Combination Oxylanthanum Carbonate and Tenapanor Synergistically Lowers Urinary Phosphate Excretion in Rats

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BACKGROUND

- End-stage kidney disease (ESKD) affects >7 million people worldwide[1] and ~70% of patients with ESKD have hyperphosphatemia[2]
- Tenapanor is a sodium/hydrogen exchanger (NHE3) inhibitor that reduces paracellular phosphate absorption by inducing conformational changes in intestinal epithelium[3]
- Oxylanthanum carbonate (OLC) is an investigational new phosphate binder being developed for the treatment of hyperphosphatemia under FDA's 505 (b)(2) regulatory pathway
- If approved, OLC will share substantially the same product label and prescribing information as reference-listed drug Fosrenol® (lanthanum carbonate), although OLC tablets are smaller in size and swallowed whole with water and not chewed

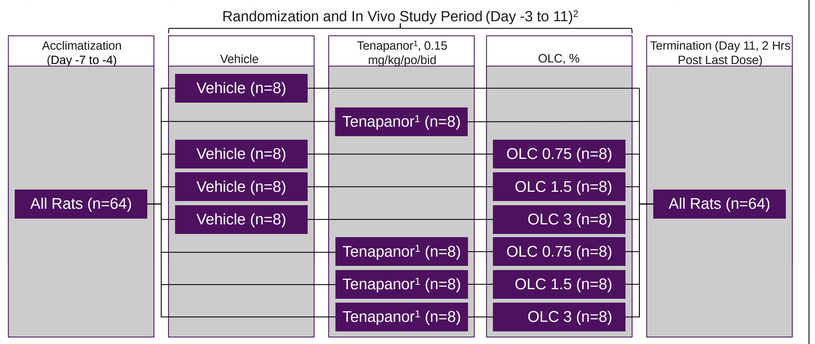
OBJECTIVE

This study evaluated effects of OLC+tenapanor on urinary phosphate excretion in rats on a high phosphorus diet

METHODS

- 64 male Sprague Dawley rats were fed standard chow for 1 week prior to study start and then spiked with additional 0.4% inorganic phosphorus [1:1 sodium:potassium salt, 1.1% (wt/wt) total phosphorus content] for rest of the study[3] **(Figure 1)**
- On study Day -1, animals were randomized into 8 groups (n=8 in each):
  - Vehicle
  - OLC 0.75%
  - OLC 1.5%
  - OLC 3%
  - Tenapanor 0.15 mg/kg
  - OLC 0.75%+tenapanor 0.15 mg/kg
  - OLC 1.5%+tenapanor 0.15 mg/kg
  - OLC 3%+tenapanor 0.15 mg/kg
- Vehicle and tenapanor were dosed PO twice daily whereas OLC was incorporated into the diets
- 24-hour urine samples were collected using metabolic cages on day 9, 10, and 11 for urinary phosphate measurements
- OLC efficacy data are presented as average of all OLC doses (0.75%, 1.5%, and 3%)

Figure 1. Study Design – OLC+Tenapanor[1] Combo Study

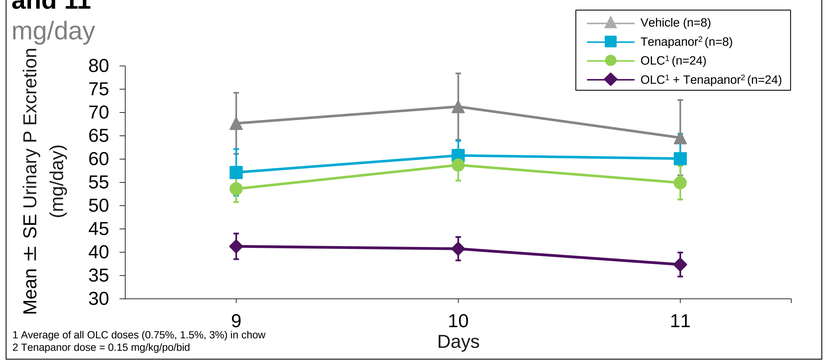


1 Chronic repeated dosing of tenapanor: PO, BID; Day 1 to termination
2 Urinary phosphate was taken on Day 9,10,11; Body weight and food intake measurements were taken once a day; Day -3 to termination

RESULTS

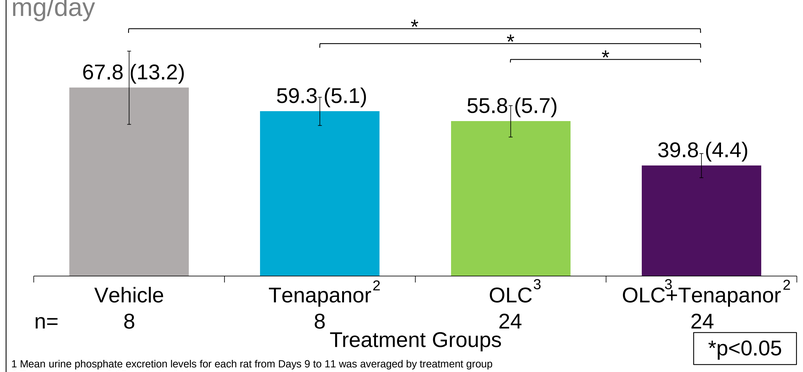
- OLC reduced 24-hour urinary phosphate excretion, with OLC + tenapanor showing lower phosphate excretion compared to vehicle, OLC only, and tenapanor only **(Figure 2)**
- In tenapanor alone and OLC only groups, urinary phosphate excretion was 8.5 and 12.0 mg/day lower, respectively, compared to vehicle **(Figure 3)**
- In OLC+tenapanor groups, urinary phosphate excretion was 28 mg/day lower compared to vehicle **(Figure 3)**
- The observed reduction in urinary phosphate excretion for the OLC+tenapanor groups (0.75% and 1.5% OLC doses) was significantly larger than the predicted reduction based on the single-agent effects in accordance with the Bliss model **(Figure 4)**

Figure 2. Mean ± SE Urinary Phosphate Excretion – Days 9, 10, and 11



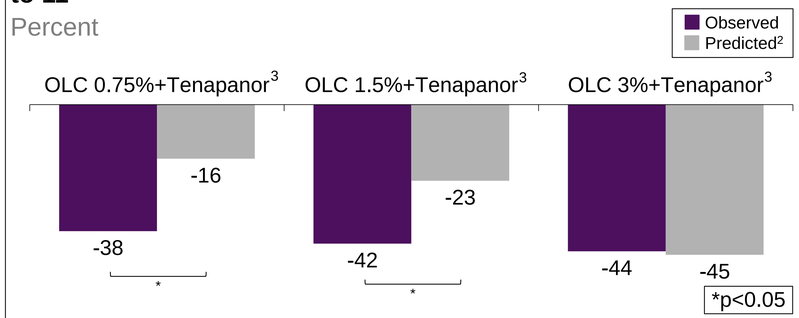
1 Average of all OLC doses (0.75%, 1.5%, 3%) in chow
2 Tenapanor dose = 0.15 mg/kg/po/bid

Figure 3. Mean[1] (95% CI) Urinary Phosphate Excretion by Treatment Group – Days 9 to 11



1 Mean urine phosphate excretion levels for each rat from Days 9 to 11 was averaged by treatment group
2 Tenapanor dose = 0.15 mg/kg/po/bid
3 Average of all OLC doses (0.75%, 1.5%, 3%) in chow

Figure 4. Mean[1] Percentage Reduction of Urinary Phosphate Excretion Relative to Vehicle Group by Treatment Group – Days 9 to 11



1 Calculated by averaging urinary phosphate excretion levels for each rat from Days 9 to 11 by dose group then subtracting mean of urinary phosphate excretion levels from Days 9 to 11 of Vehicle
2 Predicted based on the Bliss Model; the model compares the predicted combination response calculated using the complete additivity of probability theory based on the observed effect of each individual agent administered alone, with the observed effect of combination treatment
3 Tenapanor dose = 0.15 mg/kg/po/bid

CONCLUSIONS

- This study demonstrated that tenapanor alone modestly decreased urinary phosphate excretion
- OLC alone offered slightly better effects compared to tenapanor alone
- OLC+tenapanor combination achieved a much more pronounced reduction (3.3x greater vs tenapanor alone)
- We demonstrated the potent effects of the novel lanthanum-based phosphate binder OLC and found through Bliss Model analysis that OLC+tenapanor has synergistic, rather than additive, effects in rats

DISCUSSION

- OLC+tenapanor combination exhibited four- to seven-fold more synergistic effects compared to the sevelamer+tenapanor combination[4]
- The combination of OLC and tenapanor may support a pronounced inhibition of intestinal phosphate absorption by leveraging two distinct mechanisms of action;
  - OLC: an intestinal phosphate binder
  - Tenapanor: an NHE3 blocker that diminishes transcellular phosphate absorption
- Future studies should evaluate this promising treatment combination in humans with chronic kidney disease
- Additional studies in patients with ESKD and hyperphosphatemia will be required to understand the most effective and best tolerated OLC-containing regimens, as we aim to improve long-term control of hyperphosphatemia and prevent its myriad associated complications

References:
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