Rose
Living with Porphyria

Fitusiran and Givosiran Pipeline Updates

September 7, 2017

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Agenda

Welcome

- Christine Regan Lindenboom
  Vice President, Investor Relations & Corporate Communications

Introduction

- John Maraganore, Ph.D.
  Chief Executive Officer

Fitusiran and Givosiran Pipeline Updates

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

Q&A Session

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Reminder: Today at 10:30 a.m. ET

Givosiran, in development for the treatment of acute hepatic porphyrias

Featured speakers include:

- Jeff Miller, General Manager, Givosiran
- Jae Kim, M.D., Vice President, Clinical Development
- Guest Speaker: Eliane Sardh, M.D., Ph.D., Porphyria Center Sweden, Karolinska University Hospital

Visit the Investors page of alnylam.com to register for this event. Additional details, as well as replays, slides and transcripts for all past webcasts, can be accessed via the Capella section of the company's website, www.alnylam.com/capella.

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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 quarterly 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 3 Strategic Therapeutic Areas (STArs):

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

		HUMAN POC*	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL	COMMERCIAL RIGHTS
Patisiran	*Hereditary ATTR Amyloidosis*	✓		●		US, Canada, Western Europe
Fitusiran**	*Hemophilia and Rare Bleeding Disorders*	✓		●		50% US, Canada, Western Europe
Inclisiran	*Hypercholesterolemia*	✓		●		Milestones & Royalties
Givosiran	*Acute Hepatic Porphyrias*	✓		●		Global
ALN-CC5	*Complement-Mediated Diseases*	✓	●			Global
ALN-GO1	*Primary Hyperoxaluria Type 1*	✓	●			Subject to partner option rights
ALN-TTRsc02	*Hereditary ATTR Amyloidosis*	✓	●			Subject to partner option rights
ALN-HBV	*Hepatitis B Virus Infection*		●			Global

*Proof of concept defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
**Fitusiran currently on hold with intent to resume dosing as soon as possible upon agreement with regulatory authorities on risk mitigation/safety monitoring

Akshay Vaishnaw, M.D., Ph.D.,
Executive Vice President of R&D

Fitusiran and Givosiran Pipeline Updates

Fitusiran Phase 2 Open-Label Extension (OLE)

Study Design & Patient Disposition; Currently on Hold

Patients previously dosed in Phase 1* study eligible to roll over onto Phase 2 OLE^ study

Phase 1, Part B (N=12 patients with HA or HB)

15, 45, 75 mcg/kg qW x 3 SC

Phase 1, Part C (N=18 patients with HA or HB)†

225, 450, 900, 1800 mcg/kg, or 80 mg qM x 3 SC

Phase 1, Part D (N=16 patients with HA or HB with inhibitors)

50, 80 mg qM x 3 SC

Phase 2 OLE‡ (n= 33)

50 mg qM SC

80 mg qM SC

- Individual patient dose adjustment may be allowed (per SRC)
- Days between doses in Phase 1 and Phase 2 OLE ranged from 30 (no interruption in dosing) to 461

OLE, open-label extension; SC, subcutaneous

*ClinicalTrials.gov Identifier:NCT02035605; EudraCT: 2013-003135-29; Pasi KJ, et al. *N Engl J Med. 2017; epub ahead of print.*; Pasi KJ et al. *Blood*. 2016, 128: 1397

^ClinicalTrials.gov Identifier: NCT02554773; EudraCT: 2015-001395-21

†5 patients participating in Part C previously participated in Part B

‡3 patients started Phase 2 OLE at their original Phase 1 dose; later they were converted to 50 mg or 80 mg

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

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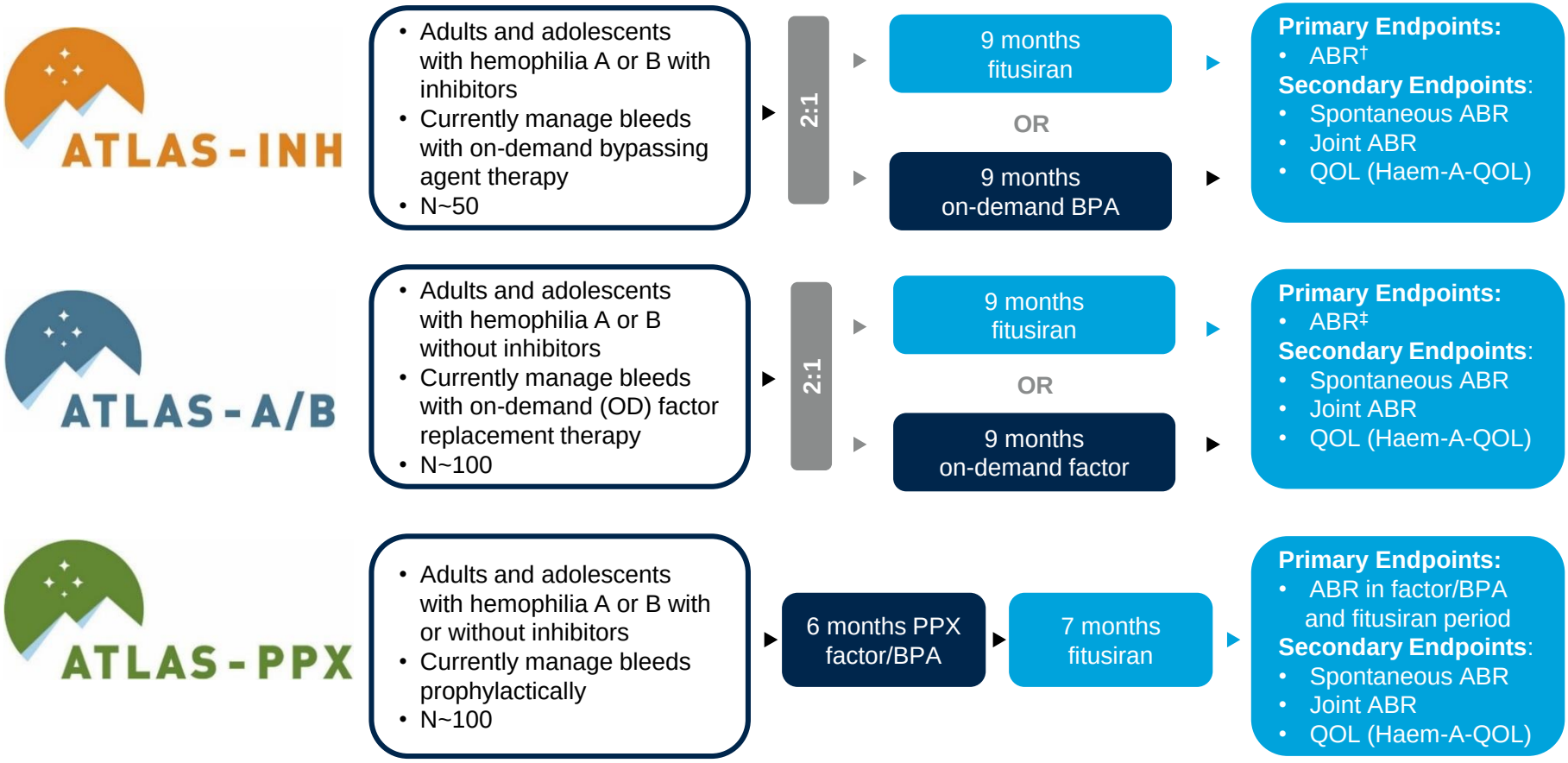
Recent Safety Update in Fitusiran Program

- Report of SAE of subarachnoid hemorrhage in Phase 2 OLE study in hemophilia A patient without inhibitors
  - Reported as unrelated to fitusiran
  - ~1 week prior to hospital admission for severe headache, patient experienced hip pain treated with 3 doses of FVIII, ranging from 31 to 46 IU/kg, on three separate days; doses are above recommended range for mild or moderate bleeds per product label
  - CT scan was read as subarachnoid hemorrhage, and patient was treated with replacement factor therapy 2-3 times daily
  - Clinical course deteriorated with subsequent cerebral edema and death
- Alnylam initiated further investigation including review of patient's CT scans by 3 independent neuro-radiologists, who all confirmed on Sept 1, 2017, that initiating event was cerebral venous sinus thrombosis, not subarachnoid hemorrhage
- Alnylam elected to temporarily suspend dosing in fitusiran studies to further investigate safety finding and develop risk mitigation plan
  - Company also notified study investigators and global regulatory authorities
- Based on fitusiran benefit-risk profile, aim to resume dosing in fitusiran studies as soon as possible, potentially in late 2017, upon agreement with global regulatory authorities, and with appropriate protocol amendments for enhanced patient safety monitoring

Fitusiran ATLAS Phase 3 Program
Initiated in July 2017; Currently on Hold*



Patients who complete the study may be eligible for fitusiran treatment in ATLAS-OLE study

*Intend to resume dosing as soon as possible upon agreement with regulatory authorities on risk mitigation/safety monitoring
†ATLAS-INH powered to detect as little as a 60% reduction from control to fitusiran
‡ATLAS-A/B powered to detect as little as a 50% reduction from control to fitusiran

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Acute Hepatic Porphyrias

Disease Overview

Acute Hepatic Porphyrias (AHP)[1,2]

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

Disease Pathophysiology

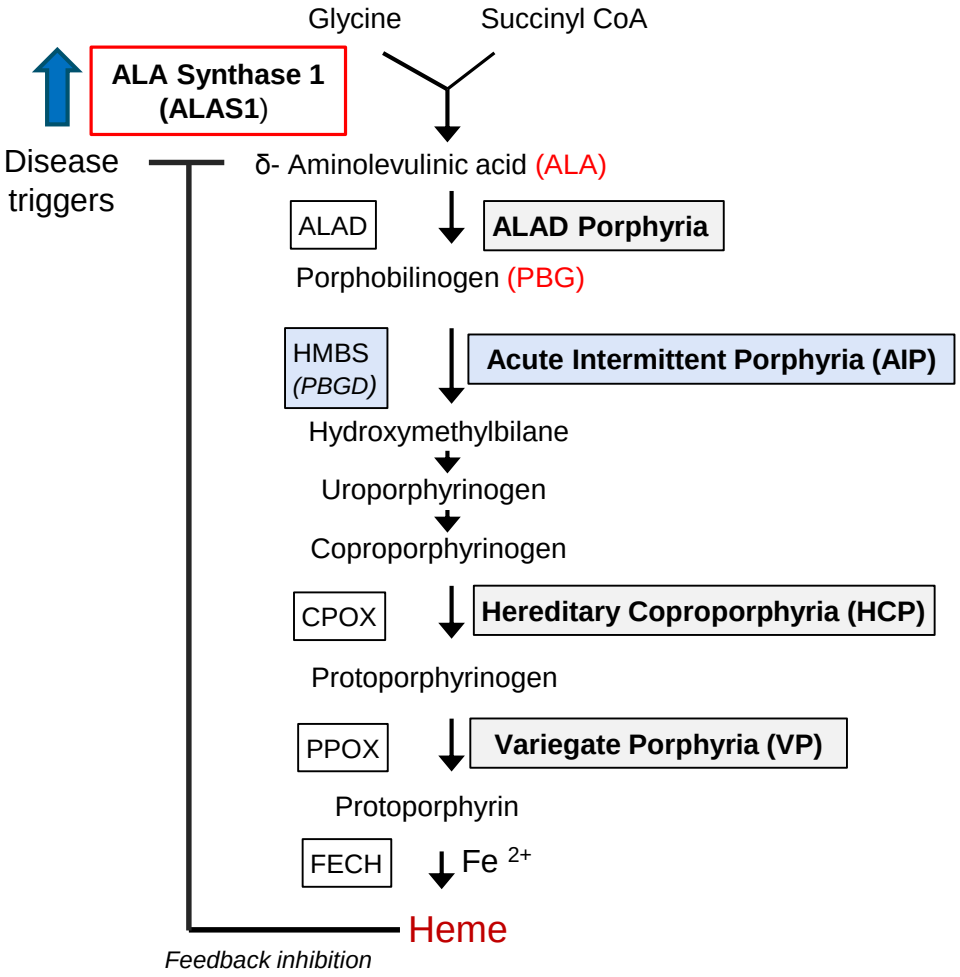
- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA/PBG that cause disease manifestations

Acute 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 more efficacious, long acting, and safer therapies to prevent attacks and improve chronic disease manifestations



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

Givosiran Interim Phase 1 Study Results*

Ongoing Randomized, Double-Blind, Placebo-Controlled Study in Recurrent Attack Porphyria Patients

Up to **79%** **lowering of ALA,** **77%** **lowering of PBG**

73% Mean Decrease in **Annualized Attack Rate**** compared with placebo

73% Mean Decrease in **Annualized Hemin Use**

Initial evidence for **further reductions in annualized attack rate** with extended dosing in OLE

DURABILITY

Monthly and possibly **quarterly** SC dose regimen

Initial Evidence for Clinical Activity in Recurrent Attack Porphyria Patients

Safety: Generally well tolerated (N=9)

- No drug-related SAEs and no discontinuations due to AEs
  - As reported previously, one patient developed acute pancreatitis complicated by pulmonary embolism resulting in death, considered unlikely related to study drug
- Majority of AEs mild-moderate in severity
- AEs possibly related include ISRs, hypersensitivity, myalgia, headache, moderate renal impairment (in patient with history of same), and erythema
- No clinically significant changes in vital signs, EKG, or clin labs

PLANNED NEXT STEPS

Start Phase 3 in late **2017**

FDA Breakthrough and EMA PRIME Designations

Alnylam retains global rights to the givosiran program

*Interim Phase 1 study results as of Apr 21, 2017; Sardh *et al.*, *ICPP*, June 2017; ** Includes attacks treated in healthcare facility or with hemin

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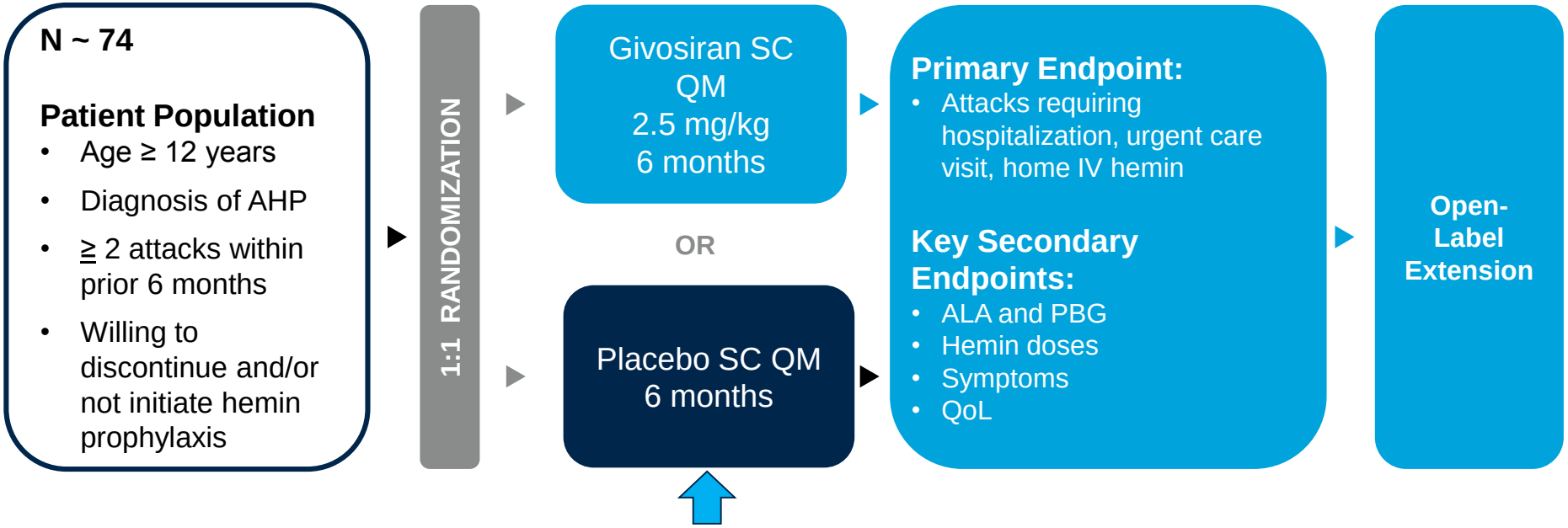
Givosiran Phase 3 Study Design; Plan to Initiate in Late ’17

Randomized, Double-Blind, Placebo-Controlled Study, Followed by Open-Label Extension



Interim analysis when 30 patients complete 3 months treatment - mid-2018 interim readout, supporting potential NDA at or around YE 2018 (if positive); potential FDA approval early-to-mid 2019

Statistical Considerations

- 70 patients will have at least 90% power to detect 45% reduction in annualized attack rate at 2-sided alpha of 0.05
- Unblinded interim analysis in 30 patients using endpoint of ALA level at 3 months
  - ➢ No plan to stop early for efficacy or futility

Global Footprint

Plan to conduct Phase 3 in ~22 countries

*Preliminary plans subject to further diligence and health authority feedback

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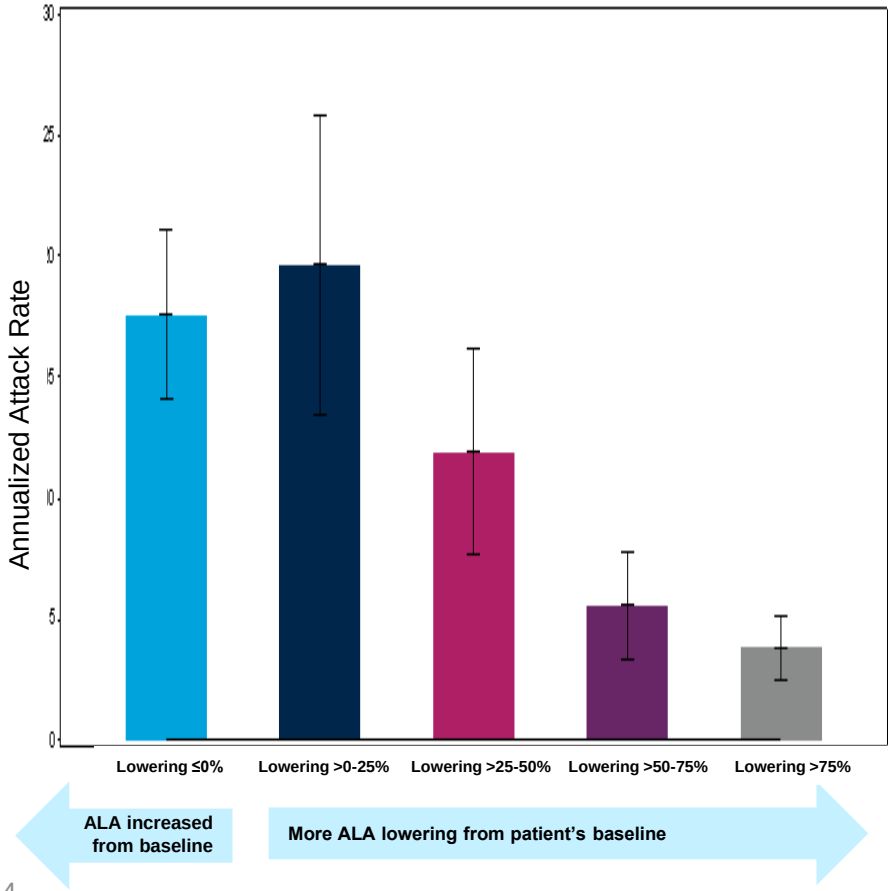
Interim Analysis in Givosiran Phase 3 Study

If Positive, Supports Potential NDA at or around YE 2018

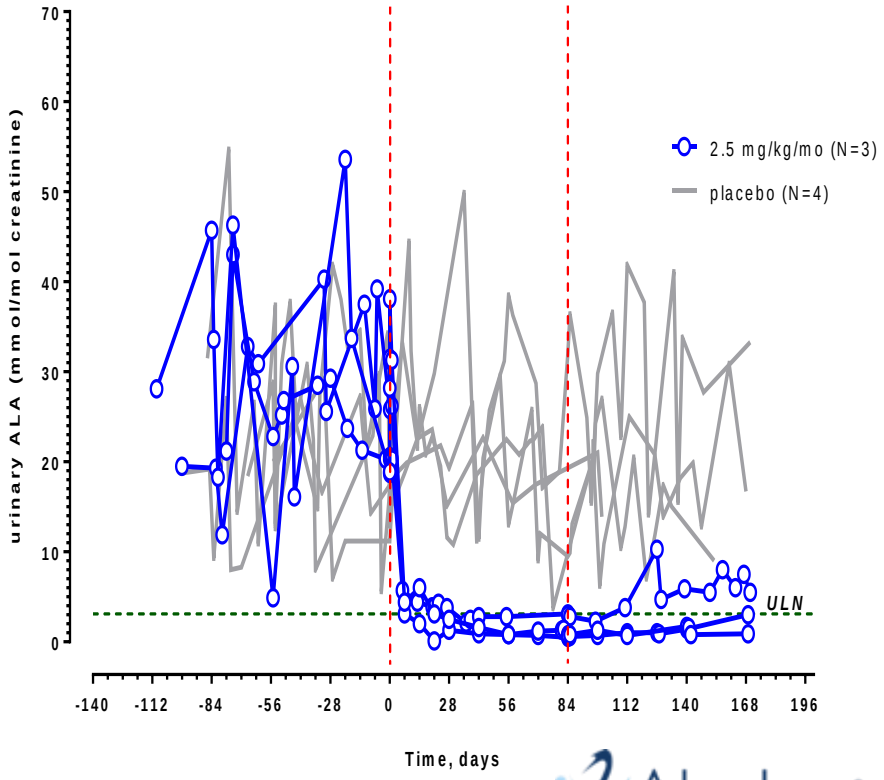
Alignment with FDA that reduction of urinary ALA is reasonably likely to predict clinical benefit

- Interim analysis with ~30 patients after 3 mo dosing; expect data in mid-2018

Relationship of ALA Lowering with Annualized Attack Rate*



ALA Lowering in Phase 1, Part C at 2.5 mg/kg qM



*Sardh *et al.*, *ICPP*, June 2017; Includes attacks treated in healthcare facility or with hemin

Q&A Session

Thank You

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