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

- Crystalline, recombinant oxalate-degrading enzyme.
- Oral delivery, not absorbed systemically.
- Degrades oxalate present in the gastrointestinal (GI) tract and reduces the amount of oxalate available for absorption, thereby decreasing urinary oxalate (UOx) excretion.

Porcine Model of Hyperoxaluria

- Pigs are more suitable than rodents for modeling HOx based on greater similarity to the human GI and genitourinary tract.
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Assessments of ALLN-177 Mechanism of Action

ALLN-177 Degrades Oxalate Primarily in Stomach

- Measurement of oxalate levels after treatment with and without ALLN-177.

Absence of Oxalobacter formigenes Colonization in Study Pigs

- Shown is PCR analysis from stool samples collected on the last day of the treatment period from representative pigs.
- Comparisons are made between pre-treatment and treatment periods.

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 provides proof of concept for a potential new therapy for severe oxalate-related disease.