Rose
Living with Porphyria

New Clinical Results with Givosiran (ALN-AS1)

2017 International Congress on Porphyrins and Porphyrias (ICPP)
June 26, 2017

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Agenda

Welcome

- Christine Lindenboom
  Vice President, Investor Relations & Corporate Communications

Introduction

- Barry Greene
  President

Givosiran Clinical Results

- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice 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 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.

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Introduction

Barry Greene
President

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Givosiran Clinical Results

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

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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

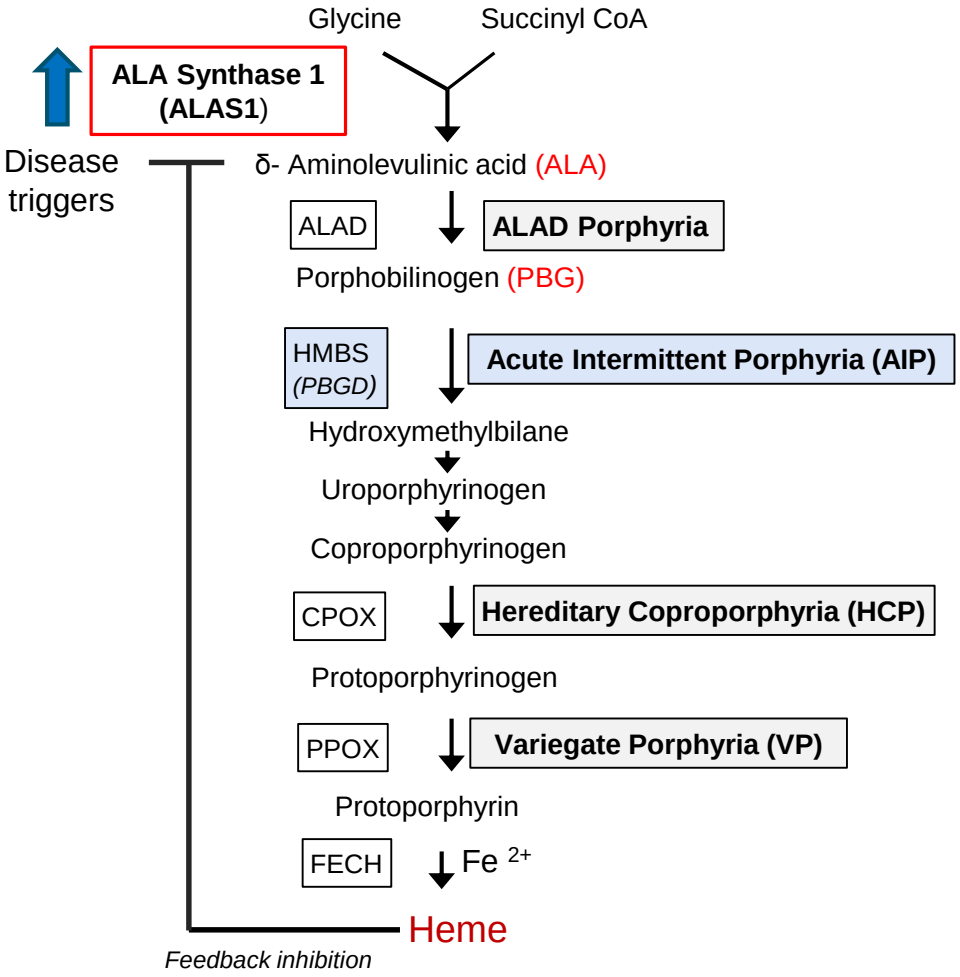
- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA/PBG that cause disease manifestations

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

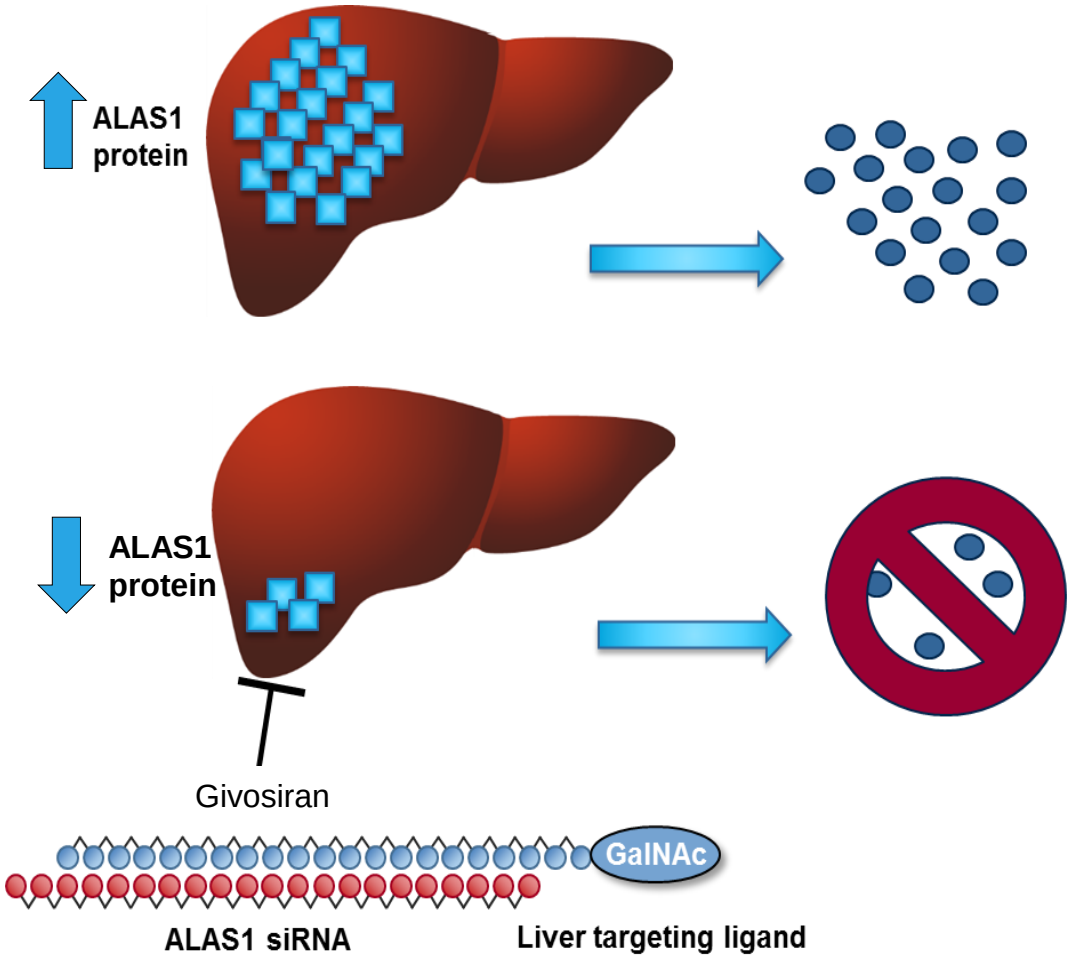


1.Bonkovsky, et al. Am J Med. 2014;127(12):1233-41; 2.Elder, et al. JIMD. 2013;36(5):849-57.

Givosiran: Investigational RNAi Therapeutic

Therapeutic Hypothesis

Reduction of Liver ALAS1 Protein to Lower ALA/PBG



ALA/PBG induce porphyria symptoms

Givosiran (ALN-AS1) results in knockdown of ALAS1 and lowers ALA/PBG production to prevent attacks and disease symptoms

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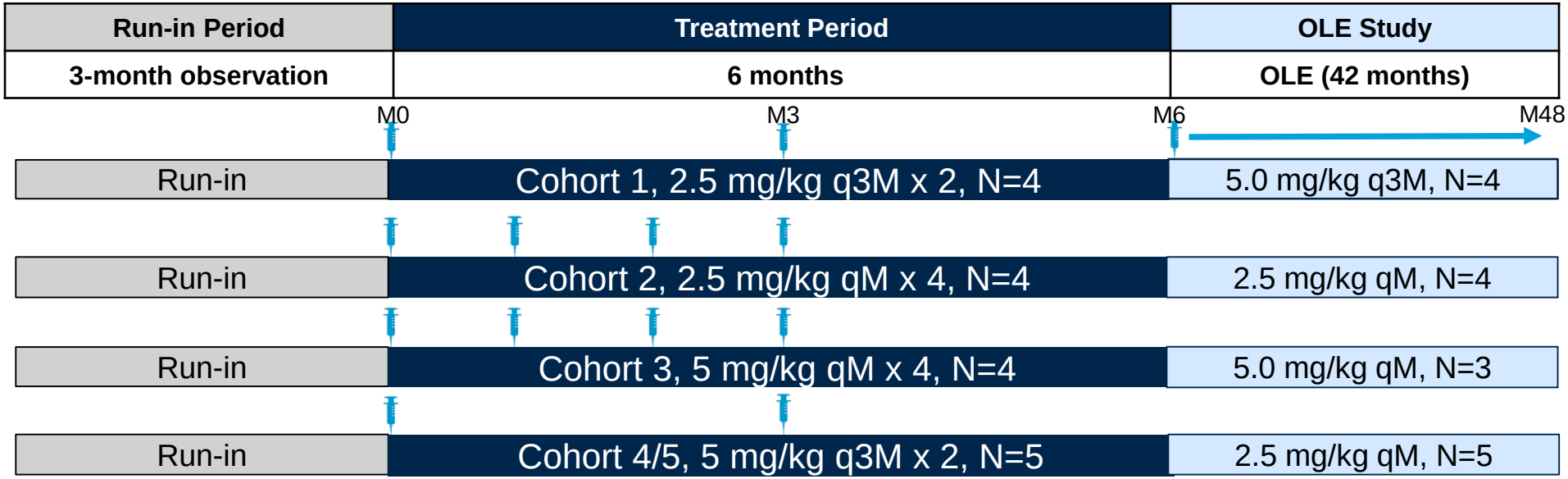
Givosiran Phase 1 (Part C and OLE) Study

Study Design and Objectives



Study Design

- Placebo-controlled, double-blind, randomized 3:1, MD in patients with AIP recurrent attacks
- Key Inclusion:
  - Genetic confirmation of AIP
  - ≥ 2 attacks in past 6 months if on-demand treatment or willing to stop hemin prophylaxis during study. One attack in run-in required for randomization

Objectives

- Safety and tolerability
- Characterize PK and PD

Exploratory Objectives

- Clinical activity on attack frequency and treatment
- Characterize circulating ALAS1 mRNA from liver in urine and serum

OLE, Open label Extension
Clinicaltrials.gov: NCT02452372

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Baseline and Run-in Disease Severity by Cohort
Part C Cohorts 1-3

Disease Characteristics	Cohort 1 (N=4)	Cohort 2 (N=4)	Cohort 3 (N=4)
Patient Reported Attacks in last 12 mos, mean (range)	22.3 (5-50)	13.5 (0-36)	8.5 (4-12)
Hemin Prophylaxis Use Prior to Study, n (%)	3 (75)	2 (50)	0
Baseline PBG, mmol/mol Cr mean, (range)*	51.8 (12.3 - 90.3)	50.8 (44.1 – 51.8)	41.4 (37.1 – 45.7)
Baseline ALA, mmol/mol Cr mean, (range)*	22.5 (2.6 – 36.7)	24.5 (17.6 – 31.5)	19.7 (14.6 – 25.6)
Run-in Period			
Annualized Attack Rate mean (SEM)	38.4 (6.4)	16.6 (4.2)	12.8 (3.4)

* ULN: ALA <3.9 or 3.8 mmol/mol Cr; PBG < 1.6 or 1.5 mmol/mol Cr depending on site

Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results

Pharmacodynamics, Urine ALA and PBG

Mean ALA* (mmol/mol Cr)

	Placebo (n=3)	Cohort 1: 2.5 mg/kg q3M (n=3)	Cohort 2: 2.5 mg/kg qM (n=3)	Cohort 3: 5 mg/kg qM (n=3)
Run-in (SD)	22.6 (6)	20.6 (11)	28.6 (2)	20.4 (4)
Treatment (SD)	20.8 (5)	11.8 (4)	6.7 (0.1)	4.3 (3)
% change	-7.6	-42.5	-76.7	-78.9

Mean PBG* (mmol/mol Cr)

	Placebo (n=3)	Cohort 1: 2.5 mg/kg q3M (n=3)	Cohort 2: 2.5 mg/kg qM (n=3)	Cohort 3: 5 mg/kg qM (n=3)
Run-in (SD)	42.8 (7)	55.5 (29)	51.1 (3)	34.2 (4)
Treatment (SD)	41.1 (6)	39.5 (21)	12.5 (1)	7.9 (6)
% change	-3.9	-28.8	-75.5	-76.9

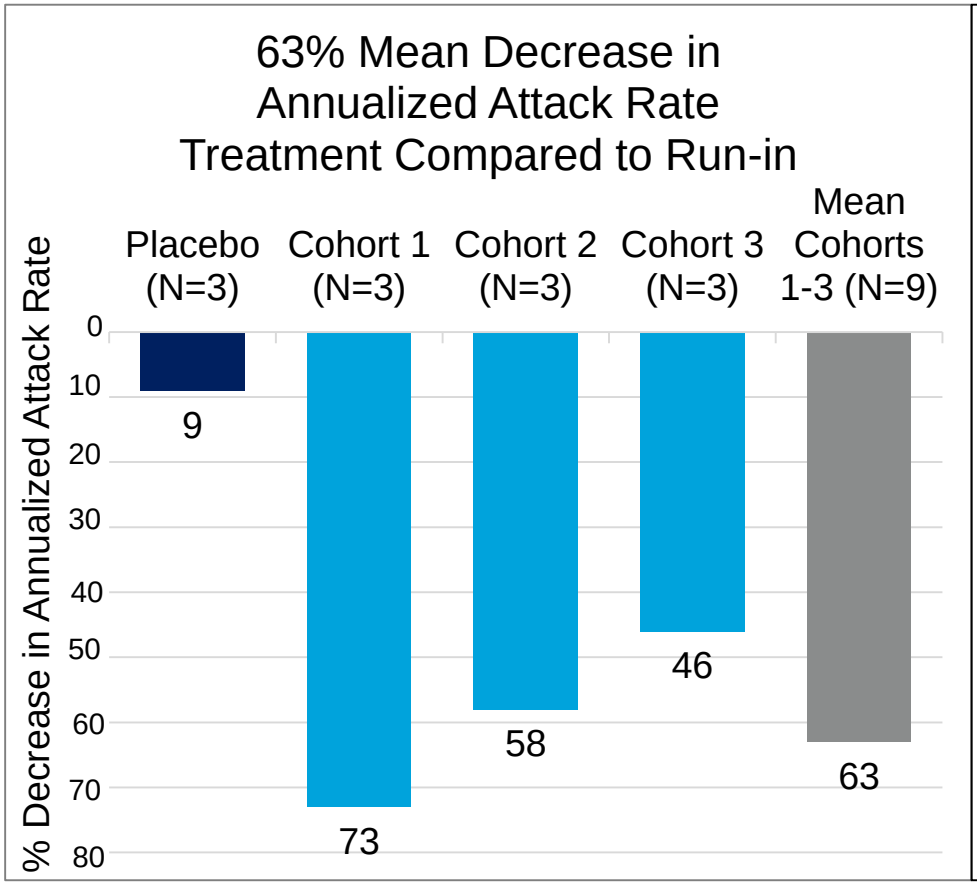
* ULN: ALA <3.9 or 3.8 mmol/mol Cr; PBG < 1.6 or 1.5 mmol/mol Cr depending on site

Data cut date of 05 May 2017

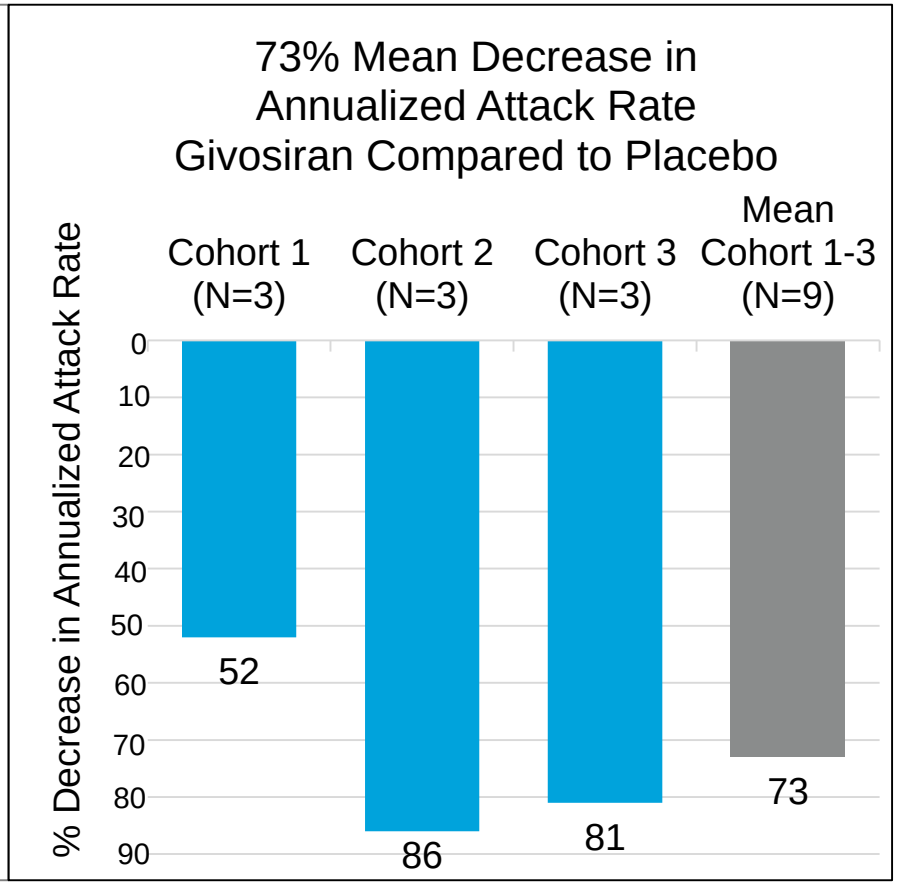
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results

Clinical Activity, Annualized Attack Rates

Decreased Annualized Attack Rates



All attacks, regardless of treatment type or treatment location



Attacks requiring hospitalization, urgent health care visit or hemin

Data cut date of 21 Apr 2017

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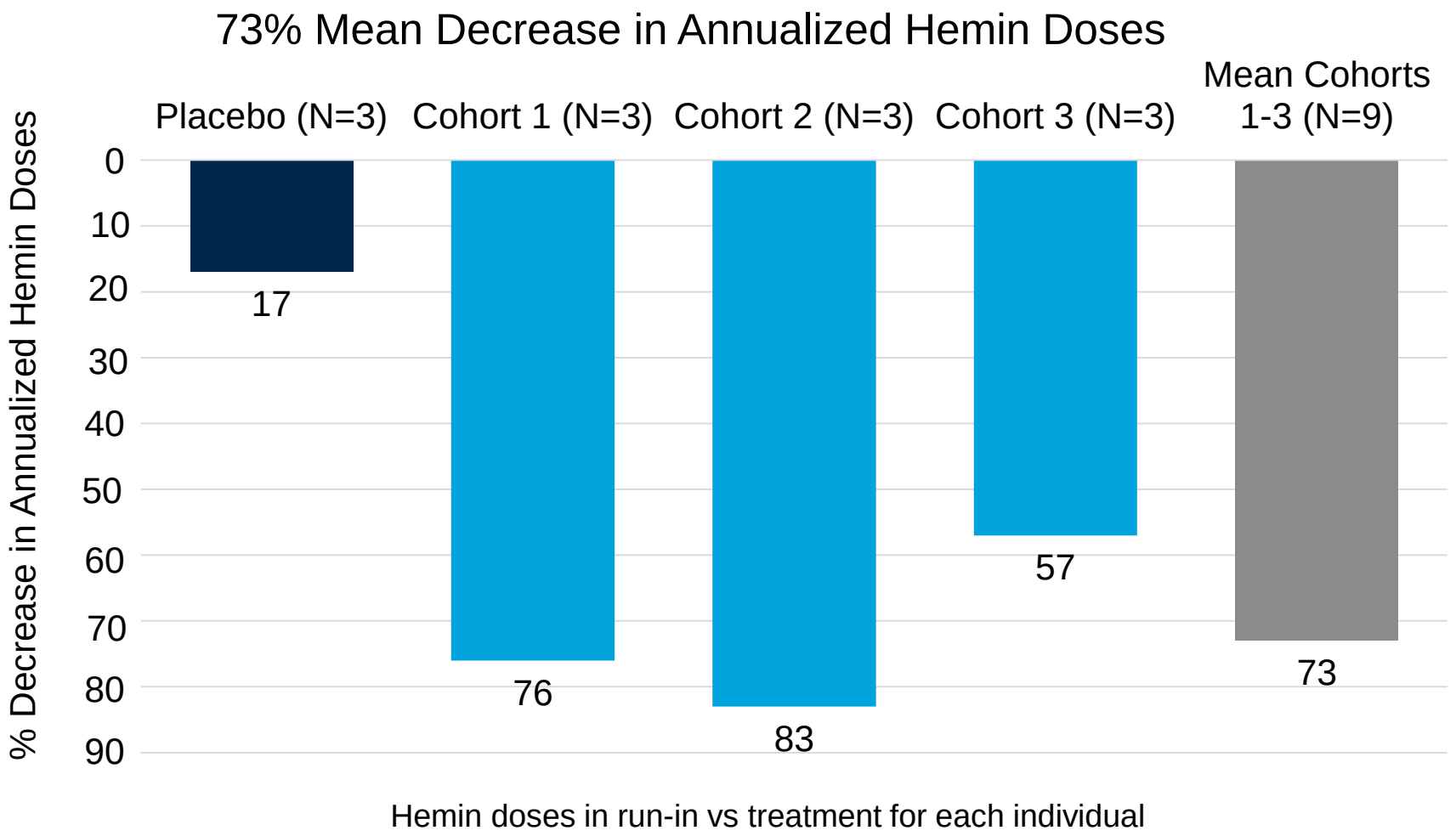
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results

Clinical Activity, Annualized Hemin Doses



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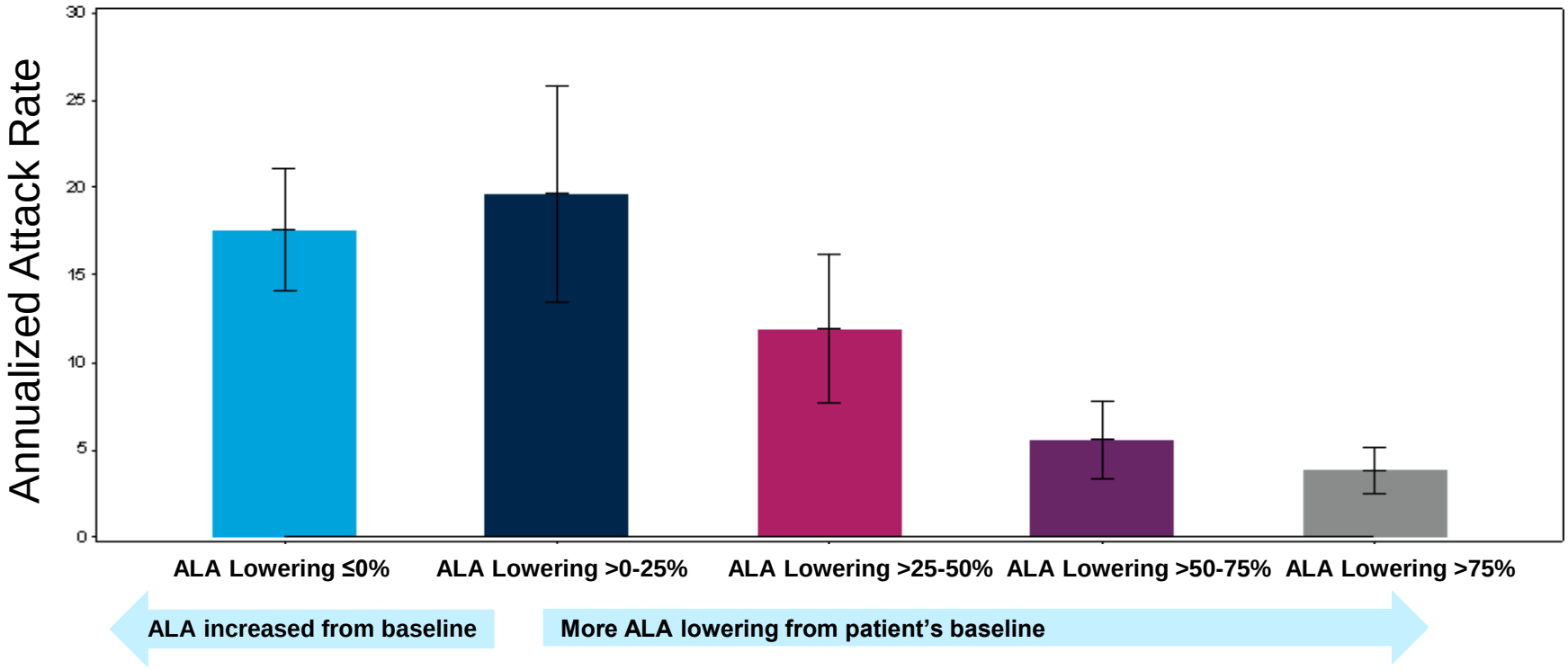
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results

Clinical Activity, Annualized Attack Rates by ALA Lowering Quartiles



	ALA % Lowering Quartile				
	≤0%	>0-25%	>25-50%	>50-75%	>75%
Mean (SEM) Annualized Attack Rate	17.6 (3.5)	19.6 (6.2)	11.9 (4.2)	5.5 (2.3)	3.8 (1.4)
Number of Attacks	25	10	8	6	8
Patient-years	1.4	0.5	0.7	1.1	2.1

Data transfer date of 14 Feb 2017

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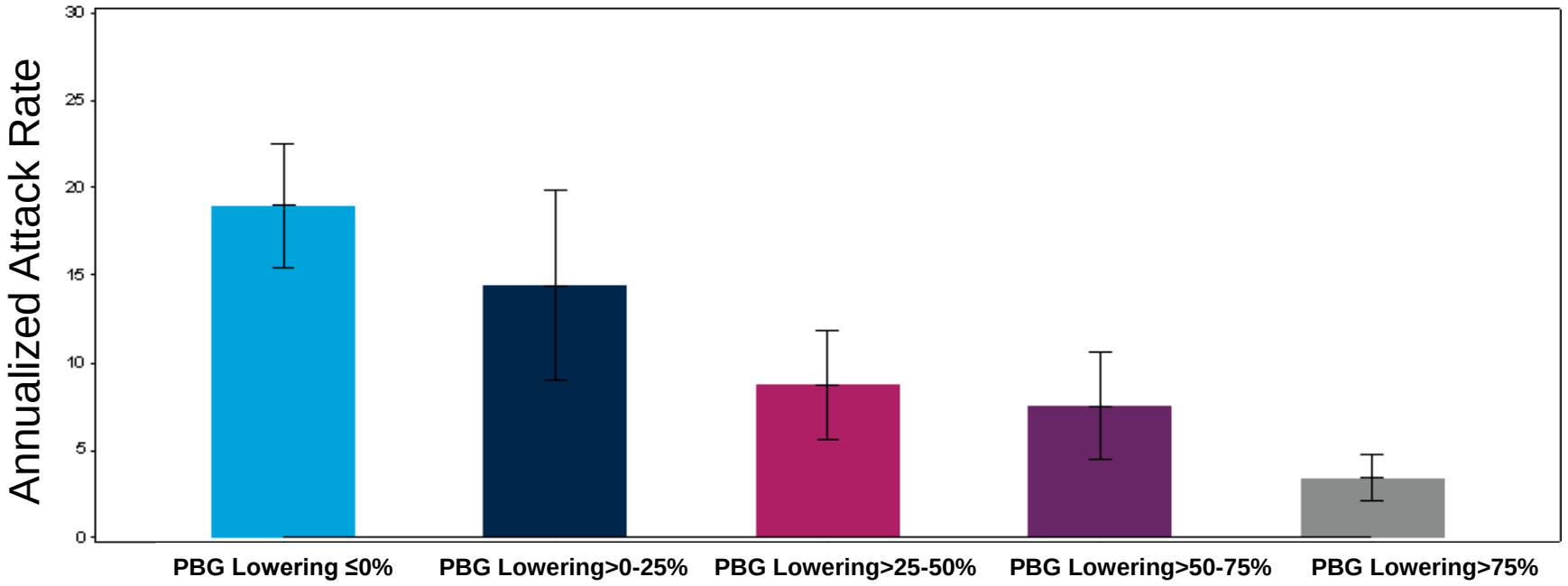
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results

Clinical Activity, Annualized Attack Rates by PBG Lowering Quartiles



	PBG % Lowering Quartile				
	≤0%	>0-25%	>25-50%	>50-75%	>75%
Mean (SEM) Annualized Attack Rate	19.0 (3.5)	14.4 (5.5)	8.7 (3.1)	7.5 (3.1)	3.4 (1.3)
Number of Attacks	29	7	8	6	7
Patient-years	1.5	0.5	0.9	0.8	2.1

Data transfer date of 14 Feb 2017

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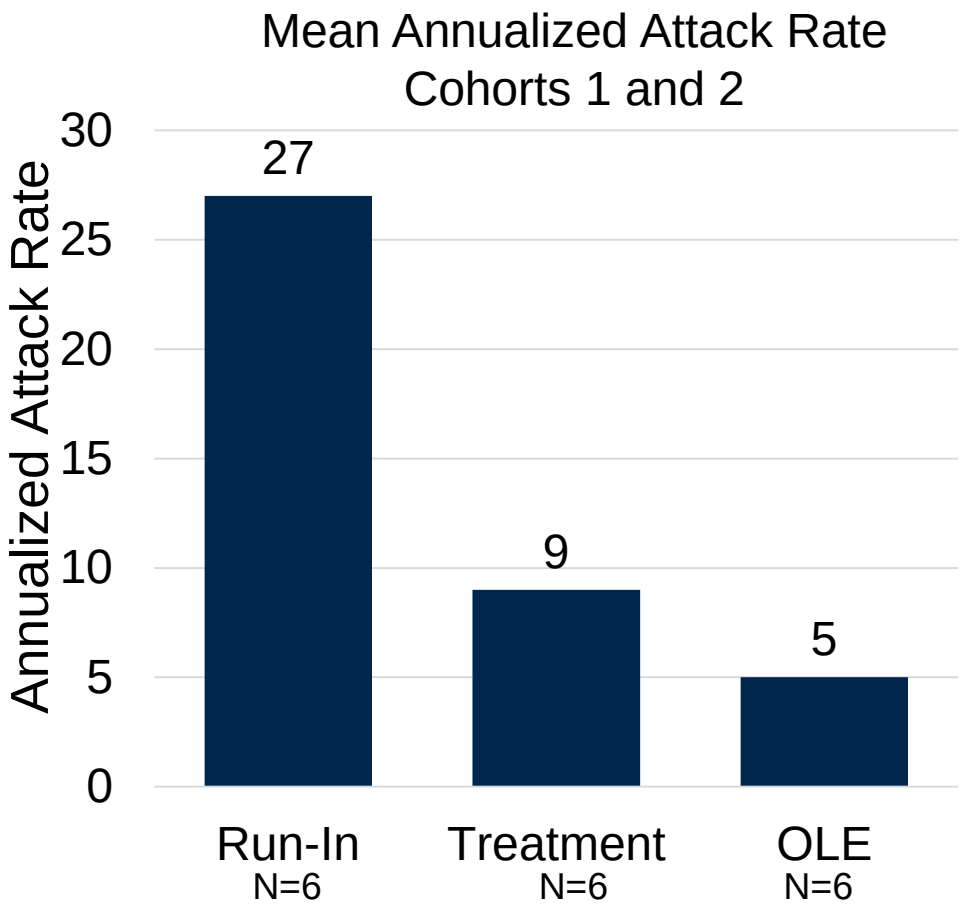
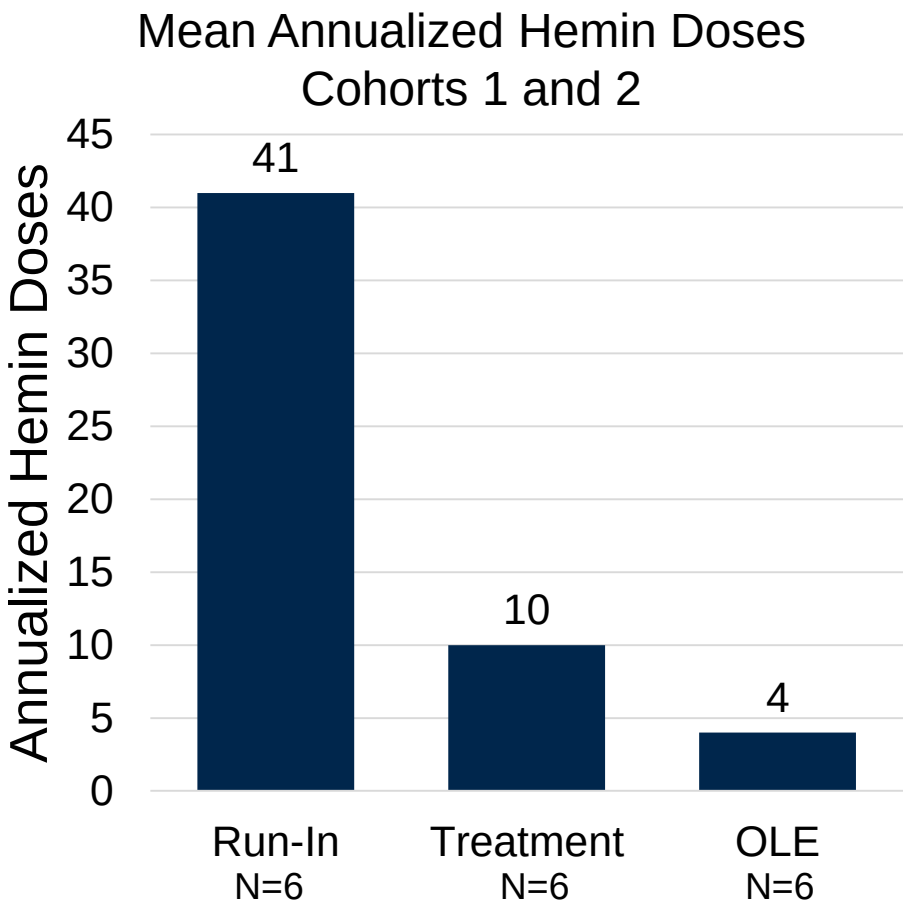
Interim Givosiran Phase 1 (Part C, Cohorts 1-2 OLE) Study Results

Clinical Activity, Annualized Attack Rates & Hemin Use

Givosiran activity maintained, potential for further reductions in attack rate with extended dosing





	Run-In	Treatment	OLE
Mean Days on Study	90	169	111

Data cut date of 21 Apr 2017

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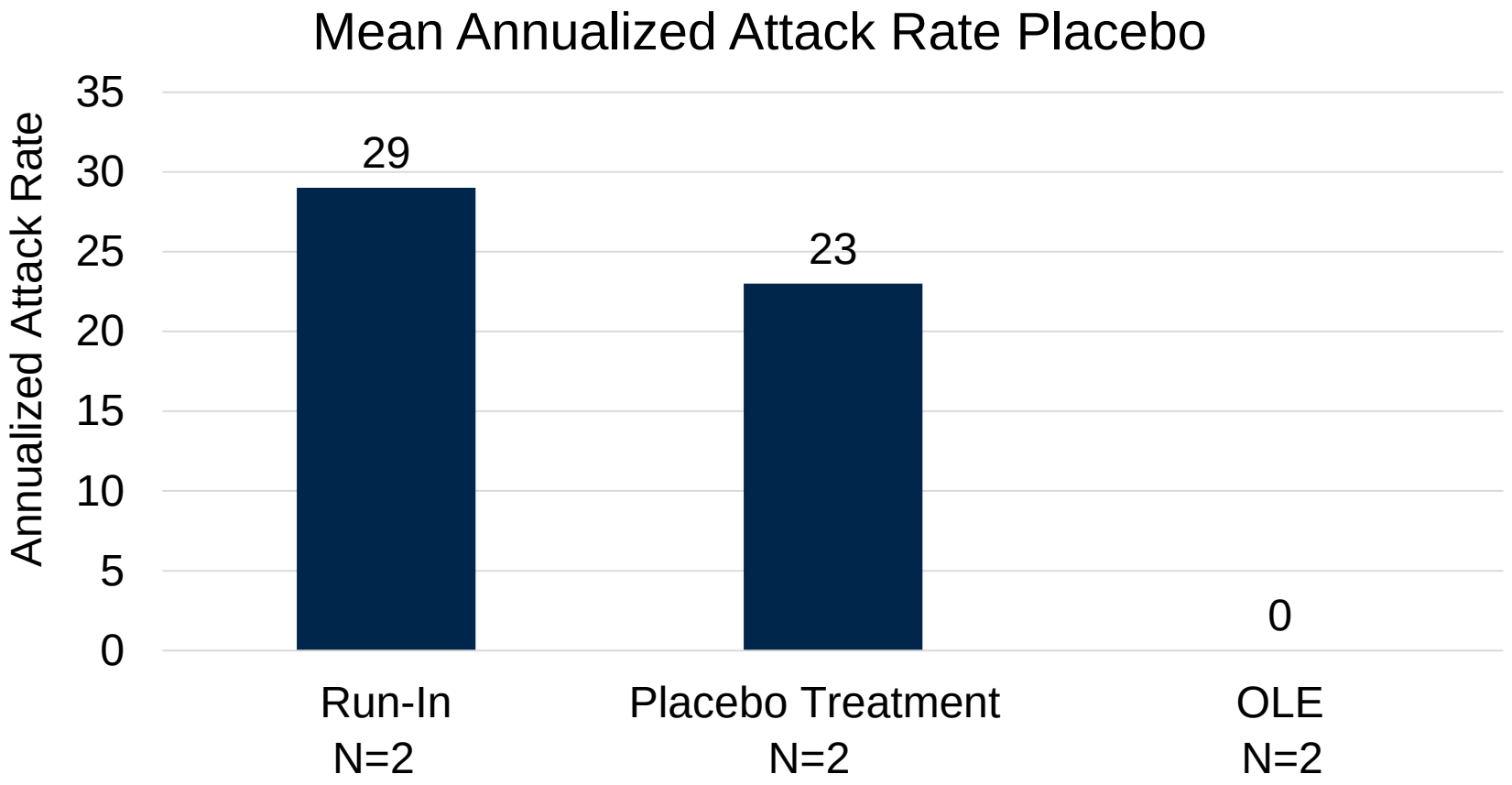
Interim Givosiran Phase 1 (Part C, Cohort 1-2 OLE) Study Results

Clinical Activity, Placebo



	Run-In	Treatment	OLE
Mean Days on Study	77	169	31

Data cut date of 21 Apr 2017

Interim Givosiran Phase 1 (Part C and OLE) Study Results

Safety and Tolerability

Part C (Cohorts 1-3)

- 3 patients had 4 SAEs (excluding porphyria attacks), none assessed as related to study drug
  - 1 patient in Cohort 3 had fatal SAE of hemorrhagic pancreatitis, complicated by pulmonary embolism, as previously reported; assessed unlikely related due to presence of gallbladder sludge
- All randomized patients reported AEs
  - Majority of AEs were mild to moderate; 25% patients had severe AEs, assessed as unrelated to study drug
  - AEs in ≥3 patients: Abdominal pain, headache, nasopharyngitis, nausea, vomiting
  - 4 patients had related AEs:
    - Injection site reactions (mild and self-limiting), hypersensitivity, myalgia, headache, moderate renal impairment (in patient with history of moderate renal impairment) and erythema
- No other discontinuations due to AEs or other clinically significant changes in EKG, clinical laboratory or physical examination

OLE (Cohorts 1-2)

- Overall safety experience in OLE is consistent with Phase 1 Study
- No SAEs (excluding porphyria attacks) or discontinuations due to AEs
- 4 patients reported AEs; most assessed as mild or moderate in severity
  - 2 patients experienced mild or moderate AEs that were considered related or possibly related to study drug (epistaxis, hypertension and renal impairment, in same patient with history of moderate renal impairment as noted above)
- No clinically significant changes in EKG, clinical laboratory, or physical examination reported

All Safety Data in database as of 5 May 2017

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EXPLORE Natural History Study

Study Design Overview

Study Design

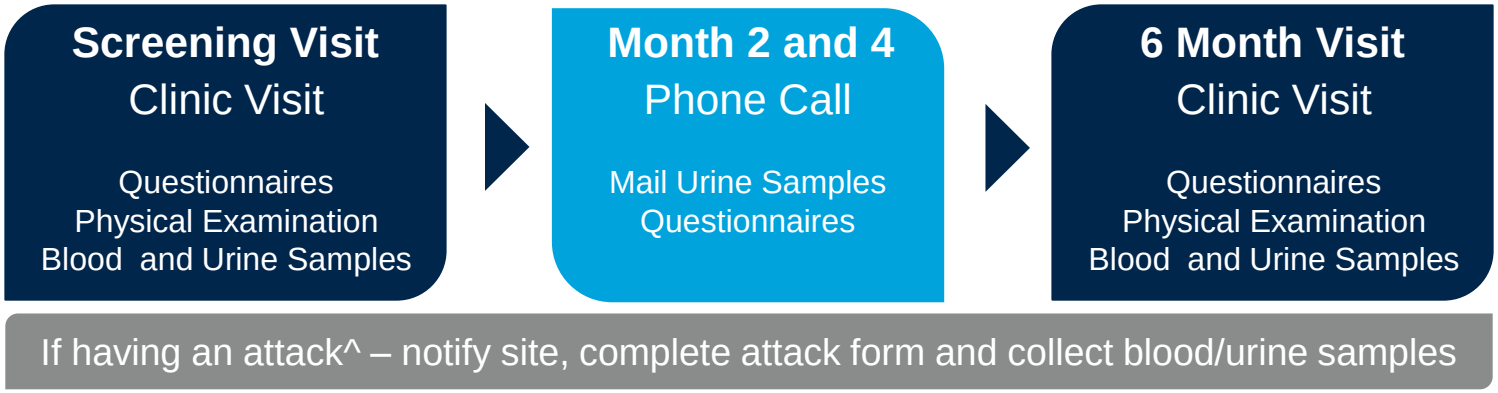
- Observational, multinational, prospective on-going natural history study

Key Eligibility Criteria

- Males or Females ≥ 18 years old
- Diagnosis of AHP by specialist, including acute intermittent porphyria (AIP), hereditary coproporphyria (HCP) and variegate porphyria (VP)
- Recurrent attacks
  - 3+ attacks^ within 12 months of screening
  - Using hemin or GnRH analog prophylactically

Key Objectives

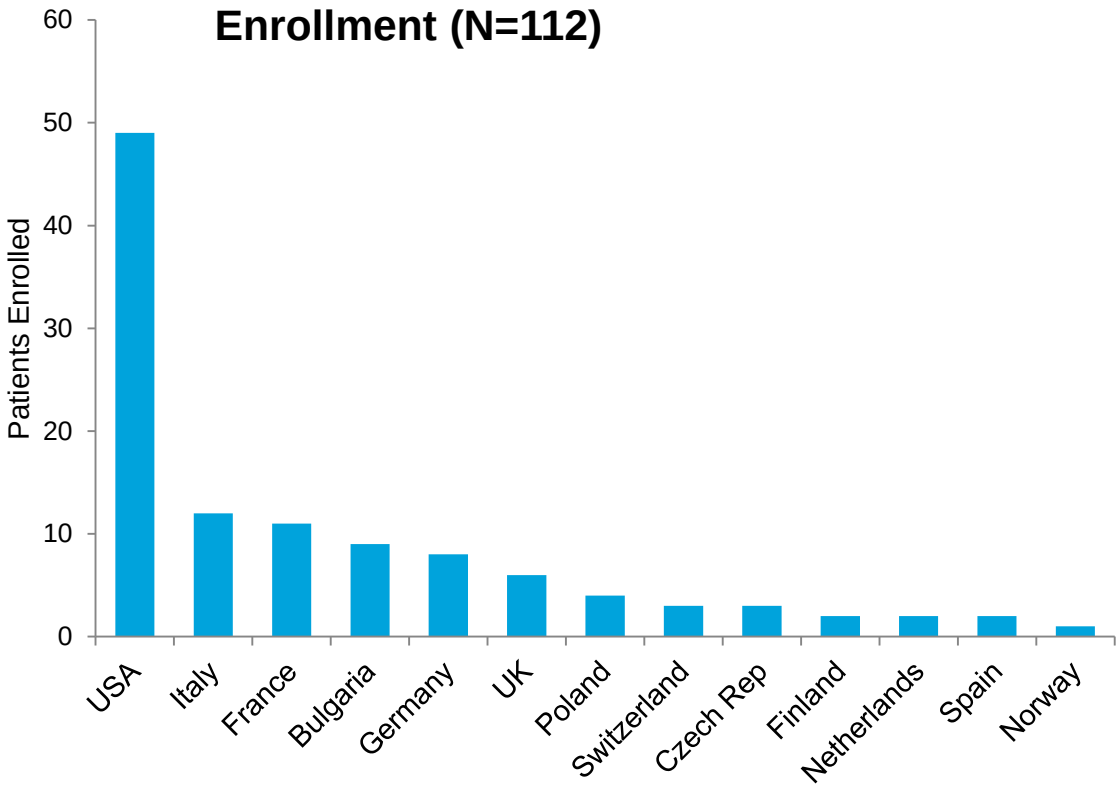
- Characterize natural history and current AHP management
  - Medical history and medication usage
  - Porphyria signs and symptoms
  - Biomarkers
  - Quality of life (QoL)

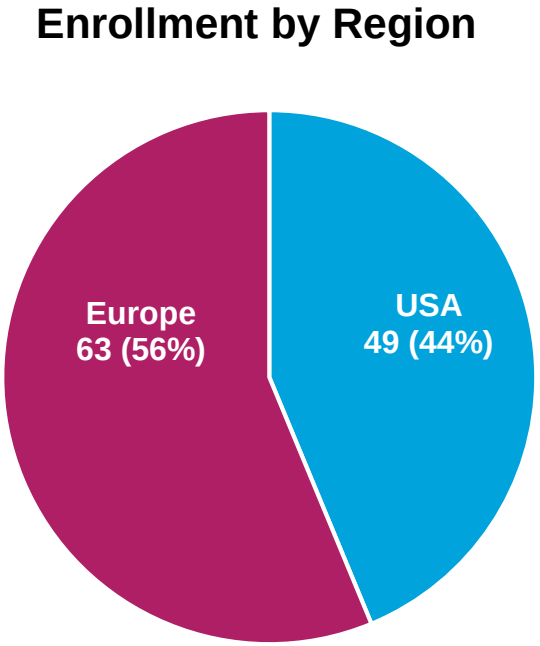


^Attacks defined as acute porphyria symptoms requiring increase in treatment (hemin, pain medications, carbohydrates) or hospitalization
ClinicalTrials.gov Identifier: NCT02240784

EXPLORE Natural History Study

12-Month Study Enrollment and Follow-Up





Follow-Up Time, n (%)	N=112
≥6 months	107 (96%)
≥12 months	80 (71%)

Data as of 11 April 2017

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EXPLORE Natural History Study
Healthcare Utilization and Cost Analysis

Healthcare Utilization Category	Average Annual Cost Per Patient
PCP Visits	$443
Specialist Visits	$1,203
ER Visits	$3,753
Hospitalizations	
Costs	$100,078
Charges	$356,853
Hemin Prophylaxis	$148,145
Hemin Acute Attacks	$141,738
Hemin Administration	$3,282
Total with Hospital Costs, mean (95% CI)	**$398,463 ($328,303 - $475,477)**
Total with Hospital Charges, mean (95% CI)	**$655,418 ($482,278 - $847,448)**

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Q&A

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Samantha
Regulatory Affairs, Alnylam

Thank You!

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