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Iron-related parameters in dialysis patients treated with sucroferric oxyhydroxide

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ABSTRACT

Background. Sucroferric oxyhydroxide is a non-calcium, iron-based phosphate binder indicated for the treatment of hyperphosphataemia in adult dialysis patients. This *post hoc* analysis of a randomized, 24-week Phase 3 study and its 28-week extension was performed to evaluate the long-term effect of sucroferric oxyhydroxide on iron parameters.

Methods. A total of 1059 patients were randomized to sucroferric oxyhydroxide 1.0–3.0 g/day ($n = 710$) or sevelamer carbonate ('sevelamer') 2.4–14.4 g/day ($n = 349$) for up to 52 weeks. The current analysis only included patients who completed 52 weeks of continuous treatment ($n = 549$). Changes in iron-related parameters and anti-anaemic product use during the study were measured.

Results. Some changes in iron-related parameters across both treatment groups were observed during the first 24 weeks of the study, and to a lesser extent with longer-term treatment. There were small, but significantly greater increases in mean transferrin saturation (TSAT) and haemoglobin levels with sucroferric oxyhydroxide versus sevelamer during the first 24 weeks (change in TSAT: +4.6% versus +0.6%, P = 0.003; change in haemoglobin: +1.6 g/L versus −1.1 g/L, P = 0.037). Mean serum ferritin concentrations also increased from Weeks 0 to 24 with sucroferric oxyhydroxide and sevelamer (+119 ng/mL and +56.2 ng/mL respectively; no statistically significant difference between groups). In both treatment groups, ferritin concentrations increased to a greater extent in the overall study population [>70% of whom received concomitant intravenous (IV) iron], compared with the subset of patients who did not receive IV iron therapy during the study. The pattern of anti-anaemic product use was similar in both treatment groups, with a trend towards higher use of IV iron and erythropoiesis-stimulating agents with sevelamer.

Conclusions. Initial increases in some iron-related parameters were observed in both treatment groups but were more pronounced with sucroferric oxyhydroxide. These differences between treatment groups with respect to changes in iron parameters are likely due to minimal iron absorption from sucroferric oxyhydroxide.

Keywords: chronic kidney disease, dialysis, iron, phosphate binder, sucroferric oxyhydroxide

ORIGINAL ARTICLE

INTRODUCTION

Sucroferric oxyhydroxide (VELPHORO®; PA21) is a non-calcium, iron-based phosphate binder that was designed to bind intestinal phosphate while minimizing iron absorption. In a Phase 2 study involving patients with no evidence of iron-deficiency anaemia, there were no significant increases in iron parameters among patients treated with sucroferric oxyhydroxide [1]. However, administration of sucroferric oxyhydroxide for up to 1 year in a Phase 3 study and subsequent extension study did result in small increases in ferritin and transferrin saturation (TSAT), compared with sevelamer carbonate [2–4]. Thus, a *post hoc* subgroup analysis was performed on data from the Phase 3 study and its extension to further examine changes in iron parameters and intravenous (IV) iron and erythropoiesis-stimulating agent (ESA) use in patients who completed 1 year of sucroferric oxyhydroxide treatment.

What are the main messages of this paper?

- This *post hoc* analysis of a 24-week Phase 3 study and its 28-week extension found initial increases in iron-related parameters among dialysis patients treated with sucroferric oxyhydroxide or sevelamer carbonate.
- There were small, but statistically significant, greater increases in TSAT and haemoglobin with sucroferric oxyhydroxide versus sevelamer carbonate and these differences are likely due to minimal iron absorption from sucroferric oxyhydroxide.
- Ferritin concentrations increased to a greater extent in the overall study population (>70% of whom received concomitant IV iron), compared with the subset of patients who did not receive concomitant IV iron, indicating that these increases were primarily driven by IV iron use.
- There appeared to be minimal risk of iron accumulation or overload with sucroferric oxyhydroxide following 1 year of treatment.
- There was a trend towards lower use of anti-anaemic products (ESA and IV iron) among patients treated with sucroferric oxyhydroxide, compared with those treated with sevelamer carbonate.

MATERIALS AND METHODS

The design of the randomized, open-label, 24-week, Phase 3 study and its 28-week extension study has been previously described [2, 3]. Briefly, the efficacy and safety of sucroferric oxyhydroxide (1.0−3.0 g/day, 2−6 tablets/day) were compared with those of sevelamer carbonate ('sevelamer'; 2.4−14.4 g/day, 3−18 tablets/day) in adult haemodialysis or peritoneal dialysis patients with hyperphosphataemia over 24 weeks of treatment. Eligible patients entered the 28-week extension study, continuing the same treatment and dose they were receiving at the end of the initial study. Patients with serum ferritin >2000 ng/mL were excluded, and oral iron therapies or supplements were not permitted during the study.

To observe the effects of long-term treatment administration on iron parameters, *post hoc* analyses included only those patients who completed at least 52 weeks of continuous treatment (completer set). To fully investigate changes in iron-related parameters throughout the study, patients were stratified by baseline serum ferritin quartiles (Q1, ≤310 ng/mL; Q2, >310 to ≤604 ng/mL; Q3, >604 to ≤920 ng/mL; Q4, >920 ng/mL). In order to evaluate the potential impact of sucroferric oxyhydroxide and sevelamer on iron-related parameters independent of IV iron use, serum levels of ferritin, TSAT and haemoglobin were also summarized for the subgroup of patients in each treatment group who did not receive IV iron during the study ('no IV iron' subgroup). Iron parameters were summarized at baseline ('Week 0') then every 4 weeks up until Week 52 (end of study). Any missing values at Weeks 24 or 52 were imputed using the last observation carried forward method.

Analysis of treatment-emergent adverse events (TEAEs) related to changes in iron parameters was performed on the safety set (patients who took one or more dose of study medication during the initial 24-week Phase 3 study and/or the 28-week extension study).

Analyses were conducted using SAS® Version 9.2 or later (SAS Institute, Inc.), and statistical tests were performed using two-sided tests at the 5% significance level. Descriptive statistics were used to analyse the safety data.

RESULTS

Baseline demographics

In the initial Phase 3 study, 1059 patients were randomized to treatment: 710 to sucroferric oxyhydroxide, 349 to sevelamer. The 52-week completer set comprised 549 patients ($n = 322$ sucroferric oxyhydroxide; $n = 227$ sevelamer). Iron parameters data were available for all patients in the completer set.

Baseline characteristics were largely similar between the two treatment groups (Table 1). A similar proportion of patients in the sucroferric oxyhydroxide and sevelamer groups received concomitant IV iron (51.2 versus 52.0%, respectively) or ESA (70.8 versus 73.6%) during the 2-week period prior to the first dose of study treatment. Baseline characteristics of the completer set were similar to those of the full analysis set (patients randomized to treatment who received one or more dose of study medication and had one or more post-baseline evaluable efficacy assessment) [2, 3].

Table 1. Baseline patient demographics and use of concomitant iron products and ESAs prior to study treatment start (completer set; $n = 549$).

	Sucroferric oxyhydroxide ($n = 322$)	Sevelamer carbonate ($n = 227$)	Total ($n = 549$)
Mean (SD) age, years	55 (13)	56 (15)	56 (14)
Sex, %			
Male	55.6	63.0	58.7
Ethnicity, %			
White	80.7	74.9	78.3
Black/African American	14.9	22.9	18.2
Other	4.4	2.2	3.5
Dialysis modality, %			
Haemodialysis	88.2	93.8	90.5
Peritoneal dialysis	11.8	6.2	9.5
Reason for end-stage renal disease, %			
Hypertension	21.4	29.1	24.6
Glomerulonephritis	26.1	23.3	25.0
Diabetic nephropathy	22.7	26.4	24.2
Other	29.8	21.1	26.2
Mean (SD) time from first dialysis, months	50 (49)	55 (60)	52 (53)
Prior phosphate binders, *n* (%)			
Calcium-based	216 (67.1)	148 (65.2)	364 (66.3)
Aluminum-based	12 (3.7)	10 (4.4)	22 (4.0)
Lanthanum	20 (6.2)	9 (4.0)	29 (5.3)
Sevelamer	99 (30.8)	83 (36.6)	182 (33.2)
Other	2 (0.6)	1 (0.4)	3 (0.6)
Use of sevelamer any time in previous 12 months	105 (32.6)	90 (39.7)	195 (35.5)
Prior use of anti-anaemic products[a], *n* (%)			
IV iron	165 (51.2)	118 (52.0)	283 (51.5)
ESA	228 (70.8)	167 (73.6)	395 (71.9)

ESA, erythropoiesis stimulating agents; IV, intravenous; SD, standard deviation.
[a]Within 2 weeks of study entry.

Overall changes in iron-related parameters

Mean ± standard errors of the mean (SEM) serum ferritin concentrations in both treatment groups during the course of the initial Phase 3 study and its 28-week extension are shown in Figure 1A. Baseline ferritin concentrations were lower in the sucroferric oxyhydroxide group compared with the sevelamer group (621.5 and 710.1 ng/mL, respectively).

Significant increases in ferritin concentrations up to Week 24 were observed in both the sucroferric oxyhydroxide and sevelamer treatment groups [+119.0 ng/mL ($P < 0.001$) and +56.2 ng/mL ($P = 0.002$), respectively]. Changes in serum ferritin from Weeks 24 to 52 were less pronounced in both treatment groups (increases of 34.8 ng/mL with sucroferric oxyhydroxide and 16.1 ng/mL with sevelamer), and were not statistically significant. There were no significant differences between treatment groups with respect to changes in ferritin concentrations during the initial Phase 3 study (Weeks 0–24) or the extension study (Weeks 24–52).

Mean ± SEM TSAT values for both treatment groups during the 1-year treatment period are shown in Figure 1B. Significant increases in TSAT up to Week 24 were observed in the sucroferric oxyhydroxide group (+4.6%, $P < 0.001$), but not in the sevelamer group (+0.6%). No significant changes in TSAT were observed from Weeks 24 to 52 with sucroferric oxyhydroxide or sevelamer [no change (0%) and +0.6%, respectively]. The differences between treatment groups with respect to changes in TSAT were statistically significant from Weeks 0 to 24 ($P = 0.003$), but not from Weeks 24 to 52.

Mean ± SEM haemoglobin concentrations over 1 year are shown in Figure 1C. Overall, no major changes in haemoglobin concentration were observed by Week 24 with sucroferric oxyhydroxide or sevelamer. However, there were small, but statistically significant increases from baseline in mean haemoglobin concentrations among patients in the sucroferric oxyhydroxide group from Weeks 0 to 24 (+1.6 g/L; $P = 0.044$) that were maintained until the end of the study (Week 52). Although the changes from baseline in haemoglobin concentrations were small, differences between the treatment groups were statistically significant at the majority of time points analysed during the 52-week treatment period (Figure 1C).

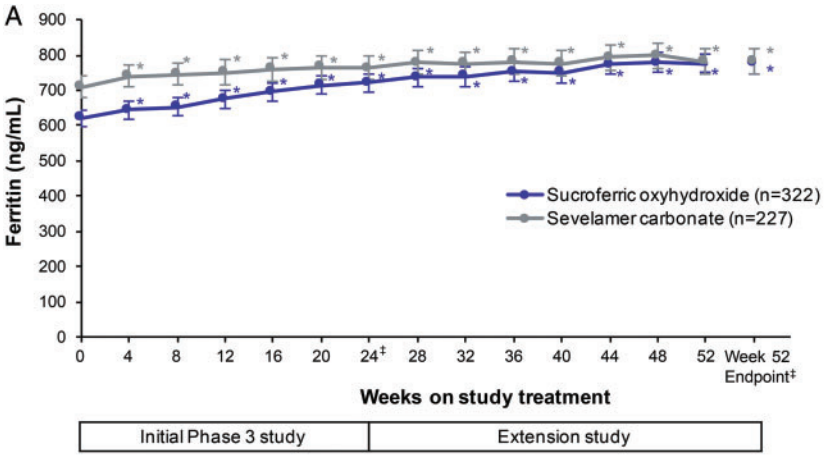
Changes in concomitant anti-anaemic product use

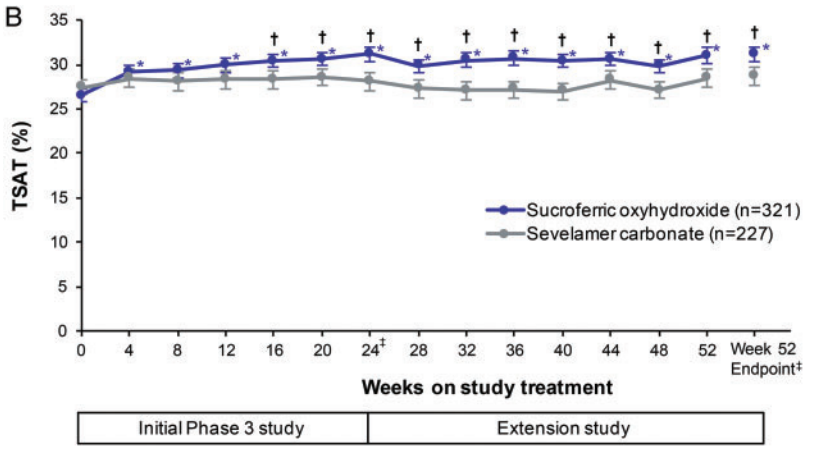
The majority of patients in the sucroferric oxyhydroxide and sevelamer groups received concomitant IV iron and/or ESA products at least once during the 1-year study (IV iron: 73.6 and 80.6% of patients, respectively; ESA: 85.4 and 89.4% of patients, respectively).

In both treatment groups, the proportion of patients receiving concomitant IV iron was greater during Weeks 0–24, compared with Weeks 24–52 (Figure 2A). Over these periods, the proportion of patients receiving IV iron and ESA was marginally higher in the sevelamer group compared with the sucroferric oxyhydroxide group (Figure 2). This difference in concomitant ESA use was statistically significant between treatment groups between Weeks 24 and 52 ($P = 0.025$).

Changes in iron-related parameters by baseline ferritin

Mean levels of iron-related parameters stratified by baseline ferritin quartile are summarized in Figure 3.





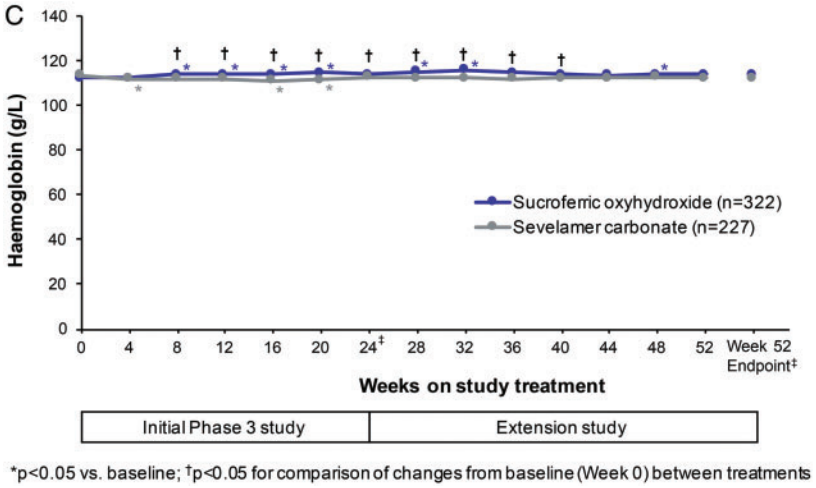


FIGURE 1: Mean (SEM) iron parameters—ferritin (**A**), TSAT (**B**) and haemoglobin (**C**)—over 1 year (completer set; $n = 549$). Only statistically significant differences are shown ($P < 0.05$). ‡Last observation carried forward, Week 24 is the Week 24 result or the latest evaluable measurement after baseline (Week 0) in the primary study when Week 24 is missing; Week 52 Endpoint is Week 52 result or the latest available measurement after extension baseline when Week 52 is missing; SEM, standard error of the mean; TSAT, transferrin saturation.

Across baseline ferritin quartiles, the greatest changes in iron parameters had generally occurred by Week 24 in both treatment groups, while smaller changes were seen from Weeks 24 to 52. Moreover, except for serum ferritin, there were no significant changes in iron parameters from Weeks 24 to 52.

Significant increases in mean ferritin concentrations were observed from Weeks 0 to 24 among patients in baseline ferritin quartiles Q1, Q2 and Q3 with both sucroferric oxyhydroxide and sevelamer ($P \leq 0.014$) (Figure 3A). In contrast, changes in serum ferritin among patients within baseline ferritin quartile

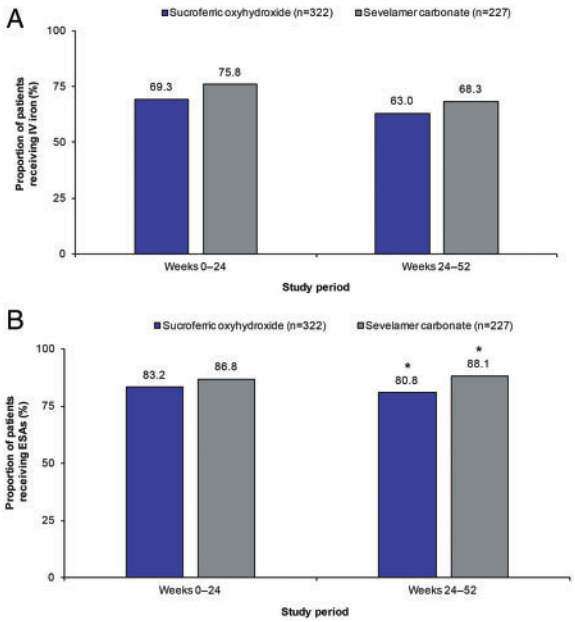


FIGURE 2: Proportion of patients receiving concomitant anti-anaemic products—IV iron (**A**) and ESAs (**B**)—at different time periods over 1 year (completer set; $n = 549$). *P = 0.0252 for sucroferric oxyhydroxide versus sevelamer carbonate. Week 0 is baseline of initial Phase 3 study. ESAs, erythropoiesis stimulating agents; IV, intravenous.

Q4 were non-significant in both treatment groups. Statistically significant increases in ferritin were observed from Weeks 24 to 52 only among patients in ferritin quartiles Q1 and Q2 with sucroferric oxyhydroxide ($P \leq 0.022$).

Significant increases in TSAT were observed from Weeks 0 to 24 among patients in baseline ferritin quartiles Q1, Q2 and Q3 with sucroferric oxyhydroxide ($P \leq 0.0164$), but not with sevelamer (Figure 3B). There was a significant difference between treatment groups only in Q1 ($P < 0.001$).

A small but significant increase in mean haemoglobin concentration was observed from Weeks 0 to 24 among patients in baseline ferritin quartile Q1 with sucroferric oxyhydroxide ($P = 0.001$), but not with sevelamer (Figure 3C). In both treatment groups, small non-significant changes in haemoglobin were observed from Weeks 0 to 24 among patients in baseline ferritin quartiles Q2, Q3 and Q4.

Changes in iron parameters in the 'no IV iron' subgroup

Approximately 26% of patients in the sucroferric oxyhydroxide group ($n = 85$) and 19% of patients in the sevelamer group ($n = 44$) did not receive any IV iron therapy during the 1-year treatment period. Mean ferritin, TSAT and haemoglobin levels for patients in this 'no IV iron' subgroup are summarized in Figure 4.

Mean ± SEM baseline ferritin concentrations in the 'no IV iron' subgroup were slightly lower in the sucroferric oxyhydroxide group (491.2 ng/mL), compared with the sevelamer group (552.4 ng/mL). There were initial reductions in serum ferritin from Weeks 0 to 24 in both the sucroferric oxyhydroxide and sevelamer treatment groups [−41.5 ng/mL ($P = 0.035$) and −60.7 ng/mL, respectively]. However, mean ferritin concentrations increased in both treatment groups from Weeks 24 to 52 [sucroferric oxyhydroxide: +71.9 ng/mL ($P = 0.003$); sevelamer: +39.7 ng/mL, respectively]. There were no significant differences between the treatment groups with respect to changes in serum ferritin at any of the time points analysed during the 1-year treatment period.

In patients who did not receive IV iron, TSAT levels increased significantly from Weeks 0 to 24 in the sucroferric oxyhydroxide group (+3.9%; $P = 0.005$), and this initial increase was maintained until the end of the study (Week 52) (Figure 4B). In contrast, TSAT levels remained unchanged in the sevelamer group during the initial Phase 3 study (Δ Weeks 0 to 24: 0.5%) and extension study (Δ Weeks 24 to 52: +0.9%).

Haemoglobin levels were generally stable among patients who did not receive concomitant IV iron in both treatment groups (Figure 4C). There were small but significant initial increases in mean haemoglobin concentrations with sucroferric oxyhydroxide between Weeks 0 and 24 (+4.3 g/L; $P = 0.006$), which were maintained up until the end of the study (Week 52). In contrast, there were no significant increases from baseline in mean haemoglobin concentrations in the sevelamer group at any time point during the study (Figure 4C).

Safety and tolerability

Overall safety and tolerability data from the Phase 3 and extension studies have been reported [2, 3]. Analysis of the safety set ($n = 1055$) showed that TEAEs related to an increase in iron parameters were reported by a similar proportion of patients in both treatment groups (sucroferric oxyhydroxide, 2.8%; sevelamer, 2.9%). The only iron parameter-related TEAE occurring in ≥2% of patients in either treatment group was increased serum ferritin (sucroferric oxyhydroxide, 2.1%; sevelamer, 2.3%). None of the iron-related TEAEs was severe, considered to be serious or led to withdrawal. Anaemia was reported in a greater proportion of patients in the sevelamer group (10.1%) than in the sucroferric oxyhydroxide group (5.2%).

Two patients in the sucroferric oxyhydroxide group had iron-related TEAEs that were considered by the investigators to be related to treatment. One patient experienced increased serum ferritin (1373.8 ng/mL), but remained on treatment with sucroferric oxyhydroxide until the end of the study, and the event was ongoing at that time. This patient was also receiving concomitant IV iron during the trial. The other patient was diagnosed with iron overload, based on elevated TSAT (80%) and iron (48.1 µmol/L) levels, although ferritin concentrations remained rather low (31.2 ng/mL). The iron overload resolved without further sequelae 14 days later, and the patient was able to remain on the full dose of sucroferric oxyhydroxide for the remainder of the study.

DISCUSSION

Initial increases in some iron-related parameters, particularly ferritin and TSAT, were observed in this *post hoc* analysis of patients who received 52 weeks of continuous sucroferric oxyhydroxide treatment. Serum ferritin reflects the amount of

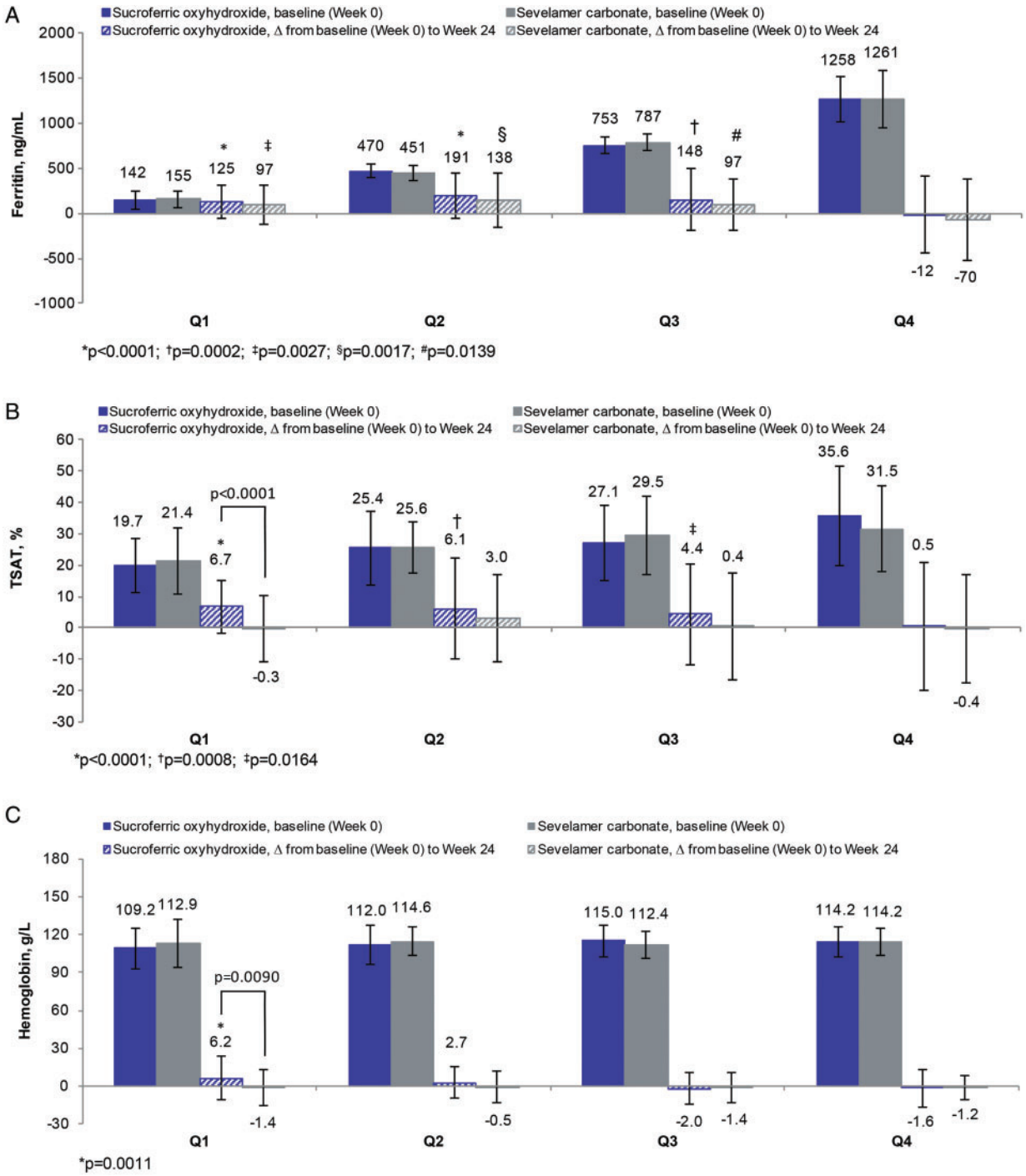
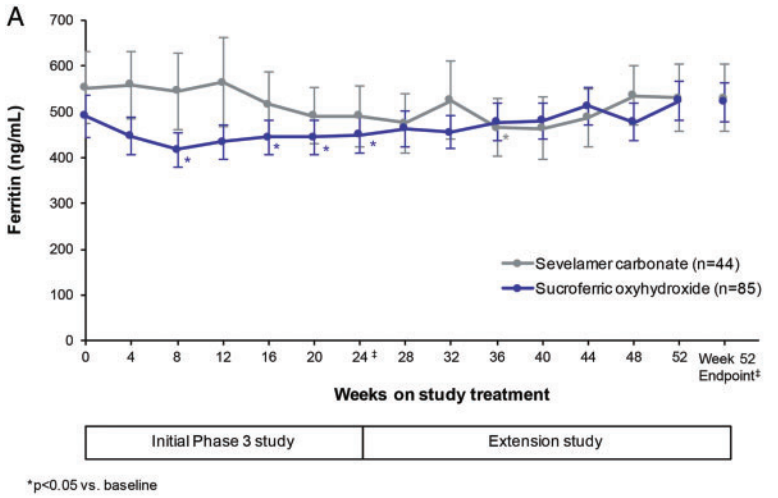
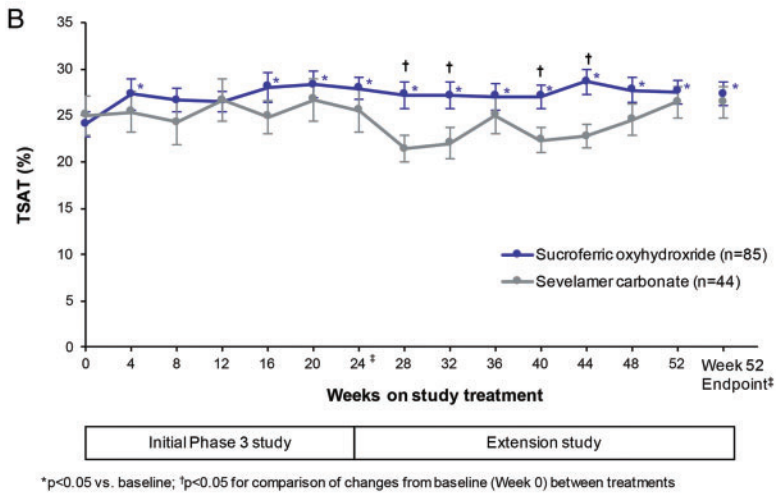


FIGURE 3: Mean (SD) values at baseline and changes in iron indices by baseline ferritin levels in the initial Phase 3 study (Weeks 0–24) (completer set; $n = 549$). (**A**) Ferritin, (**B**) TSAT and (**C**) haemoglobin. Only P-values <0.05 are shown on the graphs; all other differences were not statistically significant. SD, standard deviation; TSAT, transferrin saturation. Ferritin quartiles were defined as follows: Q1, ≤310 ng/mL; Q2, ≤604 ng/mL (median for total population at baseline); Q3, ≤920 ng/mL; Q4, >920 ng/mL.

stored iron and is also recognized as an inflammatory disease marker [5, 6]. Inflammation is common in patients with chronic kidney disease on dialysis [7]; therefore, higher threshold levels for ferritin are defined for assessment of iron stores. In this current analysis, ferritin increased in both treatment groups at Weeks 24 and 52 among patients in the overall study population, the majority of whom (>70%) received concomitant IV iron at least once during the 52-week treatment period. In contrast, in patients who did not receive IV iron during the study, there was a decline in ferritin concentrations in both treatment groups up to Week 24. These observations indicate that increases in ferritin concentrations observed among patients in the overall population were largely driven by concomitant IV iron use.





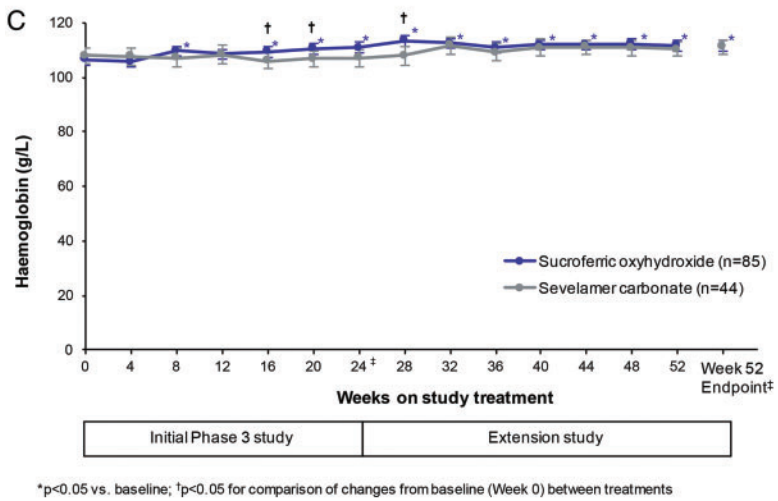


FIGURE 4: Mean (SEM) iron parameters—ferritin (**A**), TSAT (**B**) and haemoglobin (**C**)—in patients who did not receive concomitant IV iron over 1 year (non-IV iron completer set; $n = 129$). Only statistically significant differences are shown ($P < 0.05$). ‡Last observation carried forward, Week 24 is the Week 24 result or the latest evaluable measurement after baseline (Week 0) in the primary study when Week 24 is missing; Week 52 Endpoint is Week 52 result or the latest available measurement after extension baseline when Week 52 is missing. IV, intravenous; SD, standard deviation; SEM, standard error of the mean; TSAT, transferrin saturation.

Importantly, TSAT, which reflects circulating iron availability for haemoglobin production [8], increased over 1 year of sucroferric oxyhydroxide treatment, irrespective of whether or not patients received IV iron during the study. Finally, although there was a statistically significant difference between the sucroferric oxyhydroxide and sevelamer groups for the change in haemoglobin concentrations from baseline to Week 24, the absolute changes in haemoglobin in both groups appeared small and unlikely to be clinically meaningful.

The differences between treatment groups in terms of changes in iron parameters are likely due to minimal iron absorption from sucroferric oxyhydroxide. This was particularly evident from the analysis of iron parameters in the 'no IV iron' subgroup, which was performed to evaluate the impact of sucroferric oxyhydroxide and sevelamer treatment on iron-related parameters, independent of IV iron use. In this patient subgroup, there were small but significant increases from baseline in TSAT and haemoglobin among subjects treated with sucroferric oxyhydroxide, whereas no significant changes were observed in those treated with sevelamer. In addition, the use of concomitant anti-anaemic treatments, including ESAs, by the majority of the patients (72% of the completer population at baseline, and up to 88% during the study) should be considered as a factor modifying iron parameters. Across both treatment groups, the greatest changes in iron parameters occurred during the first 6 months of treatment, whereas the changes in iron parameters over the second 6 months were less pronounced and the differences between the treatment groups not statistically significant. In both treatment groups, patients with high baseline serum ferritin concentration had the least pronounced change in iron parameters, in line with knowledge that iron uptake is largely governed by iron body storage and inflammatory status [9]. Furthermore, the proportion of patients with iron-related TEAEs was similar between treatment groups, and none of these TEAEs was severe, serious or caused withdrawal from the study. The risk of iron accumulation or overload with long-term sucroferric oxyhydroxide treatment appears to be minimal. While minimal iron absorption from sucroferric oxyhydroxide may be beneficial to dialysis patients, who are often iron deficient [10, 11], this treatment does not replace the use of IV iron products that enable controlled delivery of iron to replenish and maintain iron stores.

A slightly higher proportion of patients in the sevelamer group received IV iron and ESA products during the 1-year study period, compared with those in the sucroferric oxyhydroxide group. Concomitant IV iron use in both treatment groups, as well as ESA use in the sucroferric oxyhydroxide group, was greatest during the first 6 months and declined over the next 6 months. The lack of prespecified, per-protocol data relating to dose and frequency of anti-anaemic product use makes it difficult to precisely evaluate the extent to which concomitant IV iron and ESA use were affected by sucroferric oxyhydroxide treatment. Use of IV iron in dialysis patients is influenced by several factors, including reimbursement pressures (e.g. bundling) that provide an incentive to reduce the use of more costly treatments (such as ESAs) in favour of less expensive treatments (such as IV iron) [12]. Implementation of a new bundling reimbursement policy in the USA in 2011, when the Phase 3 study was being conducted [13], may have led to a higher use of IV iron preparations in US haemodialysis patients [14], and may have impacted concomitant IV iron and ESA use during the study.

Sucroferric oxyhydroxide was developed as a phosphate binder with high potency and low iron release properties, resulting in minimal iron uptake in chronic kidney disease patients following administration of radiolabelled sucroferric oxyhydroxide [15–17]. Preclinical studies conducted in rats and dogs have also demonstrated that long-term (up to 2 years) administration of sucroferric oxyhydroxide in clinically relevant and higher doses was associated with only modest increases in tissue iron levels and no iron toxicity [16]. Findings from the current *post hoc* analysis are consistent with data from the overall patient population investigated in the previous sucroferric oxyhydroxide Phase 3 and extension studies, in which changes in some iron parameters were observed [2, 3]. Real-world observational studies of sucroferric oxyhydroxide have also reported similar findings with respect to changes in iron-related parameters. A large retrospective study of over 3000 US dialysis patients found that 3 months' treatment with sucroferric oxyhydroxide was associated with small but significant increases in serum ferritin, TSAT and haemoglobin among subjects who also received concomitant IV iron [18]. Analysis of the sucroferric oxyhydroxide-treated patients who did not receive IV iron during the 3-month treatment period revealed significant reductions in serum ferritin concentrations and no changes in TSAT or haemoglobin levels [18]. These observations are consistent with the changes in iron parameters observed in this current analysis.

Increases in iron-related parameters, including ferritin and TSAT, have been observed with another iron-based phosphate binder, ferric citrate, in short-term (8-week [19] and 12-week [20]) and longer-term (52-week [21–23]) studies. In addition, ferric citrate was associated with a reduction in the need for concomitant IV iron and ESA compared with active control, supporting the potential of this phosphate binder to increase iron stores [22, 23]. Despite IV iron therapy being stopped if patients' serum ferritin concentration exceeded 1000 ng/mL, ~20% of patients who received ferric citrate had one or more episode of elevated serum ferritin (>1500 ng/mL), compared with ~10% in the active control arm [22, 23], and a number of patients had serum ferritin concentrations >2000 ng/mL over 1 year of treatment [23].

It is not possible to make a direct comparison between ferric citrate and sucroferric oxyhydroxide in terms of their effects on iron parameters due to inherent differences between study designs. For example, in contrast to the ferric citrate studies [22, 23], IV iron therapy was not prohibited in sucroferric oxyhydroxide studies if patients' serum ferritin concentration exceeded 1000 ng/mL [2, 3]. Moreover, mean baseline ferritin was lower in patients receiving ferric citrate (<600 ng/mL) in the 52-week study [22, 23], compared with those receiving sucroferric oxyhydroxide in the Phase 3 study and its extension study (>600 ng/mL) [2, 3]. The differences between the phosphate binders

may be explained, at least in part, by their individual physicochemical properties. The active moiety in sucroferric oxyhydroxide—polynuclear iron(III)-oxyhydroxide—is practically insoluble [24], and iron release is minimal under physiological pH conditions simulating administration on a full stomach [15]. Citrate is known to chelate [25], solubilize and promote absorption of trivalent metals from the diet [26] and, thus, has the potential to enhance iron uptake from a ferric-based phosphate binder and impact physiological mechanisms of controlled iron absorption [26]. Nevertheless, preliminary data from a subgroup analysis of a ferric citrate 52-week Phase 3 study, in which patients were stratified by concomitant IV iron use versus no IV iron [27], appear to show findings that contrast with those observed with sucroferric oxyhydroxide in the current *post hoc* analysis. In particular, changes in ferritin and TSAT in patients treated with ferric citrate appeared to be similar in those who received concomitant IV iron and those who did not [27].

This study had several limitations: no specific information was available on changes in doses or frequency of IV iron and ESA; almost 50% of patients enrolled in the initial Phase 3 study were recruited in the USA and, therefore, iron-related data may have been influenced by the implementation of the new bundling reimbursement policy in the USA in 2011 [2, 3, 13].

In conclusion, initial increases in some iron-related parameters were observed in dialysis patients treated with sucroferric oxyhydroxide. Changes in iron parameters were less pronounced among patients with high serum ferritin concentrations at baseline, and the risk for iron accumulation or overload appears to be minimal following 1 year of continuous sucroferric oxyhydroxide treatment. Thus, no additional monitoring of iron parameters, beyond routine evaluation, is required. A potential modest reduction in the use of anti-anaemic products following treatment with sucroferric oxyhydroxide, compared with sevelamer, warrants more in-depth analyses in post-marketing studies.

CONFLICT OF INTEREST STATEMENT

A.C.C. has received consultancy fees or lecture fees from Vifor Pharma, Fresenius Medical Care and Amgen. J.F. has received consulting fees or lecture fees from AbbVie, Amgen, Chugai, Fresenius Medical Care, Sanofi, Shire and Vifor Pharma. M.K. has received consulting fees or lecture fees from Vifor Pharma, Fresenius Medical Care, Amgen, AbbVie, Medice, Mitsubishi Pharma, Sanofi and Shire. S.M.S. has received consultancy fees from OPKI, Vifor Pharma, Amgen, Fresenius Medical Care, Litholink Corp, and NPS Pharma and research funding from Abbott, Amgen, Shire, Cytochroma/OPKO Health, Vifor Pharma, Satellite Healthcare and Deltanoid. L.L. and V.R. are both employees of Vifor Pharma. A.R. has received consultancy fees from Fresenius Medical Care and Vifor Pharma, and lecture and consultancy fees from Sanofi. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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