New Clinical Results with Givosiran

European Association for the Study of the Liver (EASL)
53rd International Liver Congress

April 14, 2018

Alnylam® PHARMACEUTICALS

Agenda

Welcome

- Christine Lindenboom
  Vice President, Investor Relations & Corporate Communications

Overview

- John Maraganore, Ph.D.
  Chief Executive Officer

Disease Background & Givosiran Clinical Results

- Akshay Vaishnaw, M.D., Ph.D.
  President of R&D

Q&A Session

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent report on Form 10-K under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

John Maraganore, Ph.D.
Chief Executive Officer

Overview

Akshay Vaishnaw, M.D., Ph.D.

President of R&D

Disease Background & Givosiran Clinical Results

Disease Overview

Acute Hepatic Porphyrias (AHPs)[1,2]

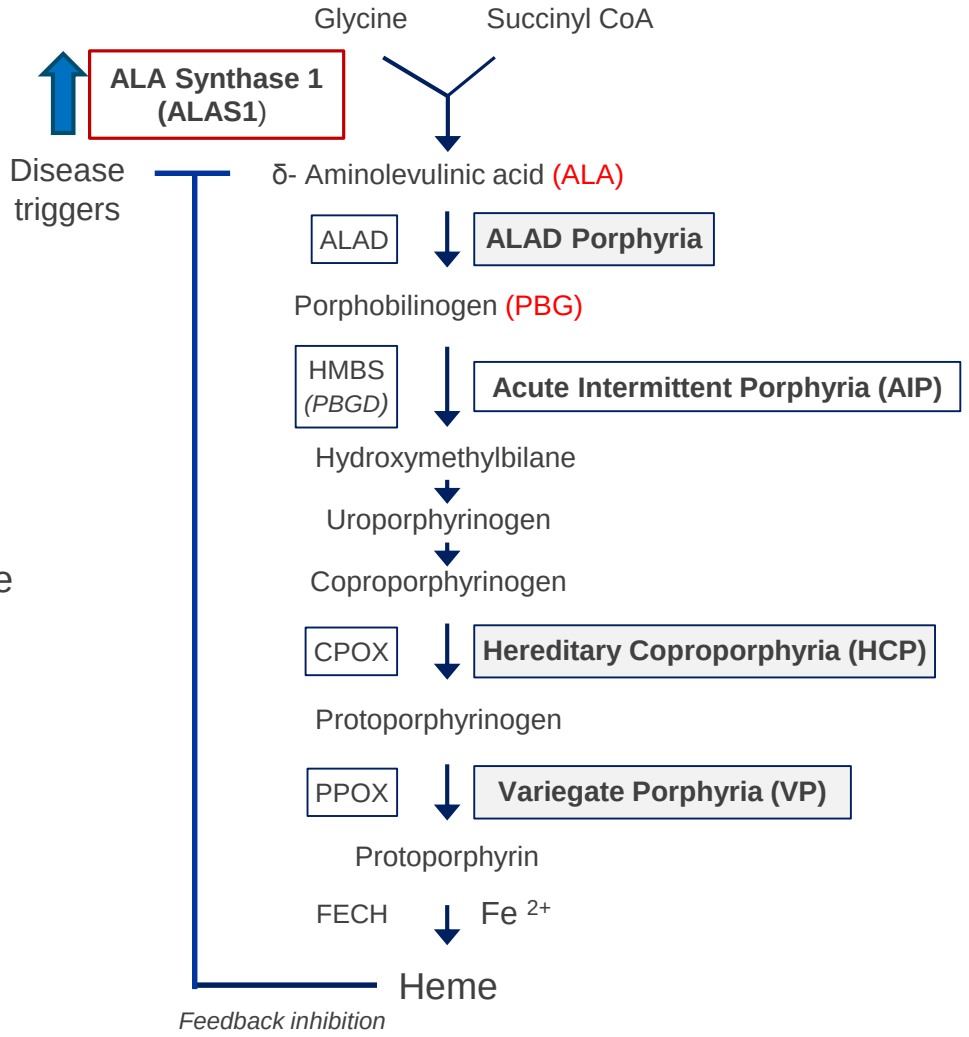
- Inborn errors of heme synthesis from liver enzyme defects
- Acute Intermittent Porphyria (AIP) most common, with a mutation in hydroxymethylbilane synthase (HMBS)

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

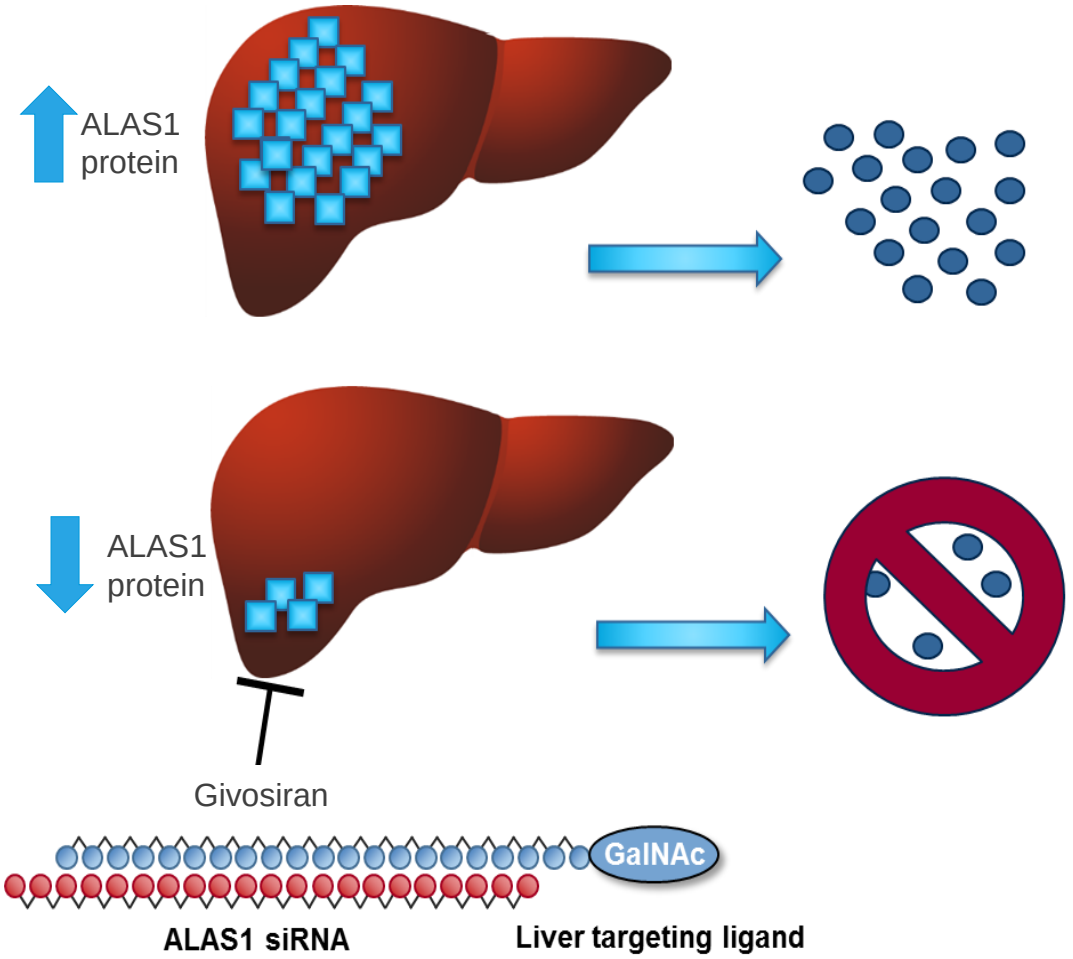
- Autonomic Nervous System
  - Severe abdominal pain, hypertension
- Central Nervous System
  - Mental status changes, seizures
- Peripheral Nervous System
  - Muscle weakness, paralysis



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

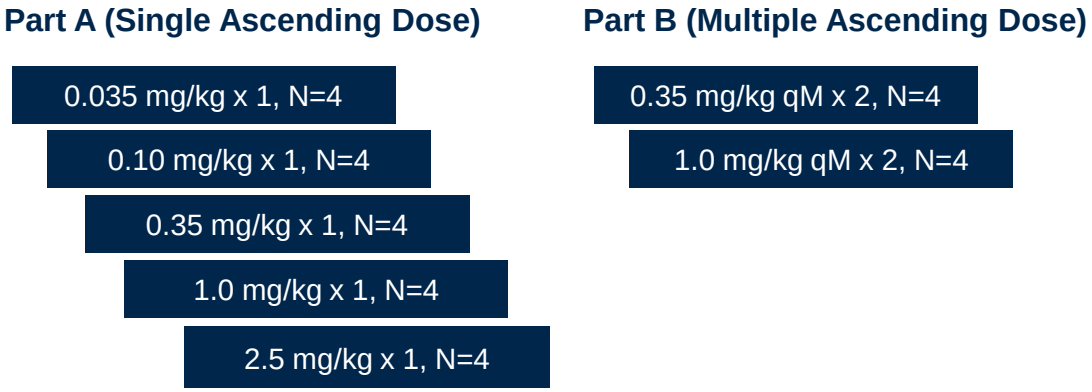


ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. ALAS1; ALA synthase 1

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

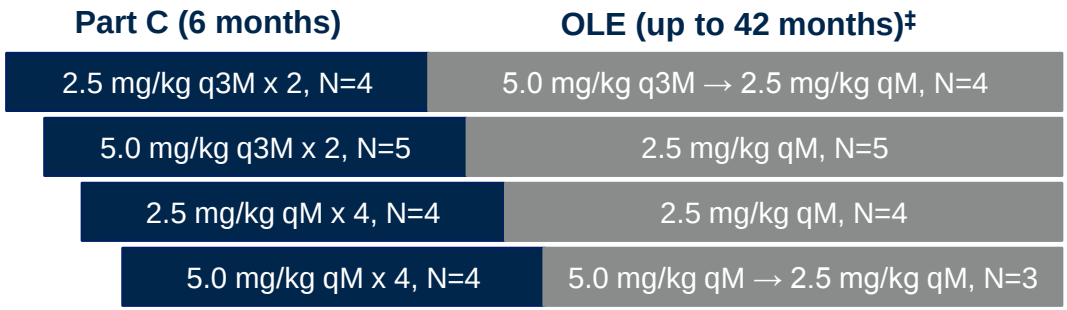
Parts A & B in Chronic High Excreter (CHE) Patients†

- 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

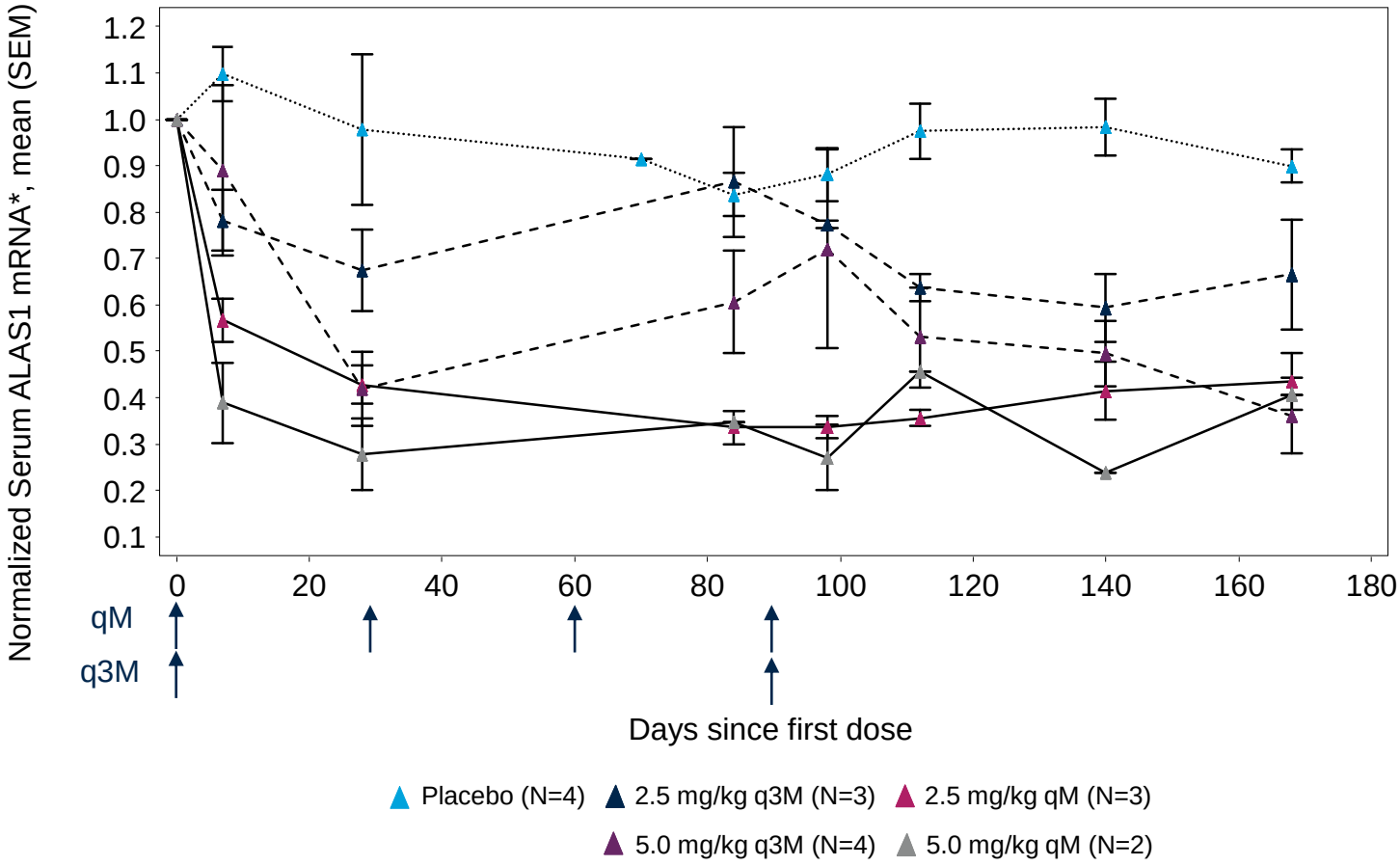
Patients Reporting Adverse Event, N (%)	Parts A & B		Part C	
	Placebo (N=6)	Givosiran (N=20)	Placebo (N=4)	Givosiran (N=13)
Any adverse event	6 (100)	17 (85)	4 (100)	13 (100)
Serious adverse event	0	3 (15)	0	3 (23)
Most common adverse events (occurring in >2 patients)				
Abdominal pain	0	2 (10)	1 (25)	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

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



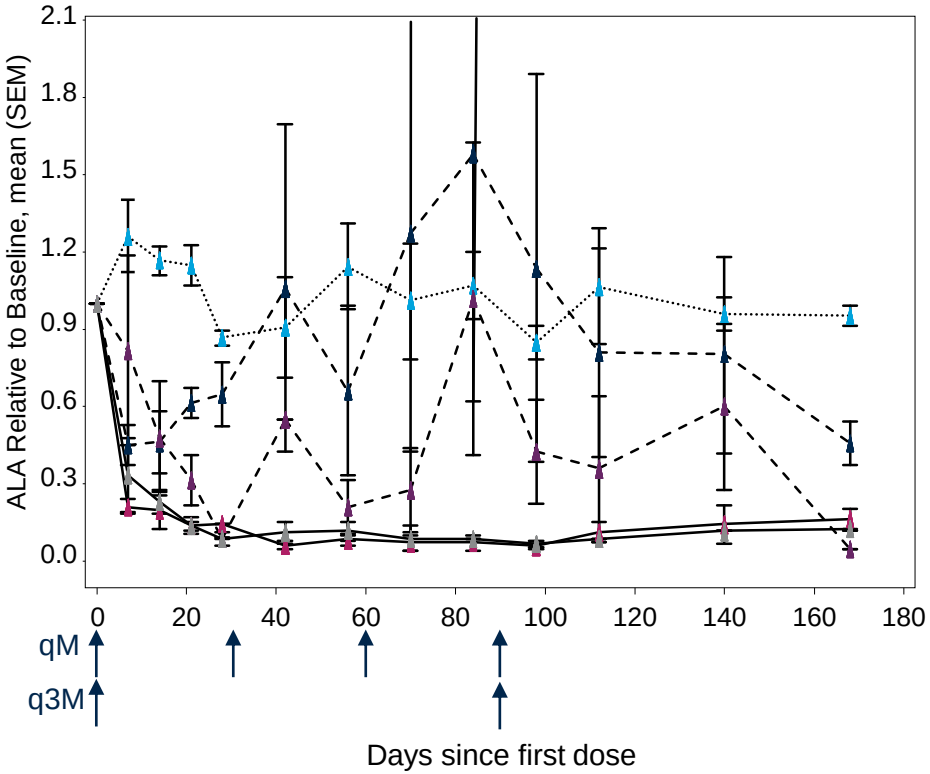
ALAS1; ALA synthase 1. SEM; Standard error of mean. qM; Monthly. q3M; Quarterly.
*Determined by Circulating Extracellular RNA Detection (cERD)

Dose-Dependent Lowering of ALA and PBG After Givosiran Dosing

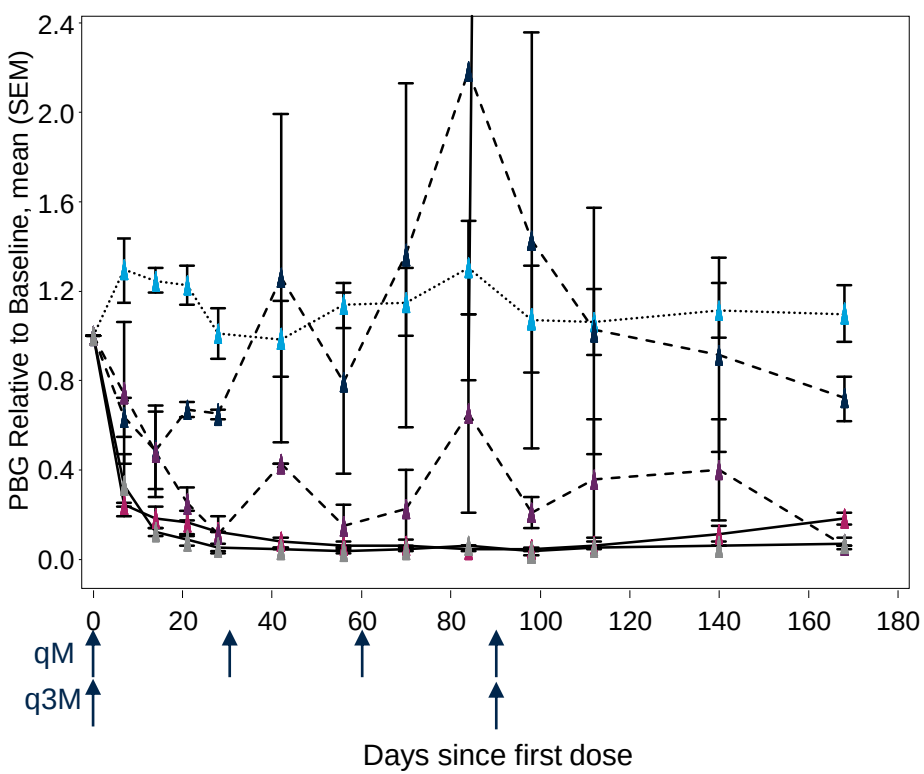
Phase 1 Study Results in Recurrent Attack Patients

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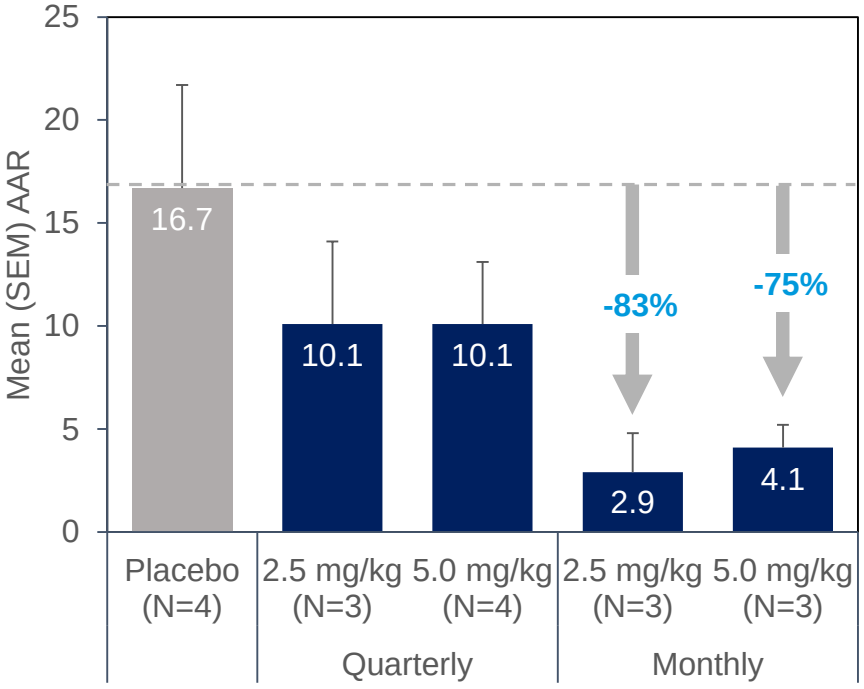
Givosiran Treatment Led to Decreased Annualized Attack Rates (AAR) and Decreased Hemin Use

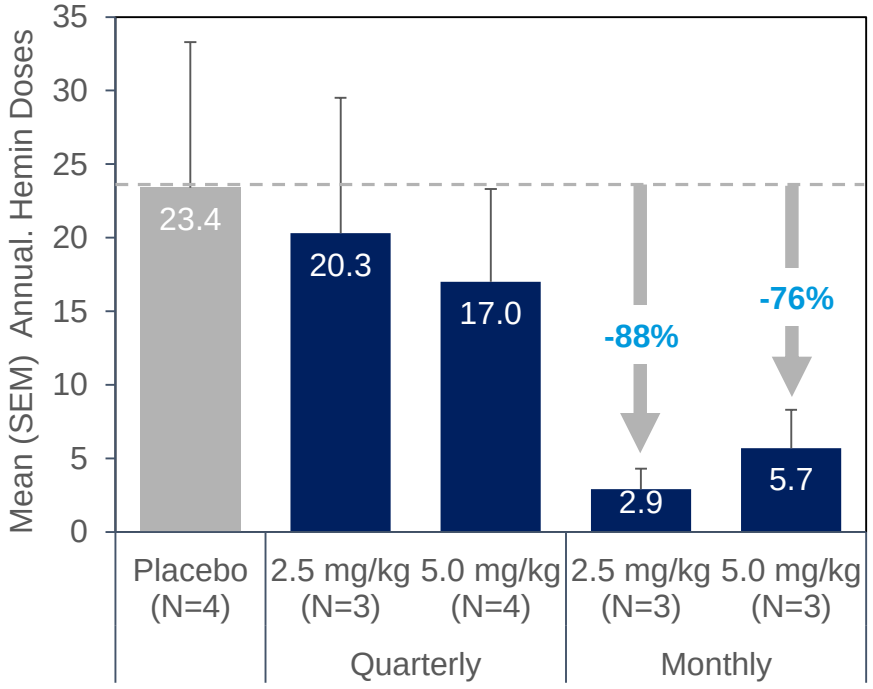
Phase 1 Study Results in Recurrent Attack Patients

- 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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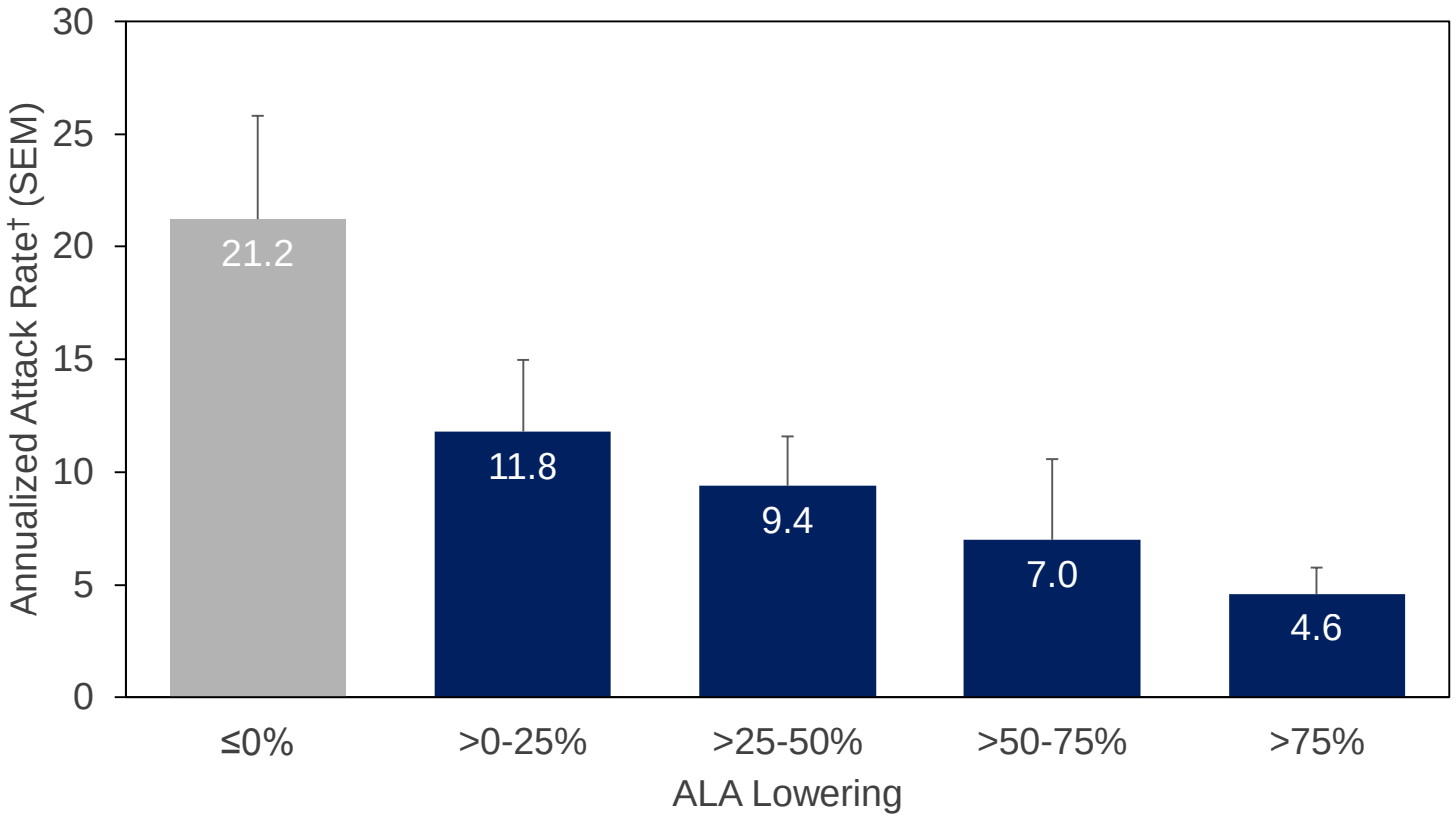
ALA Lowering is Correlated with Reductions in AAR

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

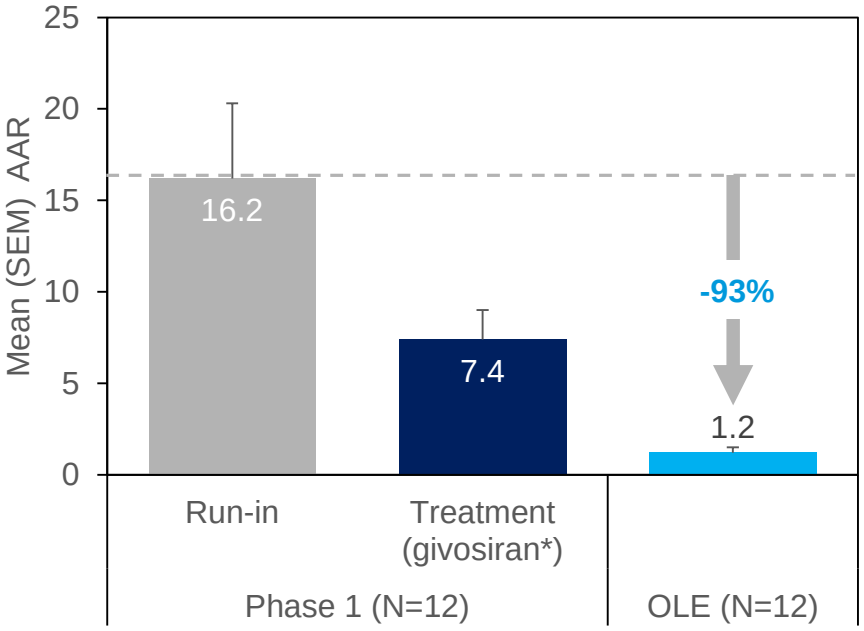
Data as of 26Feb2018
*Only case of anaphylactic reaction in >2500 patients dosed with Alnylam GalNAc-siRNAs

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

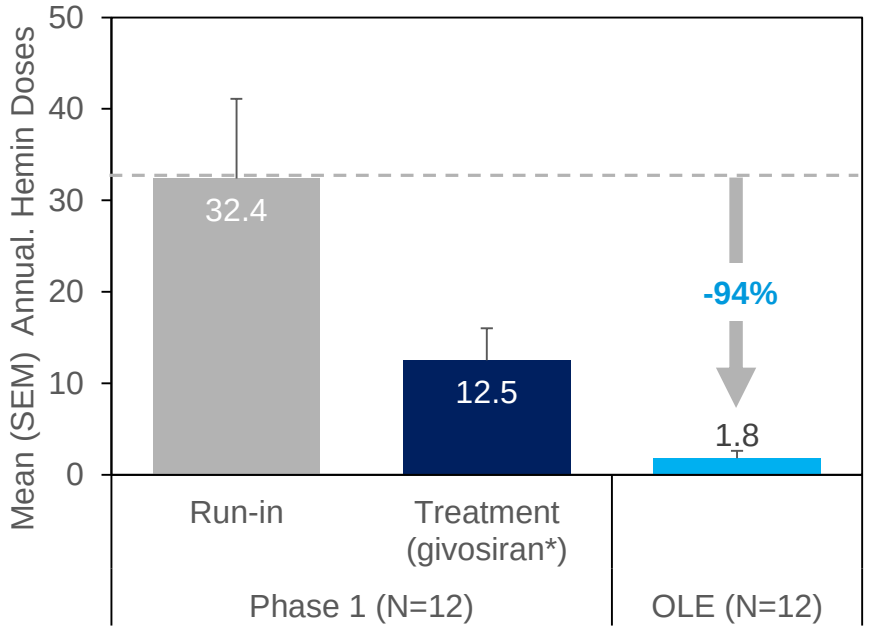
Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- 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



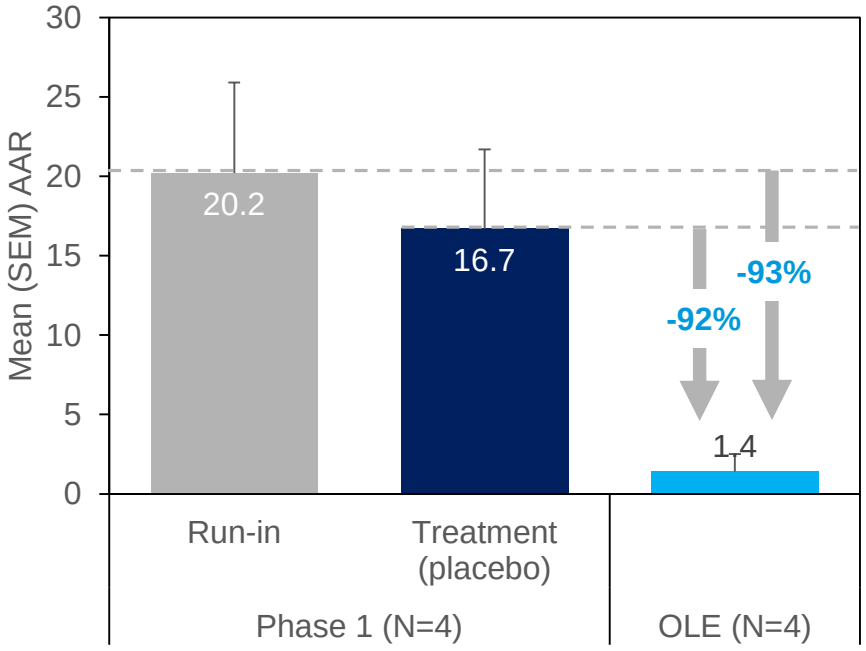
Data as of 26Feb2018. OLE; Open-label extension. AAR; Annualized attack rate.
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. *Aggregated across all dose groups.
Mean time in Phase 1 Run-in and Treatment of 103 days and 165 days, respectively; mean time in OLE of 322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

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

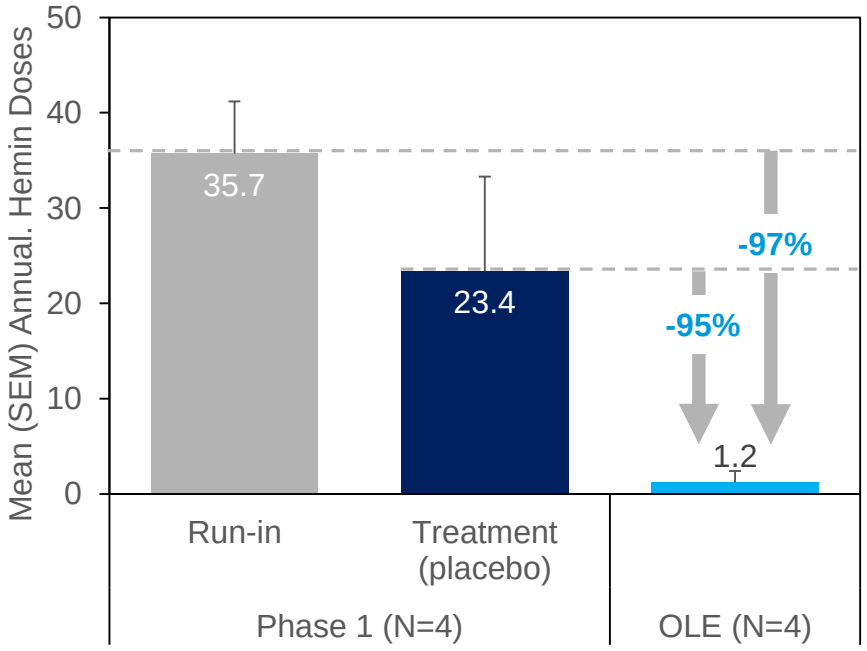
Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- 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

Givosiran Clinical Results

Q&A Session


THANK YOU
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