Orally administered
Specifically targets degradation of urate along the GI tract

Plasma Urate Urine Uric Acid
Mice renally excrete 20-40 fold more uric acid than humans

Urate Oxidase Knockout (UrOxKO) Mouse Phenotype

• Hyperuricemia, Gout and Present Therapies

• Here, we targeted gut elimination of urate that contribute to refractoriness to therapy in gout.

• and approximately 50-70% of urate is secreted via intestine.

• Gout, but also in the genesis and progression of chronic kidney disease (CKD), hypertension, coronary artery disease (CAD), and metabolic syndrome.

• Renal excretion is the major route of uric acid elimination, but the gastrointestinal (GI) tract plays an increasingly recognized role in urate homeostasis, especially in CKD where renal uric acid excretion is impaired and approximately 50-70% of urate is secreted via intestine.

• Urate is secreted from the circulation into the intestine, and it is partially reabsorbed

• Kidneys filter urate from the blood; it is either reabsorbed into the circulation or is excreted into the urine

• Healthy kidneys filter ~70% of daily uric acid turnover; the remaining ~30% are secreted via intestine

• In CKD, extra-renal, intestinal elimination increases up to 50-70%, becoming a major route of urate elimination

• Crystal deposition can cause inflammation and associated kidney damage, further contributing to decline in glomerular filtration rate

• Kidney from UrOxKO mice, a model with severe hyperuricemia, hyperuricosuria, and uric acid crystalline obstructive nephropathy.

Urate Oxidase Knockout (UrOxKO) Mouse Phenotype

• Severe hyperuricemia:
  - >14 mg/dL (6-20 mg/dL); with maintenance dose of allopurinol (ALLO), plasma urate is reduced to ~4 mg/dL (normal ~2 mg/dL)
  - >47 mg/24h; varies daily; with maintenance dose of ALLO, plasma urate is reduced to normal range of 2-3 mg/24h
  - Mice renally excrete 20-40 fold more uric acid than humans based on kg body mass
  - Mice develop diabetes insipidus, increase water intake, and excrete higher urine volume (~4-15 mL/24h)

• Oral therapy with ALLN-346 was well-tolerated and resulted in significant reduction of plasma urate and of urine uric acid excretion after 1 week of treatment in severe hyperuricemia.

• The effect on plasma urate reduction was similar to the ALLO dose of 50 mg/L and the effect on urine uric acid excretion was superior to the maintenance dose of ALLO 150 mg/L which is required to sustain this animal model.

• The underlying physiology of hyperuricemia and the extrarenal pathway of uric acid elimination corresponds to the ALLN-346 mechanism of action of degradation urate along the GI tract.

Conclusions and Future Steps

• Oral therapy with ALLN-346 was well-tolerated and resulted in significant reduction of plasma urate and normalization of uric acid excretion after 1 week of treatment in severe hyperuricemia.

• The effect on plasma urate reduction was similar to the ALLO dose of 50 mg/L and the effect on urine uric acid excretion was superior to the maintenance dose of ALLO 150 mg/L which is required to sustain this animal model.

• Future experimental studies will address the effect of ALLN-346 on fractional excretion of uric acid (FEUA) and potential renoprotection.

Study Design and Results

Objectives: Demonstrate effect of ALLN-346 on reduction of plasma urate and of urine uric acid excretion

Pre-Treatment: 7 days Treatment: 7 days Follow-up: 7 days

Discontinue ALLO

Oral therapy with ALLN-346 mixed with food (~700 units/day); ALLO (50 mg/L or 150 mg/L) in drinking water

Figure 1: Significant Reduction in Plasma Urate and Urine Uric Acid with ALLN-346 or ALLO Therapy

Plasma Urate

0 2 4 6 8 10

Pre-Treatment Treatment Follow-up

n = 25

ALLO 50 (n = 8)

ALLO 150 (n = 9)

0.001

0.001

Shown is mean (standard error), p < 0.05 for difference between pre-treatment to treatment, paired t-test

References:

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