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# Preclinical Pharmacokinetics, Pharmacodynamics and Safety of Sucroferric Oxyhydroxide

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**Abstract:** Sucroferric oxyhydroxide (VELPHORO®) is a polynuclear iron-based phosphate binder recently approved for the treatment of hyperphosphataemia in patients with chronic kidney disease (CKD). As a number of the available phosphate binders do not provide the optimal combination of good efficacy, adequate tolerability and low pill burden, sucroferric oxyhydroxide constitutes a promising alternative. Among the attributes of an ideal phosphate binder is minimal absorption and, hence, low risk of systemic toxicity. Accordingly, the iron-releasing properties and absorption, distribution, metabolism and excretion (ADME) profile of sucroferric oxyhydroxide, as well as the possibility of iron accumulation and toxicity, were investigated in a series of preclinical studies. The effect of sucroferric oxyhydroxide on the progression of vascular calcification was also investigated. Sucroferric oxyhydroxide exhibited a high phosphate-binding capacity and low iron-releasing properties across the physiological pH range found in the gastrointestinal tract. In the ADME studies, uptake of $^{59}$Fe-radiolabelled sucroferric oxyhydroxide was low in rats and dogs (<1% from a 50 mg Fe/kg bodyweight dose), with the majority of absorbed iron located in red blood cells. Long-term (up to 2 years) administration of sucroferric oxyhydroxide in rats and dogs was associated with modest increases in tissue iron levels and no iron toxicity. Moreoever, in uraemic rats, sucroferric oxyhydroxide was associated with reduced progression of vascular calcification compared with calcium carbonate. In conclusion, sucroferric oxyhydroxide offers a new option for the treatment of hyperphosphataemia, with a high phosphate-binding capacity, minimal iron release, and low potential for iron accumulation and toxicity.

**Keywords:** Chronic kidney disease (CKD), dialysis, hyperphosphataemia, phosphate, phosphate binder, preclinical, sucroferric oxyhydroxide.

## INTRODUCTION

Chronic kidney disease (CKD) is defined as prolonged damage of the kidney lasting more than 3 months, featuring structural or functional abnormalities and characterised by a reduced glomerular filtration rate (GFR), increased urinary albumin excretion, or a combination of the two [1-3]. A growing international public health concern, CKD has an estimated worldwide prevalence of 8–16% with a 5-year survival rate of just 46% for patients aged around 60 years [1, 4]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) has identified five stages of CKD according to the remaining level of kidney function, defined in terms of the GFR [2]. Patients in the latter stage of CKD (Stage 5) may experience kidney failure (end-stage renal disease, ESRD), requiring treatment with dialysis or transplantation [5].

The decline of kidney function in CKD is associated with a progressive decline in the homeostasis of various minerals and the disruption of bone metabolism, collectively known as CKD-mineral bone disorder (CKD-MBD) [6, 7]. Phosphorus homeostasis plays a key role in CKD-MBD [8]. In people with Stage 4 or Stage 5 CKD, the rate of phosphorus excretion declines until the rate of dietary intake exceeds excretion, leading to hyperphosphataemia [9]. Hyperphosphataemia occurs in almost all patients undergoing dialysis, despite dietary restriction of phosphate, and may begin in CKD Stage 3 [6, 9].

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The disturbances of mineral homeostasis found in CKD-MBD have been associated with a risk of mortality [10, 11]. In a systematic review of 35 studies, Covic *et al.* found a significant relationship between mineral parameters and all-cause mortality, cardiovascular mortality and cardiovascular events in patients with CKD [11]. Of the three mineral metabolism parameters investigated (phosphorus, calcium and parathyroid hormone [PTH]), phosphorus was associated with the greatest risk of death; of the 35 studies included in the review, 17 assessed the all-cause mortality risk associated with high serum phosphorus and all but one demonstrated a significant relationship, compared with six of nine studies for calcium and seven of eleven studies for PTH. An earlier retrospective study of 40,538 haemodialysis patients in the United States of America (USA) also found step-wise increases in the relative risk (RR) of death and the risk of cardiovascular hospitalisation with increases of serum phosphorus concentrations above 5.0 mg/dL [12]. RR of death also showed a step-wise increase with increases in serum calcium within four strata of serum phosphorus concentrations (calcium concentrations were investigated with respect to serum phosphorus concentrations due to the tendency of the serum concentrations of each mineral to rise as the other falls, and vice versa). It is notable, however, that even within the normal range (2.5–4.5 mg/dL), increases in serum phosphorus concentrations may be associated with a significantly increased risk of death [6, 13].

Beyond the increased risk of all-cause mortality, hyperphosphataemia is specifically associated with increased risk of cardiovascular morbidity and mortality [14, 15]. In the United States Renal Data System (USRDS) study of 14,829 haemodialysis

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patients, step-wise relationships were found between serum phosphorus concentrations above 4.5 mg/dL and risk of cardiovascular events, and between serum phosphorus concentrations above 6.4 mg/dL and risk of death [15]. A systematic review and meta-analysis of 47 cohort studies, meanwhile, found a 35% increase in the risk of death for every 1 mg/dL increase in serum phosphorus in three adequately-adjusted studies, with an 18% increase in the risk of death for every 1 mg/dL increase in serum phosphorus in the 13 available studies overall [14].

The strong relationship between hyperphosphataemia and cardiovascular morbidity and mortality indicates that increased serum phosphorus has a specific deleterious effect on the cardiovascular system, thought to result from accelerated calcification of the vasculature [16]. *In vitro* studies of human aortic smooth muscle cell cultures have shown that, in the presence of inorganic phosphate at hyperphosphataemic levels (>4.33 mg/dL), the expression of osteoblastic differentiation markers is heightened and calcification increases in a concentration-dependent manner, suggesting that elevated serum phosphorus may predispose vascular smooth muscle cells to calcification [17]. A study of rat aortic smooth muscle cells, meanwhile, found increased calcification in the presence of inorganic phosphate, which was enhanced by the addition of ascorbic acid [18]. The same study also found that the expression of markers of osteoblastic differentiation was increased in the presence of inorganic phosphate plus ascorbic acid. The enhancing effect of hyperphosphataemia on vascular calcifications has also been demonstrated in clinical studies. For example, the Multi-Ethnic Study of Atherosclerosis found a graded relationship between serum phosphorus concentrations and vascular calcification of the descending thoracic aorta, aortic valve and mitral valve in 439 patients with moderate CKD and no clinical cardiovascular disease at baseline [19]. Furthermore, it was found that even moderate increases in serum phosphorus levels in people with CKD may lead to cardiovascular calcification.

Given the strength of the association between hyperphosphataemia in CKD and vascular calcification, cardiovascular morbidity and mortality, and all-cause mortality, it is to be expected that correcting the phosphorus balance is an important part of the therapeutic strategy for CKD [6]. Restricting dietary phosphorus intake is difficult to maintain and insufficient to normalise serum phosphorus concentrations in the majority of patients [4, 20, 21]. Standard intermittent haemodialysis performed three times weekly is also usually unable to maintain serum phosphate at appropriate levels, necessitating the use of phosphate binder therapy in patients with CKD [22]. Phosphate binders block the intestinal absorption of phosphate by forming an insoluble complex with it or by binding it into a resin [4, 20]. Research has confirmed that treatment with phosphate binders reduces mortality in CKD patients on dialysis [20]. Phosphate binders should be effective and well tolerated, with a high efficiency across a wide pH range (such as is found in the gastrointestinal [GI] tract) [9, 23]. To be considered ideal, however, a phosphate binder should also be palatable and inexpensive, with minimal potential for systemic absorption from the digestive tract and a sufficiently low pill burden to help ensure adherence to treatment [9, 23, 24].

Available phosphate binders include aluminium-, calcium- and magnesium-based binders, in addition to sevelamer and lanthanum carbonate [4, 25]. Each of these is associated with considerable disadvantages. Aluminium salts are highly effective but may be associated with toxicity, having been linked to encephalopathy and anaemia [26, 27]. Calcium acetate and calcium carbonate are effective and inexpensive but may increase hypercalcaemia, and have been associated with the progression of vascular calcification [27-30]. Sevelamer and lanthanum, meanwhile, are expensive and may be associated with GI side effects [4, 31]. In addition, sevelamer is associated with a high pill burden and there are concerns surrounding the potential for accumulation of lanthanum from lanthanum carbonate, although these have been reduced to some extent by more recent long-term data [9, 32-34]. Consequently, it may be concluded that an ideal phosphate binder combining the optimal set of characteristics listed above is not yet available on the market.

Sucroferric oxyhydroxide (VELPHORO®) is a novel, iron-based phosphate binder, which could provide an alternative to the existing phosphate binder treatment options [35, 36]. It is a polynuclear iron(III)-oxyhydroxide (pn-FeOOH) based compound in which the addition of sucrose prevents iron(III)-oxyhydroxide from ageing, thereby maintaining its phosphate binding capacity [35]. Sucroferric oxyhydroxide contains ~ 33% (m/m) of the active moiety pn-FeOOH (corresponding to an iron content of ~ 21% [m/m]), ~ 30% (m/m) sucrose, ~ 28% (m/m) starches and ≤10% (m/m) water [37]. Iron is an essential trace element, but in its free form it is toxic due to its ability to generate reactive oxygen species, which can damage biological macromolecules such as DNA [38-40]. The nature of iron toxicity and the possibility of intestinal iron absorption are, therefore, important considerations when assessing the therapeutic potential of an iron-based phosphate binder such as sucroferric oxyhydroxide.

In order to balance the simultaneous requirement for iron and its potential toxicity, in biological systems iron is bound with ligands, such as proteins or other prosthetic groups, which reduce its reactivity and attenuate its potential to cause harm [38, 41]. In humans, iron is stored in ferritin, which consists of an iron (III)-oxyhydroxide core stabilised by a protein shell, and it is transported in transferrin, a glycoprotein consisting of a single polypeptide chain with two iron-binding sites [41, 42]. Iron is mainly stored in the liver and spleen in hepatocytes and macrophages, but the maintenance of iron levels is regulated by absorption in the small intestine [38, 43]. Absorption of iron from the diet is low – typically between 1–2 mg/day of a dietary intake of 12–18 mg/day – but excessive dietary intake can cause iron overload and toxicity [38, 43, 44]. In the iron-overloaded state, liver levels of ferritin and haemosiderin (another iron storage molecule, of which denatured ferritin subunits are a major constituent) may be markedly increased [45, 46]. Haemosiderin has been implicated in tissue damage in the iron-overloaded state [47], and the liver is the organ most likely to be affected by iron overload [48]. Non-transferrin-bound iron (NTBI), which corresponds to iron that is unbound to either transferrin, ferritin or haem (the other major protein associated with iron), also plays a major role in iron overload [41]. When the serum transferrin iron capacity is saturated, the majority of any additional iron absorbed from the intestine is deposited in the liver, with 58–75% of NTBI removed from the serum by the liver in a single pass [41]. The capacity of the liver to excrete NTBI into bile may also be reduced under iron-loaded conditions [49]. Although the pathological significance of NTBI is unclear, there is growing evidence pointing towards a damaging effect [41]. For example, NTBI has been linked with heart disease and liver damage in patients with thalassaemia [50].

In order to be considered 'ideal', therefore, an iron-based phosphate binder would need to combine high phosphate-binding capacity with minimal systemic absorption of iron and low potential

for iron-related side effects, including those that may be associated with the release of iron in the GI tract. The iron(III)-oxyhydroxide component of sucroferric oxyhydroxide was designed to be practically insoluble, with the intention of minimising intestinal absorption [51]. Nevertheless, the avoidance of iron accumulation in the body must be demonstrated for an iron-based phosphate binder if it is to be considered safe, particularly given the likelihood of long-term use.

This review summarises the results of several preclinical *in vitro* and animal studies that evaluated the pharmacological properties of sucroferric oxyhydroxide, including its phosphate-binding capacity, iron release and systemic absorption, and potential long-term effects on iron status and progression of vascular calcification.

## PRECLINICAL DATA REVIEW

The phosphate binding and iron-releasing properties of sucroferric oxyhydroxide were assessed *in vitro* under conditions simulating administration on both an empty stomach and a full stomach, across the typical pH range that sucroferric oxyhydroxide would be exposed to during passage through the GI tract [37]. Iron absorption, distribution, metabolism and excretion (ADME), meanwhile, were assessed *in vivo* in rats and dogs administered $^{59}$Fe-labelled sucroferric oxyhydroxide. Several toxicological studies (ranging from 4 weeks to 2 years) also examined the potential effects of sucroferric oxyhydroxide on iron stores and iron-related toxicity in rats and dogs. Finally, the efficacy of sucroferric oxyhydroxide in preventing vascular calcifications was assessed in a uraemic rat model with adenine-diet-induced CKD [52].

### Phosphate Binding and Iron-Releasing Properties of Sucroferric Oxyhydroxide *In Vitro*

To evaluate the expected phosphate-binding and iron-releasing properties of sucroferric oxyhydroxide when administered to human patients, a series of five experiments were conducted *in vitro* to assess these properties under physiologically relevant conditions – that is, across the pH range that would be encountered in the GI tract [37]. The first two experiments examined the phosphate-binding capacity of sucroferric oxyhydroxide under conditions simulating its administration on an empty stomach (i.e., with an excess of sucroferric oxyhydroxide over phosphate) and on a full stomach. In the first experiment, the pH was increased at five pre-determined time points, from a starting pH of 1.2 to a final pH of 7.5, with the experiment lasting 8 hours in total. In the second experiment, the pH was raised or lowered at five pre-determined time points over the course of 28 hours to simulate the physiological conditions that would be encountered during the passage of sucroferric oxyhydroxide through the GI tract. The iron-releasing properties of sucroferric oxyhydroxide were then investigated in a second set of three experiments designed to simulate administration on: 1) an empty stomach in the absence of phosphate; 2) an empty stomach in the presence of phosphate; and 3) a full stomach (in the presence of phosphate) across the pH range that sucroferric oxyhydroxide would be exposed to in the GI tract.

In the first set of experiments, sucroferric oxyhydroxide showed robust phosphate-binding capacity over the entire physiologically-relevant pH range [37]. Under conditions representative of administration on an empty stomach, phosphate adsorption was highest at pH 2.5 (0.21 mg P/mg Fe) but only slightly lower at pH 1.3 (0.18 mg P/mg Fe). Above pH 2.5, phosphate adsorption decreased slightly with increasing pH (Fig. **1a**). Under conditions simulating administration on a full stomach, it took some time for chemical equilibrium to be reached; phosphate adsorption was 0.15 mg P/mg Fe at pH 5.9 after a short, 15-minute exposure, but was higher at each time point thereafter, regardless of whether the pH was raised or lowered, including at a similar pH of 6.7 after 6 hours (0.24 mg P/mg Fe) (Fig. **1b**). The maximum bound phosphate to iron ratio was found to be 0.26 mg P/mg Fe, recorded at pH 2.6.

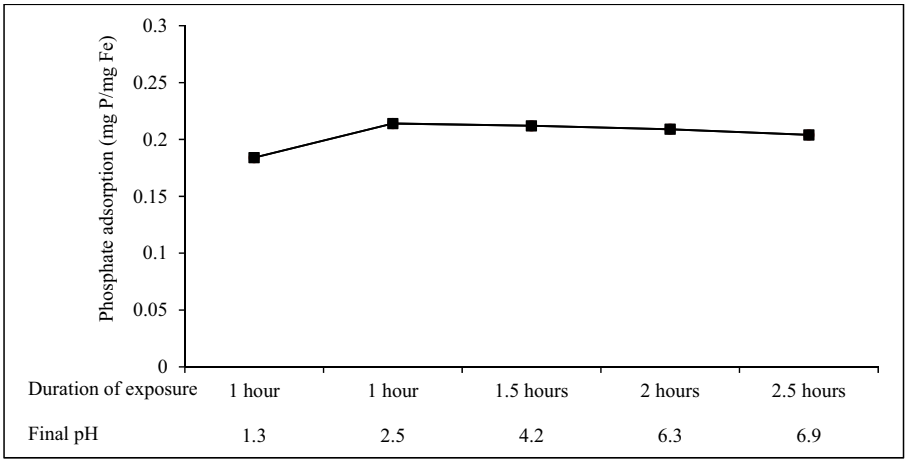
In the second set of experiments, sucroferric oxyhydroxide showed minimal iron release (≤0.35%) across a pH range of 2.6–8.0 under conditions simulating being taken on a full stomach (Fig. **2**) [37]. Although iron release was high (67%) at an initial pH of 1.2 (final pH 2.1) under conditions simulating administration on an empty stomach and in the absence of phosphate (conditions which are of a rather theoretical nature), this fell to just 6% under similar conditions (initial and final pH 1.2) in the presence of phosphate (Table **1**).

These *in vitro* experiments show that sucroferric oxyhydroxide has a robust phosphate-binding capacity across the full physiologically-relevant pH range [37]. This indicates that phosphate binding could begin in the stomach and continue throughout the length of the GI tract, thus maximising the potential for phosphate binding – and minimising the potential for phosphate absorption – at any stage during the passage of food through the digestive tract. The minimal iron release properties observed may support clinical features such as minimal iron absorption and low risk for systemic iron accumulation and toxicity. Further investigations were needed *in vivo*, however, before any firm predictions could be made about the potential of sucroferric oxyhydroxide to cause iron toxicity and accumulation with clinical use.

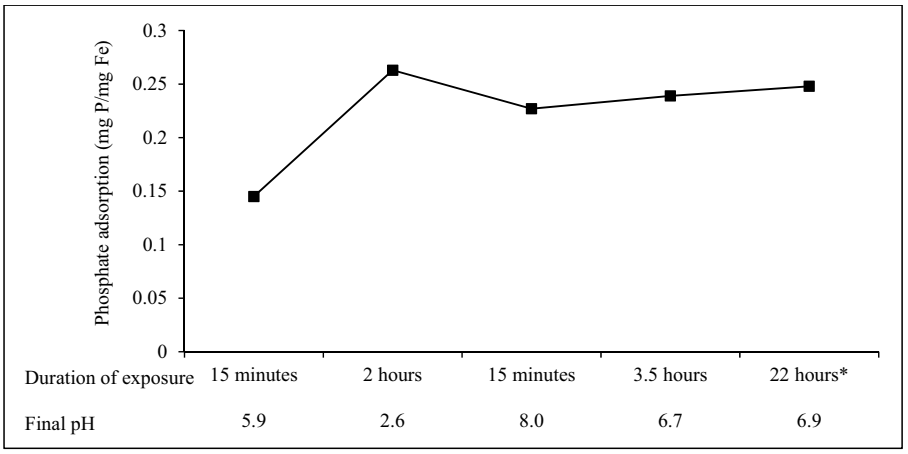
### Iron Absorption, Distribution, Metabolism and Excretion *In Vivo* in Rats and Dogs Administered $^{59}$Fe-labelled Sucroferric Oxyhydroxide

To begin to assess the potential for iron absorption and accumulation from sucroferric oxyhydroxide, two preclinical ADME studies were conducted in rats and dogs. These new data will be discussed here. Both experiments were conducted in accordance with the requirements of current, internationally recognised Good Laboratory Practice Standards, and the applicable sections of the United Kingdom (UK) Animals (Scientific Procedures) Act 1986.

Iron-replete rats and dogs were administered a 50 mg Fe/kg bodyweight dose of $^{59}$Fe radiolabelled sucroferric oxyhydroxide. For both groups of animals, a COBRA II Gamma Counter (Model 5003; Canberra Packard, Pangbourne, UK) with the capability to count low-level activity and higher energy isotopes was used to measure radioactivity. In rats, radioactivity was mainly found in the red blood cells (RBCs), with 0.62% of the total radioactivity from the administered dose found in these cells, corresponding to 78% of the total radioactivity retrieved. Some radioactivity was also found in the liver, amounting to 0.18% of the total from the administered dose and corresponding to 22% of the total amount of radioactivity retrieved (Fig. **3**). Radioactivity was measured in dogs 7 days after administration. Similar to the findings in rats, 0.82% of the total radioactivity from the administered dose was found in RBCs, corresponding to 85% of the total amount of radioactivity retrieved. In one dog, 0.14% of the total radioactivity from the administered dose was found in the spleen, corresponding to 15% of the total amount of radioactivity retrieved in that animal. No radioactivity was found in two dogs. In both rats and dogs, $^{59}$Fe was excreted exclusively in the faeces.




**1a)**




**1b)**

**Fig. (1).** Phosphate adsorption under conditions representative of administration on **1a**) an empty stomach and **1b**) a full stomach during passage through the gastrointestinal tract [37]. *Average of duplicate samples. Observed changes in final pH values are due to buffering capacity of sucroferric oxyhydroxide and the dissolution process. Reproduced from Wilhelm *et al.* 2014 with permission from Dustri-Verlag.

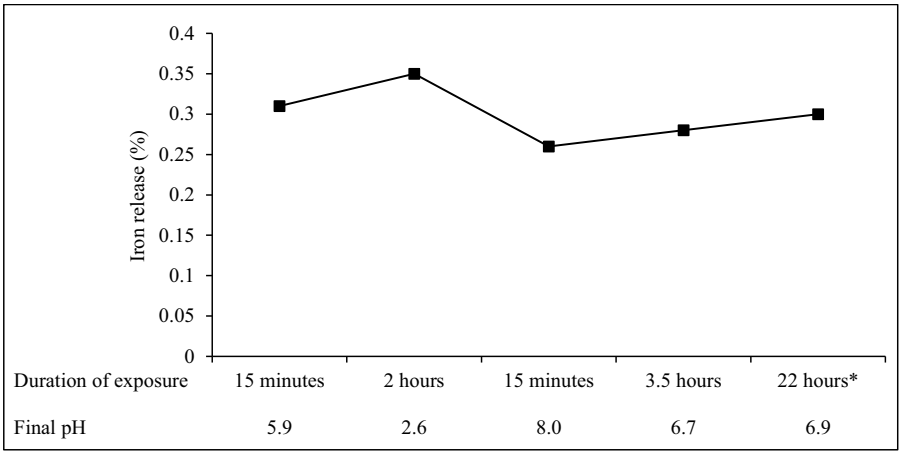



**Fig. (2).** Iron release from sucroferric oxyhydroxide under conditions representative of administration on a full stomach during passage through the gastrointestinal tract [37]. *Average of duplicate samples. Observed changes in final pH values are due to buffering capacity of sucroferric oxyhydroxide and the dissolution process.

**Table 1. Iron release from sucroferric oxyhydroxide under conditions representative of administration on a) an empty stomach in the absence of phosphate; b) an empty stomach in the presence of phosphate; c) a full stomach, in the presence of phosphate, during passage through the gastrointestinal tract [37]. Reproduced from Wilhelm *et al.* 2014 with permission from Dustri-Verlag.**

| Initial pH of samples | Final pH of samples | Duration of exposure | Iron release (%) | SD (%) |
|---|---|---|---|---|
| **a) Empty stomach: in the absence of phosphate** | | | | |
| 1.2 | 2.1 | 1 hour | 66.90 | 3.10 |
| **b) Empty stomach: in the presence of phosphate** | | | | |
| 1.2 | 1.2 | 1 hour | 6.24 | 0.59 |
| **c) Full stomach: passage of sucroferric oxyhydroxide through the GI tract (in the presence of phosphate)** | | | | |
| 4.5 | 5.9 | 15 minutes | 0.31 | N/A |
| 2.5 | 2.6 | 2 hours | 0.35 | N/A |
| 8.5 | 8.0 | 15 minutes | 0.26 | N/A |
| 6.5 | 6.7 | 3.5 hours | 0.28 | N/A |
| 7.0 | 6.9 | 22 hours | 0.30* | N/A |

*Average of duplicate samples. N/A, data not available; SD, standard deviation.
Observed changes in final pH values due to buffering capacity of sucroferric oxyhydroxide and the dissolution process.

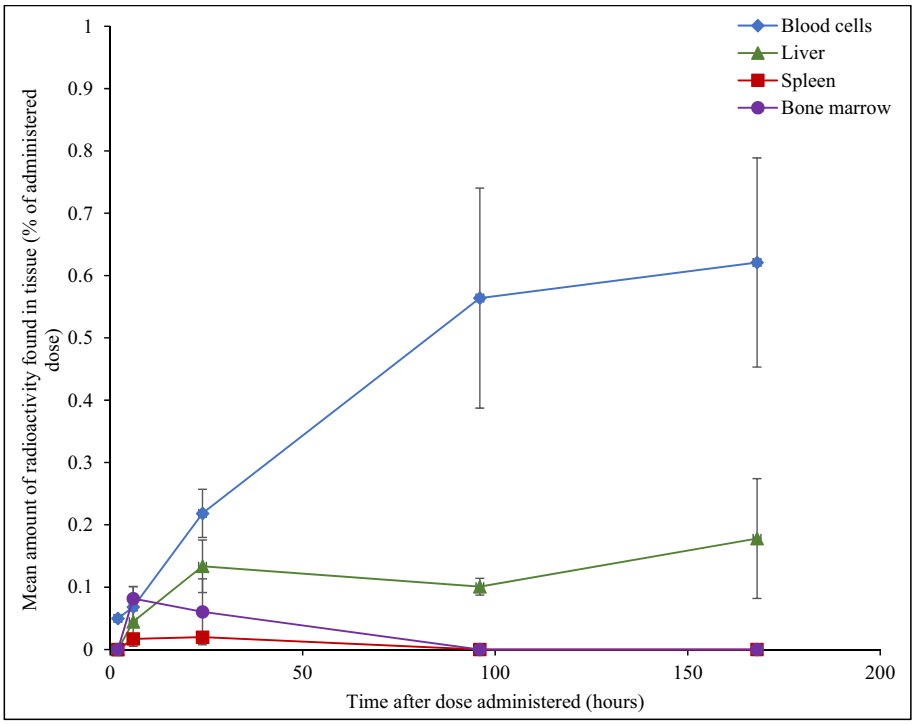



**Fig. (3).** Amount of radiolabelled iron found in red blood cells, liver, spleen and bone marrow in rats after a single dose administration of $^{59}$Fe-labelled sucroferric oxyhydroxide (50 mg Fe/kg bodyweight).

The two ADME studies in iron-replete rats and dogs demonstrated that iron uptake from sucroferric oxyhydroxide was low (≤1% from a 50 mg Fe/kg dose). In clinical practice, iron absorption depends on a number of different factors, including the saturation of iron stores and inflammatory status [44, 53-56]. The results of these animal studies may, however, suggest a low systemic impact of sucroferric oxyhydroxide on iron parameters. It is particularly interesting that what little iron was absorbed was mainly found in the RBCs. After absorption, iron is bound to transferrin and travels either to the liver, for storage in hepatocytes, or to RBCs for production of haemoglobin [43]. Thus it would appear that the low levels of iron that were absorbed from sucroferric oxyhydroxide were used for haemoglobin synthesis – a normal part of iron metabolism [43] – even though the test animals were iron-replete. If iron absorption from sucroferric oxyhydroxide is low, and what iron is absorbed is subject to the normal metabolic

processes, then it should follow that sucroferric oxyhydroxide carries a low risk of iron toxicity. As CKD is a chronic condition, however, phosphate binder use may be required over a long period of time. It was, therefore, important to evaluate the potential for iron accumulation and toxicity associated with long-term use of sucroferric oxyhydroxide.

### Toxicological Studies of the Effect of Sucroferric Oxyhydroxide on Iron Stores and Iron-related Toxicity in Rats and Dogs

The effect of sucroferric oxyhydroxide on iron accumulation and iron-related toxicity was investigated in seven sub-chronic, chronic and long-term studies in rats and dogs; new data from these studies are presented below. All studies were conducted in accordance with the requirements of current, internationally recognised Good Laboratory Practice Standards, and the applicable sections of the UK Animals (Scientific Procedures) Act 1986.

In the four rat studies, sucroferric oxyhydroxide was administered orally via the diet at clinically-relevant doses (40 mg Fe/kg bodyweight/day) or higher to equal numbers of male and female rats for periods of 4, 13 and 26 weeks, and up to 2 years. The doses administered in each of the four studies can be seen in Table **2**. During the studies, the rats' clinical condition, bodyweight, food consumption, ophthalmic condition, haematology, blood chemistry, serum vitamin analysis, urinalysis, tissue iron, bone turnover, organ weights, macropathology and histopathology were investigated. All animals were subject to detailed necropsy after sacrifice upon completion of the studies.

Dose-related increases in liver iron content were observed in treated animals relative to controls in all four rat studies. At clinically relevant doses (40 mg Fe/kg/day), however, the liver iron values of treated rats were not significantly higher than those found in control animals after 2 years of treatment (liver iron values were 8% and 16% higher in male and female treated rats than control rats, respectively; $p \geq 0.05$) (Table **2**). After 26 weeks, liver iron values were 21% and 18% higher in male and female treated rats, respectively, than in control rats. At higher doses of sucroferric oxyhydroxide, liver iron concentrations in treated animals tended to stabilise over time. For example, the relative increase in liver iron values among treated animals compared with controls was similar in the 500 mg Fe/kg/day dose groups for each of the 4-week, 26-week and 2-year studies (Table **2**). Tissue iron values were also recorded after 6 weeks of recovery at the end of the 26-week study for the high-dose group (500 mg Fe/kg/day) only. Iron values in treated rats continued to be elevated relative to controls in the liver and spleen, but did show some signs of recovery.

**Table 2. Mean liver tissue iron content in rats after administration of sucroferric oxyhydroxide for 4, 13 and 26 weeks, and 2 years.**

| Liver iron content, group mean values: rat studies | | | Male rats | | | | Female rats | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study number** | **Study duration** | | **Control group** | **Group 1 (low dose)** | **Group 2 (mid dose)** | **Group 3 (high dose)** | **Control group** | **Group 1** | **Group 2** | **Group 3** |
| 1 | 4 weeks | Dose (mg Fe/kg bodyweight/day) | - | 100 | 200 | 500 | - | 100 | 200 | 500 |
| | | Iron concentration in mg/kg (relative value compared with control) | 110 | 151* (x1.37) | 167* (x1.52) | 275* (x2.50) | 306 | 455* (x1.49) | 426* (x1.39) | 581* (x1.90) |
| 2 | 13 weeks | Dose (mg Fe/kg bodyweight/day) | - | 60 | 200 | 600 | - | 60 | 200 | 600 |
| | | Iron concentration in mg/kg (relative value compared with control) | 192 | 227* (x1.18) | 242* (x1.26) | 531* (x2.77) | 423 | 523 (x1.24) | 597* (x1.41) | 926* (x2.19) |
| 3 | 26 weeks | Dose (mg Fe/kg bodyweight/day) | - | 40 | 150 | 500 | - | 40 | 150 | 500 |
| | | Iron concentration in mg/kg (relative value compared with control)† | 174 | 210* (x1.21) | 268* (x1.54) | 477* (x2.74) | 438 | 515* (x1.18) | 610* (x1.39) | 781* (x1.78) |
| | | | 182 | | | 415* (x2.28) | 429 | | | 565 (x1.32) |
| 4 | 2 years | Dose (mg Fe/kg bodyweight/day) | - | 40 | 150 | 500 | - | 40 | 150 | 500 |
| | | Iron concentration in mg/kg (relative value compared with control) | 322 | 348 (x1.08) | 423* (x1.31) | 780* (x2.42) | 427 | 495 (x1.16) | 786* (x1.84) | 1315* (x3.08) |

* Significant when compared with untreated control group ($p<0.05$).
† Second row shows mean liver tissue iron content after 6 weeks of recovery.

Overall, there were no notable differences in kidney iron values between treated and control rats in any of the studies; small but significant increases ($p<0.01$) in kidney iron values were mainly confined to female rats at higher doses. In all four studies, the iron content of the spleen varied greatly between rats. After 2 years, spleen iron values did not differ significantly between rats administered clinically-relevant doses (40 mg Fe/kg/day) and controls ($p\geq0.05$). There were a few cases of significant spleen iron value increases ($p<0.01$) in treated rats compared with controls in each study, but these did not appear to be dose-dependent.

In the three controlled dog studies, sucroferric oxyhydroxide was administered twice daily by oral capsule at clinically-relevant doses (40 mg Fe/kg/day) or higher to equal numbers of male and female dogs for periods of 4, 13 and 26–39 weeks. Doses administered in each of the three studies can be seen in Table **3**. In addition to the investigational assessments undertaken in rats, electrocardiography and blood pressure were also assessed. As in the rat studies, all animals were subject to detailed necropsy after sacrifice upon the studies' completion.

In the dog studies, tissue iron levels varied greatly between dogs after 4, 13 and 39 weeks. Findings with respect to liver iron levels did, however, complement those from the rat studies (Table **3**). Liver iron values increased in treated animals compared with controls in each of the studies, although these increases did not appear to be dose-dependent. After 39 weeks of treatment, liver iron values were not more than 40% higher among dogs treated with clinically-relevant doses (40 mg Fe/kg/day) than controls for either sex, and did not reach statistical significance ($p\geq0.05$). Even at the highest dose of sucroferric oxyhydroxide (400 mg Fe/kg/day, around ten times higher than a human dose), liver iron values were less than 2.5 times greater in treated dogs than in controls after 39 weeks of treatment. Overall, there was no notable effect of treatment on kidney or spleen iron levels at clinically-relevant doses (40 mg Fe/kg/day) in any of the studies. At the highest dosage in the 39-week study (400 mg Fe/kg/day), increased tissue iron values compared with controls persisted after 6 weeks of recovery.

Histopathological analyses in both the rat and dog studies revealed iron to be found mainly in the reticuloendothelial system (RES). In the 2-year rat study, the degree of macrophage pigmentation (defined as minimal, slight or moderate) increased in a dose-dependent manner, but the macrophage staining was only observed in a statistically significant number of animals at doses of 150 and 500 mg Fe/kg/day ($p<0.01$). The number of rats with pigmented hepatocytes, meanwhile, did not reach statistical significance at any treatment dose. In the 39-week dog study, moderate positive staining of Kupffer cells/macrophages was observed in liver sections from dogs administered 120 mg Fe/kg/day (males only) and 400 mg Fe/kg/day (males and females) stained with Perls' Prussian blue. Positive Perls' staining of hepatocytes, meanwhile, was only observed in female dogs administered doses of 120 or 400 mg Fe/kg/day and was minimal.

Elevated haematocrit and haemoglobin concentrations were observed in the highest dose groups (500 mg Fe/kg/day) for male rats in the 2-year study, and for male and female rats in the 26-week study. These appeared to recover during the 6-week recovery period following the 26-week study. In the dog studies, there were no notable haematological differences in treated dogs compared with control dogs.

Together, the toxicity studies undertaken in rats and dogs show that iron accumulation resulting from administration of sucroferric

**Table 3. Mean liver tissue iron content in dogs after administration of sucroferric oxyhydroxide for 4, 13, 26 and 39 weeks.**

| **Liver iron content, group mean values: dog studies** | | | **Male dogs** | | | | **Female dogs** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study number** | **Study duration** | | **Control group** | **Group 1 (low dose)** | **Group 2 (mid dose)** | **Group 3 (high dose)** | **Control group** | **Group 1** | **Group 2** | **Group 3** |
| 1 | 4 weeks | Dose (mg Fe/kg bodyweight/day) | - | 100 | 200 | 400 | - | 100 | 200 | 400 |
| | | Iron concentration in mg/kg (relative value compared with control) | 393.3 | 373.3 (x0.95) | 386.7 (x0.98) | 420 (x1.07) | 296.7 | 300 (x1.01) | 406.7 (x1.37) | 380 (x1.28) |
| 2 | 13 weeks | Dose (mg Fe/kg bodyweight/day) | - | 100 | 200 | 400 | - | 100 | 200 | 400 |
| | | Iron concentration in mg/kg (relative value compared with control) | 423 | 725* (x1.71) | 595* (x1.41) | 570* (x1.35) | 308 | 445 (x1.44) | 580 (x1.88) | 420 (x1.36) |
| 3 | 26 weeks | Dose (mg Fe/kg bodyweight/day) | - | 40 | 120 | 400 | - | 40 | 120 | 400 |
| | | Iron concentration in mg/kg (relative value compared with control) | 390 | - | 703 (x1.80) | 563 (x1.44) | 370 | - | 480 (x1.30) | 683 (x1.85) |
| 4 | 39 weeks† | Dose (mg Fe/kg bodyweight/day) | - | 40 | 120 | 400 | - | 40 | 120 | 400 |
| | | Iron concentration in mg/kg (relative value compared with control) | 364 | 509 (x1.40) | 813* (x2.23) | 778* (x2.14) | 428 | 575 (x1.34) | 693 (x1.62) | 1045* (x2.44) |

* Significant when compared with untreated control group ($p<0.05$).
† Group mean values not available for 6-week recovery.

oxyhydroxide is low and below toxic levels, even with long-term use at high doses [42]. Moreover, at clinically-relevant doses of 40 mg Fe/kg/day, sucroferric oxyhydroxide was not associated with significant increases in liver, spleen or kidney iron values compared with controls after 2 years of administration in rats or after 39 weeks of administration in dogs. Histopathological analyses showed that absorbed iron tended to be found in the normal sites of iron metabolism, such as macrophages and Kupffer cells [43], components of the RES.

### Efficacy of Sucroferric Oxyhydroxide in Preventing Vascular Calcifications in a Uraemic Rat Model

The preclinical studies to assess iron release properties, phosphate binding capacity, ADME and iron toxicity were essential to establish a theoretical basis for the phosphate-binding efficacy of sucroferric oxyhydroxide and to evaluate its potential for iron toxicity. An additional preclinical study was also undertaken in a rat model of CKD to examine the possible effects of sucroferric oxyhydroxide on the progression of vascular calcification, as well as serum phosphorus, calcium, intact parathyroid hormone (iPTH) and fibroblast growth factor 23 (FGF23) concentrations, compared with calcium carbonate [52].

CKD was chemically induced in rats by the addition of adenine to their high-phosphorus diet. The rats were then administered sucroferric oxyhydroxide (at a concentration of 0.5%, 1.5% or 5.0%), calcium carbonate (at a concentration of 3%) or no treatment (CKD control group). Three additional groups also received the high-phosphorus pre-treatment diet for 4 weeks but without adenine, so CKD was not induced. The non-CKD groups then received either no treatment (non-CKD control group), sucroferric oxyhydroxide 5%, or calcium carbonate 3% for 4 weeks. After 4 weeks of treatment, blood pressure and heart rate were assessed. The rats were then sacrificed and blood was taken for biochemical analysis. Parameters measured included haematocrit and serum phosphorus, calcium, iPTH and FGF23, among others. Vascular calcifications were evaluated by histomorphometric analysis. The degree of calcification was scored semiquantitatively according to the surface of von Kossa positivity, with a score of 0 indicating no von Kossa positivity; 1, focal von Kossa positivity, larger than or not overlying a cell nucleus; 2, partially circumferential von Kossa positivity in the tunica medial of the vessel; and a score of 3 indicating von Kossa positivity in the tunica media spanning the complete circumference of the vessel.

The development of CKD was associated with an increase in serum phosphorus, although serum calcium was not higher in rats with CKD after the initial 4-week adenine diet than in non-CKD animals. CKD rats also developed hyperparathyroidism. After 4 weeks of phosphate binder treatment, mean serum phosphorus concentrations in the sucroferric oxyhydroxide 5% and calcium carbonate groups had normalised and were comparable with one another (Table **4**). There were no significant differences in serum calcium levels between any of the treatment groups and either the non-CKD control or the CKD control groups ($p>0.05$), although it is notable that serum calcium levels were highest in the non-CKD calcium carbonate group. Sucroferric oxyhydroxide produced a dose-dependent reduction in serum iPTH levels after 4 weeks of treatment. Calcium carbonate also reduced serum iPTH levels, with sucroferric oxyhydroxide 5% and calcium carbonate producing comparable serum iPTH levels after 4 weeks. FGF23 was significantly reduced in the sucroferric oxyhydroxide 5% group compared with the calcium carbonate group and the CKD control group ($p<0.05$). No significant differences in systemic blood pressure or heart rate were observed between CKD rats and non-CKD rats, or between CKD rats treated with any dose of sucroferric oxyhydroxide or calcium carbonate.

Sucroferric oxyhydroxide was found to attenuate the development of vascular calcifications (Fig. **4**). A high proportion of CKD control rats (76%, n=13), rats receiving low dose (0.5%) sucroferric oxyhydroxide (86%, n=6), and rats receiving calcium carbonate (58%, n=11) developed severe vascular calcifications with high calcification scores (scores of 2 or 3). Just 22% of rats treated with sucroferric oxyhydroxide 1.5% (n=2), and the same proportion treated with sucroferric oxyhydroxide 5% (n=4), meanwhile, had high vascular calcification scores.

This study demonstrated the efficacy of sucroferric oxyhydroxide as a treatment for hyperphosphataemia. At the 5%

**Table 4. Mean serum phosphorus, calcium and iPTH concentrations in rats with or without chronic kidney disease (CKD) after 4 weeks of treatment with sucroferric oxyhydroxide 0.5%, 1.5% or 5%, or calcium carbonate 3% [52]. Reproduced from Phan *et al.* 2013 with permission from The American Society for Pharmacology and Experimental Therapeutics.**

| | N | Calcium | Phosphorus | iPTH |
|---|---|---|---|---|
| | | (mg/dL ± SD) | | pg/mL ± SD |
| Non-CKD control | 8 | 9.60 ± 0.12 | 6.67 ± 0.34 | 105 ± 14 |
| Non-CKD sucroferric oxyhydroxide 5% | 8 | 9.72 ± 0.20 | 5.27 ± 0.37 | 134 ± 50 |
| Non-CKD calcium carbonate 3% | 8 | 10.00 ± 1.40 | 6.63 ± 0.68 | 102 ± 9 |
| CKD control | 19 | 9.52 ± 0.48 | 9.02 ± 0.74 | 3261 ± 397 |
| CKD sucroferric oxyhydroxide 5% | 20 | 9.64 ± 0.12 | 6.85 ± 0.28[a] | 1138 ± 228[a] |
| CKD sucroferric oxyhydroxide 1.5% | 9 | 8.92 ± 0.16 | 7.10 ± 0.78[b] | 2727 ± 695[c] |
| CKD sucroferric oxyhydroxide 0.5% | 9 | 9.56 ± 0.28 | 8.49 ± 1.15 | 4830 ± 624[c] |
| CKD calcium carbonate 3% | 19 | 9.56 ± 0.24 | 6.39 ± 0.34[a] | 1299 ± 300[a] |

CKD, rats with chronic kidney disease; iPTH, intact parathyroid hormone; Non-CKD, rats without chronic kidney disease; SD, standard deviation. a, $p\leq0.001$ vs CKD control; b, $p<0.05$ vs CKD control; c, $p<0.05$ vs CKD sucroferric oxyhydroxide 5% or calcium carbonate 3%.

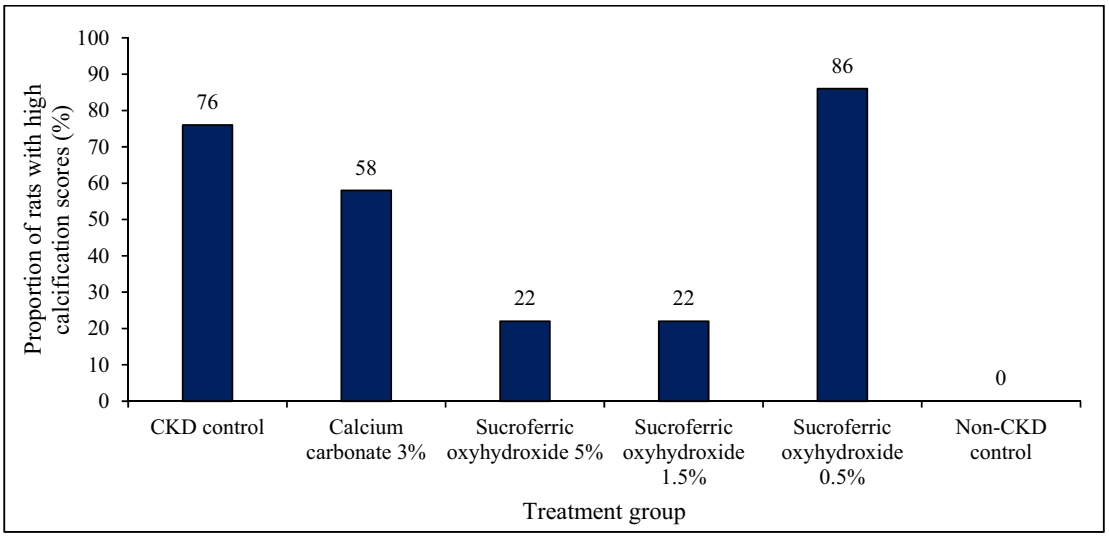



**Fig. (4).** Percentages of rats with high vascular calcification scores (scores of 2 or 3 on a scale from 0–3, with 0 representing no von Kossa activity and 3 representing von Kossa positivity in the tunica media spanning the complete circumference of the vessel) after 4 weeks of treatment with sucroferric oxyhydroxide 0.5%, 1.5% or 5%, or calcium carbonate 3% [52]. CKD, chronic kidney disease.

dose, it showed comparable efficacy to calcium carbonate in reducing levels of serum phosphorus. Sucroferric oxyhydroxide was also shown to be superior to calcium carbonate at reducing the extent of vascular calcifications. While calcium carbonate did produce a reduction of vascular calcifications in CKD rats, there were significantly fewer animals with severe calcifications observed after treatment with sucroferric oxyhydroxide 5% ($p=0.045$), and sucroferric oxyhydroxide 1.5% also produced a significant reduction in the number of animals with severe calcifications compared with CKD controls ($p=0.002$).

The *in vivo* study described here appears to demonstrate that sucroferric oxyhydroxide has the potential to reduce the progression of vascular calcification in comparison with the calcium-based phosphate binder calcium carbonate. While calcium carbonate did reduce the progression of vascular calcification relative to untreated CKD controls, it is possible that calcium-based phosphate binders may in some way contribute to the progression of vascular calcifications. Further studies are required in humans to evaluate its potential with respect to reducing the progression of vascular calcifications but, as a non-calcium-based phosphate binder, sucroferric oxyhydroxide does constitute an attractive alternative for the management of hyperphosphataemia in dialysis patients.

## DISCUSSION

This review has provided an overview of preclinical data gathered *in vitro* and *in vivo* on the use of sucroferric oxyhydroxide as a phosphate binder for the treatment of hyperphosphataemia in CKD. The first study to be reviewed investigated the phosphate-binding capacity and iron-releasing properties of sucroferric oxyhydroxide *in vitro* [37]. Sucroferric oxyhydroxide was shown to have potent phosphate-binding capacity and low iron release over the pH range present in the GI tract. New data from *in vivo* ADME studies in rats and dogs using $^{59}$Fe-labelled sucroferric oxyhydroxide subsequently demonstrated iron uptake to be low. The majority of radiolabelled iron that was absorbed was found in RBCs in both species. Overall, most of the radiolabelled iron was excreted in the faeces. This indicates both that the iron in sucroferric oxyhydroxide is predominantly utilised to bind phosphate in the GI tract, and that the small amount of iron which is absorbed is processed via normal metabolic pathways, with the majority being found in RBCs.

The potential toxicity of sucroferric oxyhydroxide was investigated in a series of seven sub-chronic, chronic and long-term studies conducted in rats and dogs. Data from these studies presented in this review show that long-term (up to 2 years) administration of sucroferric oxyhydroxide is associated with modest increases in tissue iron levels that fall well below those associated with iron toxicity [42]. Absorption of iron in the GI tract plays a key role in the maintenance of iron levels and, in the normal state, increasing iron stores tend to inhibit intestinal iron absorption [44, 56]. Despite this, excessive dietary intake or abnormally increased intestinal absorption can still lead to iron overload in the liver and other tissues [56-58]. The small increases in tissue iron levels observed in the rat and dog studies described here suggest that uptake of iron released from sucroferric oxyhydroxide proceeds via the normal metabolic pathways, thus limiting excessive absorption. The fact that most of the iron found in the liver and the spleen was in the cells of the RES also supports the conclusion that iron absorbed from sucroferric oxyhydroxide is directed to normal metabolism; in humans, macrophages of the spleen and Kupffer cells of the liver are responsible for recycling around 25 mg of iron from ageing RBCs per day, while hepatocytes provide an iron storage facility [43].

It is also notable that the maximum increases in liver iron values were no more than 3.1 times greater in treated rats than in controls, and no more than 2.5 times greater in treated dogs than in controls. To put this into context, a toxicity study of a parenteral iron preparation in dogs found that signs of iron overload toxicity appear only when levels of liver iron rise to between 13 and 50 times greater than those observed in controls [42].

Based on the low iron release observed in the *in vitro* study, and the low absorption and accumulation of iron seen in the animal studies, it can be expected that sucroferric oxyhydroxide will exhibit a favourable long-term safety profile in the clinical setting. Indeed, Phase I and III clinical studies in CKD patients have shown that sucroferric oxyhydroxide is associated with minimal systemic

absorption and low risk of iron overload [35, 59]. In the Phase I study, serum phosphorus levels decreased in non-dialysis CKD patients and haemodialysis patients over 7 days of treatment with 10 g/day sucroferric oxyhydroxide, while uptake of iron from a single $^{59}$Fe-labelled dose was very low: at 21 days after administration of the radiolabelled dose, median iron uptake was 0.06% (range: 0.008–0.44%) in non-dialysis-dependent CKD patients and 0.02% (range: 0–0.04%) in haemodialysis patients [35]. This was approximately ten-fold lower than iron uptake in healthy control subjects with low iron stores, in whom the median iron uptake was 0.43% (range: 0.16–1.25%). In all groups, the increase in $^{59}$Fe plateaued at approximately 2 weeks after administration. There were also no changes in iron indices after a week of treatment.

In the Phase III study, sucroferric oxyhydroxide was found to be non-inferior to sevelamer carbonate at reducing serum phosphorus in haemodialysis and peritoneal dialysis patients after 24 weeks of treatment, with no evidence of iron overload [59]. While sucroferric oxyhydroxide was associated with increases in ferritin and transferrin concentrations, increases in ferritin were also observed among patients receiving sevelamer carbonate. As increases in these parameters occurred early during the study and flattened out over time, it was concluded that no iron accumulation was taking place. The absorption of a small amount of iron from sucroferric oxyhydroxide could not be ruled out, however. Although over 70% of the overall study population (patients receiving sucroferric oxyhydroxide or sevelamer carbonate) were receiving concomitant intravenous iron during the study, which may account for some of the observed increases in iron parameters, increases in serum ferritin and transferrin were slightly higher among patients receiving sucroferric oxyhydroxide than sevelamer carbonate. Thus it would appear that a small amount of iron was being absorbed, in line with the findings of the Phase I study. In a long-term extension of the Phase III trial, no evidence for iron accumulation or overload was observed with up to 1 year of treatment with sucroferric oxyhydroxide [60].

The preclinical uraemic rat model study discussed in this review showed that sucroferric oxyhydroxide may prevent the progression of vascular calcifications [52]. The study compared the effects of sucroferric oxyhydroxide and an existing calcium-based phosphate binder, calcium carbonate, on rats with adenine-induced CKD. Sucroferric oxyhydroxide reduced serum phosphorus levels in a dose-dependent manner, and after 4 weeks both sucroferric oxyhydroxide 1.5% and 5%, and calcium carbonate 3%, had significantly reduced serum phosphorus levels relative to untreated CKD controls. Although both sucroferric oxyhydroxide and calcium carbonate were also comparable in their effects on serum calcium and iPTH levels, sucroferric oxyhydroxide 5% was associated with a significantly reduced progression of vascular calcifications in comparison with calcium carbonate.

One possible explanation for the reduced vascular calcification in rats treated with sucroferric oxyhydroxide compared with calcium carbonate could be that the protective effect of the calcium-based phosphate binder is limited by the absorption of calcium [52], which can alter the calcium balance and may lead to calcification of vascular smooth muscle cells [61, 62]. The observation that serum calcium levels were comparable between CKD rats treated with sucroferric oxyhydroxide and those treated with calcium carbonate would appear to argue against this explanation. It should be noted that similar observations have been reported previously by Spiegel *et al*. in a human study of patients with Stage 3–4 CKD, which found that increasing calcium intake from 800 to 2000 mg did not result in a concomitant increase in serum calcium levels [62]. As serum calcium concentrations are known to be tightly regulated, it may be argued that high calcium intake may cause calcium overload in the tissues without increasing the serum calcium concentration [62]. Indeed, this is what was found by Spiegel *et al.*, who reported that the overall calcium balance (defined as oral calcium intake less urinary and faecal calcium output) did increase when the calcium intake was increased to 2000 mg, despite the lack of an increase in serum calcium levels. As a non-calcium based phosphate binder, sucroferric oxyhydroxide may help to avoid the increases in calcium balance that could potentially be caused by the uptake of calcium from calcium-based phosphate binders such as calcium carbonate, and which may precipitate or worsen vascular calcification [52, 62].

Another possibility is that, rather than affecting vascular calcification directly, sucroferric oxyhydroxide and calcium carbonate affect the progression of calcification by differentially modulating serum levels of FGF23. Raised serum levels of FGF23 have previously been shown to be correlated with severe vascular calcifications in haemodialysis patients, and it has been argued that FGF23 is independently associated with vascular calcification [63, 64]. In the preclinical study described here, treatment with sucroferric oxyhydroxide was associated with lower levels of FGF23 than was treatment with calcium carbonate, even though serum phosphorus, calcium and iPTH levels were comparable [52]. It may be suggested that calcium uptake from calcium carbonate causes an increase in serum levels of FGF23, which then enhances the development of vascular calcifications. Indeed, FGF23 levels have been found to correlate positively with both ionised calcium and the calcium phosphate product (which is an independent predictor for coronary calcifications) in human patients with CKD aged over 12 years [65]. Calcium deficiency, meanwhile, has previously been shown to reduce FGF23 levels in rats with normal renal function [66]. Despite this, the evidence for a modulatory role of FGF23 on vascular calcifications is equivocal. A recent study into the association between FGF23 and arterial calcification in patients with CKD showed that, after adjustment for the traditional coronary risk factors associated with elevated FGF23, higher plasma FGF23 was not associated with coronary artery calcifications [67]. In the same study, mRNA expression of FGF23 or its coreceptor, klotho, could not be found in either human or mouse smooth muscle cells, or in normal or calcified mouse aorta. Interestingly, the severity, but not the presence, of thoracic artery calcification was found to be associated with levels of FGF23, but this latter finding may have been an artefact of the complex data modelling required in this study.

The question of whether or not calcium-based phosphate binders should be used in clinical practice has become the subject of extensive debate. In a recent systematic review and meta-analysis of 847 reports, including 14 randomised trials, Jamal *et al.* found that calcium-based phosphate binders are associated with an increased risk of all-cause mortality in people with CKD compared with non-calcium-based phosphate binders [68]. In the 11 randomised trials included in this analysis that reported an outcome of mortality, patients who were assigned to non-calcium-based phosphate binders had a 22% reduction in all-cause mortality compared with those assigned to calcium-based phosphate binders. Similar reductions in mortality were observed for patients assigned to non-calcium-based, rather than calcium-based, phosphate binders in non-randomised trials and when pre-dialysis and dialysis patients

were considered separately. Jamal *et al.* also reported an increase in coronary artery calcification among patients treated with calcium-based phosphate binders versus those receiving non-calcium-based phosphate binders. Earlier reviews of the literature have also reported a greater progression of vascular calcification with the use of calcium-based, rather than non-calcium-based, phosphate binders [69].

The meta-analysis by Jamal *et al*. did not determine whether the increased mortality observed among patients administered calcium-based phosphate binders was due to an increase in cardiovascular events [68]. Vascular calcification is known to be a risk factor for ischaemic heart disease in non-uremic individuals, however, and vascular calcifications have been directly linked to the prevalence of cardiovascular events [70].

Calcium-based phosphate binders, such as calcium carbonate, have been shown to affect the calcium balance [28], and have also been associated with hypercalcaemia [71] and vascular calcifications [69]. As a non-calcium-based phosphate binder, sucroferric oxyhydroxide may help to reduce the progression of vascular calcification by avoiding contributing to these processes. It is essential that further studies are undertaken in human subjects to properly assess the potential for sucroferric oxyhydroxide to slow the progression of vascular calcifications in the clinical setting. As discussed earlier in this review, further research is also needed to determine the mechanism(s) by which calcium-based phosphate binders contribute to the development of vascular calcification.

The high phosphate-binding capacity, minimal iron release and low toxicity of sucroferric oxyhydroxide observed in preclinical studies, along with its positive effect on the development of vascular calcification, recommend it as a strong candidate for the treatment of hyperphosphataemia in clinical practice. Indeed, Phase II and Phase III trials have confirmed its efficacy and safety in clinical practice [36, 59]. In the Phase II trial, sucroferric oxyhydroxide significantly reduced serum phosphorus in haemodialysis patients at doses of 1.0–2.5 g Fe/day with an adverse event rate similar to that of sevelamer hydrochloride [36]. In the Phase III trial, sucroferric oxyhydroxide was shown to be non-inferior to sevelamer carbonate at reducing and maintaining serum phosphorus, with a substantially lower pill burden (on average, 3.1 versus 8.1 pills per day for sucroferric oxyhydroxide- and sevelamer carbonate-treated patients, respectively) [59]. The percentage of patients that reported at least one treatment-emergent adverse event (TEAE) was, however, found to be slightly higher with sucroferric oxyhydroxide (83.2%) than with sevelamer carbonate (76.1%).

In addition to good efficacy, efficiency regardless of pH, minimal absorption in the digestive tract and/or deposition in the tissues, and minimal side effects, other attributes that could identify a phosphate binder as an ideal treatment include good palatability and a sufficiently low pill burden to help ensure adherence to treatment [9, 23, 24]. As mentioned above, sucroferric oxyhydroxide is associated with a considerably lower pill burden than sevelamer carbonate [59]. Consideration was also given to patient preferences and practicality when designing the dosage form. Surveys suggest that patients prefer a single dosage form to multiple tablets for swallowing, which may also be impractical when a treatment is typically administered in high doses [51]. In addition, avoiding excess water intake – such as might be required for swallowing whole tablets – is advantageous for patients with CKD. Disintegration of a chewable tablet is also important to ensure that efficacy is not lost should chewing be incomplete after administration. Considering these factors, sucroferric oxyhydroxide has been designed as a chewable tablet that disintegrates readily into smaller particles to allow for optimal adsorption of phosphate. *In vitro* assessments of the chewability of sucroferric oxyhydroxide tablets showed them to be able to withstand the high breaking forces required to achieve low friability, while still being adequately chewable [51].

In conclusion, sucroferric oxyhydroxide is a new, iron-based phosphate binder that offers high phosphate-binding capacity over the physiologically-relevant pH range and minimal iron release *in vitro* [37]. *In vivo* studies have indicated a good long-term safety profile, with no iron toxicity and minimal accumulation associated with long-term use. An *in vivo* study using a uraemic rat model has also indicated that sucroferric oxyhydroxide may slow the progression of cardiovascular calcifications in rats [52], although this finding requires further evaluation in human trials before conclusions can be drawn about its clinical significance. The safety and efficacy of sucroferric oxyhydroxide have been confirmed in Phase I, II and III clinical trials, which have also demonstrated a low pill burden and possible improved treatment adherence in comparison with sevelamer carbonate [35, 36, 59]. Furthermore, the chewability of sucroferric oxyhydroxide [51] offers a dosage form which may be more amenable to patients and more practical in terms of administration. Sucroferric oxyhydroxide therefore constitutes a promising new alternative to the available phosphate binder treatments.

## CONFLICT OF INTEREST

Mario Cozzolino has received research grants from Abbvie and Shire. He has attended advisory boards for Abbvie, Amgen, Genzyme/Sanofi, Keryx, Shire and Vifor Pharma/Fresenius Medical Care, and has received lecture honoraria from Abbvie, Amgen, Genzyme/Sanofi, Roche and Shire. Isaac Teitelbaum attended an advisory board for Vifor Pharma. Olivier Phan received congress travel expenses cover from Vifor (International) Ltd., St. Gallen. Viatcheslav Rakov and Felix Funk are employees of Vifor Pharma Ltd. This review article was funded by Vifor Pharma Ltd.

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## ABBREVIATIONS

| | | |
|---|---|---|
| ADME | = | Absorption, distribution, metabolism and excretion |
| CKD | = | Chronic kidney disease |
| CKD-MBD | = | Chronic kidney disease mineral bone disorder |
| ESRD | = | End-stage renal disease |
| FGF23 | = | Fibroblast growth factor 23 |
| GFR | = | Glomerular filtration rate |
| GI | = | Gastrointestinal |
| iPTH | = | Intact parathyroid hormone |
| K/DOQI | = | Kidney Disease Outcomes Quality Initiative |
| NTBI | = | Non-transferrin-bound iron |

| | | |
|---|---|---|
| PTH | = | Parathyroid hormone |
| RBC | = | Red blood cell |
| RES | = | Reticuloendothelial system |
| RR | = | Relative risk |
| TEAE | = | Treatment-emergent adverse event |

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