non-dialysis patients with CKD. As a result, the iron status of patients administered this compound should be regularly assessed [12].

Conclusion

Clinical studies have shown that sucroferric oxyhydroxide is potent, being at least as effective in lowering serum phosphorus levels as sevelamer carbonate. The same studies showed that equivalent efficacy was attained by sucroferric oxyhydroxide with a pill burden almost a third lower than that required with sevelamer carbonate. This lower pill burden may result in increased patient compliance and, thus, ultimately better phosphate control. Sucroferric oxyhydroxide was generally well tolerated and demonstrated a robust safety profile. It was associated with discolored feces, as can be expected for an oral iron-based compound, and an increased frequency of mild diarrhea at the start of treatment, which was self-limiting. Further safety analysis showed that sucroferric oxyhydroxide administration led to minimal iron absorption without risk for iron overload or iron accumulation. Therefore, the use of sucroferric oxyhydroxide as a treatment to control serum phosphorous concentrations does not necessitate any additional monitoring of iron stores or iron-related parameters. The results obtained from clinical studies investigating this new phosphate binder will need corroborating with data derived from observations and evaluations conducted in the 'real-life' clinical practice setting. In summary, the recently approved iron-based phosphate binder sucroferric oxyhydroxide is a valuable new option for the treatment of hyperphosphatemia in CKD patients requiring hemodialysis or peritoneal dialysis.

Future perspective

Over the past decade, observational and *in vitro* cell culture studies linked hyperphosphatemia with cardiovascular morbidity and mortality in patients with CKD undergoing dialysis [43–46]. This link was demonstrated with a 42% mortality reduction in association with phosphate binder therapy in the well-known ArMORR study in incident dialysis patients (n = 8610) [8]. Recent studies aim toward measurement of alternate biomarkers, such as FGF-23 [47], and its relationship to hyperphosphatemia, as well as the use of phosphate binder therapy in the stage 3 and 4 CKD population [48–50]. Some of these studies have demonstrated that treatment with non-calcium-based phosphate binders, such as lanthanum carbonate, is associated with reductions of serum FGF-23 [48], and similar results have been observed with sucroferric oxyhydroxide [51]. Analysis of the initial Phase III study and its 28-week extension showed that over 1 year, baseline FGF-23 concentrations decreased in both the sucroferric oxyhydroxide and sevelamer carbonate treatment groups [51]. As a better understanding of the underlying physiologic mechanisms between hyperphosphatemia and vascular mineralization emerges, it is important for clinicians to adapt multiple elements of the therapeutic approach to controlling phosphorus levels including dietary phosphate restriction, intensified hemodialysis, and the use of novel phosphate binders.

Dietary phosphate restriction appears to be a practical adjunct to phosphate binders and a recent prospective study, by Sullivan *et al.*, found that reduction in phosphate additives in an incident dialysis population led to a significant reduction in phosphorus levels (-0.6 mg/dl after 3 months versus placebo) [52]. However, the application of dietary restriction of phosphate is difficult due to lack of patient compliance, the inability to regulate and label foods properly, and the risk of malnutrition. Phosphorus containing additives are increasingly being used in processed and fast foods in order to maintain color, moisture, and flavor. Therefore, individual phosphate consumption in the USA is rising [53] and it is hoped that the FDA will mandate labeling of phosphate content. Better educating both patients and their physicians of dietary exposure to inorganic phosphate may lead to limiting phosphate intake and possibly ultimately reduce the overall use of these additives by food-makers.

In addition to decreasing phosphate exposure, the use of more effective regimens of dialysis should be expanded. Increasing both the frequency and/or duration of hemodialysis sessions has been shown to enhance phosphorus clearance. Preliminary data have demonstrated that extended nocturnal hemodialysis on 5–6 days weekly results in a decrease in serum phosphorus of up to 1.24 mg/dl in comparison to conventional hemodialysis [54]; however, the issues of cost and availability have thus far made this a difficult option.

The evolution of phosphate binders has led to a number of studies comparing calcium and non-calcium-based phosphate binders, including sevelamer, lanthanum, and magnesium-based compounds. The RIND study [55] on

hemodialysis patients, as well as a recent, randomized study on non-dialysis patients (CKD Stage 3–4), demonstrated reduced all-cause mortality with sevelamer. However, none of the available phosphate binders are ideal because, as stated above, they are associated with large pill burden, have variable GI absorption and tolerance, and have possible side effects of increased cardiovascular risk and hepatotoxicity. Thus, a new generation of phosphate binders, including colestilan, niacin/nicotinamide, and iron-based compounds are a welcomed addition to our current armamentarium. Colestilan is a well-known drug for the treatment of hyperlipidemia and has a similar mechanism of anion exchange as sevelamer, and has received regulatory approval for the treatment of hyperphosphatemia. Another medication, nicotinamide, which is an inhibitor of the intestinal sodium-phosphate cotransporter-2b (NaPi-2b), has also shown encouraging results for lowering serum phosphorus, when used alone or as an add-on to established phosphate binder therapy [56–58]. The potential of salivary phosphate secretion as a marker of hyperphosphatemia [6,59], and the use of salivary phosphate binders as a means of reducing serum phosphorus concentration in CKD patients [7], have been proposed. Preliminary studies with chitosan-loaded chewing gum initially showed reductions in serum phosphorus concentrations [60,61]; however, subsequent controlled studies have yet to affirm its effectiveness [62–64]. Finally, iron-based phosphate binders such as sucroferric oxyhydroxide and ferric citrate are potential new alternatives for treating hyperphosphatemia. Both sucroferric oxyhydroxide and ferric citrate have been approved for the control of serum phosphorus concentrations in dialysis patients. Sucroferric oxyhydroxide, in addition to being effective and generally well tolerated, has also been shown to have a low pill burden compared with ferric citrate. Clearly, future studies are required to determine if these therapies are able to reduce cardiovascular morbidity and mortality, in addition to controlling hyperphosphatemia, in patients with CKD and those undergoing dialysis.

Financial & competing interests disclosure

This study was funded by Vifor Pharma. VR is an employee of Vifor Pharma Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support provided by AXON Communications (Richmond, UK) funded by Vifor Pharma Ltd.

Executive summary

- The use of oral phosphate binders in Stage 4 and 5 chronic kidney disease is a mainstay of therapy for hyperphosphatemia, and is associated with a significant reduction in mortality. The properties of an ideal phosphate binder include a high phosphate-binding capacity in the gastrointestinal tract, low pill burden, and a good safety profile.
- Sucroferric oxyhydroxide (Velphoro®) is a novel, iron-based phosphate binder approved for the control of serum phosphorus levels in chronic kidney disease patients receiving dialysis.
- In a Phase II clinical trial, the efficacy of sucroferric oxyhydroxide was examined and the primary end point of the study was met, with a significant decrease in serum phosphorus concentrations observed in four active dosing groups.
- In a Phase III program, a two-stage, randomized, international, multicenter, open-label study compared sucroferric oxyhydroxide to sevelamer carbonate in the management of hyperphosphatemia in patients undergoing hemodialysis or peritoneal dialysis. In both treatment groups, rapid reductions in mean serum phosphorus were observed and maintained at the week 24 end point, with the non-inferiority of sucroferric oxyhydroxide to sevelamer carbonate demonstrated with a 97.5% confidence interval. In addition, an extension study enrolling 659 patients demonstrated that serum phosphorus control was maintained with both sucroferric oxyhydroxide and sevelamer carbonate following 1 year of treatment.
- One advantage of sucroferric oxyhydroxide is its association with a low pill burden in comparison to sevelamer carbonate in Phase III clinical trials (mean 3.1 vs 8.1 pills/day), allowing for better adherence.
- With regard to safety and tolerability, adverse events reported more frequently in a Phase III clinical trial with sucroferric oxyhydroxide, included diarrhea, discolored stools, and hyperphosphatemia. However, incidences of severe and serious treatment-emergent adverse events were similar between the sucroferric oxyhydroxide and sevelamer carbonate groups. Finally, a subgroup analysis revealed that treatment with sucroferric oxyhydroxide was generally well tolerated among both hemodialysis and peritoneal dialysis patients.
- In conclusion, clinical studies have shown that sucroferric oxyhydroxide is at least as effective in lowering serum phosphorus levels as the established phosphate binder, sevelamer carbonate, but with a lower pill burden and similar safety profile. Further clinical studies with the use of iron-based phosphate binders will be necessary to continue to explore this valuable treatment option for the treatment of hyperphosphatemia in patients with advanced chronic kidney disease.

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