A Randomized, Single-Blind, Placebo-Controlled, Phase 1/2 Study of ALN-AAT, an Investigational RNAi Therapeutic for the Treatment of Alpha-1 Antitrypsin Deficiency Associated Liver Disease: Interim Study Results

12th Annual Meeting of the Oligonucleotide Therapeutics Society (OTS)
28 September 2016

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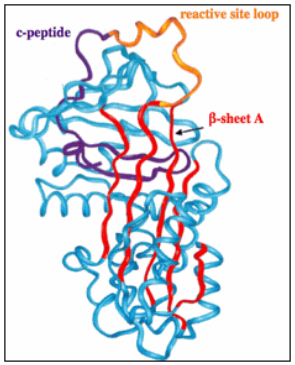
Alpha 1 Antitrypsin (AAT) Deficiency
Background



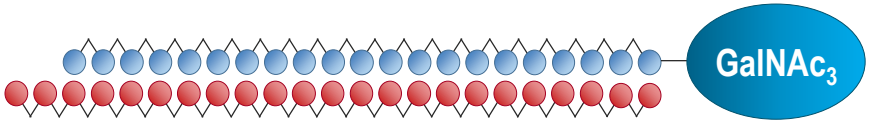
AAT is a serine proteinase inhibitor (serpin)
- Inhibits neutrophil elastase, trypsin, thrombin, chymotrypsin, etc
- Abundant plasma protein , primarily synthesized in hepatocytes

AAT deficiency
- “PiZZ” phenotype accounts for 95% of AAT-deficient patient population
- Z allele likely arose in N Europe, present in up to 5% of the population
- Z allele has point mutation Glu342Lys
- Autosomal codominant inheritance of disease

- PiZ has slow rate of protein folding, permitting polymerization of intermediate which accumulates in hepatocyte ER
- Failure of secretion results in peripheral deficiency
  - Lack of protease inhibition primarily manifests as lung disease: early onset emphysema
- Hepatocyte accumulation results in liver disease
  - Infantile cholestatic hepatitis - usually self-limiting, but progressive liver disease in minority
  - Progressive liver fibrosis
  - Cirrhosis
  - Hepatocellular carcinoma

ALN-AAT

Therapeutic Hypothesis



ALN-AAT

Z-AAT mRNA expression in hepatocytes

Reduced Z-AAT polymers in hepatocytes

Reduced hepatocyte damage

Decrease in liver fibrosis and HCC

Suppression of hepatocyte Z-AAT protein production permits clearance of the accumulated abnormal protein from the liver, permitting stabilization and potentially reversal of liver disease

ALN-AAT Phase 1/2 Study Design

Part A: Single-Ascending Dose (SAD) | Randomized 3:1, Single-blind, Placebo-controlled

- 0.1 mg/kg x 1 SC, N=4
- 0.3 mg/kg x 1 SC, N=4
- 1.0 mg/kg x 1 SC, N=4
- 3.0 mg/kg x 1 SC, N=4
- 6.0 mg/kg x 1 SC, N=4

Healthy adult volunteers
Outcome evaluations: Safety and Pharmacodynamic Response (reduction in plasma AAT level)

Part B: Multiple-Ascending Dose (MAD) | Randomized 4:2, Single-blind, Placebo-controlled

- 1.0 mg/kg, q28d ×4 SC, N=6

Healthy adult volunteers
Outcome evaluations: Safety and Pharmacodynamic Response (reduction in plasma AAT level)

Clinicaltrials.gov identifierNCT02503683

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ALN-AAT Phase 1/2 Interim Study Results

Demographics: Part A + B (Healthy Volunteers)

Demographic	Results
Number enrolled	N=26 (ALN-AAT:Placebo = 19:7)
Median Age	28 years (range: 18 - 60)
Gender, n	Female: 13 Males: 13
Race, n	White / Caucasian: 13 African: 5 Asian: 3 Other: 5

ALN-AAT Phase 1/2 Interim Study Results
Summary of Safety

ALN-AAT was generally well-tolerated in Parts A and B of Study ALN-AAT-001

No drug-related serious adverse events (SAEs) or discontinuations due to adverse events (AEs)

Part A: Total of 57 AEs reported in 5 placebo and 14 ALN-AAT subjects

- 15 related or possibly related AEs were reported in 7 subjects
  - Diarrhea, dyspnea (normal spirometry), nasopharyngitis, elevated ALT/AST, elevated CK, influenza, worsening allergy, headache, injection site bruise, injection site dysesthesia, abdominal pain
- No injection site reactions were reported

Part B: Total of 23 AEs reported in 2 placebo and 4 ALN-AAT subjects

- 6 related or possibly related AEs were reported in 2 subjects*
  - Nasopharyngitis, headache, injection site bruise, oropharyngeal pain, psoriasis, subacute spongiotic dermatitis
- No injection site reactions were reported

No clinically significant changes in vital signs or EKG

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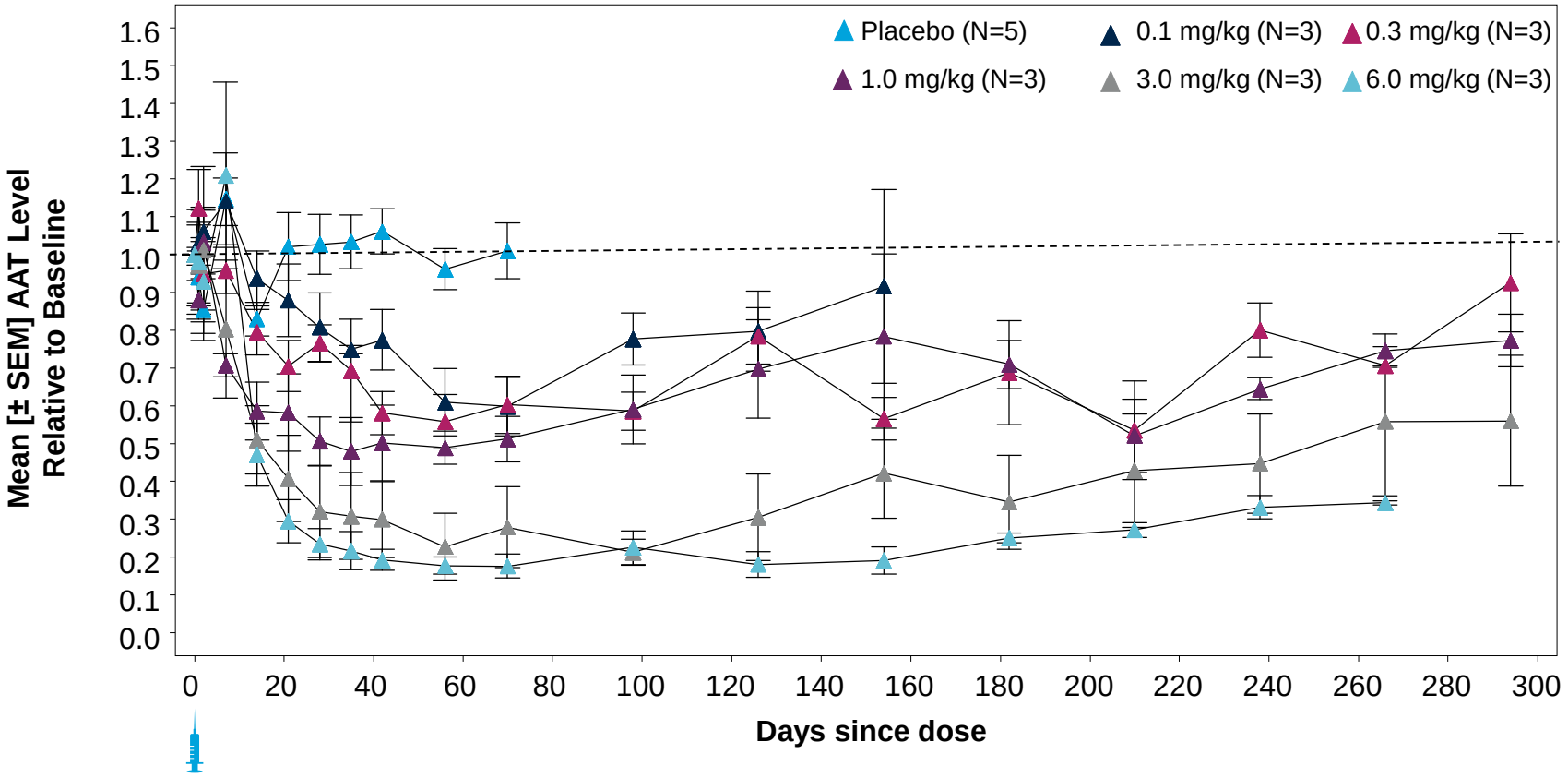
*One AE of ligament sprain with missing relatedness assessment is not included in this count

ALN-AAT Phase 1/2 Interim Study Results

Pharmacodynamics: Serum AAT Levels, Part A (Single Dose)



6.0 mg/kg dose group -

- Max AAT knockdown (KD): 88.9%
- Mean maximal KD: 83.9 ± 2.6%
- Mean AAT KD at ~6 months: 75.0 ±1.2%

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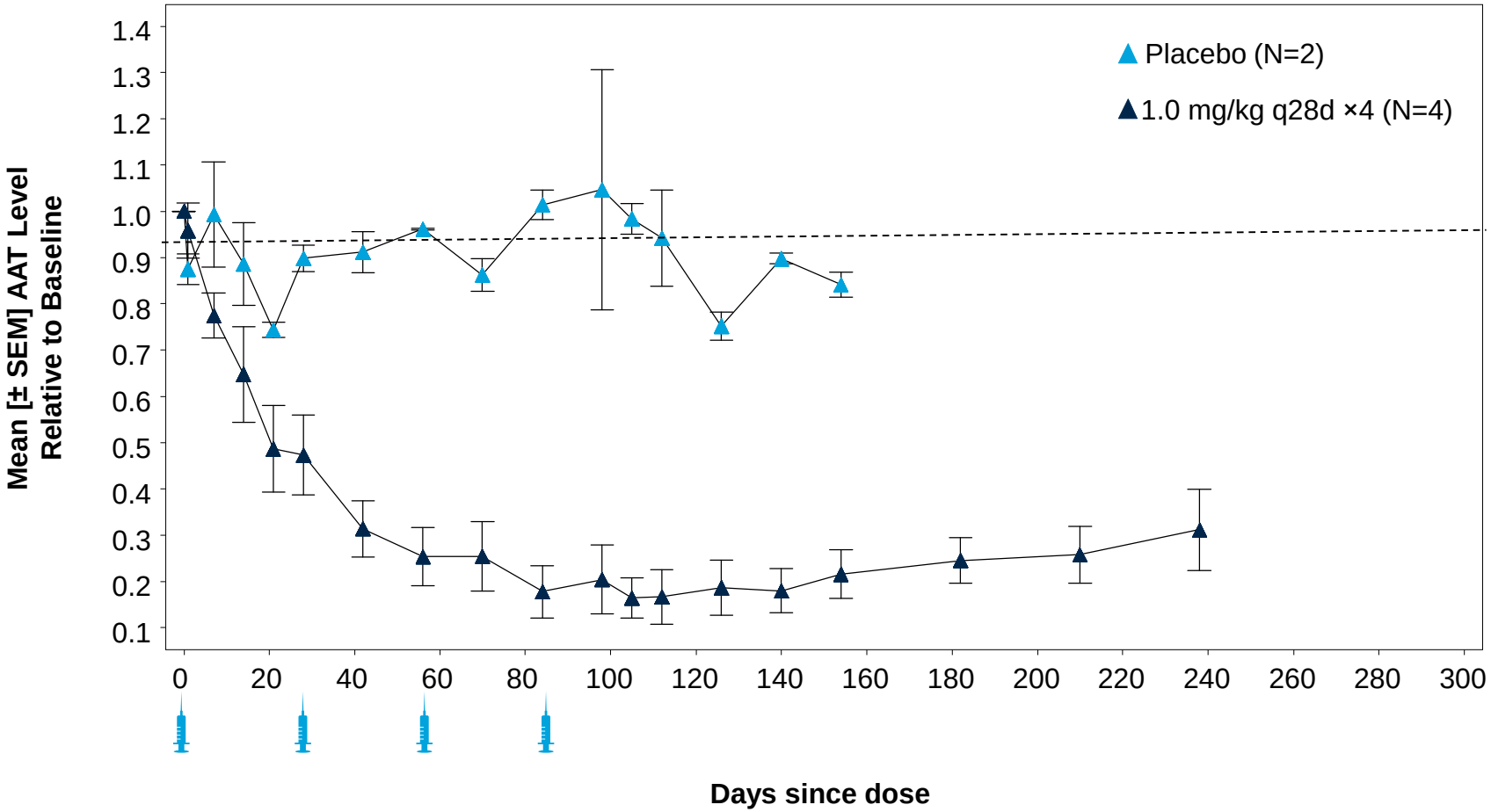
ALN-AAT Phase 1/2 Interim Study Results

Pharmacodynamics: Serum AAT Levels, Part B (Multiple Doses)



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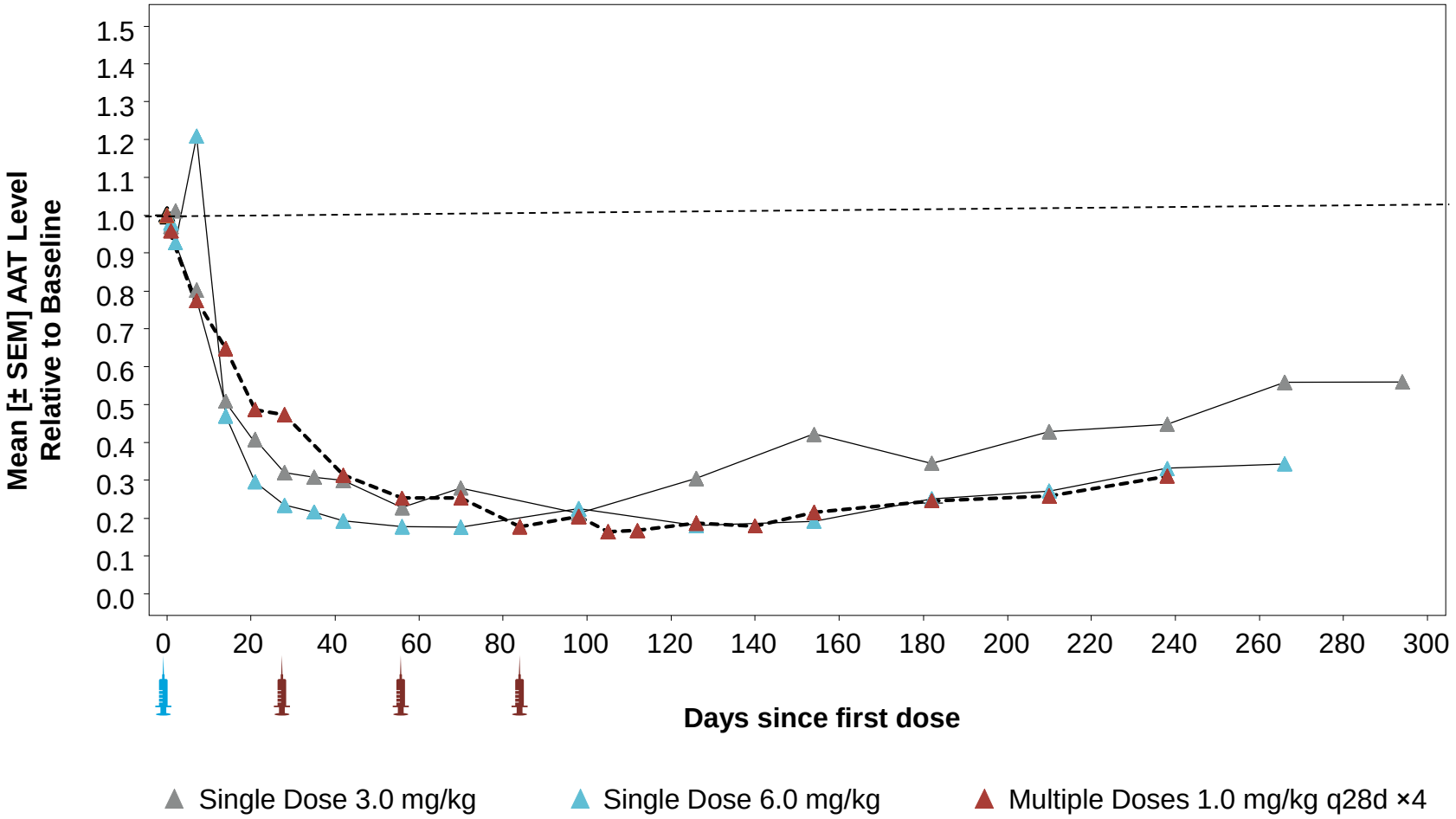
ALN-AAT Phase 1/2 Interim Study Results

Pharmacodynamics: Serum AAT Levels, Part A + B

AAT Knockdown at 1mg/kg multidose comparable to 3 and 6 mg/kg single doses



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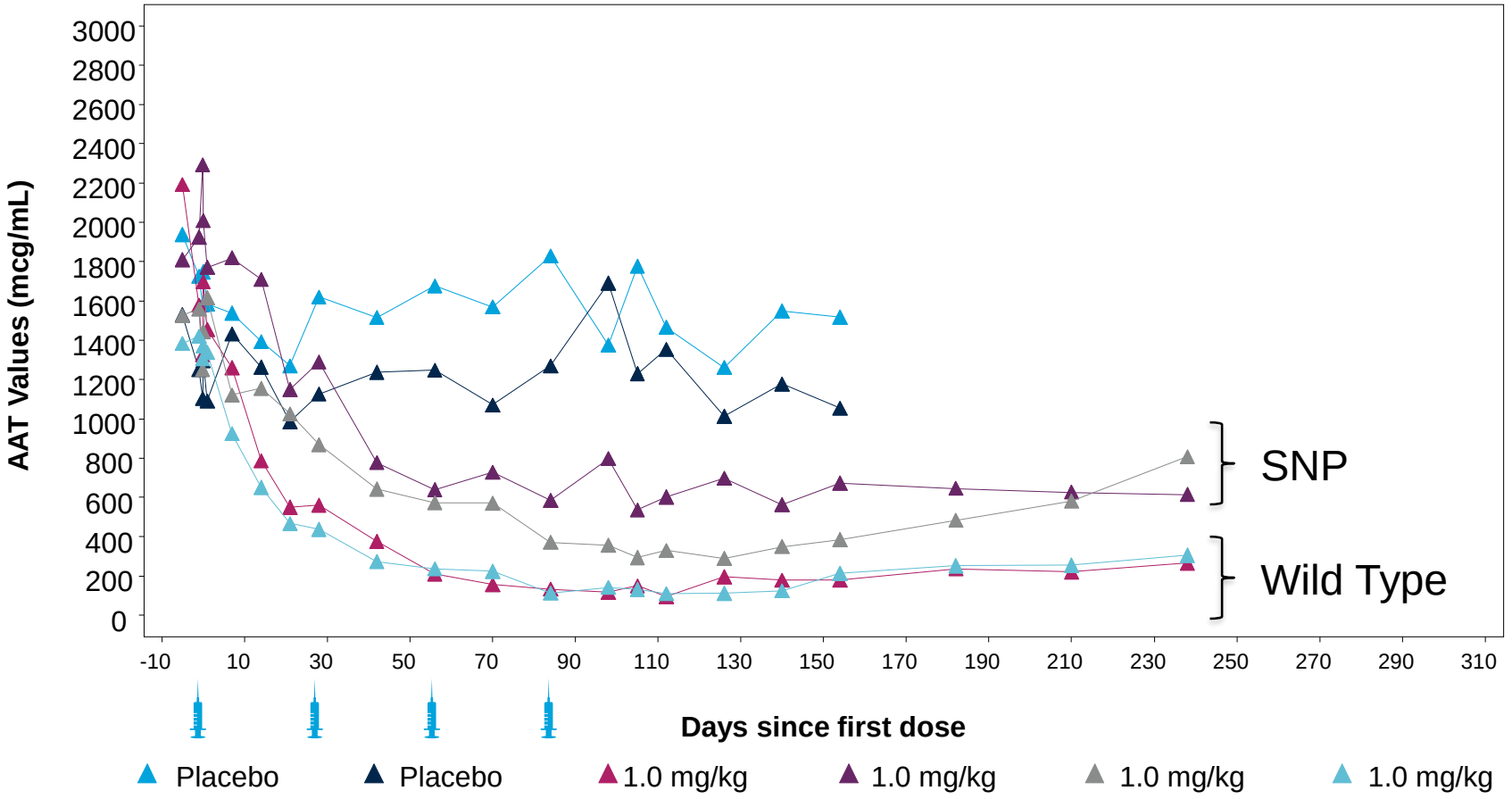
ALN-AAT Phase 1/2 Interim Study Results

Pharmacodynamics: Dichotomous Pattern Explained by Target SNP

SNP confers a single base mismatch between drug and target

Prevalence up to 30% in some populations

SNP is not co-inherited with Z allele



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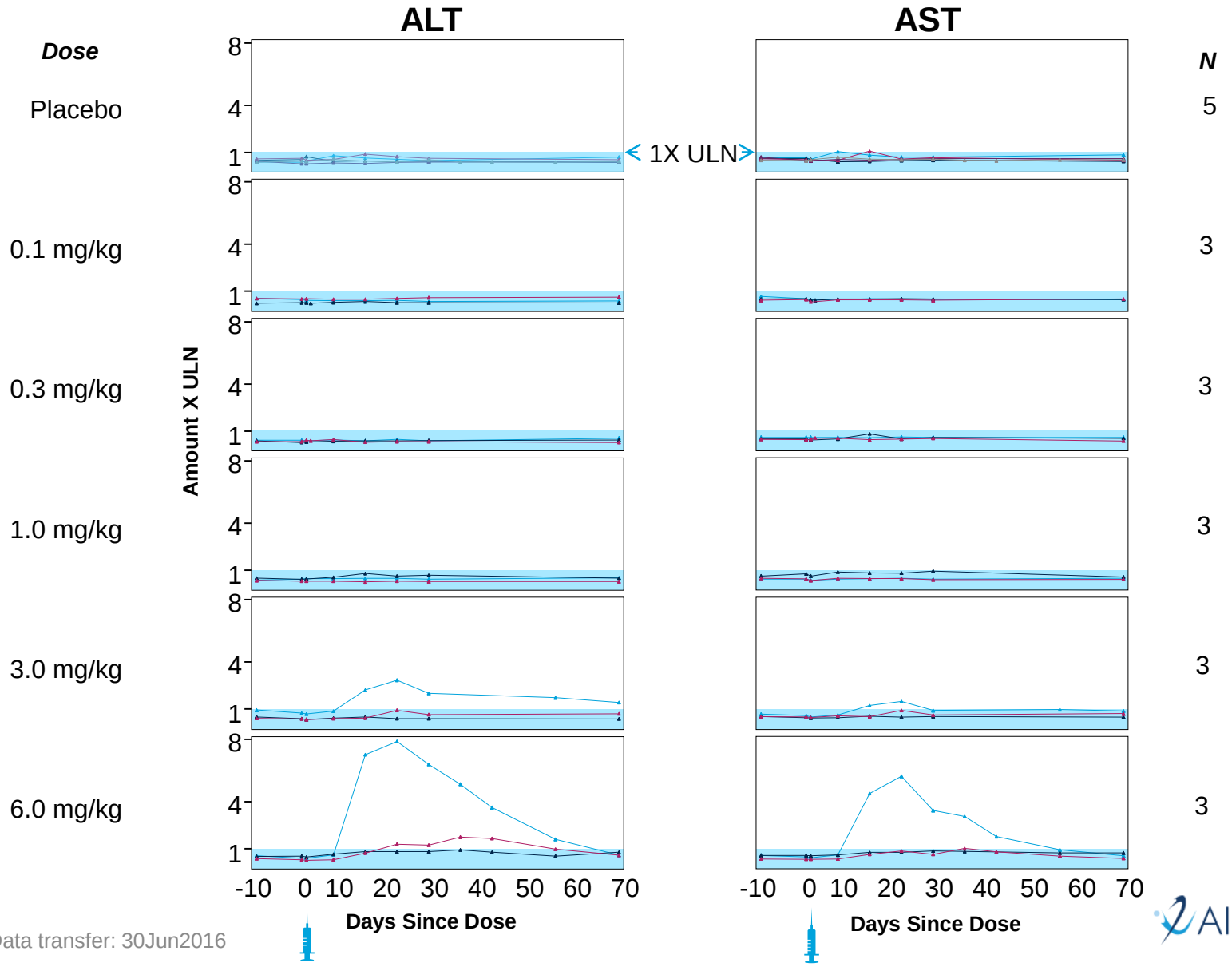
ALN-AAT Phase 1/2 Interim Study Results

Liver Transaminases, Part A



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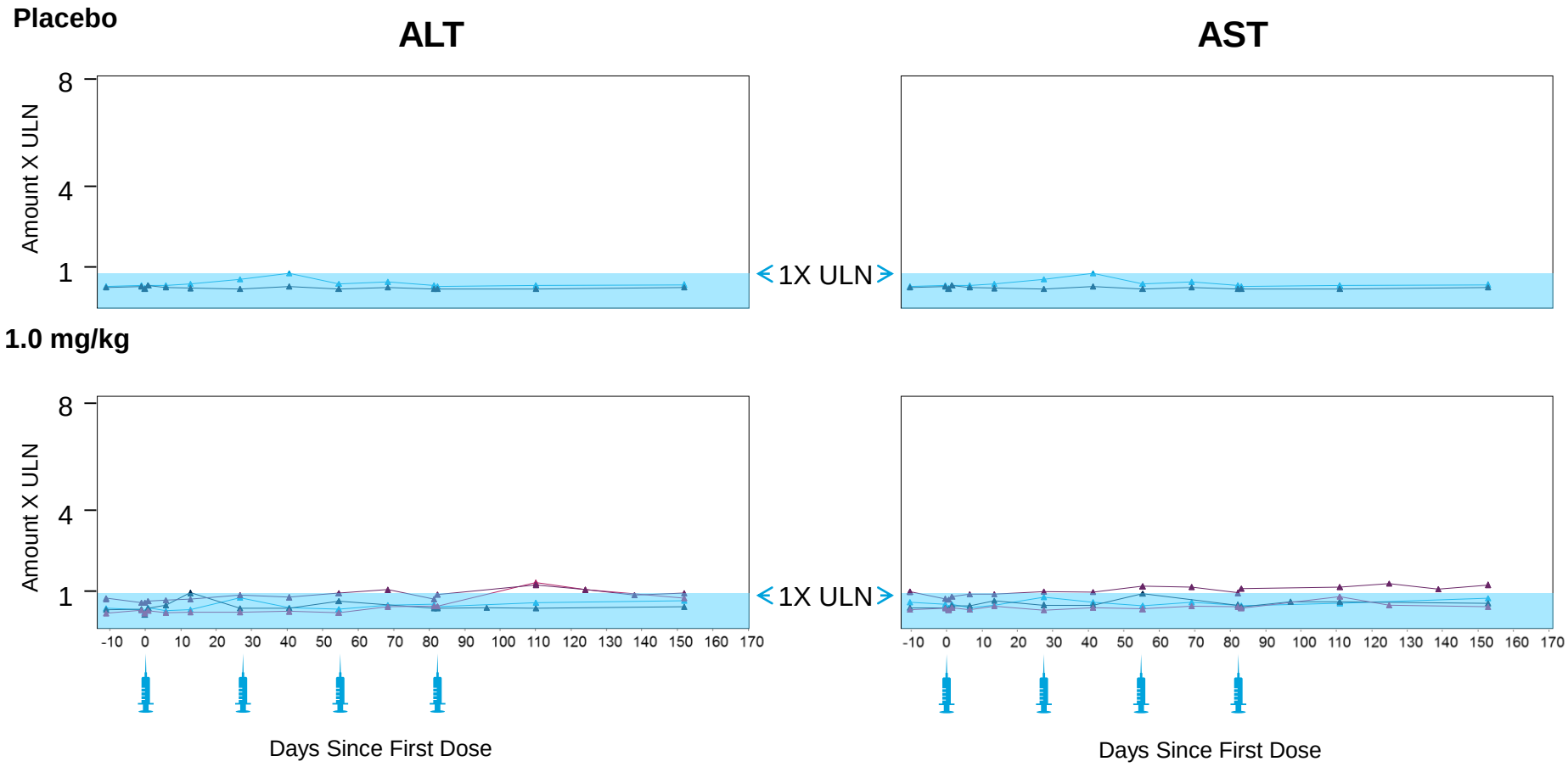
ALN-AAT Phase 1/2 Interim Study Results

Liver Transaminases, Part B



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ALN-AAT Phase 1/2 Interim Study Results
Summary and Next Steps

ALN-AAT clinically well tolerated with single or multiple (4) doses

Dose-dependent , potent and durable suppression of AAT was observed

Diminution of PD effect in presence of SNP in target sequence demonstrates specificity of drug mechanism

Asymptomatic, reversible, dose-dependent increase in hepatic transaminase observed

Next Steps

- Since the target patient population has established liver disease, plan to hold further development of this molecule
- Identification of a 2nd generation molecule is in progress, CTA expected in 2017

Thank you

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