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SUCROFERRIC OXYHYDROXIDE DOES NOT IMPACT THE iPTH-LOWERING EFFECTS OF ORAL VDRAS OR CINACALCET: A *POST HOC* ANALYSIS OF A PHASE 3 STUDY

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INTRODUCTION

- Many patients with chronic kidney disease (CKD) have hyperphosphataemia and secondary hyperparathyroidism (SHPT), which are major contributors to CKD-mineral and bone disorder (MBD)[1,2]
- Oral phosphate binders are required by the majority of patients on dialysis for the control of serum phosphorus levels,[3] while patients who develop SHPT are prescribed oral vitamin D receptor agonists (VDRAs) and/or cinacalcet therapy for the reduction of parathyroid hormone (PTH) levels[4,5]
- Concomitant administration of these agents may result in drug–drug interactions, reducing their therapeutic efficacy; therefore, it is important that oral phosphate binders not only have high binding affinity for phosphate, but also display minimal interaction with other medications and nutritional supplements[6]
- In an open-label, randomised 24-week, Phase 3 study and its 28-week extension, the non-calcium, iron-based phosphate binder sucroferric oxyhydroxide (VELPHORO®) demonstrated similar efficacy and tolerability to sevelamer carbonate (Renvela®), but with a lower pill burden[7,8]

STUDY OBJECTIVE

- This *post hoc* analysis of these Phase 3 studies evaluated the potential interactions between sucroferric oxyhydroxide or sevelamer carbonate and oral VDRAs and/or cinacalcet therapy, based on changes in CKD-MBD parameters during the 1-year treatment period

METHODS

Design

- This Phase 3 study was a two-stage, randomised, active-controlled, parallel-group, multicentre, open-label, 24-week study which compared sucroferric oxyhydroxide with sevelamer carbonate, followed by a 28-week extension study, in dialysis patients with hyperphosphataemia[7,8]
- Full details of the study design have been described previously[7]

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
- Key exclusion criteria at screening:
  - Serum iPTH levels >88 pmol/L or planned parathyroidectomy
  - Hypercalcaemia (serum calcium >11.0 mg/dL), or hypocalcaemia (<7.6 mg/dL) in patients receiving non-calcium-based phosphate binders at screening
  - Significant gastrointestinal (GI) or hepatic disorders, or major GI surgery, likely to influence study outcome

Study treatment

- Randomisation took place after a 2–4 week washout period; 1059 patients were randomised 2:1 to receive sucroferric oxyhydroxide 1.0–3.0 g/day (starting dose: 1.0 g/day [2 tablets/day]) or sevelamer carbonate 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
- Eligible patients completing the initial 24-week study could enter the 28-week extension, continuing on the same treatment and dosage they were receiving at the end of the initial study
- In accordance with local clinical practice, doses of concomitant oral VDRA and cinacalcet were unchanged during the study period as far as possible

Post hoc analysis

- This analysis was performed on the full analysis set (defined as patients who received ≥1 dose of study medication and had ≥1 post-baseline evaluable efficacy assessment during the initial Phase 3 and/or extension study)
- Two separate patient populations were analysed:
  - Population 1: patients who received ≥1 dose of oral VDRA and/or cinacalcet during the 52-week treatment period
  - Population 2: patients who did not receive oral VDRAs or cinacalcet during the study
- Mean ± standard deviations (SD) serum levels of phosphorus, intact PTH (iPTH) and calcium at baseline, Week 24 and Overall Endpoint (and changes versus baseline) were summarised by study treatment, for both analysis populations
- 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 (full analysis set; n=1041)

	Population 1: Concomitant oral VDRA and/or cinacalcet* (n=372)		Population 2: No concomitant oral VDRA and/or cinacalcet (n=669)	
	Sucroferric oxyhydroxide (n=234)	Sevelamer carbonate (n=138)	Sucroferric oxyhydroxide (n=460)	Sevelamer carbonate (n=209)
Mean (SD) age, years	56.0 (13.4)	55.6 (14.2)	56.4 (13.4)	56.0 (14.9)
Sex, %				
Male	125 (53.4)	77 (55.8)	258 (56.1)	142 (67.9)
Mean (SD) weight, kg	81.8 (20.7)	85.9 (23.2)	81.8 (20.7)	85.9 (23.2)
Dialysis modality, %				
Haemodialysis	30 (12.8)	17 (12.3)	434 (94.3)	198 (94.7)
Peritoneal dialysis	204 (87.2)	121 (87.7)	26 (5.7)	11 (5.3)
Mean (SD) time from first dialysis to screening, months	53.6 (54.5)	54.3 (58.9)	50.5 (45.7)	53.2 (52.5)
Reason for ESRD, n (%)				
Hypertension	41 (17.5)	29 (21.0)	117 (25.4)	59 (28.2)
Glomerulonephritis	66 (28.2)	40 (29.0)	89 (19.3)	47 (22.5)
Diabetic nephropathy	59 (25.2)	33 (23.9)	137 (29.8)	61 (29.2)
Polycystic kidney disease	27 (11.5)	12 (8.7)	39 (8.5)	9 (4.3)
Other	41 (17.5)	24 (17.2)	78 (17.0)	33 (15.8)
Mean (SD) 25(OH)D, ng/mL	25.2 (15.0)	24.6 (14.1)	22.0 (12.3)	23.6 (12.1)
Mean (SD) $1,25(OH)_2D$, pg/mL	14.0 (11.0)	12.9 (11.0)	13.9 (13.5)	14.0 (9.8)
Mean (SD) total calcium, mg/dL	8.8 (0.7)	8.8 (0.8)	8.8 (0.8)	8.8 (0.8)
Mean (SD) iPTH, pmol/L	47.8 (29.5)	43.7 (27.0)	45.3 (33.0)	42.3 (30.2)

*Summary of concomitant VDRA / calcimimetic usage in Population 1: oral VDRA only (n=311); cinacalcet only (n=39); oral VDRAs + cinacalcet (n=22).

ESRD, end-stage renal disease; iPTH, intact parathyroid hormone; SD, standard deviation; VDRA, vitamin D receptor agonist 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D.

RESULTS

Patient baseline characteristics

- A total of 1041 patients from the full analysis of the Phase 3 study were analysed *post hoc*:
  - 372 patients (35.7%) received concomitant oral VDRAs and/or cinacalcet during the study (Population 1), while the remaining 669 patients (64.3%) did not receive oral VDRAs or cinacalcet (Population 2)
- The majority of patients (83.6%) in the concomitant VDRA and/or cinacalcet group (Population 1) received oral VDRAs only
- Patient demographics in both groups in the analysis and across treatment groups were similar (Table 1)

Changes in serum phosphorus levels

- Decreases in serum phosphorus were maintained over 52 weeks with sucroferric oxyhydroxide and sevelamer carbonate, irrespective of concomitant VDRA and/or cinacalcet use, and similar reductions were observed in Populations 1 and 2 (Figure 1)

Changes in serum iPTH levels

- In the concomitant oral VDRA and/or cinacalcet group (Population 1), mean serum iPTH decreased from baseline to Week 24 and Week 52 among sucroferric oxyhydroxide-treated patients, whereas in sevelamer carbonate-treated patients, iPTH levels significantly increased from baseline up to Week 52 (P=0.02; Figure 2)
- In the no concomitant oral VDRA and/or cinacalcet group (Population 2), similar decreases in iPTH levels were observed with sucroferric oxyhydroxide and sevelamer carbonate treatment from baseline to Week 24; from baseline to Week 52, serum iPTH levels increased to above-baseline values with both treatments

Changes in serum calcium levels

- No major changes in serum calcium concentrations were observed with sucroferric oxyhydroxide or sevelamer carbonate in either analysis population (Figure 3)

Conclusions

- The results of this *post hoc* analysis demonstrate that both sucroferric oxyhydroxide and sevelamer carbonate maintained serum phosphorus control over 1 year, irrespective of oral VDRA or cinacalcet use
- Furthermore, compared with patients treated with sucroferric oxyhydroxide, there was a non-significant trend towards a smaller iPTH-lowering effect of oral VDRAs or cinacalcet among sevelamer carbonate-treated patients. This finding is consistent with a pharmacokinetic study which demonstrated that sevelamer reduced the bioavailability of oral calcitriol when these agents were administered concomitantly[9]

FIGURE 1: Mean ± SD serum phosphorus levels and changes versus baseline during the study period in each analysis population. (A) Oral VDRA and/or cinacalcet (Population 1) (N=372). (B) No oral VDRA and/or cinacalcet (Population 2) (N=669)

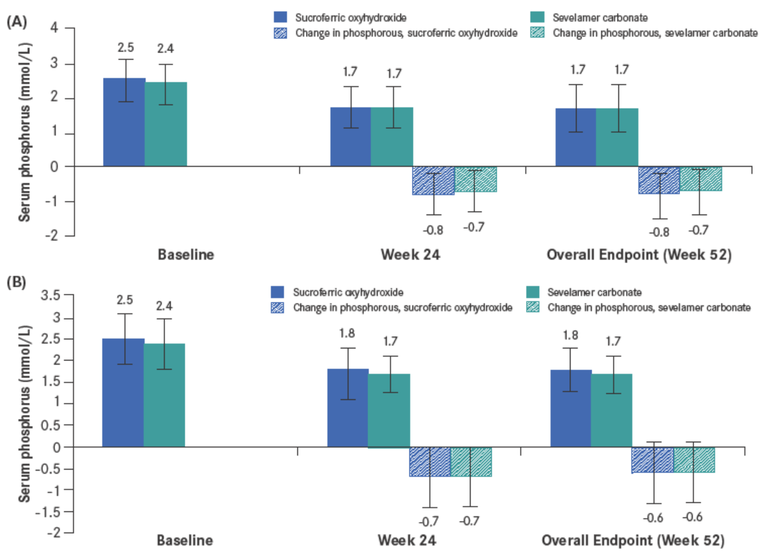


FIGURE 2: Mean ± SD iPTH levels and changes versus baseline during the study period in each analysis population. (A) Oral VDRA and/or cinacalcet (Population 1) (N=372). (B) No oral VDRA and/or cinacalcet (Population 2) (N=669)

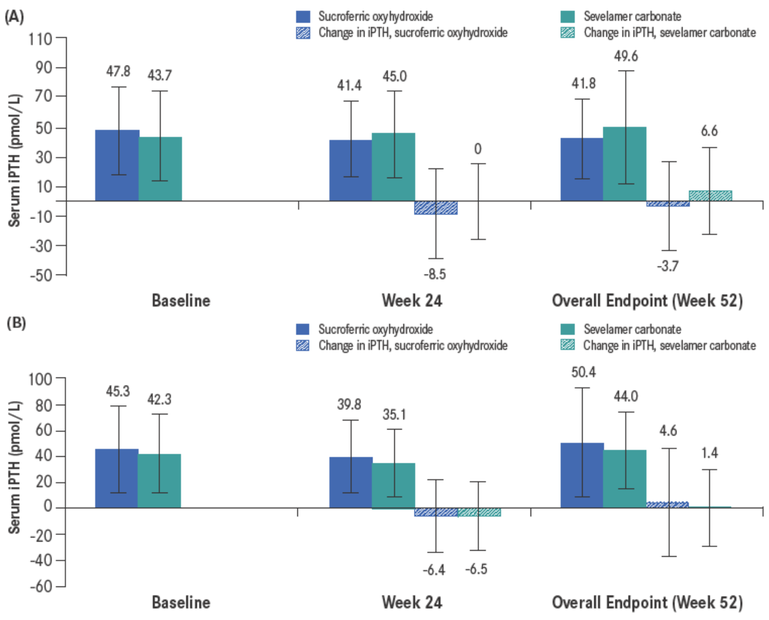
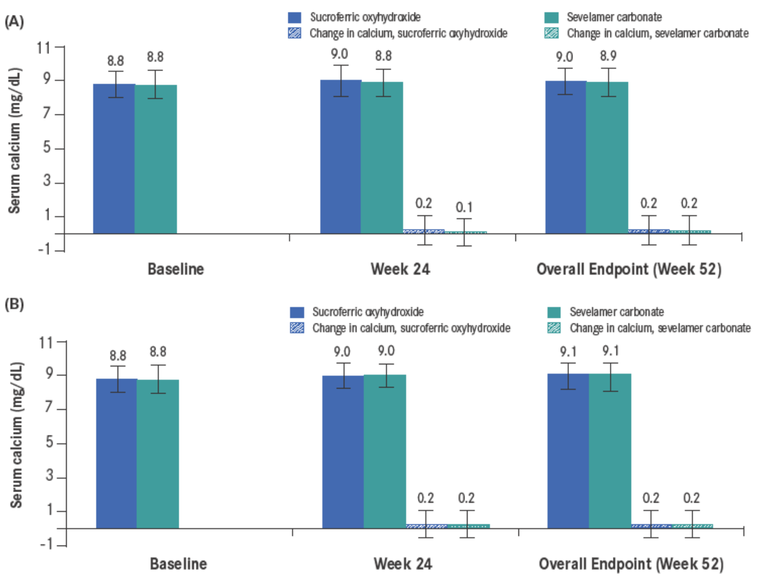


FIGURE 3: Mean ± SD serum calcium levels and changes versus baseline during the study period in each analysis population. (A) Oral VDRA and/or cinacalcet (Population 1) (N=372). (B) No oral VDRA and/or cinacalcet (Population 2) (N=669)



REFERENCES

1. Sprague SM, et al. *Am J Nephrol* 2014; **40**:535-45.
2. Nigwekar SU, et al. *Bonekey Rep* 2014; **3**:498.
3. Hutchison AJ, et al. *Nat Rev Nephrol* 2011; **7**:578-89.
4. Sprague SM, Coyne D. *Clin J Am Soc Nephrol* 2010; **5**:512-8.
5. Akizawa T, et al. *Sci Rep* 2016; **6**:19612.
6. Wu-Wong J and Mizobuchi M. *Expert Opin Investig Drugs* 2014; **23**:1465–75.
7. Floege J, et al. *Kidney Int* 2014; **86**:638-47.
8. Floege J, et al. *Nephrol Dial Transplant* 2015; **30**:1037-46.
9. Pierce D, et al. *Nephrol Dial Transplant* 2011; **26**:1615-21.

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