Development of RNAi Therapeutics for Rare Diseases

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Emerging Technologies for Rare Diseases
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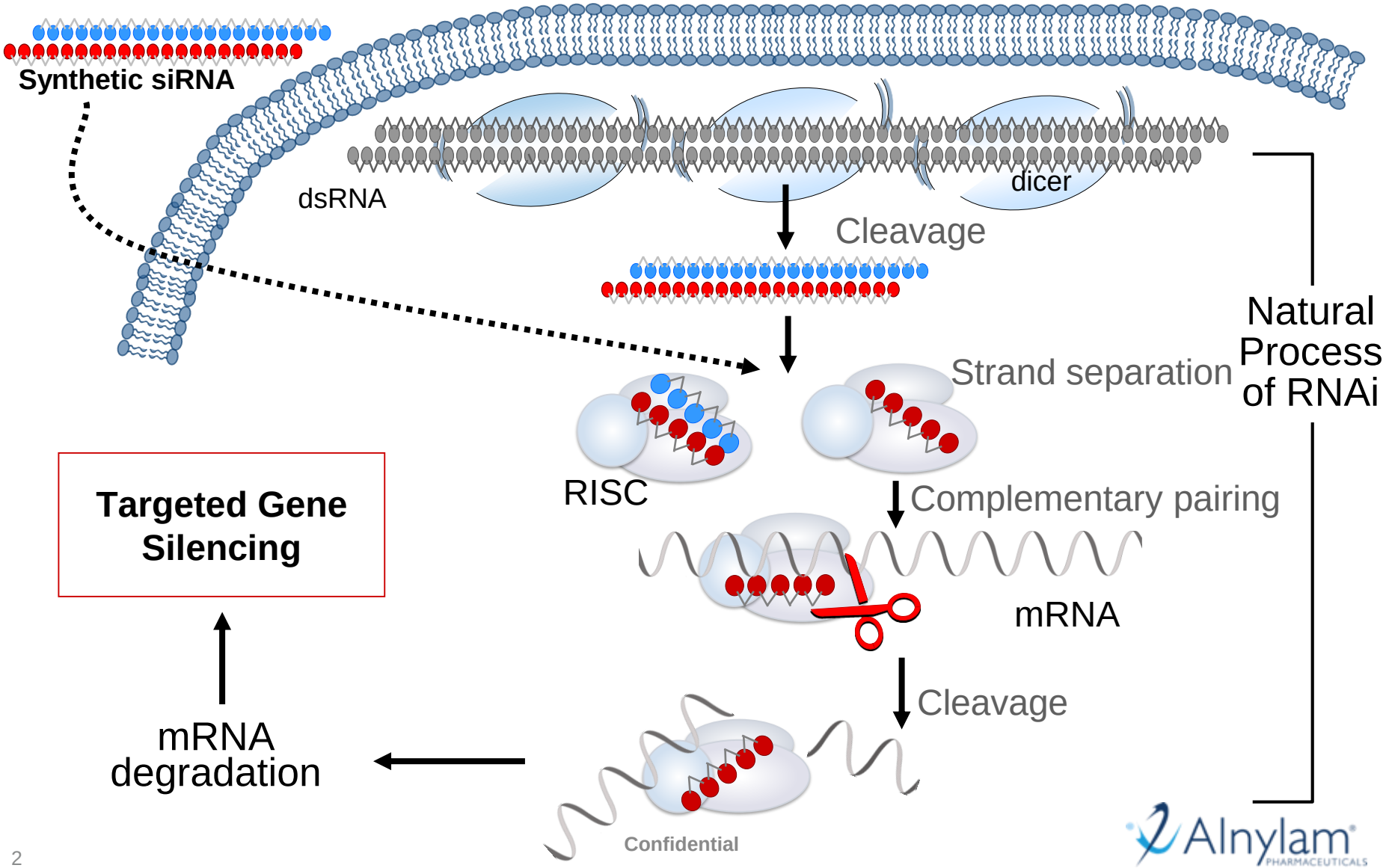
Mechanism of RNA Interference (RNAi), A Natural Endogenous Pathway



Alnylam Platform and R&D Strategy

Building a Pipeline of Potentially Transformative Medicines

Genetically validated, liver-expressed target gene

Biomarker for Proof of Concept in Phase 1

Definable path to potential approval and patient access

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Hereditary ATTR (hATTR) Amyloidosis

DESCRIPTION

Orphan multi-system disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart, GI tract, and other tissues

Significant morbidity and fatal within **2-15** years from symptom onset

PATIENT POPULATION*

~50,000 worldwide

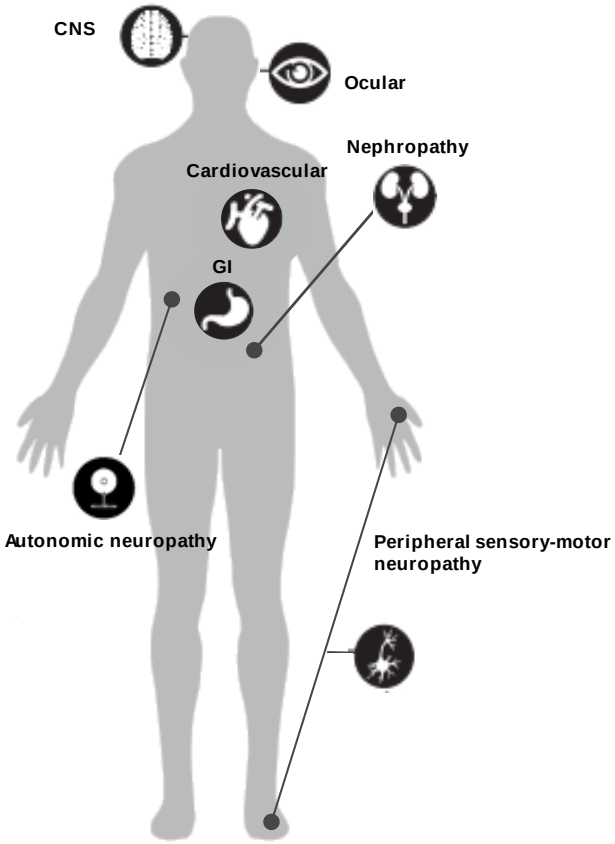
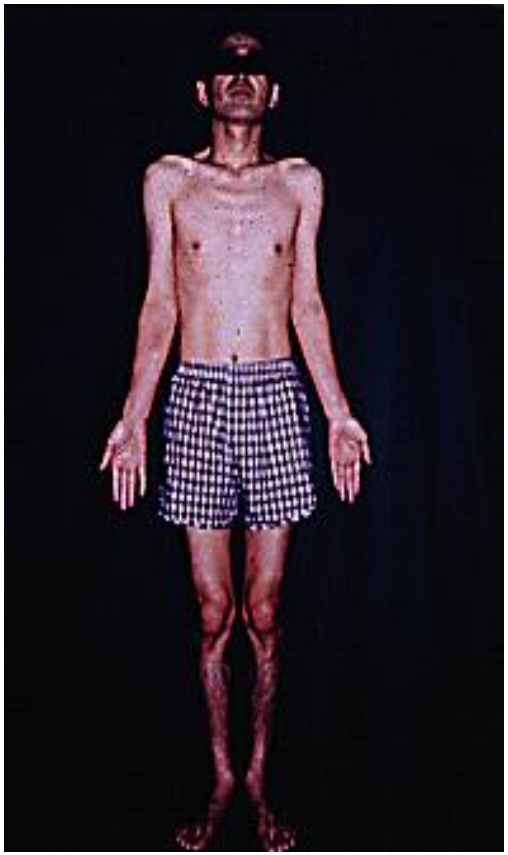
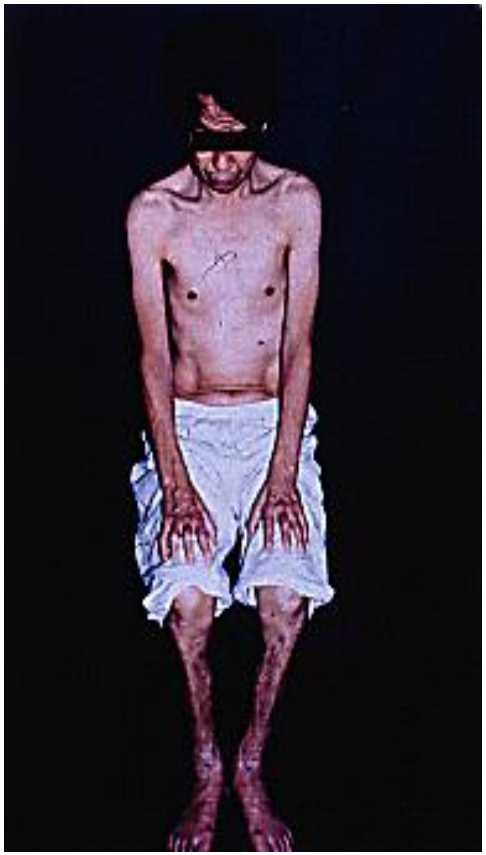
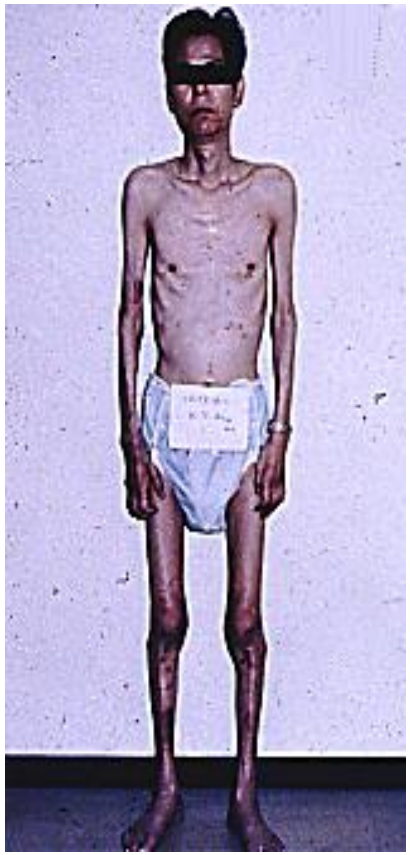
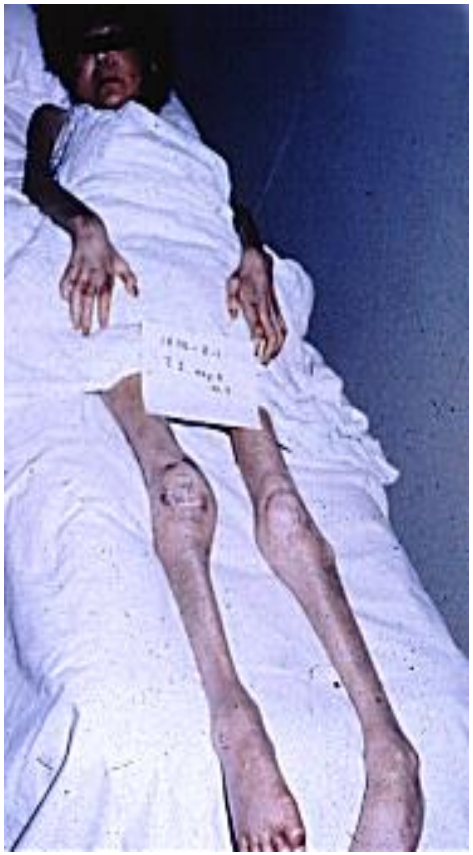


Image based on Conceicao *et al*., *J Peripher Nerv Syst*, 2016;21:5–9
*Ando *et al., Orphanet J Rare Dis*, 2013; Ruberg *et al., Circulation*, 2012

Peripheral Neuropathy in hATTR Amyloidosis

Stage 1 → (4-5 years) → Stage 2: Early → (2-3 years) → Stage 2: Late → (1-2 years) → Stage 3

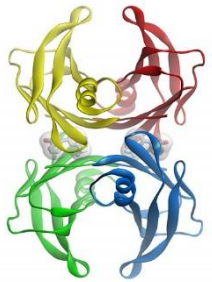
Patisiran in Development for hATTR Amyloidosis

Potential for Disease Modification by Reducing Pathogenic Protein

Genetically validated, liver-expressed target gene

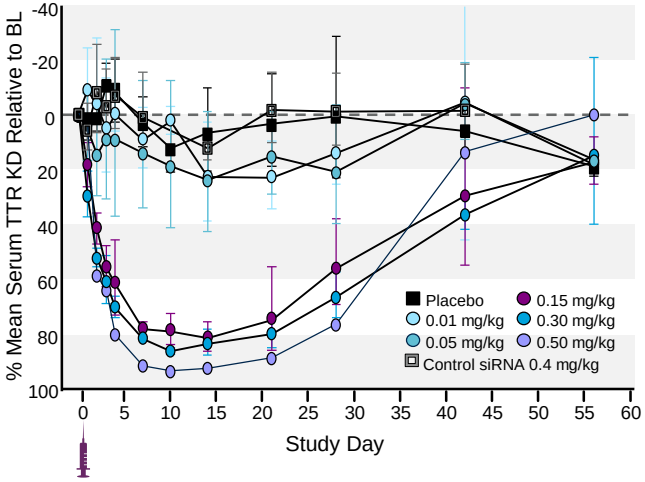
Biomarker for POC in Phase 1

Definable path to potential approval and patient access



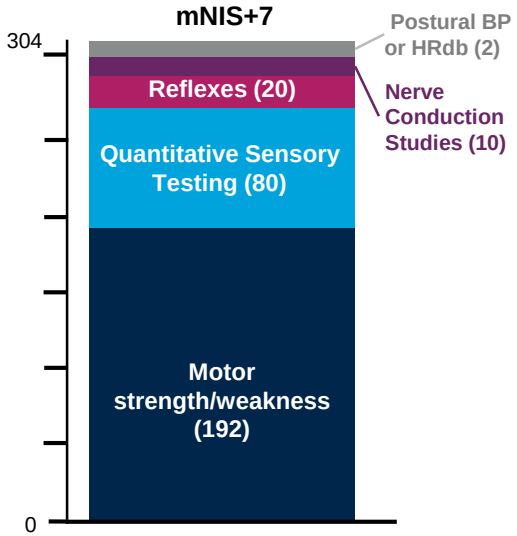
Mutant **Transthyretin (TTR)** is disease-causing protein

Serum Biomarker
TTR

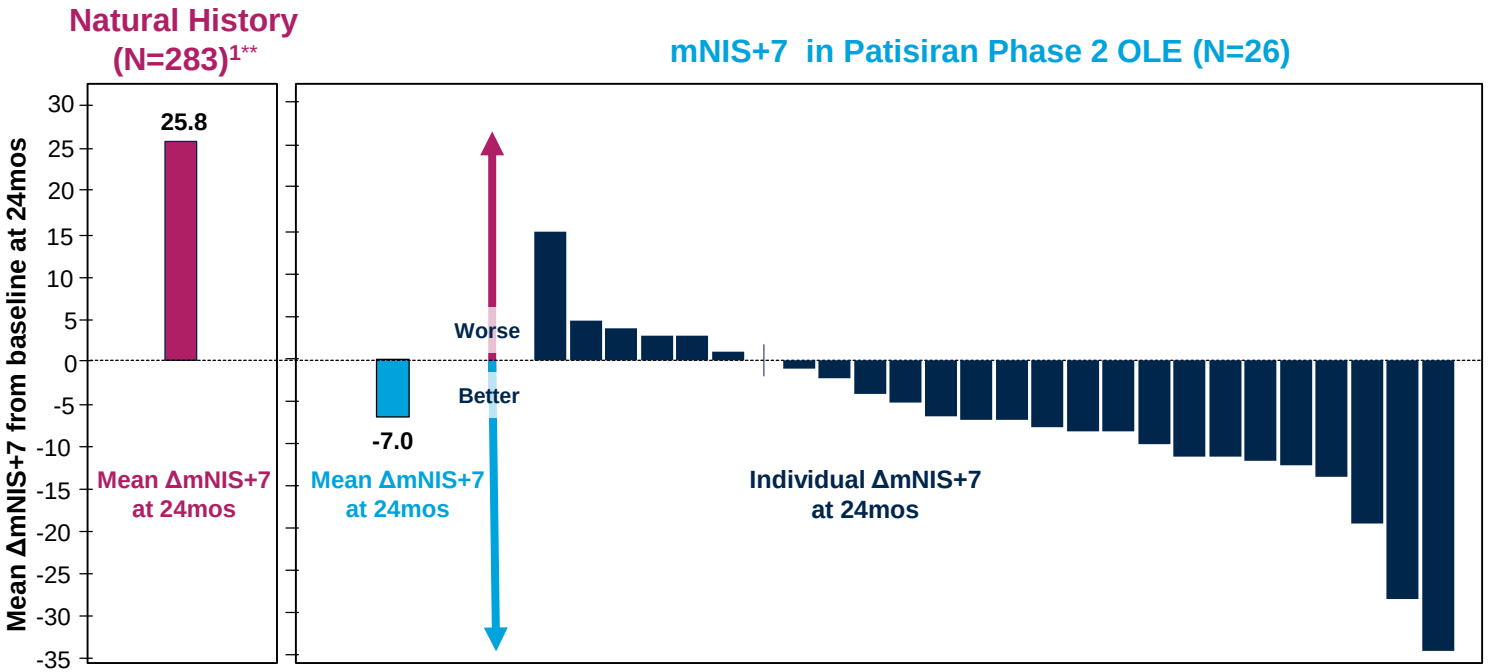


Patisiran Phase 1 results: Coelho *et al., N Engl J Med*;369:819-29 (2013)

Clinical Endpoint
Neurological Impairment Score



Patisiran Final Phase 2 OLE Study Results*
Study in hATTR Amyloidosis Patients with Polyneuropathy



Safety: Generally well tolerated out to 25 months (N=27)

- 10 non-drug related SAEs in 7 patients
- Majority of AEs mild to moderate, including mild flushing (22.2%) and mild infusion-related reactions (22.2%)
- No significant lab findings; no drug-related discontinuations
- No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

* Modified Neuropathy Impairment Score (mNIS+7) -Final Phase 2 OLE results; Adams *et al.*, *AAN*, April 2017

[1]Adams D *et al.*, *Neurology. 85;675-682* (2015); **Predicted progression of median NIS value from Gompertz curve fit

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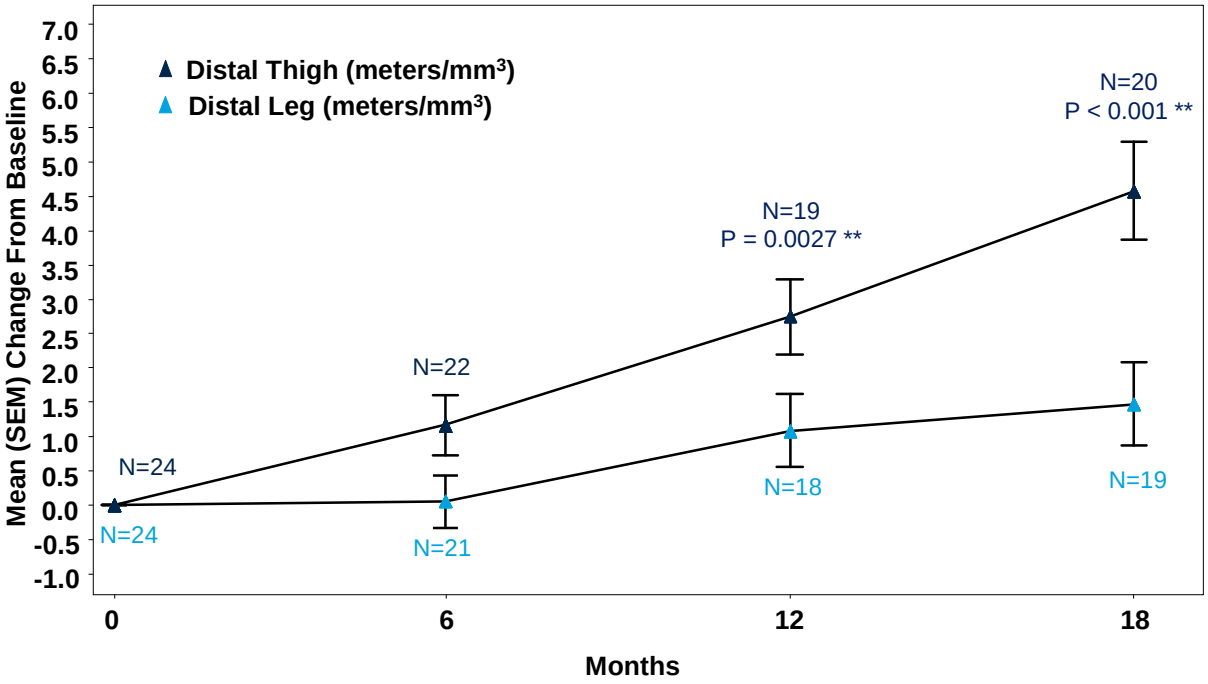
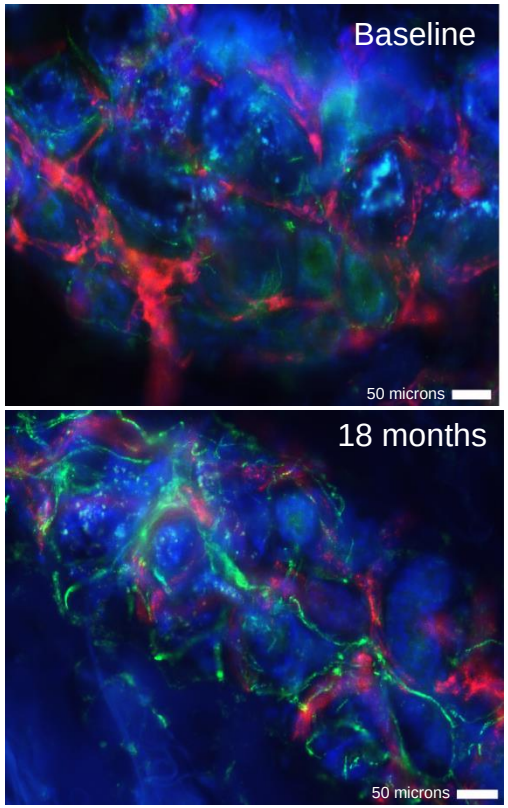
Patisiran Phase 2 OLE Preliminary Study Results*

Sweat Gland Nerve Fiber Density (SGNFD): Lower Limb



Distal thigh sweat gland innervation† in Patient 050-0005



†Green: PGP 9.5 (nerve fibers)
Red: CD31 (blood vessels)
Blue: DAPI (nuclei)

** 2-sided p values from paired t-test comparing post-baseline vs baseline
[1]Chao C et al., Ann Neurol. 78:272-83 (2015)
**Data as of February 23, 2016*

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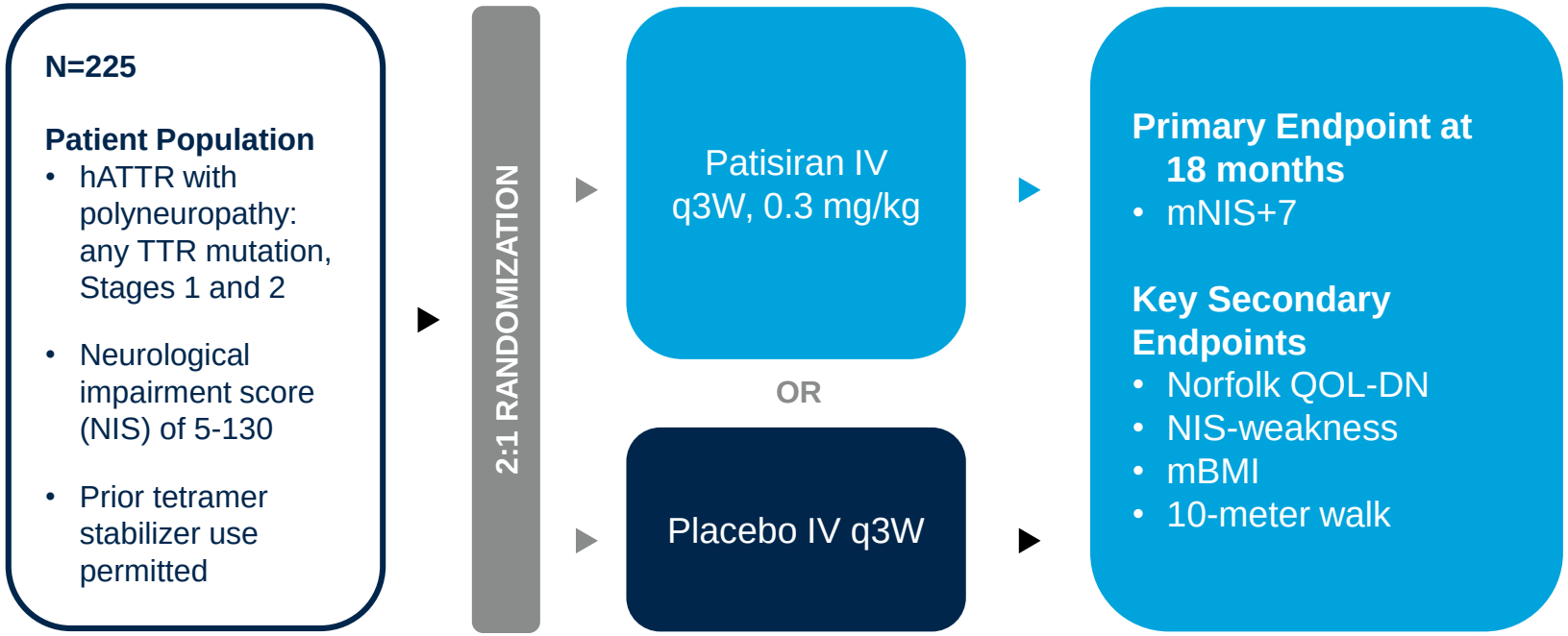
APOLLO Phase 3 Study Design



All completers eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE)

Enrollment completed; mid-2017 top-line data readout, supporting 2017 NDA/MAA if positive

Statistical Considerations

- Placebo-estimated mNIS+7 progression rate of 17.8 points/year derived from natural history study of 283 hATTR patients with polyneuropathy
- 90% Power to detect a 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha=0.05
  - Based on original target enrollment of 200 patients

Clinicaltrials.gov # NCT01960348

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Hemophilia and Rare Bleeding Disorders

DESCRIPTION

Genetic deficiency resulting in inability to generate thrombin and stop bleeding

PATIENT POPULATION*

Hemophilia A and B

200,000 **worldwide**

~4,000 **with inhibitors**

Highest need is **prophylaxis** for **inhibitor** patients and to **avoid** inhibitor **formation** in **all** patients

Global need due to **frequent IV infusions, ability to manufacture,** and **cold chain**

*World Federation of Hemophilia, *Report on the Annual Global Survey 2014,* October 2015

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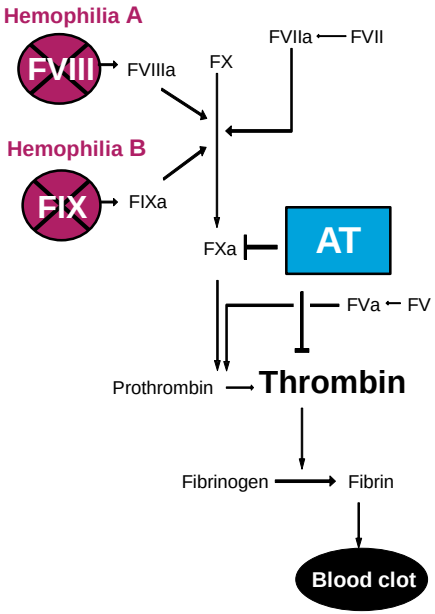
Fitusiran in Development for Hemophilia

Potential to Restore Hemostasis in Hemophilia

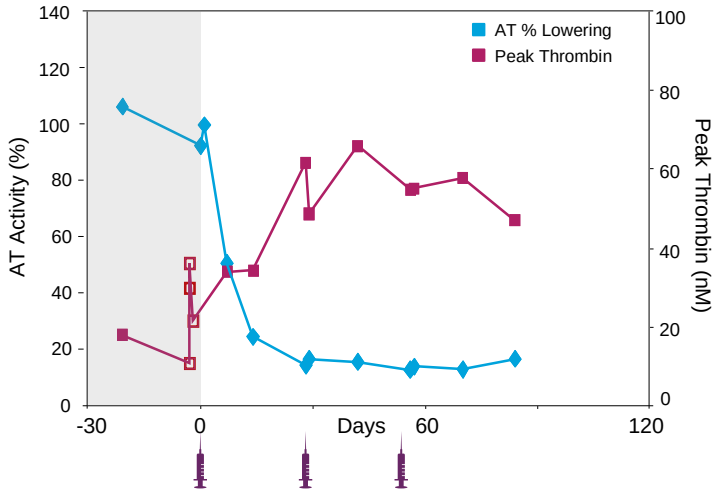
Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to potential approval and patient access



Plasma Biomarkers Antithrombin Lowering, Thrombin Generation



Fitusiran Phase 1 results: Pasi *et al.*, *WFH*, July 2016

Established Endpoint Annualized Bleeding Rate (ABR)

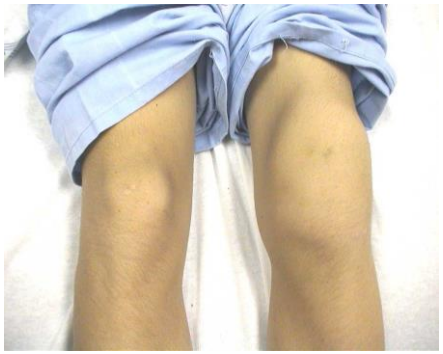
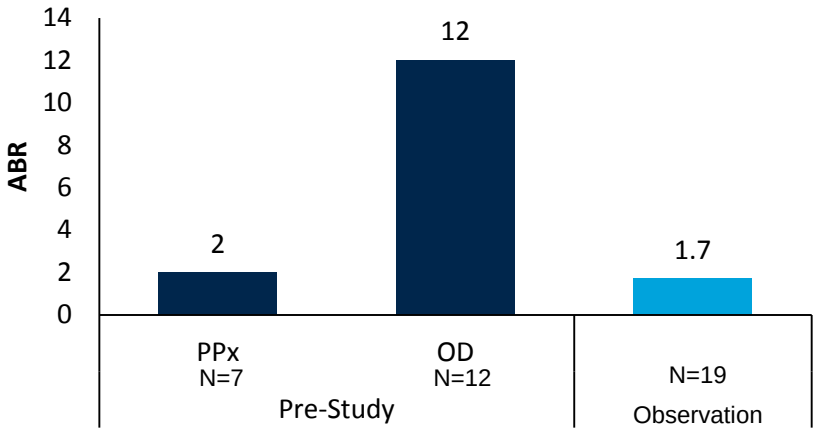


Photo courtesy of Guy Young, M.D. Director, Hemostasis & Thrombosis Center at Children's Hospital Los Angeles and Professor of Pediatrics, USC Keck School of Medicine

Fitusiran Phase 2 OLE Study Results*

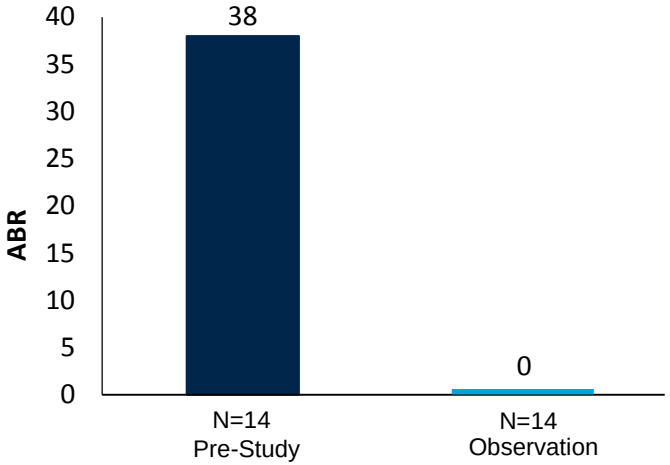
Ongoing Study in Hemophilia A & B Patients, Including Inhibitors; Currently on Hold

Summary of Median ABRs in Patients without Inhibitors



- Median duration in observation period: 13 months [range: 2 –19]
- Mean AT activity in observation period (relative to baseline): 22%

Summary of Median ABRs in Patients with Inhibitors



- Median duration in observation period: 6 months [range: 1 –11]
- Mean AT activity in observation period (relative to baseline): 18%

Updated Safety in Phase 2 OLE (N=33)

- 3 SAEs considered possibly related to study drug
  - Fatal cerebral venous sinus thrombosis resulting in suspension of dosing and evaluation of enhanced safety monitoring, currently in planning
  - Asymptomatic transaminase elevation in HCV infected patient and seizure in patient with seizure history
- Majority of AEs mild or moderate in severity, unrelated to study drug
  - Mild ISRs in 6 (18%) patients
- ALT increases >3x ULN observed in 11 (33%) patients
  - All asymptomatic, with no concurrent elevations of bilirubin >2x ULN
  - Reversible; all patients had medical history of HCV
- No instances of anti-drug antibody formation

*Clinical results as of Jun 15, 2017; Pasi *et al.*, *ISTH*, July 2017; updated to reflect cerebral venous sinus thrombosis case noted in safety box

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
- Patient had higher FVIII exposure than any other patient in study
- Alnylam and its partner Sanofi Genzyme elected to 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

Acute Hepatic Porphyrias

DESCRIPTION

Family of ultra-rare orphan diseases causing incapacitating and potentially fatal attacks

PATIENT POPULATION*

~5,000 Patients with **sporadic attacks** in U.S./EU

~1,000 Patients with **recurrent attacks** in U.S./EU

Disease burden includes:

- Acute, Severe Abdominal Pain
- Frequent Hospitalizations
- Peripheral and Autonomic Neuropathy
- Neuropsychiatric Symptoms
- Chronic Pain

Predominantly **female,** commonly misdiagnosed

*ORPHANET; The Porphyria Consortium

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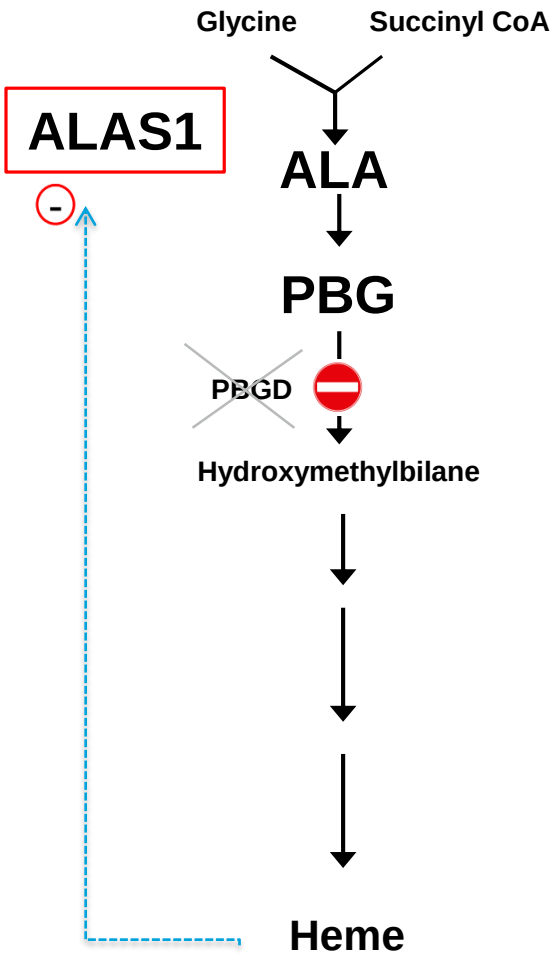
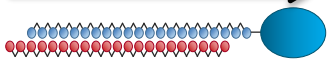
Givosiran Therapeutic Hypothesis

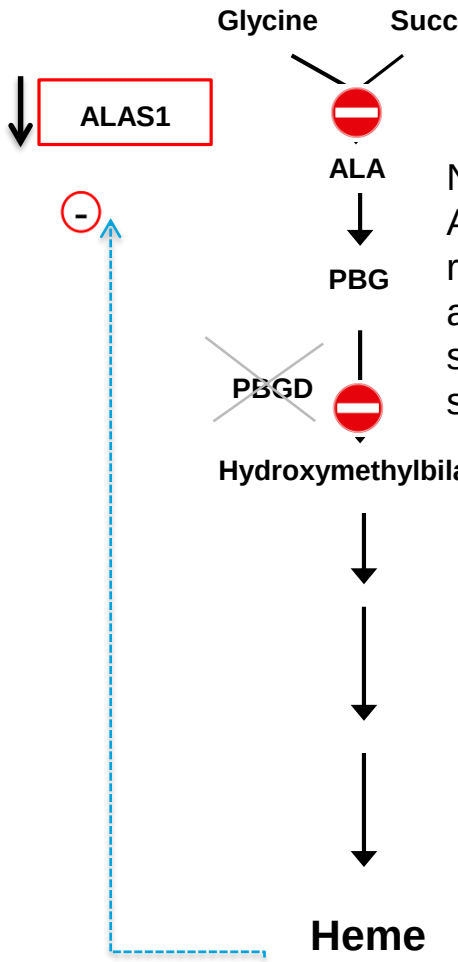
Heme Synthetic Pathway in AIP



Givosiran siRNA



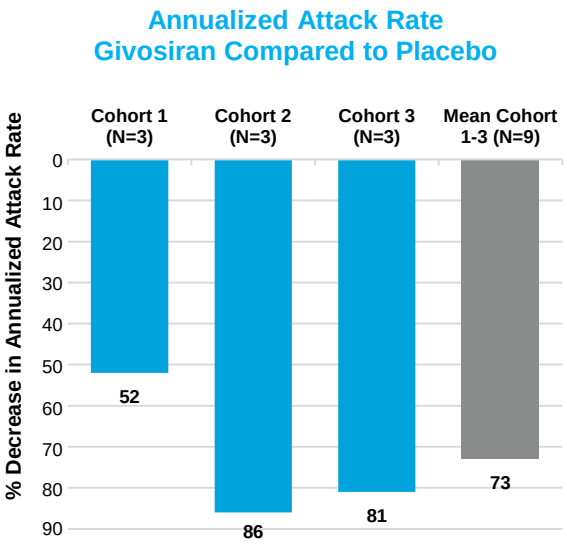
ALN-AS1 Effect in AIP

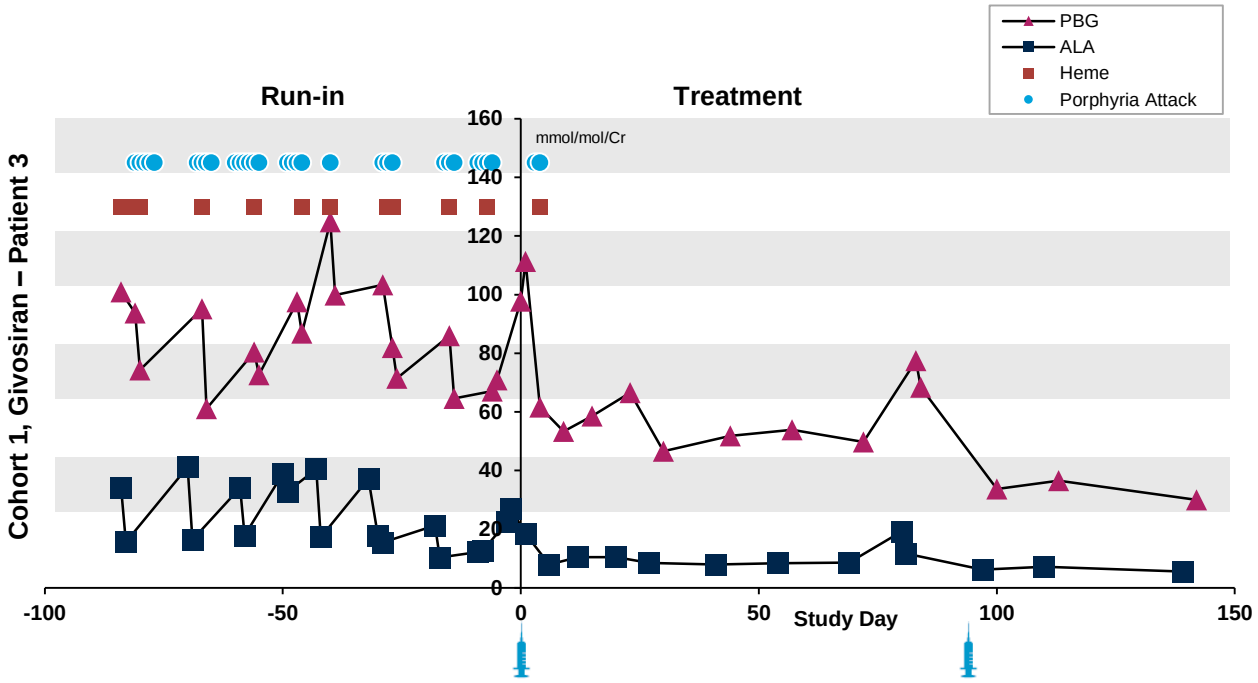


Normalization of ALN & PBG levels results in amelioration of signs and symptoms of AIP

Givosiran Interim Phase 1 Study Results*

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





Safety: (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

FDA Breakthrough and EMA PRIME Designations

*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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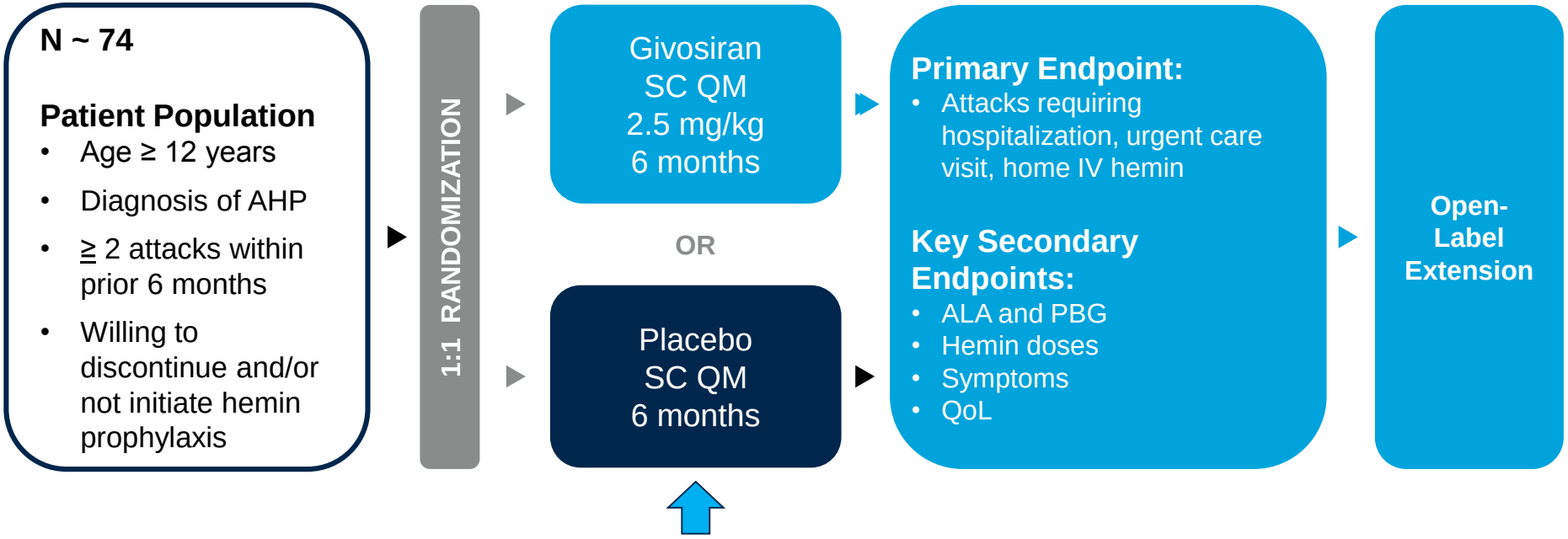
Givosiran Phase 3 Study Design

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



Interim analysis when 30 patients complete 3 months treatment*

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 reduction in urinary ALA level at 3 months
  - ➢ No plan to stop early for efficacy or futility

*Preliminary plans subject to further diligence and health authority feedback

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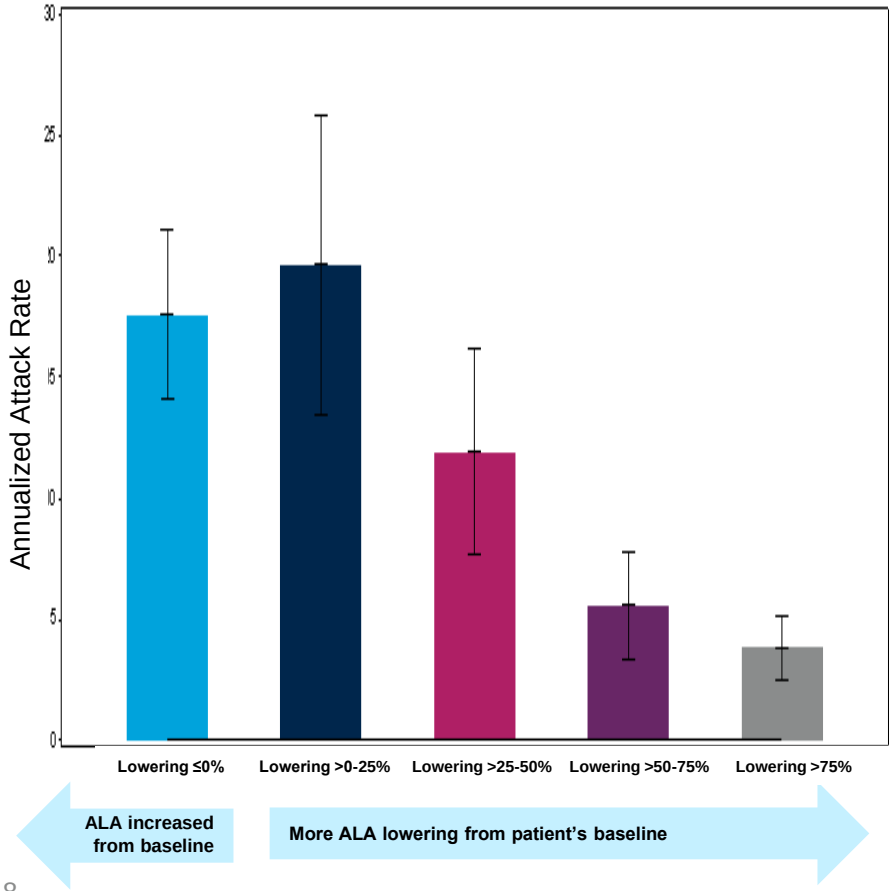
ALA Lowering and Clinical Outcome in Phase 1 Study

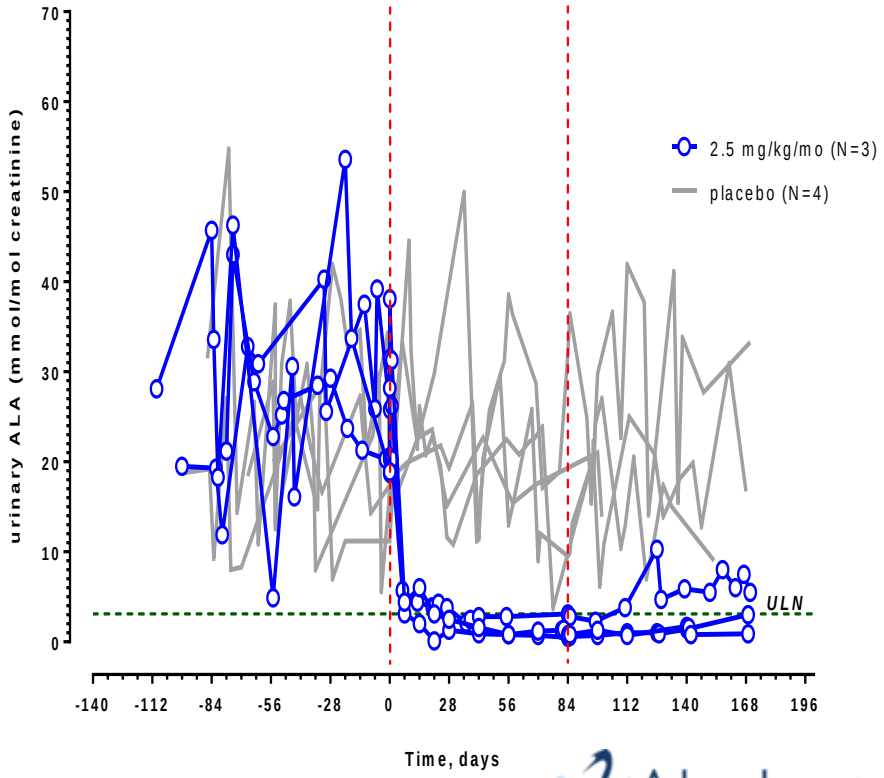
Alignment with FDA that reduction of urinary ALA is reasonably likely to predict clinical benefit

- Interim analysis with ~30 patients after 3 months dosing

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

Summary

RNAi Platform

- Reproducible, modular drug development platform
- Applicable to any gene in the genome
  - 8 POCs achieved in the clinic
- Rapid path from concept to clinic
- Significant platform efficiencies in nonclinical, CMC and clinical development
- Over 1400 patients and healthy volunteers dosed across 10 programs
  - Relevance of safety learnings from one program to others in pipeline

Lessons Learned in Orphan Disease Space

- Patient input and engagement key at all phases of development cycle
  - Understanding unmet need, target product profile, natural history, study design, product presentation, outreach and education
- Potential for accelerated drug development
  - e.g., givosiran program biomarker-based interim analysis for acute hepatic porphyrias
- Aligning study design and endpoint structure between regulators, patients and payers key
- Value of Breakthrough (US) and Prime (EU) Designation

Thank You

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