A Phase 1/2 Trial of ALN-GO1, an Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1 (PH1)

Interim Study Results from Part A (Healthy Volunteers)

17th Congress of the International Pediatric Nephrology Association (IPNA 2016)
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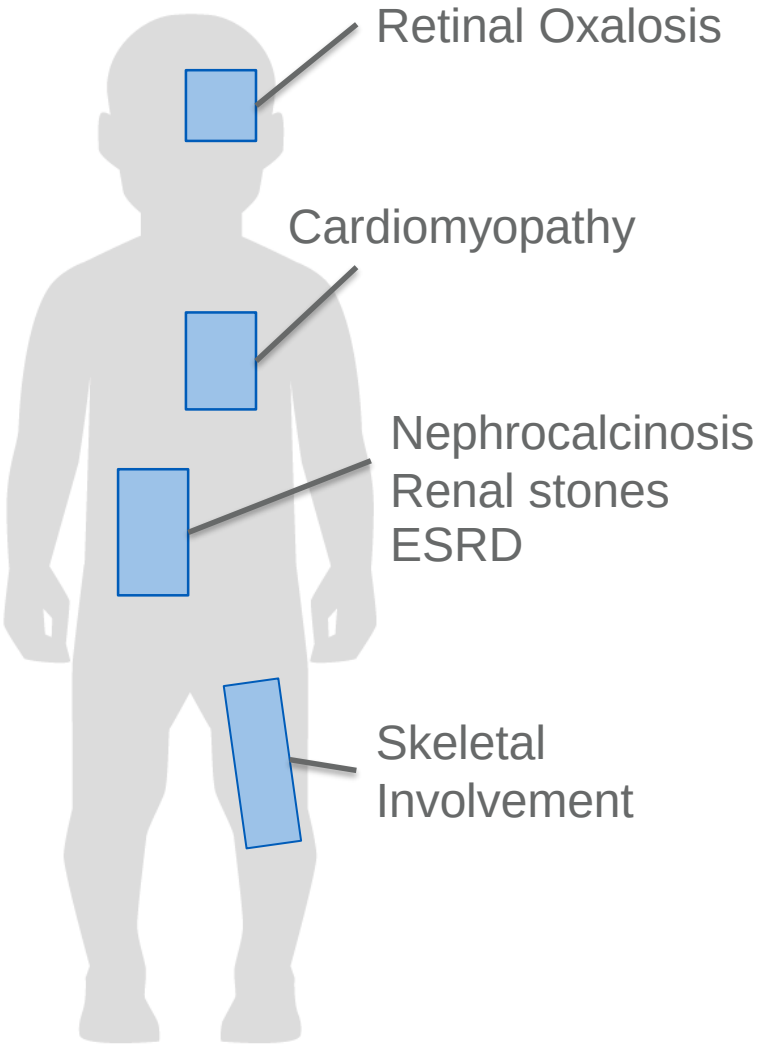
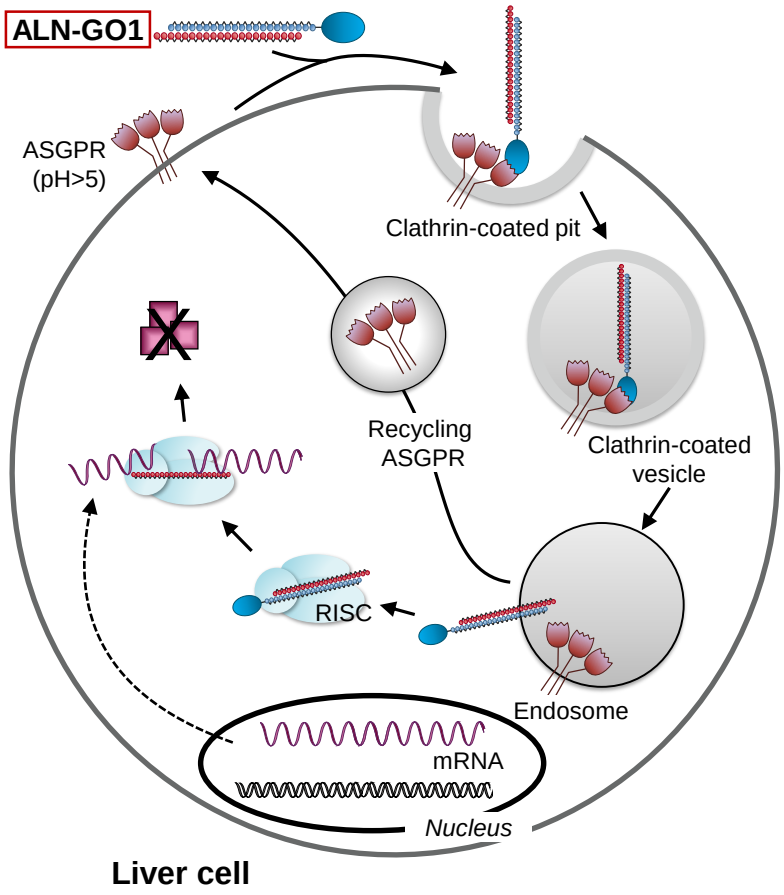
Primary Hyperoxaluria Type 1 (PH1)

- Rare, autosomal recessive disease
- Prevalence of 1-3:1,000,000
- Deficiency of hepatic alanine-glyoxylate aminotransferase (AGT) leads to excessive hepatic oxalate production
- Systemic oxalosis occurs as renal function declines
- Minority of patients respond to Vitamin B6, a co-factor of AGT
- Conservative therapy with hyperhydration and crystallization inhibitors
- Metabolic correction requires liver transplantation, typically performed in combination with renal transplant



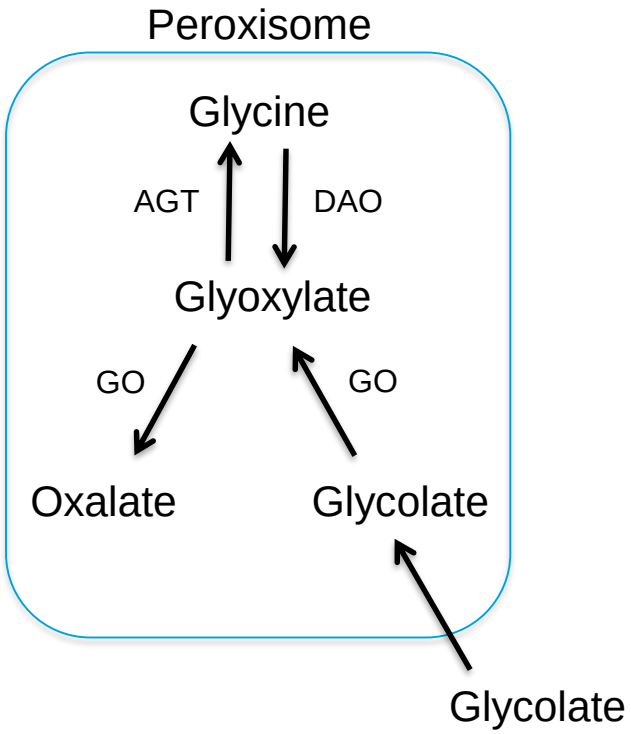
Investigational Therapeutic Approach: RNAi

- Harness a natural pathway of gene silencing to regulate protein production
- Sequence-dependent degradation of target mRNA confers exquisite specificity
- Conjugation to the sugar GalNAc allows efficient delivery to hepatocytes and subcutaneous administration
- General approach clinically validated with human proof-of-concept in multiple clinical development programs

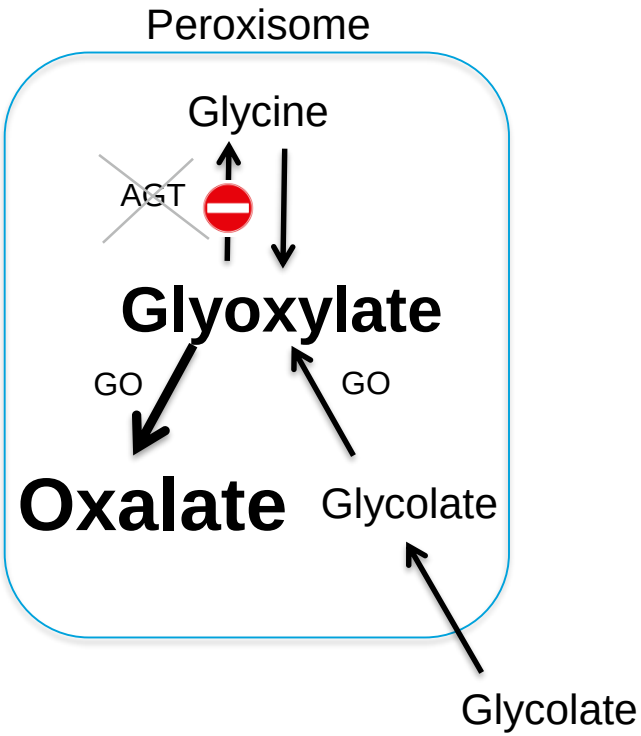


PH1 Pathophysiology

Healthy Pathway

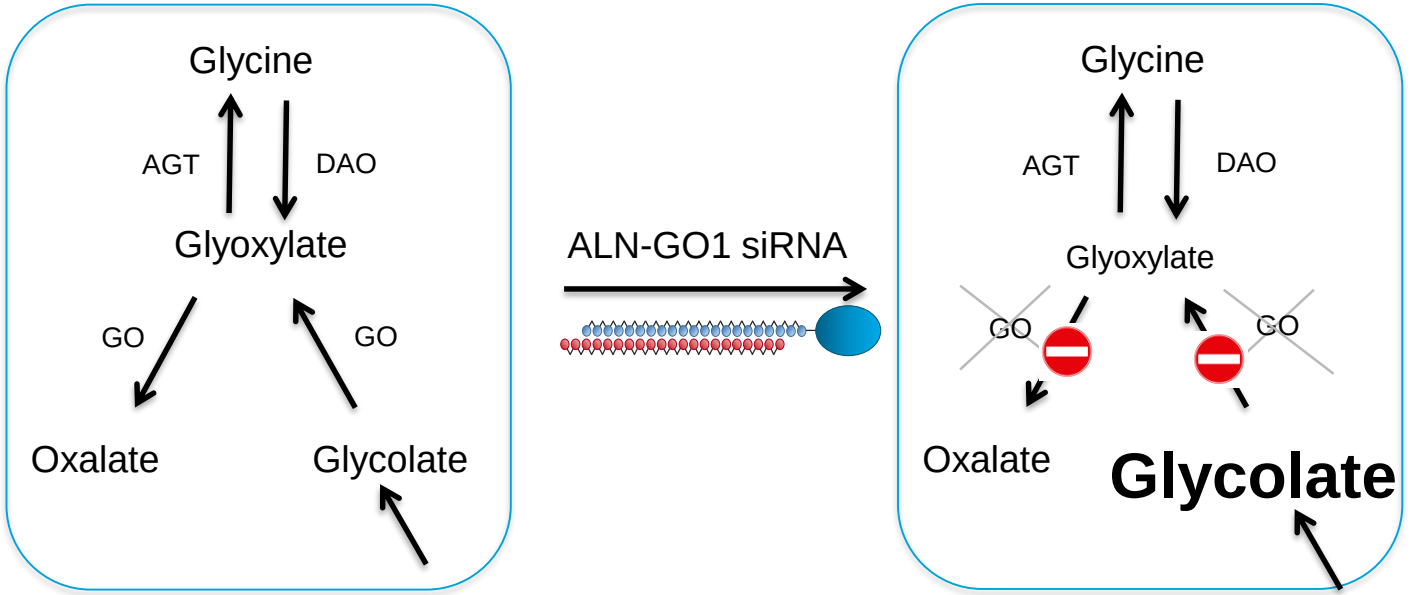


PH1 Pathway

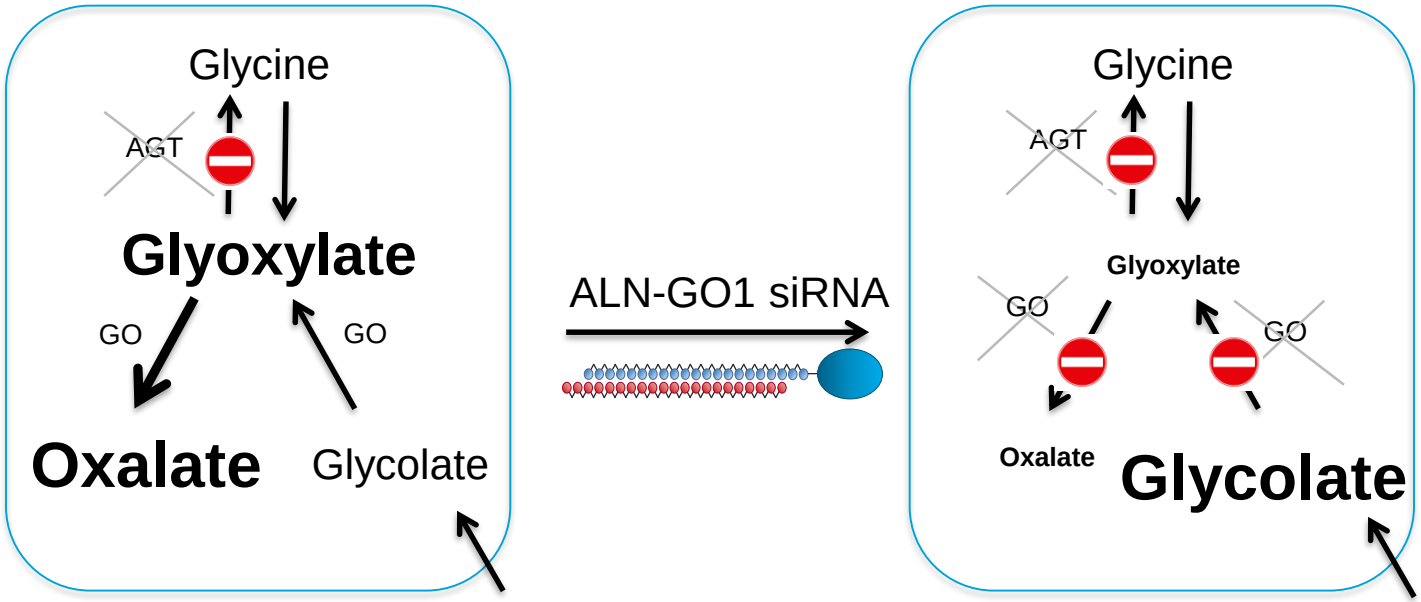


ALN-GO1 Therapeutic Hypothesis

Knockdown of Liver GO Enzyme to Reduce Oxalate

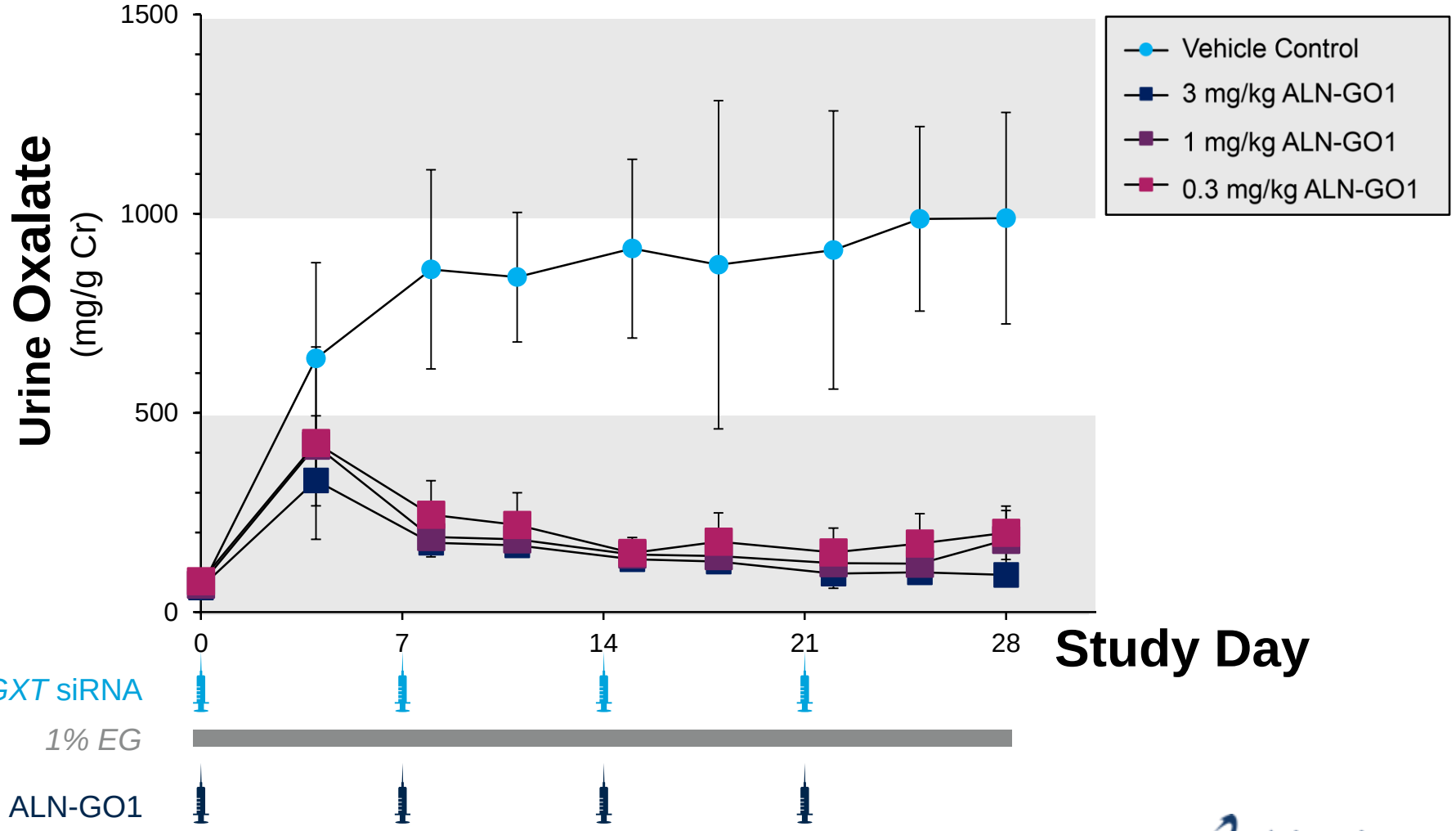


ALN-GO1 Effect in healthy volunteers



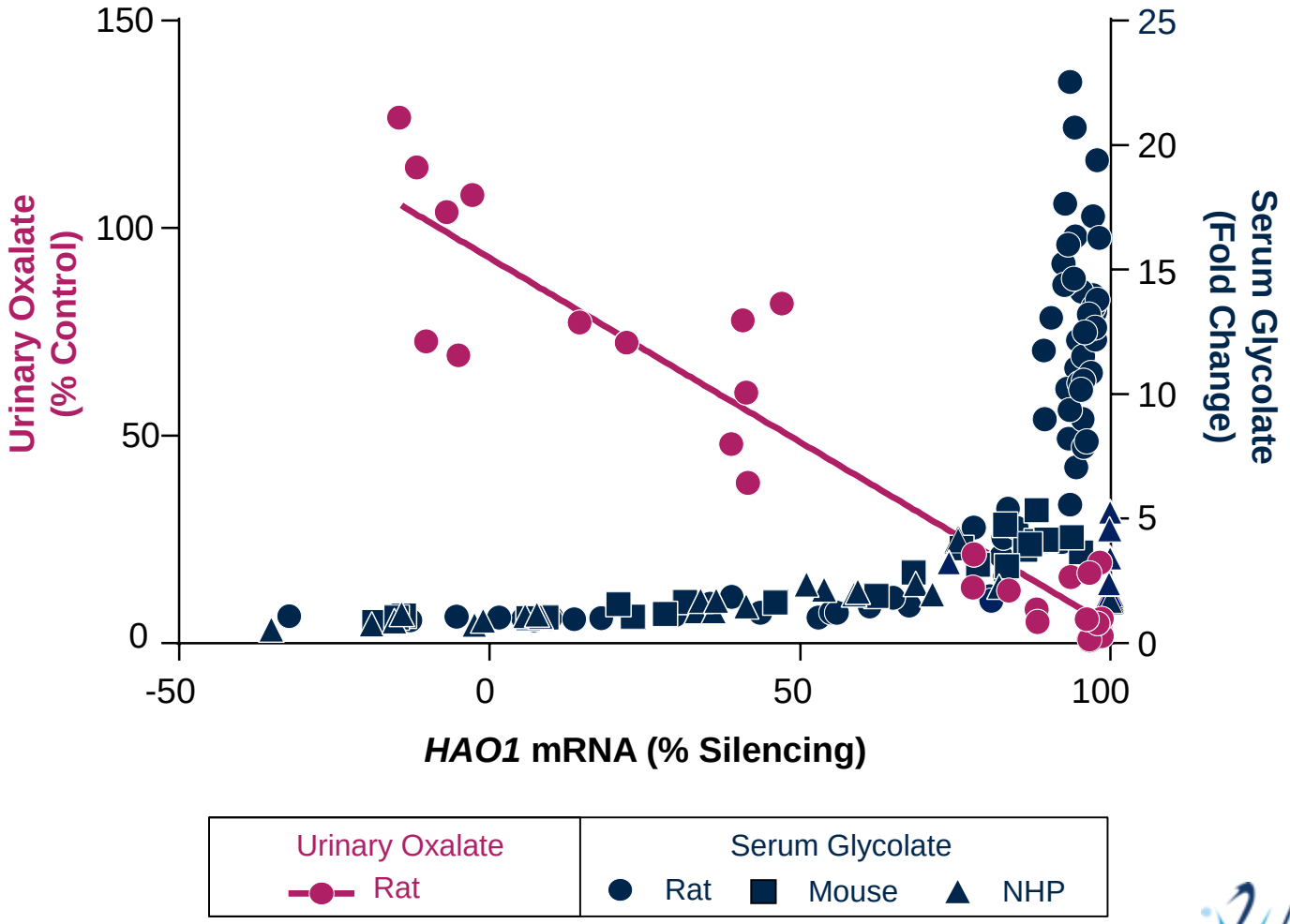
ALN-GO1 Effect in PH1 patients

ALN-GO1 Lowered Urine Oxalate in Rat PH1 Model induced with *AGXT* siRNA



CR: Creatinine; EG: Ethylene Glycol
Liebow et al., 2016 J Am Soc Nephrol

Effective Response of Metabolites in Model Organisms with *HAO1* Silencing



ALN-GO1 Phase 1/2 Study Design

Part A: Single-Ascending Dose (SAD) | Randomized 6:2, Single-blind, Placebo-controlled

- 0.3 mg/kg x 1 SC, N=8
- 1.0 mg/kg x 1 SC, N=8
- 3.0 mg/kg x 1 SC, N=8
- 6.0 mg/kg x 1 SC, N=8

Healthy adult volunteers
Outcome evaluations: Safety and Pharmacodynamics

Part B: Multiple-Ascending Dose (MAD) | Randomized 3:1, Single-blind, Placebo-controlled

- 1.0 mg/kg, q28d x 3 SC, N=4

PH1 patients, ages 6-64 years
GFR>45 ml/min/1.73m^2
Outcome evaluations: Safety and Pharmacodynamics

Clinicaltrials.gov identifier: NCT02706886

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ALN-GO1 Phase 1/2 Interim Study Results*
Demographics: Part A (Healthy Volunteers)

Demographic	
Number enrolled	N=32 (ALN-GO1:Placebo = 24:8)
Median Age (range)	29 years (22 - 42)
Gender	16 females, 16 males
Race (n)	White / Caucasian 25 Asian 2 African 2 Other 3

*Data as of: 17 August 2016

ALN-GO1 Phase 1/2 Interim Study Results*
Safety: Part A (Healthy Volunteers)

ALN-GO1 was generally well-tolerated in healthy volunteers

No drug-related SAEs or discontinuations due to AEs

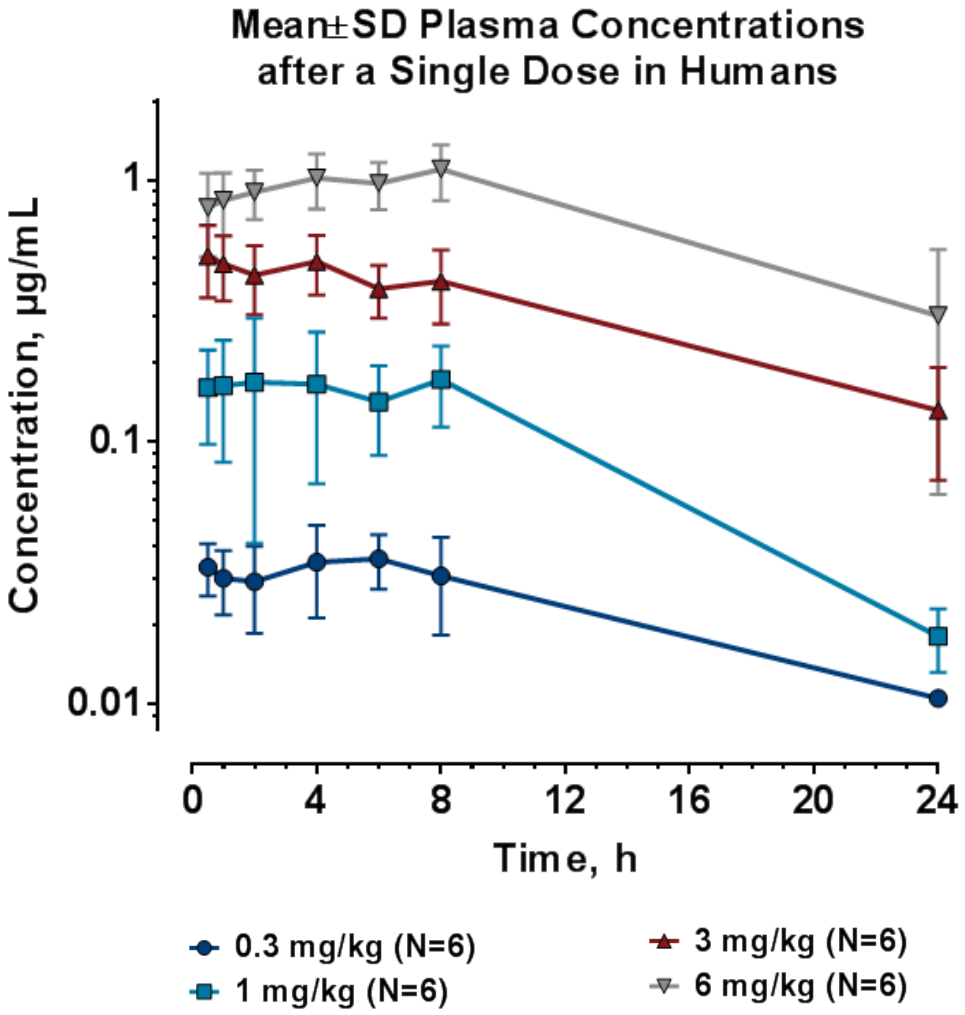
Total of 61 AEs reported in 5 placebo and 21 ALN-GO1 treated healthy volunteers

- AEs occurring in greater than 10% of ALN-GO1 treated subjects included nasopharyngitis (N=6), headache (N=5), and transient injection site pain (N=4).
  - All AEs were mild to moderate with the exception of one healthy volunteer in the lowest dose cohort who had transient, asymptomatic CPK elevation which was unrelated to study drug.

No clinically significant changes in vital signs or EKG

*Data as of: 17 August 2016

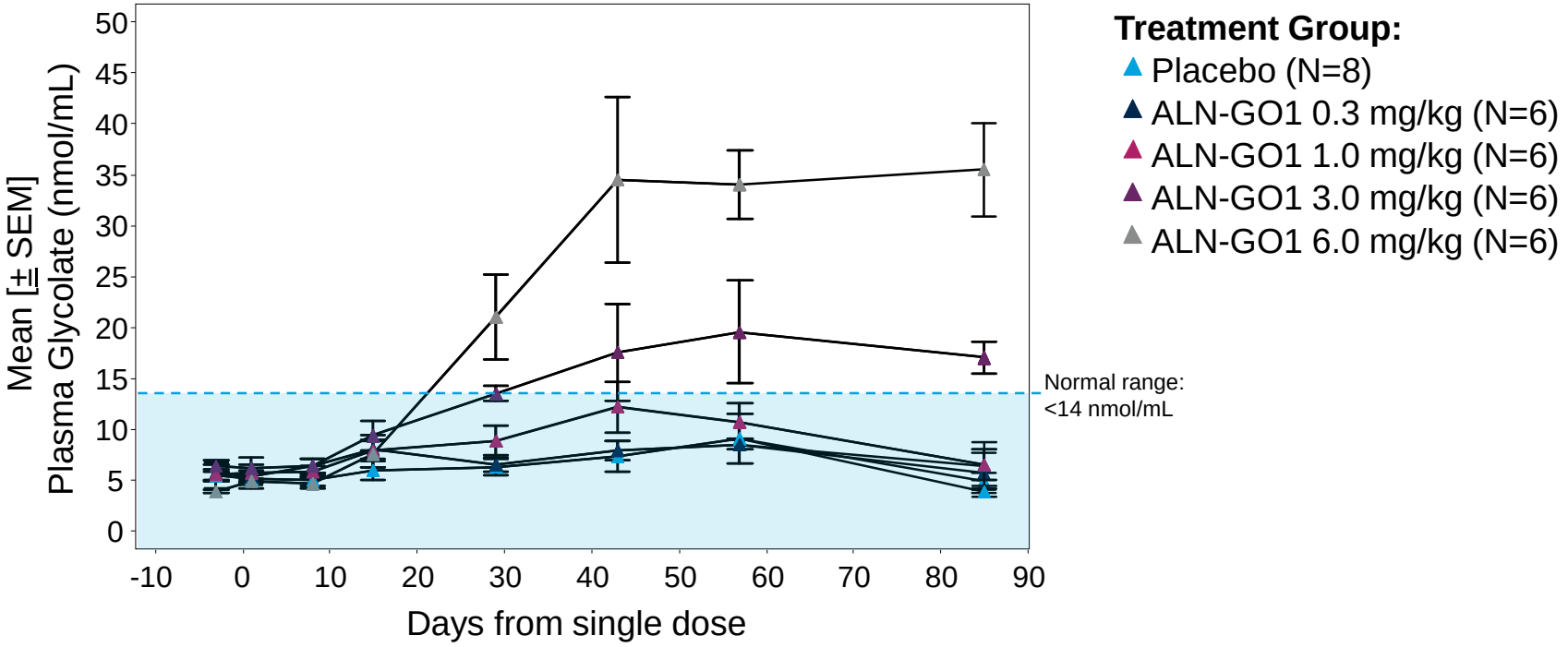
ALN-GO1: Plasma Pharmacokinetics
Part A (Healthy Volunteers)



- ALN-GO1 was rapidly absorbed after subcutaneous injection with mean plasma t_{max} of approximately 3 to 6 hours
- Plasma exposures increased proportionally with dose
- Plasma concentrations declined rapidly after t_{max} with a short elimination $t_{1/2}$ (~ 3.5 to 7 hours), consistent with rapid uptake by the liver

ALN-GO1 Phase 1/2 Interim Study Results*

Plasma Glycolate: Part A (Healthy Volunteers)



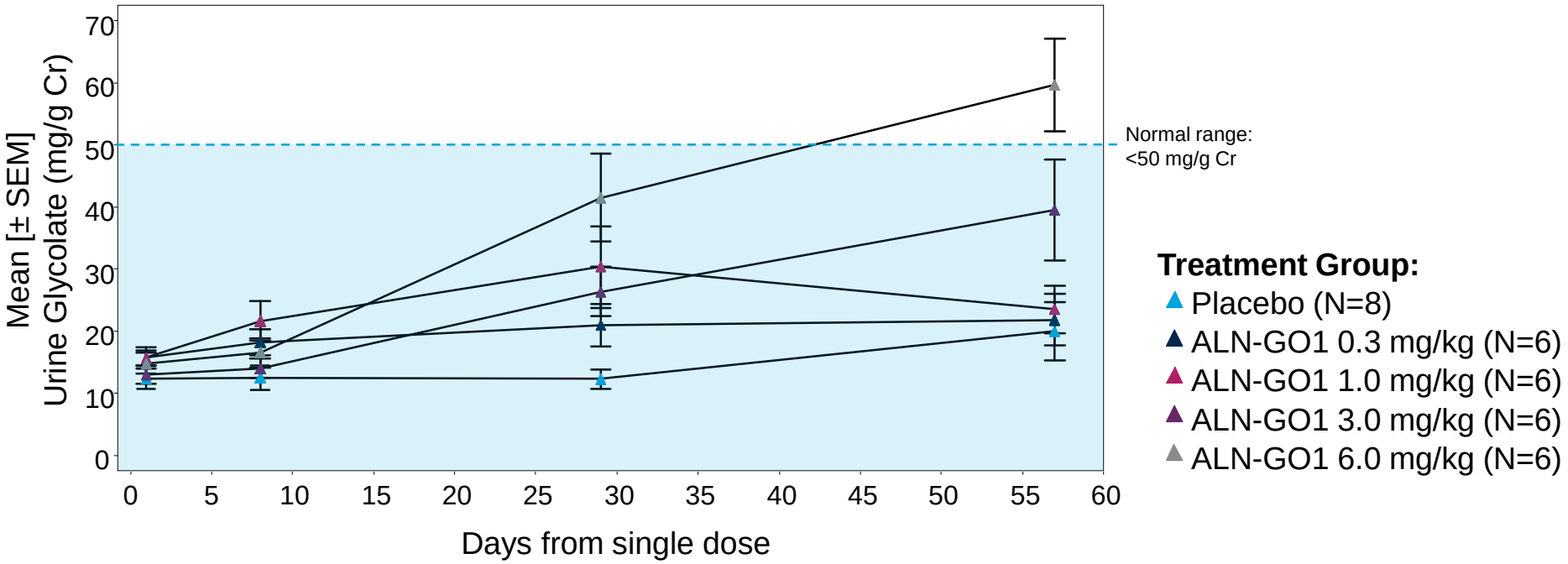
- A dose-dependent increase in plasma glycolate levels is observed, with earliest onset of activity at higher doses evident by Day 29 post dose and sustained until Day 85
- The lowest dose with appreciable glycolate increase is 1 mg/kg

SEM; Standard error of the mean

*Data as of: 02 September 2016

ALN-GO1 Phase 1/2 Interim Study Results*

Urine Glycolate: Part A (Healthy Volunteers)



- A dose-dependent increase in urine glycolate activity is observed, with onset of activity evident by Day 29 post dose

SEM; Standard error of the mean; Cr: Creatinine

*Data as of: 02 September 2016

ALN-GO1 Phase 1/2 Interim Study Results

Summary: Part A (Healthy Volunteers)

- ALN GO1 is a novel, subcutaneously administered investigational RNAi therapeutic designed to reduce the hepatic production of oxalate in PH1 patients
- Preliminary data in healthy adult volunteers suggest that single doses of ALN-GO1 are generally well tolerated
- ALN-GO1 demonstrates dose-dependent and sustained pharmacodynamic activity, with the expected effect of increasing plasma and urine glycolate levels in healthy volunteers
- A starting regimen for the investigation of PH1 patients will be 1.0 mg/kg q28 days, where the increased glycolate levels observed in healthy volunteers is expected to translate into a reduction in urinary oxalate excretion in patients

Acknowledgements

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