Two-Way Crossover Study to Establish Pharmacodynamic Bioequivalence Between Oxylanthanum Carbonate and Lanthanum Carbonate

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BACKGROUND

- End-stage renal disease (ESRD) affects more than 7 million people worldwide[1] and approximately 70% of patients with ESRD have hyperphosphatemia[2]
- In patients with CKD G3a through G5D with hyperphosphatemia, current Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend treatments such as dietary intervention, phosphate binders, and dialysis to lower elevated serum phosphate concentrations toward the normal range while avoiding hypercalcemia (calcium levels above 10.2 mg/dL [>2.55 mmol/L])[3]
- Phosphate binders (PB) are integral to the management of hyperphosphatemia in patients with end-stage kidney disease. Effectiveness of PBs is adversely affected by non-adherence and limitations of phosphate-binding capacity relative to dietary intake
- Lanthanum carbonate (LC): approved PB; must be chewed completely
- Oxylanthanum carbonate (OLC): oral tablet phosphate binder designed to be swallowed whole as opposed to being chewed
- For equivalent-phosphate-binding dose volumes of 1000 mg, referred to as the active moiety, oxylanthanum carbonate demonstrates a significant reduction in pill volume when contrasted with LC, measuring 2.3 cm^3 for the former and 8.0 cm^3 for the latter. Thus, formulations with smaller pill sizes are possible[4]

OBJECTIVE

Demonstrate the pharmacodynamic (PD) equivalence of orally administered OLC 1000 mg TID to LC 1000 mg TID in healthy subjects

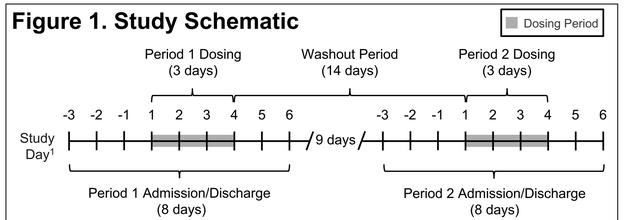
METHODS

- Phase 1, single-center, randomized, open-label, controlled, 2-way crossover study in healthy volunteers designed to establish the pharmacodynamic equivalence between OLC swallowable tablets 1000mg TID and LC chewable tablets 1000 mg TID
- The study consisted of a screening period (28 days before Day -4 of Period 1), 2 dosing periods separated by a 14-day washout period, and a follow-up period 7 days after last study drug dose**(Figure 1)**
- Study subjects were housed in an inpatient clinical research unit from Days -3 to 5 of each treatment period
- Randomization was 1:1 to order of treatment (i.e., OLC/LC or LC/OLC)
- Each treatment period included a 2-day Baseline (BL) Period (Days -2 and -1) during which the 24-hour baseline urine P was established and a 3-day Evaluation Period (Days 1 to 3)
- Subjects receive one 1000 mg tablet TID of OLC (swallowed whole) or LC (chewed) after each of 3 meals on Days 1 to 3
- All subjects received the same standardized meals, controlled for daily P (1400 mg/day) during the in-unit period, starting at Day -3
- 24-hour urine samples were collected for 5 days beginning Day -2
- Primary outcome variable was Least Squares (LS) mean change in daily urinary P excretion from BL (48 hrs prior to dosing) to Evaluation Period (Days 1-3)
- Primary pharmacodynamic variable was assessed using a mixed-effect linear model with fixed effects for sequence, period, and study drugs; random effect for individual within-sequence & baseline as a covariate

METHODS (CONT.)

- Based on the mixed-effect linear model, a standard 90% CI was constructed for the difference in LSM of change in urinary phosphorous excretion from the Baseline Period to the Evaluation Period
- In addition, a reference interval (acceptance range) for the treatment (effect) was defined as ±20% of the LSM of the primary pharmacodynamic variable for LC

Figure 1. Study Schematic

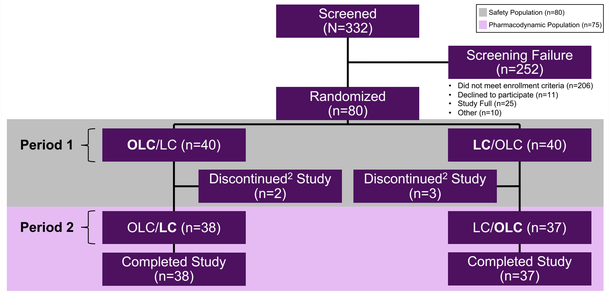


1 All durations start at the start of the day, and end at the end of the day
Note: Phosphorous controlled diet for both periods 1 and 2 are from Day -3 to 4 (7 days); Urine measurements for both periods 1 and 2 are from Day -2 to 4 (6 days)

RESULTS

- 75 of 80 randomized subjects were analyzed for the primary (equivalence) endpoint**(Figure 2)**
- BL characteristics balanced between OLC/LC & LC/OLC sequences**(Table 1)**
- Mean daily P declined over time to a similar extent in both groups**(Figure 3)**
- The change from BL to the Evaluation Period in the LS mean 24-hour urine P excretion was -320.4 mg/day for OLC and -324.0 mg/day for LC**(Figure 4)**
- The 90% CI for the LS mean change in urinary P excretion from BL (treatment difference) was (-37.8, 45.1), which was entirely contained within the predefined ±20% acceptance range of (-64.8, 64.8)**(Figure 5)**
- Incidence of treatment-emergent adverse events (TEAEs), regardless of relatedness to the study drugs was 35% in both groups; related adverse events (AE) were reported in 25% in each group**(Table 2)**
- No AEs resulted in treatment discontinuation and none were serious/severe

Figure 2. CONSORT[1] Diagram



1 Consolidated Standards of Reporting Trials
2 Meal non-compliance

Table 1. Baseline Characteristics

Population Dataset		Treatment Sequence OLC/LC (n=40)	Treatment Sequence LC/OLC (n=40)	Total (N=80)
Age[1] (years)	Mean (SD)	35.1(9.6)	33.7(9.6)	34.4(9.6)
	Median (Min-Max)	35.5(18-55)	33.0(18-53)	34.5(18-55)
Gender[1] (%)	Male	50.0	55.0	52.5
Race[1] (%)	White or Caucasian	87.5	92.5	90.0
	Black or African American	12.5	2.5	7.5
	Other	0.0	5.0	2.5
BMI[1] (kg/m^2)	Mean (SD)	26.0(3.6)	27.3(2.8)	26.6(3.3)
	Median (Min-Max)	26.4(18.1-31.6)	27.4(21.0-31.2)	26.9(18.1-31.6)
24-Hour Urine Phosphorous[2] (mg/day)	Mean (SD)	678.7(214.4)	668.6(207.9)	673.7(211.3)
	Median (Min-Max)	681.0(268.9-1,074.8)	681.9(183.3-1,216.0)	681.9(183.3-1,216.0)
Calcium[2] (mg/dL)	Mean (SD)	9.8(0.4)	9.9(0.3)	9.8(0.3)
	Median (Min-Max)	9.7(9.1-10.6)	9.9(9.2-10.5)	9.8(9.1-10.6)
Phosphate[2] (mg/dL)	Mean (SD)	3.5(0.5)	3.4(0.5)	3.5(0.5)
	Median (Min-Max)	3.6(2.7-5.0)	3.5(2.2-4.6)	3.5(2.2-5.0)
Vitamin D[2] (ng/L)	Mean (SD)	49.0(13.0)	46.7(13.5)	47.9(13.3)
	Median (Min-Max)	48.0(24.0-79.0)	45.0(18.0-75.0)	46.5(18.0-79.0)
Parathyroid Hormone (PTH)[2] (ng/L)	Mean (SD)	41.2(15.2)	37.3(12.1)	39.2(13.9)
	Median (Min-Max)	39.0(20.0-70.0)	36.0(16.0-62.0)	36.0(16.0-70.0)
Est. Glomerular Filtration Rate (eGFR)[1] (mL/min)	Mean (SD)	104.9(12.9)	108.0(12.4)	106.4(12.6)
	Median (Min-Max)	103.5(85-133)	110.0(85-128)	106.5(85-133)

1 Screening
2 Period 1 baseline

Figure 3. Mean (±SD) Daily Urinary Phosphorus Excretion Over Time (Pharmacodynamic Population)

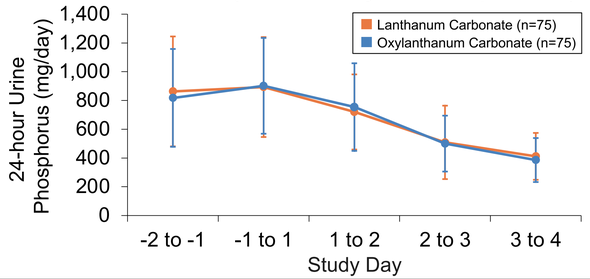
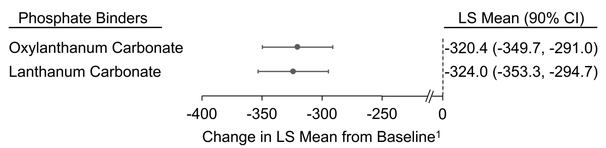


Figure 4. Change in LS Mean Urinary Phosphorus Excretion Between Baseline[1] to the Evaluation Period[2]

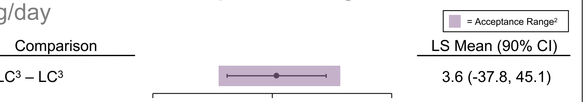
mg/day



1 Baseline was defined as the 48-hour period starting on Day -2 and ending on Day 1 of each Treatment Period
2 The evaluation period of the study was defined as the 72-hour period starting on Day 1 and ending on Day 4

Figure 5. Difference of Change[1] in Urinary Phosphorus Excretion Within Acceptance Range[2]

mg/day



1 Change between baseline to the evaluation period (72-hour period starting on Day 1 and ending on Day 4)
2 The acceptance range for equivalence was the 90% CI of the treatment difference (-64.80, +64.80)
3 OLC = Oxylanthanum Carbonate; LC = Lanthanum Carbonate
4 Baseline was defined as the 48-hour period starting on Day -2 and ending on Day 1 of each Treatment Period

Table 2. Treatment-Emergent Adverse Events (TEAE) in ≥2 Subjects

Number (Percent) of Subjects

TEAE Preferred Term	OLC (N=80)	LC (N=80)
Any Treatment-Related TEAE[1]	20 (25.0)	20 (25.0)
Nausea	8 (10.0)	5 (6.3)
Back Pain	3 (3.8)	3 (3.8)
Vomiting	3 (3.8)	1 (3.1)
Diarrhea	2 (2.5)	0 (0.0)
Eructation	2 (2.5)	0 (0.0)
Abdominal Distension	1 (1.3)	3 (3.8)
Lip Dry	0 (0.0)	2 (2.5)
Somnolence	0 (0.0)	2 (2.5)

1 Includes subjects with ≥1 treatment-related AE

CONCLUSIONS

- In this randomized, crossover study, both OLC and LC increased urinary P excretion similarly and were found to be bioequivalent
- Declines in daily urinary phosphorus excretion after treatment were similar for OLC and LC

IMPLICATIONS

- Although the majority of patients with ESKD in the United States are managed with phosphate binders, the optimal strategies for garnering the greatest effectiveness from these drugs while minimizing pill burden and adverse effects for patients are yet to be defined
- The higher intrinsic phosphate binding capacity of lanthanum without the potential variability introduced by the need to completely chew tablets may provide an additional option for patients with hyperphosphatemia for whom chewing tablets is disliked, inconvenient, or difficult

References:
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2. K/DOQI. *Am J Kidney Dis.* 2003. Oct.
3. KDIGO. *Kidney Int Suppl.* 2017. Jul.
4. McClure ST, et al., *Nutrients.* 2017. Jan.

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