



# Givosiran, for the Treatment of Acute Hepatic Porphyria



September 14, 2020

# Agenda

## Welcome

- Joshua Brodsky – Director, Investor Relations & Corporate Communications

## Introduction & GIVLAARI<sup>®</sup> (givosiran) Overview

- Akin Akinc, Ph.D. – Vice President & General Manager, Givosiran

## GIVLAARI U.S. Commercial Progress

- Gail Hartigan – Senior Director, U.S. Business Lead

## 12-Month Interim Data from ENVISION Phase 3 Study

- Amy Simon, M.D. – Vice President, Clinical Research

## 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](http://www.alnylam.com/capella)**

# 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: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; 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 and our marketed products, including GIVLAARI; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner's ability to obtain regulatory approval for our product candidates, including lumasiran and inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO® (patisiran) and GIVLAAR® (givosiran); our progress in continuing to establish a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI, and achieve net product revenues for ONPATTRO within our further revised expected range during 2020; 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 within the reduced ranges of guidance provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products, Ironwood, for assistance with the education about and promotion of GIVLAARI, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. 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

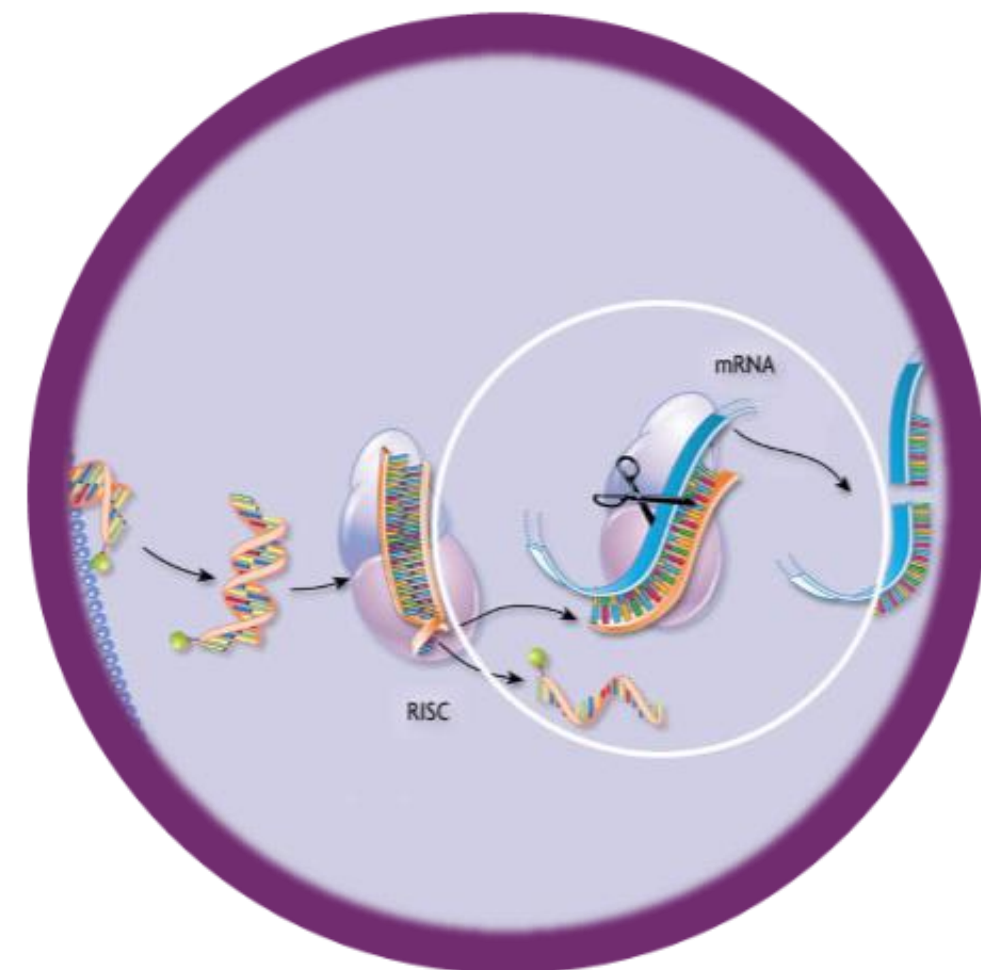
**Nobel Prize-winning science**

**Silence any gene in genome**

**Potent and durable mechanism of action**

**Product engine for sustainable innovation**

**Multiple products impacting patients globally**



# Anylam Commercial Products and Late Stage Clinical Development Pipeline

## Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

**BREAKTHROUGH  
DESIGNATION**

**LATE STAGE**  
(Phase 2 – Phase 3)

**REGISTRATION**

**COMMERCIAL**

**COMMERCIAL  
RIGHTS**



*hATTR Amyloidosis<sup>1</sup>*



Global



*Acute Hepatic Porphyria<sup>2</sup>*



Global

**Lumasiran**

*Primary Hyperoxaluria Type 1*



Global

**Inclisiran**

*Hypercholesterolemia*



Milestones & up to  
20% Royalties<sup>3</sup>  
(Novartis)

**Patisiran**

*ATTR Amyloidosis  
Label Expansion*



Global

**Fitusiran**

*Hemophilia and Rare  
Bleeding Disorders*



15-30% Royalties  
(Sanofi)

**Vutrisiran**

*ATTR Amyloidosis*



Global

<sup>1</sup> Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

<sup>2</sup> Approved in the U.S. and Brazil for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older












<sup>3</sup> As part of Blackstone strategic financing collaboration, 50% of inclisiran royalty revenue will be payable to Blackstone



# Alnylam Early Stage Clinical Development and 2020 IND Pipeline

## Focused in 4 Strategic Therapeutic Areas (STArS):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		HUMAN POC <sup>1</sup>	BREAKTHROUGH DESIGNATION	2020 IND CANDIDATES	EARLY STAGE (Phase 1 – Phase 2)	COMMERCIAL RIGHTS
<b>Cemdisiran</b>	<i>Complement-Mediated Diseases</i>					50-50 (Regeneron)
<b>Cemdisiran/Pozelimab Combo<sup>2</sup></b>	<i>Complement-Mediated Diseases</i>					Milestone/Royalty (Regeneron)
<b>ALN-AAT02</b> (DCR-A1AT) <sup>3</sup>	<i>Alpha-1 Liver Disease</i>					Ex-U.S. option post-Phase 3 (Dicerna)
<b>ALN-HBV02</b> (VIR-2218)	<i>Hepatitis B Virus Infection</i>					50-50 option post-Phase 2 (Vir)
<b>ALN-AGT</b>	<i>Hypertension</i>					Global
<b>ALN-HSD</b>	<i>NASH</i>					50-50 (Regeneron)
<b>ALN-COV</b> (VIR-2703)	<i>COVID-19</i>					50-50 option post-Phase 2 (Vir)

**2-4** *INDs per year planned from organic product engine*

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

<sup>2</sup> Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

<sup>3</sup> Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development



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# Acute Hepatic Porphyria (AHP)

Family of Rare Genetic Diseases with Significant Disease Burden

## Description

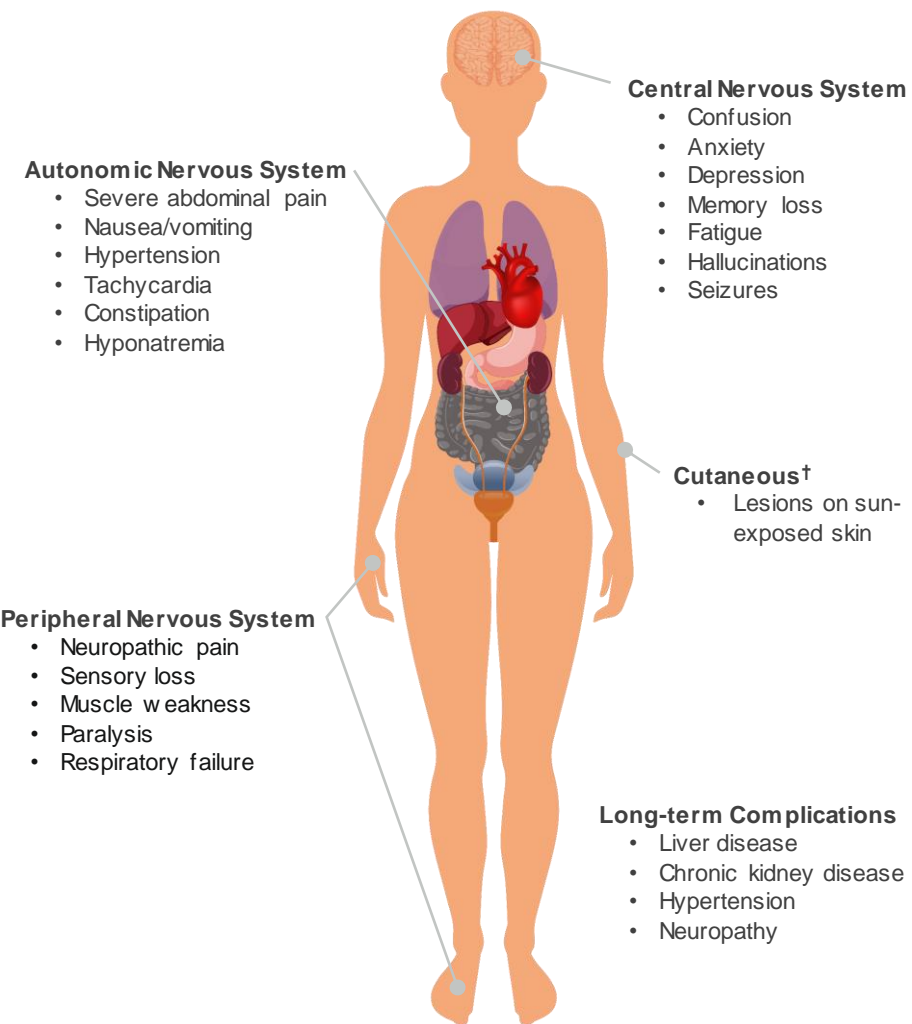
Causes potentially life-threatening attacks and chronic manifestations that negatively impact quality of life

Predominantly  
**female**  
commonly misdiagnosed

Patient Population

**~3,000**

diagnosed in U.S./EU with active disease<sup>1,2</sup>



<sup>1</sup> Elder et al. J Inherit Metab Dis 2013;36:849–57; 2. Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database

† Symptoms specific to hereditary coproporphyria and variegate porphyria

# Acute Hepatic Porphyria (AHP)

## Disease Overview

- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in the liver<sup>1,2</sup>
- AIP is the most common type, with mutation in *hydroxymethylbilane synthase (HMBS)* gene<sup>3,4</sup>

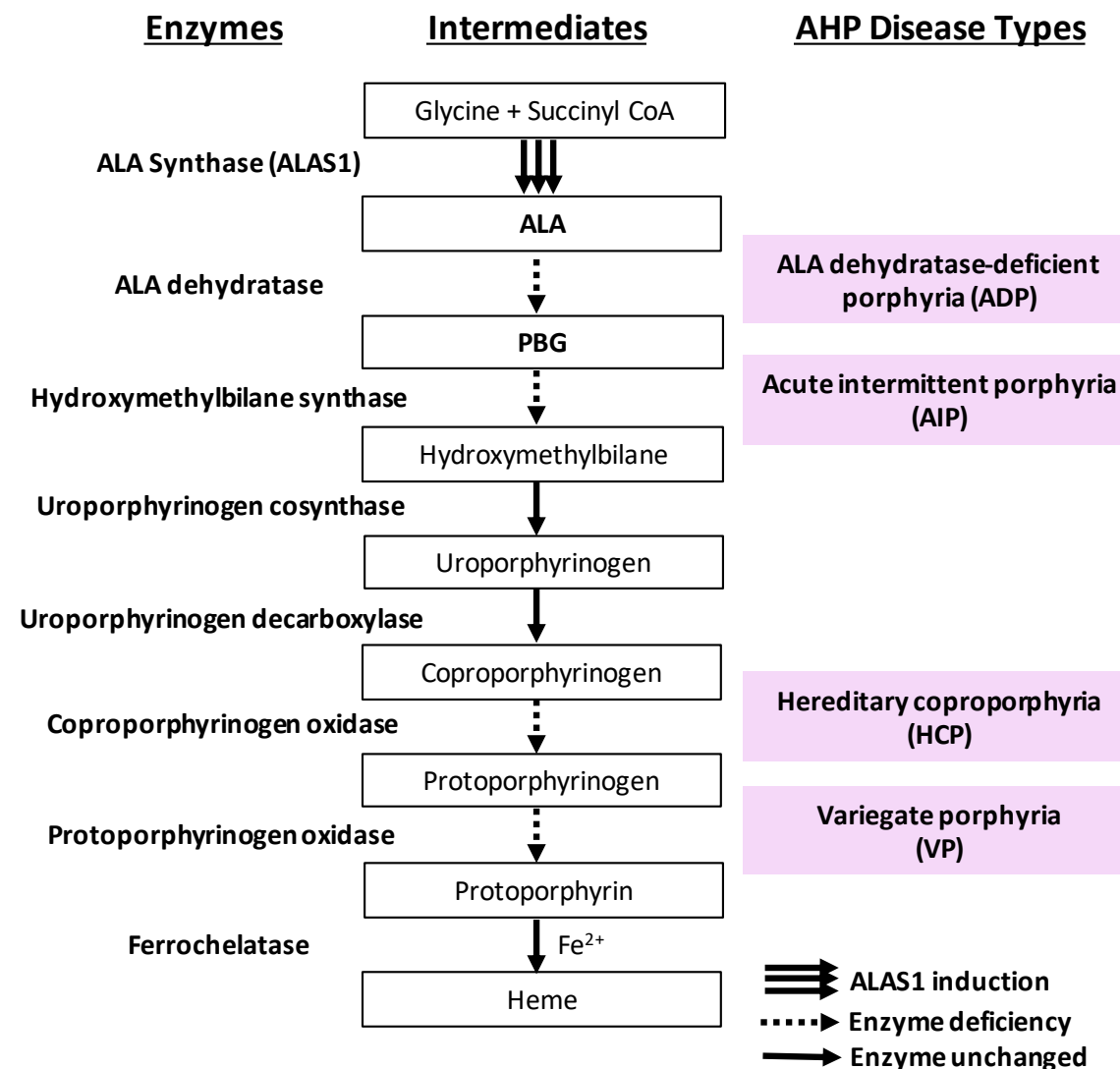
## Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA/PBG<sup>1,2</sup>
- Accumulation of ALA/PBG is believed to cause disease manifestations<sup>2,5</sup>

## Attacks, Chronic Manifestations, and Comorbidities

Patients can experience:

- Acute neurovisceral attacks which commonly manifest as severe abdominal pain and can be life-threatening<sup>6,7</sup>
- Debilitating chronic symptoms (pain, fatigue, nausea, and anxiety)<sup>6–8</sup>
- Hypertension, chronic kidney disease, and liver disease<sup>3,6,9–11</sup>
- Disability, diminished quality of life, and social isolation common among those with attacks<sup>6–8</sup>



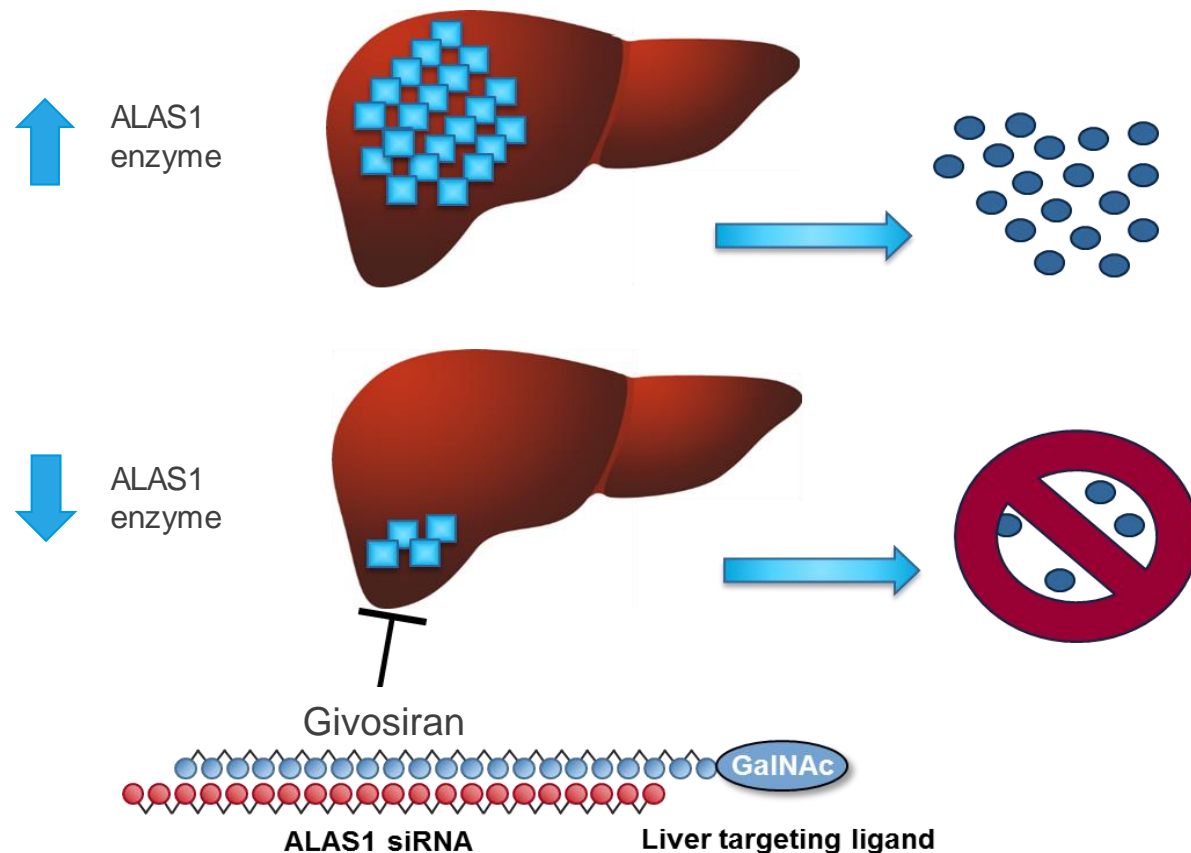
<sup>1</sup> Puy et al. *Am J Hum Genet* 1997;60:1373–83; <sup>2</sup> Balwani & Desnick. *Blood* 2012;120:4496–504; <sup>3</sup> Bonkovsky et al. *Am J Med* 2014;127:1233–41; <sup>4</sup> Elder et al. *JIMD* 2013;36:849–57; <sup>5</sup> Bissell et al. *Am J Med* 2015;128:313–7; <sup>6</sup> Gouya et al. *Hepatology* 2019; DOI:10.1002/hep.30936; <sup>7</sup> Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; <sup>8</sup> Simon et al. *Patient* 2018;11:527–37; <sup>9</sup> Stewart. *J Clin Pathol* 2012;65:976–80; <sup>10</sup> Pallet et al. *Kidney Int* 2015;88:386–95; <sup>11</sup> Andersson et al. *J Intern Med* 1996;240:195–201

AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; CoA, coenzyme A; PBG; porphobilinogen

# Givosiran: An RNAi Therapeutic for AHP<sup>1,2</sup>

## Therapeutic Hypothesis

### Reduction of Liver ALAS1 Enzyme to Lower ALA and PBG



ALA/PBG induces porphyria symptoms

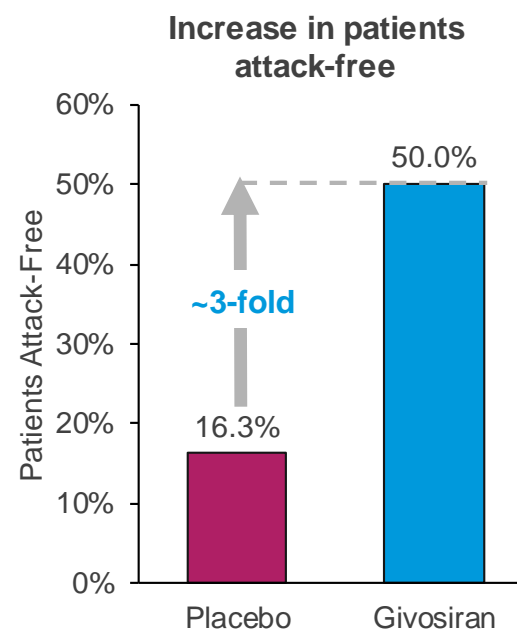
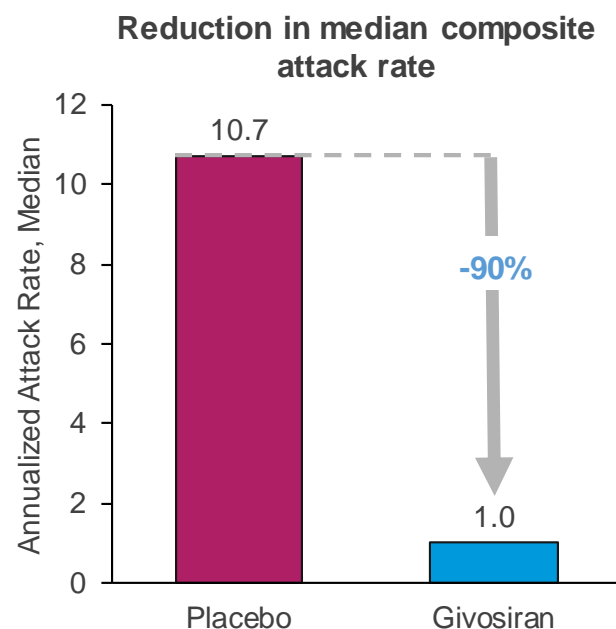
Givosiran results in reduction of ALAS1 mRNA and lowers ALA/PBG accumulation to prevent attacks and disease symptoms

# Givosiran <sup>ENVISION</sup> Phase 3 Study

Givosiran Meets Primary Endpoint with Encouraging Profile in High Unmet Need Disease

Primary Endpoint*	Givosiran (N=46)	Placebo (N=43)	Rate Ratio	P-Value
Composite <sup>†</sup> Annualized Attack Rate, Mean	3.2	12.5	0.26	6.04 x 10 <sup>-9</sup>

Adverse Event, n of patients (%)	Placebo (N = 46)	Givosiran (N = 48)
Adverse Event (AE)	37 (80.4%)	43 (89.6%)
Serious Adverse Event (SAE)	4 (8.7%)	10 (20.8%)
Deaths	0 (0.0%)	0 (0.0%)
Discontinuations Due to AEs	0 (0.0%)	1 (2.1%)



- Two SAEs in givosiran patients reported as study drug related
  - 1 abnormal liver function test, and 1 chronic kidney disease
- Common AEs (>10% in either arm)
  - More common in givosiran than placebo: nausea, injection site reaction, chronic kidney disease, fatigue
  - More common in placebo than givosiran: headache, vomiting, urinary tract infection, pyrexia
- ALT elevations >3x ULN occurred in 7 givosiran patients compared to 1 placebo
  - Majority mild to moderate in severity; occurred after first 3 to 5 doses of givosiran
  - One givosiran-treated patient discontinued due to ALT >8x ULN, a protocol-defined stopping rule, with subsequent resolution; remaining 6 patients had resolution with continued dosing (n=5) or after brief interruption (n=1)
- Small and mostly reversible increases in creatinine and decreases in eGFR more common in givosiran than placebo; none led to discontinuation
- 93/94 (99%) patients entered Open Label Extension (OLE) period

Completed primary analysis as of April 13, 2019; see Balwani, et al., EASL Meeting, April 13, 2019 for full ENVISION study results

\* Efficacy endpoints evaluated in AIP patients, unless otherwise noted

<sup>†</sup> Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home

# Givosiran Phase 3 Data Published in *The New England Journal of Medicine*



The NEW ENGLAND  
JOURNAL of MEDICINE

## Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria

Manisha Balwani, M.D., Eliane Sardh, M.D., Ph.D., Paolo Ventura, M.D., Paula Aguilera Peiró, M.D., David C. Rees, F.R.C.P., Ulrich Stölzel, M.D., D. Montgomery Bissell, M.D., Herbert L. Bonkovsky, M.D., Jerzy Windyga, M.D., Ph.D., Karl E. Anderson, M.D., Charles Parker, M.D., Samuel M. Silver, M.D., Ph.D., et al., for the ENVISION Investigators\*

June 11, 2020

N Engl J Med 2020; 382:2289-2301

DOI: 10.1056/NEJMoa1913147



# The second RNAi therapeutic is **APPROVED IN THE U.S., EU & BRAZIL**

 **GIVLAARI**<sup>®</sup>  
(givosiran) injection for subcutaneous use  
189 mg/mL

 **GIVLAARI**<sup>®</sup>  
189 mg/mL solution for injection givosiran

 **GIVLAARI**<sup>®</sup>  
(givosirana sódica) injeção para uso  
subcutâneo  
189 mg/mL

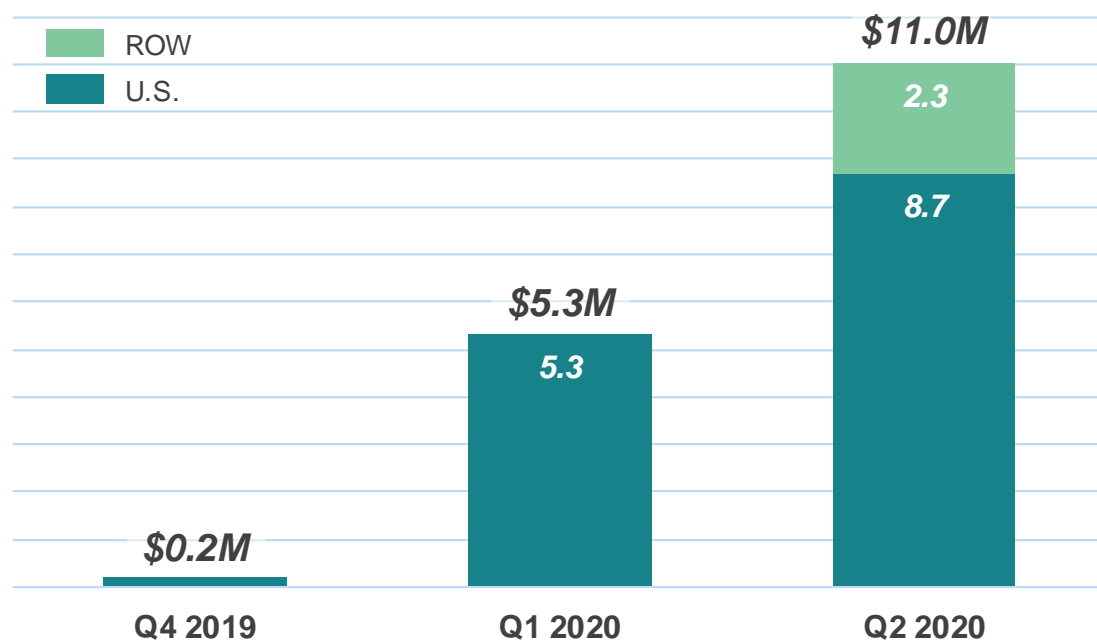


# GIVLAARI® Launch Update: Q2 2020

Strong Initial Demand

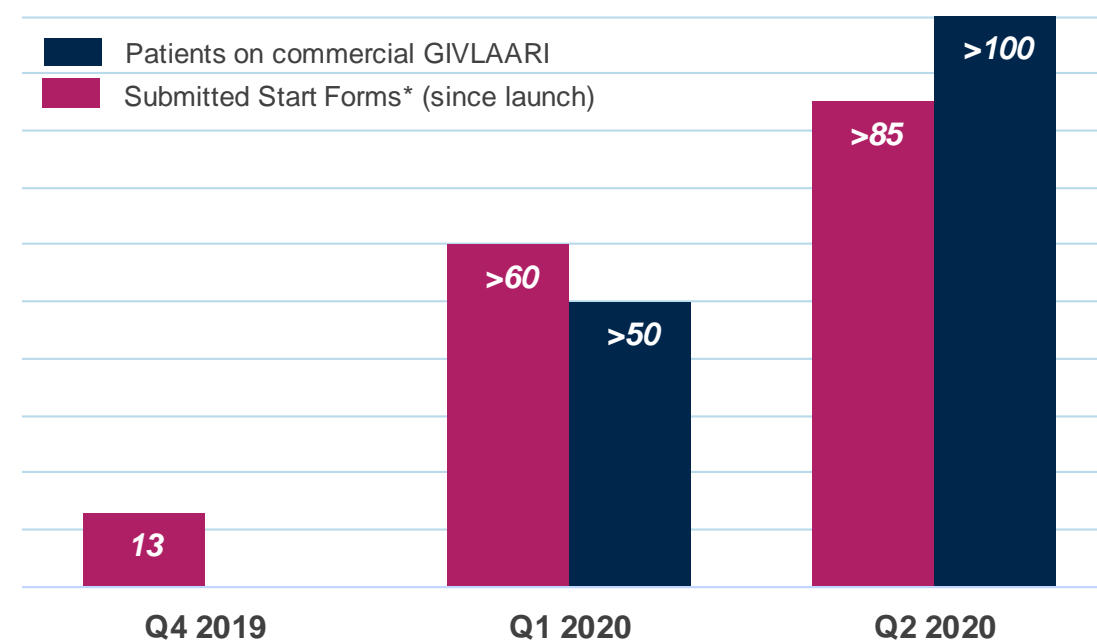
## \$11.0M

GIVLAARI Q2  
Net Product Revenues



## >100

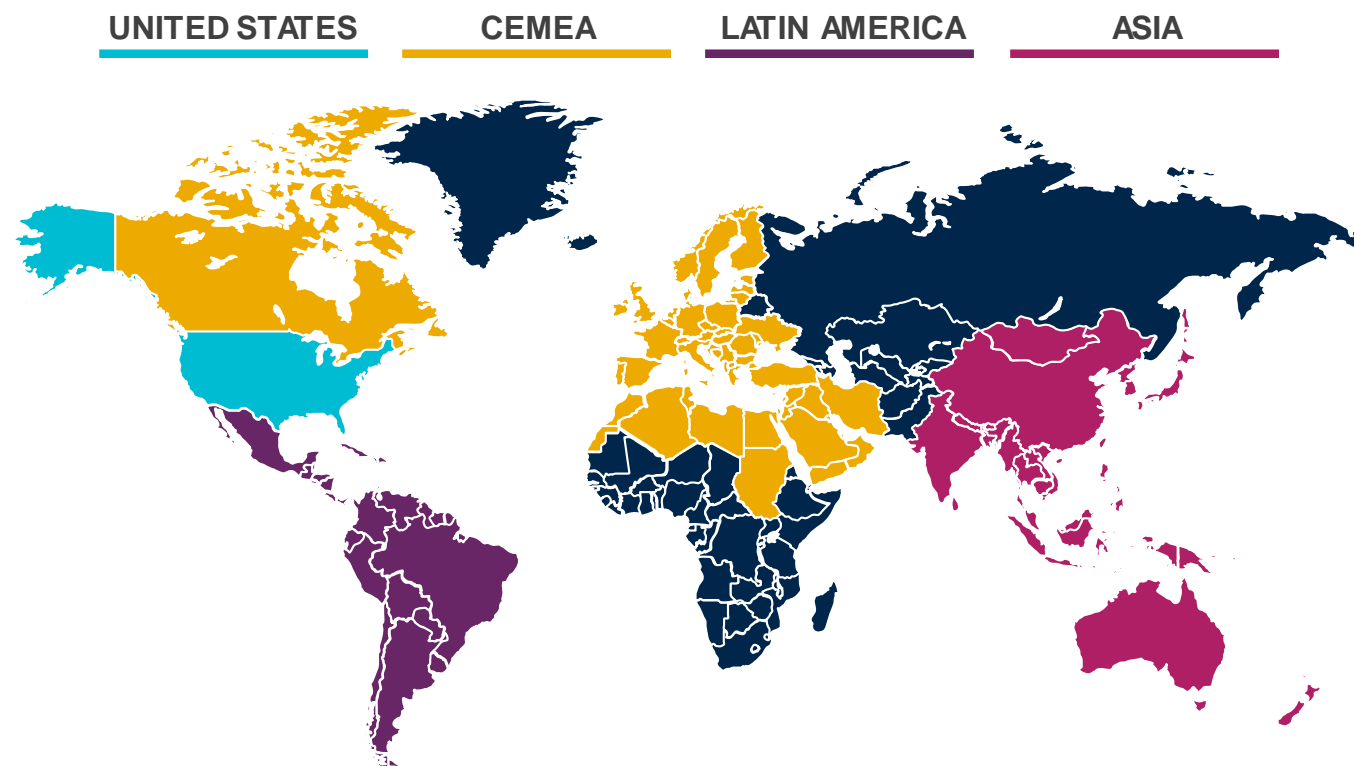
Patients on Commercial GIVLAARI  
at end of Q2 2020



# GIVLAARI Global Commercialization

Ensuring GIVLAARI Availability Around the World

- Now approved in Brazil
- Initial launch underway in Germany
- Named patient sales in France and other countries
  - ASMR II granted by HAS in France
- Working with physicians on their requests in multiple regions to provide pre-approval access via Expanded Access Program (EAP)
- MAAs submitted in Canada, Switzerland, and Israel
- Planned JNDA submission in Japan in late 2020



**GIVLAARI**<sup>®</sup>  
(givosiran) injection for subcutaneous use  
189 mg/mL

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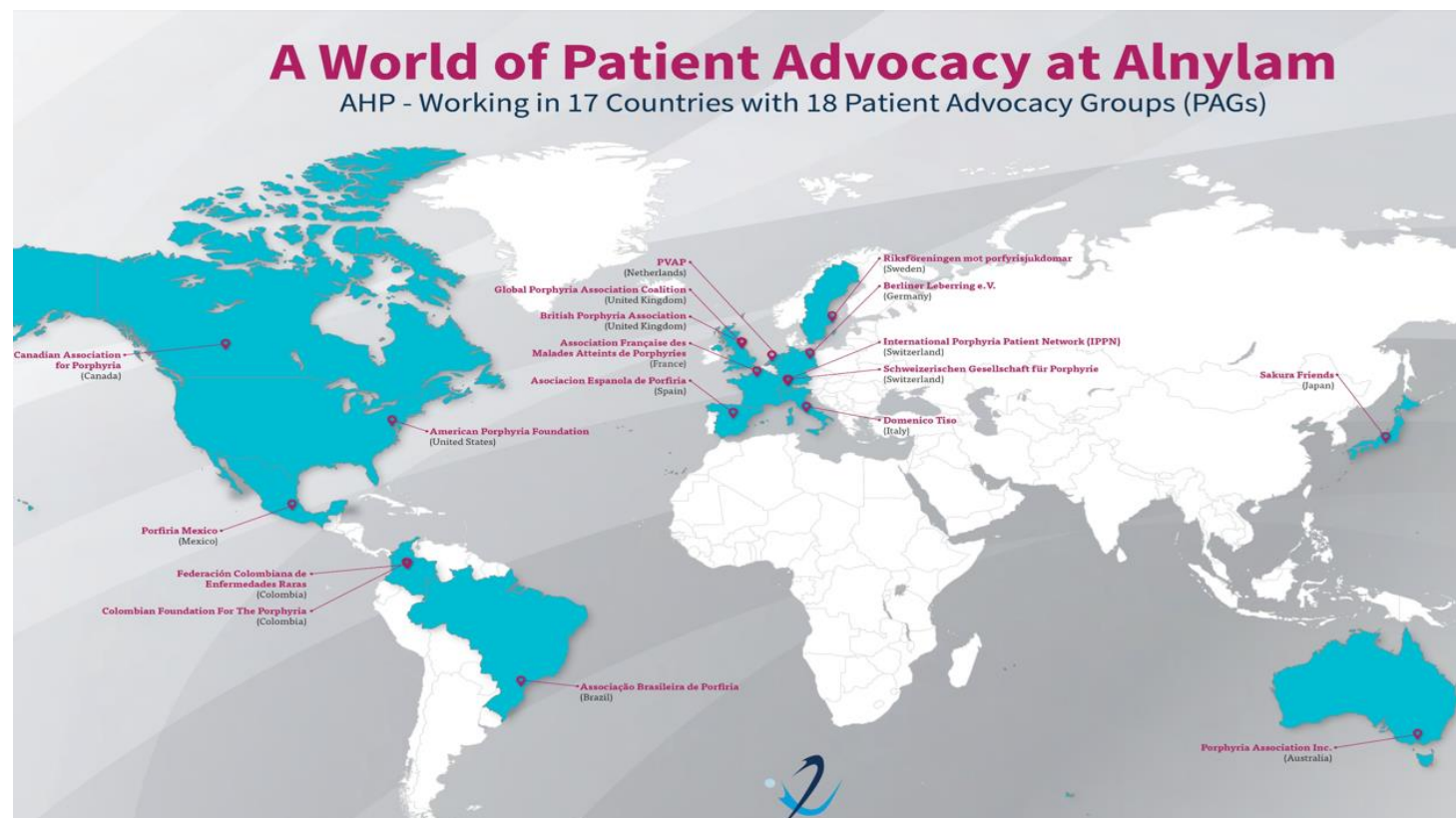
## Q&A Session

# Educating on AHP and Launching GIVLAARI



# Collaborating with Patient Community

- Co-presented with American Porphyria Foundation at Patients as Partners conference on best practices for patient community and industry collaborations
- Engaged patient groups worldwide to understand how COVID-19 is impacting members and operations
- Increased use of digital platforms to continue to get timely input from patient groups, patients and caregivers



# Leveraging Combination of Innovative Data, Technology, and Digital Efforts to Facilitate Diagnosis and Patient Identification

## Data



Data from Medical/Pharmacy Claims, EMR, Genetic/Biochemical Tests, etc.



## Technology

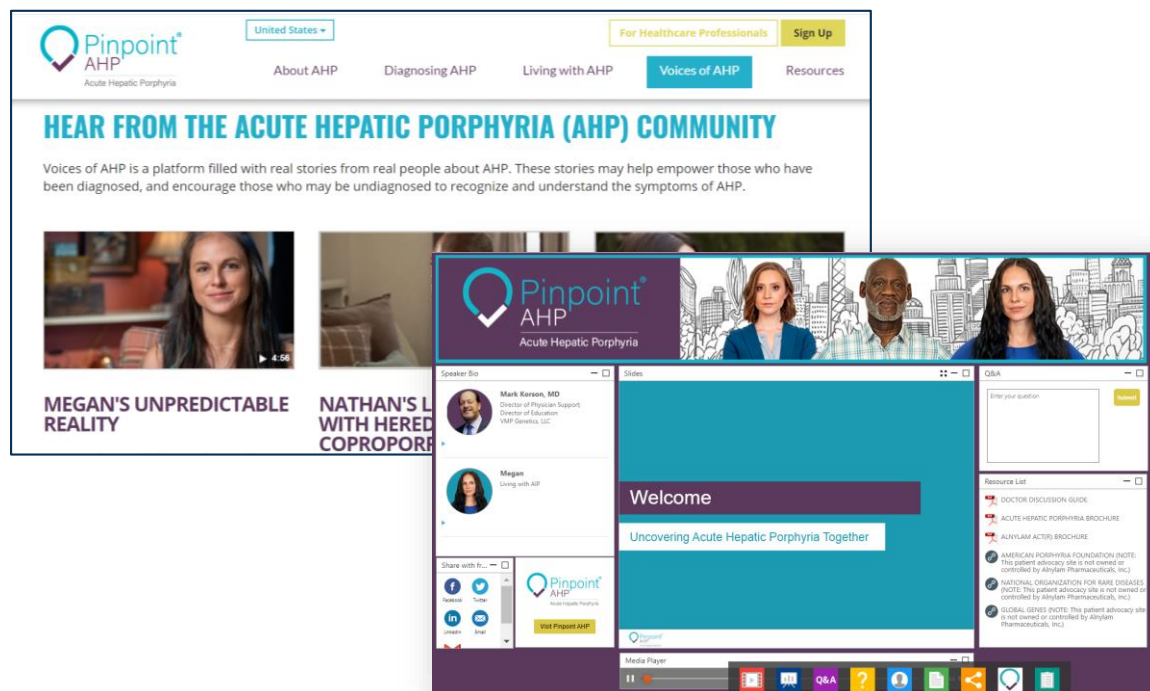


- Optimize testing availability in EMR
- Establish informational instruction guides for healthcare providers to facilitate earlier diagnosis

## Digital

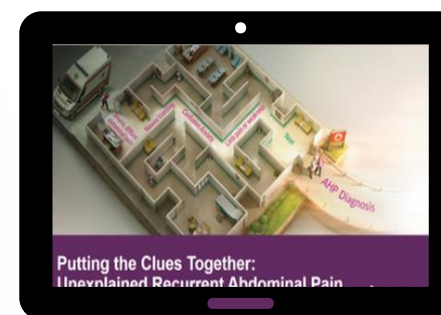


# Connecting with Consumers and Healthcare Providers via Webinars



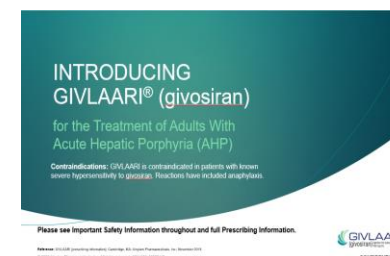
- Ability to register for patient events on PinpointAHP.com
- Patient webinar topics include Living Healthfully and Uncovering AHP

## Healthcare Provider Disease Education Programs



- Raise awareness about AHP
- Improve patient identification through symptom recognition
- Educate HCPs on commonly used tests to help inform diagnosis of AHP

## Healthcare Provider Product Education Programs



- Introduce GIVLAARI® (givosiran) for the treatment of adults with AHP
- Increase awareness of GIVLAARI with specialties who treat adult patients with AHP



# Leveraging Social Media to Help Connect Patients to AHP Disease Resources

## 3rd Party Social Media Programs

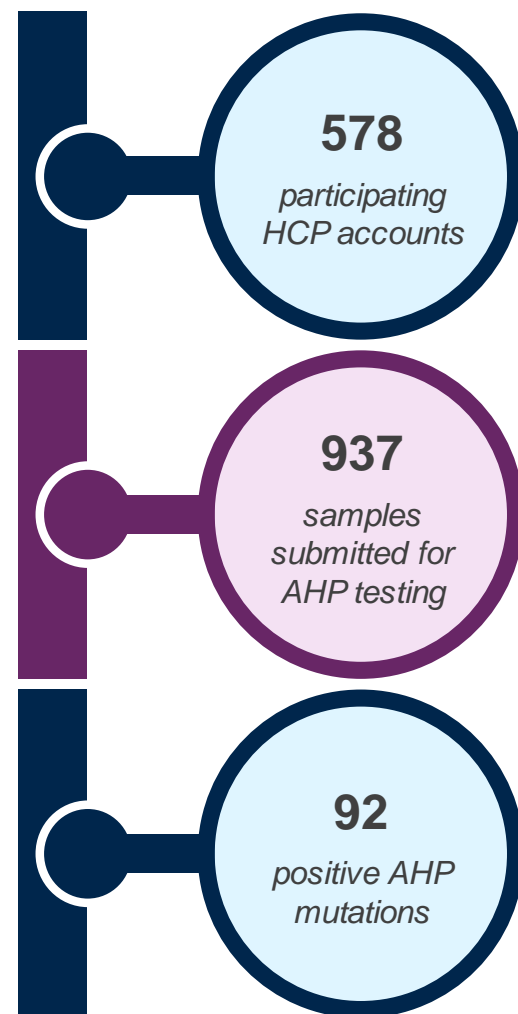
## PinpointAHP.com



- Voices of AHP added to website with NEW videos from patient ambassadors
- Doctor Discussion Guide downloaded over 3,600 times
- MOD video watched over 11,000 times

# Alnylam Act® – Acute Hepatic Porphyria

Third-Party Genetic Testing and Counseling Program Sponsored by Alnylam



Reduce barriers to genetic testing and counseling to help people make more informed decisions about their health

Tests and services are performed by independent third parties

Available in U.S. and Canada (genetic counseling service available in U.S.)

Healthcare professionals who use this program have **no obligation** to recommend, purchase, order, prescribe, promote, administer, use or support any Alnylam product

More information regarding this program  
available at: [www.alnylamact.com](http://www.alnylamact.com)

# Alnylam **Patient Services Programs\***

Our Focus on Patient Support

## Supporting Patients Directly

Evaluate **patients' coverage** and translate benefit details to patients

Facilitate **reimbursement process**

Provide information regarding **financial assistance** programs

Manage ongoing access, **treatment administration support**, and patient/caregiver education



## Working with HCPs to Support Patients

Evaluate **patients' coverage** and translate benefit details to HCPs

**Facilitate communication** between HCPs, patients, insurance companies, and drug distribution providers, as needed

Provide information regarding **financial assistance programs**

Educate about the **claims and appeals** requirements and processes

# GIVLAARI® U.S. Launch Update: Q2 2020

Strong Initial Demand and Patient Access

## Demand



>85

U.S. Start Forms submitted

76%

New U.S. starts from new writers\*

## Patient Access



### INNOVATIVE PRICING

Proactively seeking Value Based Agreements (VBAs) with Prevalence Based Adjustment (PBA) option to link value delivered with real world drug performance and patient prevalence

7

VBAs completed

>75%

U.S. lives with confirmed access to GIVLAARI, if prescribed





## ***GIVLAARI® launch off to strong start, even in midst of pandemic***

- Leveraging of digital channels to educate on AHP, with content tailored to patients and HCPs
- Field teams continue to interact with customers, both virtually and in-person, where possible
- Very good progress on access
- Alnylam Assist® program to help support patients

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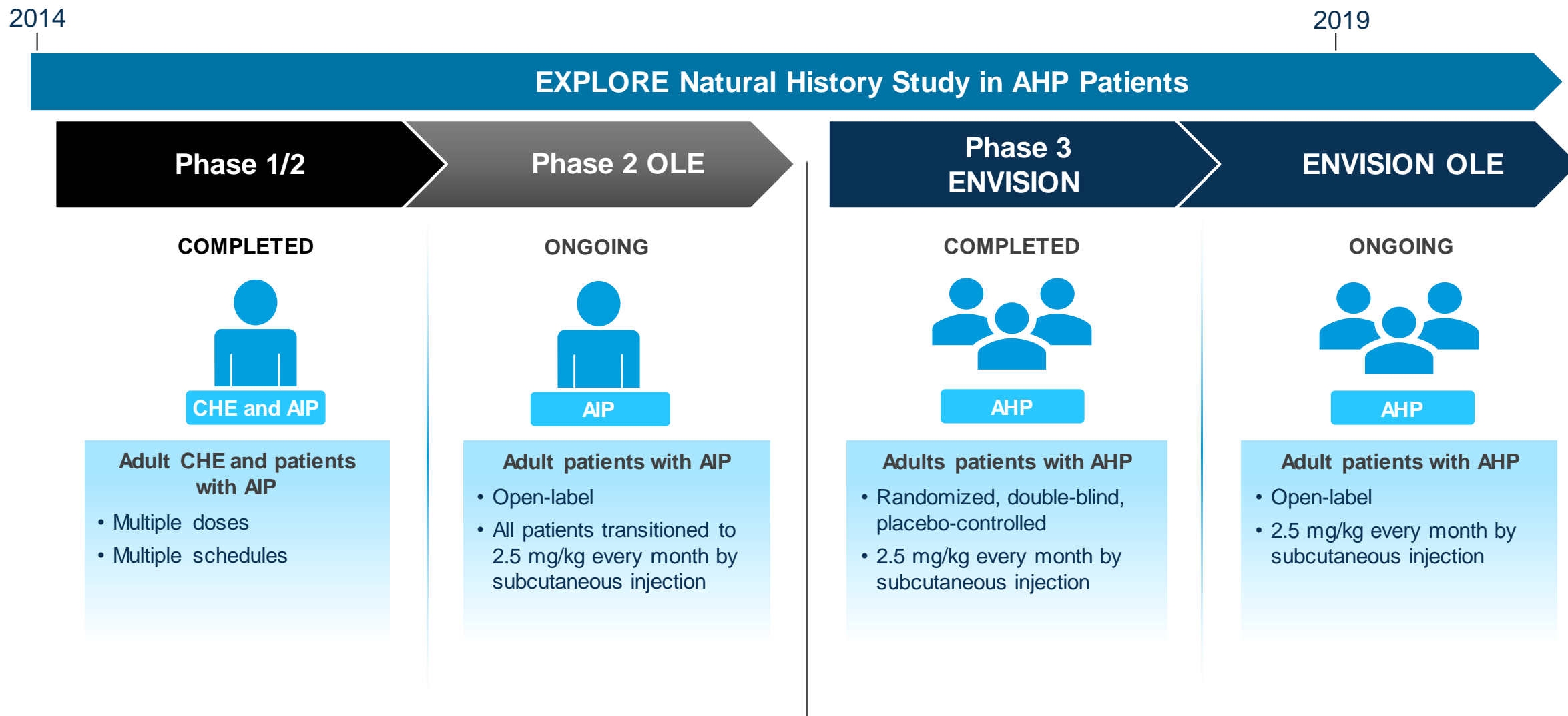
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# Givosiran Clinical Development Program

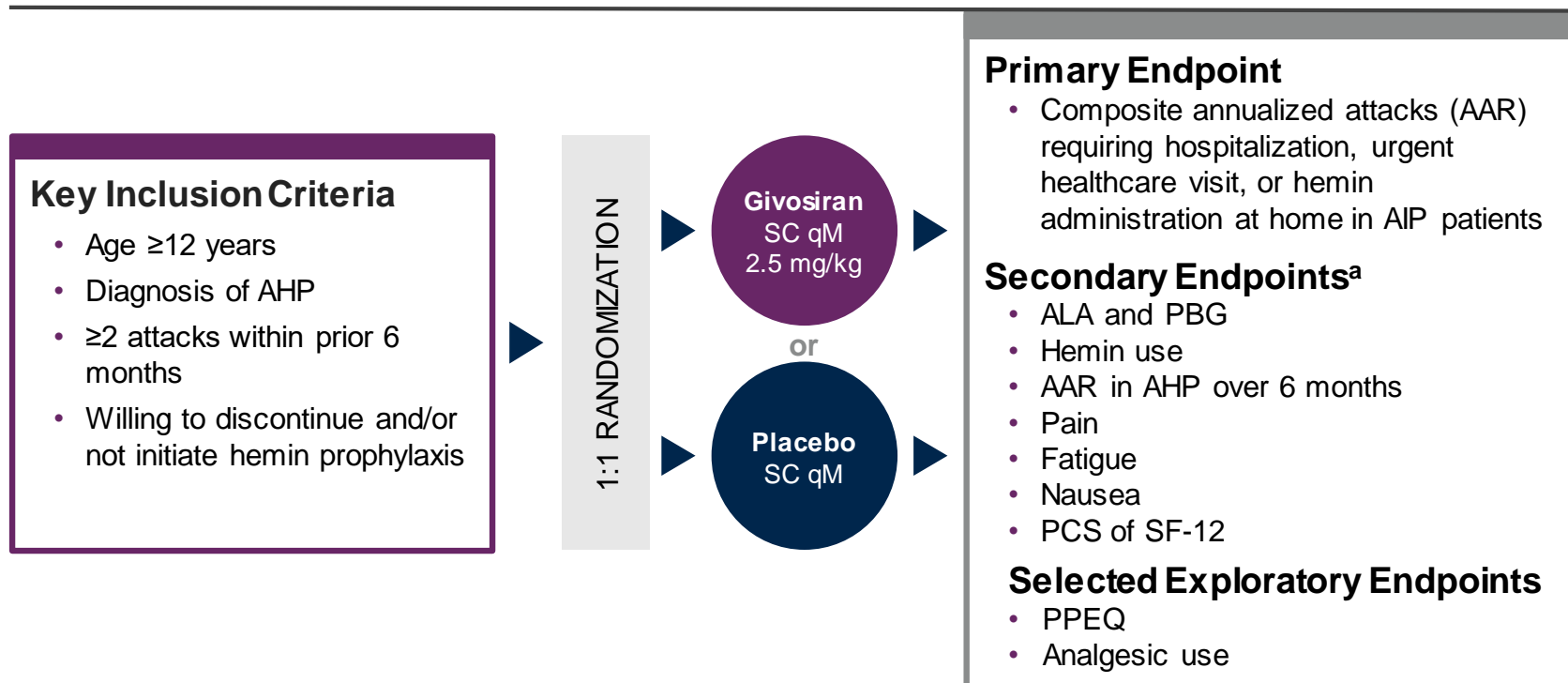




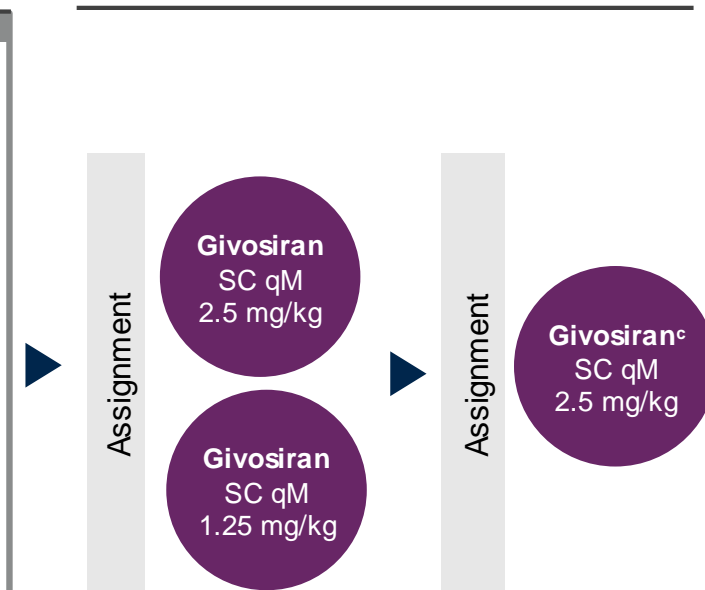
# ENVISION Phase 3 Study Design

- 94 patients with AHP enrolled in ENVISION at 36 sites in 18 countries
- All patients completed 6-month double-blind (DB) period; all eligible patients (n=93) entered 30-month open label extension (OLE) period

## 6-Month DB Period



## 30-Month OLE Period<sup>b</sup>



<sup>a</sup> Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted, at 6 months

<sup>b</sup> All endpoints listed above were considered exploratory in OLE period

<sup>c</sup> Amendment 5 increased the dose of all patients to 2.5 mg/kg monthly

Balwani et al. *International Liver Congress* 2019. Oral

ALA, delta-aminolevulinic acid; AAR, annualized rate of composite porphyria attacks; DB, double-blind; PBG; porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire qM, every month; SC, subcutaneous; SF-12, Short Form (12-item) Health Survey; OLE, Open Label Extension

# Demographics and Baseline Characteristics of AHP Patients

- Baseline characteristics were generally balanced between groups

Characteristic	Placebo Crossover Patients (n=46)	Givosiran Patients (n=48)
Age at screening, years, median (range)	36 (20, 60)	42 (19, 65)
Female, n (%)	41 (89)	43 (90)
Years since diagnosis, median (range)	6.46 (0.1, 38.5)	6.98 (0.2, 43.3)
Prior hemin prophylaxis, n (%)	18 (39)	20 (42)
Historical AAR <sup>a</sup> , median (range)	7.0 (0 <sup>b</sup> , 46)	8.0 (4, 34)
Chronic symptoms daily or most days between attacks, n (%)	26 (57)	23 (48)
Opioid use daily or most days between attacks, n (%)	13 (28)	14 (29)
Baseline urinary ALA (mmol/mol), median (range)	16.4 (1.4, 41.5)	16.4 (1.8, 88.9)
Baseline urinary PBG (mmol/mol), median (range)	39.3 (3.6, 87.7)	39.6 (0.4, 150.0)

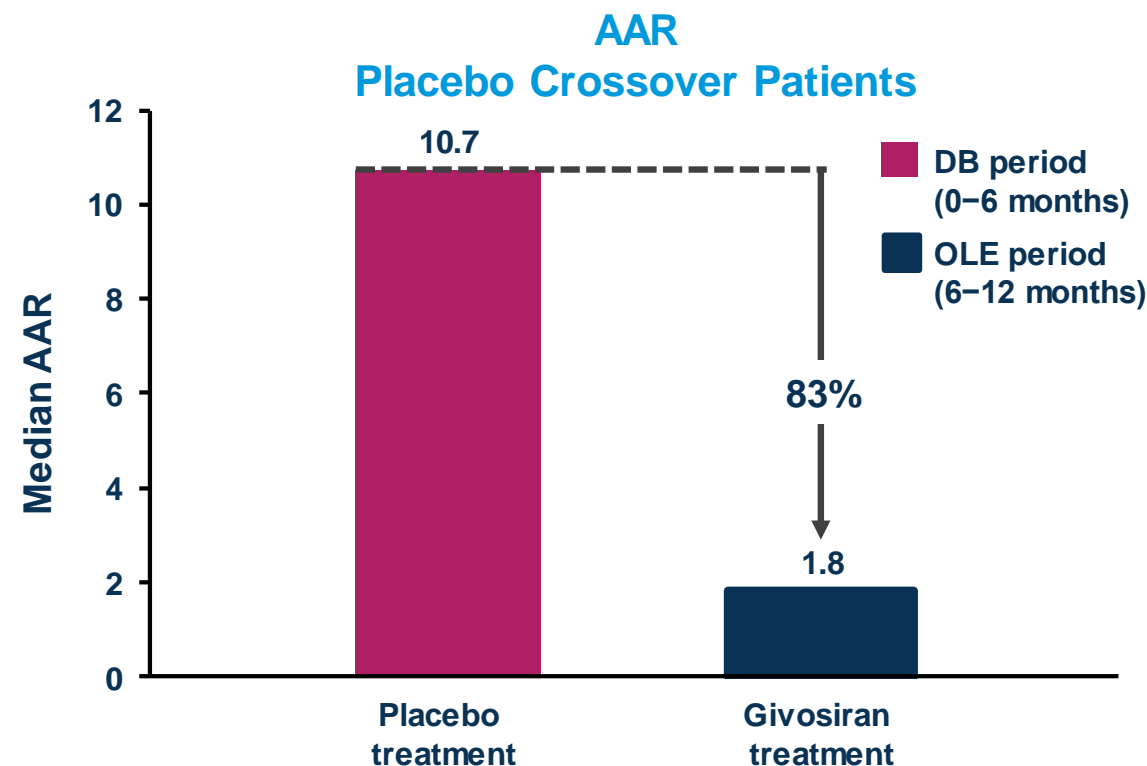
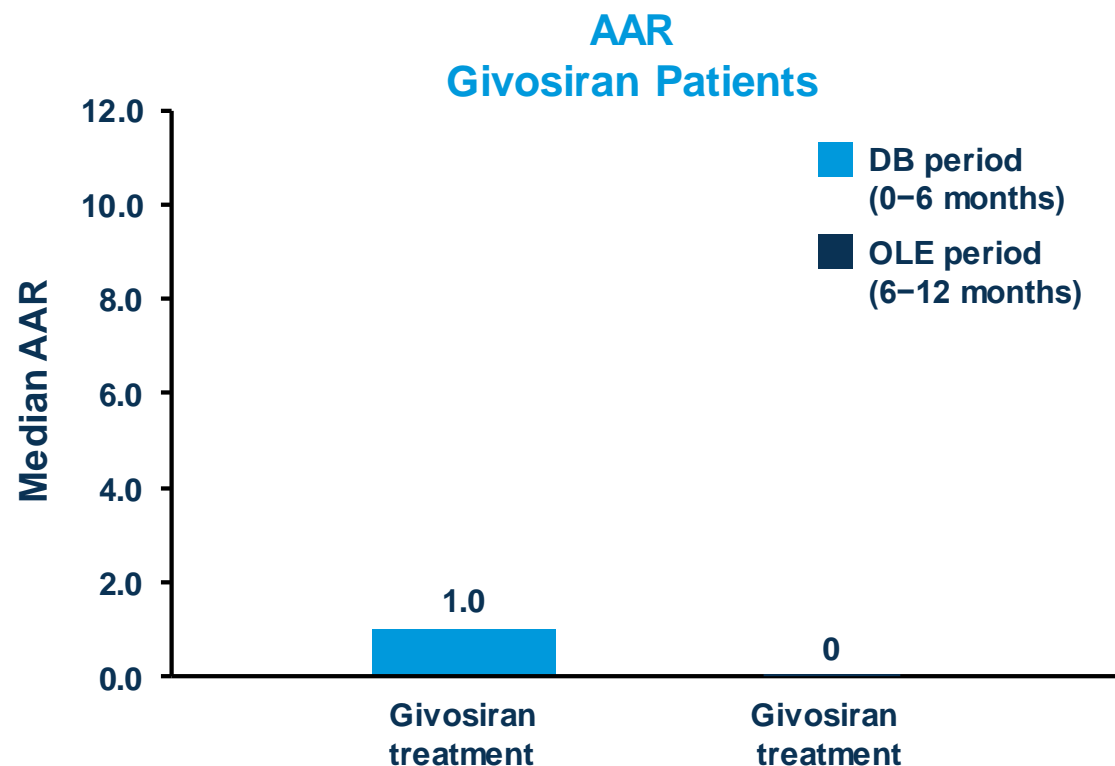
<sup>a</sup> Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home

<sup>b</sup> One patient in the placebo group did not meet inclusion criterion of  $\geq 2$  attacks requiring hospitalization, urgent healthcare visit or intravenous hemin at home within 6 months prior to screening (patient had 2 attacks that were treated at home without intravenous hemin). This was identified as a protocol deviation

AAR, annualized rate of composite porphyria attacks; IV, intravenous

## Sustained AAR Reduction with Long-Term Dosing

- Continued givosiran treatment led to sustained AAR reduction during the OLE
- Placebo crossover patients had similar AAR reduction in OLE period as givosiran patients in DB period<sup>a</sup>
  - Trend towards increased efficacy in placebo crossover patients for 2.5 mg/kg<sup>b</sup> dose compared to 1.25 mg/kg<sup>c</sup> dose (Intra-patient AAR reduction of 79% vs 67%, respectively)



<sup>a</sup> Descriptive analysis

<sup>b</sup> Placebo crossover patients receiving 2.5mg/kg (n=29)

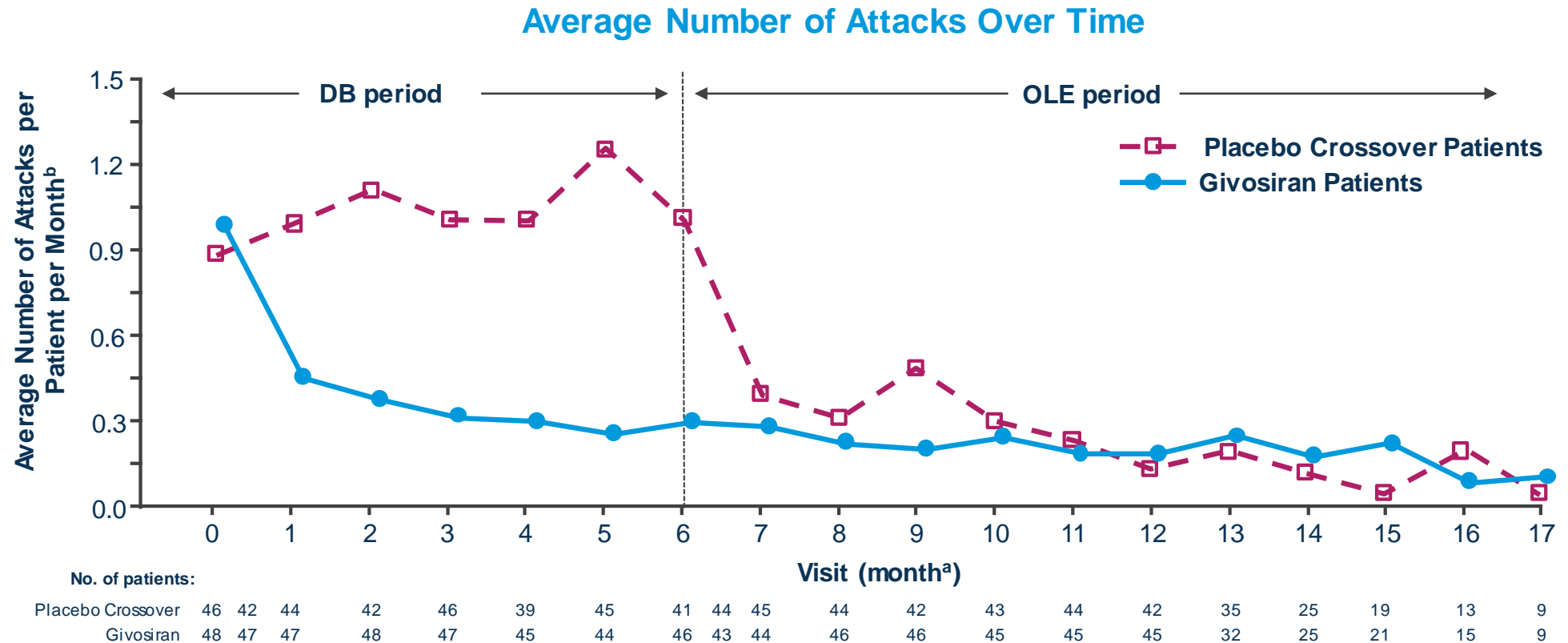
<sup>c</sup> Placebo crossover patient receiving 1.25mg/kg (n=17)

Balwani et al. International Liver Congress 2019. Oral

OLE, open label extension; AAR, annualized rate of composite porphyria attacks

# Givosiran Treatment Led to Rapid Reduction of Attacks Sustained Over Time

- Patients who continued givosiran treatment had sustained or enhanced reduction in average attacks per month over time
- Placebo crossover patients had similar attack reduction during OLE period as givosiran patients in DB period



<sup>a</sup> Month = 28 days

<sup>b</sup> OLE Data for 1.25mg/kg and 2.5mg/kg are pooled

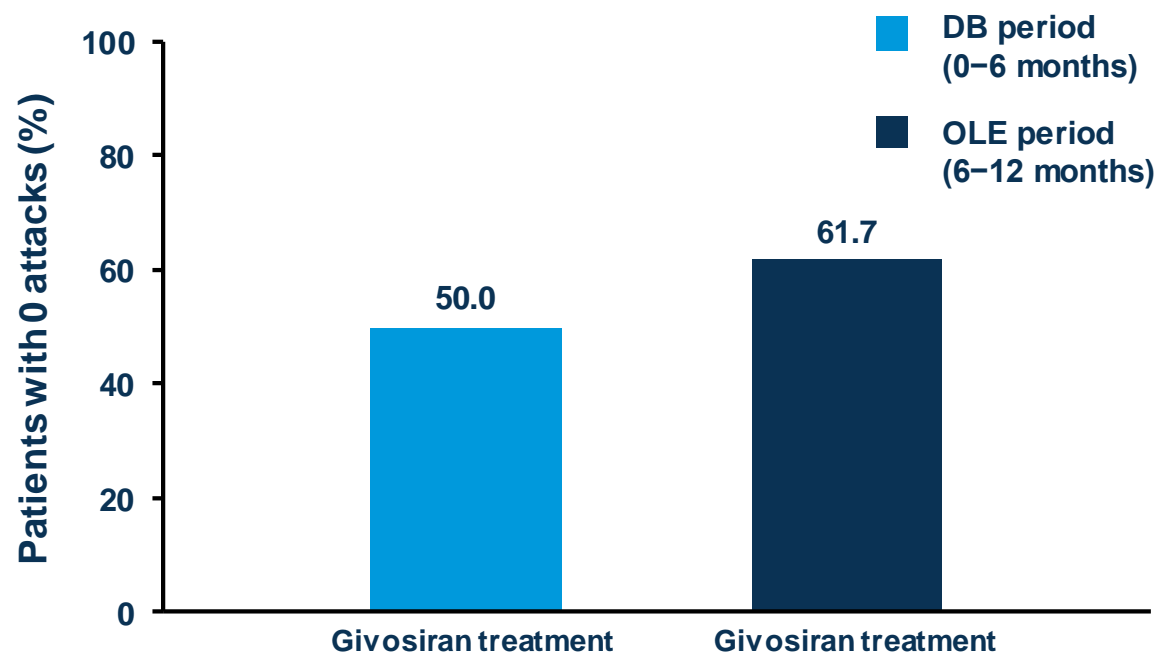
Balwani et al. International Liver Congress 2019. Oral

DB, double-blind; OLE, open label extension

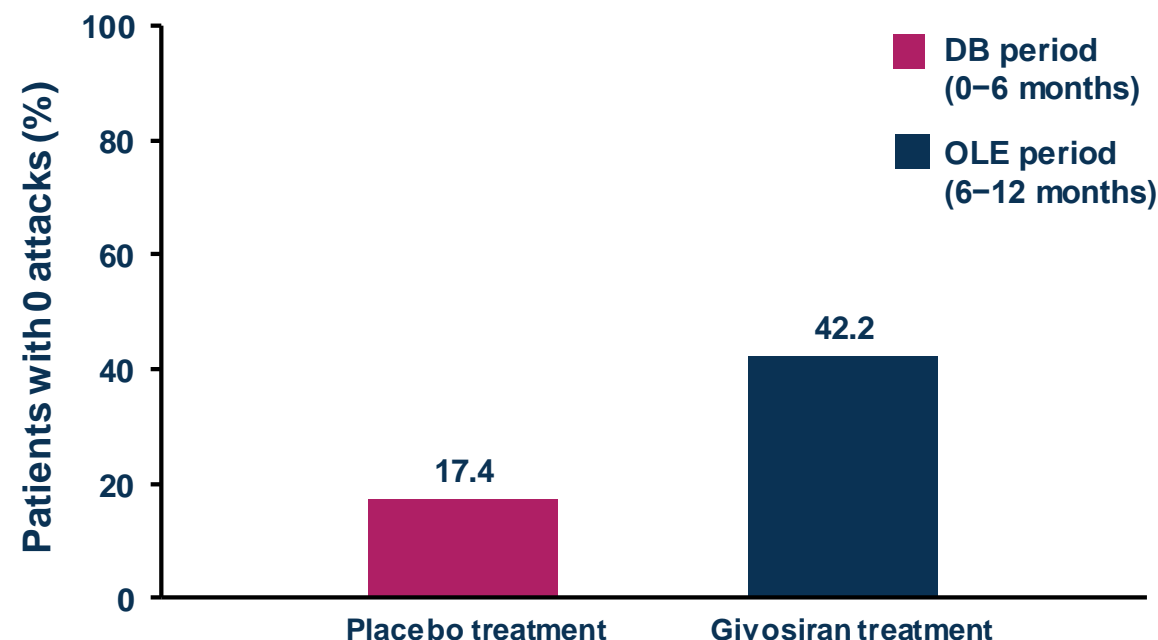
# Increased Number of Patients with Zero Attacks with Long-Term Dosing

- Proportion of patients with zero attacks\* (61.7%) increased with continued givosiran treatment
- Proportion of placebo crossover patients with zero attacks\* (42.2%) increased with givosiran treatment in OLE period

**Patients with 0 Attacks  
Givosiran Patients**



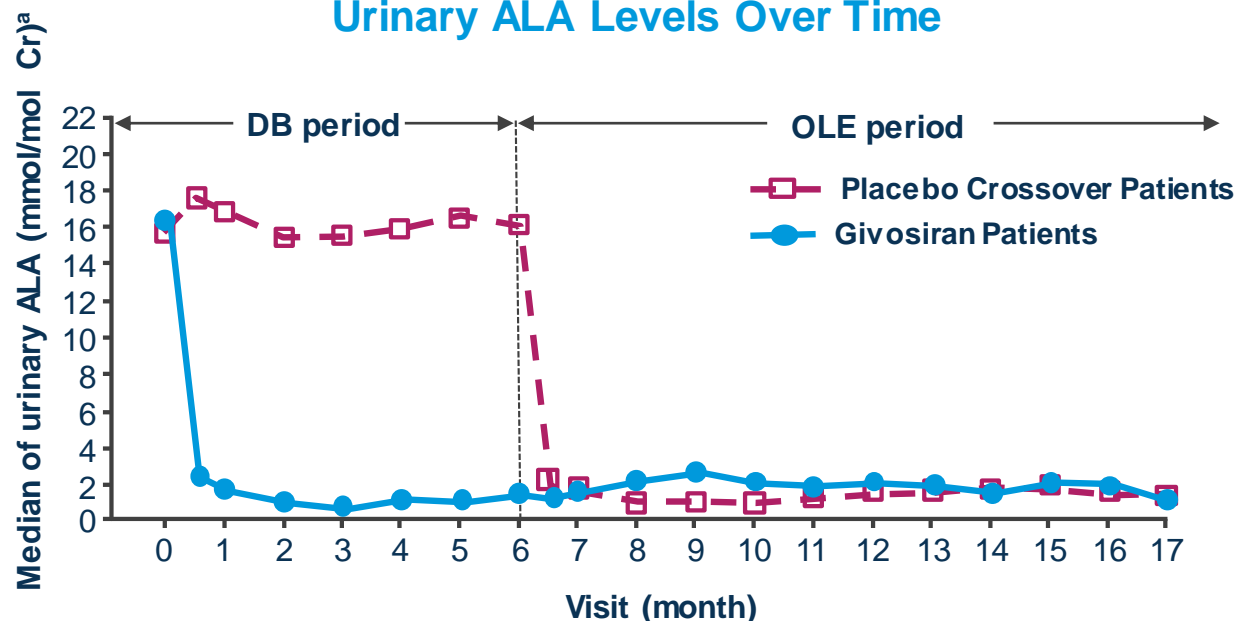
**Patients with 0 Attacks  
Placebo Crossover Patients**



# Rapid & Sustained Lowering of ALA & PBG Levels with Long-Term Dosing

- Continued givosiran treatment led to sustained ALA and PBG reduction during OLE period
- Placebo crossover patients had >75% reduction in median ALA and PBG levels compared to baseline, consistent with data in givosiran patients during DB period<sup>1</sup>

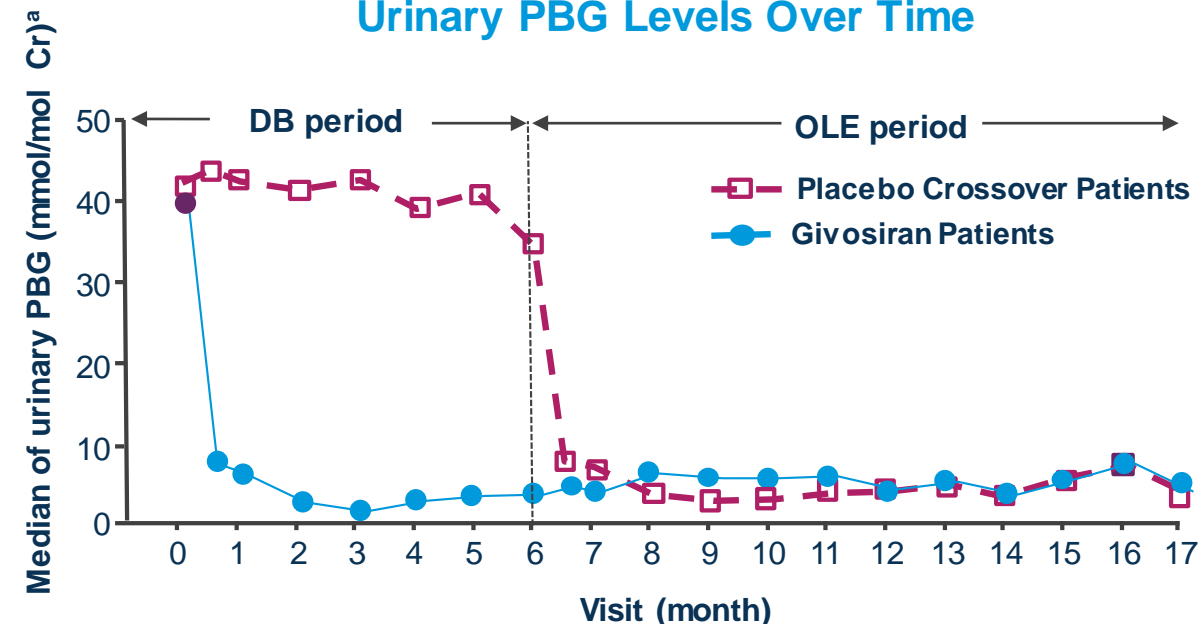
## Urinary ALA Levels Over Time



No. of patients:

PBO Crossover	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9
Givosiran	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9

## Urinary PBG Levels Over Time



No. of patients:

PBO Crossover	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9
Givosiran	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9

<sup>1</sup> Balwani et al. International Liver Congress 2019. Oral

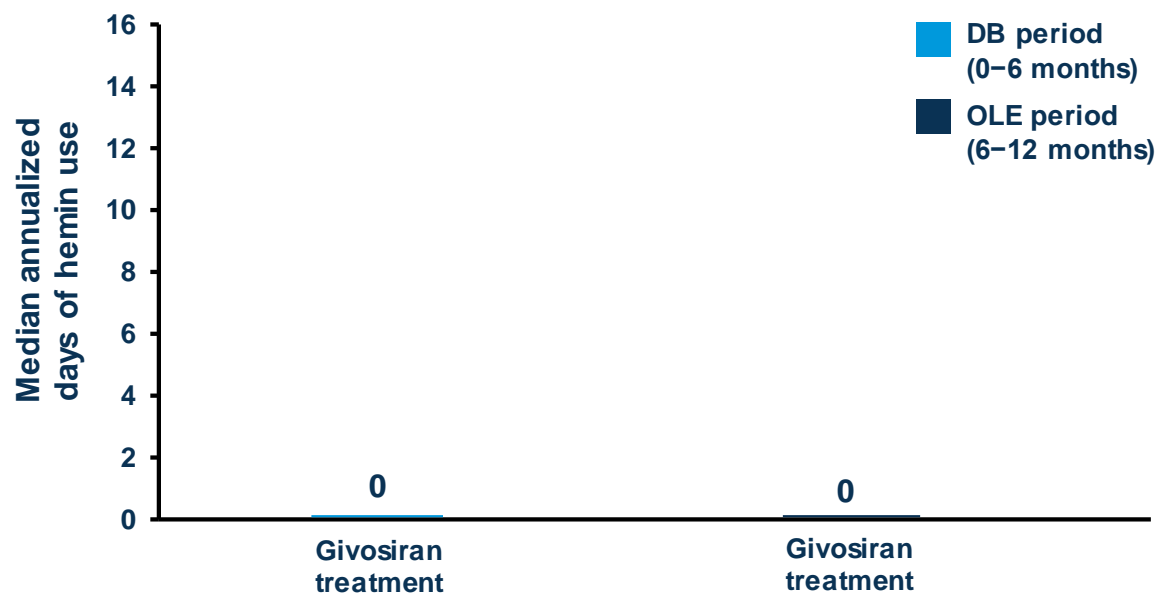
<sup>a</sup> OLE Data for 1.25mg/kg and 2.5mg/kg are pooled

ALA, delta-aminolevulinic acid; DB, double-blind period; Cr, creatinine; No., number; OLE, open label extension; PBG, porphobilinogen; PBO, Placebo

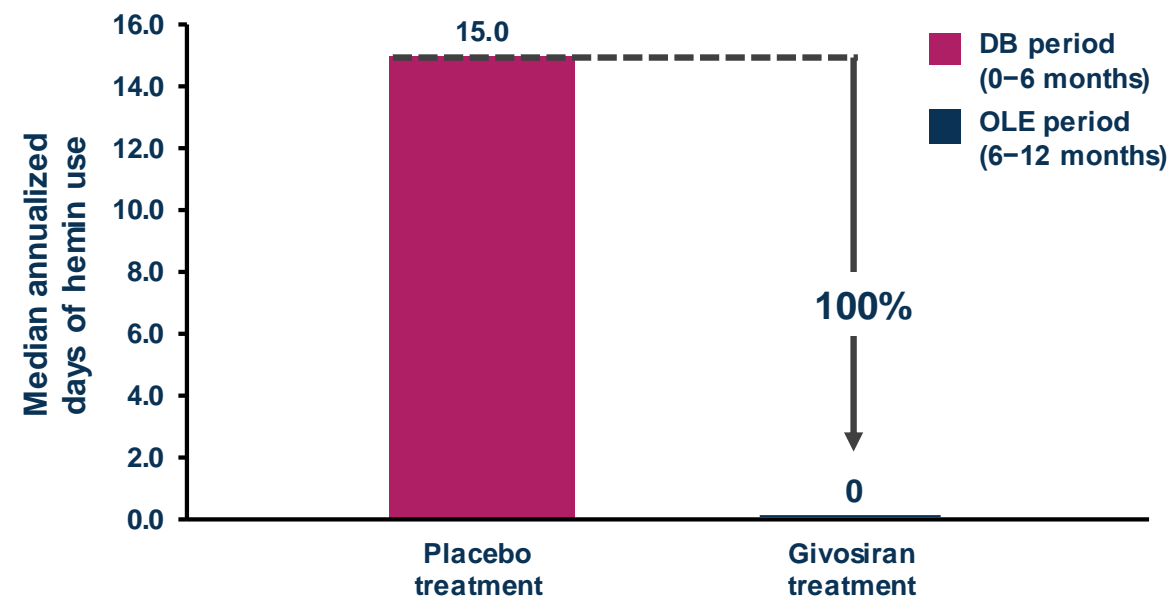
# Sustained Reductions in Hemin Use with Long-Term Dosing

- Continued givosiran treatment led to sustained reductions in hemin use in OLE period, with 70% of patients requiring zero days of hemin
- Placebo crossover patients had 100% reduction in median annualized days of hemin use during OLE period, consistent with data in givosiran patients during DB period<sup>1</sup>
- Proportion of patients with 0 days of hemin use increased in OLE compared with DB period

**Annualized Days of Hemin Use  
Givosiran Patients**



**Annualized Days of Hemin Use  
Placebo Crossover Patients**



<sup>1</sup> Balwani et al. International Liver Congress 2019. Oral  
DB, double-blind; OLE, open label extension



## Daily Worst Pain Decreased with Long-Term Dosing

- Continued givosiran treatment led to a further decrease in patient-reported daily worst pain score during the OLE period
- Placebo crossover patients had a decrease in patient-reported daily worst pain score and proportion of days with analgesics use, consistent with data in givosiran patients during DB period<sup>1</sup>

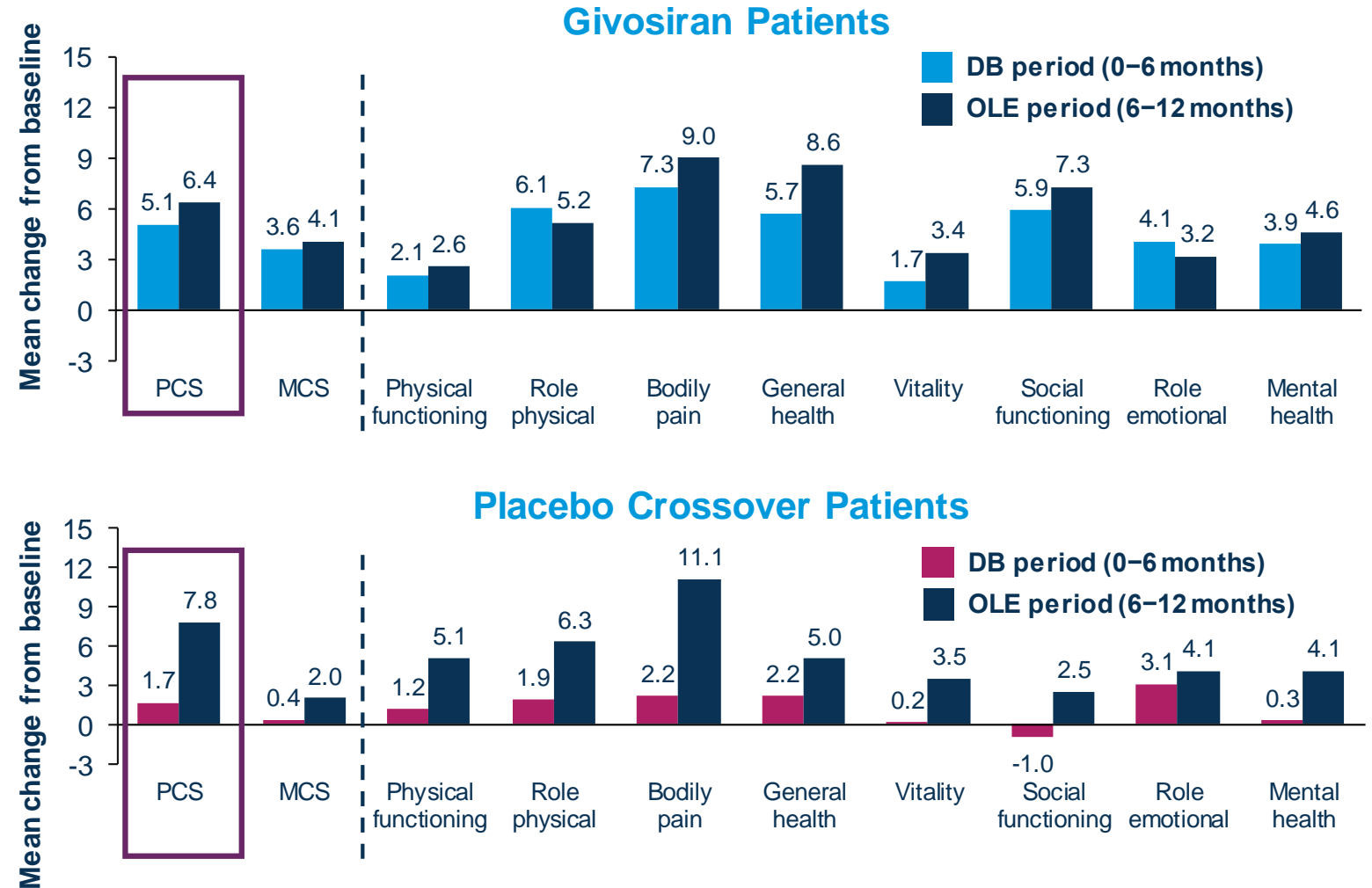
Period	Placebo Crossover Patients (N=46)	Givosiran Patients (N=48)
Baseline Pain score (NRS), median	3.50	2.29
DB period (0–6 months), median change from baseline	+0.10	–0.34
OLE period (6–12 months), median change from baseline	–0.54	–0.77

<sup>1</sup> Balwani et al. *International Liver Congress* 2019. Oral

NRS, numerical ratingscale for assessing pain intensity; OLE, open label extension

# Improvement in Physical Health (SF-12) with Long-Term Dosing

- Continued givosiran treatment resulted in improvements in SF-12 scores, with most impact on role physical, bodily pain, general health and social functioning<sup>a</sup>
- Placebo crossover patients had improvement in SF-12 scores<sup>a</sup>, consistent with givosiran treated patients during DB period<sup>1</sup>
- Research from chronic diseases suggests a 2–5 point increase in PCS scores represents a clinically meaningful difference<sup>2,3</sup>

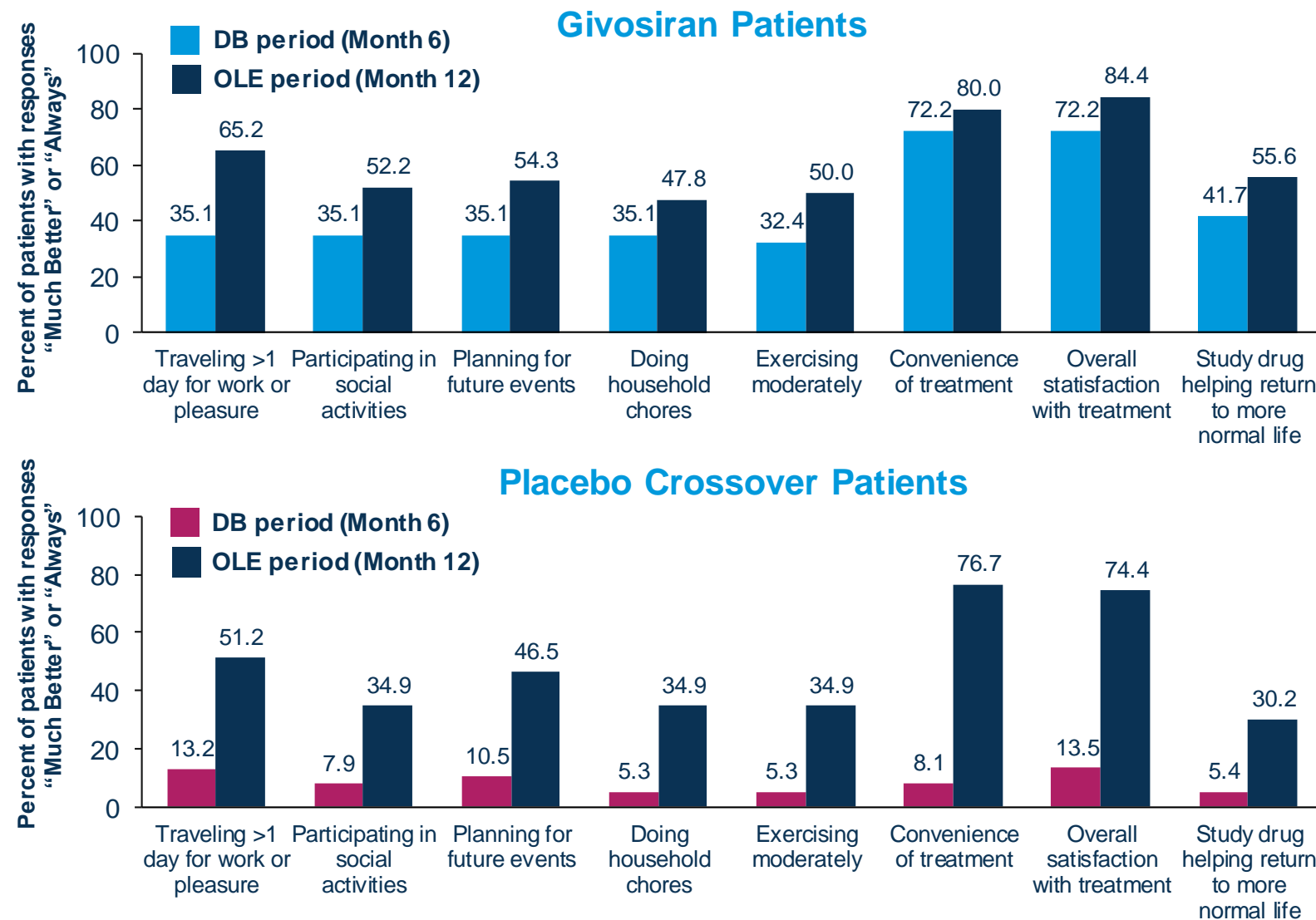


<sup>a</sup> Higher scores represent an improvement in that summary or domain  
DB, double-bind; MCS, mental component summary; OLE, open label extension; PCS, physical component summary; SF-12, Short Form (12-item) Health Survey

<sup>1</sup> Sardh et al. *International Congress on Porphyrins and Porphyrins* 2019. Oral; 2. Clement et al. *Knee Surg Sports Traumatol Arthrosc* 2014;22:1933–9; 3. Parker et al. *J Neurosurg Spine* 2012;16:471–8

# Improvement in PPEQ with Long-Term Dosing

- Custom questionnaire that used global rating of change scale, with questions asked at month 6 and month 12, looking back at entire study period
- Continued givosiran treatment led to further improvements in every PPEQ category at Month 12<sup>a</sup>
- Placebo crossover patients had improvement in all PPEQ categories, consistent with data in givosiran patients during the DB period<sup>a,1</sup>



<sup>a</sup> Higher scores represent an improvement in that category

DB, double-blind; OLE, open label extension; PPEQ, Porphyria Patient Experience Questionnaire

<sup>1</sup> Sardh et al. Presented at *International Congress on Porphyrins and Porphyrias* 2019. Oral

# Safety in AHP Patients with Ongoing Dosing

## Safety Profile of Givosiran Remained Acceptable with No New Safety Concerns

- Overall exposure: 11.22 months (median; range 1.8 to 19.5 months); cumulative exposure of 84.5 person-years<sup>a</sup>
  - 87 patients treated for ≥6 months, 36 patients treated for ≥12 months and 3 patients ≥18 months
- Majority of AEs were mild or moderate in severity
- Most common related AEs (≥ 10%) were ISRs, nausea and fatigue
- ISRs in 33% of patients; 7.4% of injections
  - Erythema, pruritus, rash, pain, and swelling most common
- SAEs in ≥ 2% were CKD and urinary tract infection (2 patients each)
  - SAEs of CKD reported during the DB period
- 1 patient with SAE of LFT abnormal discontinued treatment during the DB period per protocol-specified rules
- No other treatment discontinuations due to AEs; no deaths
- Safety profile was acceptable at both 2.5 mg/kg and 1.25 mg/kg doses

Patients with at least 1 event, n (%)	Placebo Crossover Patients (N=46)	Givosiran Patients (N=48)	All Patients (N=94)
AEs	42 (91)	46 (96)	88 (94)
SAEs	6 (13)	14 (29)	20 (21)
Severe AEs	9 (20)	11 (23)	20 (21)
AE leading to treatment discontinuation	0	1 (2)	1 (1)
AE leading to study withdrawal	0	1 (2)	1 (1)
Deaths	0	0	0

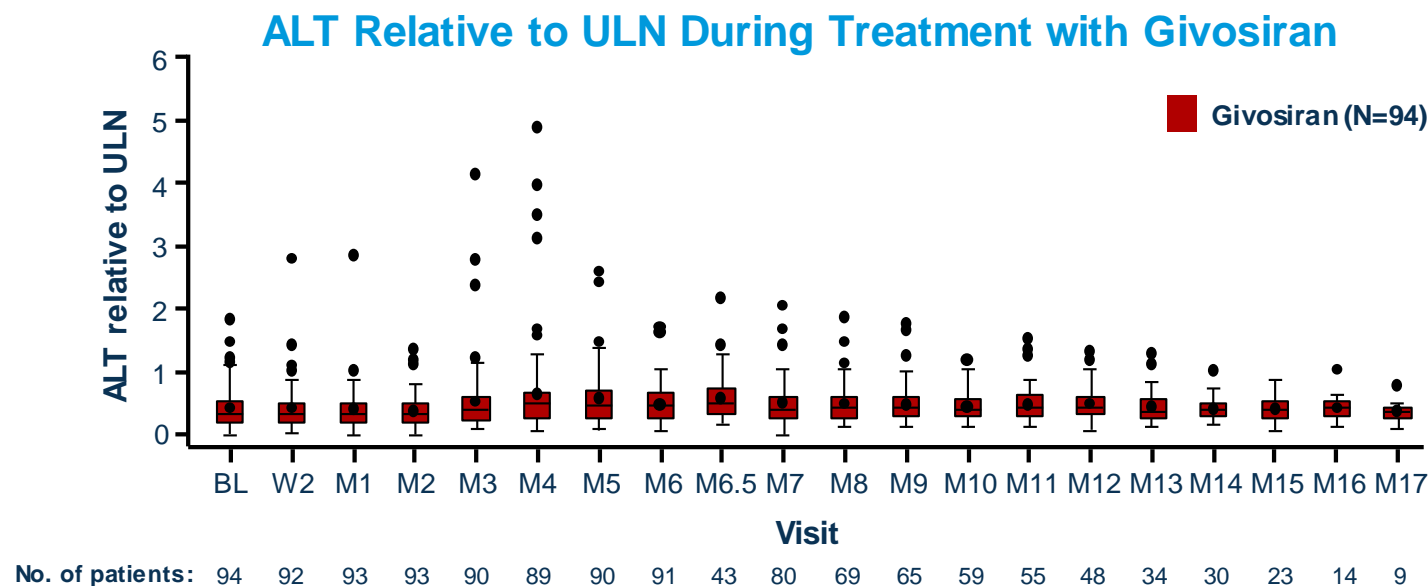
Safety data from first dose of givosiran to data cut-off date (23 July 2019)

<sup>a</sup> For calculating exposure: 1 Month=30.44 days

AE, adverse event; ALT, alanine aminotransaminase; CKD, chronic kidney disease; ISR, injection site reaction; LFT, liver function test; SAE, serious adverse event

# Hepatic Events in AHP Patients

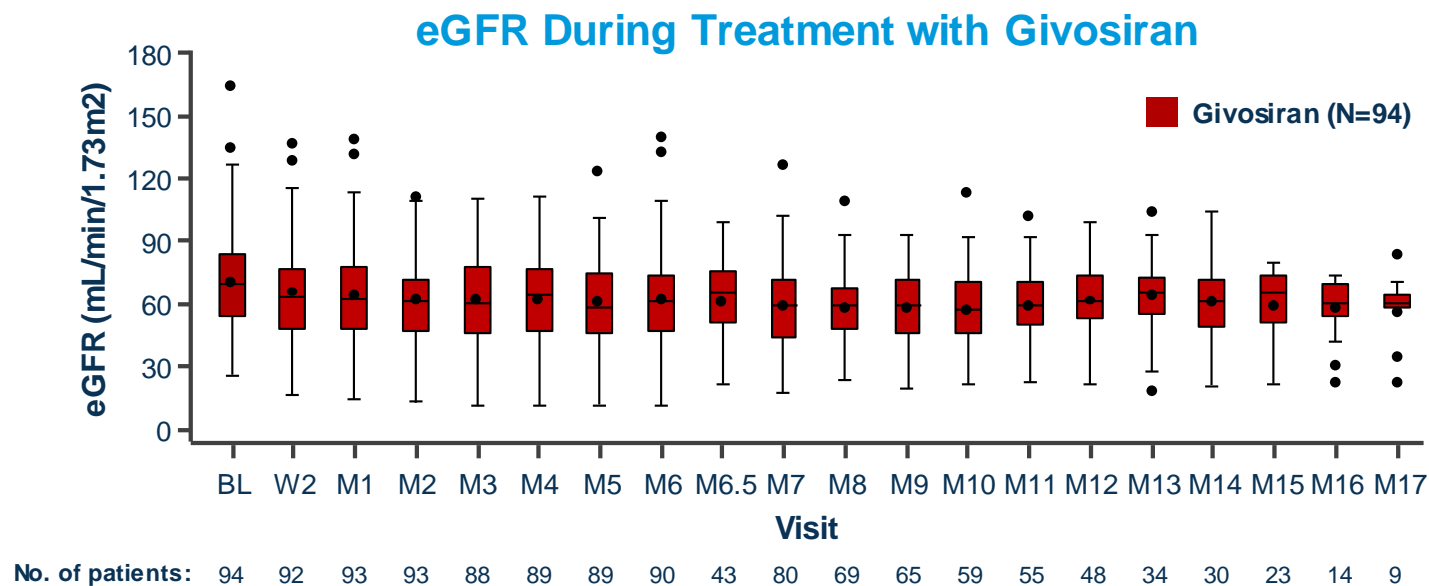
- Hepatic AEs were reported in 16 patients (17%)<sup>a</sup>, all were mild or moderate in severity
  - Majority were elevations of serum aminotransferases
- ALT >3×ULN in 10 patients (10.6%), of whom 3 (3.2%) had ALT >5×ULN
  - 1 patient with ALT >8×ULN, discontinued treatment due to protocol-defined stopping rule in DB period
  - 2 patients with ALT of >5×ULN:
    - 1 patient on 2.5 mg/kg had dose interruption during DB period with resumption at 1.25 mg/kg
    - 1 patient on 1.25 mg/kg during OLE period had resolution during ongoing dosing
  - 7 patients with ALT >3×ULN: 6 patients with resolution during ongoing dosing and 1 patient with transient interruption
- ALT elevations mostly occurred ~3 to 6 months after givosiran started; majority resolved with ongoing dosing, suggesting liver adaptation



<sup>a</sup> Hepatic AEs included any AEs within the Drug-related hepatic disorders Standardized MedDRA query  
AE, adverse events; ALT, alanine aminotransferase; BL, baseline; M, month; ULN, upper limit of normal; W, week

## Renal Events in AHP Patients

- 10 patients (11%) had renal AEs<sup>a</sup>, characterized by increased serum creatinine and/or decreased eGFR
  - Majority of AEs mild or moderate in severity
  - None led to discontinuation of study treatment
- Small increases in serum creatinine were observed at Month 6 and 12
  - Median change 0.09 mg/dL at Month 6 and 0.11 mg/dL at Month 12
- Mean eGFR was generally stable over time
- A decrease in eGFR has been observed in some patients with pre-existing renal disease



<sup>a</sup> Renal AEs included custom search for any AEs of blood creatinine increased, glomerular filtration rate decreased, chronic kidney disease, nephropathy, renal impairment, renal failure  
eGFR, estimated glomerular filtration rate



## ENVISION 12-Month OLE Summary

- Reductions in annualized rate of composite porphyria attacks in patients with AHP sustained or enhanced during OLE
  - 61.7% of patients who continued on givosiran had zero attacks during 6 month OLE period
- Givosiran treatment led to sustained lowering of ALA and PBG levels through month 12 in OLE
- Reductions in annualized days of hemin use in patients with AHP were sustained during OLE
  - 70% of patients who continued on givosiran reported no hemin use during OLE period
- Givosiran treatment led to reductions in daily worst pain and analgesic use, and improvements in quality of life compared to placebo according to PCS of SF-12 and PPEQ measurements
- Safety profile of givosiran remained acceptable with no new safety findings identified

# Two GIVLAARI® (givosiran) Patient Stories

Individual Experiences May Differ



*“Since starting treatment with GIVLAARI, I haven’t experienced any AIP attacks. I still have some symptoms and get waves of nausea out of nowhere. But I feel like AIP isn’t controlling my life anymore.”*

Donna was pregnant with her third child when her AIP attacks became so severe and consistent that she had to move her family into her parents’ home so they could help raise her children. She couldn’t be the mother and wife she wanted to be.

Donna didn’t give up and eventually discovered that a pharmaceutical company was researching a treatment for AHP. She joined the clinical trial for givosiran and hasn’t had an attack since.

In clinical trials, the most common side effects of GIVLAARI were nausea and injection site reactions, risks that she and her doctor have discussed.

*“Since starting treatment, I have not had to be hospitalized for an AHP attack. During the week of the month that I’d normally get an attack, I do feel more tired and sometimes get a little nauseous.”*



Amalia started having AIP attacks during her first week of college. Her mental health quickly declined as doctors couldn’t figure out what was causing her excruciating pain. She had to take time off college to recover and began to see her dreams slip away as AIP became a constant presence in her life. During attacks she would be hospitalized with excruciating pain and nausea. Between attacks she felt deep and constant anxiety, waiting for the next attack.

She heard about the approval of GIVLAARI in 2019 and began the process with Anylam Assist®. She started treatment in February 2020.

Before starting treatment, her doctor told her about risks of GIVLAARI, including the possibility of severe allergic reaction, liver problems, kidney problems, and injection site reactions.

# Agenda

## Welcome

- Joshua Brodsky – Director, Investor Relations & Corporate Communications

## Introduction & GIVLAARI<sup>®</sup> (givosiran) Overview

- Akin Akinc, Ph.D. – Vice President & General Manager, Givosiran

## GIVLAARI U.S. Commercial Progress

- Gail Hartigan – Senior Director, U.S. Business Lead

## 12-Month Interim Data from ENVISION Phase 3 Study

- Amy Simon, M.D. – Vice President, Clinical Research

## Q&A Session







To those who say “impossible, impractical,  
unrealistic,” we say:

**CHALLENGE ACCEPTED**