Phase 1/2 and Open Label Extension Studies of Givosiran, an Investigational RNA Interference (RNAi) Therapeutic, in Patients with Acute Intermittent Porphyria

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Disease Overview

Acute Hepatic Porphyrias (AHPs)[1,2]

- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis
- Acute Intermittent Porphyria (AIP) most common, with a mutation in hydroxymethylbilane synthase (HMBS)

Disease Pathophysiology

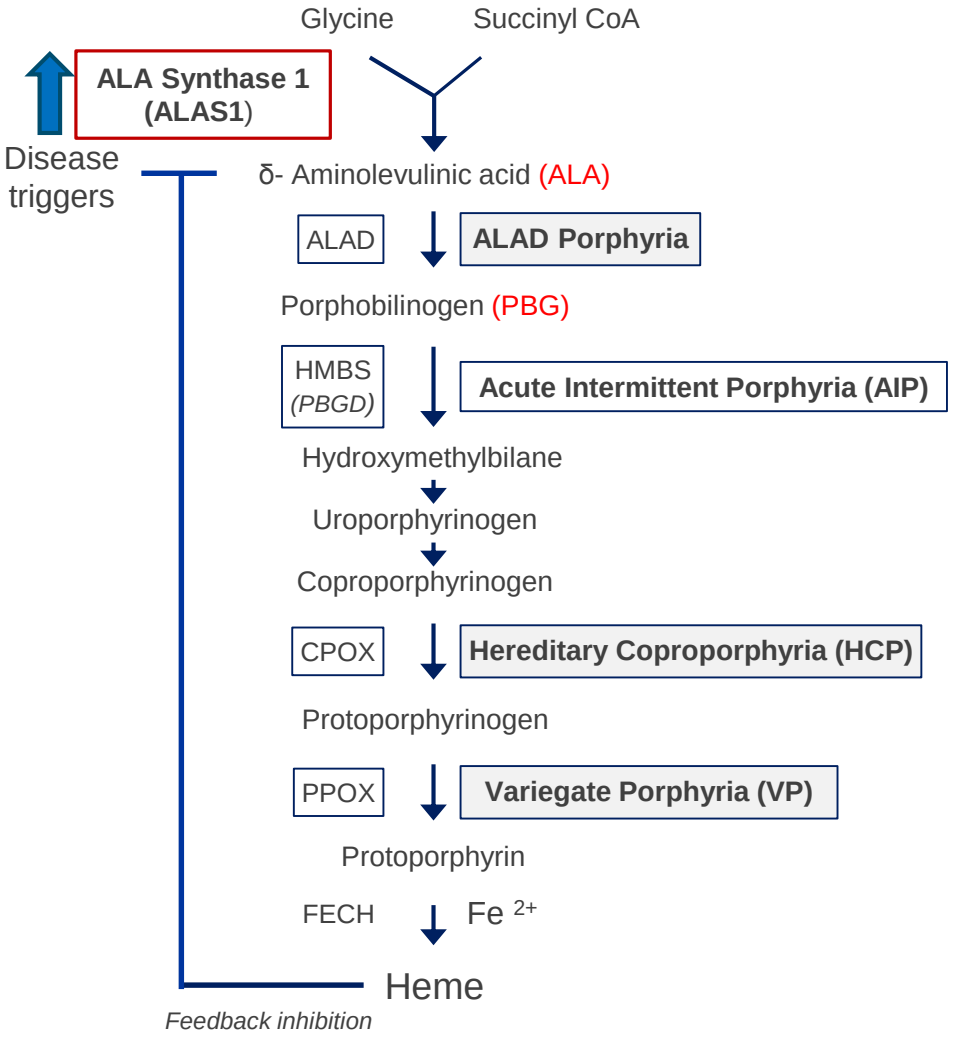
- Induction of ALAS1 leads to accumulation of neurotoxic heme intermediates ALA/PBG
- ALA believed to be primary neurotoxic intermediate that causes disease manifestations

Attacks and Chronic Manifestations

- Autonomic Nervous System (severe abdominal pain, hypertension)
- Central Nervous System (mental status changes, seizures)
- Peripheral Nervous System (muscle weakness, paralysis)

Treatment and Unmet Need

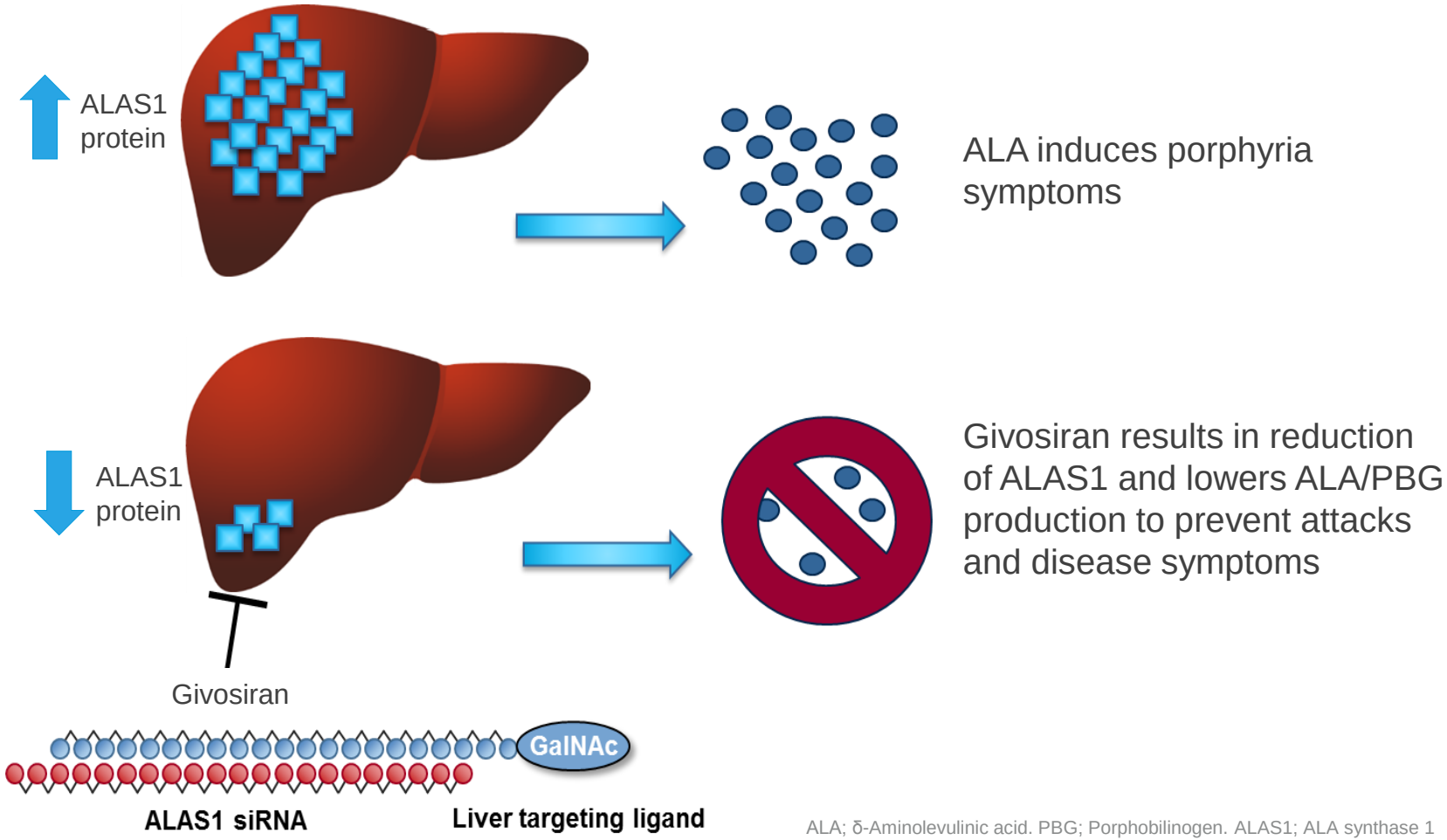
- Glucose and hemin used to treat acute attacks and by some specialists to prevent attacks
- Unmet need for therapies to prevent attacks and improve chronic disease manifestations



1. Bonkovsky, et al., Am J Med. 2014;127:1233-41; 2. Elder, et al., JIMD. 2013;36:849-57

Therapeutic Hypothesis for Givosiran, an Investigational RNAi Therapeutic for AHPs

Reduction of Liver ALAS1 Protein to Lower ALA and PBG

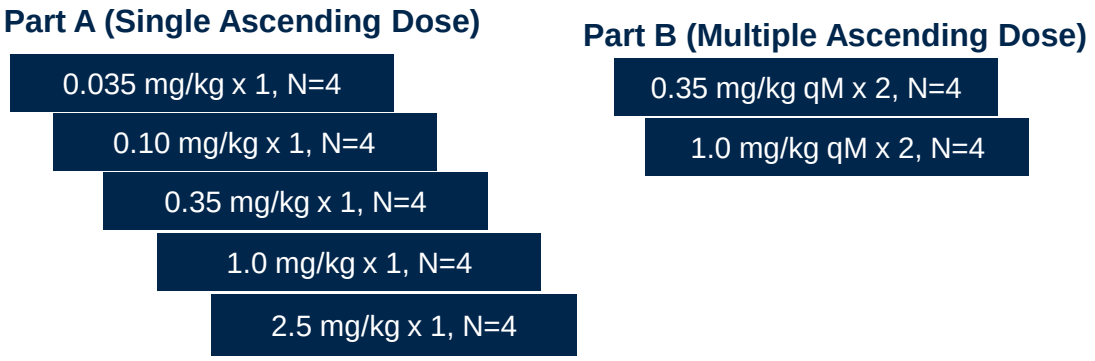


ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. ALAS1; ALA synthase 1

Phase 1 and Open-Label Extension (OLE) Study Design

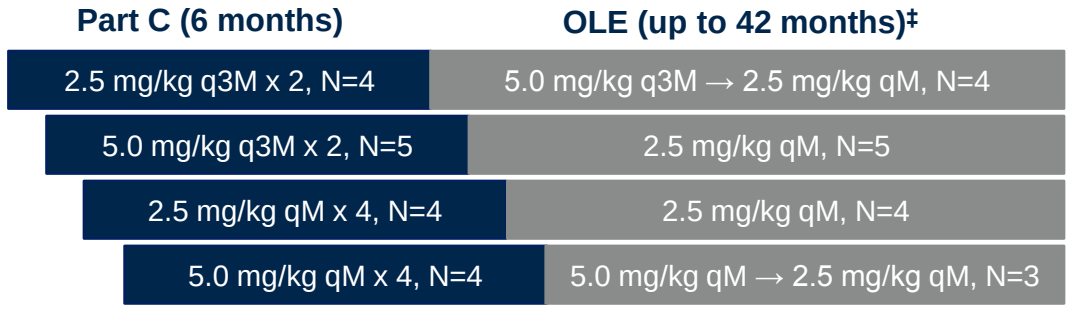
Parts A & B in Chronic High Excreter (CHE) Patients†

- Randomized 3:1 (givosiran:placebo), single blind design
- Genetic confirmation of AIP
- Urine PBG level >4 mmol/mol Cr
- No attacks within 6 months of study drug



Part C and OLE in Recurrent Attack Patients

- Randomized 3:1 (givosiran:placebo), double-blind design
- Genetic confirmation of AIP
- Observational run-in (3 month) without scheduled hemin
- ≥2 attacks in past 6 months OR on prior hemin prophylaxis. One attack in run-in required for randomization
- Patients completing Part C eligible to enroll in OLE



Clinicaltrials.gov: NCT02452372. AIP, Acute Intermittent Porphyria. PBG; Porphobilinogen. Cr; Creatinine. qM; Monthly. q3M; Quarterly.

†2 patients participated twice in Part A and 3 patients participated in both Part A and Part B

‡All patients in OLE transitioned to 2.5 mg/kg qM; Safety Review Committee authorization before all dose escalations

Alnylam PHARMACEUTICALS

Demographics and Baseline Characteristics

Phase 1 Study Results

	Parts A & B	Part C	
	(N=23†)	Placebo (N=4)	Givosiran (N=13)
Age, years, median (range)	47 (30–64)	42 (27–60)	36 (21–59)
Female, n (%)	18 (78)	2 (50)	13 (100)
Weight, kg, mean (SD)	75.9 (15.9)	91.4 (20.8)	70.9 (14.5)
Race, n (%)			
White/Caucasian	22 (96)	4 (100)	10 (77)
Asian	1 (4)	0 (0)	1 (8)
Black/African American	0 (0)	0 (0)	2 (15)
Prior porphyria therapy, n (%)			
Hemin prophylaxis		2 (50)	6 (46)
GnRH analogue use	NA	0 (0)	4 (31)
Chronic opioid use		2 (50)	7 (54)
Porphyria attacks in past 12 months, median (range)	NA	10.0 (5–50)	9.0 (0–36)
ALA, mmol/mol Cr, mean (SEM)‡	10.3 (1.5)	18.7 (5.5)	17.5 (4.0)
PBG, mmol/mol Cr, mean (SEM)‡	23.8 (3.6)	43.8 (4.6)	48.1 (7.1)
ALAS1 mRNA, fold relative to normal, mean (SEM) [1]	2.4 (0.2)	2.8 (0.3)	3.7 (0.3)

†2 patients participated twice in Part A and 3 patients participated in both Part A and Part B
‡Upper Limit of Normal: ALA=1.5 mmol/mol Cr; PBG=0.14 mmol/mol Cr determined based on samples collected from 150 normal healthy subjects analyzed by LC-MS/MS
SD; Standard deviation. GnRH; Gonadotropin-releasing hormone. Cr; Creatinine. ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. SEM; Standard error of mean. ALAS1; ALA synthase 1

1. Chan, et al., Molecular Therapy—Nucleic Acids. 2015;4:e263

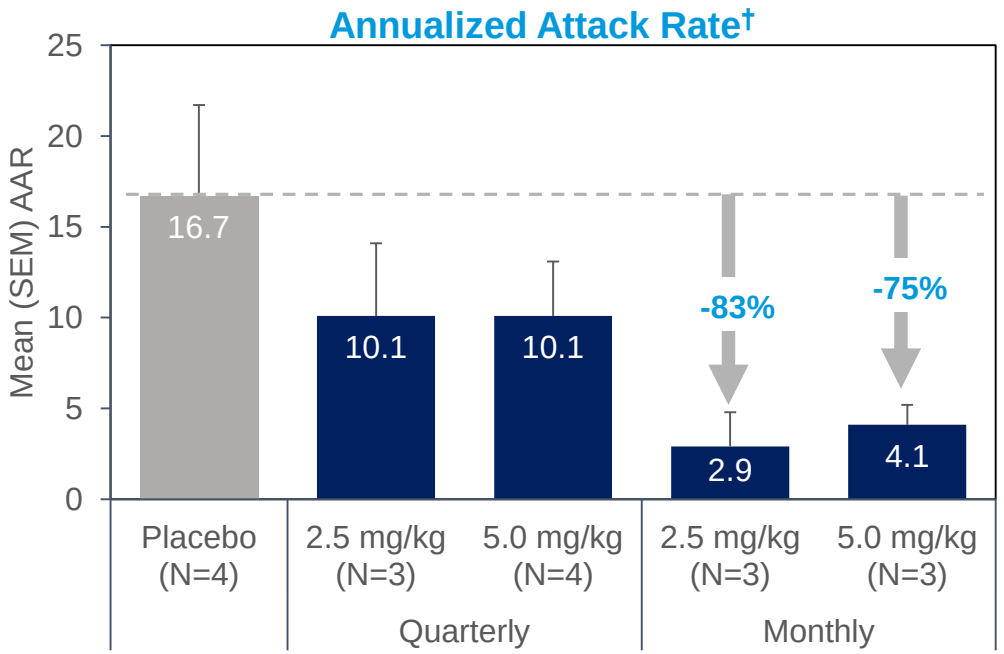
Summary of Phase 1 Study Results*

Clinical Activity and Safety

Clinical Activity in Recurrent Attack Patients (Part C)

Monthly dosing resulted in:

- Approximately 60-70% reduction of induced ALAS1 mRNA
- Robust and sustained lowering of ALA and PBG of >80%
- Mean reductions in AAR up to 83% and annualized hemin use up to 88% relative to placebo



Safety

- 6 patients had SAEs, with none assessed as related to study drug
  - Part A: 2 patients (0.035 and 0.10 mg/kg) had abdominal pain requiring hospitalization
  - Part B: 1 patient (1 mg/kg) had miscarriage 7 weeks post-conception and 90 days post-dose
  - Part C: 3 patients
    - 1 patient (2.5 mg/kg qM) had opioid bowel dysfunction
    - 1 patient (5 mg/kg q3M) had influenza infection
    - 1 patient (5 mg/kg qM) had bacteremia from portacath, associated with auditory hallucinations. Patient subsequently had fatal hemorrhagic pancreatitis, assessed as unlikely related to study drug due to presence of gallbladder sludge (previously reported)
- No other discontinuations due to AEs or other clinically significant changes in EKG, clinical laboratory or physical examination
- Review of AEs reveals no clear relationship to dose

*Sardh *et al*. EASL Meeting, Apr 2018
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home

Phase 1/2 Open Label Extension (OLE) Study Patient Overview

- All eligible patients from Phase 1 Part C enrolled into OLE
- Mean time in OLE of 13.6 months (median 14.3 months)
- Max time in OLE of 19 months, with max of 25 months of total treatment in Phase 1 and OLE

Data as of 7Jun2018

Safety and Tolerability

Interim Phase 1/2 OLE Study Results

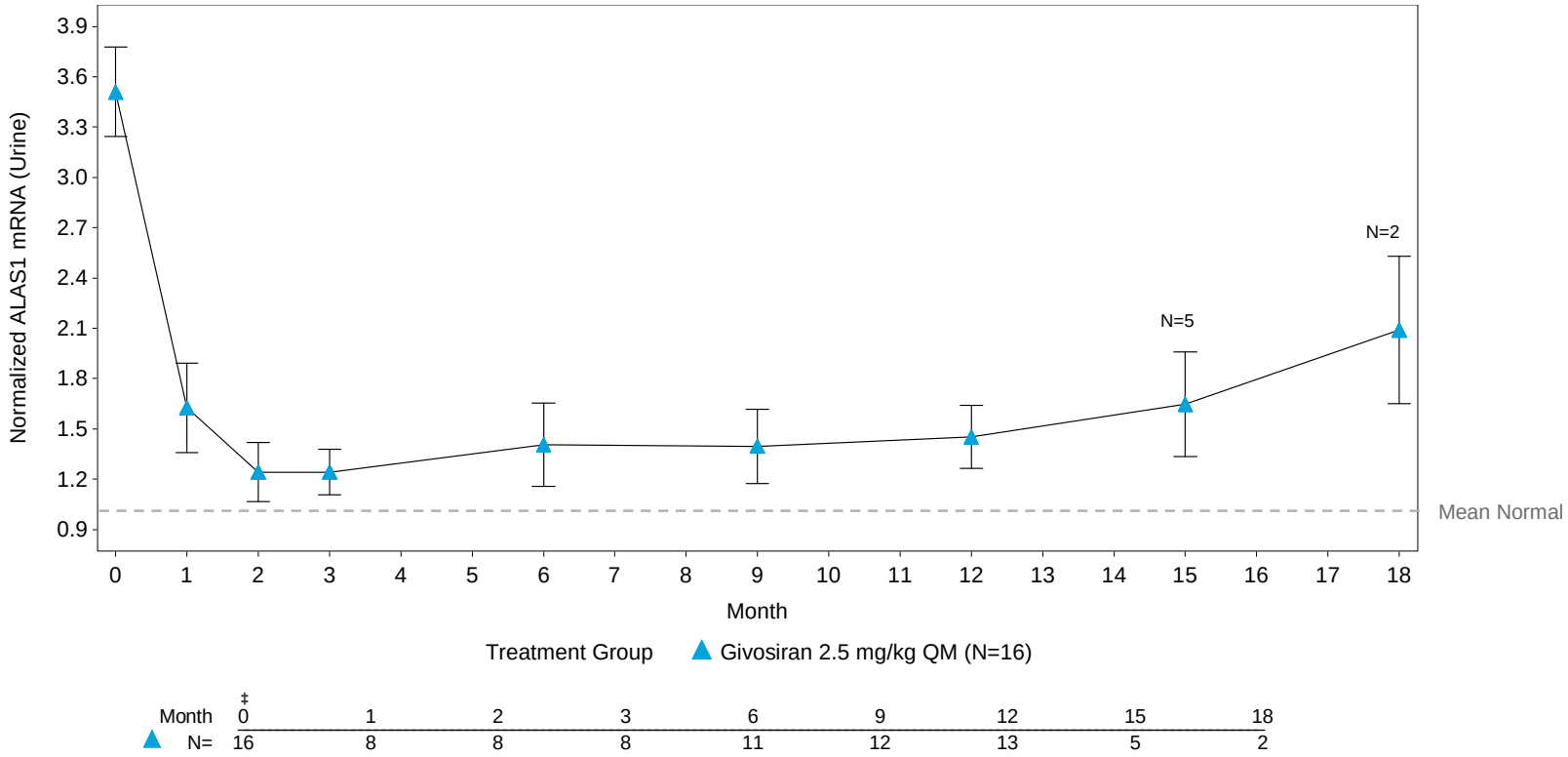
- 100% (16/16) patients reported at least 1 AE
- 4 patients with 5 SAEs
  - 1 patient with upper extremity DVT, unlikely related to study drug due to prior indwelling central venous catheter and venous damage from chronic hemin usage*
  - 1 patient with anaphylactic reaction, assessed as definitely related to study drug*:
    - Occurred after third dose of givosiran (first dose in OLE at 2.5 mg/kg); patient previously received two doses (5 mg/kg q3M) in Phase 1 study
    - Past history of asthma and atopy
    - Event resolved with medical management, and patient permanently discontinued from study
  - 1 patient had two events: two episodes of pyrexia related to suspected PaC infection and chlamydia bronchitis; all events assessed as unlikely related
  - 1 patient with change in mental status due to possible glucocorticoid toxicity for an acute bacterial sinusitis, assessed as unlikely related
- AEs in >3 patients: abdominal pain, fatigue, injection site erythema, nausea, myalgia, diarrhea, headache, and nasopharyngitis
- 6 patients had injection site reactions, most commonly erythema and all mild to moderate
- No clinically significant increases in LFTs or lipase with ongoing dosing

Data as of 7Jun2018
*Previously reported Sardh *et al*. EASL Meeting, Apr 2018

Consistent and Durable Lowering of Induced ALAS1 mRNA Levels With Long-term Givosiran Dosing

Interim Phase 1/2 OLE Study Results

- Monthly dosing at 2.5 mg/kg led to robust and sustained lowering of ALAS1 mRNA, with a reduction from baseline of 61% at Month 12



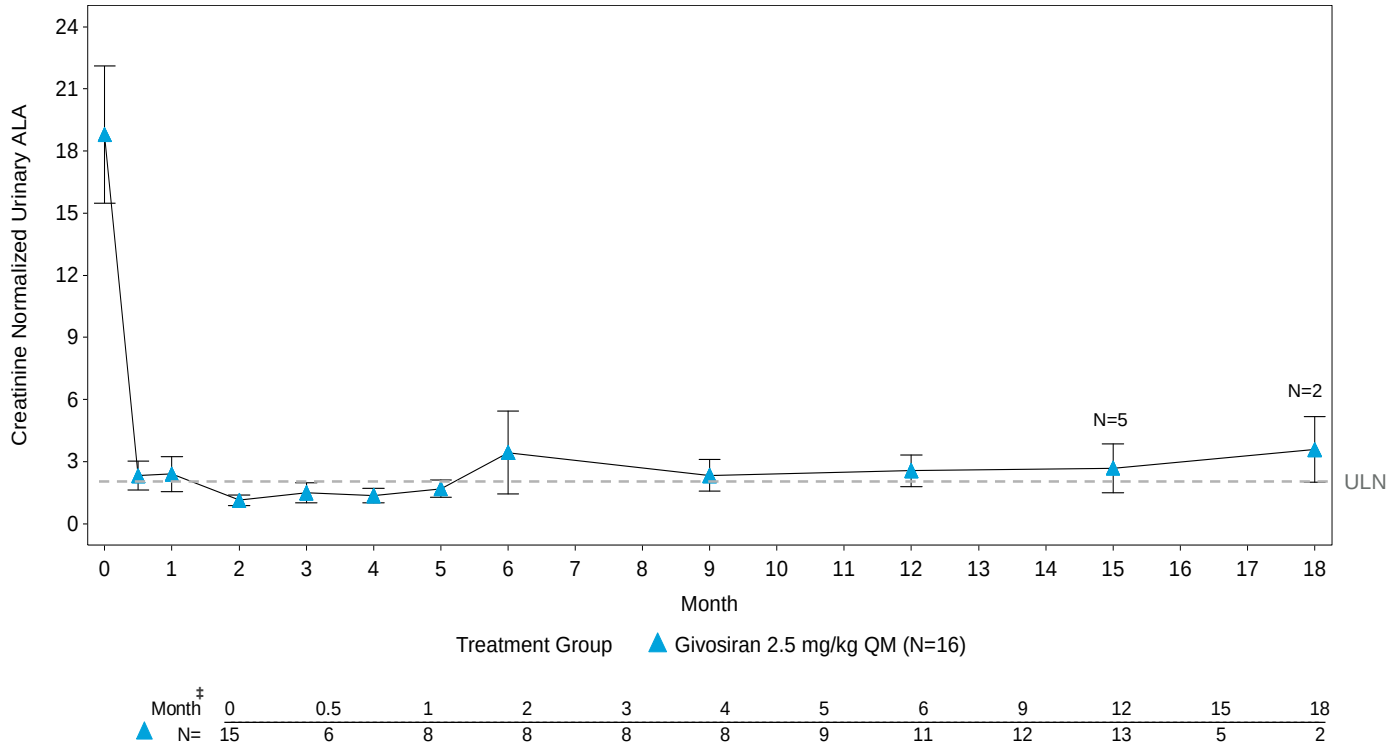
Data as of 7Jun2018

‡The different Ns at each month reflect differences in (1) when patients transitioned to 2.5 mg/kg dose on study, and (2) the duration of patients on study.

Consistent and Durable Lowering of ALA Toward Normal Levels With Long-term Givosiran Dosing

Interim Phase 1/2 OLE Study Results

- Monthly dosing at 2.5 mg/kg led to robust and sustained lowering of ALA toward normal levels, with a reduction from baseline of 87% at Month 12
- Similar reductions were seen with PBG, with a reduction from baseline of 83% at Month 12 (data not shown)

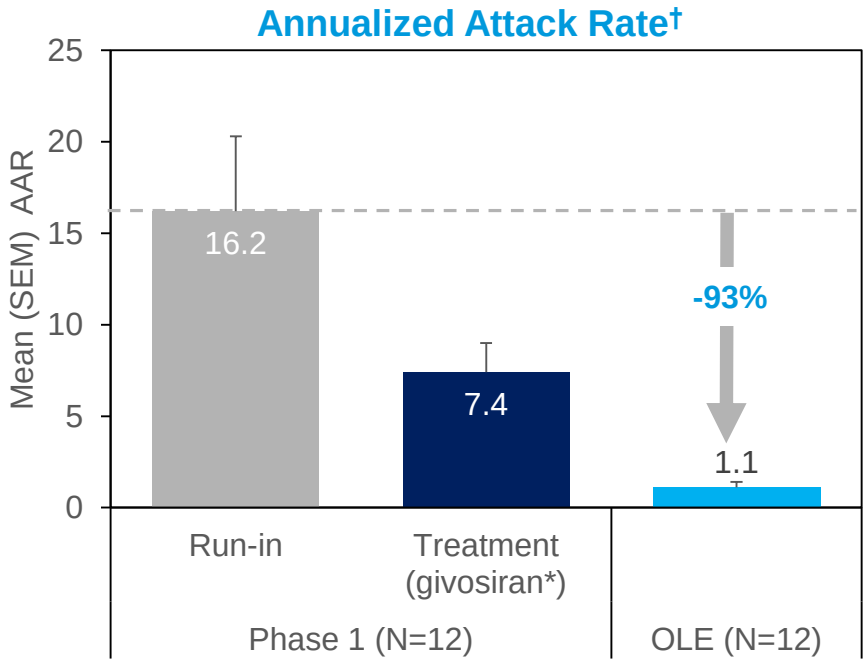


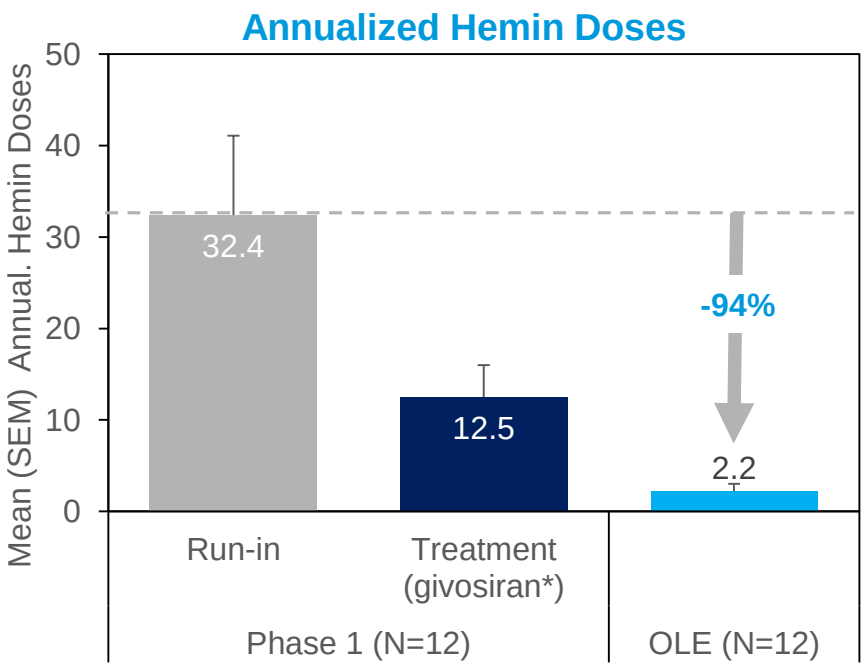
Data as of 7Jun2018
[1]Upper Limit of Normal (ULN): ALA=1.5 mmol/mol Cr
‡The different Ns at each month reflect differences in (1) when patients transitioned to 2.5 mg/kg dose on study, and (2) the duration of patients on study. The N=15 at 0 month reflects a missing data point at pre-study baseline.

Clinical Activity Maintained or Enhanced in Givosiran Treated Patients with Extended Dosing in OLE Study

Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- Mean reductions in AAR of 93% and annualized hemin use of 94% observed in OLE relative to Phase 1 Run-in
- 5/12 (42%) patients with AAR = 0, for a mean of 7.4 months



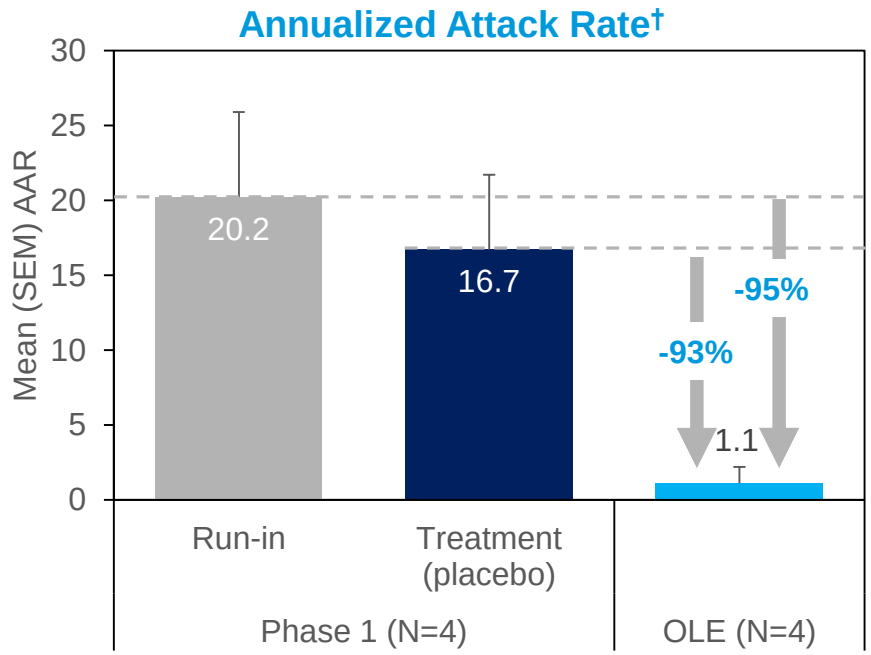


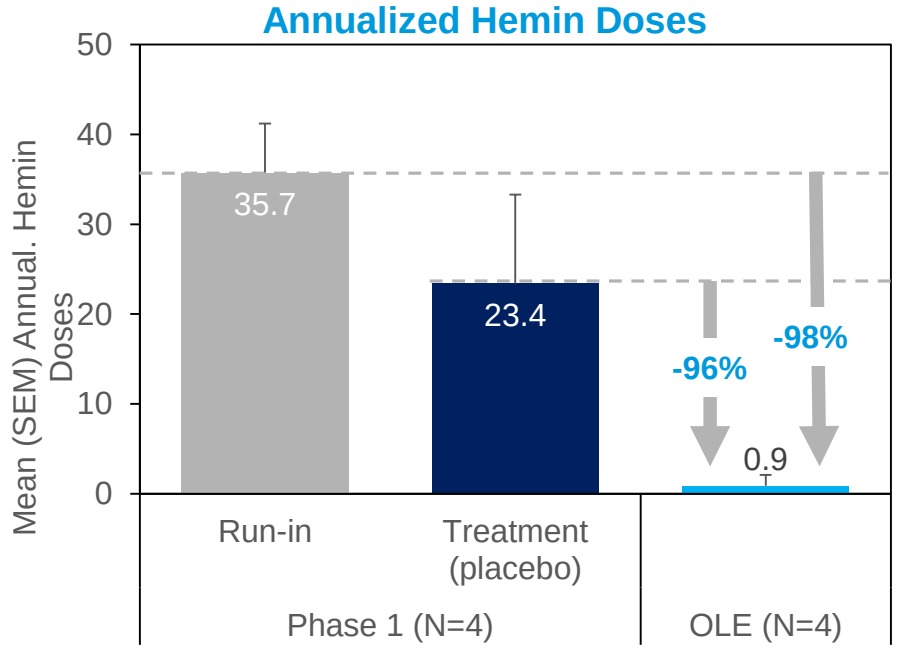
Data as of 7Jun2018. OLE: Open-label extension. AAR: Annualized attack rate
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. *Aggregated across all dose groups. Mean time in Phase 1 Run-in and Treatment of 103 days and 165 days, respectively; mean time in OLE of 415 days.

Clinical Activity Demonstrated in Placebo Patients Crossing Over to Givosiran Treatment in OLE

Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- Upon crossing over to givosiran in OLE, prior Phase 1 placebo patients had a 95% mean reduction in AAR and 98% mean reduction in annualized hemin use relative to both Phase 1 Run-in and Treatment periods
- 2/4 (50%) patients with zero attacks, for a mean of 14.6 months

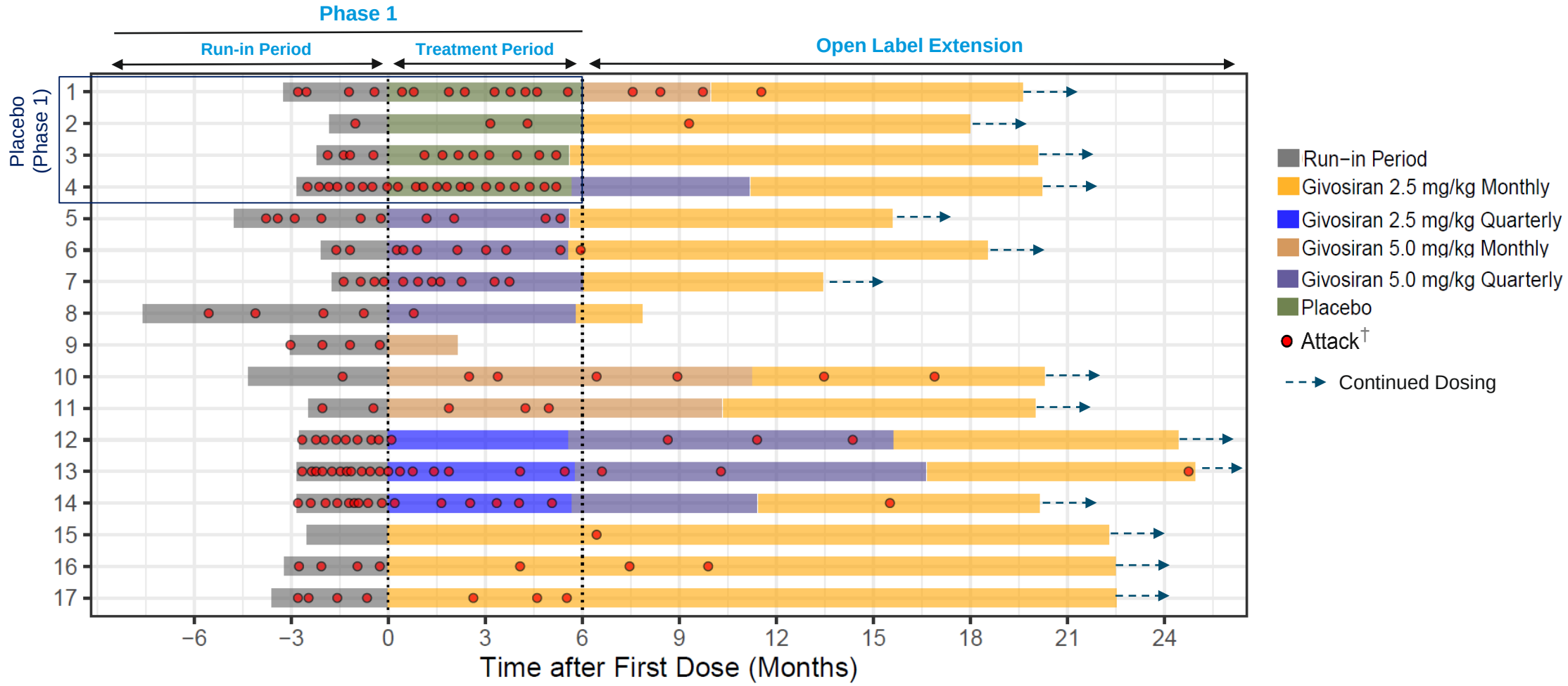




Data as of 7Jun2018. OLE: Open-label extension. AAR: Annualized attack rate
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. Mean time in Phase 1 Run-in and Treatment of 77 days and 175 days, respectively; mean time in OLE of 416 days

Clinical Activity in Recurrent Attack Patients

Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

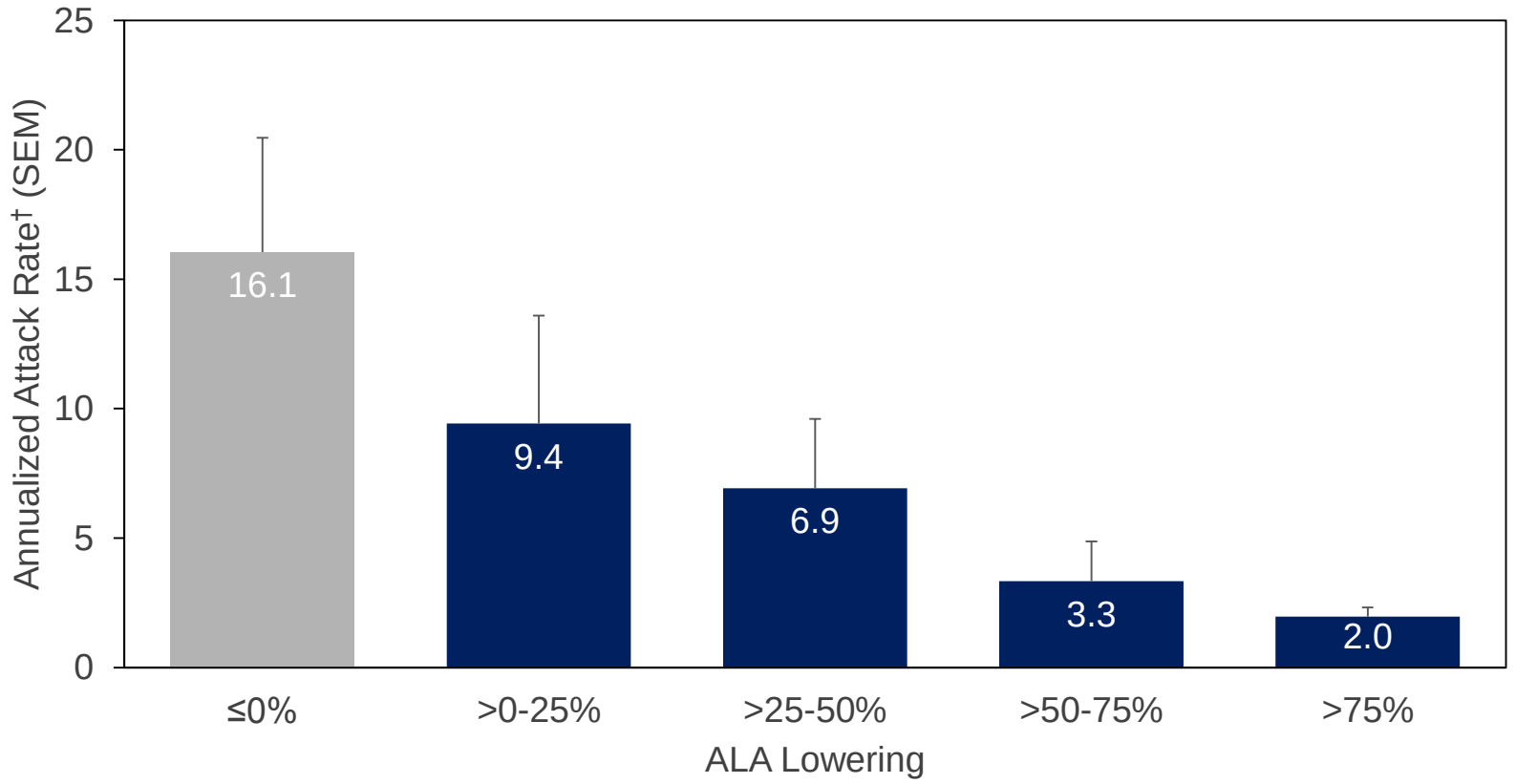


Data as of 7Jun2018. OLE: Open-label extension
Note: Duration between Phase 1 and OLE studies is not shown
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home.

ALA Lowering is Associated with Reductions in AAR

Phase 1 and Phase 1/2 OLE Study Results in Recurrent Attack Patients

- Graded relationship between AAR and ALA lowering



Data as of 7Jun2018. OLE: Open-label extension. AAR: Annualized attack rate
ALA; δ-Aminolevulinic acid. SEM; Standard error of mean. AAR; Annualized attack rate.
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home

Summary

- In Phase 1 study, givosiran treatment lowered induced ALAS1, with corresponding reductions in both elevated ALA and PBG, and reduced attacks and hemin use in recurrent attack patients
- Dose regimen of 2.5 mg/kg qM was selected for Phase 1/2 OLE and further clinical development
- Increasing patient experience, with mean time in Phase 1/2 OLE of 13.6 months and up to 25 months of total treatment in Phase 1 and Phase 1/2 OLE
- Interim Phase 1/2 OLE study results demonstrated:
  - Maintenance, and potentially enhancement, of clinical activity with continuous monthly dosing at 2.5 mg/kg
    - Consistent and durable ALA and PBG lowering of >80% at Month 12
    - Reductions in AAR and hemin use of >90%
  - Safety profile supportive of continued clinical development
- Graded relationship observed between ALA lowering and AAR in Phase 1 and Phase 1/2 OLE, supporting therapeutic hypothesis and ALA as a biomarker reasonably likely to predict clinical benefit

Planned Next Steps

- ENVISION Phase 3 study in patients with AHP is ongoing; enrollment completed with 94 patients, 36 sites, 18 countries
- Topline results from complete ENVISION study in early 2019
- Initiation of rolling NDA submission in 2018 with addition of full clinical results in mid-2019; MAA submission in mid-2019

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Investigators	Institution	Location
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