Long-term efficacy and safety of sucroferric oxyhydroxide in African American dialysis patients

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Abstract

Introduction: Sucroferric oxyhydroxide (SFOH) is a non-calcium, iron-based phosphate binder that demonstrated sustained serum phosphorus (sP) control, good tolerability, and lower pill burden, vs. sevelamer carbonate (“sevelamer”), in a Phase 3 study conducted in dialysis patients with hyperphosphatemia. This analysis evaluates the efficacy and safety of SFOH and sevelamer among African American (AA) patients participating in the trial.

Methods: Post hoc analysis of a 24-week, Phase 3, open-label trial (NCT01324128) and its 28-week extension study (NCT01464190). Patients were randomized 2:1 to SFOH (1.0–3.0 g/day) or sevelamer (2.4–14.4 g/day) for up to 52 weeks.

Findings: Of 549 patients who completed the Phase 3 study and extension, 100 (18.2%) AA patients were eligible for efficacy analysis (SFOH, n = 48; sevelamer, n = 52). sP concentrations decreased rapidly and comparably with both treatments by Week 8 (mean ± standard deviation change from baseline: –1.9 ± 1.9 mg/dL for SFOH and –2.2 ± 1.8 mg/dL for sevelamer). These reductions were maintained for 52 weeks (–2.1 ± 2.6 and –2.1 ± 1.6 mg/dL) and achieved with a lower mean pill burden (3.4 ± 1.4 vs. 7.6 ± 2.9 tablets/day) with SFOH vs. sevelamer. Treatment adherence rates (adherence within 70%–120% of expected medication intake) were 79.2% with SFOH and 59.6% with sevelamer. The proportion of patients reporting serious adverse events (AEs) was 27.7% with SFOH and 30.7% with sevelamer. More patients withdrew due to treatment-emergent AEs with SFOH vs. sevelamer (18.5% vs. 8.0%). The most common AEs with both treatments were gastrointestinal-related: diarrhea and discolored feces with SFOH, and nausea, vomiting, and constipation with sevelamer.

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Discussion: SFOH is an efficacious and well-tolerated treatment for hyperphosphatemia in AA dialysis patients, with a lower pill burden and an improved adherence rate vs. sevelamer. These findings were consistent with the wider US patient population and the overall study population.

Key words: Phosphate binder, chronic kidney disease, hyperphosphatemia, sucroferric oxyhydroxide, hemodialysis

INTRODUCTION

Hyperphosphatemia is a common and serious complication in patients with advanced chronic kidney disease (CKD), contributing to changes in bone and mineral metabolism. These changes ultimately result in the emergence of CKD-mineral bone disorder (CKD-MBD). Abnormal serum levels of CKD-MBD markers, including phosphorus, fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH) and vitamin D, are frequently observed in patients with CKD, and are associated with adverse clinical outcomes.

Although African Americans comprise only 13% of the US population, they constitute approximately one-third of patients receiving dialysis. It is important, therefore, to assess the efficacy and safety of new treatments used in dialysis patients in this population. Disordered mineral metabolism is often more severe in African American dialysis patients, which leads to a higher rate of disease progression. Some studies have shown lower levels of 25-hydroxyvitamin D and FGF-23, and higher levels of PTH and serum phosphorus, in African American compared with non-African American dialysis patients. The risk of all-cause and cardiovascular mortality due to elevated serum phosphorus and FGF-23 levels has been shown to be greater in African American patients than in their non-African American counterparts.

Phosphate binders are required by most patients on dialysis to control serum levels of phosphorus and CKD-MBD markers. Desirable properties of a phosphate binder include a high capacity for binding dietary phosphorus in the gastrointestinal (GI) tract, a low pill burden, and good safety and tolerability profiles.

Sucroferric oxyhydroxide (SFOH) is a non-calcium, iron-based, oral phosphate binder. A randomized, open-label, Phase 3 study and its 28-week extension conducted in dialysis patients demonstrated similar efficacy and tolerability of SFOH vs. sevelamer carbonate (“sevelamer”), but with a lower pill burden. The objective of this post hoc analysis was to evaluate the efficacy and safety of SFOH vs. sevelamer in the subset of African American patients who completed the Phase 3 study and its extension (i.e., at least 52 weeks of continuous treatment).

METHODS

Design

The initial Phase 3 study was a 24-week, 2-stage, randomized, active-controlled, parallel-group, multicenter, open-label trial comparing the efficacy and safety of SFOH against sevelamer in dialysis patients with hyperphosphatemia (NCT01324128). This initial study was followed by a 28-week extension which could be entered by eligible patients who completed 24 weeks of treatment (NCT01464190). Doses of both study treatments were titrated to achieve the predefined serum phosphorus concentrations of 3.5–5.5 mg/dL, as recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI).

The protocols were reviewed by Independent Ethics Committees/Institutional Review Boards, and the study was conducted in accordance with the Principles of the Declaration of Helsinki. Full details of the study designs have been described previously.

Participants

Full inclusion and exclusion criteria have been described elsewhere. Briefly, key inclusion criteria were: age ≥ 18 years; history of hyperphosphatemia and prescription of stable doses of phosphate binders for ≥ 1 month before screening; maintenance hemodialysis 3 times per week or peritoneal dialysis ≥ 3 months before screening; and washout phase serum phosphate levels ≥ 6.0 mg/dL (≥ 1.94 mmol/L). Key exclusion criteria were: intact PTH (iPTH) levels > 800 ng/L at screening, or planned parathyroidectomy; serum ferritin levels > 2000 μg/L at screening; and hypercalcemia (serum calcium > 10.5 mg/dL) in patients receiving non-calcium-based phosphate binders, or hypocalcemia (< 7.6 mg/dL) at screening.

Study treatment

Following a 2- to 4-week washout period, patients with serum phosphorus concentrations of ≥ 6.0 mg/dL (≥ 1.94
mmol/L) were randomized 2:1 to receive SFOH 1.0–3.0 g/day (2–6 tablets/day based on iron content; starting dose 1.0 g/day [2 tablets/day]; n = 710) or sevelamer 2.4–14.4 g/day (3–18 tablets/day; starting dose 4.8 g/day [6 tablets/day]; n = 349) for an 8-week dose titration, followed by 4 weeks without dose change (Weeks 1–12) and then 12 weeks’ maintenance (Weeks 12–24) (Stage 1). After 24 weeks, patients in the SFOH group were re-randomized (1:1) to continue receiving their maintenance dose (n = 50, median dose 1.5 g/day) or receive low-dose SFOH (n = 49; 250 mg/day [ineffective control]) for 3 weeks (Stage 2).

All patients who completed the initial Phase 3 study (Stage 1 or 2) and met the eligibility criteria could enter the extension study, with the exception of those patients re-randomized to low-dose SFOH in Stage 2. Patients who entered the extension study continued the same randomized treatment and dosage they were receiving at the end of the initial study. Use of IV iron and erythropoiesis-stimulating agents (ESAs) was permitted in line with local guidelines.

**Assessments**

Serum concentrations of circulating biochemical parameters were assessed at baseline, predefined time points over 1 year, and end of study (Week 52). The parameters measured were change in concentrations of serum phosphorus, FGF-23, iPTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D3 (calcitriol), total calcium and iron-related parameters (ferritin, transferrin saturation [TSAT] and hemoglobin), and pill burden (the number of tablets taken per day). Analysis of serum samples was performed at 1 of 2 central laboratories using standard validated methods.

**Post hoc analysis**

The analyses reported in this article were performed on data from African American patients who completed at least 52 weeks of continuous treatment in the initial Phase 3 study and its extension study. To investigate whether treatment responses to phosphate binder therapy among African American patients were consistent with the wider study population, the efficacy analyses (change in serum phosphorus levels), pill burden, and adherence rates were also presented descriptively for 2 other patient populations: the “US completers” population, which consisted of all randomized patients enrolled from study sites in the United States and who had completed at least 52 weeks of continuous treatment, and the “overall completers” population, comprised of all randomized patients who completed at least 52 weeks of treatment.

Adherence to study medication was calculated as the number of tablets dispensed and returned, i.e.,

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

Patients were classed as adherent if their level of adherence to study medication was 70%–120%.

Treatment-emergent adverse events (TEAEs) were summarized for the “African American safety set” that comprised all African American patients who took ≥ 1 dose of study medication during the initial Phase 3 study and/or extension study. Safety analyses were also performed on the overall US patient population (“US safety set”) and the overall study population (“Overall safety set”) to describe potential differences in safety outcomes among African American patients.

The Week 52 endpoint was defined as the last post-baseline non-missing value across both the Phase 3 and extension studies (i.e., last observation carried forward). T-tests for the change from baseline within and between treatment groups were performed using 2-sided tests at the 5% significance level. The analyses were conducted using SAS® version 9.3 (SAS Institute, Cary, NC, USA).

**RESULTS**

**Patient disposition and baseline demographics**

In the initial Phase 3 study, a total of 1059 patients were randomized to treatment, with 710 patients assigned to SFOH and 349 to sevelamer.

A total of 549 patients completed the trial (overall completers population), of whom 100 were African Americans (African American completers population; Table 1). The distribution of these patients between treatment groups was approximately equal, despite a 2:1 treatment randomization (n = 48, SFOH; n = 52, sevelamer). This was due, in part, to the higher proportion of African American patients who withdrew during Stage 1 of the initial Phase 3 study in the SFOH group (n = 37, 28.5%), compared with the sevelamer group (n = 13, 17.3%) (Figure 1). In addition, the allocation of patients for Stage 2 of the initial...
Phase 3 study resulted in a relatively large proportion of African American patients (n = 18, 19.4%) who completed Stage 1 being randomized into the low-dose (250 mg) SFOH group; these patients were subsequently ineligible to participate in the 28-week extension study. Together, these factors account for the similar number of African American completers in the SFOH and sevelamer treatment groups.

The most frequent reasons for withdrawals of African American patients during the 52-week study included TEAEs other than phosphorus or calcium level-related events (46.5% of withdrawals in the SFOH group vs. 30.0% in the sevelamer group), withdrawn consent (9.3% vs. 20.0%), protocol violation (11.6% vs. 20.0%), and renal transplant (9.3% vs. 15.0%) (Figure 1).

A total of 253 enrolled US patients completed at least 52 weeks of study treatment (US completers population).

Baseline characteristics of African American patients were similar between the SFOH and sevelamer groups (Table 1). Most patients were male and receiving hemodialysis. The most common reasons for end-stage renal disease were hypertension and diabetic nephropathy (in 56% and 27% of patients, respectively). The vast majority (>92%) of African American patients received ESA or IV iron therapy at least once during the study, while oral vitamin D supplements were taken by >40% of patients.

Baseline clinical characteristics of the African American completers population were generally similar to those of the US completers and overall completers populations, although there were some variations (Table 1).

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**Table 1** Baseline patient characteristics and concomitant medications (African American completers, n = 100; US completers, n = 253; overall completers, n = 549)

|                          | African American completers (N = 100) | US completers (N = 253) | Overall completers (N = 549) |
|--------------------------|----------------------------------------|--------------------------|-----------------------------|
|                          | Sucroferric oxyhydroxide (n = 48)      | Sevelamer carbonate (n = 52) | Sucroferric oxyhydroxide (n = 133) | Sevelamer carbonate (n = 120) | Sucroferric oxyhydroxide (n = 322) | Sevelamer carbonate (n = 227) |
| Mean (SD) age, y         | 55.3 (12.0)                            | 55.9 (14.2)              | 58.1 (13.5)                  | 58.1 (14.1)                  | 55.3 (13.1)                  | 55.7 (14.9)                  |
| Sex, n (%)               |                                        |                          |                             |                             |                             |                             |
| Male                     | 30 (62.5)                              | 29 (55.8)                | 78 (58.6)                   | 74 (61.7)                   | 179 (55.6)                  | 143 (63.0)                  |
| Mean (SD) weight, kg     | 93.1 (22.9)                            | 92.2 (24.5)              | 89.0 (22.2)                 | 90.2 (23.2)                 | 81.9 (19.6)                 | 84.3 (21.8)                 |
| Dialysis status, n (%)   |                                        |                          |                             |                             |                             |                             |
| Hemodialysis             | 48 (100.0)                             | 49 (94.2)                | 121 (91.0)                  | 113 (94.2)                  | 284 (88.2)                  | 213 (93.8)                  |
| Peritoneal dialysis      | 0 (0.0)                               | 3 (5.8)                  | 12 (9.0)                    | 7 (5.8)                     | 38 (11.8)                   | 14 (6.2)                    |
| Mean (SD) time from first dialysis to screening, months | 59.0 (47.9) | 67.1 (64.3) | 45.2 (41.9) | 55.7 (55.6) | 49.9 (48.6) | 55.0 (59.6) |
| Reason for ESRD, n (%)   |                                        |                          |                             |                             |                             |                             |
| Hypertension             | 27 (56.3)                              | 29 (55.8)                | 44 (33.1)                   | 48 (40.0)                   | 69 (21.4)                   | 66 (29.1)                   |
| Diabetic nephropathy     | 12 (25.0)                              | 15 (28.8)                | 47 (35.3)                   | 46 (38.3)                   | 73 (22.7)                   | 60 (26.4)                   |
| Glomerulonephritis       | 5 (10.4)                               | 5 (9.6)                  | 18 (13.5)                   | 14 (11.7)                   | 84 (26.1)                   | 53 (23.3)                   |
| Pyelonephritis           | 0 (0.0)                               | 0 (0.0)                  | 0 (0.0)                     | 0 (0.0)                     | 12 (3.7)                    | 8 (3.5)                     |
| Congenital               | 0 (0.0)                               | 1 (1.9)                  | 2 (1.5)                     | 1 (0.8)                     | 5 (1.6)                     | 5 (2.2)                     |
| Interstitial nephritis   | 0 (0.0)                               | 1 (1.9)                  | 2 (1.5)                     | 2 (1.7)                     | 11 (3.4)                    | 7 (3.1)                     |
| Hydronephrosis           | 0 (0.0)                               | 0 (0.0)                  | 0 (0.0)                     | 0 (0.0)                     | 6 (1.9)                     | 1 (0.4)                     |
| Polycystic kidney disease| 1 (2.1)                               | 0 (0.0)                  | 5 (3.8)                     | 2 (1.7)                     | 35 (10.9)                   | 13 (5.7)                    |
| Other                    | 3 (6.3)                               | 1 (1.9)                  | 15 (11.3)                   | 7 (5.8)                     | 27 (8.4)                    | 14 (6.2)                    |
| Concomitant medications used during the study, n (%) | | | | | | |
| ESA                      | 46 (95.8)                              | 51 (98.1)                | 127 (95.5)                  | 116 (96.7)                  | 275 (85.4)                  | 203 (89.4)                  |
| IV iron                  | 46 (95.8)                              | 48 (92.3)                | 125 (94.0)                  | 112 (93.3)                  | 237 (73.6)                  | 183 (80.6)                  |
| Oral vitamin D           | 20 (41.7)                              | 23 (44.2)                | 46 (34.6)                   | 44 (36.7)                   | 110 (34.2)                  | 96 (42.3)                   |
| IV vitamin D             | 3 (6.3)                               | 1 (1.9)                  | 5 (3.8)                     | 3 (2.5)                     | 6 (1.9)                     | 3 (1.3)                     |
| Cinacalcet               | 1 (2.1)                               | 0 (0.0)                  | 3 (2.3)                     | 1 (0.8)                     | 19 (5.9)                    | 8 (3.5)                     |

ESA = erythropoiesis-stimulating agent; ESRD = end-stage renal disease; IV = intravenous; SD = standard deviation.

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The mean length of time on dialysis prior to study entry was longer among African American patients, in comparison with the US completers and the overall study populations.

In addition, the proportions of patients who received concomitant IV iron or ESA products during the Phase 3 study were also higher in both the African American and the US patient populations, vs. the overall study population.

**Serum phosphorus**

In African American completers, rapid reductions to a plateau in mean ± standard deviation (SD) serum phosphorus concentrations occurred by Week 8 in both treatment groups: −1.9 ± 1.9 mg/dL in the SFOH group and −2.2 ± 1.8 mg/dL in the sevelamer group. These initial reductions were maintained over the remainder of the...
1-year study in both treatment groups, with similar reductions from baseline being observed at Weeks 24 and 52 (Figure 2).

Mean baseline serum phosphorus concentrations in the African American completers population were similar to those of the US completers and the overall completers populations, and the reductions in serum phosphorus levels achieved with SFOH and sevelamer from baseline to Weeks 24 and 52 were comparable across all 3 patient populations (Figure 2).

Pill burden and treatment adherence

Mean (SD) daily pill burden was lower for African American patients in the SFOH group vs. the sevelamer group from baseline to Week 24 (3.1 ± 1.2 vs. 7.1 ± 2.5 tablets/day) and from Weeks 24 to 52 (3.6 ± 1.6 vs. 8.1 ± 3.7 tablets/day) (Figure 3). Over 52 weeks of study treatment, the mean (SD) pill burden was 3.4 ± 1.4 tablets/day in the SFOH group compared with 7.6 ± 2.9 tablets/day in the sevelamer group. Similar differences in pill burden between the SFOH and sevelamer groups.
were observed in the US completers and overall completers populations.

In African American completers, treatment adherence (adherence within 70% and 120% of expected tablet intake) was 79.2% in the SFOH group and 59.6% in the sevelamer group over the 1-year treatment period. Similar adherence rates over 1 year were observed in the US completers population (SFOH group: 78.2%; sevelamer group: 65.8%), although adherence rates in the overall completers population were slightly higher (SFOH: 90.1%; sevelamer: 81.1%), compared with the African American completers and overall completers populations.

Safety

Overall, in the African American patient population, the incidence of severe and serious TEAEs, including death, was similar in both treatment groups (Table 2).

GI-related TEAEs were the most common TEAEs in both treatment groups. Diarrhea and discolored feces were more common among patients treated with SFOH, whereas constipation, nausea, vomiting, dyspepsia, and abdominal discomfort were more frequent in the sevelamer group. Diarrhea and discolored feces events associated with SFOH administration were transient and were observed primarily during the titration phase of the initial Phase 3 study. In total, 61% of discolored feces events and 25% of diarrhea events of the totals reported during the Phase 3 study were reported during Week 1. The first 4 weeks of the Phase 3 study also encompassed 89% of discolored feces events and 45% of the diarrhea events.

Hyperparathyroidism (9.2% vs. 14.7%) and anemia (1.5% vs. 9.3%) were both reported less frequently in the SFOH group than in the sevelamer group, respectively (Table 2).

The incidence of treatment withdrawals due to TEAEs was higher in the SFOH group than in the sevelamer group (18.5% vs. 8.0%) (Table 2). The most common class of TEAEs leading to withdrawal of patients in the SFOH group were GI disorders, resulting in treatment discontinuations in 6.9% of patients (n = 9), compared with 2.7% of patients (n = 2) discontinuing treatment due to GI disorders in the sevelamer group. In addition, abnormal product taste led to the withdrawal of 3.9% (n = 5) of SFOH-treated patients, but did not account for any treatment discontinuations in the sevelamer group. TEAEs leading to withdrawals of patients in the sevelamer group were distributed across several different System Organ Classes.

Table 2  Incidence of treatment-emergent adverse events (African American safety set, N = 205; US safety set, N = 513; overall safety set N = 1055)

|                      | African American safety set (N = 205) | US safety set (N = 513) | Overall safety set (N = 1055) |
|----------------------|---------------------------------------|-------------------------|-------------------------------|
|                      | SFOH oxyhydroxide (n = 130)           | Sevelamer carbonate (n = 75) | SFOH oxyhydroxide (n = 343) | Sevelamer carbonate (n = 170) | SFOH oxyhydroxide (n = 707) | Sevelamer carbonate (n = 348) |
| N (%)                |                                       |                         |                               |                              |                               |                              |
| Any TEAE             | 121 (93.1)                            | 66 (88.0)               | 322 (93.9)                    | 155 (91.2)                   | 628 (88.8)                    | 308 (88.5)                   |
| Serious TEAEs        | 36 (27.7)                             | 23 (30.7)               | 113 (32.9)                    | 65 (38.2)                    | 188 (26.6)                    | 103 (29.6)                   |
| Severe TEAEs         | 19 (14.6)                             | 15 (20.0)               | 69 (20.1)                     | 39 (22.9)                    | 113 (16.0)                    | 61 (17.5)                    |
| Withdrawal due to TEAEs | 24 (18.5)                         | 6 (8.0)                 | 73 (21.3)                     | 14 (8.2)                     | 148 (20.9)                    | 36 (10.3)                    |
| Death                | 4 (3.1)                               | 2 (2.7)                 | 8 (2.3)                       | 7 (4.1)                      | 20 (2.8)                      | 14 (4.0)                     |
| GI TEAE              | 56 (43.1)                             | 33 (44.0)               | 187 (54.5)                    | 82 (48.2)                    | 371 (52.5)                    | 149 (42.8)                   |
| Diarrhea             | 20 (15.4)                             | 8 (10.7)                | 82 (23.9)                     | 24 (14.1)                    | 167 (23.6)                    | 40 (11.5)                    |
| Nausea               | 12 (9.2)                              | 11 (14.7)               | 41 (12.0)                     | 29 (17.1)                    | 69 (9.8)                      | 50 (14.4)                    |
| Discolored feces     | 18 (13.9)                             | 1 (1.3)                 | 59 (17.2)                     | 1 (0.6)                      | 114 (16.1)                    | 1 (0.3)                      |
| Vomiting             | 9 (6.9)                               | 7 (9.3)                 | 25 (7.3)                      | 21 (12.4)                    | 42 (5.9)                      | 32 (9.2)                     |
| Constipation         | 5 (3.9)                               | 6 (8.0)                 | 21 (6.1)                      | 19 (11.2)                    | 36 (5.1)                      | 29 (8.3)                     |
| Dyspepsia            | 2 (1.5)                               | 4 (5.3)                 | 7 (2.0)                       | 7 (4.1)                      | 26 (3.7)                      | 16 (4.6)                     |
| Abdominal discomfort | 2 (1.5)                               | 6 (8.0)                 | 4 (1.2)                       | 8 (4.7)                      | 8 (1.1)                       | 10 (2.9)                     |
| Hyperparathyroidism  | 12 (9.2)                              | 11 (14.7)               | 25 (7.3)                      | 19 (11.2)                    | 61 (8.6)                      | 49 (14.1)                    |
| Anemia               | 2 (1.5)                               | 7 (9.3)                 | 12 (3.5)                      | 14 (8.2)                     | 28 (4.0)                      | 29 (8.3)                     |

GI = gastrointestinal; TEAE = treatment-emergent adverse event.
Overall, the safety and tolerability profile of SFOH and sevelamer in the African American population was generally consistent with that observed for the US safety set and overall safety set populations (Table 2).

**CKD-MBD markers in African American completers**

In African American completers, mean serum concentrations of FGF-23 were higher at baseline in the SFOH group compared with the sevelamer group (Table 3). In both treatment groups, FGF-23 was significantly reduced from baseline to Week 52 (SFOH: P < 0.0001; sevelamer: P = 0.0032), although these changes were not significantly different between the treatment groups (P > 0.05).

Mean serum concentrations of iPTH in African American completers were also higher at baseline in the SFOH group compared with the sevelamer group (Table 3). Decreases from baseline in serum iPTH were observed in both treatment groups at Week 52, reaching statistical significance.

### Table 3: Mean (SD) serum concentration and change from baseline for CKD-MBD markers by treatment group (African American completers, N = 100)

|                          | African American completers (N = 100) |                      |                      |
|--------------------------|----------------------------------------|----------------------|----------------------|
|                          | Sucroferric oxyhydroxide (n = 48)      | Sevelamer carbonate (n = 52) |
| **FGF-23, μg/L**         |                                        |                      |
| Baseline                 | 234.3 (297.7)                          | 136.5 (242.0)        |
| Week 52                  | 62.6 (121.8)                           | 49.1 (93.8)          |
| Δ from baseline          | −174.2 (253.4)***                     | −90.0 (202.8)**      |
| **iPTH, pg/mL**          |                                        |                      |
| Baseline                 | 608.3 (343.0)                          | 494.3 (318.8)        |
| Week 52                  | 540.5 (403.3)                          | 410.3 (319.9)        |
| Δ from baseline          | −67.8 (433.6)                          | −84.0 (296.6)*       |
| **Calcium, mg/dL**       |                                        |                      |
| Baseline                 | 8.8 (0.7)                              | 9.0 (0.7)            |
| Week 52                  | 9.1 (0.8)                              | 9.4 (0.6)            |
| Δ from baseline          | 0.4 (0.9)*                             | 0.4 (0.7)***         |
| **25-hydroxyvitamin D, ng/mL** |                                  |                      |
| Baseline                 | 26.6 (13.7)                            | 27.5 (18.3)          |
| Week 52                  | 25.9 (12.8)                            | 25.3 (12.4)          |
| Δ from baseline          | −0.7 (11.9)                            | −2.3 (14.1)          |
| **1,25-dihydroxyvitamin D₃ (calcitriol), pg/mL** |                                  |                      |
| Baseline                 | 16.8 (21.4)                            | 13.6 (8.9)           |
| Week 52                  | 19.0 (17.6)                            | 16.9 (16.8)          |
| Δ from baseline          | 2.2 (18.4)                             | 3.3 (11.5)*          |

Δ from baseline: *P < 0.05; **P < 0.01; ***P < 0.001 (T-test).
iPTH = intact parathyroid hormone; SD = standard deviation.
There were no statistically significant differences between the treatment groups with respect to changes in serum iPTH concentrations.

There were small but statistically significant increases in serum calcium levels observed in both treatment groups at Week 52 (SFOH: \(P < 0.0114\); sevelamer: \(P < 0.0001\)).

Table 4  Mean (SD) serum concentration and change from baseline for iron-related indices by treatment group (African American completers, \(N = 100\))

| Mean (SD)                  | Sucroferric oxyhydroxide (n = 48) | Sevelamer carbonate (n = 52) |
|----------------------------|-----------------------------------|------------------------------|
| Ferritin, ng/mL            |                                   |                              |
| Baseline                  | 822.7 (426.2)                     | 1010.3 (401.4)               |
| Week 52                   | 1083.6 (380.0)                    | 1013.5 (318.3)               |
| \(\Delta\) from baseline  | 260.9 (313.1)**†                  | 3.2 (405.6)†                 |
| TSAT, %                   |                                   |                              |
| Baseline                  | 33.1 (17.4)                       | 29.4 (11.3)                  |
| Week 52                   | 32.4 (16.0)                       | 32.7 (15.5)                  |
| \(\Delta\) from baseline  | 0.7 (23.5)                       | 3.3 (15.9)                   |
| Hemoglobin g/L            |                                   |                              |
| Baseline                  | 117.2 (9.7)                       | 115.3 (7.3)                  |
| Week 52                   | 113.2 (12.8)                      | 113.9 (9.4)                  |
| \(\Delta\) from baseline  | −4.0 (12.0)*                      | −1.4 (10.6)                  |

\(\Delta\) from baseline: \(*P < 0.05\); \(**P < 0.001\) (T-test).
Comparison between treatment groups (sucroferric oxyhydroxide–sevelamer carbonate): †\(P < 0.001\) (T-test).
SD = standard deviation; TSAT = transferrin saturation.

Significance in the sevelamer group \((P = 0.0464)\). There were no statistically significant differences between the treatment groups with respect to changes in serum iPTH concentrations.

There were small but statistically significant increases in serum calcium levels observed in both treatment groups at Week 52 (SFOH: \(P = 0.0114\); sevelamer: \(P = 0.0001\)).

There was no change in 25-hydroxyvitamin D concentrations from baseline to Week 52 in the SFOH group (Table 3). Small reductions in 25-hydroxyvitamin D were observed in the sevelamer group, but these were not statistically significant.

Small increases in serum calcitriol concentrations were observed in both treatment groups over 1 year, only reaching significance for sevelamer \((P = 0.0431)\). However, no statistically significant differences were observed between the groups for either parameter.

Iron-related indices in African American completers

In African American completers, mean serum ferritin at baseline was higher in the sevelamer group, compared with the SFOH group (Table 4). Significant increases in serum ferritin at Week 52 were observed in the SFOH group, but not in the sevelamer group. These differences between the treatment groups were statistically significant \((P < 0.001)\).

TSAT levels remained generally stable over 52 weeks of treatment (Table 4), with no statistically significant changes from baseline or between treatment groups observed \((P > 0.05)\). Hemoglobin levels decreased slightly from baseline in both treatment groups at Week 52, and only reached statistical significance for the SFOH group at Week 52 (Table 4). There were no significant differences between treatment groups with respect to changes in hemoglobin levels during the study \((P > 0.05)\).

DISCUSSION

This post hoc analysis of African American dialysis patients showed that treatment with SFOH resulted in rapid reductions of serum phosphorus levels, and that this control was sustained throughout the 52 weeks of the study. Comparable reductions in serum phosphorus measurements were observed in the sevelamer group, but these were not statistically significant. Significantly increased serum calcium levels were observed in both treatment groups at Week 52, with greater increases observed in the sevelamer group compared with the SFOH group. No statistically significant differences were observed between treatment groups with respect to changes in serum calcium, 25-hydroxyvitamin D, or calcitriol concentrations.

African American completer patients showed significantly higher baseline serum ferritin concentrations compared with the SFOH group. Significant increases in serum ferritin were observed only in the SFOH group at Week 52. There were no statistically significant differences between treatment groups with respect to changes in hemoglobin levels during the study.

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concentrations were observed in those patients treated with sevelamer. Our analyses showed that these observations are consistent with those of the wider US study population and those previously reported for the overall study population.\textsuperscript{12,13}

Despite providing similar control of serum phosphorus, the pill burdens and levels of adherence associated with SFOH and sevelamer were markedly different. Over 52 weeks, the pill burden remained substantially lower among African American patients receiving SFOH, compared with those receiving sevelamer. Our analyses demonstrated that these data were generally consistent and similar for the wider US study population and the overall study population.\textsuperscript{12,13}

The low pill burden and serum phosphorus control achieved with SFOH in the current analysis is consistent with observations in real-world patient populations. A retrospective US database analysis evaluating real-world effectiveness of SFOH among hemodialysis patients previously treated with other phosphate binder therapy found that treatment with SFOH for 3 or 6 months was associated with a significant decline in pill burden, coupled with a significant improvement in the proportion of patients achieving mean phosphorus \( \leq 5.5 \text{ mg/dL} \).\textsuperscript{14} A separate sub-analysis, of 1015 African American hemodialysis patients who switched from a different phosphate binder, demonstrated that 3 months’ treatment with SFOH was associated with significantly improved serum phosphorus control (57% increase in patients with in-range serum phosphorus levels [3.5–5.5 mg/dL]; \( P < 0.001 \)) and a significant reduction in pill burden (reduction from 8.5 tablets/day to 3.7 tablets/day; \( P < 0.001 \)).\textsuperscript{15}

The safety and tolerability profiles observed in this sub-analysis of African American patients were comparable with those of the US study population and that reported for the overall study population.\textsuperscript{12,13} The safety profiles were broadly similar between study treatments, with respect to rates of serious TEAEs, severe TEAEs, and deaths. For GI-related TEAEs, as for the overall study population, rates of diarrhea and discolored feces were higher in the SFOH group, whereas incidences of nausea and constipation were higher in the sevelamer group.\textsuperscript{12,13}

Our analyses also showed that, in line with the overall study population, the incidences of these GI-related TEAEs peaked within the first few weeks of treatment and decreased over time.\textsuperscript{12,13}

The rate of study withdrawals associated with TEAEs was higher in the SFOH group, compared with the sevelamer group. This difference between the groups was predominantly driven by the higher proportion of African American patients in the SFOH group who withdrew due to GI disorders (6.9%), and, to a lesser extent, abnormal product taste (3.9%). These findings are in line with the overall population where GI disorders and taste abnormalities accounted for approximately 9.9% and 1.8% of withdrawals in SFOH-treated patients, respectively. Overall, the proportion of patients who withdrew due to TEAEs during the study in the African American population was similar to the overall population for both treatment groups.

Circulating levels of FGF-23 progressively decreased over 52 weeks of treatment, possibly reflecting the sustained reductions in serum phosphorus levels.\textsuperscript{16,17} The precise role of FGF-23 in CKD-MBD pathogenesis remains to be elucidated; however, reducing levels may be of clinical benefit in CKD patients.\textsuperscript{7,17} There is evidence to suggest that higher FGF-23 levels are associated with a greater risk of mortality in African American dialysis patients than in non-African American patients.\textsuperscript{9} Therefore, control of FGF-23 concentrations may be of particular clinical importance in this patient population.

Serum iPTH concentrations among African American patients decreased in both treatment groups during the 52-week treatment period, although the reductions were small and not consistently statistically significant. These reductions in iPTH may have been partly due to the serum phosphorus-lowering effect of phosphate binder treatment and improved management of hyperphosphatemia of patients enrolled in the study. Levels of serum total calcium were generally stable over 1 year and, although statistically significant increases were observed, these are unlikely to have been clinically significant.

With respect to iron parameters, the greater increases in serum ferritin observed in the SFOH group vs. the sevelamer group are comparable with observations in the overall study population.\textsuperscript{18} This between-group difference may have been partly due to minimal iron absorption from SFOH, although it should be noted that baseline serum ferritin concentrations were higher in the sevelamer than SFOH group.

Serum ferritin concentrations in both treatment groups were, on average, greater than those reported for the overall study population.\textsuperscript{18} This observation probably reflects the high rate of IV iron usage. Almost all (~95%) of African American patients received concomitant IV iron at least once during the study. In the overall US study population it was shown that 94% of patients received IV iron, and 96% received ESA. Only minimal changes were observed in TSAT and hemoglobin levels, and these are likely to be clinically insignificant. There was no evidence...
of iron accumulation or overload over 52 weeks of treatment.

The limitations of the study include the relatively low number of patients in this patient subpopulation and significant variability across these subsets in parameter values. There was also considerable interpatient variability. Even taking these factors into account, the general findings were similar to those observed for the overall study population. The efficacy analysis was performed on the completers population in order to evaluate the long-term effects of SFOH and sevelamer over a 1-year treatment period. A limitation of this approach was that it preselected patients who completed 1 year of continuous treatment and excluded from the analysis those patients who withdrew before the end of the study due to TEAEs or other reasons.

In conclusion, the impact of elevated serum phosphorus on mortality has been shown to be greater for African Americans than for non-African Americans. Thus, there is a need for treatments with a low pill burden that effectively reduce and maintain serum phosphorus levels in this patient population. The results of this post hoc analysis of African American patients are consistent with those from the overall study population, and demonstrate that SFOH is an efficacious and well-tolerated treatment for hyperphosphatemia in African American dialysis patients, with a lower pill burden and a higher adherence rate compared with sevelamer.

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