

Oxalate Degrading Enzyme in Clinical Trials

Kenneth M. Attie¹ and Danica Grujic²
Departments of ¹Clinical Development and ²Product Research,
Altus Pharmaceuticals Inc., Waltham, MA.

Introduction: Hyperoxaluria is a major risk factor for urolithiasis and nephrocalcinosis. Current therapies for patients with primary (PH) and enteric (EH) hyperoxaluria are limited and may not forestall disease progression. ALTU-237 is an orally delivered, crystalline, cross-linked formulation of oxalate decarboxylase that is being developed for the treatment of hyperoxaluria and the prevention of kidney stones. It is intended to reduce both dietary and endogenous sources of oxalate. ALTU-237 is active over a broad pH range and stable against proteolytic degradation. In animal models of EH (diet-induced or Cl⁻-oxalate exchanger deficient) and PH (AGT1 knockout ± ethylene glycol), ALTU-237 reduced urinary oxalate levels and prevented nephrocalcinosis. A Phase I clinical trial was recently conducted to test the safety and tolerability of ALTU-237 in healthy adult volunteers.

Methods: This was a placebo-controlled, double-blind, dose-escalation study in normal healthy males and females, ages 18-60 years. The primary objective was to determine the safety and tolerability of ALTU-237 compared to placebo. A secondary objective was to assess clinical activity in terms of urinary oxalate levels. Subjects consumed a low-oxalate diet (with no drug treatment) for 5 days, followed by a 7-day double-blind treatment period during which they consumed a high oxalate/low calcium diet and drug administered with meals. Subjects (n = 58) were randomized to receive one of four doses of ALTU-237 (900; 3600; 10,800; or 18,000 units/day) or placebo. A followup visit was performed on Day 19.

Results: ALTU-237 achieved a favorable safety profile and was well tolerated. No serious or severe adverse events were reported and there were no clinically significant laboratory abnormalities attributable to the drug. The high oxalate diet resulted in mean urinary oxalate levels near the upper limit of normal. The treatment did not result in a substantial or dose-dependent reduction in urinary oxalate levels at the doses administered.

Conclusions: ALTU-237 is effective in lowering oxalate levels in animal models of PH and EH. It was found to be safe and well tolerated in a Phase I clinical study. Urinary oxalate levels were increased on a high oxalate diet and did not decrease substantially with ALTU-237 at the doses tested. Further proof-of-concept studies in humans are planned.

Support: This work was funded by Altus Pharmaceuticals Inc.
