Enteral Administration of ALLN-346, a Recombinant Urate-Degrading Enzyme, Decreases Serum Urate in a Pig Model of Hyperuricemia

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Hyperuricemia, Gout, and Present Therapies

- Hyperuricemia refers to abnormally high levels of uric acid in the blood. Gout is the most recognized clinical manifestation with well-understood pathophysiology, but hyperuricemia has also been associated with progression of chronic kidney disease, hypertension, coronary artery disease, and metabolic syndrome.[1,2]
- Uric acid homeostasis is determined as a balance between urate production, renal excretion, and intestinal secretion. Approximately 2/3 of uric acid is excreted by the kidneys, while the remaining 1/3 is secreted by the intestine (extra-renal elimination).[3] With impaired kidney function and hyperuricemia, extra-renal elimination increases to ~50%-70%, and intestinal secretion plays a predominant role in maintaining urate homeostasis.[3-5]
- Existing urate-lowering therapies including oral xanthine oxidase inhibitors, uricosurics, and intravenous uricase agents have limitations either in efficacy or tolerability that contribute to refractoriness to therapy.
- ALLN-346 is an orally administered, non-absorbed, engineered urate-specific enzyme designed to degrade urate in the intestinal tract and thereby reduce hyperuricemia.
- Previously, we demonstrated in urate oxidase knock-out mice that 7 days of oral therapy with ALLN-346 reduced plasma uric acid levels comparably to allopurinol therapy.[6]
- Here, we tested whether enteral administration of ALLN-346 to pigs with acutely induced hyperuricemia[7] could reduce plasma urate (pUA) and urine uric acid (uUA) excretion.

Model of Acute Hyperuricemia in Juvenile Pigs

Why Pigs?

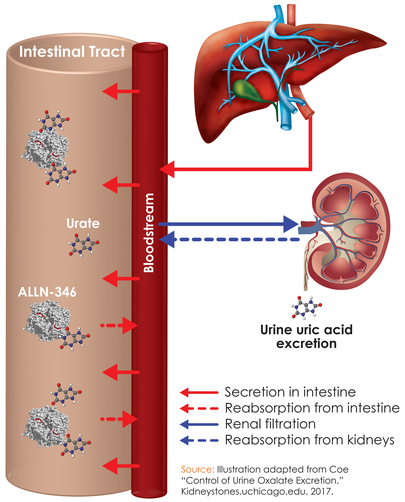
- Similarities:
  - Porcine gastrointestinal tract features, kidney filtration, and urate efflux transporters that regulate urate homeostasis, similar to humans[8,9]
  - ABCG2 urate transporters present in the intestine have similar tissue distribution to humans[9]
- Differences:
  - Humans lack uricase unlike pigs, rodents, and most primates

Acutely induced severe hyperuricemia and hyperuricosuria by chronic infusion of uric acid of 10 mg/kg in 40% glucose over 8 hours:

- pUA ~8 mg/dL (normal in pigs: <1 mg/dL)
  - Similar to humans with hyperuricemia
- uUA >1,000 mg/day (normal in pigs: <100 mg/day)

ALLN-346: Engineered Urate Oxidase

- Specific urate-degrading enzyme optimized for stability in gastric compartment and activity along intestine
  - Orally administered
  - Not expected to be systemically absorbed
  - Specifically degrades urate along the small intestine



Source: Illustration adapted from Coe "Control of Urine Oxalate Excretion." Kidneystones.uchicago.edu. 2017.

- Liver releases daily production of urate into the bloodstream
  - 500-700 mg from purine metabolism
  - 150-200 mg from diet
- **Healthy kidneys** filter ~70% of daily uric acid turnover; the remaining ~30% is secreted via intestine
- **In CKD**, extra-renal (intestinal) elimination increases to 50%-70%, becoming a major route of urate elimination
- **ALLN-346 MOA:** degradation of urate along the intestinal tract; suitable to reduce systemic urate burden by targeting intestinal elimination of urate

Study Design

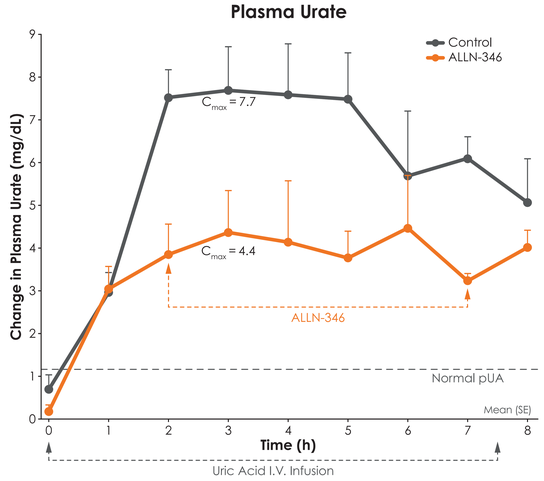
Objective: Demonstrate effect of enteral (duodenal) ALLN-346 administration on plasma urate

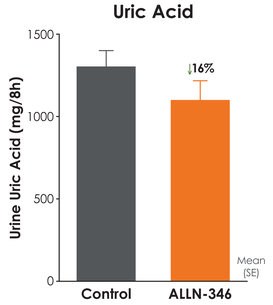
Study Design:

Pig Characteristics	Chronic Hyperuricemia & ALLN-346 Treatment
Juvenile pigs (n=7) Age: 3 months Mean body weight: 17.3 kg Feeding Schedule: 2h before and in middle of 8h study	Jugular vein catheters for: • Uric acid infusion (10 mg/kg from 40% glucose suspension) Duodenal port for: • Bolus, hourly ALLN-346 administration (6×10,560 U) pUA measurement: • Hourly during 8h study uUA measurement: • Once during 8h study

Results

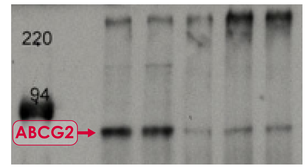
Figure 1: Enteral Administration of ALLN-346 Reduces Plasma Urate and Uric Acid Excretion





	Control	ALLN-346	%
AUC_{0-8h}	44.3	27.5	↓38%
	P < 0.0156		

Figure 2: Analysis of ABCG2 Expression



WB analysis confirms that expression of ABCG2, a major intestinal urate transporter, is the highest in the jejunum and ileum, similar to humans.

Conclusion and Future Steps

- The results of this pilot experiment in pigs with acute hyperuricemia suggest:
  1) Small intestine plays an active role in urate elimination in conditions of severe hyperuricemia
  2) The potential for oral therapy with ALLN-346 to degrade urate in the intestinal tract, and as a result reduce pUA and overall urate burden in people with hyperuricemia and gout
- Future clinical trials are warranted to test ALLN-346 oral enzyme therapy in patients with hyperuricemia

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