ALLN-177, a Novel Oral Enzyme Therapy, Reduces Urinary Oxalate Excretion and Plasma Oxalate in a Porcine Dietary Model of Severe Hyperoxaluria

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Hyperoxaluria
- Oxalate is an end-product of carbohydrate and amino acid metabolism, and it is also absorbed from the diet. There is obligatory renal excretion of the metabolic and dietary oxalate load.
- Hyperoxaluria (HOx) is a major risk factor for kidney stones, nephrocalcinosis, and oxalate nephropathy, which may lead to chronic kidney disease and end-stage renal disease.
- Secondary HOx is caused by excess oxalate absorption from diet and can be:
  - Enteral: Primarily associated with bariatric surgery, resection of the small intestine, diseases of the small intestine, or pancreatic insufficiency.
  - Idiopathic: Unknown etiology.
- There are no pharmacological agents approved to treat any type of HOx.

ALLN-177: Oxalate Decarboxylase
- ALLN-177 degrades oxalate primarily in the stomach. Absence of oxalate in the small intestine. Degrades oxalate present in the gastrointestinal (GI) tract and reduces the amount of oxalate available for absorption, thereby decreasing urinary oxalate (UOx) excretion.

Study Design

Baseline Characteristics:
- Twelve juvenile pigs, 8 male and 4 female; 8-10 weeks of age (Polish Landrace x Yorkshire x Hampshire x Petreum).
- Mean ± SD body weight at randomization: 21.8 ± 6.2 kg.
- Twelve pigs were assigned to treatment groups, with 3 replicates per group.
- Mean ± SD body weight at randomization: 21.8 ± 6.2 kg.
- Food intake and body weight were recorded daily.
- Oxalate excretion was measured before and after treatment.

Treatment:
- 22,500 u ALLN-177 with feed, 3x7,500 u/meal; same dose used in the clinical trials, poster #TH-PO1073.

Primary endpoint:
- Mean within-pig difference from pre-treatment to on-treatment in 24h UOx expressed as mg/gCr/day calculated from a single collection at the end of pre-treatment and treatment periods.

Secondary endpoints:
- Change in plasma oxalate (POx).
- Oxalobacter formigenes colonization assessed by PCR.

Conclusions
- A high-fat diet enriched with rhubarb induced hyperoxaluria and hyperoxalemia in the pigs, with a >50% increase in both urine and plasma oxalate levels.
- ALLN-177 therapy for 7 days normalized urinary oxalate excretion and reduced plasma oxalate to the normal range.
- Changes in oxalate levels occurred in the absence of Oxalobacter formigenes colonization.
- Oral ALLN-177 was well-tolerated, with no observable effects on growth, food or water intake, or macroscopic changes in the GI tract or kidneys.
- The reductions demonstrated in both plasma and urine oxalate with ALLN-177 treatment in a large animal model of severe hyperoxaluria provide proof of concept for a potential new therapy for severe oxalate-related disease.