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Enhanced Urinary Phosphorous Reduction: Comparative Study of Oxylanthanum Carbonate and Tenapanor in Rats

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BACKGROUND

- End-stage renal disease (ESRD) affects >7M people worldwide[1] and ~70% of patients with ESRD have hyperphosphatemia[2]
- Current hyperphosphatemia treatment options are dietary phosphate (P) restriction, dialysis, and P binders. However, not only are these hyperphosphatemia treatment options not highly effective for P control, they also negatively impact patient quality of life
- Thus, there is an unmet need for novel therapeutic innovations that maintain efficacy while reducing the required number of tablets and adverse effects, thereby increasing adherence and potentially improving clinical outcomes
- Tenapanor is a sodium hydrogen exchanger inhibitor used to reduce serum P in adults with chronic kidney disease (CKD) on dialysis as an add-on therapy with P binders[3]. Tenapanor has a unique mechanism of action that blocks paracellular absorption, thus reducing intestinal P absorption
- Combination treatments, especially those employing therapies with distinct mechanisms of action, may improve P control while reducing the negative characteristics of current P binders
- A previous study conducted by King et al.[4] found that when administered together, tenapanor and sevelamer decreased urinary P excretion significantly more than either tenapanor or sevelamer alone across all sevelamer dose levels
- Oxylanthanum carbonate (OLC) is a novel nanotechnology product that combines lanthanum, which has highest binding capacity vs other P binders, with smaller pill size that is swallowed with water vs chewed[5]

OBJECTIVE

The objective of our study was to evaluate the effects of tenapanor and OLC on P excretion in rats

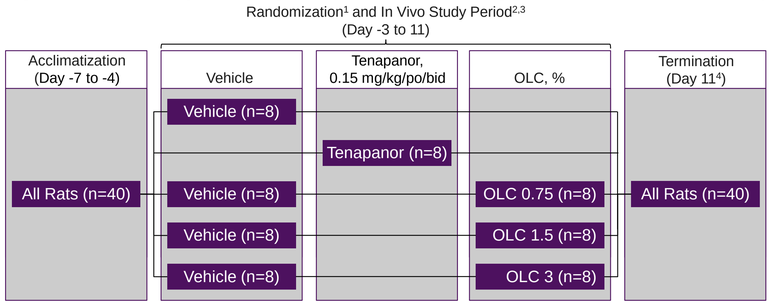
METHODS

- In our study, we utilized the study design and dosage regimen from King et al. involving sevelamer and tenapanor
- The study consisted of acclimatization, randomization, in vivo study period, and termination **(Figure 1)**
- 40 male Sprague Dawley rats fed standard chow 1 week prior to study start

METHODS (Cont.)

- On study Day -1, rats were randomized into study groups (n = 8): 1) Vehicle, 2) tenapanor 0.15 mg/kg, 3) Vehicle + OLC 0.75%, 4) Vehicle + OLC 1.5%, 5) Vehicle + OLC 3% **(Figure 1)**
- From 11 days, Vehicle and tenapanor were dosed orally (PO) twice/day via oral gavage whereas OLC was incorporated into the diets
- Food intake was measured daily from study Day -3 until study Day 11, when the animals were euthanized
- 24-hour urine samples were collected using metabolic cages on Days 9, 10, and 11 for urinary P measurements
- Mean urine P excretion concentrations for each animal from Days 9 to 11 were averaged by treatment group

Figure 1. Study Design – OLC + Tenapanor Combo Study

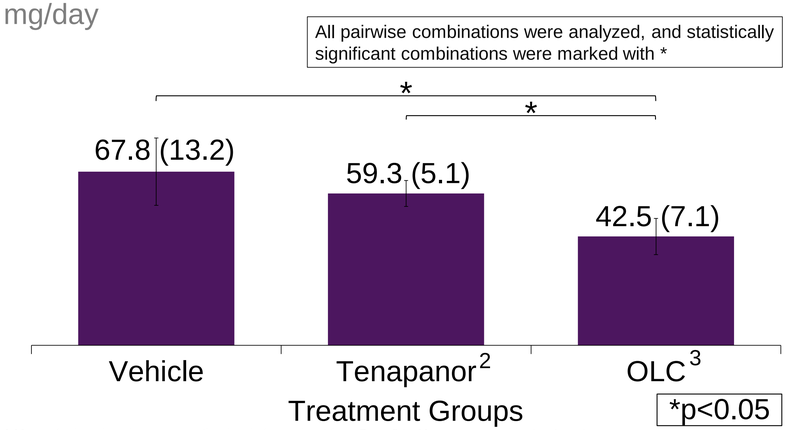


1 Bodyweight and food intake: QD day -3 to termination
2 Chronic repeated dosing: PO, BID day 1 to termination
3 Urine phosphate was taken on Day 9,10,11
4 2 hrs post last dose

RESULTS

- Reduction of urinary P excretion with tenapanor was not significantly different compared to Vehicle **(Figure 2)**
- Compared to Vehicle alone (group 1), tenapanor demonstrated 8.5 mg/day less urinary P excretion while OLC demonstrated 25.3 mg/day less urinary P excretion, a significantly greater reduction in urinary P excretion with OLC compared to tenapanor ($p<0.05$) **(Figure 2)**

Figure 2. Mean[1] (±95% CI) of Urinary Phosphorus Excretion by Treatment Group – Days 9 to 11 (n=8 per Treatment Group)



1 Mean of urine phosphorous 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 OLC dose = 3% in chow

CONCLUSIONS

- Tenapanor did not significantly reduce urinary P excretion
- OLC demonstrated 3x more effective urine P reduction vs tenapanor
- Subsequent analyses will focus on examining the combination of tenapanor and OLC
- OLC and tenapanor utilize 2 different mechanisms of action to manage P levels. The combination may lead to synergistic effects on lowering P levels while providing patients with the benefit of reduced pill burden
- Future studies should evaluate tenapanor + OLC in humans with CKD

References:

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