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CHARACTERISTICS OF RESPONDERS AND NON-RESPONDERS TO TREATMENT WITH SUCROFERRIC OXYHYDROXIDE: *A POST HOC* ANALYSIS OF A PHASE 3 STUDY

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INTRODUCTION

- Hyperphosphataemia is a frequent and serious complication in advanced-stage chronic kidney disease (CKD), and is a major contributor to CKD-mineral and bone disorder (CKD-MBD)[1] which is characterised by abnormalities in other serum markers of bone and mineral metabolism, including fibroblast growth factor-23 (FGF-23) and parathyroid hormone[1,2]
- The majority of CKD patients on dialysis require treatment with oral phosphate binders to maintain control of serum phosphorus levels and CKD-MBD[3,4]
- Identifying the key characteristics of responders and non-responders to phosphate binder therapy for hyperphosphataemia may help optimise treatment selection for dialysis patients
- Sucroferric oxyhydroxide (VELPHORO®; SFOH) is a non-calcium, iron-based phosphate binder used for the treatment of hyperphosphataemia in dialysis patients
- A Phase 3 study and subsequent extension study in dialysis patients with hyperphosphataemia showed that SFOH was non-inferior to sevelamer carbonate (Renvela®; SEV), in terms of serum phosphorus control after 12 weeks of treatment,[5] and the phosphorus-lowering effect of SFOH was maintained over 1 year[6]

STUDY OBJECTIVE

- This *post hoc* analysis of the Phase 3 study and its extension evaluated the clinical and biochemical characteristics associated with treatment response to phosphate binder therapy among patients randomised to SFOH or SEV

METHODS

Design

- This was a two-stage, randomised, active-controlled, parallel-group, multicentre, open-label, 24-week, Phase 3 study, with a 28-week extension study, that compared SFOH with SEV in dialysis patients with hyperphosphataemia[5,6]
- Full details of the study design have been described previously[5]

Participants

- Key inclusion criteria:
  - Age ≥18 years
  - History of hyperphosphataemia and prescription of stable doses of phosphate binders for ≥1 month before screening
  - Maintenance haemodialysis three times per week or peritoneal dialysis ≥3 months before screening
  - Serum phosphate levels ≥1.94 mmol/L (≥6.0 mg/dL) during washout
- Exclusion criteria have been described elsewhere[5]

Study treatment

- Following a 2–4 week washout period, 1059 patients were randomised 2:1 to receive SFOH 1.0–3.0 g/day (starting dose: 1.0 g/day [2 tablets/day]) or SEV 2.4–14.4 g/day (starting dose: 4.8 g/day [6 tablets/day]) for 12 weeks' dose titration followed by 12 weeks' maintenance
- Treatment doses were titrated to achieve pre-defined serum phosphorus concentrations of between 0.81 mmol/L and 1.78 mmol/L
- After the initial 24-week efficacy and safety study, eligible patients were allowed to enter a 28-week safety extension study; patients in the extension study continued on the same treatment, with the same dose, that they were receiving at the end of the initial study

Post hoc analysis

- The *post hoc* analysis was performed using data for those patients in the full analysis set (FAS) of the Phase 3 study who had a serum phosphorus measurement available at Week 52
- Responders to SFOH or SEV treatment were defined as patients achieving serum phosphorus levels of 1.78 mmol/L [≤5.5 mg/dL] at Week 52
- Mean serum concentrations of phosphorus, intact parathyroid hormone (iPTH) and FGF-23 were summarised at baseline, Week 24 and Week 52 Endpoint in responders and non-responders
- Baseline demographic and clinical characteristics data for these two subgroups were also compared
- The Week 52 Endpoint was defined as the last post-baseline non-missing value across both the Phase 3 and the extension study (last observation carried forward)
- Statistical 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

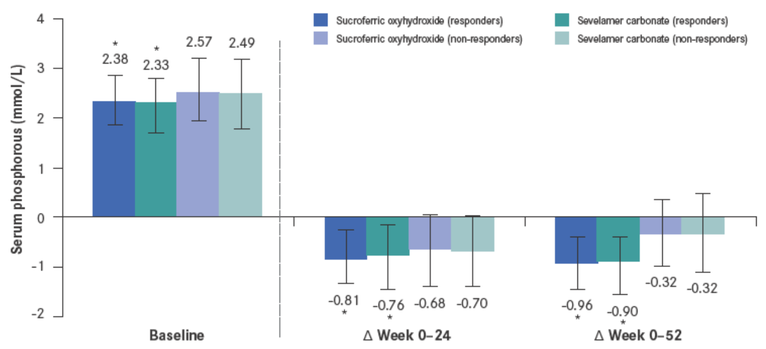
TABLE 1: Baseline patient demographics and clinical characteristics (N=497)

	Responders (N=302)		Non-responders (N=195)	
	Sucroferric oxyhydroxide (N=172)	Sevelamer carbonate (N=130)	Sucroferric oxyhydroxide (N=115)	Sevelamer carbonate (N=80)
Mean (SD) age, years	57.2 (12.9)*	56.6 (15.1)	52.3 (13.0)*	55.0 (14.1)
Sex, %				
Male	94 (54.7)	86 (66.2)	66 (57.4)	49 (61.3)
Race, %				
White	142 (82.6)	97 (74.6)	92 (80.0)	63 (78.8)
Black/ African American	22 (12.8)	29 (22.3)	19 (16.5)	16 (20.0)
Other	4 (2.3)	4 (3.1)	4 (1.4)	1 (1.3)
Mean (SD) weight, kg	80.9 (19.5)	82.9 (21.8)	83.0 (19.3)	84.4 (22.0)
Dialysis modality, %				
Haemodialysis	152 (88.4)	121 (93.1)	103 (89.6)	77 (96.3)
Peritoneal dialysis	20 (11.6)	9 (6.9)	12 (10.4)	3 (3.8)
Reason for end-stage renal disease, n (%)				
Hypertension	39 (22.7)	40 (30.8)	20 (17.4)	21 (26.3)
Glomerulonephritis	39 (22.7)	33 (25.4)	35 (30.4)	16 (20.0)
Diabetic nephropathy	39 (22.7)	30 (23.1)	28 (24.3)	26 (32.5)
Polycystic kidney disease	17 (9.9)	7 (5.4)	14 (12.2)	5 (6.3)
Other	38 (22.0)	20 (15.4)	18 (15.7)	12 (15.0)
Mean (SD) time from start of ESRD, months	64.0 (59.0)	71.6 (78.7)	60.3 (66.6)	62.2 (59.3)
Mean (SD) time from first dialysis, months	55.1 (54.9)*	57.0 (66.0)	42.7 (40.8)*	51.9 (47.9)
Mean (SD) initial daily number of tablets taken	3.6 (1.2)	8.7 (3.3)	4.0 (1.2)	9.5 (3.9)

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

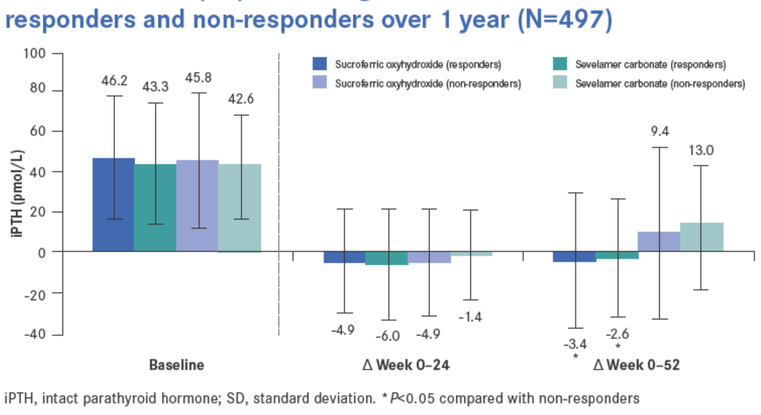
*P<0.05 for comparison between responder and non-responders

FIGURE 1: Mean (SD) and changes from baseline in serum phosphorus levels in responders and non-responders over 1 year (N=497)



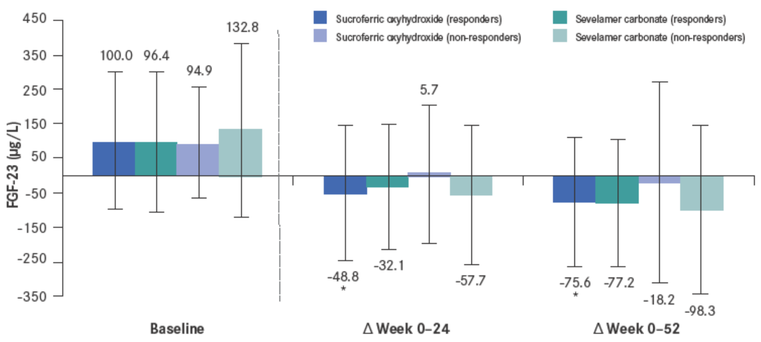
SD, standard deviation. *P<0.05 compared with non-responders

FIGURE 2: Mean (SD) and change from baseline in iPTH levels in responders and non-responders over 1 year (N=497)



iPTH, intact parathyroid hormone; SD, standard deviation. *P<0.05 compared with non-responders

FIGURE 3: Mean (SD) and change from baseline in FGF-23 levels in responders and non-responders over 1 year (N=497)



FGF-23, fibroblast growth factor-23; SD, standard deviation. *P<0.05 compared with non-responders

RESULTS

Patient baseline characteristics

- Of the 1041 patients comprising the FAS of the initial Phase 3 study, 497 (48%) had a serum phosphorus measurement available at Week 52 and were eligible for inclusion in this *post hoc* analysis (Table 1)
- The proportion of responders was similar in both treatment groups:
  - 172/287 (60%) patients treated with SFOH
  - 130/210 (61%) patients treated with SEV
- In both groups, the time period on dialysis was longer for responders versus non-responders (P<0.05 in the SFOH group); furthermore, responders to SFOH tended to be older than non-responders in this treatment group (P<0.05)

Serum phosphorus

- Mean baseline serum phosphorus levels were significantly lower in responders versus non-responders in both the SFOH and SEV groups (P<0.05) (Figure 1)
- Decreases in serum phosphorus from baseline to Weeks 24 and 52 were greater among responders versus non-responders (P<0.05) in both treatment groups, with the greatest reductions observed in SFOH-treated responders

Serum iPTH

- Mean iPTH levels decreased significantly from baseline to Week 52 in responders in both treatment groups (P<0.05); in contrast, iPTH levels increased in non-responders following 1 year of treatment (Figure 2)

Serum FGF-23

- Mean serum FGF-23 levels decreased to a greater extent in responders versus non-responders within the SFOH group from baseline to Weeks 24 and 52 (P<0.05)
- In contrast, mean reductions in serum FGF-23 levels among patients in the SEV group were similar between responders and non-responders (Figure 3)

Pill burden

- Pill burden was lower for responders versus non-responders in both treatment groups, but this difference was only statistically significant in the SFOH group (mean: 3.6 versus 4.0 tablets/day; P<0.05)

Conclusions

- The findings of this *post hoc* analysis suggest that hyperphosphataemia may be more challenging to manage in younger patients who have been on dialysis for a shorter period of time
- Baseline serum phosphorus levels appeared to be predictive of treatment effect with SFOH and SEV
- The findings also indicate that more pronounced decreases in serum phosphorus may be associated with greater reductions in iPTH and FGF-23, although the impact of other therapies that may affect these parameters should also be evaluated

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