Phase 1/2, Randomized, Placebo Controlled 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]

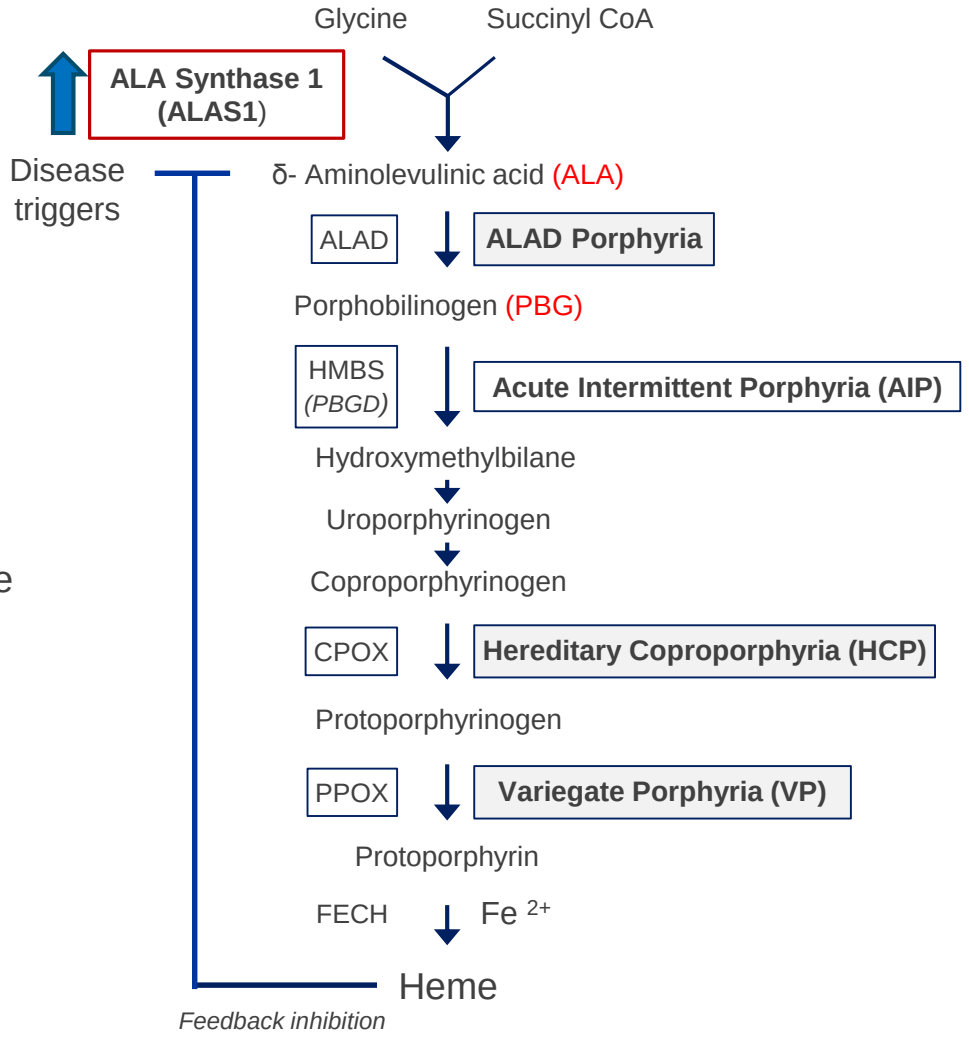
- Inborn errors of heme synthesis from liver enzyme defects
- Acute Intermittent Porphyria (AIP) most common, with a mutation in hydroxymethylbilane synthase (HMBS)

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

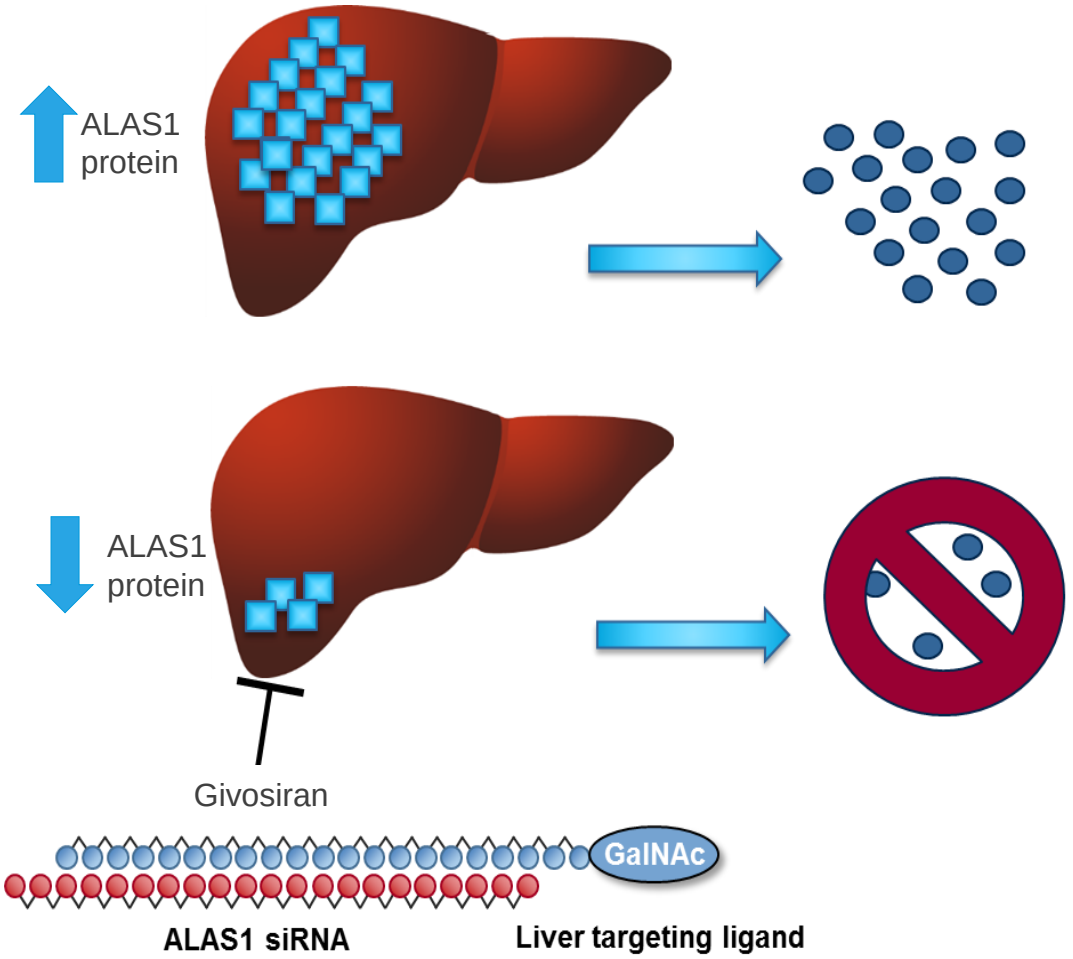
- Autonomic Nervous System
  - Severe abdominal pain, hypertension
- Central Nervous System
  - Mental status changes, seizures
- Peripheral Nervous System
  - Muscle weakness, paralysis



1.Bonkovsky, et al. Am J Med. 2014;127(12):1233-41; 2.Elder, et al. JIMD. 2013;36(5):849-57.

Therapeutic Hypothesis for Givosiran, an Investigational RNAi Therapeutic for AHPs

Reduction of Liver ALAS1 Protein to Lower ALA and PBG

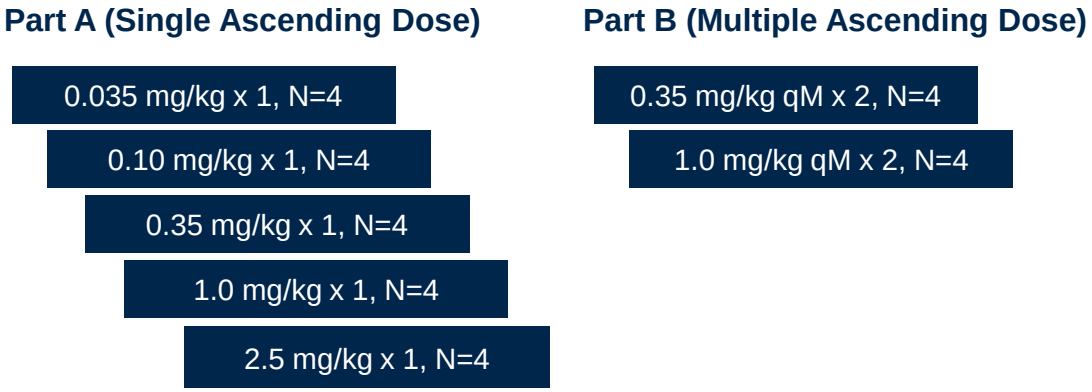


ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. ALAS1; ALA synthase 1

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

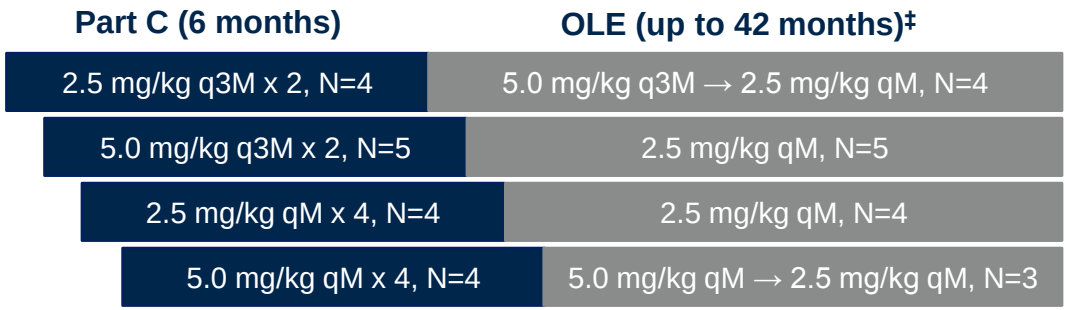
Parts A & B in Chronic High Excreter (CHE) Patients†

- 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

Demographics and Baseline Characteristics

	Parts A & B (N=23†)	Part C	
		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)‡	23.1 (3.1)	43.1 (9.8)	37.8 (6.5)
PBG, mmol/mol Cr, mean (SEM)‡	24.8 (3.6)	39.2 (4.6)	38.9 (5.8)
ALAS1 mRNA, fold relative to normal, mean (SEM)	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<3.9 or 3.8 mmol/mol Cr; PBG<1.6 or 1.5 mmol/mol Cr (site dependent)
SD; Standard deviation. GnRH; Gonadotropin-releasing hormone. Cr; Creatinine. ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. SEM; Standard error of mean. ALAS1; ALA synthase 1.

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Safety and Tolerability

Phase 1 Study Results

Patients Reporting Adverse Event, N (%)	Parts A & B		Part C	
	Placebo (N=6)	Givosiran (N=20)	Placebo (N=4)	Givosiran (N=13)
Any adverse event	6 (100)	17 (85)	4 (100)	13 (100)
Serious adverse event	0	3 (15)	0	3 (23)
Most common adverse events (occurring in >2 patients)				
Abdominal pain	0	2 (10)	1 (25)	6 (46)
Nasopharyngitis	1 (17)	4 (20)	1 (25)	5 (39)
Nausea	0	0	1 (25)	5 (39)
Back pain	0	0	0	3 (23)
Injection site reaction	0	0	0	3 (23)
Vomiting	0	0	2 (50)	3 (23)
Rash	0	3 (15)	0	0

- 6 patients with 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

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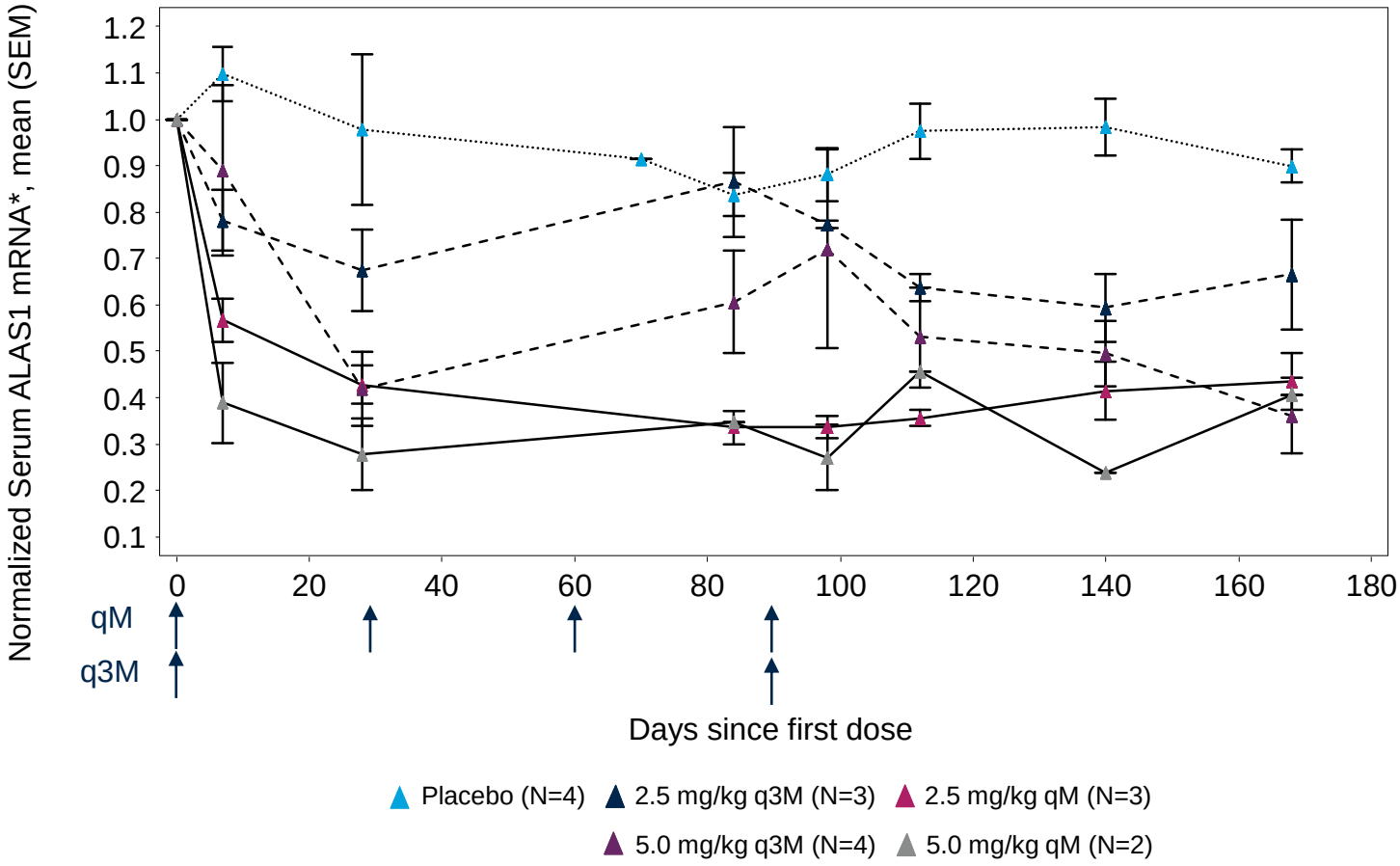
Rapid, Dose-Dependent, and Durable ALAS1 mRNA Silencing After Givosiran Dosing

Phase 1 Study Results in Recurrent Attack Patients

- Approximately 60-70% ALAS1 mRNA silencing with monthly dosing



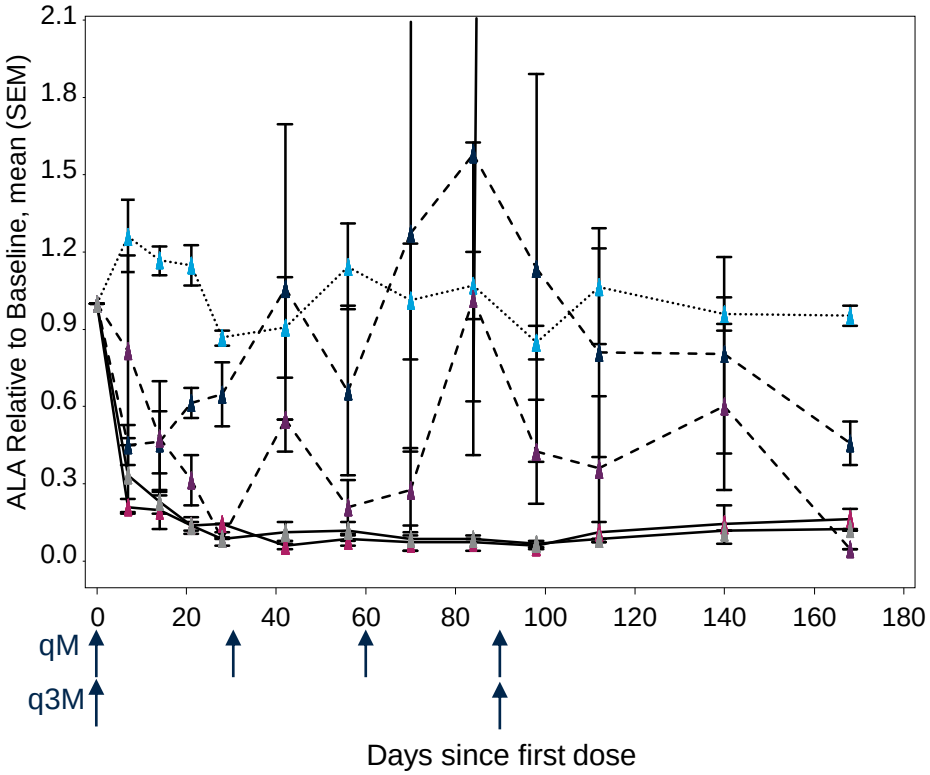
ALAS1; ALA synthase 1. SEM; Standard error of mean. qM; Monthly. q3M; Quarterly.
*Determined by Circulating Extracellular RNA Detection (cERD)

Dose-Dependent Lowering of ALA and PBG After Givosiran Dosing

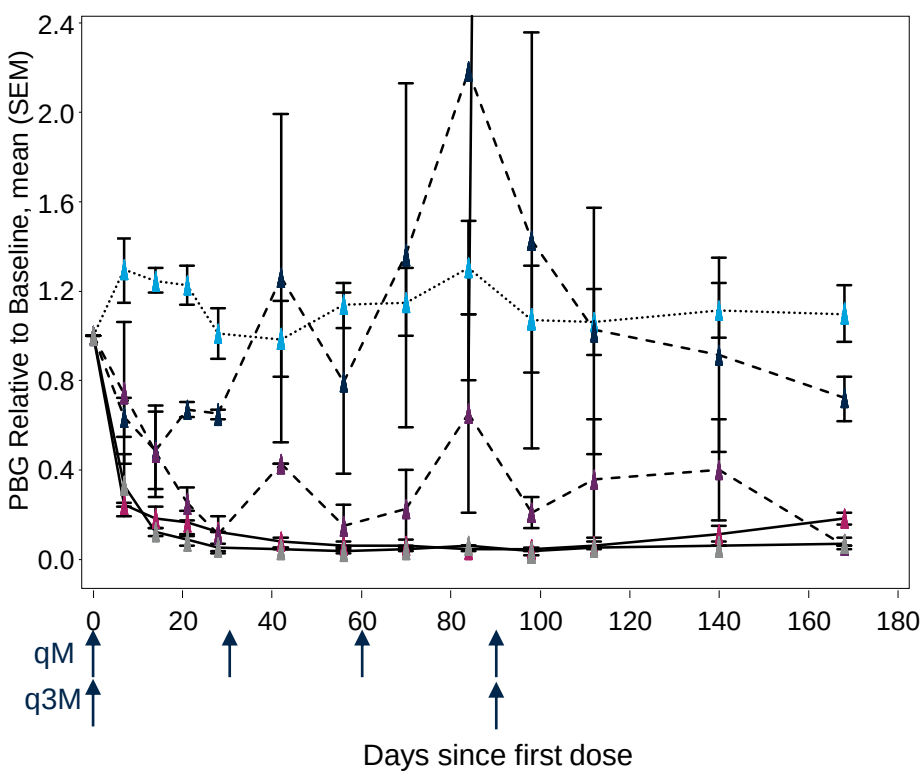
Phase 1 Study Results in Recurrent Attack Patients

- Monthly dosing led to consistent and sustained lowering of ALA and PBG of >80%
- Increasing monthly dose from 2.5 mg/kg to 5.0 mg/kg did not lead to further lowering

Urine ALA Levels



Urine PBG Levels



Placebo (N=4) 2.5 mg/kg q3M (N=3) 2.5 mg/kg qM (N=3)
5.0 mg/kg q3M (N=4) 5.0 mg/kg qM (N=2)

ALAS1, ALA synthase 1. ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. SEM; Standard error of mean
qM; Monthly. q3M; Quarterly.

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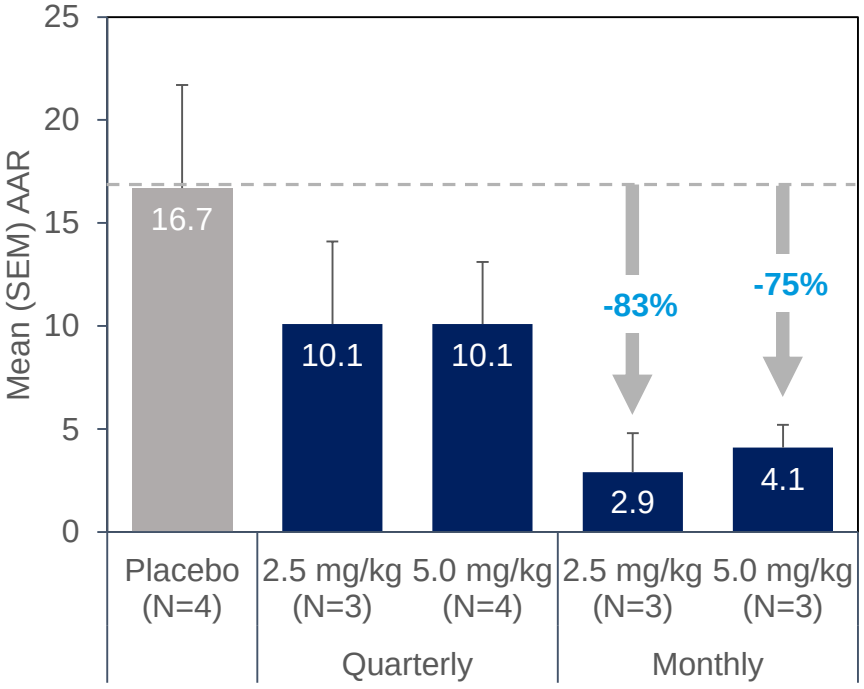
Givosiran Treatment Led to Decreased Annualized Attack Rates (AAR) and Decreased Hemin Use

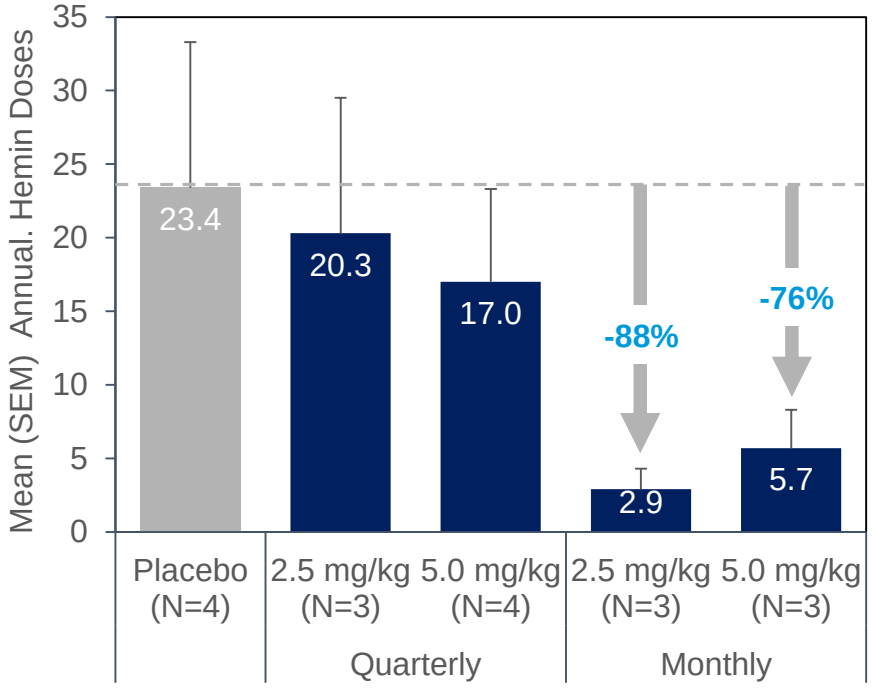
Phase 1 Study Results in Recurrent Attack Patients

- Monthly dosing led to greater mean reductions in AAR (up to 83%) and annualized hemin use (up to 88%) relative to placebo

Annualized Attack Rate†



Annualized Hemin Doses



†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home

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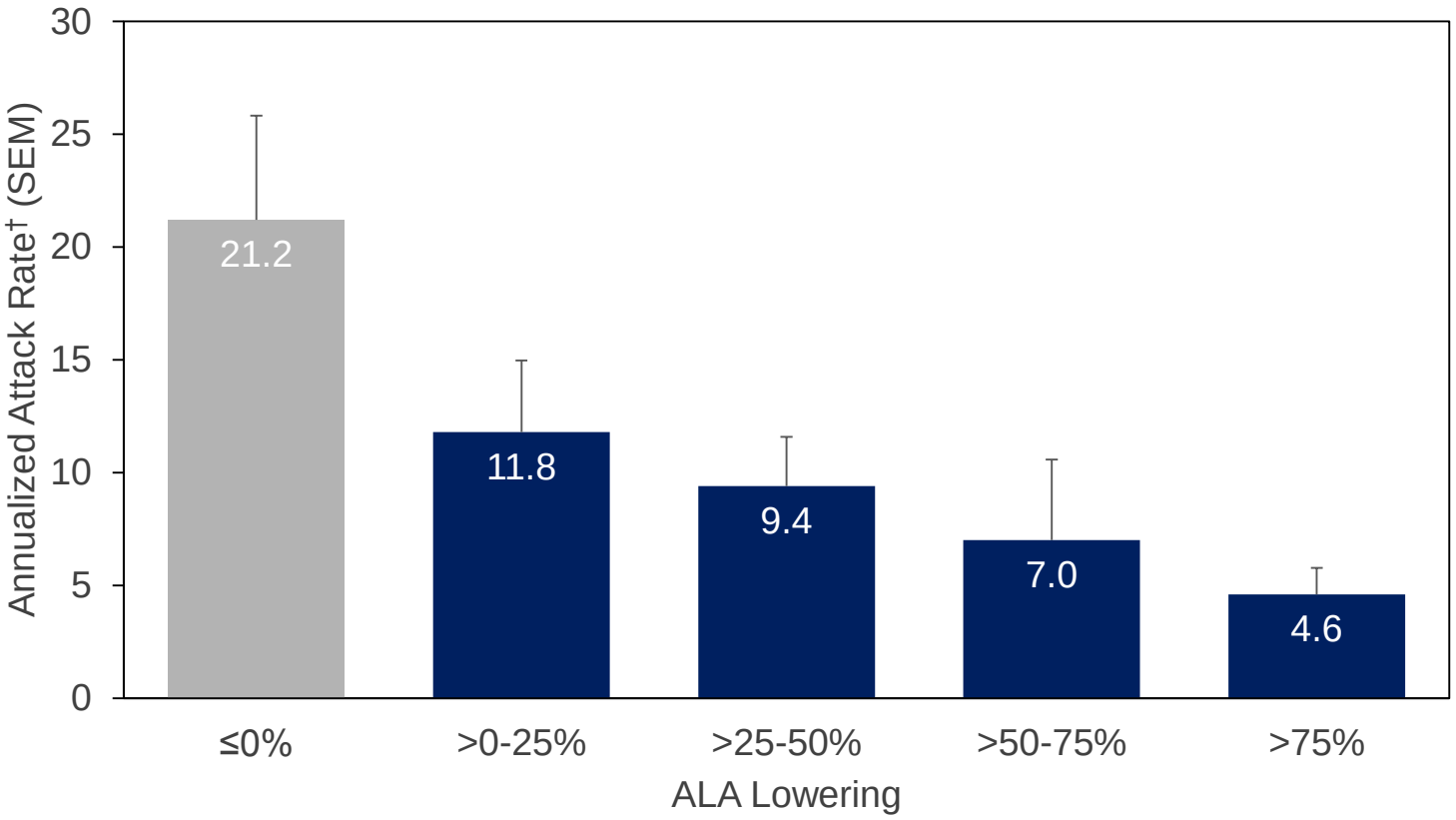
ALA Lowering is Correlated with Reductions in AAR

Phase 1 Study Results in Recurrent Attack Patients

- Continuous relationship between AAR and ALA lowering



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

Safety and Tolerability

Interim Phase 1/2 OLE Study Results

- 15/16 (94%) patients reported AEs
- 2 patients with SAEs
  - 1 patient (5.0 mg/kg q3M) with upper extremity DVT, assessed as unlikely related to study drug due to prior indwelling central venous catheter and venous damage from chronic hemin usage
  - 1 patient (2.5 mg/kg qM) 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, oral allergy syndrome, and prior allergic reactions to acne cream and possibly latex gloves
    - Event resolved with medical management, and patient discontinued from study
- AEs in >3 patients: abdominal pain, nausea, injection site erythema, headache, injection site pruritus, fatigue, nasopharyngitis
- No clinically significant increases in LFTs or lipase with ongoing dosing

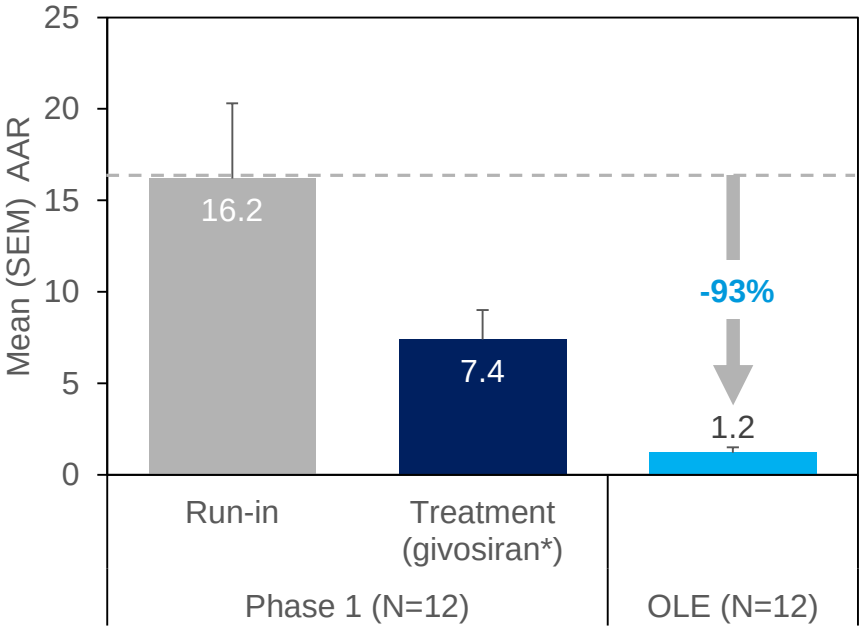
Data as of 26Feb2018
*Only case of anaphylactic reaction in >2500 patients dosed with Alnylam GalNAc-siRNAs

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

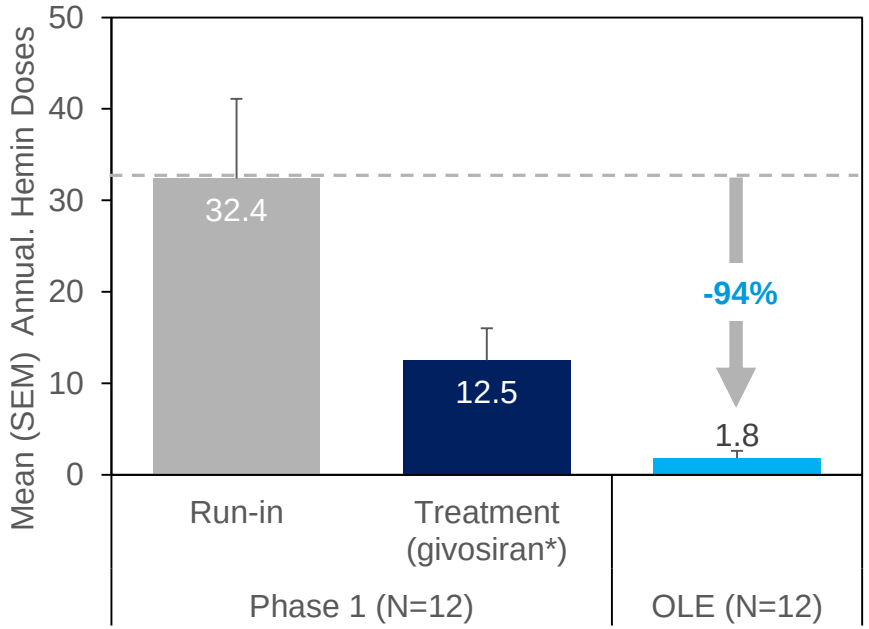
Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- Mean time in OLE of 10.6 months, with up to 22 months of total treatment in Phase 1 and OLE
- Continuous dosing at 2.5 mg/kg monthly regimen in OLE (all patients transitioned to 2.5 mg/kg qM) potentially leads to enhanced clinical activity
- ALA and PBG lowering >80% maintained with continued dosing in OLE
- 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

Annualized Attack Rate†



Annualized Hemin Doses



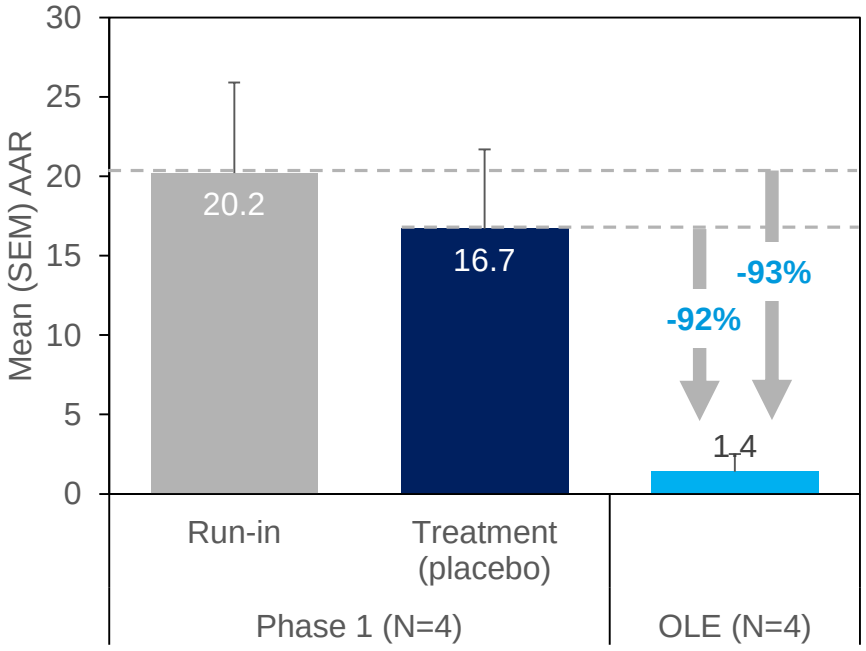
Data as of 26Feb2018. OLE; Open-label extension. AAR; Annualized attack rate.
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. *Aggregated across all dose groups.
Mean time in Phase 1 Run-in and Treatment of 103 days and 165 days, respectively; mean time in OLE of 322 days.

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

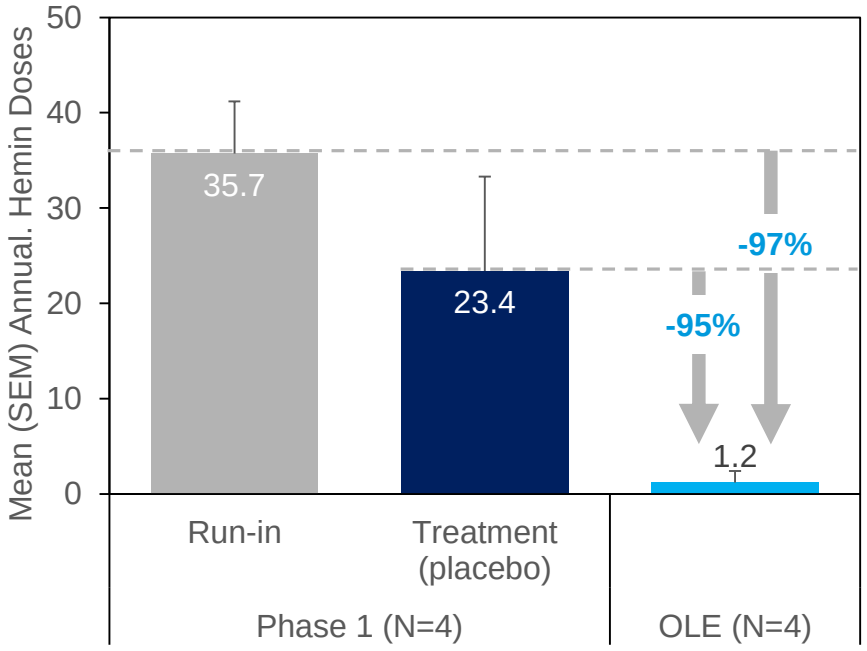
Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- Upon crossing over to givosiran in OLE, prior Phase 1 placebo patients experienced >90% mean reduction in AAR and annualized hemin use relative to both Phase 1 Run-in and Treatment periods
- 2/4 (50%) patients with AAR = 0, for a mean of 11.2 months

Annualized Attack Rate†



Annualized Hemin Doses



Data as of 26Feb2018. 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 316 days

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Summary

- In Phase 1 study, givosiran lowered induced ALAS1, with corresponding reductions in both ALA and PBG, and reduced attacks and hemin use in recurrent attack patients
- Dose regimen of 2.5 mg/kg qM was selected for OLE and further clinical development
- Interim Phase 1/2 OLE study results demonstrate maintenance, and potentially enhancement, of clinical activity with continuous monthly dosing
- Clinical activity and safety profile support continued clinical development
- ENVISION Phase 3 study in patients with AHPs is enrolling

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Montgomery Bissell Bruce Wang	University of California, San Francisco	San Francisco, CA

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