A Randomized, Placebo Controlled, Phase 1 Study of ALN-AS1, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias

Interim presentation of Safety and Pharmacodynamic Results

SSIEM Annual Symposium 07 September 2016

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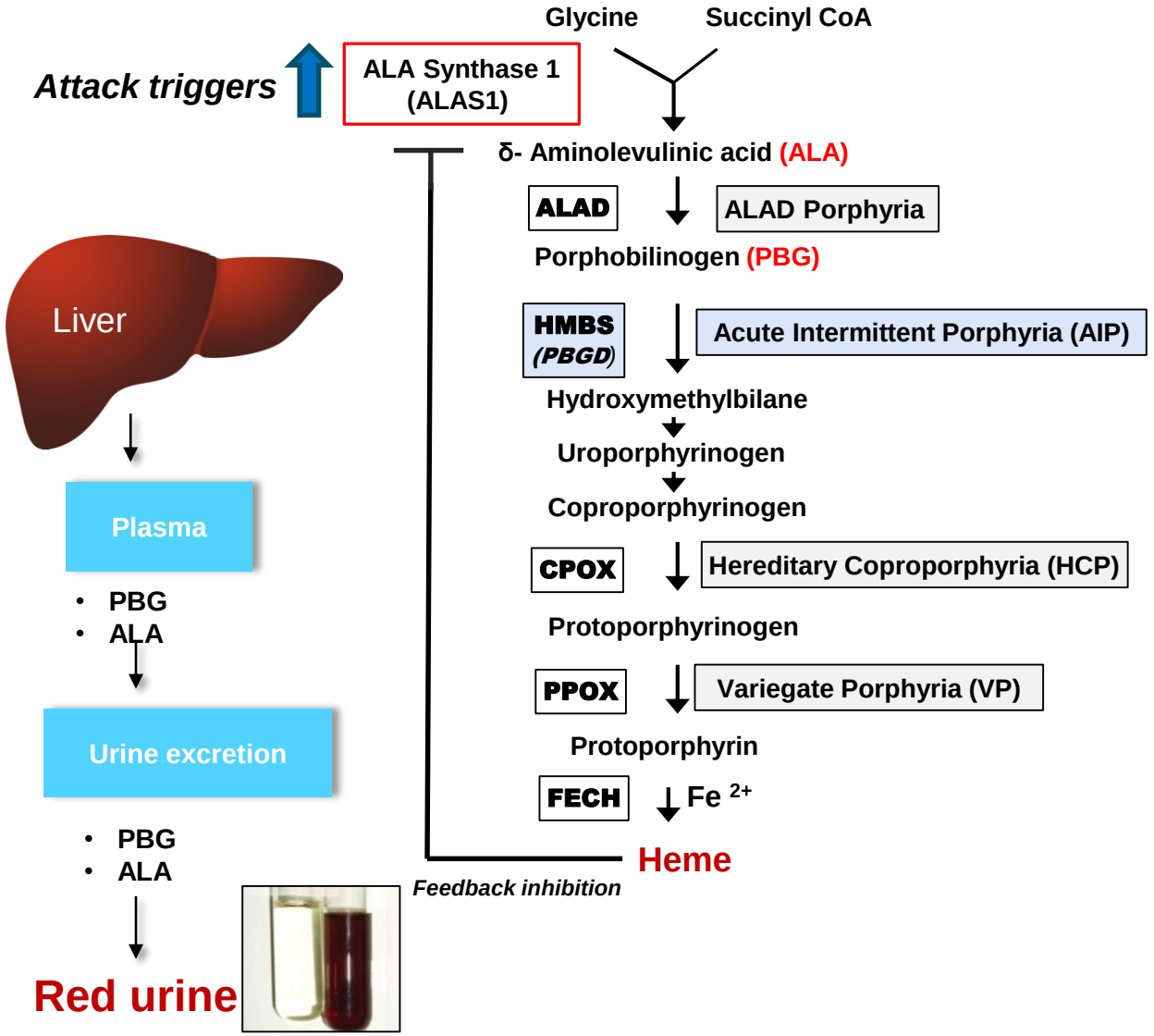
Acute Hepatic Porphyrias Pathophysiology



Acute Hepatic Porphyrias (AHP)

Inborn errors of heme synthesis resulting from enzyme defects in the liver

- **Acute Intermittent Porphyria (AIP)**
  - Most common AHP: prevalence 2-5 per 100,000, ~5-10% with manifest disease
  - Autosomal dominant mutation in the HMBS (PBGD) *gene* : 50% of activity
- **Disease Pathophysiology**
  - ALA synthase (ALAS1) is induced, leading to accumulation of toxic heme intermediates ALA and PBG that cause nerve damage and acute attacks
- **Affecting**
  - Central Nervous System (seizures, PRES)
  - Autonomous Nervous System (abdominal pain, hypertension, tachycardia)
  - Peripheral Nervous System (muscle weakness, paralysis)
- **Treatment**
  - Human hemin

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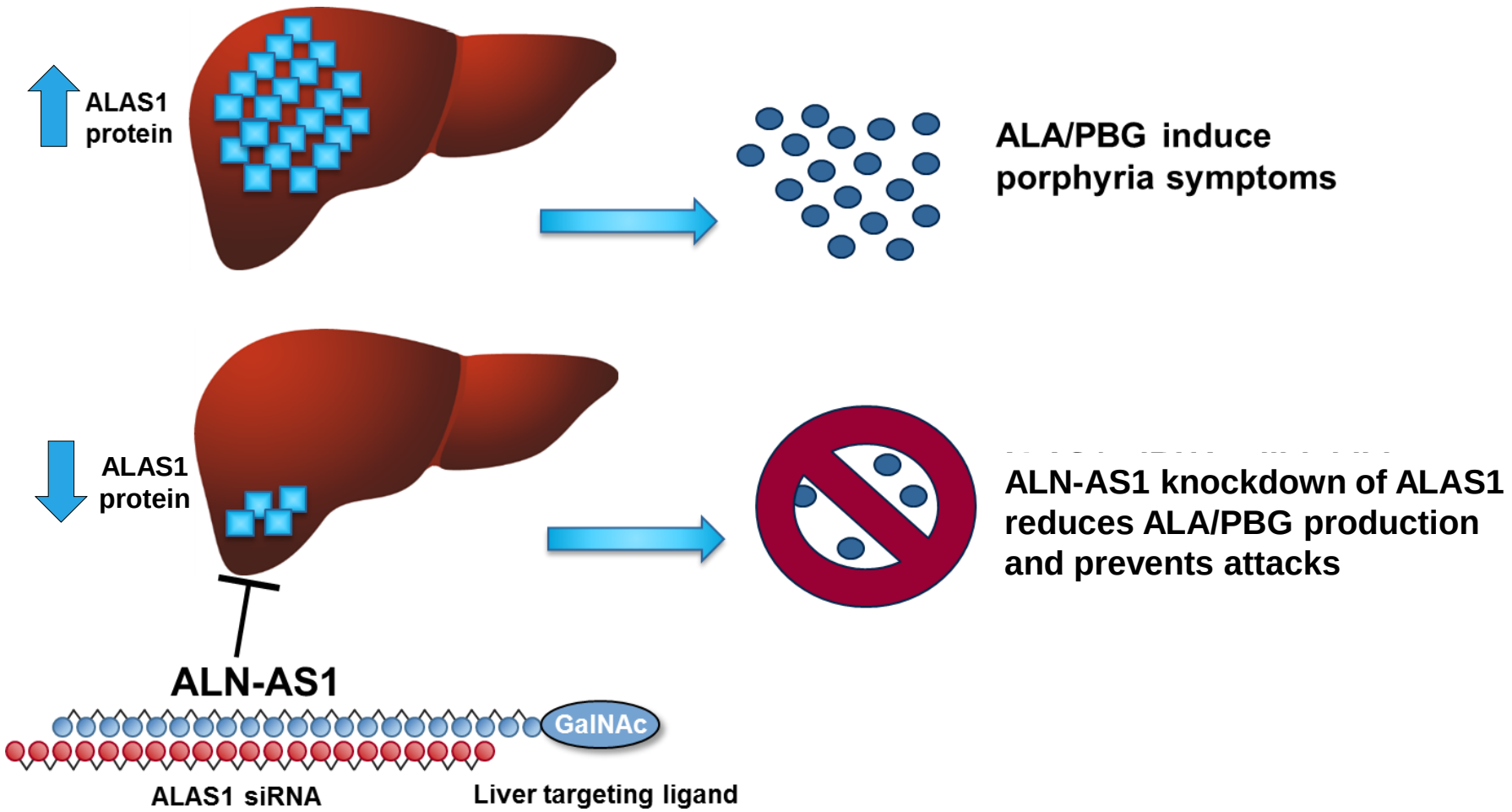
ALN-AS1: RNAi Therapeutic Hypothesis

Knockdown of Liver ALAS1 Protein to Reduce ALA/PBG



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ALN-AS1 Phase 1 Study: AIP patient populations

Asymptomatic High Excreters (ASHE)

- Persistently elevated ALA/PBG
- More clinically relevant than healthy volunteers
- Ability to measure key biomarkers
- Medically stable patient population for initial safety evaluation (studied in prior enzyme replacement trial)

Recurrent attack patients

- Highest unmet medical need
- Evaluate safety and dose regimen in small subset of patients

Sardh et al. Clin Pharmacokinet;46(4):335-49.

ALN-AS1 Phase 1 Study: Design and Objectives

Parts A and B (SAD/MAD) in ASHE patients

Study Design

- Randomized, single-blind, placebo-controlled **single and multiple ascending dose** study in ASHE patients

Primary Objective

- Safety and tolerability of ALN-AS1

Secondary Objectives

- Characterize ALN-AS1 pharmacokinetics (PK) and pharmacodynamics (PD), i.e. ALA and PBG lowering

Exploratory Objectives

- Characterize circulating ALAS1 mRNA from the liver in urine and serum using a circulating RNA detection (cERD) assay

Part C (MD) in recurrent attack patients

Study Design

- Placebo-controlled **multiple dose study** in recurrent attacks patients

Primary Objective

- Safety and tolerability of ALN-AS1

Secondary Objectives

- Characterize ALN-AS1 PK and PD

Exploratory Objectives

- Clinical activity of ALN-AS1 on attack characteristics and treatment, and patient quality of life
- Characterize circulating ALAS1 mRNA from the liver in urine and serum

ALN-AS1 Phase 1 Study: Key Eligibility Criteria

Part A and B Inclusion

- Male or female, ages 18-65 years
- Acute intermittent porphyria (AIP), with genetic diagnosis of HMBS mutation
- Urine PBG > 4 mmol/mol creatinine at screening

Part A and B Exclusion

- Attack* within 6 months of screening
- Heme use in past 6 months
- Subjects with new prescription medication regimen within 3 months of screen

Part C Only Inclusion

- Experienced at least 2 porphyria attacks in past 6 months or on heme prophylaxis to prevent attacks
- If on heme prophylaxis, willing to stop during study

*Attack definition: intense abdominal or back pain requiring hospitalization, heme use or treatment consisting of increased carbohydrate intake or pain medication

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ALN-AS1 Phase 1 Study Progress

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

- 0.035 mg/kg x 1 SC, N=4 ✓
- 0.10 mg/kg x 1 SC, N=4 ✓
- 0.35 mg/kg x 1 SC, N=4 ✓
- 1.0 mg/kg x 1 SC, N=4 ✓
- 2.5 mg/kg x 1 SC, N=4 ✓

*The 0.035 mg/kg SAD cohort was dosed after the 0.10 and 0.35 mg/kg cohorts

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

- 0.35 mg/kg, qMx2 SC, N=4 ✓
- 1.0mg/kg, qMx2 SC, N=4 ✓

Part C: Multiple-Dose (MD) | Randomized 3:1, Double-blind, Placebo-controlled in AIP patients with recurrent attacks

Run-in Observation (1 to 6 months)

- Cohort 1 N=4
- Cohort 2 N=4
- Cohort 3 N=4

ongoing

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ALN-AS1 Phase 1 Study Part A and Part B

Demographics and Baseline Disease Characteristics

Part A and B	
Characteristic	**Result**
Number of Patients	N=23* (ALN-AS1:Placebo=21:7)
Median Age (range)	47 years (30-64)
Gender	18 Females, 5 Males
Race n	22 White/Caucasian 1 Asian
Genotype (n)	8 different mutations identified**: • HMBS_593G>A (13) • HMBS_87+1G>A (4) • HMBS_499-1G>A (1) • HMBS_517C>T (1) • HMBS_647G>A (1) • HMBS_847_848delTG (1) • 673C>T variant exon 11(1) • Exon 3 shift IVS3+1G>T(1)
Mean baseline ALA (range)	11.0 mmol/mol Cr (2.9-24.6) ^
Mean baseline PBG (range)	22.0 mmol/mol Cr (4.5-50.5) ^

**5 subjects had >1 treatment assignment: 2 subjects repeated Part A; 3 subjects enrolled in Part A and Part B*

** 3 mutations added to database post data cut and W198X collapsed into HMBS_593G>A

^Upper Limit of Normal: ALA <3.9 or 3.8 mmol/mol Cr; PBG < 1.6 or 1.5 mmol/mol Cr depending on site

Biorad assay performed at Porphyria Centers in Sweden and UK

Data in database as of 28 Jun 2016

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ALN-AS1 Phase 1 Study Interim Results
Part A (SAD) and Part B (MAD) Safety and Tolerability

ALN-AS1 was generally well-tolerated in Parts A and B of Study ALN-AS1-001

No drug-related SAEs or discontinuations due to AEs

- Two SAD subjects (0.035 and 0.10 mg/kg dose groups) were hospitalized for SAE of “abdominal pain”. Both events were assessed as unlikely related to ALN-AS1 by the investigators
- One MAD* subject (1 mg/kg dose group) experienced a miscarriage 7 weeks post-conception (90 days post-ALN-AS1) during the extended follow-up period which was assessed as unlikely related by the investigator

SAD: Total of 49 AEs reported (10 AEs in 5 PBO subjects; 39 AEs in 11 ALN-AS1 subjects)

- All AEs were mild or moderate in severity with the exception of one severe AE of abdominal pain (same subject noted above with SAE at 0.10 mg/kg dose).
- AEs reported in ≥2 subjects were abdominal pain, diarrhea, and hypoesthesia
- 8 related or possibly related AEs were reported in 5 subjects
  - Diarrhea, dyspepsia, hematochezia, hypoesthesia, injection site erythema, injection site pain, decreased GFR and elevated Cr
- Injection site reactions (erythema and pain) were seen in 2 subjects–both mild and transient

MAD: Total of 29 AEs reported (4 AEs in 1 PBO subject; 25 AEs in 6 ALN-AS1 subjects)

- All reported AEs were mild or moderate in severity
- AEs reported in ≥2 subjects were nasopharyngitis and rash
- 8 related or possibly related AEs were reported in 3 subjects
  - Pruritus only (1 subject), rash only (1 subject) and pruritus and rash (1 subject)
- No injection site reactions were reported

No clinically significant changes in vital signs, EKG, clinical laboratory or physical examination

**All Safety Data in database as of 28 Jun 2016 with the exception of the MAD SAE which was as of 03 Sept 2016*

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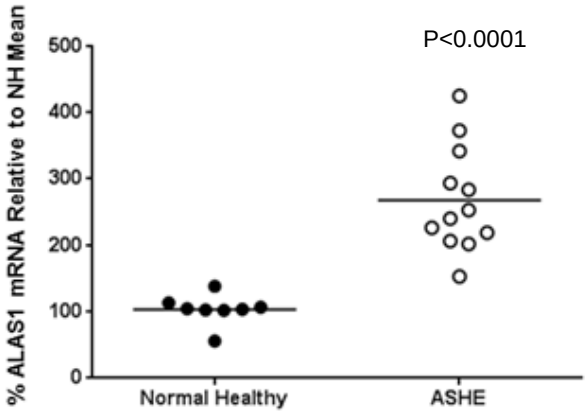
ALN-AS1 Phase 1 Study Interim Results

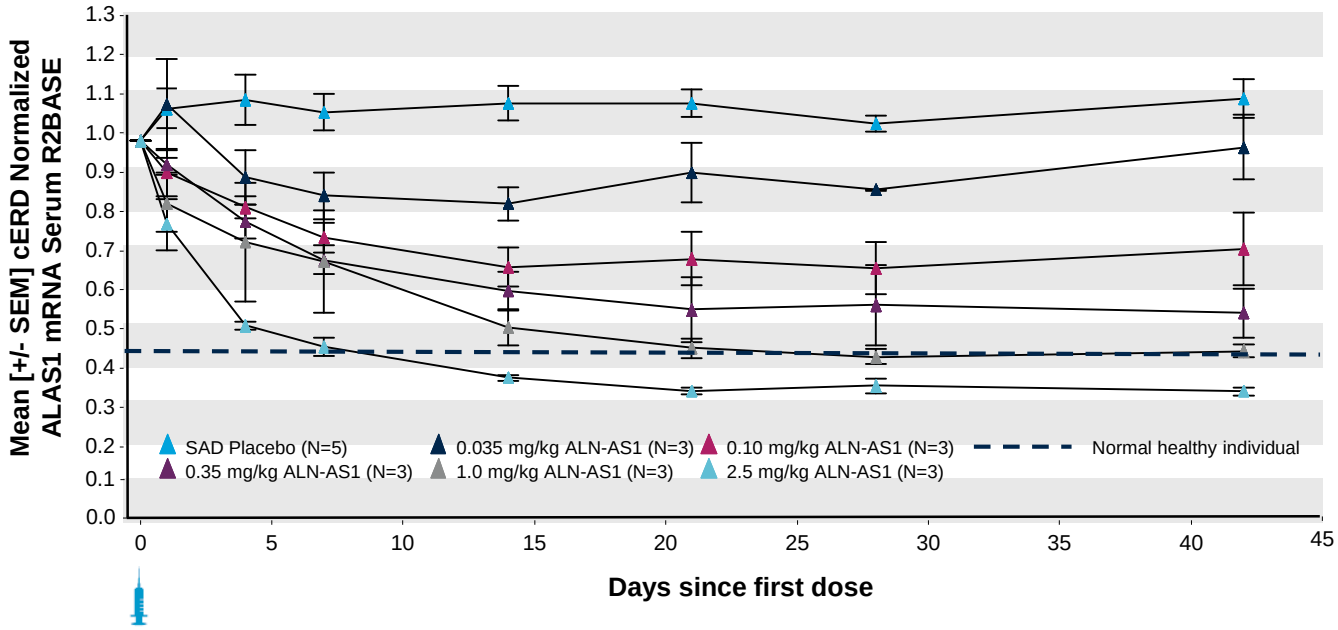
SAD Pharmacodynamic Data: Serum ALAS1 mRNA by cERD

ALAS1 mRNA induced approximately 3-fold in ASHE compared to normal healthy volunteers

Rapid, dose-dependent, and durable ALAS1 mRNA lowering after single dose

- 64 ± 1% mean (SEM) maximal reduction in 2.5 mg/kg dose group
- Remaining ALAS1 mRNA levels after highest dose similar to levels in normal healthy individuals





Data in database as of 28 Jun 2016

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ALN-AS1 Phase 1 Study Interim Results

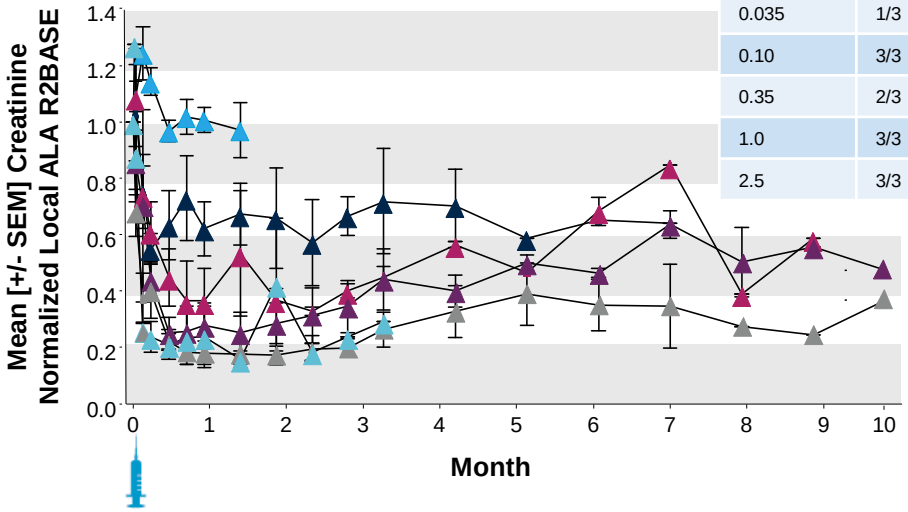
SAD Pharmacodynamic Data: Urinary ALA and PBG

Rapid, dose-dependent, and durable ALA and PBG lowering after single dose

- Mean (SEM) maximal reduction in 2.5 mg/kg group: 86± 2% (ALA) and 95± 0.4% (PBG)
- Prolonged ALA and PBG lowering with single dose supporting monthly or quarterly dosing
- Normalization of ALA/PBG achieved at higher dose levels

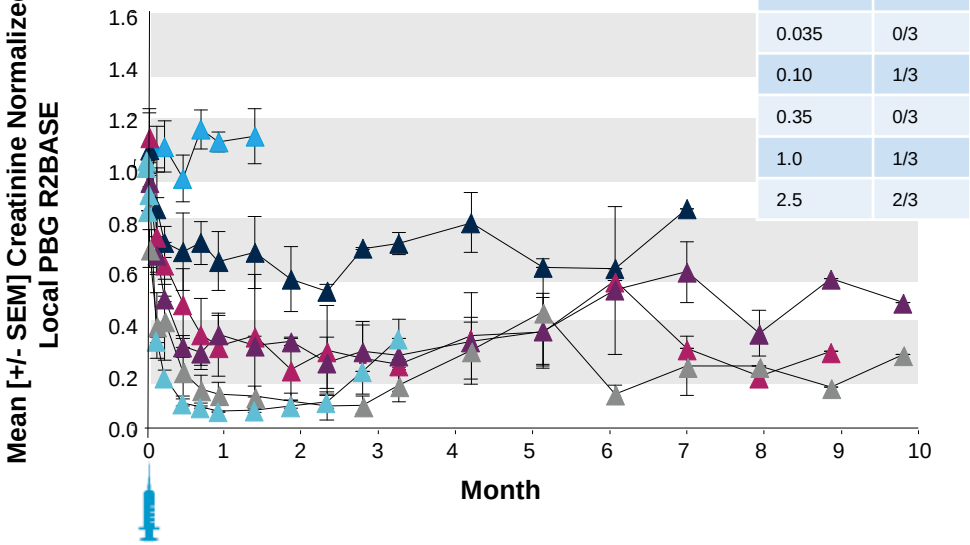
ALA

Dose (mg/kg)	ALA
Placebo	0/5
0.035	1/3
0.10	3/3
0.35	2/3
1.0	3/3
2.5	3/3



PBG

Dose (mg/kg)	PBG
Placebo	0/5
0.035	0/3
0.10	1/3
0.35	0/3
1.0	1/3
2.5	2/3



Excluding subject 201-0002, Day 0: 0-6 hour ALA measurement

SAD Placebo (N=5)
0.035 mg/kg ALN-AS1 (N=3)
0.10 mg/kg ALN-AS1 (N=3)
0.35 mg/kg ALN-AS1 (N=3)
1.0 mg/kg ALN-AS1 (N=3)
2.5 mg/kg ALN-AS1 (N=3)

ALA Assay URL: < 3.9 or 3.8 mmol/mol Cr at sites 101 or 201
PBG Assay URL: < 1.6 or 1.5 mmol/mol Cr at sites 101 or 201

Data in database as of 28 Jun 2016

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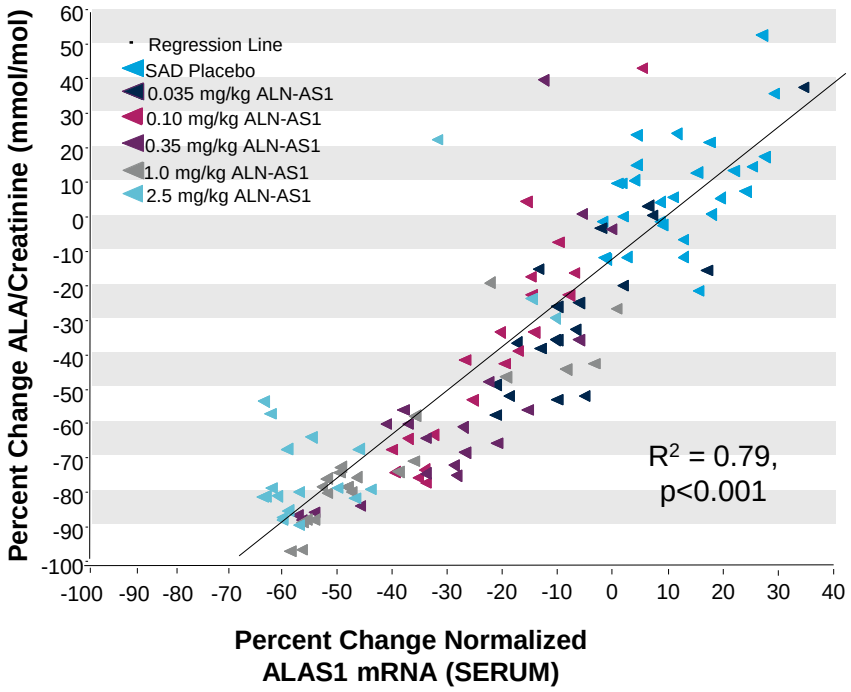
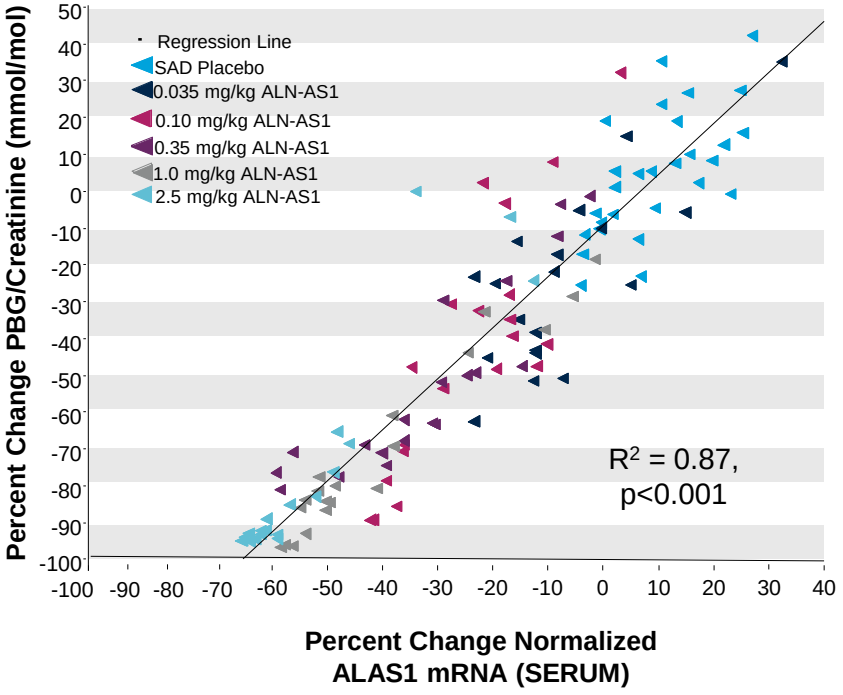
ALN-AS1 Phase 1 Study Interim Results

SAD: Changes in Serum ALAS1 mRNA and Urinary ALA/PBG Highly Correlated

ALAS1 mRNA vs ALA



ALAS1 mRNA vs PBG



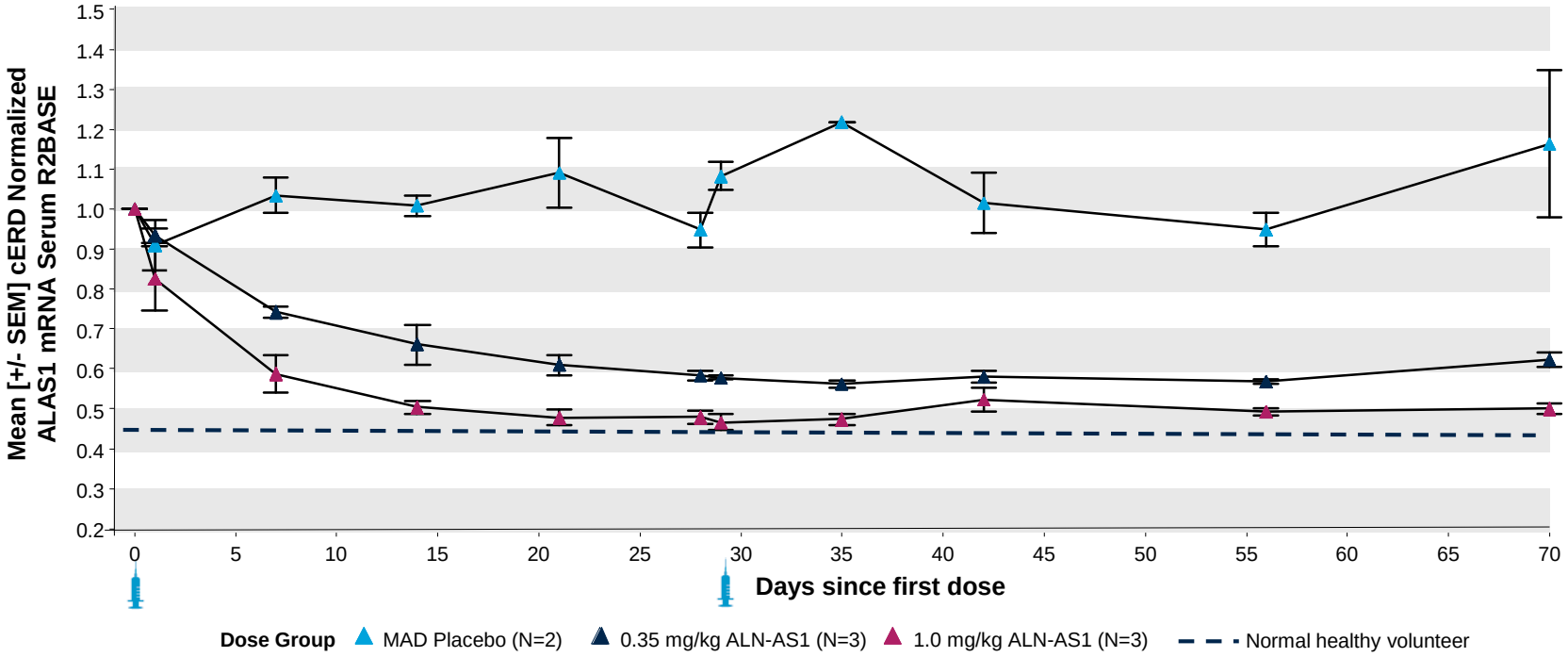
Data in database as of 28 Jun 2016

ALN-AS1 Phase 1 Study Interim Results

MAD Pharmacodynamic Data: Serum ALAS1 mRNA by cERD

Rapid, dose-dependent, and durable ALAS1 mRNA lowering

- 54 ± 2% mean (SEM) maximal reduction relative to baseline in 1.0 mg/kg dose group
- ALAS1 mRNA reduction seen with 2 doses similar to single dose



Data in database as of 28 Jun 2016

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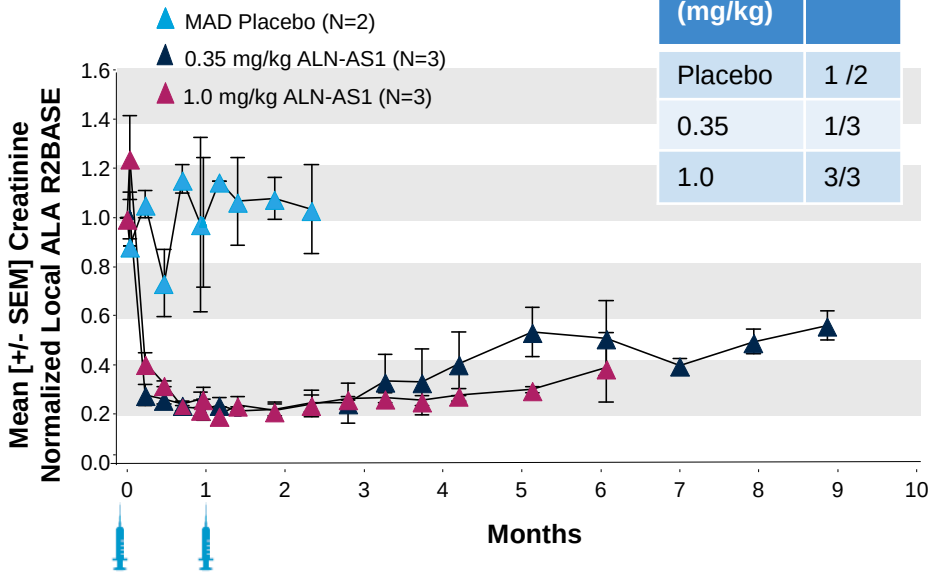
ALN-AS1 Phase 1 Study Interim Results
MAD Pharmacodynamic Data: Urinary ALA and PBG

Rapid, dose-dependent, and durable ALA and PBG lowering after multiple doses

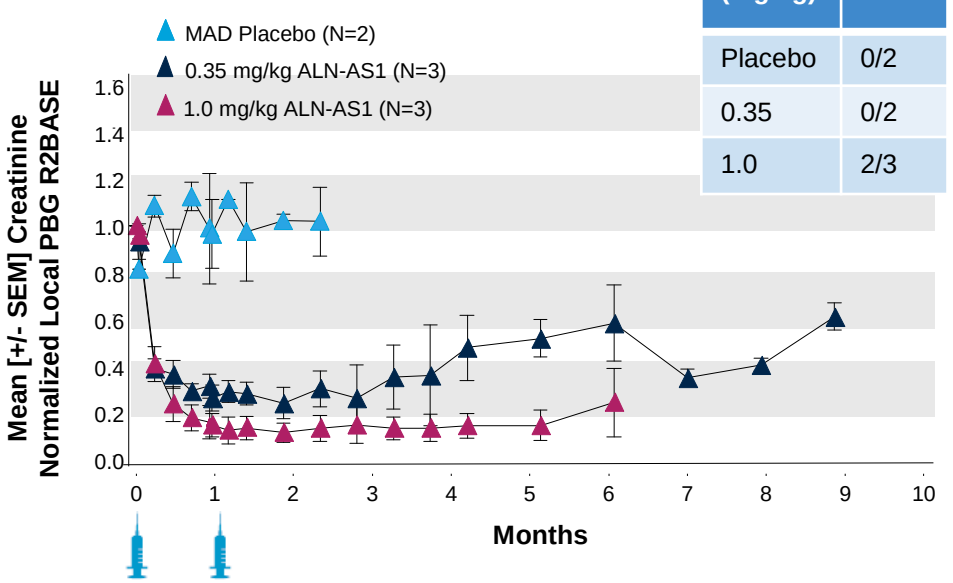
- Mean (SEM) maximal reduction in 1 mg/kg group: 84 ± 2% (ALA) and 89 ± 5% (PBG)
- Multiple doses without additive effect in either dose group
- Normalization of ALA/PBG achieved at higher dose levels

ALA



Dose (mg/kg)	ALA
Placebo	1 /2
0.35	1/3
1.0	3/3

PBG



Dose (mg/kg)	PBG
Placebo	0/2
0.35	0/2
1.0	2/3

Data in database as of 28 Jun 2016

ALA Assay URL: < 3.9 or 3.8 mmol/mol Cr at sites 101 or 201
PBG Assay URL: < 1.6 or 1.5 mmol/mol Cr at sites 101 or 201

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ALN-AS1 Phase 1 Study Initial Results
Summary

ALN-AS1 generally well tolerated with single or multiple (2) doses

- No drug-related SAEs or discontinuations due to AEs
- No dose-dependent AEs or clinically significant changes in vital signs, EKG, clinical laboratory or physical examination

Non-invasive cERD assay to quantify liver ALAS1 mRNA expression demonstrated

- ASHE have 3-fold ALAS1 mRNA induction compared to normal healthy individuals
- Rapid, dose-dependent, and durable ALAS1 mRNA lowering with single and multiple doses of ALN-AS1; highly correlated with changes in ALA and PBG
  - 64% with a single 2.5 mg/kg dose and 54% with multiple 1.0 mg/kg doses

Rapid, dose-dependent, and durable lowering of urinary ALA and PBG with single and multiple doses of ALN-AS1

- 86% and 95%, respectively, with a single 2.5 mg/kg dose
- 84% and 89%, respectively with multiple 1.0 mg/kg doses

Next Steps

- Part A/B, (SAD/MAD) continue to monitor ALA, PBG and ALAS1 recovery
- Part C, MD portion in recurrent attack patients ongoing in Sweden, UK and US

Data in database as of 28 Jun 2016

Acknowledgements

Phase 1 Investigators

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The AIP patients who participated In this Phase 1 Study