

Givosiran, in Development for the Treatment of Acute Hepatic Porphyrias

July 24, 2018



Agenda

Welcome

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

Introduction

- Akin Akinc, Ph.D., General Manager, Givosiran

Disease Overview & Givosiran Phase 1/Open-Label Extension Results

- Jae Kim, M.D., Vice President, Clinical Development

Patient Perspective

- Mary, patient living with Acute Intermittent Porphyria

Givosiran Program Opportunity & Status

- Akin Akinc, Ph.D., General Manager, Givosiran

Q&A Session

Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the 'Ask a Question' field on the webcast interface.

Replay, slides and transcript available at www.alnylam.com/capella

Anylam 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-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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RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

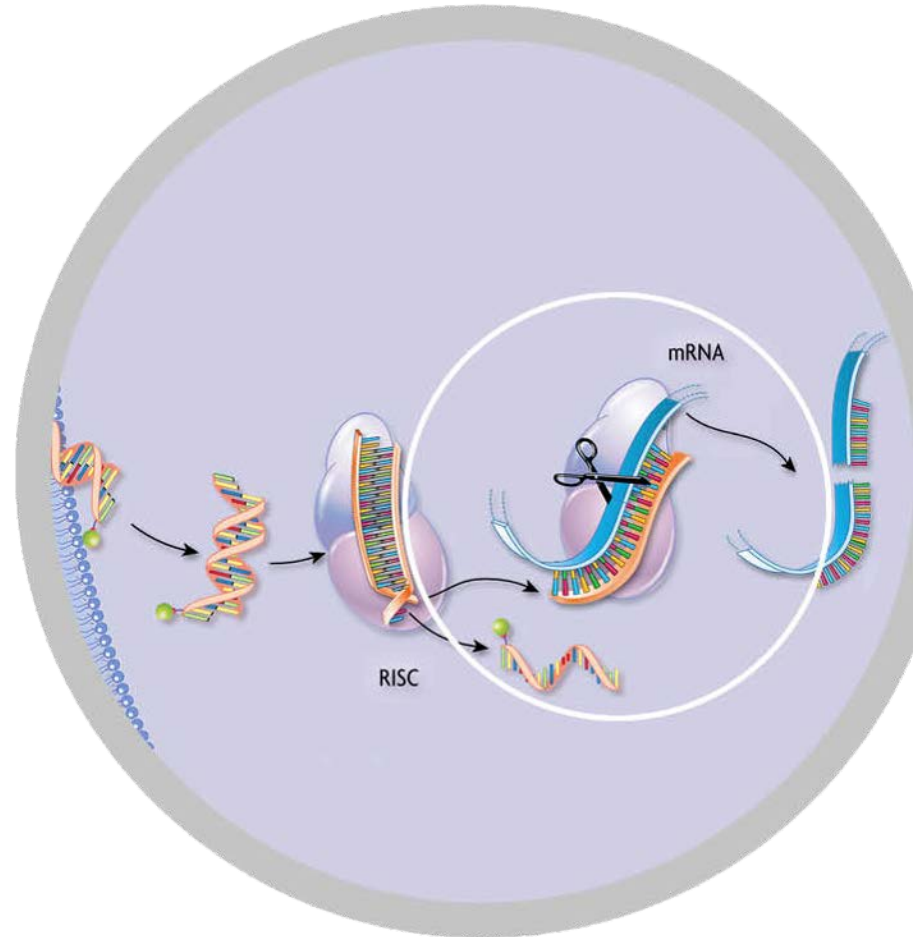
Nobel Prize-winning science

Silence any gene in genome

Potent and durable mechanism of action

Product engine for sustainable pipeline

Now entering commercial stages



Anylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STAr):

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

		HUMAN POC ¹	BREAKTHROUGH DESIGNATION	EARLY STAGE <i>(IND or CTA Filed-Phase 2)</i>	LATE STAGE <i>(Phase 2-Phase 3)</i>	REGISTRATION/ COMMERCIAL ²	COMMERCIAL RIGHTS
Patisiran	<i>Hereditary ATTR Amyloidosis</i>					●	Global
Givosiran	<i>Acute Hepatic Porphyrias</i>				●		Global
Fitusiran	<i>Hemophilia and Rare Bleeding Disorders</i>				●		15-30% Royalties
Inclisiran	<i>Hypercholesterolemia</i>				●		Milestones & up to 20% Royalties
ALN-TTRsc02	<i>ATTR Amyloidosis</i>			●			Global
Lumasiran	<i>Primary Hyperoxaluria Type 1</i>			●			Global
Cemdisiran	<i>Complement-Mediated Diseases</i>			●			Global

¹POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies

²Includes marketing application submissions

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Givosiran for Acute Hepatic Porphyrias

Rationale for RNAi Therapeutic



1

Genetically validated, liver-expressed target gene

ALAS1 is the liver-expressed, initial enzyme of the heme biosynthesis pathway; it is upstream of the genetic enzyme deficiencies that are responsible for acute hepatic porphyrias

Up-regulation of **ALAS1** results in accumulation of toxic intermediates **ALA** and **PBG** that drive disease



2

Biomarker for POC in Phase 1

Serum and urinary biomarkers:

- **ALA**
- **PBG**



3

Definable path to approval and market

Single pivotal study in AHP patients

Primary endpoint:

- Attacks requiring hospitalization, urgent care visit, home IV hemin at 6 months

Secondary endpoints:

- ALA and PBG levels
- Hemin usage
- Symptoms
- QoL

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Disease Overview

Acute Hepatic Porphyrias (AHPs)^{1,2}

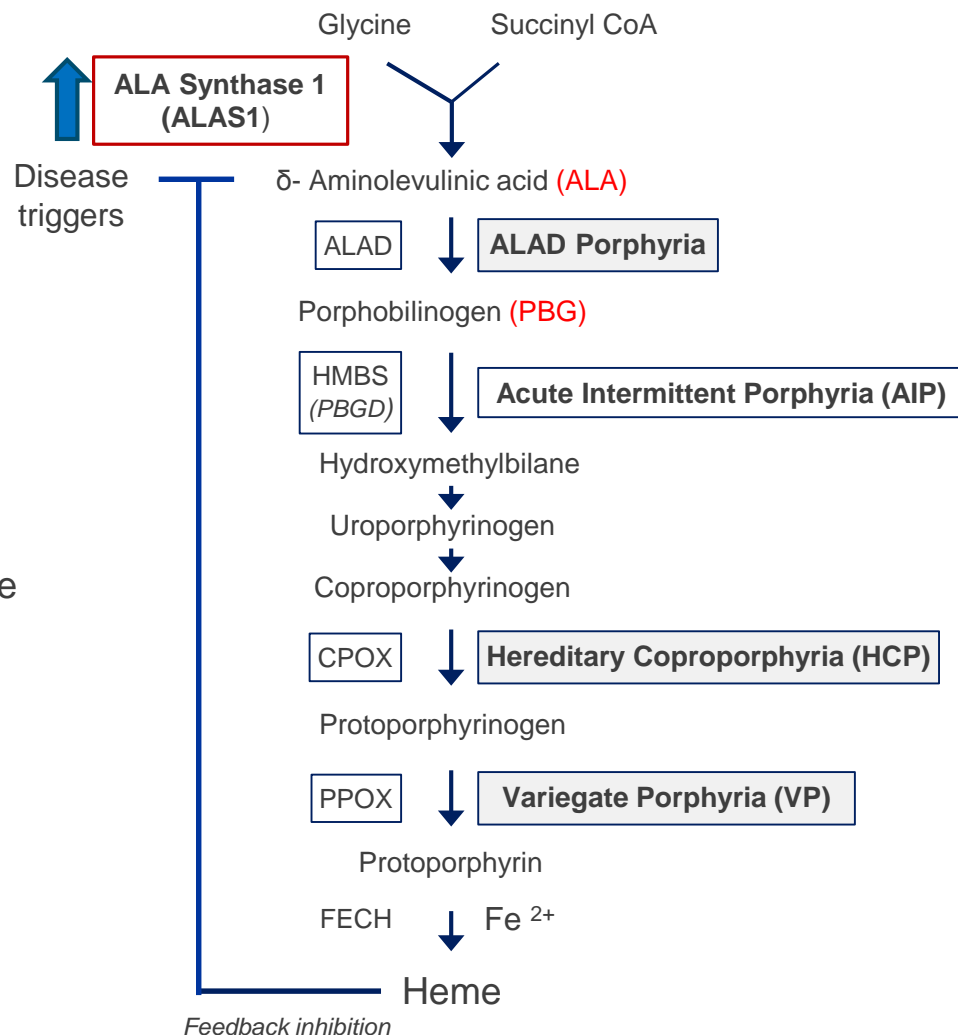
- Inborn errors of heme synthesis from liver enzyme defects
- Acute Intermittent Porphyria (AIP) most common, with a mutation in hydroxymethylbilane synthase (HMBS)

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

- Acute neurovisceral attacks that can be life-threatening
- Chronic pain and discomfort
- High prevalence of anxiety/depression
- Disability and social isolation common



AHPs: Acute Neurovisceral Crisis

Autonomic neuropathy

- Abdominal pain, nausea, vomiting, abdominal distension and constipation
- Tachycardia, cardiac arrhythmia, labile hypertension, postural hypotension
- Sweating, hoarse voice

Acute peripheral neuropathy

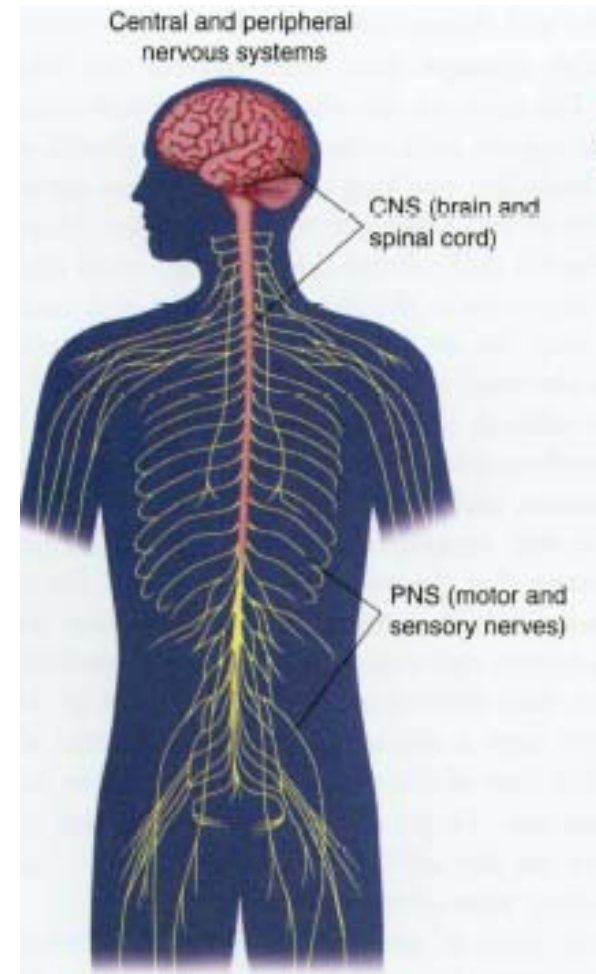
- Diffuse muscle weakness
- Pain in back and limbs
- Neuropathic sensory loss
- Cranial neuropathy (mainly III, VI, IX and X)
- Respiratory paresis due to diaphragm paresis

CNS manifestations

- Mental symptoms; anxiety, insomnia, depression, confusion, agitation, hallucinations
- Acute encephalopathy; headache, somnolence, altered consciousness and behaviour, seizures

Metabolic manifestations

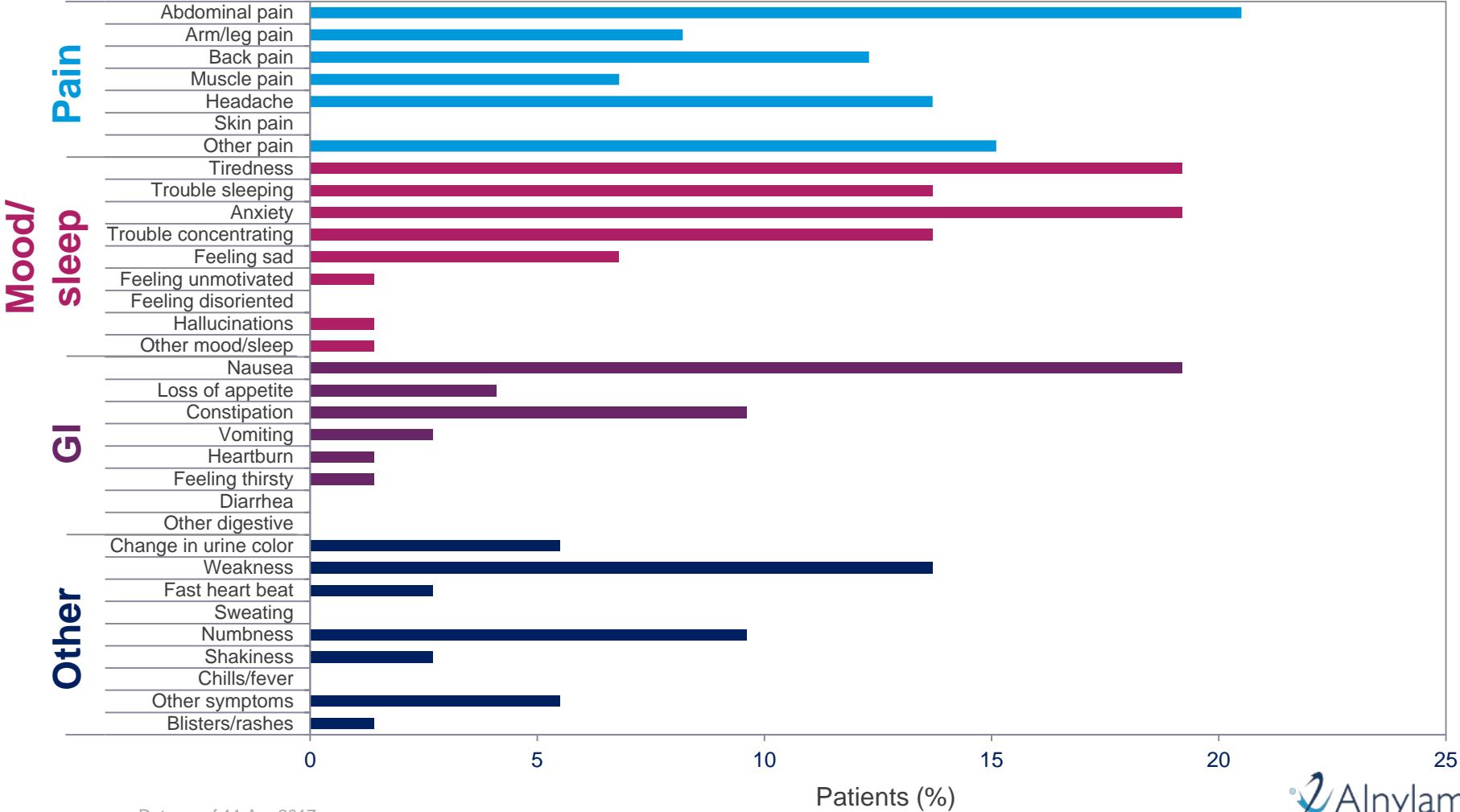
- Hyponatremia
- Mild LFT elevation



EXPLORE Natural History Study

Baseline Patient-Reported Chronic Symptoms

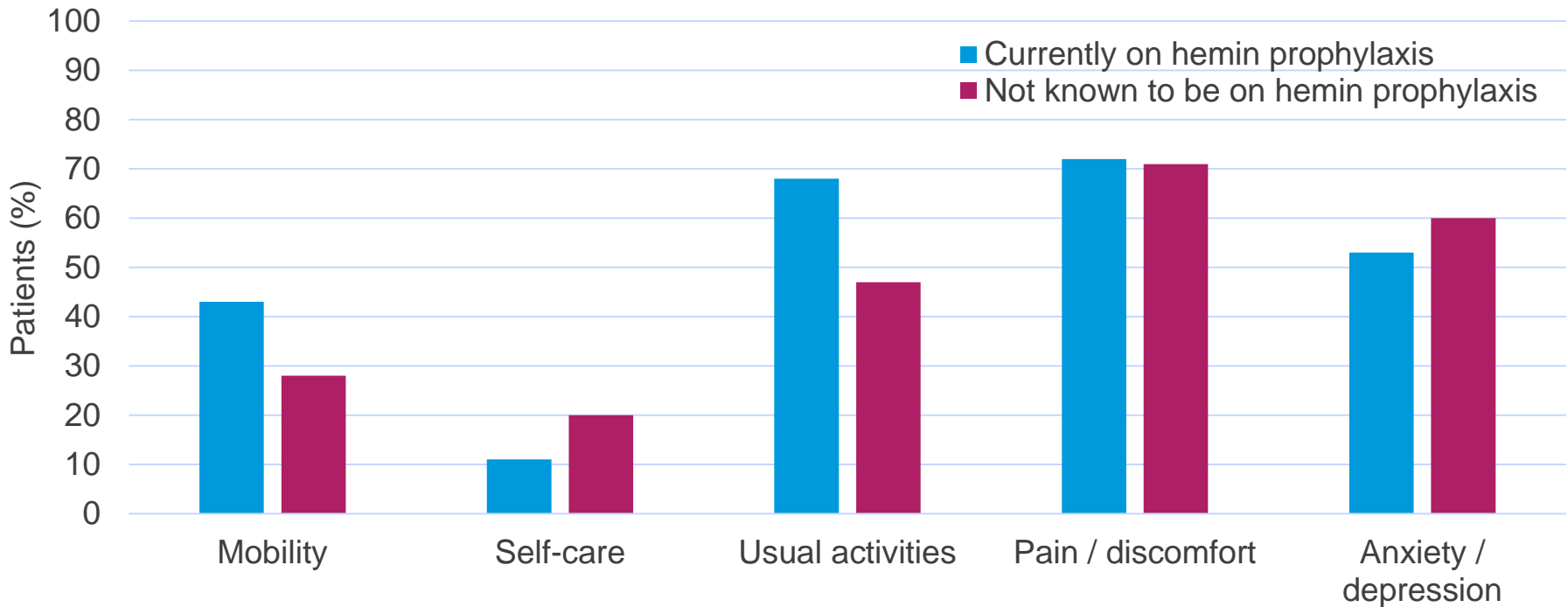
- 65% patients with chronic symptoms, most commonly pain, tiredness, anxiety and nausea, with 46% reporting daily symptoms



EXPLORE Natural History Study

Baseline QoL Using EQ-5D-5L Domains

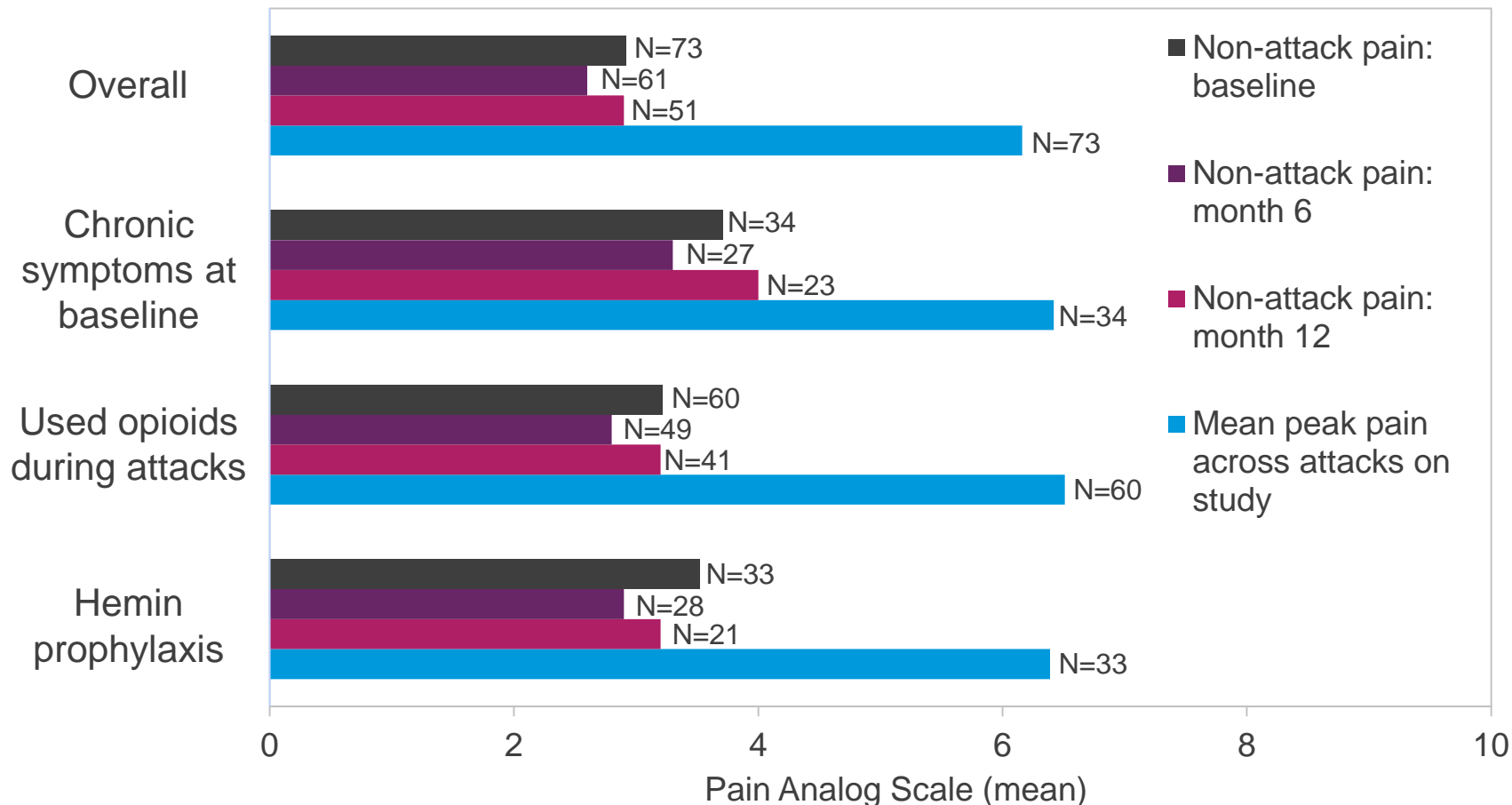
Percent of Patients Reporting Problem in Domain†



- Health status domains of usual activities, pain/discomfort and anxiety/depression are most impacted
- Domains not impacted by hemin prophylaxis treatment status

EXPLORE Natural History Study

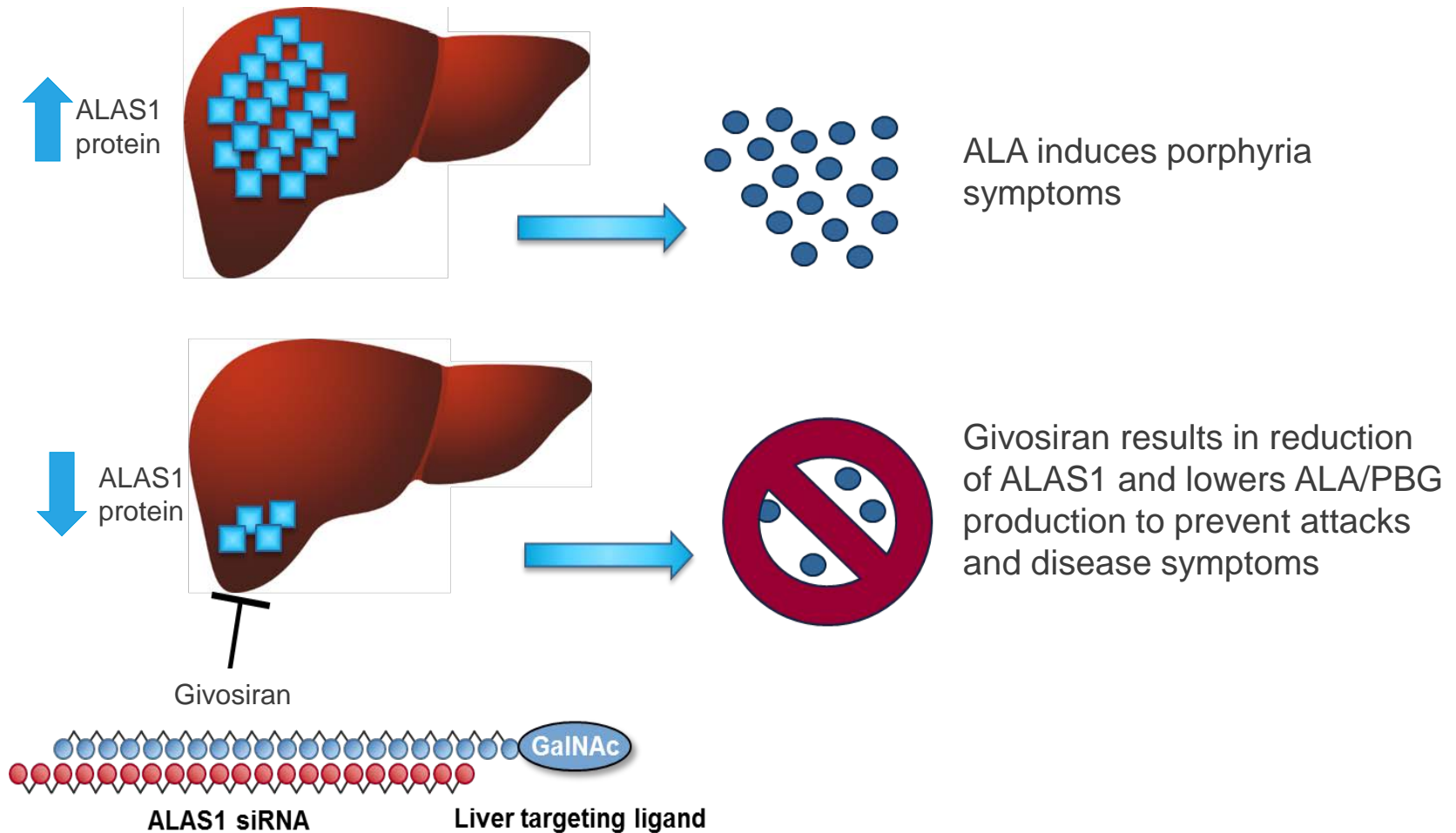
Pain Characteristics on Study



- Patients had chronic pain (3.5/10) in between attacks that increased during attacks (6.4/10)
- Non-attack pain persists at month 6 and month 12 regardless of porphyria treatment (hemin prophylaxis and opioids)

Therapeutic Hypothesis for Givosiran, an Investigational RNAi Therapeutic for AHPs

Reduction of Liver ALAS1 Protein to Lower ALA and PBG

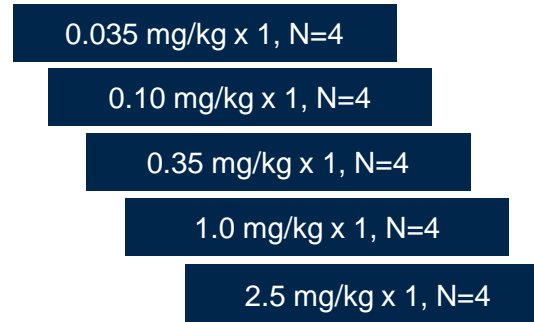


Phase 1 and Open-Label Extension (OLE) Study Design

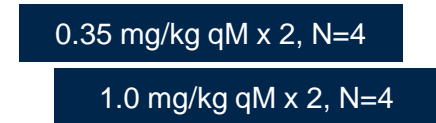
Parts A & B in Chronic High Excreter (CHE) Patients[†]

- 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 A (Single Ascending Dose)



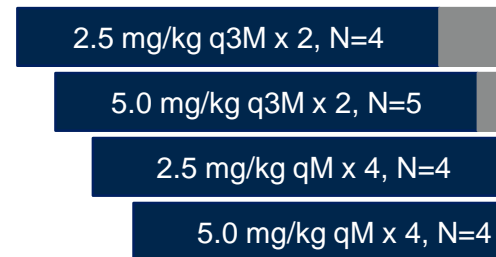
Part B (Multiple Ascending Dose)



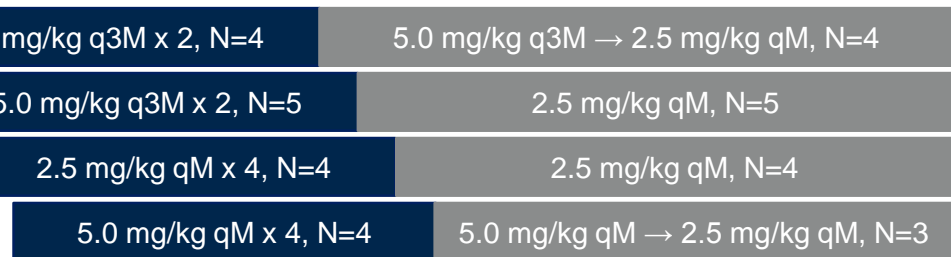
Part C and OLE in Recurrent Attack Patients

- 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

Part C (6 months)



OLE (up to 42 months)[‡]



Sardh *et al.* EASL Meeting, Apr 2018

Clinicaltrials.gov: NCT02452372. AIP, Acute Intermittent Porphyrin. 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)

Sardh *et al.* EASL Meeting, Apr 2018

[†]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.

Safety and Tolerability

Phase 1 Study Results

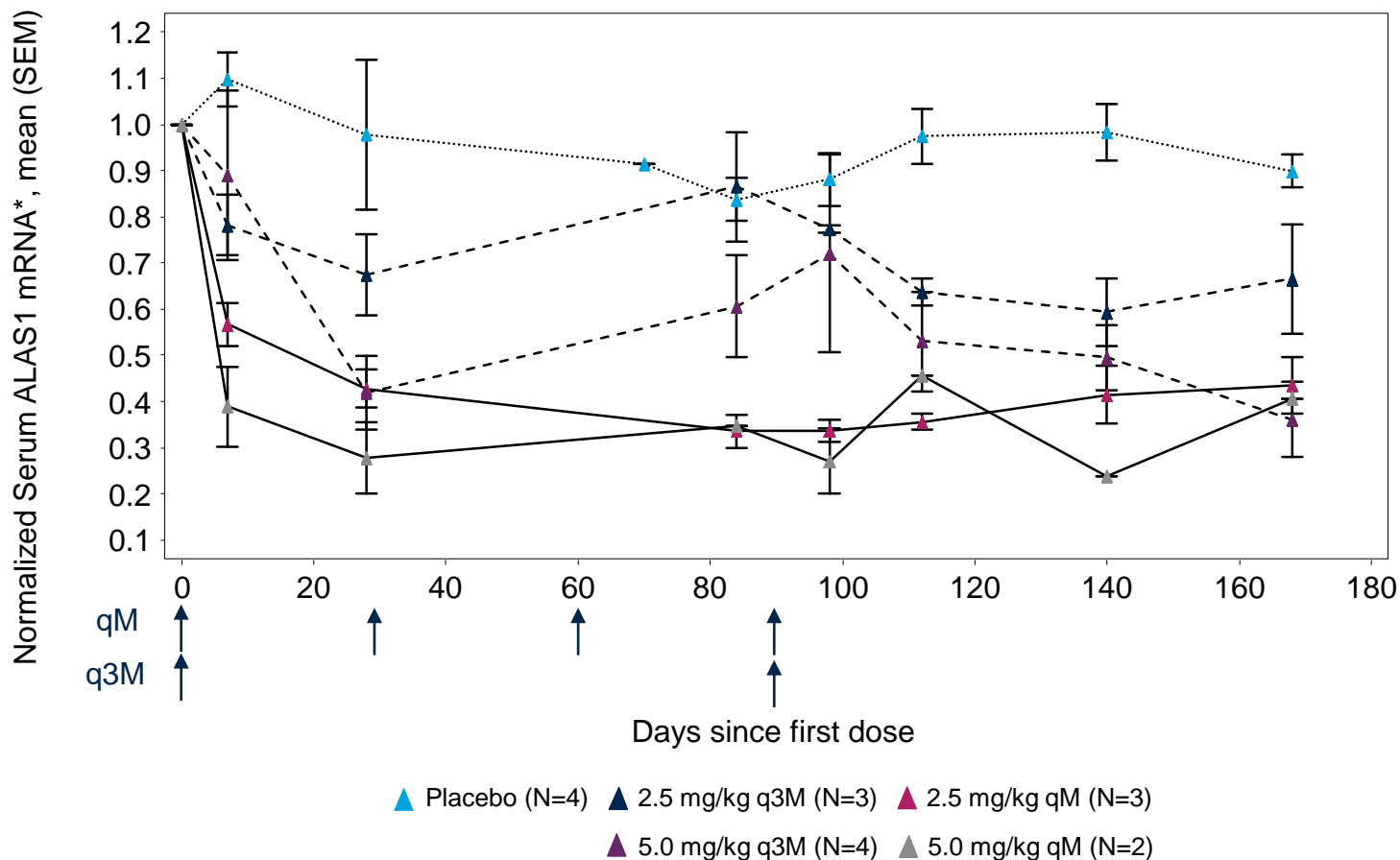
Patients Reporting Adverse Event, N (%)	Parts A & B		Part C	
	Placebo (N=6)	Givosiran (N=20)	Placebo (N=4)	Givosiran (N=13)
Any adverse event	6 (100)	17 (85)	4 (100)	13 (100)
Serious adverse event	0	3 (15)	0	3 (23)
Most common adverse events (occurring in >2 patients)				
Abdominal pain	0	2 (10)	1 (25)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



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ALAS1; ALA synthase 1. SEM; Standard error of mean. qM; Monthly. q3M; Quarterly.

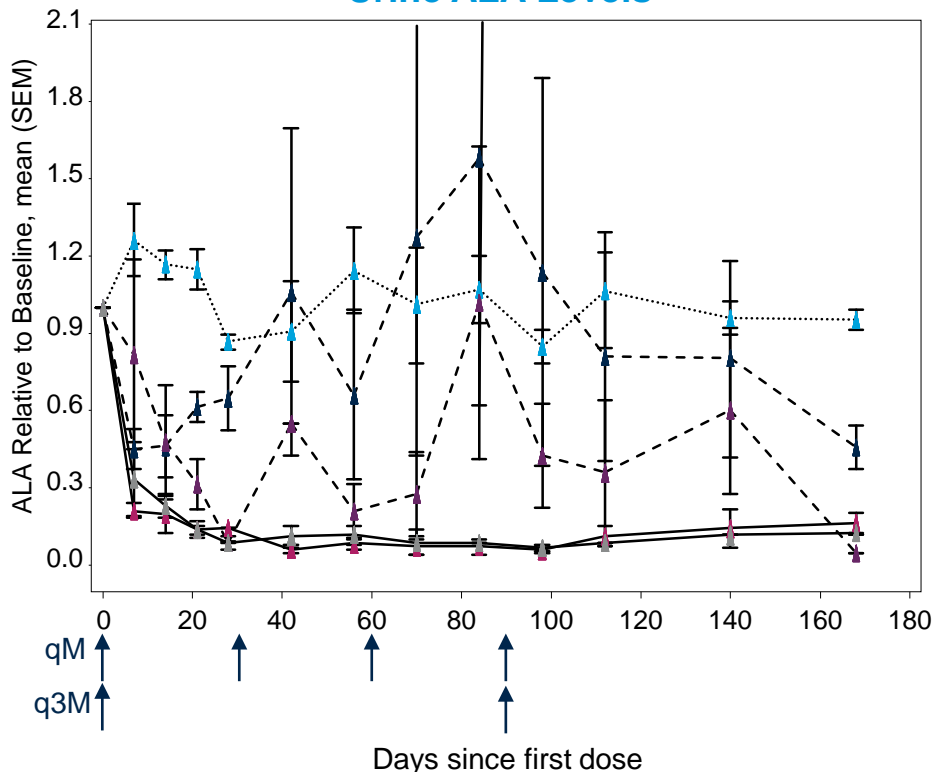
*Determined by Circulating Extracellular RNA Detection (cERD)

Dose-Dependent Lowering of ALA and PBG After Givosiran Dosing

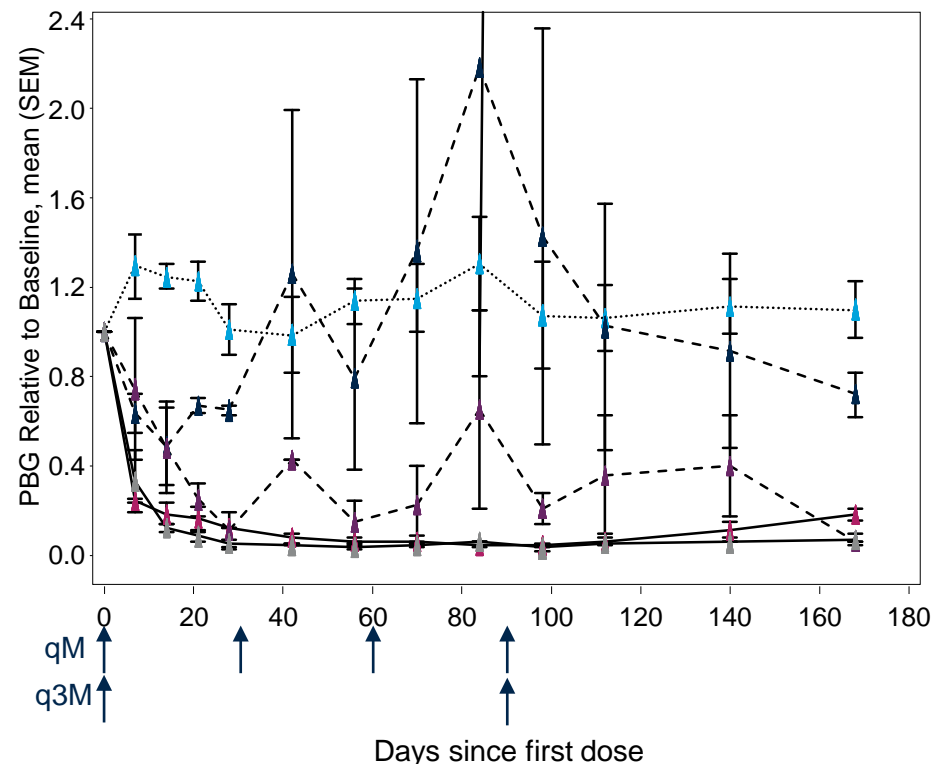
Phase 1 Study Results in Recurrent Attack Patients

- 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)

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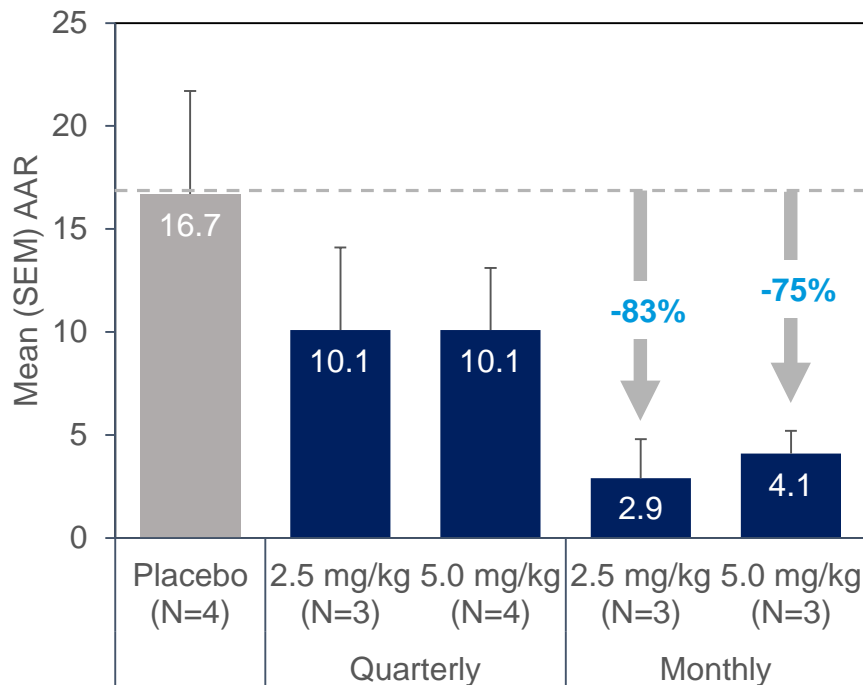
ALAS1, ALA synthase 1. ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. SEM; Standard error of mean qM; Monthly. q3M; Quarterly.

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

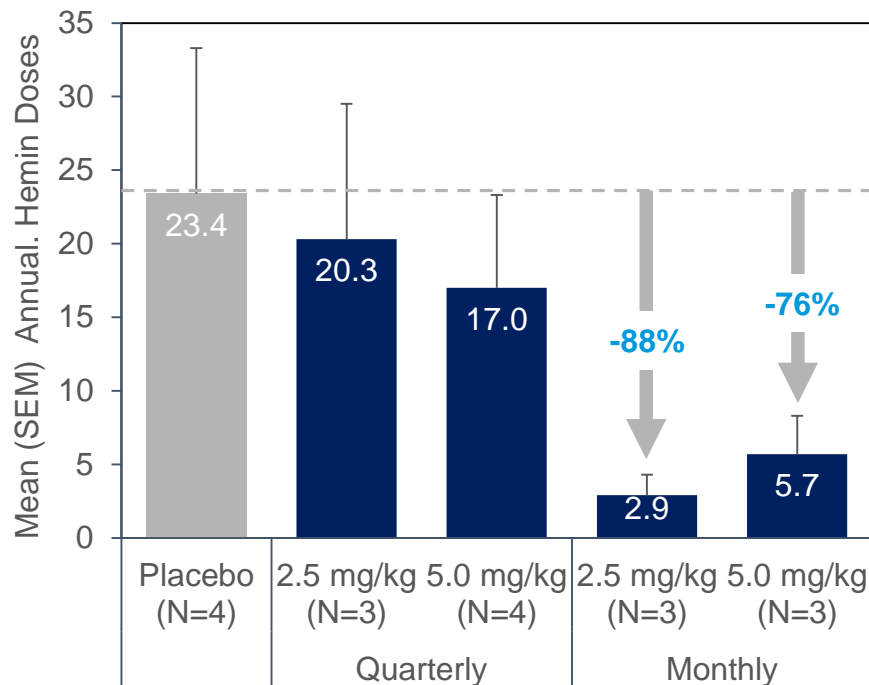
Phase 1 Study Results in Recurrent Attack Patients

- 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†



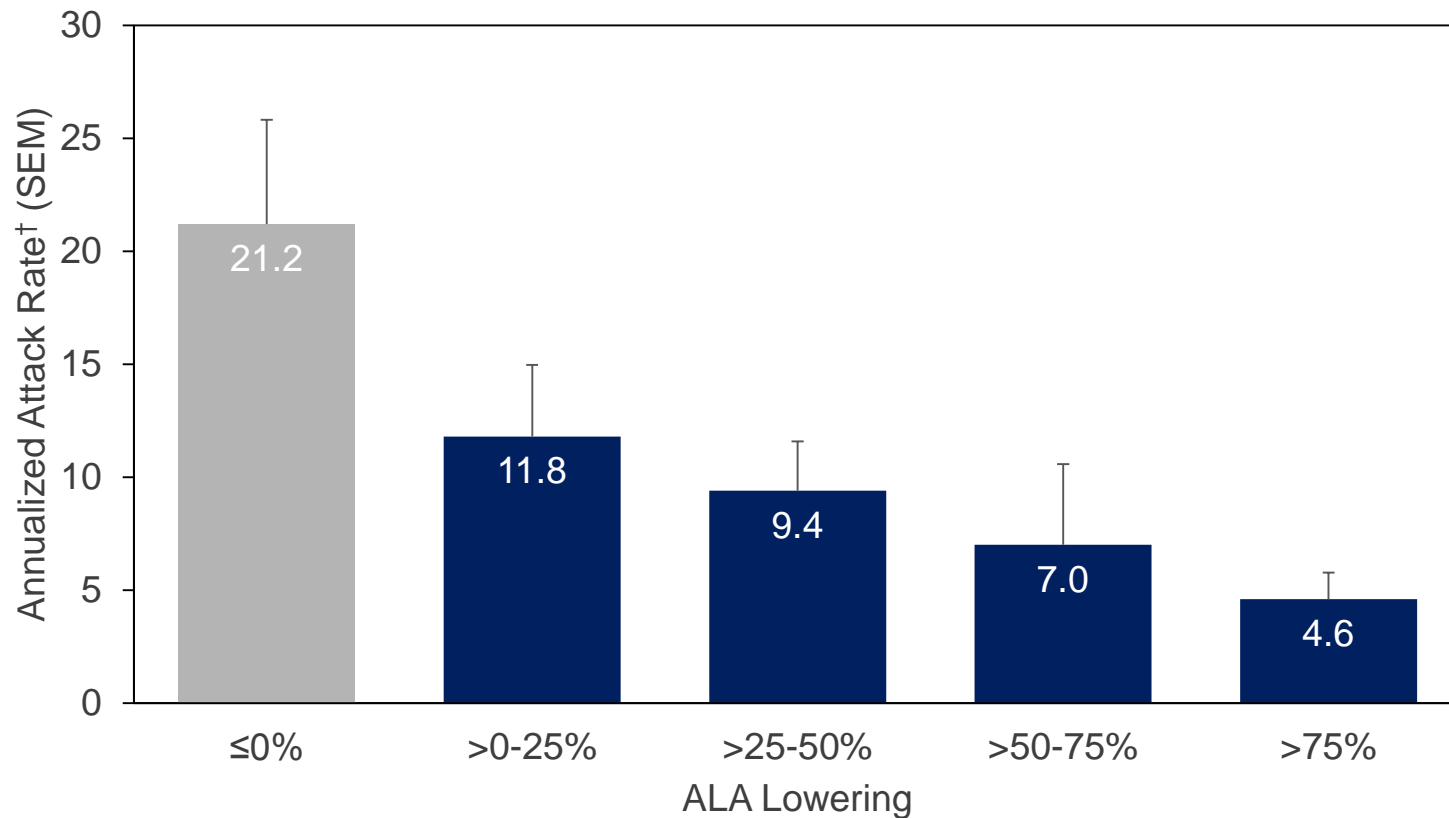
Annualized Hemin Doses



ALA Lowering was Correlated with Reductions in AAR

Phase 1 Study Results in Recurrent Attack Patients

- Continuous relationship between AAR and ALA lowering



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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*

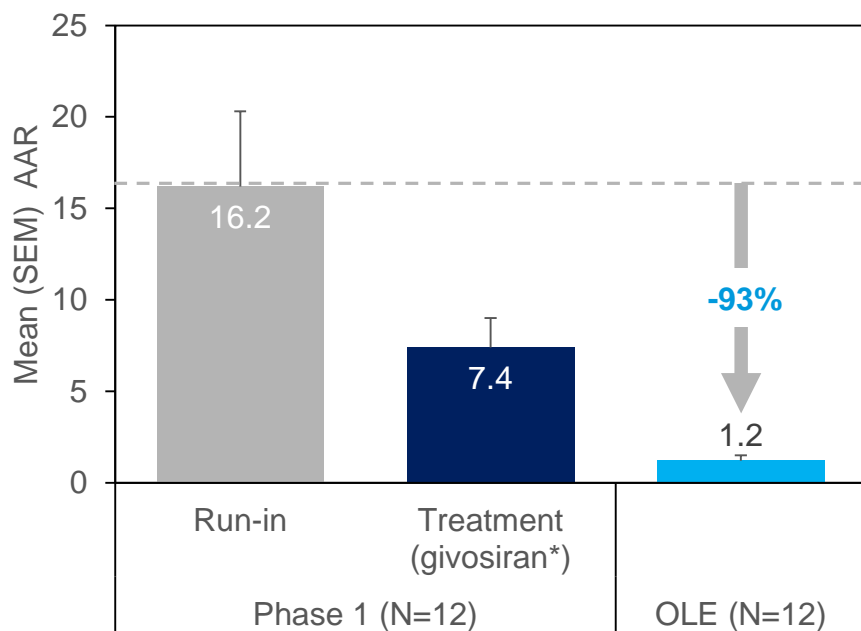
- 15/16 (94%) patients reported AEs
- 2 patients with SAEs
 - 1 patient (5.0 mg/kg q3M) with upper extremity DVT, assessed as unlikely related to study drug due to prior indwelling central venous catheter and venous damage from chronic hemin usage
 - 1 patient (2.5 mg/kg qM) with anaphylactic reaction, 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

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

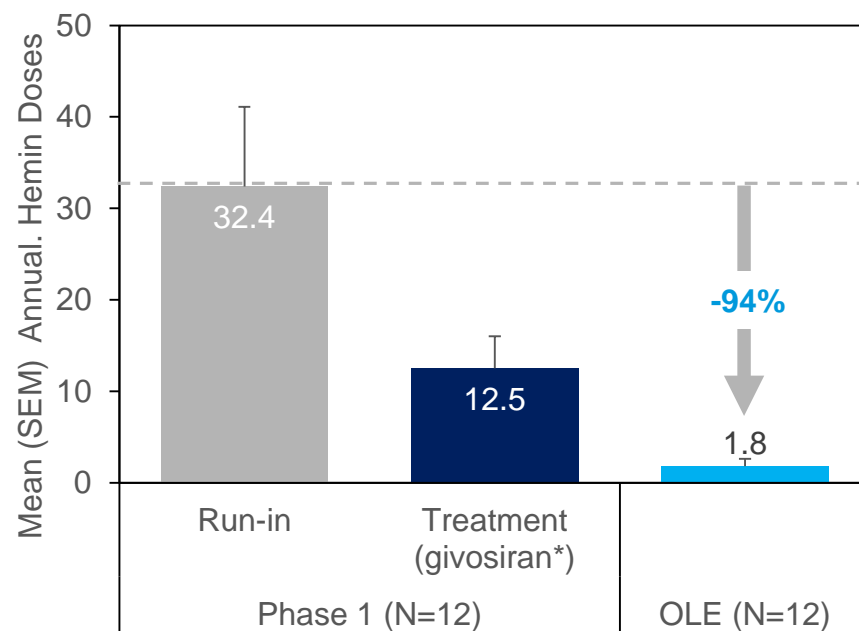
Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- 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. Sardh *et al.* EASL Meeting, Apr 2018

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.

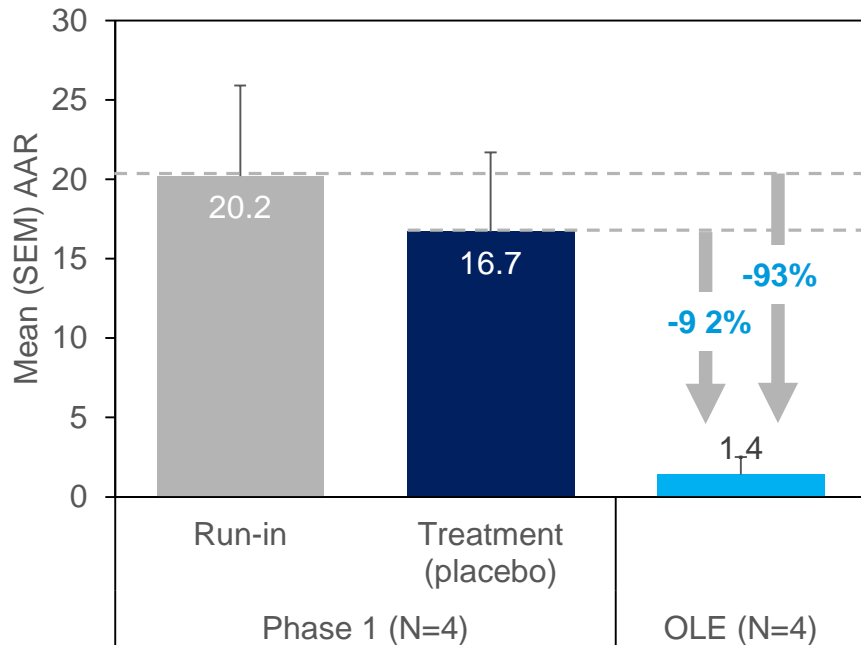
Mean time in Phase 1 Run-in and Treatment of 103 days and 165 days, respectively; mean time in OLE of 322 days.

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

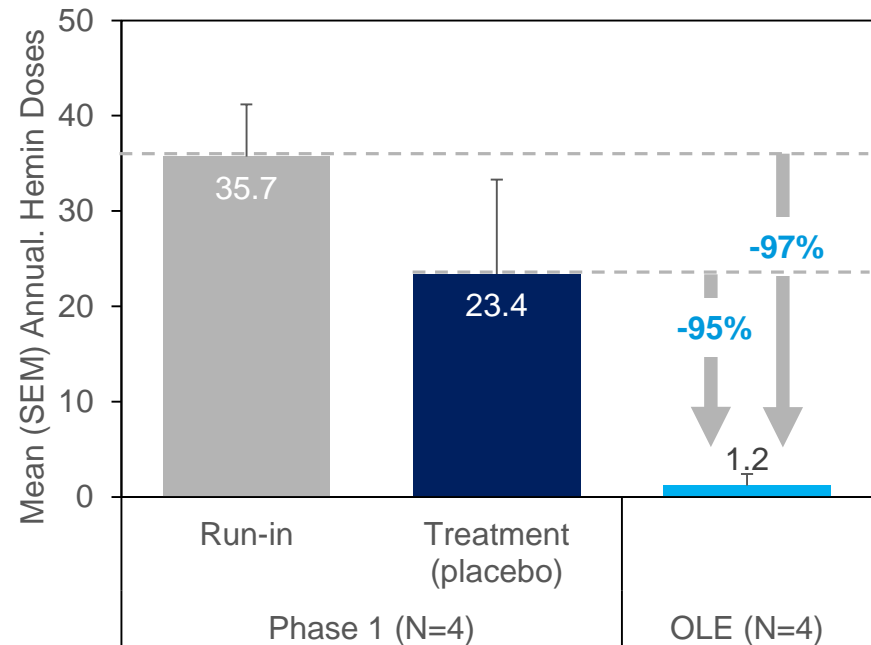
Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- 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. Sardh *et al.* EASL Meeting, Apr 2018

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

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 demonstrated 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

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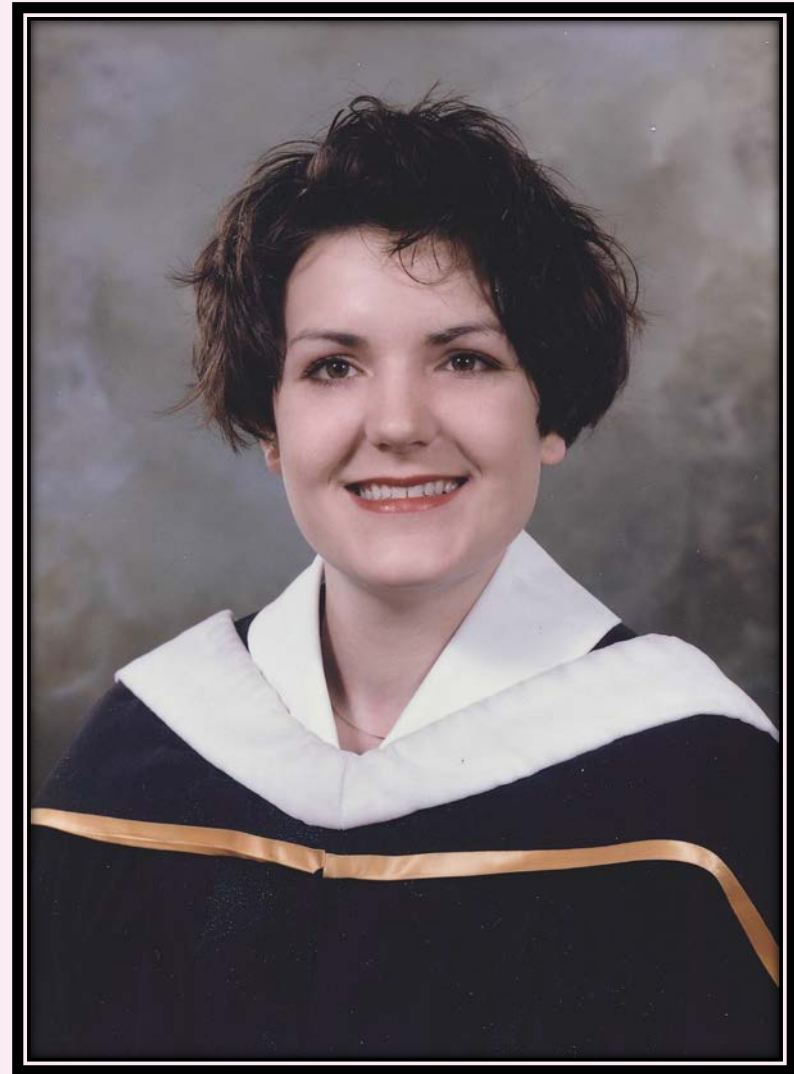
Patient Perspective

- Mary, patient living with Acute Intermittent Porphyria

Givosiran Program Opportunity & Status

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Q&A Session



- A perfectly healthy child. My good health lasted through my college years.



- After college, and before my porphyria awoke at age 28, I indulged my wanderlust and visited 38 countries for business and pleasure.



- For the last 23 years, my life has been reduced from the wide world to a 15x12 bedroom.



- A rare, 'invisible' disease like porphyria can be extremely isolating. Patients can only turn down invitations from friends so many times before they stop calling.

- Thank goodness for pets!
Without their unconditional love, porphyria would be very lonely.



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AHP Patient Population

- Consensus estimated prevalence of 2-5:100,000[†]
- Predominantly female
- ~5% of patients may be severely affected with frequent attacks (~1,000 patients with recurrent attacks in US/EU[‡])
- Many more have sporadic attacks and likely have chronic symptoms and impaired quality of life between attacks
- AHPs are challenging to diagnose, and most patients currently remain undiagnosed
 - Rare disease with low awareness, highly variable, with constellation of non-specific symptoms
 - Often misdiagnosed, with lengthy delays in diagnosis up to 15 years

[†]Anderson KE, Metabolic & Molecular Bases of Inherited Disease, 2001
[‡]ORPHANET; The Porphyria Consortium

AHP Market Landscape

No approved therapy for prevention of attacks

Hemin is only available therapy; not approved for prophylactic use

- Approved for treatment of acute attacks; has short duration of activity (half-life of 11 hours)
 - In EXPLORE study, mean of 4.0 attacks per year on hemin prophylaxis vs. 5.5 attacks per year without
- Side effects including nausea, vomiting, headache, phlebitis
- Risk of iron overload
- Risk of venous destruction or complications from venous port (e.g. infection, clots)

Normosang [product label]. Puteaux, France: Orphan Europe; 2017.

Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

Anderson KE, Bloomer JR, Bonkovsky HL, et al. *Ann Intern Med*. 2005;142:439-450.

Balwani M, Desnick RJ. *Blood*. 2012;120:4496-4504.

Bonkovsky HL. *Am Soc Hematol Educ Program*. 2005:24-30.

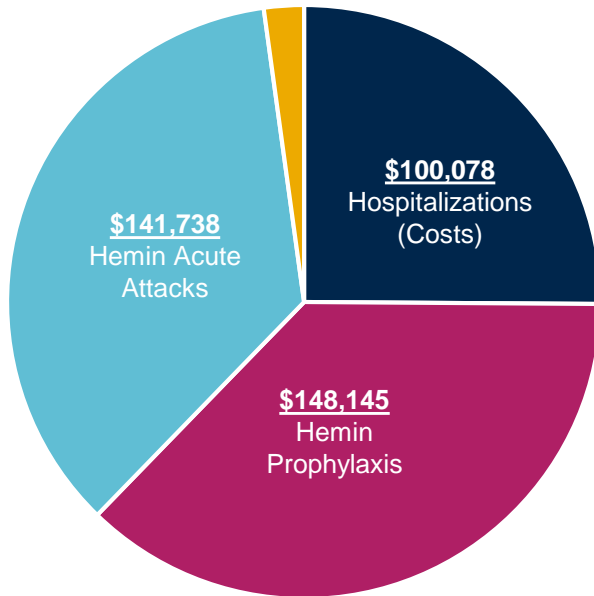
Schmitt C, Lenglet H, Yu A, et al. *J Intern Med*. 2018; 284: 78-91

Wahlin S, Harper P. In: Ferreira GC, Kadish KM, Smith KM, Guillard R, eds. *Handbook of porphyrin science*. Vol 29. 2014.

Significant Economic Burden of AHPs

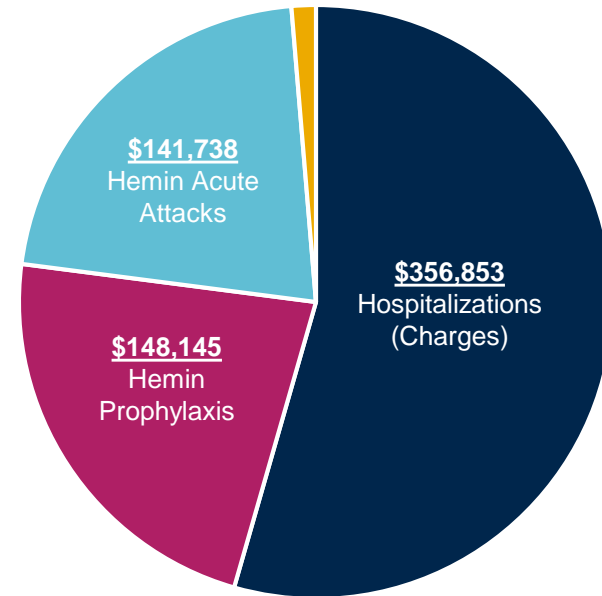
Healthcare Utilization and Cost Analysis* (EXPLORE Natural History Study)

Hospitalizations as Costs



Mean **\$398,463**
(95% CI) **(\$328,303 - \$475,477)**

Hospitalizations as Charges



Mean **\$655,418**
(95% CI) **(\$482,278 - \$847,448)**

*Annual expenditure per patient; based on both hospitalization charges (amount billed) and costs (amount paid)

Opportunities for Facilitating Patient Identification and Improving Patient Care



Increase Disease Awareness & Knowledge



Streamline Testing & Diagnosis



Improve Care Networks & Support Current/New CoEs



Redefine Expectations for Treatment of Patients



Ensure Access

AInylam Act™

- **No-charge third-party genetic testing and counseling program***
- **Recently expanded to include testing and counseling for individuals who may carry a gene mutation known to be associated with the acute hepatic porphyrias**

123
Tests
Submitted**

16
Positive
Samples**

AInylamAct™

- Blood or saliva samples submitted by physicians on behalf of patients that experience symptoms consistent with an acute hepatic porphyria
- Genetic screening performed by CLIA-certified clinical diagnostic laboratory
- Genetic counseling offered before, during, or after genetic testing



More information can be found at www.alnylamact.com

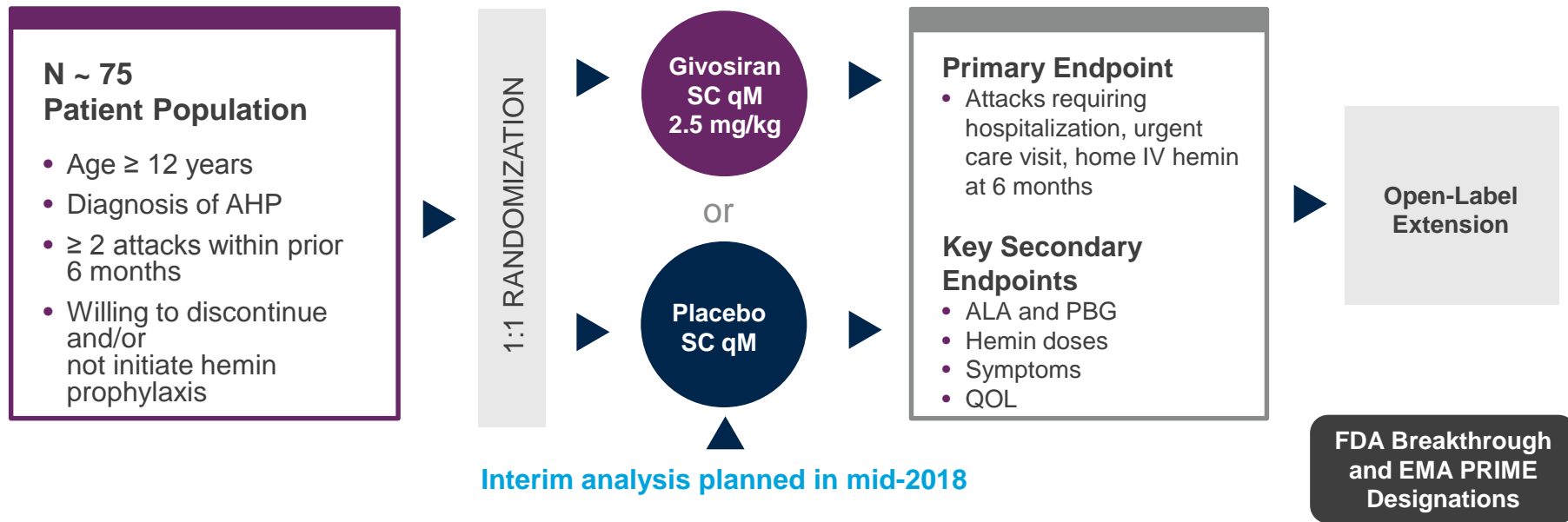
*Genetic testing available in the United States and Canada. Genetic counseling only available in the United States.

**As of 13 July 2018

At no point does Alnylam receive patient-identifiable information; Alnylam receives contact information for physicians using the Program

ENVISION Phase 3 Study Design

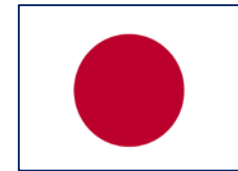
Randomized, Double-Blind, Placebo-Controlled Study in Acute Hepatic Porphyria Patients



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
 - Includes blinded assessment to adjust sample size for primary endpoint

Approval Timeline Assumptions



+ROW

Agenda

Welcome

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

Introduction

- Akin Akinc, Ph.D., General Manager, Givosiran

Disease Overview & Givosiran Phase 1/Open-Label Extension Results

- Jae Kim, M.D., Vice President, Clinical Development

Patient Perspective

- Mary, patient living with Acute Intermittent Porphyria

Givosiran Program Opportunity & Status

- Akin Akinc, Ph.D., General Manager, Givosiran

Q&A Session

Upcoming RNAi Roundtables

Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

- Wednesday, August 15th, 10:30 AM ET

Patisiran & ALN-TTRsc02, for the Treatment of Transthyretin-Mediated Amyloidosis

- Tuesday, September 11, time TBD

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella.



Thank You

