Interim Analysis Results from ENVISION Phase 3 Study of Givosiran

September 27, 2018

Alnylam® PHARMACEUTICALS

Agenda

Welcome

- Christine Lindenboom
  Vice President, Investor Relations & Corporate Communications

Introduction

- John Maraganore, Ph.D.
  Chief Executive Officer

ENVISION Phase 3 Study & Interim Analysis 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; our ability to successfully launch, market and sell our approved products globally; our ability to successfully expand the indication for ONPATTRO in the future; 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-Q 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

Introduction

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases
- CNS Diseases

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[3]	COMMERCIAL RIGHTS
onpattro® (patisiran) lipid complex injection	*hATTR Amyloidosis*[2]	✓	✓			●	Global
Givosiran	*Acute Hepatic Porphyrias*	✓	✓		●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% Royalties
Inclisiran	*Hypercholesterolemia*	✓			●		Milestones & up to 20% Royalties
ALN-TTRsc02	*ATTR Amyloidosis*	✓		●			Global
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	✓	●			Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			Global

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Approved in the U.S. for the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy
[3] Includes marketing application submissions
As of September 2018

Alnylam® PHARMACEUTICALS

JOIN US!

Alnylam R&D Day

Thursday, December 6, 2018
Westin Times Square
270 W 43rd St, NYC
8:00 am – 1:00 pm

Additional details forthcoming

Alnylam PHARMACEUTICALS

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

President of R&D

ENVISION Phase 3 Study Interim Analysis Results

Disease Overview

Acute Hepatic Porphyrias (AHPs)[1,2]

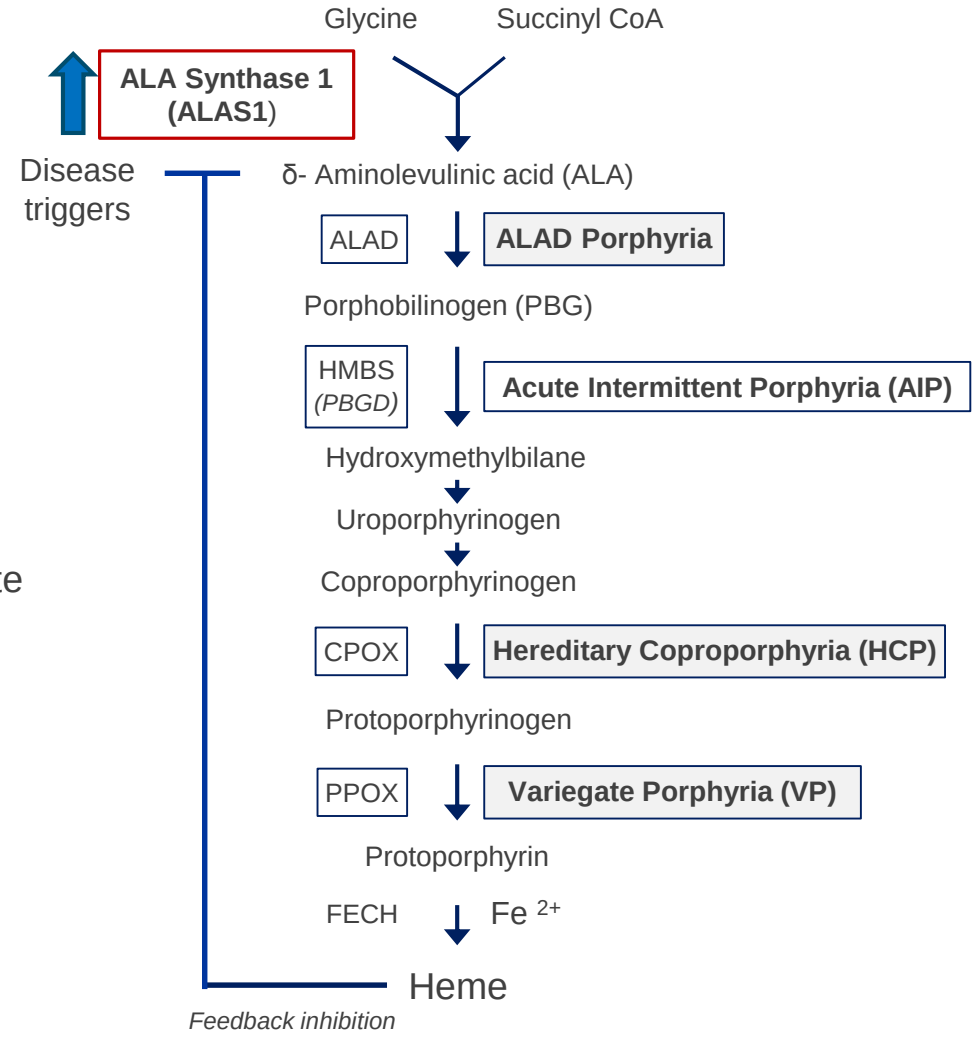
- Inherited hepatic enzymopathies of the heme synthetic pathway
- Acute Intermittent Porphyria (AIP) most common, with a mutation in hydroxymethylbilane synthase (HMBS)

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

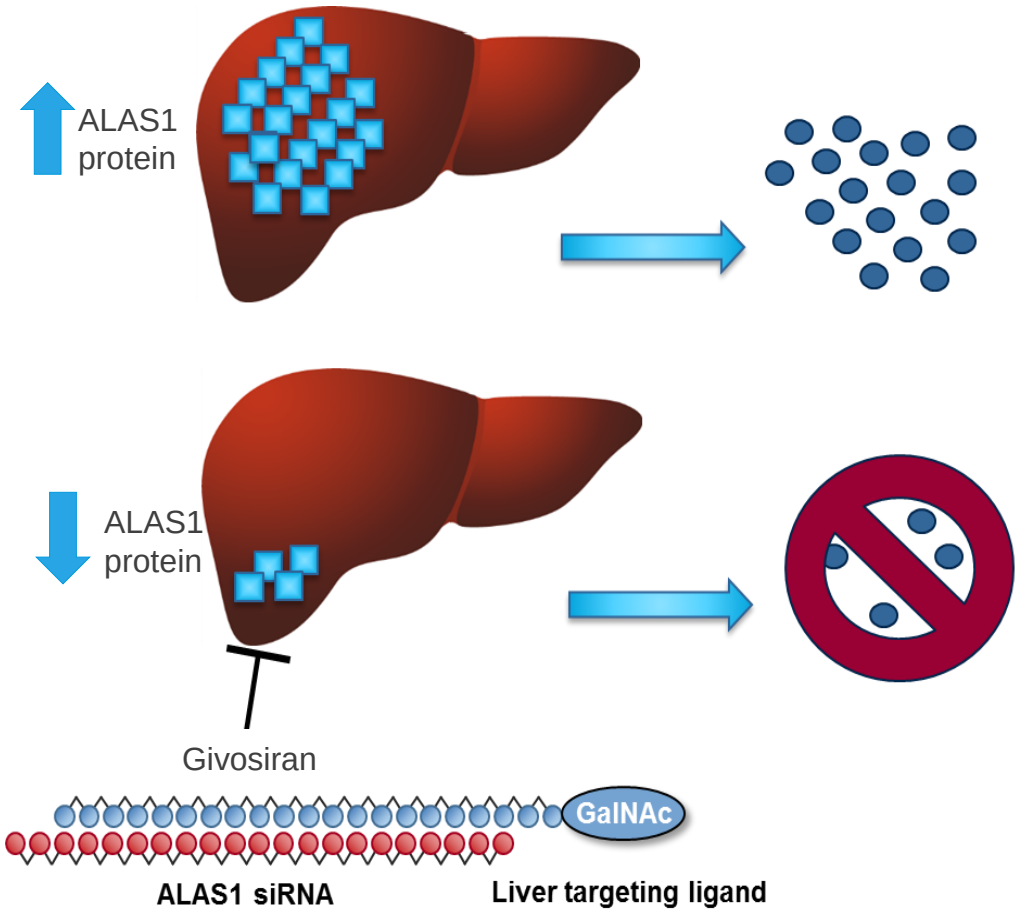
- Autonomic Nervous System
  - Severe abdominal pain, hypertension
- Central Nervous System
  - Mental status changes, seizures
- Peripheral Nervous System
  - Muscle weakness, paralysis



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

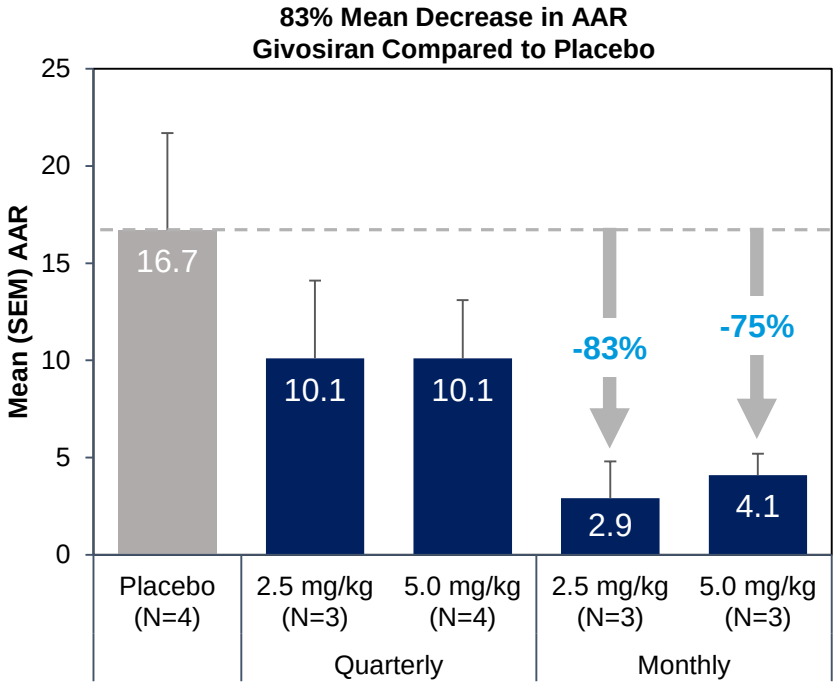
Reduction of Liver ALAS1 Protein to Lower ALA and PBG

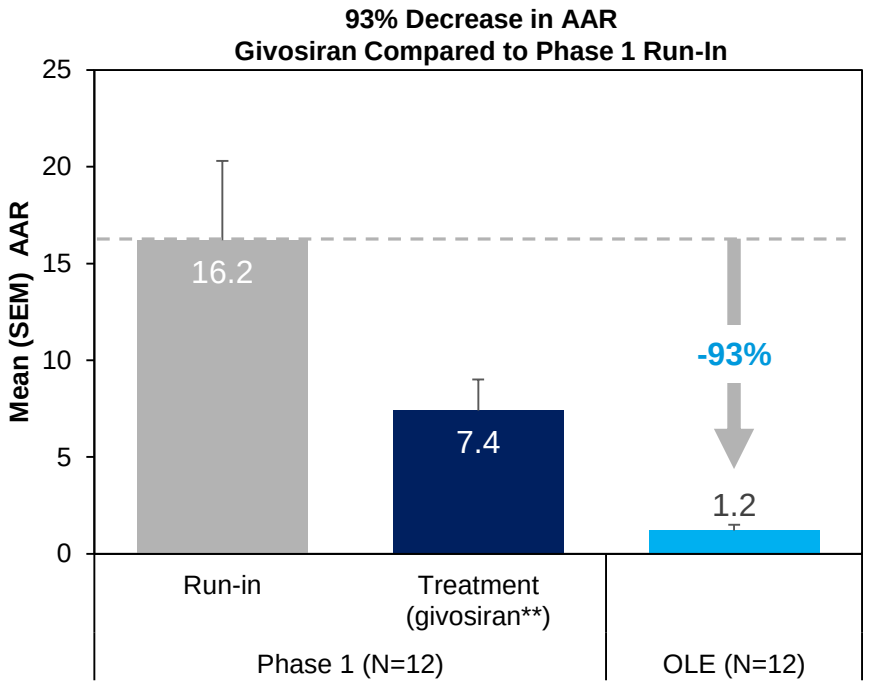


ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. ALAS1; ALA synthase 1

Givosiran Interim Phase 1 and OLE Study Results

Decreased Annualized Attack Rate (AAR)* Observed with up to 22 Months of Total Treatment in Phase 1 and OLE





Phase 1 and OLE Safety:
In OLE study (N=16):
- Two patients with SAEs, including one with anaphylactic reaction, assessed as definitely related to study drug. Patient had past history of asthma, oral allergy syndrome, and prior allergic reactions to acne cream and possibly latex gloves; patient discontinued from study
- Most common AEs: abdominal pain, nausea, injection site erythema, headache, injection site pruritis, fatigue, nasopharyngitis

In Phase 1 (N=40):
- Six patients with SAEs, including one who developed acute pancreatitis complicated by pulmonary embolism resulting in death, considered unlikely related to study drug
- Majority of AEs mild-moderate in severity

DURABILITY
Monthly SC dose regimen

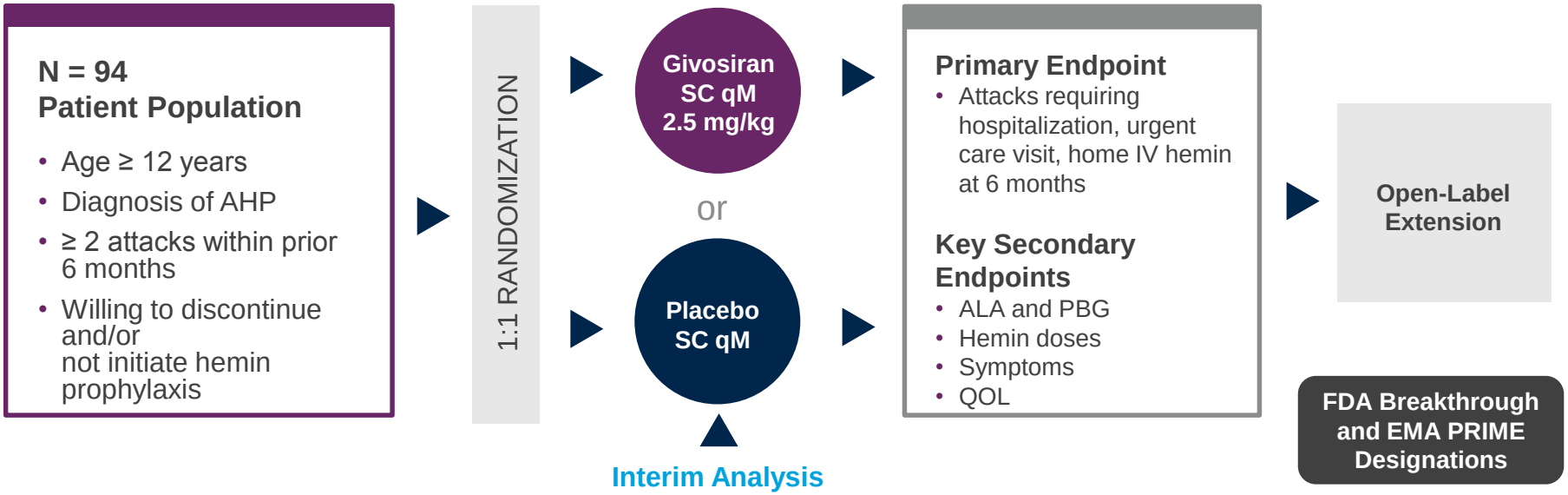
† Phase 1 and interim OLE study results as of Feb 26, 2018; Sardh *et al*., *EASL*, April 2018
* Includes attacks treated in healthcare facility or with hemin
** Aggregated across all dose groups
Mean time in Phase 1 run-in and treatment of 103 days and 165 days, respectively; mean time in OLE of 322 days

Alnylam PHARMACEUTICALS

ENVISION Phase 3 Study Design

Randomized, Double-Blind, Placebo-Controlled Study in Acute Hepatic Porphyria Patients

Enrollment completed well ahead of schedule – 94 AHP patients, 36 sites, 18 countries



Statistical Considerations:

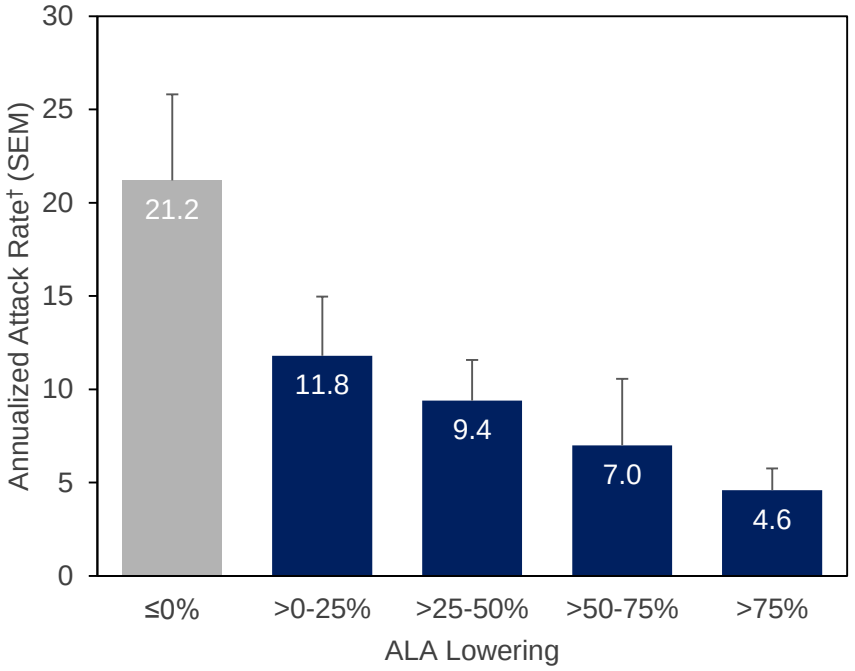
- N = 70 patients results in at least 90% power to detect 45% reduction in annualized attack rate at 2-sided alpha of 0.05
- Unblinded interim analysis of urinary ALA levels in 30 patients at 3 months

Alnylam PHARMACEUTICALS

Lowering ALA is Reasonably Likely to Predict Clinical Benefit

- ALA believed to be primary causal factor in disease manifestations*
  - Shown to induce oxidative stress, inflammation, vascular damage and cell death in multiple cell types
  - Demonstrated binding to γ-aminobutyric acid (GABA) receptors; hypothesized agonist activity in CNS
  - Similar symptoms occur in hereditary tyrosinemia and lead poisoning, associated with increased urinary ALA
  - Observational studies show higher ALA levels are associated with greater disease activity, while ALA lowering interventions (e.g., hemin or liver transplantation) result in acute attack resolution
- Alignment with FDA that reduction of urinary ALA is reasonably likely to predict clinical benefit

- Graded relationship observed between ALA lowering and AAR in givosiran Phase 1**



*Bissell et al., Am J Med, 2015. 128(3): 313-7.; Muller et al., Ann Neurol 1977;2:340-2; Monteiro et al., Biochim Biophys Acta 1986;881:100-6; Pallet et al. Kidney Int 2015;88:386-95.; Kauppinen, et al., Clin Chem 2002;48:1891-900.
**Sardh et al. EASL Meeting, Apr 2018
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home

ENVISION Interim Results*

Interim Efficacy Analysis & Safety

Interim analysis cohort

- N = 43 AHP patients (41 AIP; 1 VP; 1 HCP)
  - 23 randomized to givosiran; 20 randomized to placebo
- Treatment period: ≥3 months

Interim efficacy analysis (ALA levels at 3 months in AIP patients)

- Statistically significant reduction in urinary ALA, relative to placebo ($p < 0.001$)

Safety

- No deaths
- Serious Adverse Events (SAE) reported in:
  - 5/23 (22%) of patients on givosiran
  - 2/20 (10%) of patients on placebo
- One patient (4%) on givosiran discontinued treatment based on a protocol-defined stopping rule due to >8x ULN increase in liver transaminase, which resolved
- No treatment discontinuations in placebo group

*Data cut-off date of August 22, 2018

Givosiran, an Investigational RNAi Therapeutic for AHPs

Next Steps

Continued execution of ENVISION study

- Enrollment completed August 2018
- Topline results on full study expected early 2019

Engage with FDA to discuss potential NDA filing for Accelerated Approval

- Potential Accelerated Approval filing at or around year-end 2018
- 4-6 month timing impact if filing delayed for completed Ph 3 study attack data compared with an NDA for accelerated approval

ENVISION Interim Analysis

Q&A Session


THANK YOU
Alnylam
PHARMACEUTICALS