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Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients

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ABSTRACT

Background. Hyperphosphatemia necessitates the use of phosphate binders in most dialysis patients. Long-term efficacy and tolerability of the iron-based phosphate binder, sucroferric oxyhydroxide (previously known as PA21), was compared with that of sevelamer carbonate (sevelamer) in an open-label Phase III extension study.

Methods. In the initial Phase III study, hemo- or peritoneal dialysis patients with hyperphosphatemia were randomized 2:1 to receive sucroferric oxyhydroxide 1.0−3.0 g/day (2−6 tablets/

day; $n = 710$) or sevelamer 2.4−14.4 g/day (3−18 tablets/day; $n = 349$) for 24 weeks. Eligible patients could enter the 28-week extension study, continuing the same treatment and dose they were receiving at the end of the initial study.

Results. Overall, 644 patients were available for efficacy analysis ($n = 384$ sucroferric oxyhydroxide; $n = 260$ sevelamer). Serum phosphorus concentrations were maintained during the extension study. Mean ± standard deviation (SD) change in serum phosphorus concentrations from extension study baseline to Week 52 end point was 0.02 ± 0.52 mmol/L with sucroferric oxyhydroxide and 0.09 ± 0.58 mmol/L with sevelamer. Mean serum phosphorus concentrations remained within Kidney Disease Outcomes Quality Initiative target range (1.13–1.78 mmol/L) for both treatment groups. Mean (SD) daily tablet number over the 28-week extension study was lower for sucroferric oxyhydroxide (4.0 ± 1.5) versus sevelamer (10.1 ± 6.6). Patient adherence was 86.2% with sucroferric oxyhydroxide versus 76.9% with sevelamer. Mean serum ferritin concentrations increased over the extension study in both treatment groups, but transferrin saturation (TSAT), iron and hemoglobin concentrations were generally stable. Gastrointestinal-related adverse events were similar and occurred early with both treatments, but decreased over time.

Conclusions. The serum phosphorus-lowering effect of sucroferric oxyhydroxide was maintained over 1 year and associated with a lower pill burden, compared with sevelamer. Sucroferric oxyhydroxide was generally well tolerated long-term and there was no evidence of iron accumulation.

Keywords: hemodialysis, peritoneal dialysis, sucroferric oxyhydroxide

INTRODUCTION

Hyperphosphatemia is a serious consequence of chronic kidney disease (CKD) that is associated with CKD-mineral bone disorder (CKD-MBD) [1], an increased risk of cardiovascular events [2] and death [3–6]. Treatment with phosphate binders is required by most dialysis patients to maintain serum phosphorus control and is associated with increased survival [7–9]. However, a high pill burden associated with most available phosphate binders is linked to low adherence and can reduce health-related quality of life [10–12].

The novel, non-calcium-, iron-based phosphate binder, sucroferric oxyhydroxide (VELPHORO®; PA21), has been shown to have a high phosphate-binding capacity over a wide pH range [13]. It is formulated as a chewable tablet containing 500 mg iron. In Phase I clinical studies, sucroferric oxyhydroxide was well tolerated and associated with minimal gastrointestinal (GI) iron absorption [13]. A Phase II study showed that doses of 1.0−2.5 g/day (based on iron content) substantially lowered serum phosphorus concentrations and reaffirmed its tolerability profile [14]. A Phase III study in patients undergoing hemodialysis or peritoneal dialysis showed that sucroferric oxyhydroxide was non-inferior to sevelamer, in terms of serum phosphorus control, after 12 weeks of treatment [15]. Treatment effect was achieved with approximately 62% fewer sucroferric oxyhydroxide tablets than sevelamer tablets and

was maintained over 24 weeks. Patients who completed the Phase III study, and who were eligible, had the option of entering a 28-week extension study. In this paper, we present long-term efficacy and safety data from this extension study, including an examination of its effect on iron parameters.

## MATERIALS AND METHODS

Trial design

The initial Phase III study (NCT01324128) and its extension (NCT01464190; date of registration: 12 September 2011) were multicenter, Phase III, open-label, randomized, active-controlled trials (Figure 1). The design of the initial study has been described previously [15]; in brief, after 2−4 weeks of washout from previous phosphate binders, eligible patients with serum phosphorus concentrations ≥1.94 mmol/L were randomized (2:1) to receive sucroferric oxyhydroxide [1.0−3.0 g/day (2−6 tablets/day); $n = 710$] or sevelamer carbonate ['sevelamer' 2.4−14.4 g/day (3−18 tablets/day), starting dose 4.8 g/day; $n = 349$]. The dose was titrated for 8 weeks, then adjusted only for tolerability during Weeks 9−12 and subsequently for efficacy and tolerability during Weeks 13−24 (Stage 1). After 24 weeks, 99 hemodialysis patients in the sucroferric oxyhydroxide group were re-randomized (1:1) to continue receiving their maintenance dose ($n = 50$, median dose 1.5 g/day) or receive low-dose sucroferric oxyhydroxide [$n = 49$; 250 mg/day (ineffective control)] for 3 weeks (Stage 2).

The extension study was conducted in 143 of the 174 initial study sites [USA, 56; EU, 43; other countries (Croatia, Russia, Serbia, South Africa and the Ukraine), 44]. All patients of the initial study that fullfiled the eligibility criteria were allowed to enter the extension study, except those re-randomized to low-dose sucroferric oxyhydroxide. Patients continued their randomized treatments at their maintenance doses for an additional 28 weeks (Figure 1). Dose modifications were allowed for tolerability and efficacy (target serum phosphorus 0.81−1.78 mmol/L).

Protocols were reviewed by Independent Ethics Committees or Institutional Review Boards and the study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, Committee for Proprietary Medicinal Products guideline (CPMP/ICH/135/95). Written informed consent was obtained before study-specific procedures were performed.

Participants

Eligibility criteria for the initial study have been described previously [15]. Patients were ineligible for the extension study if, at the previous study visit in the initial study, they had hypercalcemia [total serum calcium > 2.75 mmol/L (>11.0 mg/dL)], hypocalcemia [total serum calcium < 1.9 mmol/L (<7.6 mg/dL)], alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of the normal range, or serum ferritin > 4494 pmol/L (>2000 μg/L). Patients were also excluded if, in the opinion of the investigator, they
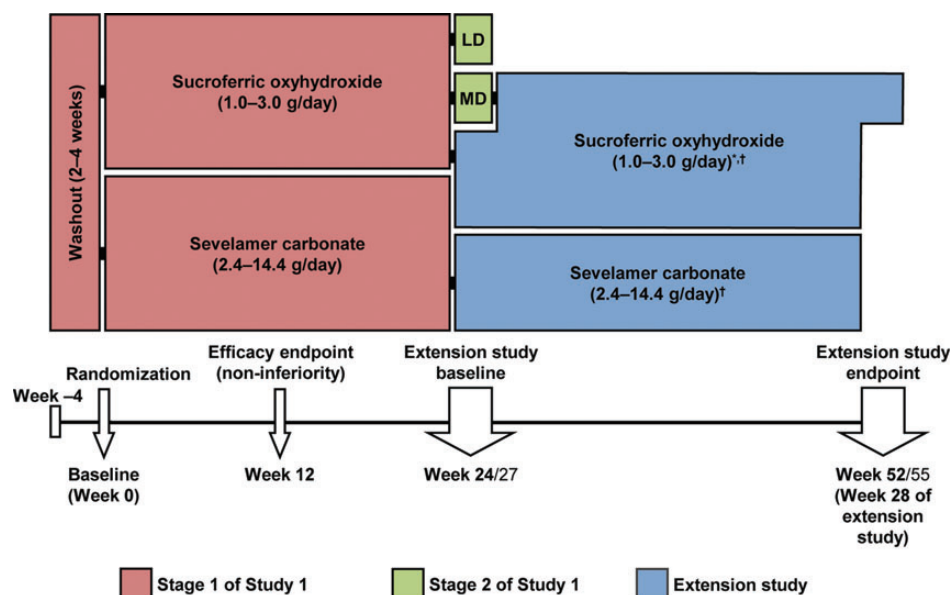
FIGURE 1: Study design. *Patients from the MD group in Stage 2 entered into the extension study at Week 27. † Patients not participating in Stage 2 continued directly into the extension study at Week 24. LD, low dose; MD, maintenance dose.

had uncontrolled diabetes, unstable angina or hypertension, or an estimated life expectancy of less than 12 months.

Patients in both treatment groups were instructed that their dietary restrictions (e.g. phosphorus and calcium intake) should remain unchanged as far as possible throughout the study period. Antacids containing aluminum, calcium or magnesium, and oral iron therapies and iron supplements were not permitted. Intravenous iron and erythropoietin-stimulating agents were permitted in accordance with local guidelines. Patients were withdrawn if serum phosphorus concentrations exceeded 2.75 mmol/L (8.5 mg/dL) or decreased below 0.81 mmol/L (2.5 mg/dL), or if total serum calcium concentrations exceeded 2.75 mmol/L (11.0 mg/dL) despite appropriate interventions, confirmed by a repeat measurement 1 week later.

Assessments and outcomes

Efficacy and safety assessments were performed every 4 weeks. Extension study efficacy end points included change in serum phosphorus concentration from baseline (last measurement before entry into extension study). Safety end points were treatment-emergent adverse event (TEAE) profiles, iron-related parameters, bone markers and hematology and biochemical laboratory parameters (analyses were performed at one of two central laboratories). Blood samples were analyzed using standard validated methods. Treatment adherence was calculated based on the number of tablets dispensed and returned:

Treatment adherence

$$= \frac{\text{Total actual number of tablets taken during a period} \times 100}{\text{Number of tablets expected to be taken during a period}}$$

Sample-size calculations and statistics

The sample-size calculation for the initial study has been described previously [15]. Based on an assumed withdrawal rate of up to 50% in the initial study, it was anticipated that ≥450

patients (300 in the sucroferric oxyhydroxide group and 150 in the sevelamer group) would be enrolled in the extension study. No replacement of patients was allowed.

Extension study data were analyzed separately. However, data collected from both the initial Phase III and extension studies were also pooled for an integrated analysis of efficacy [including change in serum phosphorus concentration from initial study baseline, (i.e. Week 0), and serum phosphorus control defined by the proportion of patients with serum phosphorus within the Kidney Disease Outcomes Quality Initiative (KDOQI) recommended target range (1.13−1.78 mmol/L; 3.5–5.5 mg/dL)], pill burden (number of tablets/day) and safety over 1 year of treatment. Analysis sets were assessed as follows:

- Full-analysis set (FAS): randomized patients who received ≥1 dose of study medication and had ≥1 post-baseline evaluable efficacy assessment during the initial study.
- Full-analysis set-extension (FAS-ext): patients who received ≥1 dose of extension study medication and had ≥1 evaluable efficacy assessment during the extension study.
- Safety set (SS): randomized patients who took ≥1 dose of study medication during the Phase III study.
- Safety set-extension (SS-ext): patients who took ≥1 dose of study medication during the extension study.
- Completers: patients who completed at least 52 weeks of continuous treatment in the initial Phase III study and the extension study.

Changes in serum phosphorus concentrations for the FAS-ext study population were compared between treatment groups using analysis of covariance (ANCOVA). The proportion of patients with serum phosphorus concentrations in the KDOQI target range (responders) were summarized by treatment group. All statistical analyses were performed using 2-sided
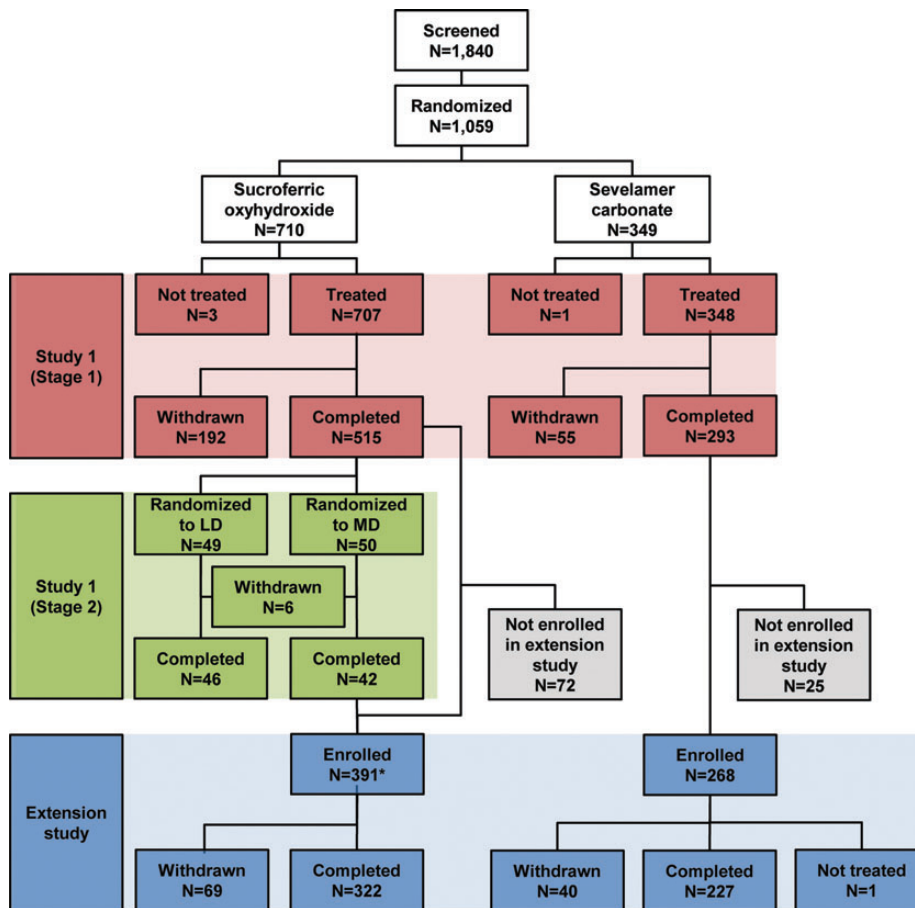
FIGURE 2: Patient disposition. *Comprises 344 patients who progressed directly to the extension study from Stage 1 of the initial Phase III study, 42 patients who completed Stage 2, as well as 5 patients who received extension study drug in error during Stage 2 and were subsequently transferred into the extension study. LD, low dose; MD, maintenance dose.

tests. Tests were at the alpha 0.05 level with no adjustments made for multiplicity, and 95% confidence intervals (CIs) of the difference in serum phosphorus concentrations between treatment groups were calculated. Analyses were conducted using SAS® version 9.2 or later (SAS Institute, Inc.). Descriptive statistics were used to analyze safety data. Demographic and adherence data were not tested for statistical significance and are descriptive only.

RESULTS

Patient disposition

Overall, 466 patients (515 patients who completed Stage 1 of the initial Phase III study minus 49 low-dose sucroferric oxyhydroxide patients excluded after Stage 2) receiving sucroferric oxyhydroxide and 293 patients receiving sevelamer completed the initial study and were eligible for the extension study (Figure 2). In total, 391 patients receiving sucroferric oxyhydroxide were enrolled and treated in the extension study; 268 patients receiving sevelamer were enrolled in the extension study, of which one patient was not treated. There were no major differences in demographic baseline characteristics between patients enrolled in the extension study and those in the initial Phase III study. Overall, the number of patients not entering the

extension study based on serum ferritin levels, as per protocol-defined exclusion criteria, was low in each treatment group ($n = 3$ for sucroferric oxyhydroxide and $n = 1$ for sevelamer). No patients in either treatment group were excluded because of alanine aminotransferase or aspartate aminotransferase levels. Of the 659 patients enrolled in the extension study, 17.6% ($n = 69$) of patients in the sucroferric oxyhydroxide group and 15.3% ($n = 41$; including 1 patient not treated) in the sevelamer group were withdrawn. The main reasons for withdrawal included adverse events other than phosphorus, calcium or potassium level-related TEAEs [24.6% for sucroferric oxyhydroxide; predominantly GI disorders ($n = 7$ patients), of whom only 2 patients discontinued treatment due to diarrhea] versus 9.8% for sevelamer (adverse events were distributed across several different System Organ Classes), hyperphosphatemia (17.4 versus 17.1%), renal transplant (15.9 versus 17.1%), withdrawal of consent (13.0 versus 19.5%) and death (8.7 versus 12.2%).

Demographics of patients enrolled in the extension study were similar between treatment groups (Table 1; FAS-ext). Of 644 patients in the FAS-ext ($n = 384$ for sucroferric oxyhydroxide and $n = 260$ for sevelamer), the proportion of patients adherent at the 70–120% level was 86.2 and 76.9% in the sucroferric oxyhydroxide and sevelamer groups, respectively. Low adherence (<70%) in the FAS-ext was 13.3 and 21.2% in

Table 1. Demographics of patients enrolled in the extension study (FAS-ext, N = 644)

Parameter	Sucroferric oxyhydroxide (n = 384)	Sevelamer carbonate (n = 260)	Total (N = 644)
Mean (SD) age, years	55.2 (13.2)	55.6 (14.6)	55.4 (13.8)
Mean (SD) weight, kg	81.5 (19.4)	83.9 (20.9)	82.4 (20.0)
Sex, n (%)			
Male	217 (56.5%)	160 (61.5%)	377 (58.5%)
Female	167 (43.5%)	100 (38.5%)	267 (41.5%)
Race, n (%)			
White	318 (82.8%)	196 (75.4%)	514 (79.8%)
Black/African American	51 (13.3%)	58 (22.3%)	109 (16.9%)
Other	15 (3.9%)	6 (2.3%)	21 (3.3%)
Ethnicity, n (%)			
Hispanic/Latino	43 (11.2%)	31 (11.9%)	74 (11.5%)
Non-Hispanic/Latino	341 (88.8%)	229 (88.1%)	570 (88.5%)
Dialysis status, n (%)			
Hemodialysis	341 (88.8%)	243 (93.5%)	584 (90.7%)
Peritoneal dialysis	43 (11.2%)	17 (6.5%)	60 (9.3%)
Mean (SD) time from first dialysis, months	49.3 (47.7)	54.9 (57.8)	51.6 (52.0)
Reason for ESRD, n (%)			
Hypertension	76 (19.8%)	72 (27.7%)	148 (23.0%)
Glomerulonephritis	95 (24.7%)	67 (25.8%)	162 (25.2%)
Diabetic mellitus	96 (25.0%)	66 (25.4%)	162 (25.2%)
Other	117 (30.5%)	55 (21.2%)	172 (26.7%)

ESRD, end-stage renal disease; SD, standard deviation.

the sucroferric oxyhydroxide and sevelamer groups, respectively. Over the 1-year period, the proportion of adherent patients (at 70−120% in the FAS; n = 694 for sucroferric oxyhydroxide and n = 347 for sevelamer) was 83.0 and 79.5% in the sucroferric oxyhydroxide and sevelamer groups, respectively.

Efficacy

Serum phosphorus control was maintained with sucroferric oxyhydroxide and sevelamer throughout the extension study (Figure 3A and Table 2) and over 1 year of treatment (Figure 3B). There was no significant difference between treatment groups in change in serum phosphorus concentrations from the start of the extension study to Week 52 end point (P = 0.14; Table 2).

Over 1 year, from the start of the initial Phase III study, mean [standard deviation (SD)] serum phosphorus concentrations among completers (N = 549; sucroferric oxyhydroxide, n = 322; sevelamer, n = 227) decreased by 0.70 (0.66) mmol/L for sucroferric oxyhydroxide [baseline: 2.45 (0.55) mmol/L; Week 52 end point: 1.74 (0.50) mmol/L] and by 0.66 (0.68) mmol/L for sevelamer [baseline: 2.38 (0.57) mmol/L; Week 52 end point: 1.72 (0.45) mmol/L]. These changes in serum phosphorus concentrations were not significantly different between treatment groups (P = 0.45).

At each timepoint throughout the extension study, mean serum phosphorus concentrations remained within the KDOQI target range (1.13–1.78 mmol/L) for both treatment groups (Figure 3A). Of 549 patients who completed ≥1 year of continuous treatment, the proportion within the KDOQI target range (1.13–1.78 mmol/L) was 52% for sucroferric oxyhydroxide and 55% for sevelamer at Week 52. Of the patients who

completed ≥1 year of continuous treatment, the proportion below the KDOQI upper limit (≤1.78 mmol/L) was 60% for sucroferric oxyhydroxide and 62% for sevelamer at Week 52.

Control of serum phosphorus concentrations throughout the extension study was achieved with an overall lower mean (SD) pill burden of 4.0 (1.5) tablets/day for sucroferric oxyhydroxide, compared with 10.1 (6.6) tablets/day for sevelamer (Figure 3C). Over 1 year, the overall mean (SD) number of tablets taken per day was 3.3 (1.3) for sucroferric oxyhydroxide and 8.7 (3.6) for sevelamer.

Mineral and bone metabolism parameters

Bone parameters during the extension study are summarized in Table 3. Mean serum intact parathyroid hormone (iPTH) concentrations increased slightly during the extension study in both sucroferric oxyhydroxide and sevelamer treatment groups. However, it should be noted that mean serum iPTH concentrations in both treatment groups were high at baseline (i.e. Week 0) in the initial Phase III study and a small decrease in serum iPTH concentrations was observed in both treatment groups during the course of the initial study [15].

Mean bone-specific alkaline phosphatase concentrations decreased in both treatment groups during the extension study, with a more pronounced decrease in the sucroferric oxyhydroxide group. However, there was no significant difference between treatment groups in change from extension study baseline to Week 52 end point.

Total serum calcium concentrations were generally stable during the extension study: i.e. no significant change in concentrations was observed in either sucroferric oxyhydroxide or sevelamer treatment groups, and no significant differences between treatment groups were observed.

Iron status

Iron-related parameters during the extension study are summarized in Figure 4. Mean serum ferritin concentrations increased slightly over the extension study in both treatment groups, with a more pronounced increase in the sucroferric oxyhydroxide group. However, there was no significant difference between treatment groups in change in mean serum ferritin concentrations from extension study baseline to Week 52 end point.

Mean serum transferrin saturation (TSAT), iron and hemoglobin concentrations were generally stable throughout the extension study. There was no significant change in mean serum TSAT, iron or hemoglobin from extension study baseline to Week 52 end point in either the sucroferric oxyhydroxide or sevelamer treatment groups.

Adverse events

The most frequent TEAEs over the extension study are summarized in Table 4. During the extension study, TEAEs considered related to treatment were observed in 14.6% (n = 57) of patients receiving sucroferric oxyhydroxide and 9.0% (n = 24) of those receiving sevelamer. The most common treatment-related TEAEs occurring in ≥2.0% of patients were hypophosphatemia (4.6% with sucroferric oxyhydroxide versus 2.6% with sevelamer) and hyperphosphatemia (2.0% versus 1.1%).
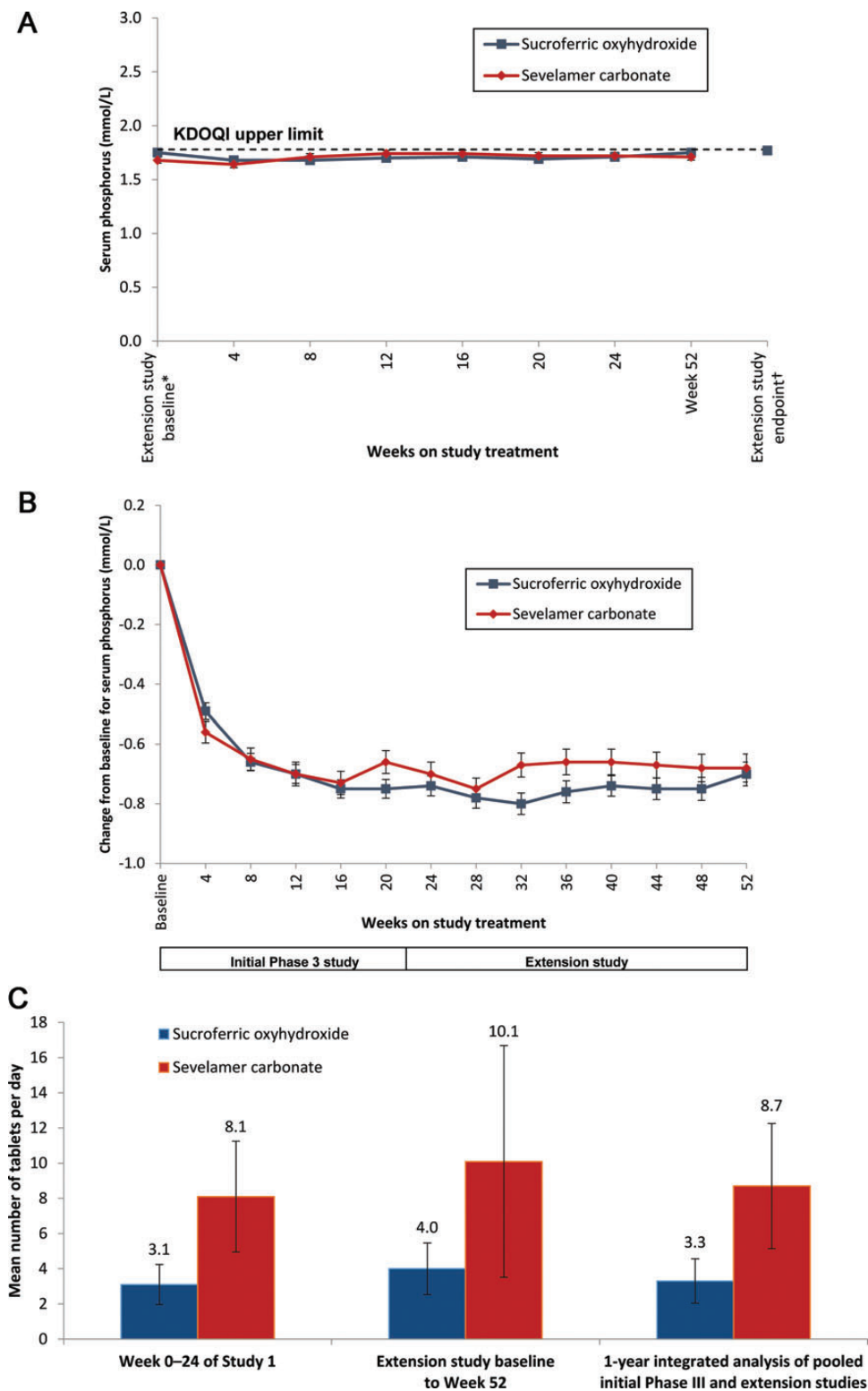
FIGURE 3: Serum phosphorus control and pill burden. (**A**) Mean (± standard error of the mean) serum phosphorus concentrations during the extension study (FAS-ext; $N = 644$). *Last available value prior to or on the date of the first extension study drug intake; [†]Last observation carried forward; KDOQI, Kidney Disease Outcomes Quality Initiative. (**B**) Mean change (± standard error of the mean) from baseline in serum phosphorus concentrations over 1 year (FAS-ext; $N = 644$). (**C**) Mean (± standard deviation) number of phosphate binder tablets per day (SS-ext; $N = 658$).

Incidences of severe and serious TEAEs and deaths were similar between treatment groups during the extension study. Few serious (sucroferric oxyhydroxide, 0.3%; sevelamer, 0.4%) or severe (sucroferric oxyhydroxide, 0.0%; sevelamer, 0.4%) TEAEs were considered related to study treatment. All severe or serious treatment-related TEAEs were GI-related disorders. A total of 14

Table 2. Summary of serum phosphorus (FAS-ext; $N = 644$) during the extension study

Parameter	Assessment timepoint	Sucroferric oxyhydroxide ($n = 384$)	Sevelamer carbonate ($n = 260$)	P-value: sucroferric oxyhydroxide versus sevelamer
		Mean (SD) mmol/L	Mean (SD) mmol/L	
Phosphorus	Extension study baseline[a] (sucroferric oxyhydroxide, $n = 384$; sevelamer carbonate, $n = 260$)	1.75 (0.48)	1.68 (0.46)	–
	Week 52 end point[b] (sucroferric oxyhydroxide, $n = 384$; sevelamer carbonate, $n = 260$)	1.77 (0.54)	1.77 (0.52)	–
	Change from extension study baseline to Week 52 end point[b] (sucroferric oxyhydroxide, $n = 384$; sevelamer carbonate, $n = 260$)	0.02 (0.52); $P = 0.42$	0.09 (0.58); $P = 0.02$	0.14

[a]Extension study baseline is the last non-missing value prior to or on the date of the first extension study drug intake.
[b]Last observation carried forward, Week 52 end point is Week 52 result or the latest available measurement after extension baseline when Week 52 is missing; –, not applicable; SD, standard deviation.

Table 3. Summary of mineral and bone metabolism parameters (SS-ext; $N = 658$) during the extension study

Parameter	Assessment timepoint	Sucroferric oxyhydroxide ($n = 391$)	Sevelamer carbonate ($n = 267$)	P-value: sucroferric oxyhydroxide versus sevelamer
		Mean (SD)	Mean (SD)	
iPTH, pmol/L	Extension study baseline[a] (sucroferric oxyhydroxide, $n = 391$; sevelamer carbonate, $n = 267$)	40.0 (30.0)	39.3 (28.4)	–
	Week 52 end point[b] (sucroferric oxyhydroxide, $n = 383$; sevelamer carbonate, $n = 260$)	46.1 (40.8)	46.0 (34.9)	–
	Change from extension study baseline to Week 52 end point[b] (sucroferric oxyhydroxide, $n = 383$; sevelamer carbonate, $n = 260$)	6.1 (29.3); $P < 0.001$	7.4 (28.8); $P < 0.001$	0.60
Bone-specific alkaline phosphatase, ng/mL	Extension study baseline[a] (sucroferric oxyhydroxide, $n = 391$; sevelamer carbonate, $n = 267$)	18.6 (15.4)	20.0 (17.2)	–
	Week 52 end point[b] (sucroferric oxyhydroxide, $n = 348$; sevelamer carbonate, $n = 251$)	16.5 (14.4)	17.7 (14.5)	–
	Change from extension study baseline to Week 52 end point[b] (sucroferric oxyhydroxide, $n = 348$; sevelamer carbonate, $n = 251$)	−2.4 (11.5); $P < 0.001$	−1.5 (13.1); $P = 0.07$	0.40
Total serum calcium, mmol/L	Extension study baseline[a] (sucroferric oxyhydroxide, $n = 391$; sevelamer carbonate, $n = 267$)	2.2 (0.2)	2.2 (0.2)	–
	Week 52 end point[b] (sucroferric oxyhydroxide, $n = 368$; sevelamer carbonate, $n = 258$)	2.3 (0.2)	2.3 (0.2)	–
	Change from extension study baseline to Week 52 end point[b] (sucroferric oxyhydroxide, $n = 368$; sevelamer carbonate, $n = 258$)	0.0 (0.2); $P = 0.09$	0.0 (0.2); $P = 0.07$	0.77

[a]Extension study baseline is the last non-missing value prior to or on the date of the first extension study drug intake.
[b]Last observation carried forward, Week 52 end point is Week 52 result or the latest available measurement after extension baseline when Week 52 is missing; –, not applicable; iPTH, intact parathyroid hormone; SD, standard deviation.

deaths were reported (sucroferric oxyhydroxide, 1.8%; sevelamer, 2.6%); however, none was considered related to study treatment. The causes of death during the extension study were generally consistent with medical conditions of this patient population, with cardiac-related disorders accounting for three of them.
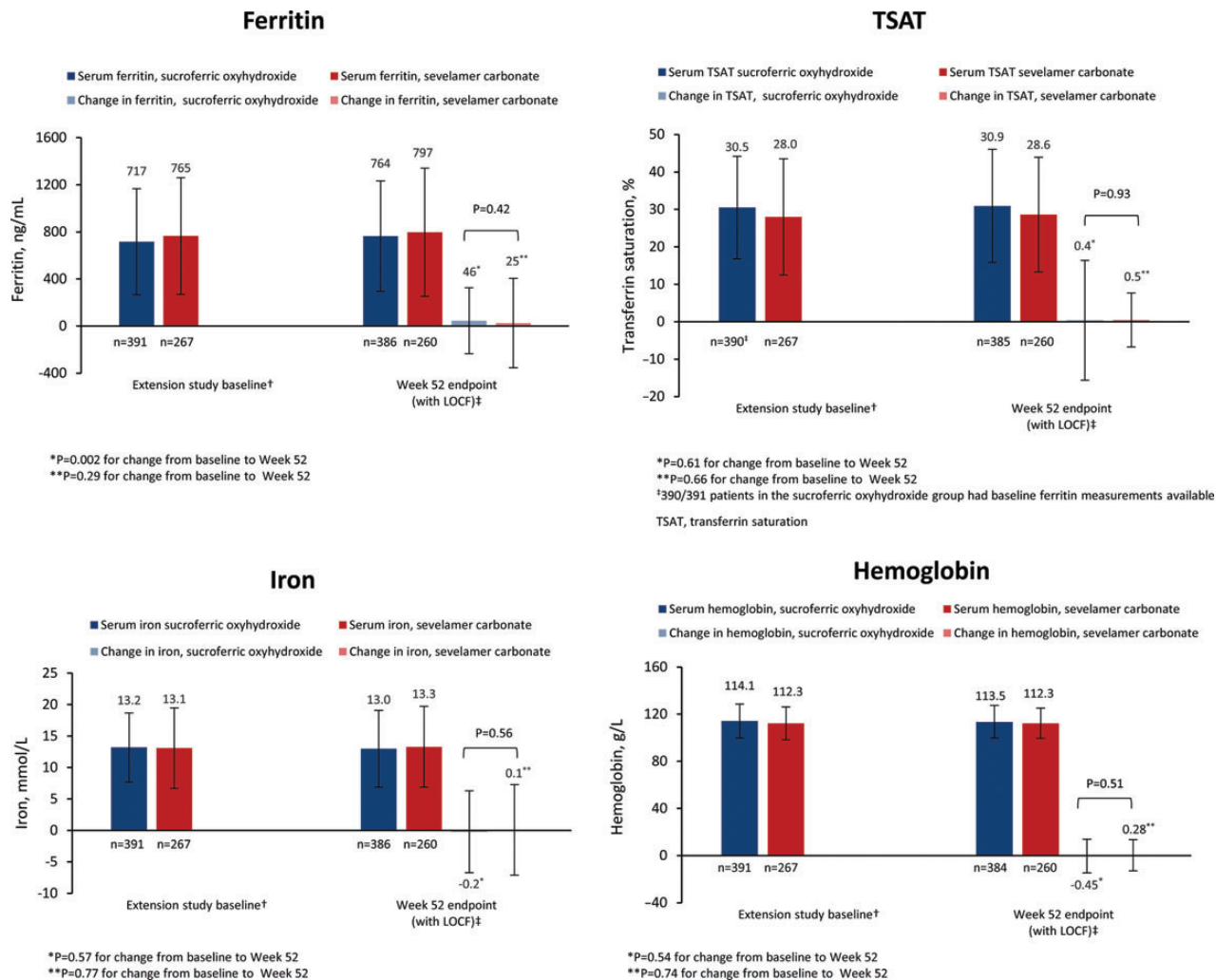
Treatment-emergent adverse events leading to withdrawal during the extension study occurred in 8.2% of patients receiving sucroferric oxyhydroxide and 4.9% of those receiving sevelamer (Table 4). Hyperphosphatemia was the most common TEAE leading to withdrawal from both treatment groups, accounting for the discontinuation of 2.8% ($n = 11$) sucroferric oxyhydroxide recipients and 2.6% ($n = 7$) sevelamer recipients. Seven (1.8%) patients receiving sucroferric oxyhydroxide withdrew due to GI TEAEs [including two patients (0.5%) who withdrew because of diarrhea], compared with one (0.4%) patient receiving sevelamer. All GI TEAEs leading to withdrawal were mild to moderate in severity except for a GI hemorrhage in a patient receiving sevelamer.

Over 1 year (integrated analysis of pooled data), a higher incidence of TEAEs leading to withdrawal was observed with sucroferric oxyhydroxide (20.9 versus 10.3% for sevelamer), reflecting the higher withdrawal rate due to TEAEs during the first 6 months (16.1% of sucroferric oxyhydroxide patients in the initial study versus 8.2% in the extension study). These TEAEs in the sucroferric oxyhydroxide group during the first 6 months were mainly attributable to mild and transient diarrhea [15].

DISCUSSION

Extension study data demonstrate that the efficacy of sucroferric oxyhydroxide for controlling serum phosphorus

Ferritin

■ Serum ferritin, sucroferric oxyhydroxide   ■ Serum ferritin, sevelamer carbonate
■ Change in ferritin, sucroferric oxyhydroxide   ■ Change in ferritin, sevelamer carbonate

Ferritin, ng/mL

717 765 — Extension study baseline†
764 797 46* 25** P=0.42 — Week 52 endpoint (with LOCF)‡
n=391 n=267   n=386 n=260

*P=0.002 for change from baseline to Week 52
**P=0.29 for change from baseline to Week 52

TSAT

■ Serum TSAT sucroferric oxyhydroxide   ■ Serum TSAT sevelamer carbonate
■ Change in TSAT, sucroferric oxyhydroxide   ■ Change in TSAT, sevelamer carbonate

Transferrin saturation, %

30.5 28.0 — Extension study baseline†
30.9 28.6 0.4* 0.5** P=0.93 — Week 52 endpoint (with LOCF)‡
n=390‡ n=267   n=385 n=260

*P=0.61 for change from baseline to Week 52
**P=0.66 for change from baseline to Week 52
‡390/391 patients in the sucroferric oxyhydroxide group had baseline ferritin measurements available
TSAT, transferrin saturation

Iron

■ Serum iron sucroferric oxyhydroxide   ■ Serum iron, sevelamer carbonate
■ Change in iron, sucroferric oxyhydroxide   ■ Change in iron, sevelamer carbonate

Iron, mmol/L

13.2 13.1 — Extension study baseline†
13.0 13.3 -0.2* 0.1** P=0.56 — Week 52 endpoint (with LOCF)‡
n=391 n=267   n=386 n=260

*P=0.57 for change from baseline to Week 52
**P=0.77 for change from baseline to Week 52

Hemoglobin

■ Serum hemoglobin, sucroferric oxyhydroxide   ■ Serum hemoglobin, sevelamer carbonate
■ Change in hemoglobin, sucroferric oxyhydroxide   ■ Change in hemoglobin, sevelamer carbonate

Hemoglobin, g/L

114.1 112.3 — Extension study baseline†
113.5 112.3 -0.45* 0.28** P=0.51 — Week 52 endpoint (with LOCF)‡
n=391 n=267   n=384 n=260

*P=0.54 for change from baseline to Week 52
**P=0.74 for change from baseline to Week 52

FIGURE 4: Mean (± standard deviation) values of iron-related parameters (SS-ext; $N = 658$) during the extension study. †Extension study baseline is the last non-missing value prior to or on the date of the first extension study drug intake; ‡Last observation carried forward, Week 52 end point is Week 52 result or the latest available measurement after extension baseline when Week 52 is missing.

concentration was robust, maintained over the long-term (1 year), and similar to that of sevelamer. The efficacy of sucroferric oxyhydroxide in the extension study was largely unaffected by geographical region, sex, age and race (data not shown).

Sucroferric oxyhydroxide was generally well tolerated over 1 year. TEAEs with sucroferric oxyhydroxide were generally more frequent during the initial Phase III study [15] than in the extension study, indicating that those who better tolerated the drug at study start continued to do so for the remainder of the 1-year period. Hyperphosphatemia was the most common class of TEAE for both sucroferric oxyhydroxide and sevelamer, which contrasted with the first 6 months of treatment, in which GI disorders were the predominant class of TEAE [15]. Diarrhea and discolored feces were the most frequent GI-related TEAEs with sucroferric oxyhydroxide over the first weeks of treatment [15], but their incidence decreased over time. Nausea, vomiting and constipation were reported more frequently with sevelamer than sucroferric oxyhydroxide in the first 6 months of treatment [15], but their incidence also diminished over time. Moreover, fewer patients were withdrawn due to TEAEs during the extension study in both the sucroferric

oxyhydroxide and sevelamer treatment groups (8.2 and 4.9%, respectively), compared with the first 6 months of treatment (16.1 and 6.6%, respectively) [15]. This indicates that, in general, patients who tolerated the treatments in the initial study continued to tolerate them for the next 6 months during the extension study. The incidence of serious or severe TEAEs and deaths were similar in both treatment groups during the extension study and over the 1-year period overall. It should be noted that a large number (one-third) of study participants were treated with sevelamer prior to inclusion in the initial Phase III study, so could be considered preadapted to this drug.

A representative proportion (9.3%) of patients receiving peritoneal dialysis was included in this long-term analysis of phosphate binders. Sucroferric oxyhydroxide appeared to be similarly efficacious and well tolerated in peritoneal dialysis and hemodialysis patients [16].

The pill burden over 1 year of treatment was 62% lower with sucroferric oxyhydroxide than with sevelamer, which may have implications for long-term adherence to phosphate-binder treatment. In this randomized study, there was a trend towards higher adherence (based on tablet numbers dispensed and

Table 4. Treatment-emergent adverse events (in order of frequency for sucroferric oxyhydroxide group) occurring in ≥5% of patients in either treatment arm during the extension study (SS-ext; $N = 658$)

Event, n (%)	Sucroferric oxyhydroxide (n = 391)	Sevelamer carbonate (n = 267)
Any TEAE	289 (73.9)	205 (76.8)
Any related TEAE	57 (14.6)	24 (9.0)
Any serious TEAE	78 (19.9)	52 (19.5)
Any severe TEAE	40 (10.2)	27 (10.1)
Withdrawals due to TEAEs	32 (8.2)	13 (4.9)
Death	7 (1.8)	7 (2.6)
Hyperphosphatemia	47 (12.0)	29 (10.9)
Hypertension	38 (9.7)	20 (7.5)
Diarrhea	32 (8.2)	15 (5.6)
Muscle spasms	26 (6.6)	16 (6.0)
Nausea	23 (5.9)	11 (4.1)
Hypophosphatemia	22 (5.6)	14 (5.2)
Headache	20 (5.1)	8 (3.0)
Hypotension	19 (4.9)	21 (7.9)
Hyperkalemia	17 (4.3)	16 (6.0)
Secondary hyperparathyroidism	15 (3.8)	23 (8.6)
Anemia	15 (3.8)	15 (5.6)

TEAE, treatment-emergent adverse event.

returned) with sucroferric oxyhydroxide. However, assessing adherence according to number of tablets returned has limited reliability, so the findings should be interpreted with caution. Moreover, as adherence within a study is generally better than in daily practice, pill burden may influence adherence differently in the real-life setting. The association between higher pill burden and lower adherence was affirmed in a recent retrospective observational study of pharmacy management program data from 8616 hemodialysis patients in the USA [17]. Findings also indicated a link between lower adherence and higher mean serum phosphorus levels [17]. Therefore, long-term adherence to phosphate-binder treatment is an important consideration in order to avoid potentially harmful sequelae to raised serum phosphorus concentrations.

Generally, iron-related parameters remained stable during the extension study. During the first 6 months of treatment (i.e. initial Phase III study), increases from baseline in serum ferritin were observed in both treatment groups, and increases from baseline in TSAT and iron were observed in the sucroferric oxyhydroxide group [15]. The use of intravenous iron, which was higher in patients from the USA (who represented almost half of all randomized patients), may provide an explanation for the increase in these iron-related parameters [15]. A short-term Phase I study indicated minimal iron absorption from sucroferric oxyhydroxide in CKD patients [13]. This finding may explain an additional impact on the iron indices observed in the Phase III studies. However, iron-related parameters appeared to plateau during the extension study and hemoglobin concentrations remained stable during long-term treatment in both treatment groups, indicating no evidence of iron accumulation. The changes in iron status are consistent across early- and late-stage clinical studies and do not indicate a safety concern. In the initial Phase III study, pronounced differences were observed between geographic regions in the use of intravenous iron

products and their impact on iron-related indices among study participants [15].

In conclusion, sucroferric oxyhydroxide as a new, non-calcium-, iron-based phosphate binder demonstrated a maintained serum phosphorus control over the long-term (1 year), with good tolerability and a lower pill burden, compared with sevelamer carbonate. Sucroferric oxyhydroxide has the potential to improve adherence and, hence, clinical outcomes for patients when used in routine clinical practice.

CONFLICT OF INTEREST STATEMENT

J.F., A.C., M.K., J.M., A.R., B.S. and S.S. were study investigators and received research funds from Vifor Pharma. J.F., A.C., M.K., A.R. and S.S. are also consultants for Vifor Pharma.

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