The Novel, Non-Aluminium, Non-Calcium Phosphate Binder, Lanthanum Carbonate (Fosrenol™), is an Effective Treatment for Hyperphosphataemia and has a Good Safety Profile

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Introduction

- Hyperphosphataemia is a frequent consequence of chronic renal failure (CRF). It is associated with significantly increased morbidity (e.g. hyperparathyroidism and bone pathology) and mortality[1,2]
- Furthermore, hyperphosphataemia and an elevated calcium x phosphate product are associated with an increased risk of vascular calcification, which can lead to adverse cardiovascular effects[1,3,4]
- Calcium-based phosphate binders are frequently prescribed to treat hyperphosphataemia, but can, in fact, increase risk of hypercalcaemia and vascular calcification[3,5]
- Lanthanum carbonate (Fosrenol™) is a novel, non-calcium phosphate binder. Phase I and II clinical trials have demonstrated that lanthanum effectively reduces serum phosphorus, is well tolerated, and is not associated with hypercalcaemia[6–10]
- Here, we present findings from a large-scale, Phase III study that compared the efficacy, safety and tolerability of lanthanum carbonate with calcium carbonate for treating hyperphosphataemia in haemodialysis patients

Methods

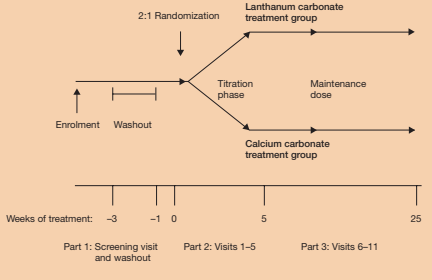
Patients

- Men and women aged 18 years or over with CRF who had been undergoing regular haemodialysis for 3 months

Study design

- A 6-month, randomized, open-label, active comparator-controlled, parallel-group trial carried out in 67 European centres
- The trial comprised three parts (Figure 1):
  - Part 1: 1- to 3- week screening and washout period
  - Part 2: 5-week dose-titration period. Patients with serum phosphorus levels > 1.80 mmol/L (5.6 mg/dL) after washout were randomized (2:1) to receive lanthanum carbonate or calcium carbonate. Titration schedules are shown in Table 1
  - Part 3: maintenance period. Phosphorus-controlled patients continued therapy for a further 20 weeks (Figure 1)

Figure 1. Study profile



Assessments

- The aim of the study was to assess serum phosphorus control, defined as serum phosphorus levels ≤ 1.80 mmol/L (5.6 mg/dL), during the titration and maintenance periods
- Serum phosphorus, calcium, lanthanum and parathyroid hormone levels were evaluated from blood samples taken throughout the study
- Adverse events (AEs) were monitored throughout

Table 1. Summary of dosing scheme specified in protocol

Study period	Step*	Daily dose of lanthanum carbonate (mg)	Tablet strength (mg)	Daily dose of calcium carbonate (mg)	Tablet strength (mg)
Part 1	-	ND	–	ND	–
Part 2	1	375	125	1500	500
	2	750	250	3000	500
	3	1500	250	4500	500
	4	2250	250	6000	500
	5	3000	250	9000	500
Part 3	6–11	Individual dose providing phosphate control†	250	Individual dose providing phosphate control†	500

*Doses raised at approximately weekly intervals, depending on clinicians' judgement
†Serum phosphorus levels ≤ 1.80 mmol/L (5.6 mg/dL).
ND, no drug (phosphate binder) administered.

Results

Patients

- In total, 805 patients completed the 3-week screening and washout phase, and were randomized to receive study medication
- The clinical characteristics of the two treatment groups were similar at baseline (Table 2)
- 44.3% of lanthanum-treated patients and 46.1% of calcium-treated patients completed both the titration and maintenance phase over a total of 24 weeks

Table 2. Patient demographic and other baseline characteristics (intention-to-treat population)

Characteristic	Treatment group: Lanthanum carbonate (*n* = 510)	Calcium carbonate (*n* = 257)
Age, years,		
Mean (SD)	57.0 (14.3)	58.4 (13.38)
Range	19–87	21–85
Gender, *n* (%) male	341 (66.9)	164 (63.8)
Body weight, kg,		
Mean (SD)	75.1 (15.4)	73.7 (14.9)
Range	40.4–153.4	37.6–138.0
Renal disease characteristics		
Months on haemodialysis, Mean (SD)	42.9 (39.0)	43.8 (43.9)
Patients with residual renal function, *n* (%)	300 (62.0)	154 (63.6)
Patients with previous kidney transplant, *n* (%)	63 (12.4)	33 (12.8)

Efficacy

Serum phosphorus levels

- Mean serum phosphorus levels in lanthanum- and calcium-treated patients up to Month 6 are summarized in Figure 2
  - At the end of titration, the reduction in mean serum phosphorus achieved with lanthanum was slightly lower than that achieved with calcium, possibly because of a sub-optimal starting dose in the lanthanum arm (375 mg)
  - By Week 9, however, higher doses of lanthanum following titration showed similar decreases in serum phosphorus *vs.* calcium carbonate. Phosphorus levels were similar in both groups for the remainder of the study
- Similar proportions of lanthanum- and calcium-treated patients achieved serum phosphorus control between study Weeks 9 and 25 (Table 3)

Drug dosage

- Smaller doses of lanthanum carbonate compared with calcium carbonate were required to achieve serum phosphorus control (median dose 2250 mg *vs.* 3000 mg, respectively)

Figure 2. Mean serum phosphorus levels during titration and maintenance treatment (ITT population)

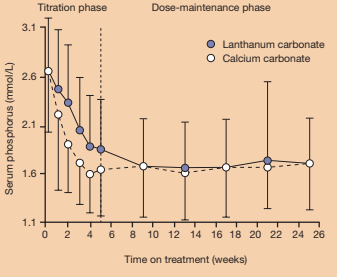


Table 3. Proportions of phosphate-controlled patients during maintenance treatment

Weeks on treatment	Treatment group: Lanthanum carbonate (*n** = 277)		Calcium carbonate (*n** = 152)		*p* value**
	n	%	*n*	%	
9	188/277	67.9	100/152	65.8	0.66
13	179/255	70.2	104/138	75.4	0.28
17	166/242	68.6	90/131	68.7	0.98
21	158/228	69.3	85/117	72.6	0.52
25	146/222	65.8	78/122	63.9	0.73

*Total number of patients entering maintenance phase; **Chi-square test.

Calcium x phosphate product

- Lanthanum carbonate was associated with greater decreases in calcium x phosphate product compared with calcium carbonate at Week 9 ($p = 0.009$ *vs.* calcium) and Week 25 ($p = 0.061$ *vs.* calcium)

Safety and tolerability

- The incidence of treatment-emergent AEs was similar in both groups (Table 4)
  - AEs were mostly mild to moderate in severity
  - Gastrointestinal AEs were reported most frequently

Table 4. Percentage of patients reporting AEs during titration and maintenance treatment at a frequency ≥ 5% (ITT safety population)

Body system	WHO preferred term	Treatment group: Lanthanum carbonate (*n* = 533)	Calcium carbonate (*n* = 257)
AE			
Cardiovascular disorders	Hypotension	7.5	9.0
Central and peripheral nervous system disorders	Headache	5.1	6.4
Dialysis complication	Dialysis graft occlusion	4.1	6.4
Gastrointestinal system disorders	Constipation	6.0	6.7
	Diarrhoea	12.6	9.7
	Nausea	15.9	12.7
	Vomiting	18.4	11.2
Metabolic and nutritional disorders	Hypercalcaemia	0.4	20.2
Musculo-skeletal system disorders	Cramps	7.1	6.4
	Bronchitis	4.7	5.6
Respiratory system disorders	Rhinitis	6.9	6.0
Total patients reporting ≥ 1 AE		77.7	79.8

WHO, World Health Organization; ITT, intention-to-trent

- A significantly greater incidence of hypercalcaemic episodes (i.e. serum calcium values > 2.6 mmol/L) was seen in calcium-treated patients (almost 40%) compared with lanthanum-treated patients (6%) ($p < 0.001$)
- Overall, fewer serious AEs were reported with lanthanum carbonate (21.4%) compared with calcium carbonate (30.0%)
- Systemic absorption of lanthanum carbonate was low (< 0.001% of administered dose)

Conclusions

- **Lanthanum carbonate, 750–3000 mg/day, is well tolerated and has comparable efficacy to calcium carbonate, 1500–9000 mg/day, for the control and maintenance of serum phosphorus for up to 6 months in CRF patients undergoing haemodialysis**
- **Lanthanum carbonate was associated with a significantly lower rate of hypercalcaemic episodes than calcium carbonate. It may also be more effective in reducing calcium x phosphate product than calcium carbonate**
- **Treatment with lanthanum carbonate may offer reduced dose requirements compared with traditional calcium-based phosphate binders**
- **An ongoing, 6-month extension to this trial is expected to define further the long-term effectiveness and continuing tolerability of lanthanum carbonate**

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