Chronic kidney disease mineral bone disorder (CKD-MBD), present in dialysis patients, is a complex syndrome involving mineral and bone laboratory abnormalities, clinical and histological bone disease and cardiovascular calcifications associated with increased risk of cardiovascular morbidity and mortality [1]. Not all components of CKD-MBD are present in all patients at all times, but they are highly interrelated. Hyperphosphatemia is one of its most frequent components that have traditionally been managed with dietary restriction and phosphate binding in the gut, but the beneficial effects of phosphate reduction on mortality and cardiovascular outcomes in CKD stage 5D are still unknown. Studies analyzing prospective observational cohorts (DOPPS and COSMOS) have shown that phosphate binder administration decreases all-cause and cardiovascular mortality risk [2, 3]. These association studies need to be confirmed by randomized controlled trials to prove the observed beneficial effect.

Advantages and disadvantages with currently available phosphate binders
Phosphate binders, both calcium-based and calcium-free, are recommended to lower serum phosphate and prevent hyperphosphataemia in CKD patients. Evidence supports that phosphate binders are equally efficacious in lowering serum phosphate concentrations if they are adequately titrated. Because of the absence of evidence of improved survival rate by any one of the calcium-free intestinal phosphate binders, and because of their more than 50–70-fold lower cost, the Kidney Disease Improving Global

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Outcomes (KDIGO) guidelines has recommend the use of calcium-based phosphate binders as first-line treatment in CKD5D patients [4]. However, the new concept of CKD-MBD has clearly influenced clinical guidelines. KDOQI guidelines from the National Kidney Foundation recommended in 2003 that calcium-based phosphate binders should be avoided to treat hyperphosphatemia in the presence of cardiovascular calcifications [5]. In 2009, the KDIGO and other international guidelines reinforced and extended this recommendation by stating that it is reasonable to choose oral phosphate binder therapy taking into consideration other components of CKD-MBD: In the presence of vascular/valvular calcification, calcium-free phosphate binders should be preferred.

A recent meta-analysis has combined data from randomized trials to update the effect of calcium-based versus calcium-free phosphate binders on all-cause mortality in patients with CKD as the primary outcome [6]. Analysis of the 11 randomized trials (4622 patients) that reported an outcome of mortality showed that patients assigned to calcium-free binders (sevelamer and lanthanum carbonate) had a 22% reduction in all-cause mortality compared with those assigned to calcium-based phosphate binders (odd ratio 0.78, 95% CI 0.61–0.98). However, further studies are needed to identify if the reduction in mortality is due to reduced cardiovascular mortality (probably in relation to decreased progressive arterial calcification) and to assess whether mortality differs by type of calcium-free phosphate binder.

In addition to this important aspect of phosphate binder therapy, there are other aspects that should be considered. The first aspect is the potential for gastrointestinal (GI) absorption of the active moieties that could be harmful or beneficial in the body. The second aspect is whether the phosphate binders can bind not only phosphate but also harmful or useful substances in the gut. The third aspect is the compliance to phosphate binder therapy. Finally, the fourth aspect is the effect of different phosphate binders on all-cause mortality shown in Table 2.

### Iron-based phosphate binders

Iron-based phosphate binders represent a new class of phosphate binders recently introduced. Several iron-based phosphate binders have undergone testing in clinical trials: Ferric Citrate (JTT-751, Zerenex®), Sucroferric oxhydroxide (PA21- Velphoro®), Ferragate, SBR759 and PT20. Ferragate (iron-magnesium hydroxycarbonate) and SBR759 development are currently on hold (Table 1).

**Ferric citrate (JTT-751—ZERENEX®)**

Ferric citrate is approved for anemia management in ESRD in Japan and has recently been approved by the US Food and Drug Administration as an oral treatment for hyperphosphatemia in CKD. The summary of published studies seen in Table 2.

**Animal studies.** Normal rats fed a diet containing 0.3, 1 or 3% ferric citrate (JTT-751) for 7 days had increased fecal phosphorus excretion with reduced phosphorus absorption and urinary phosphorus excretion. After feeding CRF rats (induced by a 0.75% adenine diet) for 35 days with ferric citrate (1 or 3%) in the dietary admixture, serum phosphorus levels, calcium-phosphorus product and calcium content in the aorta were reduced. Serum intact PTH levels and the incidence and severity of parathyroid hyperplasia were also decreased. This was also associated with a reduction in femoral bone fibrosis, porosity and osteoid formation [26].
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Table 1. Main characteristic of iron-based intestinal phosphate binders

<table>
<thead>
<tr>
<th>Name</th>
<th>Composition</th>
<th>Recommended daily dose</th>
<th>Mean daily number of pills</th>
<th>Main side effects</th>
<th>Pros/Cons</th>
<th>Pharmaceutical company</th>
</tr>
</thead>
<tbody>
<tr>
<td>VELPHORO PA21</td>
<td>Sucroferric oxyhydroxide coordination complex</td>
<td>1500 mg</td>
<td>Three pills per day</td>
<td>Discolored feces diarrhea, nausea</td>
<td>Iron not absorbed</td>
<td>Vifor (Fresenius)</td>
</tr>
<tr>
<td>ZERENEX JTT-751</td>
<td>Ferric citrate</td>
<td>6000 mg</td>
<td>Six pills per day</td>
<td>Discolored feces diarrhea, nausea</td>
<td>Iron absorbed risk of higher ferritin</td>
<td>Keryx Biopharmaceuticals</td>
</tr>
<tr>
<td>ALPHAREN Farmagate SBR-759 PT20</td>
<td>Iron-magnesium hydroxycarbonate Polymeric iron (III) Ferric oxide adipate</td>
<td>3000 mg</td>
<td>Three pills per day</td>
<td>Discolored feces gastrointestinal</td>
<td>Elevation in serum Mg levels</td>
<td>Shire</td>
</tr>
</tbody>
</table>

Table 2. Summary of published trials with ferric citrate

<table>
<thead>
<tr>
<th>Author/journal year</th>
<th>Study phase</th>
<th>Subjects enrolled</th>
<th>Comparator</th>
<th>Duration</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokoyama K Am J Nephrol 2012 [21]</td>
<td>Dose-response</td>
<td>192</td>
<td>Placebo</td>
<td>28 days</td>
<td>Pi decrease is dose-dependent up to 6 g/day Pi decreased –2.16 with 3 g/day, Pi &lt; 5.5 in 50% with 3 g/day FC 6 g/day decrease Pi –1.9 ± 1.7 mg/dL and 8 g/day, –2.1 ± 2.0 mg/dL Pi –0.82 mmol/L with FC and –0.78 with sevelamer (non-inferiority) with sig. increase in ferritin and transferrin saturation</td>
</tr>
<tr>
<td>Dwyer JP Am J Kid Dis 2013 [22]</td>
<td>Dose-response</td>
<td>151</td>
<td>None</td>
<td>28 days</td>
<td>FC 6 g/day decrease Pi –1.9 ± 1.7 mg/dL and 8 g/day, –2.1 ± 2.0 mg/dL Pi –0.82 mmol/L with FC and –0.78 with sevelamer (non-inferiority) with sig. increase in ferritin and transferrin sat</td>
</tr>
<tr>
<td>Yokoyama K Nephrol Dial Transp 2014 [23]</td>
<td>III</td>
<td>230</td>
<td>Sevelamer HC 3–9 g/day</td>
<td>12 weeks</td>
<td>Pi decrease with 4 and 6 g/day; increase in ferritin and transferrin sat</td>
</tr>
<tr>
<td>Lee CT Nephrol 2014 [24]</td>
<td>III</td>
<td>166</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>Pi decrease with 4 and 6 g/day; increase in ferritin and transferrin sat</td>
</tr>
<tr>
<td>Lewis JB JASN 2014 [25]</td>
<td>III</td>
<td>441</td>
<td>Active control</td>
<td>52 weeks</td>
<td>Pi –2.2 mg/dL compared to Placebo and similar to active control but higher mean iron parameters with less IV iron</td>
</tr>
</tbody>
</table>

Clinical studies. A phase–2, open-label study was conducted in hemodialysis patients to evaluate the short-term safety, tolerability and iron absorption of ferric citrate when used as a phosphate binder. Fifty-five subjects were enrolled in two periods. Subjects discontinued their previous binders and started 4.5 g/day of ferric citrate (period 1) or 6 g/day (period 2) and were titrated for 4 weeks to maintain phosphorus between 3.5 and 5.5 mg/dL. Ferric citrate was well tolerated. The subjects’ mean dose of ferric citrate was 7.1 ± 2.4 g/day at the end of 4 weeks. Mean phosphorus was 5.9 ± 1.4 mg/dL at baseline on their previous phosphate binder and was not significantly different at 4 weeks on ferric citrate (5.4 ± 1.4 mg/dL). GI adverse events included stool discoloration (69%), constipation (15%) and bloating (7%). Mean iron parameters (ferritin, iron and iron saturation) increased significantly at the end of follow-up [27].

Three phase-3 prospective randomized trials have been published recently in hemodialysis patients comparing ferric citrate efficacy and safety in phosphate control. The first study investigated the dose-response and safety of ferric citrate (JTT-751) among Japanese hemodialysis patients. This was a multicenter, randomized, placebo-controlled, double-blind, parallel-group, comparative study that included a total of 192 subjects with serum phosphorus (P) levels between 6.1 and 10.0 mg/dL [21]. Patients were randomized to receive ferric citrate (1.5, 3 or 6 g/day) or placebo treatment for 28 days. Serum P levels were significantly reduced in a dose-dependent manner up to 6 g/day. In the full analysis set, the mean change in serum P level at week 4 was 0.04, −1.28, −2.16 and −4.10 mg/dL in the placebo, 1.5-, 3- and 6-g/day groups, respectively. Overall, a reduction in serum P levels to ≤3.5 mg/dL was achieved in 25, 16.7, 50.0 and 92.6% of subjects, in the placebo, 1.5-, 3- and 6-g/day groups, respectively. The most common adverse events were mild and GI in nature. In 25 patients, treatment was discontinued due to increased transferrin saturation ≥50%; however, this was not considered to be a safety issue [21].

The second was a prospective, multicenter, open-label, randomized clinical trial performed in 151 maintenance hemodialysis patients with hyperphosphatemia. A fixed dose of ferric citrate was taken orally as a phosphate binder for up to 28 days (1, 6 or 8 g/day). The primary outcome was the dose-response of ferric citrate on serum P level; secondary outcomes were safety and tolerability. Mean baseline phosphorus levels were above 7 mg/dL in all groups. Phosphorus levels decreased in a dose-dependent manner (mean change at the end of treatment, −0.1 ± 1.3 mg/dL in the 1-g/day group, −1.9 ± 1.7 mg/dL in the 6-g/day group and −2.1 ± 2.0 mg/dL in the 8-g/day group). The mean difference in reduction in P levels between the 6- and 1-g/day groups was 1.3 mg/dL (95% CI 0.69–1.9; P < 0.001). The most common adverse event was stool discoloration [22].

In a third Phase-3, multicenter, open-label, parallel-group study, a total of 230 patients with a serum phosphate ≥1.97 and <3.23 mmol/L were randomized to ferric citrate (doses between 1.5 and 6.0 g/day) or sevelamer hydrochloride (doses between 3.0 and 9.0 g/day) for 12 weeks. The primary outcome was change in serum P from
baseline to end of treatment. Secondary outcomes included the changes in corrected serum calcium and intact PTH. The changes in ferritin, transferrin saturation and erythropoiesis-stimulating agent (ESA) dose were additional outcomes. Changes in serum P at the end of treatment were −0.82 mmol/L in the JTT-751 group and −0.78 mmol/L in the sevelamer group, establishing non-inferiority of ferric citrate to sevelamer. Corrected serum calcium increased and PTH decreased from baseline within both groups; changes between groups were similar. GI disorders were the most common adverse events in both groups; the incidence of diarrhea was higher in ferric citrate, while constipation occurred frequently in the sevelamer group. Treatment with ferric citrate resulted in significant relative increases in serum ferritin and transferrin saturation [23].

In another prospective, double-blind, placebo-controlled, randomized trial study carried out in five hospitals in Taiwan, 166 hemodialysis patients completed the 56-day study. Serum phosphorus levels declined while serum ferritin level/transferrin saturation increased significantly in both ferric citrate 4 and 6 g/day groups (P < 0.05 for 4 and 8 weeks). Most adverse events were mild to moderate and were comparable among the three groups [24].

In another sequential, randomized trial, 441 subjects on dialysis were randomized to ferric citrate or active control in a 52-week active control period followed by a 4-week placebo control period, in which subjects on ferric citrate who completed the active control period were re-randomized to ferric citrate or placebo. The primary analysis compared the mean change in phosphorus between ferric citrate and placebo during the placebo control period. A sequential gatekeeping strategy controlled study-wise type 1 error for serum ferritin, transferrin saturation, and intravenous iron and erythropoietin-stimulating agent usage as pre-specified secondary outcomes in the active control period. Ferric citrate better controlled phosphorus compared with placebo, with a mean treatment difference of −2.2 ± 0.2 mg/dL (mean ± SEM) (P < 0.001). Active control period phosphorus was similar between ferric citrate and active control, with comparable safety profiles. Subjects on ferric citrate achieved higher mean iron parameters [ferritin = 899 ± 488 ng/mL (mean ± SD); transferrin saturation = 39 ± 17%] versus subjects on active control [ferritin = 628 ± 367 ng/mL (mean ± SD); transferrin saturation = 30 ± 12%; P < 0.001 for both]. Subjects on ferric citrate received less intravenous elemental iron (median = 12.95 mg/week ferric citrate; 26.88 mg/week active control; P < 0.001) and less erythropoietin-stimulating agent (median epoetin-equivalent units per week: 5306 units/week ferric citrate; 6951 units/week active control; P = 0.04). Hemoglobin levels were statistically higher on ferric citrate. Thus, ferric citrate is an efficacious and safe phosphate binder that increases iron stores and reduces intravenous iron and erythropoietin-stimulating agent use while maintaining hemoglobin [25].

Pharmacoeconomic studies. A cost-effective study from a managed-care perspective by Mutell et al. [28] demonstrated the potential for cost savings with the use of ferric citrate compared with other phosphate binders in that study, monthly ESA cost was projected to be reduced by 8.15%, and IV iron cost by 33.2%. A Monte Carlo simulation demonstrated a reduction of US$160 per month in overall dialysis cost per patient with the use of ferric citrate. In another study, the projected cost reduction for ESA and iron for ESRD, based on the use of ferric citrate as a phosphate binder agent was modeled. They found that ferric citrate usage could result in a 20% reduction in ESA usage and 40% reduction in IV iron usage, resulting in 0.9–1.1 billion USD savings [29]. Presently, IV iron and ESAs are part of the bundled dialysis payment in the US, while phosphate binders are paid by private insurers, Medicare part D or the patient. Thus, the cost savings would be for the dialysis units while the cost of phosphate binder therapy (ferric citrate) would be for other payers.

Ferric citrate may be more suited for chronic treatment of hyperphosphatemia in CKD patients requiring iron supplements but its use may produce negative effects as the increased risk of aluminum absorption due to the presence of citrate in the salt [30].

Sucroferric oxyhydroxide (PA21—Velphoro®) Sucroferric oxyhydroxide is an iron-based calcium-free chewable phosphate binder developed by Vifor Pharma recently approved by the US FDA for the treatment of hyperphosphatemia of CKD patients on dialysis. In June 2014, the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending marketing authorization for this iron phosphate binder. The summary of published studies seen in Table 3.

Animal studies. The efficacy of PA21, Sucroferric oxyhydroxide, was evaluated in controlling calcium/phosphate disorders and preventing vascular calcifications in uremic rats. Rats with adenine-diet-induced CRF were randomized to receive PA21 0.5, 1.5 or 5% or CaCO3 3% in the diet for 4 weeks, and were compared with uremic and non-uremic control groups. After 4 weeks of phosphate...
binder treatment, serum P was reduced with CaCO3 3%, PA21 1.5% and PA21 5% compared to CRF controls. Intact PTH was strongly reduced in the PA21 5% and CaCO3 3% CRF groups to a similar extent versus CRF controls. A lower serum fibroblast growth factor 23 concentration was observed in the PA21 5%, compared with CaCO3 3% and CRF, control groups. PA21 5% CRF rats had a lower vascular calcification score compared with CaCO3 3% CRF rats and CRF controls [33].

**Phosphate-binding capacity studies.** The iron-based agent PA21 has high phosphate-binding capacity in vitro. Phosphate adsorption and Fe release were assessed under conditions simulating administration of PA21 on an empty stomach and full stomach across a pH range to which PA21 would be exposed during passage through the GI tract. PA21 showed a robust phosphate-binding capacity over the entire physiologically relevant pH range. The high binding capacity at low pH indicates that phosphate binding could begin in the stomach. In that experimental setting, the maximal bound phosphate to Fe ratio was 0.47 mmol P/mmol Fe. The largest amount of Fe release was observed at the lowest pH without phosphate and was much lower in the presence of phosphate. These results are in line with the formation of iron phosphate at low pH, as indicated by X-ray photoelectron spectroscopy and thermodynamic calculations. Fe release was minimal (≤ 0.35%) across pH 2.5–8.5. These studies demonstrate that PA21 has potent phosphate-binding capacity and low iron release over a physiologically relevant pH range in the GI tract [34].

**Iron absorption studies.** A study was undertaken to investigate the uptake of iron after oral administration of PA21 in order to identify any potential risk of iron overload in the clinical setting, and to assess the effect of PA21 on serum P levels prior to larger trials over a longer treatment period. An open-label, Phase I study was undertaken in which PA21 0.0 g/day was administered for 7 days to 8 non-dialysis-dependent CKD patients (Stages 3–4), 8 maintenance hemodialysis patients and 8 healthy subjects. In addition, a single dose of radiolabeled PA21 was administered to determine iron uptake. Median iron uptake (range) was 0.06% (0.008–0.44%), 0.02% (0–0.04%) and 0.43% (0.16–1.25%) in the non-dialysis-dependent CKD patients, hemodialysis patients and healthy subjects, respectively [35].

**Clinical studies.** A randomized, active-controlled, multi-center, open-label, dose-finding study was undertaken at 50 clinical sites in Europe and the United States. Hemodialysis patients were randomized to receive PA21 at dosages of 1.25, 5.0, 7.5, 10.0 or 12.5 g/day or sevelamer-HCl 4.8 g/day for 6 weeks. The primary efficacy endpoint was the change in serum P concentration from baseline. There were 154 participants who were randomized and received the study drug. All groups except PA21 1.25 g/day showed a significant decrease in serum P. Mean decreases in serum P in PA21 10 g/day and 12.5 g/day were −2.00 ± 1.71 mg/dL and −1.69 ± 1.81 mg/dL, respectively. A similar decrease to sevelamer-HCl (−1.06 ± 1.35 mg/dL) was seen with PA21 5.0 g/day (−1.08 ± 2.12 mg/dL) and 7.5 g/day (−1.25 ± 1.21 mg/day). Overall, 60.9% of participants randomized to PA21 and 57.7% randomized to sevelamer-HCl reported ≥1 adverse event. The most frequent adverse events were hypophosphatemia (18.0%) and discolored feces (11.7%) for the pooled PA21 dose groups, and diarrhea, hypophosphatemia and hypotension (each 11.5%) for sevelamer-HCl. Discontinuation due to adverse events occurred at a similar rate in PA21-treated (21.1%) and sevelamer-HCl-treated (23.1%) participants. PA21 5–12.5 g/day significantly reduces serum phosphorus in hemodialysis patients. The 5 g/day and 7.5 g/day dosages showed similar efficacy to 4.8 g/day of sevelamer-HCl [31].

The efficacy of PA21 was compared with that of sevelamer carbonate in an open-label, randomized, active-controlled phase III study. Seven hundred and seven hemodialysis patients with hyperphosphatemia received PA21 1.0–3.0 g per day and 348 received sevelamer 4.8–14.4 g per day for an 8-week dose titration, followed by 4 weeks without dose change, and then 12 weeks maintenance. Serum phosphorus reductions at week 12 were −0.71 mmol/L with PA21 and −0.79 mmol/L with sevelamer, demonstrating non-inferiority of, on average, three tablets of PA21 versus eight of sevelamer. Efficacy was maintained to week 24. Non-adherence was 15.1% (PA21) versus 21.3% (sevelamer). The percentage of patients that reported at least one treatment-emergent adverse event was 83.2% with PA21 and 76.1% with sevelamer. A higher proportion of patients withdrew due to treatment-emergent adverse events with PA21 (15.7%) versus sevelamer (6.6%). Mild, transient diarrhea, discolored feces and hyperphosphatemia were more frequent with PA21; nausea and constipation were more frequent with sevelamer. After 24 weeks, 99 hemodialysis patients on PA21 were re-randomized into a 3-week superiority analysis of PA21 maintenance dose in 50 patients versus low dose [250 mg per day (ineffective control)] in 49 patients. The PA21 maintenance dose was superior to the low dose in maintaining serum phosphorus control. Thus, PA21 was effective in lowering serum phosphorus in dialysis patients, with similar efficacy to sevelamer carbonate, a lower pill burden and better adherence [32].

CKD patients often have multiple comorbidities that may necessitate the daily use of several types of medication. Therefore, the potential pharmacokinetic drug–drug interactions between sucroferric oxyhydroxide and selected drugs commonly taken by dialysis patients were investigated. Five Phase I, single-center, open-label, randomized, three-period crossover studies in healthy volunteers investigated the effect of a single dose of sucroferric oxyhydroxide 1 g (based on iron content) on the pharmacokinetics of losartan 100 mg, furosemide 40 mg, metoprolol 40 mg, digoxin 0.5 mg and warfarin 10 mg. Pharmacokinetic parameters [including area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinite time (AUC∞)] and from 0 to 24 h (AUC0–24)] for these drugs were determined: alone in the presence of food; with sucroferric oxyhydroxide in the presence of food; 2 h after food and sucroferric oxyhydroxide administration. Systemic exposure based on AUC0–∞ for all drugs, and AUC0–24 for all drugs except metoprolol (for which AUC 0–8 h was measured), was unaffected to a clinically significant extent by the presence of sucroferric oxyhydroxide.
omeprazole (based on AUCon. There is also a low risk of drug
interactions between sucroferric oxyhydroxide and losartan, furosemide, digoxin and warfarin. There is also a low risk of drug–drug interaction with omeprazole (based on AUCon. Therefore, sucroferric oxyhydroxide may be administered concomitantly without the need to adjust the dosage regimens of these drugs [36].

Finally, it should be noted that the use of Velphoro in diabetic patients, in particular those treated by peritoneal dialysis, could interfere with capillary glucose tests and induce false results, since some of the saccharides contents of Velphoro could be metabolized to glucose, fructose and maltose.

Conclusion

Both ferric citrate and Sucroferric oxyhydroxide are effective phosphate binders, non-inferior to currently used phosphate binders. Ferric citrate may be more suited for the treatment of chronic hyperphosphatemia in CKD patients requiring iron supplements but its use may have been hampered by potential aluminum absorption. Sucroferric oxyhydroxide may be more suited for hyperphosphatemic CKD patients not requiring iron supplementation and its major benefit would be a low pill burden.

Conflict of interest statement. None declared.

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