Givosiran, for the Treatment of Acute Hepatic Porphyria

August 4, 2021

RNAi ROUNDTABLE 2021

Alnylam PHARMACEUTICALS

Agenda

Welcome
- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction & GIVLAARI® (givosiran) Overview
- Akin Akinc, Ph.D. – Vice President & General Manager, Givosiran

18-Month Interim Data from ENVISION Phase 3 Study
- Marianne Sweetser, M.D., Ph.D. – Senior Distinguished Fellow, Clinical Development

Disease Awareness, Patient Identification & Geographic Expansion
- Laurent Placidi, Ph.D., PharmD. – Senior Director, Global Marketing, 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

Alnylam Forward Looking Statements and Disclosures

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, including expectations regarding our aspiration to become a leading biotech company, and the planned achievement of our “Alnylam P5x25” strategy, plans for additional global regulatory filings and the continuing product launches of our approved products, the potential of GIVLAARI (givosiran) as a treatment option for patients with AHP, estimates of the AHP patient population, plans for additional global regulatory filings and the continuing launch of GIVLAARI in additional territories to drive growth, and the potential of global, multi-channel initiatives underway to improve AHP disease awareness. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including givosiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products, including GIVLAARI, globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO (and potentially vutrisiran) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines 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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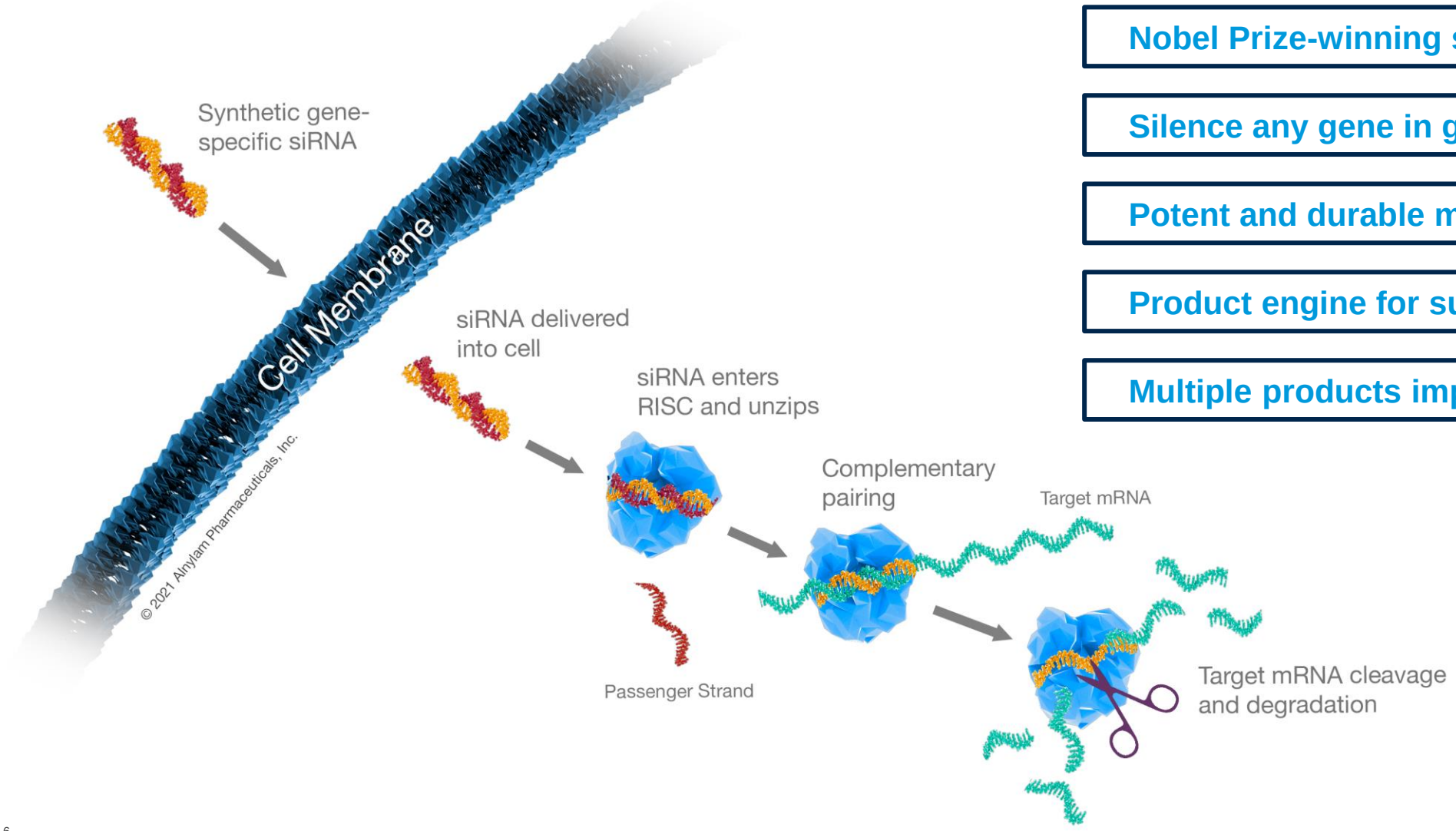
RNAi Therapeutics: New Class of Innovative Medicines

Clinically and Commercially Established Proven Approach with Transformational Potential



- **Nobel Prize-winning science**
- **Silence any gene in genome with siRNAs**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products impacting patients globally**

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6*]	*Complement-Mediated Diseases*	●			Milestone/Royalty
Belcesiran[7*]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8*]	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; 3 Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and the EU, Israel, Japan, and Switzerland for the treatment of AHP in adults and adolescents aged 12 years and older; 4 Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; 5 Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of July 2021

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As of July 2021

APPROVED IN U.S., EU, BRAZIL & JAPAN[1]

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

GIVLAARI® 189 mg/mL solution for injection givosiran

GIVLAARI® (givosirana sódica) injeção para uso subcutâneo 189 mg/mL

急性肝性ポルフィリン症治療薬 薬価基準未収載
ギブラーリ® 皮下注 189mg
GIVLAARI® Subcutaneous Injection
ギボシランナトリウム注射液 劇薬、処方箋医薬品 注意－医師等の処方箋により使用すること

[1] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and the EU, Israel, Japan, and Switzerland for the treatment of AHP in adults and adolescents aged 12 years and older

GIVLAARI® (givosiran) Launch Update: Q2 2021

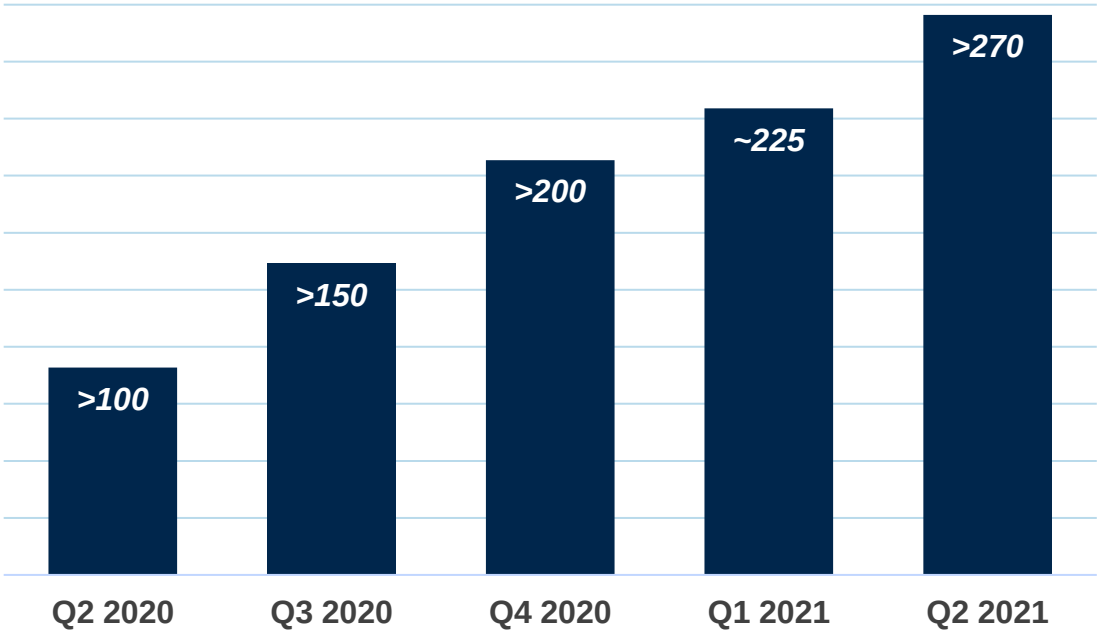
Continued Progress with Uptake and Access

$31M

GIVLAARI Global Q2 2021 Net Product Revenues

>270

Patients Worldwide on Commercial GIVLAARI at end of Q2 2021



Q2 U.S. Highlights

- Significant growth driven by net new patient adds
- Continued expansion of prescriber base, including new writers, from community centers and COEs

Lydia
Diagnosed with AHP (Switzerland)

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

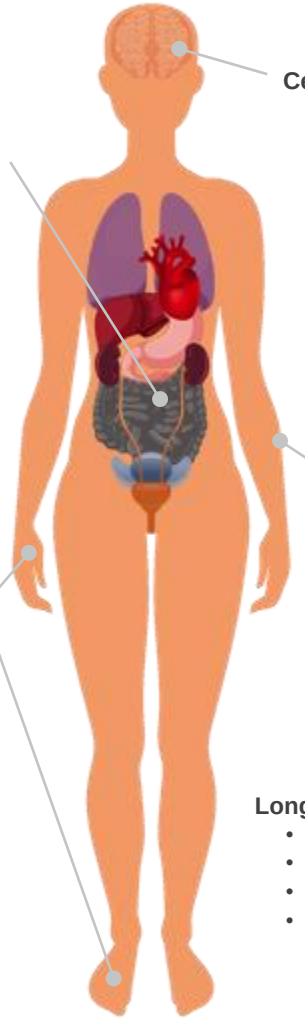
female

commonly misdiagnosed

Patient Population

~3,000

diagnosed in U.S./EU with active disease[1,2]



Central Nervous System
- Confusion
- Anxiety
- Depression
- Memory loss
- Fatigue
- Hallucinations
- Seizures

Autonomic Nervous System
- Severe abdominal pain
- Nausea/vomiting
- Hypertension
- Tachycardia
- Constipation
- Hyponatremia

Cutaneous†
- Lesions on sun-exposed skin

Peripheral Nervous System
- Neuropathic pain
- Sensory loss
- Muscle weakness
- Paralysis
- Respiratory failure

Long-term Complications
- Liver disease
- Chronic kidney disease
- Hypertension
- Neuropathy

[1] 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 coproprophyria 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[1,2]
- AIP is the most common type, with mutation in *hydroxymethylbilane synthase* (*HMBS*) gene[3,4]

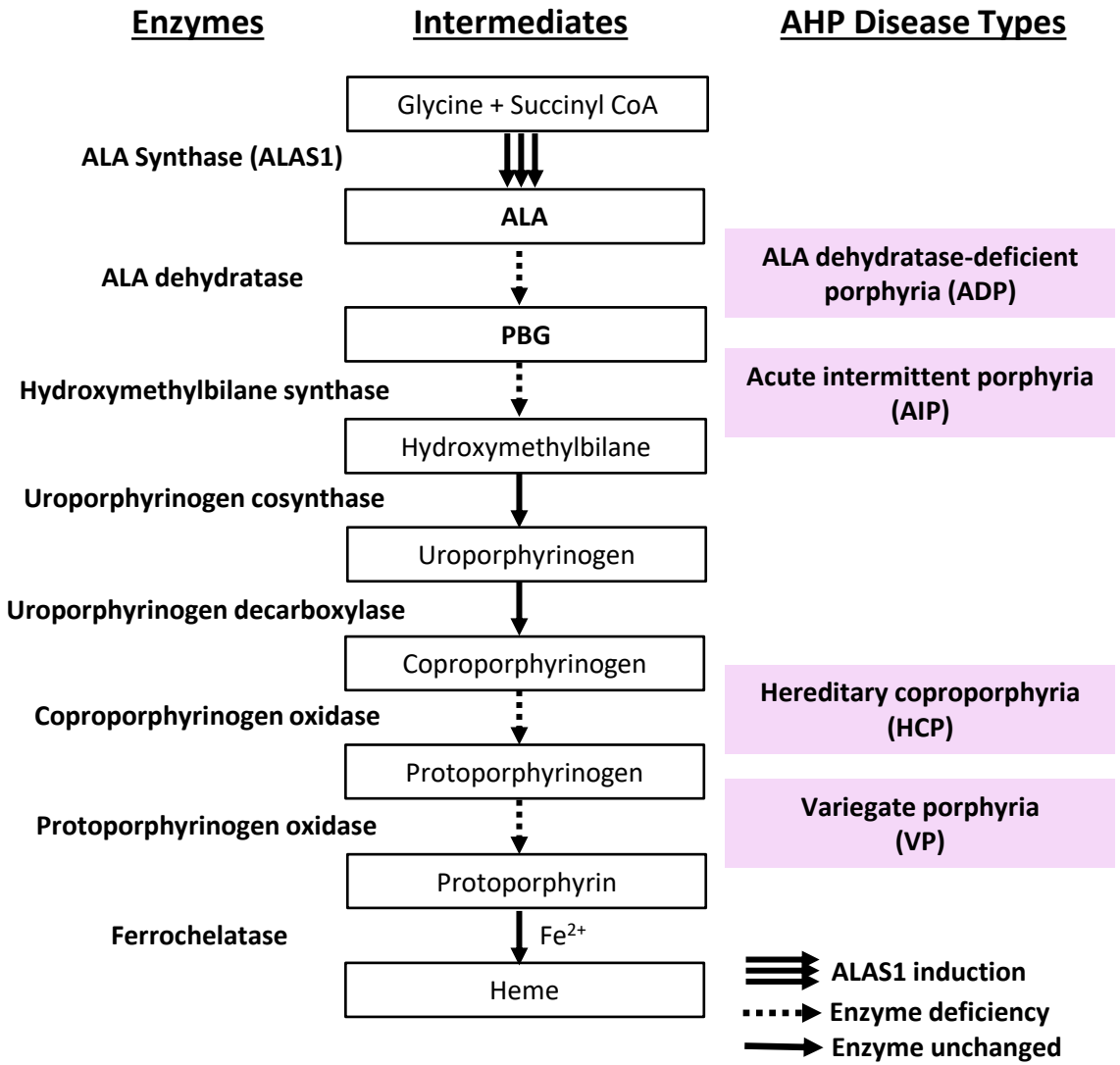
Disease Pathophysiology

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

Attacks, Chronic Manifestations, and Comorbidities

Patients can experience:

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



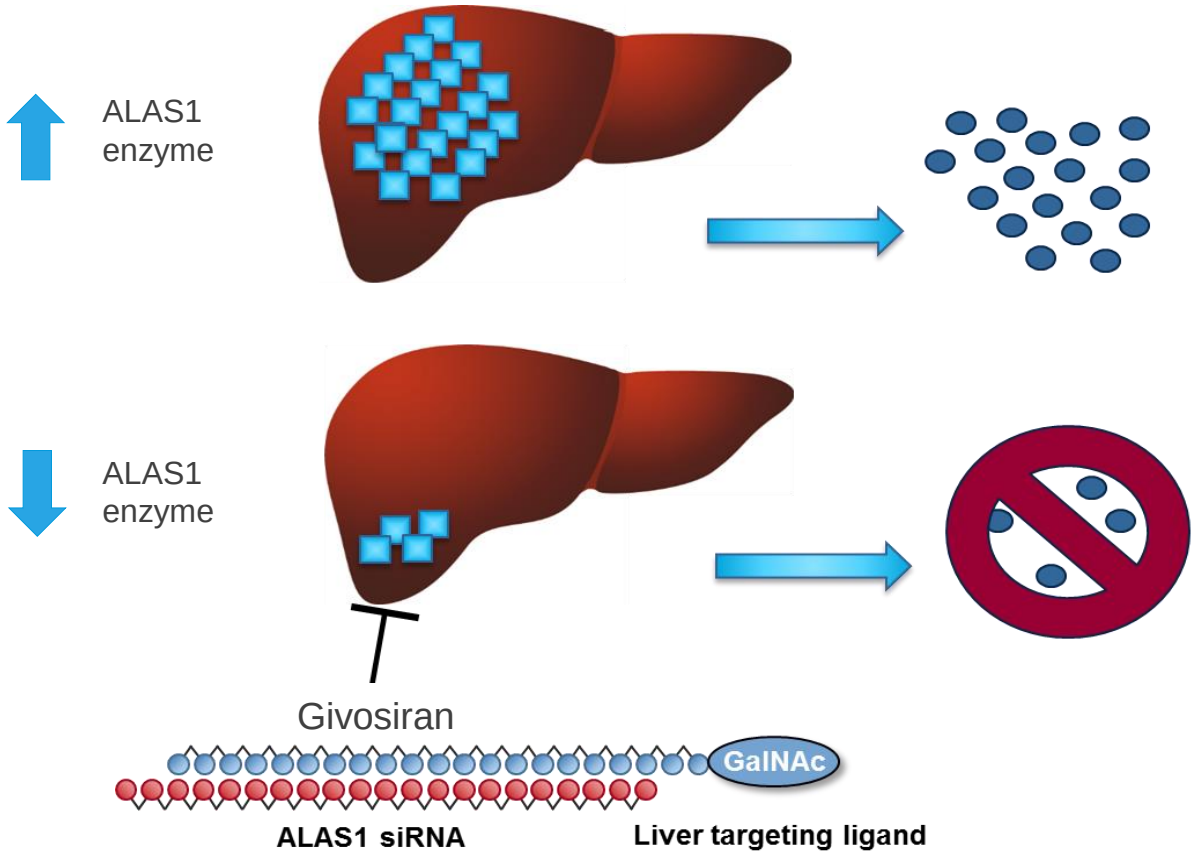
[1] Puy et al. *Am J Hum Genet* 1997;60:1373–83; [2] Balwani & Desnick. *Blood* 2012;120:4496–504; [3] Bonkovsky et al. *Am J Med* 2014;127:1233–41; [4] Elder et al. *JIMD* 2013;36:849–57; [5] Bissell et al. *Am J Med* 2015;128:313–7; [6] Gouya et al. *Hepatology* 2019; DOI:10.1002/hep.30936; [7] Pischik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

Mechanism of Action

Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference



ALA and PBG are neurotoxic intermediates associated with attacks or other disease manifestations

Givosiran reduces the elevated levels of liver ALAS1 mRNA. This leads to reduced circulating levels of ALA and PBG

ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; GalNAc, *N*-Acetylgalactosamine; mRNA, messenger RNA; PBG; porphobilinogen; RNAi, RNA interference; siRNA, small interfering RNA

1. GIVLAARI US Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf (accessed March 19, 2020); 2. GIVLAARI EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (accessed March 19, 2020)

GIVLAARI® (givosiran) Indication and Important Safety Information[1]

- GIVLAARI is indicated in the U.S. for the treatment of adults with acute hepatic porphyria

- Important Safety Information
  - Contraindications: Severe hypersensitivity to givosiran
  - Warnings and Precautions:
    - Anaphylactic Reaction: Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms. If anaphylaxis occurs discontinue GIVLAARI and administer appropriate medical treatment
    - Hepatic Toxicity: Measure liver function at baseline and periodically during treatment with GIVLAARI. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations
    - Renal Toxicity: Monitor renal function during treatment with GIVLAARI as clinically indicated
    - Injection Site Reactions: May occur, including recall reactions. Monitor for reactions and manage clinically as needed

For complete product information, please see the full Prescribing Information available at www.givlaari.com

1. GIVLAARI US Prescribing Information. Available at: https://www.alnylam.com/wp-content/uploads/pdfs/GIVLAARI-Prescribing-Information.pdf

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Givosiran Clinical Development Program

2014 — 2019

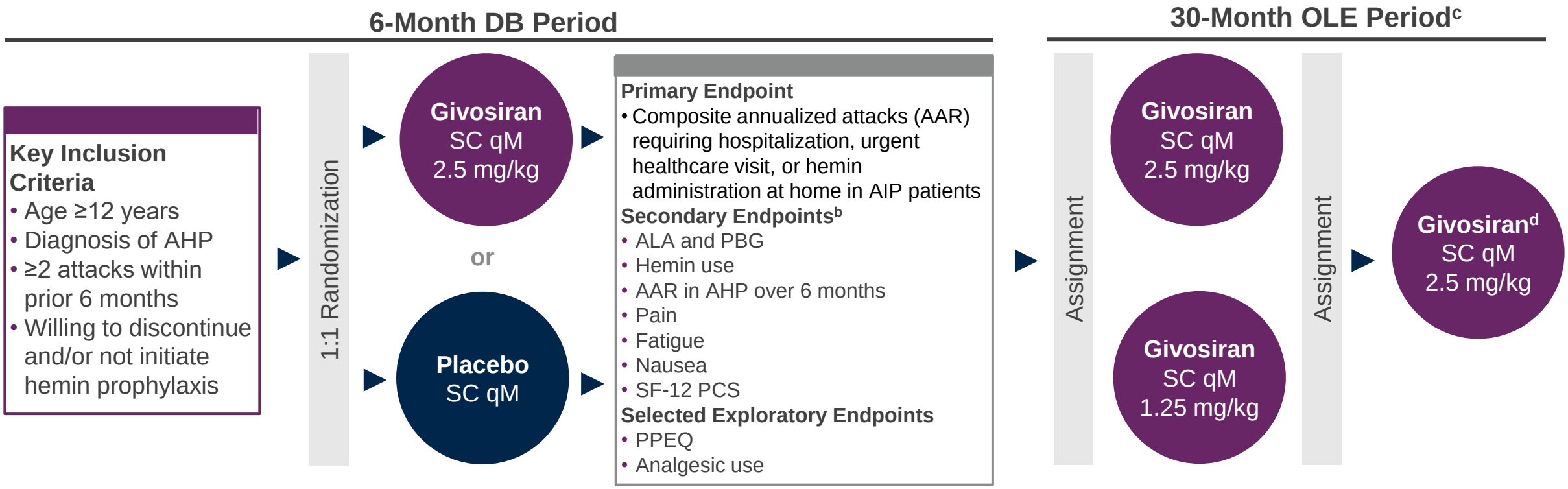
EXPLORE Natural History Study in AHP Patients

Phase 1/2	Phase 2 OLE	Phase 3 ENVISION	ENVISION OLE
COMPLETED	**ONGOING**	**COMPLETED**	**ONGOING**
CHE and AIP	AIP	AHP	AHP
Adult CHE and patients with AIP • Multiple doses • Multiple schedules	**Adult patients with AIP** • Open-label • All patients transitioned to 2.5 mg/kg every month by subcutaneous injection	**Adults patients with AHP** • Randomized, double-blind, placebo-controlled • 2.5 mg/kg every month by subcutaneous injection	**Adult patients with AHP** • Open-label • 2.5 mg/kg every month by subcutaneous injection

CHE, chronic high excretors; EAP, expanded access program; OLE, open-label extension

ENVISION Study Design

- 94 patients with AHP enrolled in ENVISION at 36 sites in 18 countries
- All patients completed the 6-month double-blind (DB) period; all eligible patients (n=93) entered the 30-month open-label extension (OLE) period; here we present results from an 18-month interim analysis[a]



[a]Data from the timepoint after which all patients had completed at least their Month 18 visit (January 10, 2020). [b]Endpoints evaluated in patients with genetically confirmed AIP, unless otherwise noted, at 6 months. [c]All endpoints listed above were considered exploratory in the OLE period. [d]A protocol amendment increased the dose of all patients to 2.5 mg/kg monthly

AAR, annualized attack rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire; qM, every month; SC, subcutaneously; SF-12, Short Form (12-item) Health Survey

Gouya et al. Presented at the International Congress on Porphyrins and Porphyrias, September 2019; Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

Baseline Characteristics Generally Balanced Between Groups

Baseline Demographics and Disease Characteristics of Patients in ENVISION

Characteristic	Placebo Crossover (N=46)	Givosiran (N=48)	All Patients (N=94)
Age at screening, years, median (range)	36 (20, 60)	42 (19, 65)	38 (19, 65)
Female, n (%)	41 (89)	43 (90)	84 (89)
AIP with identified mutation, n (%)	43 (93)	46 (96)	89 (95)
Years since diagnosis, median (range)	6.46 (0.1, 38.5)	6.98 (0.2, 43.3)	6.55 (0.1, 43.3)
Prior hemin prophylaxis, n (%)	18 (39)	20 (42)	38 (40)
Historical AAR[a], median (range)	7.0 (0[b], 46)	8.0 (4, 34)	8.0 (0[b], 46)
Chronic symptoms daily or most days between attacks, n (%)	26 (57)	23 (48)	49 (52)
Opioid use daily or most days between attacks, n (%)	13 (28)	14 (29)	27 (29)
Baseline urinary ALA (mmol/mol Cr), median (range)	16.4 (1.4, 41.5)	16.4 (1.8, 88.9)	16.4 (1.4, 88.9)
Baseline urinary PBG (mmol/mol Cr), median (range)	39.3 (3.6, 87.7)	39.6 (0.4, 150.0)	39.6 (0.4, 150.0)

[a]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home. [b]One patient in the placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home within 6 months prior to screening (patient had 2 attacks that were treated at home without IV hemin). This was identified as a protocol deviation

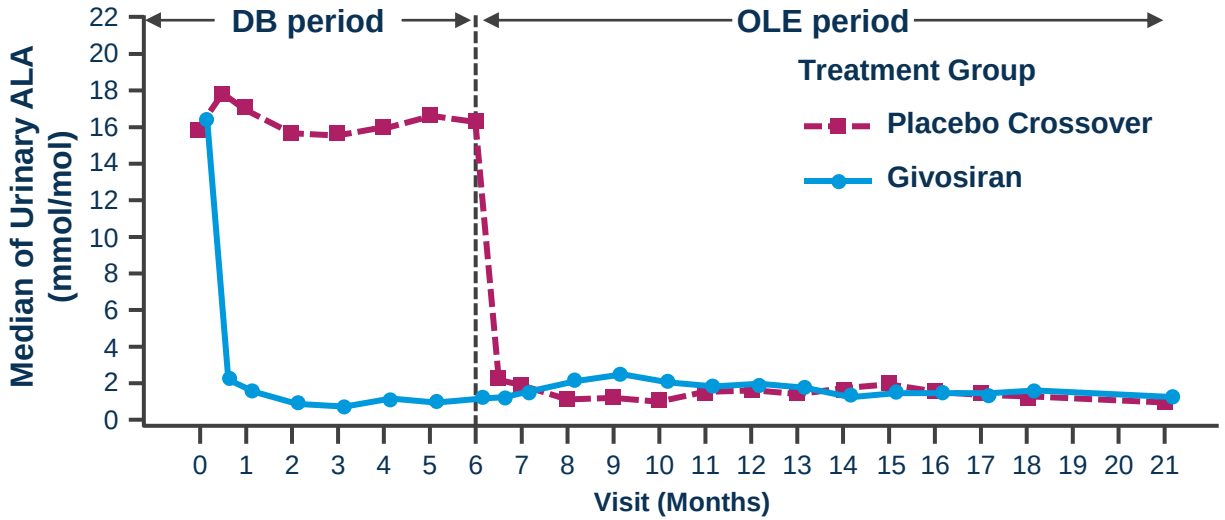
AAR, annualized attack rate; ALA, δ-aminolevulinic acid, Cr, creatinine; IV, intravenous; PBG, porphobilinogen

Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

Sustained Lowering of ALA and PBG Levels with Long-Term Dosing

- During the OLE, givosiran treatment led to sustained reductions in ALA and PBG levels through Month 18
- Patients with AHP achieved near normalization or normalization of ALA and PBG levels with givosiran treatment[1]

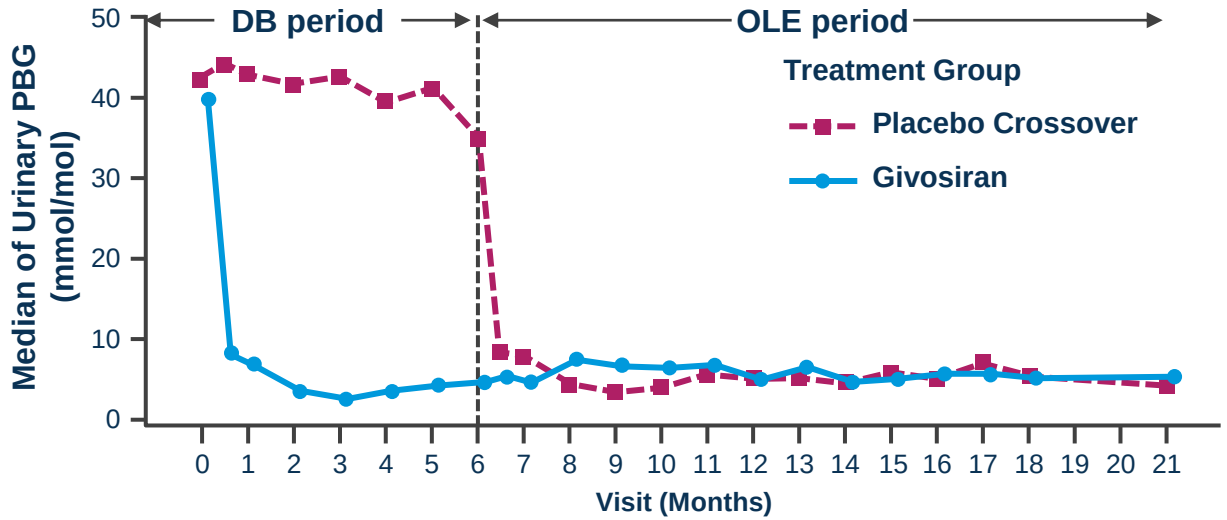
Median Urinary ALA Levels over Time[a]



No. of patients:

PBO/Givo	46	42	44	42	46	39	45	41	44	45	44	42	43	43	41	42	40	41	41	40	39	19
Givo/Givo	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	44	43	44	46	45	45	19

Median Urinary PBG Levels over Time[a]



No. of patients:

PBO/Givo	46	42	44	42	46	39	45	41	44	45	44	42	43	43	41	42	40	41	41	40	39	19
Givo/Givo	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	44	43	44	46	45	45	19

[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled

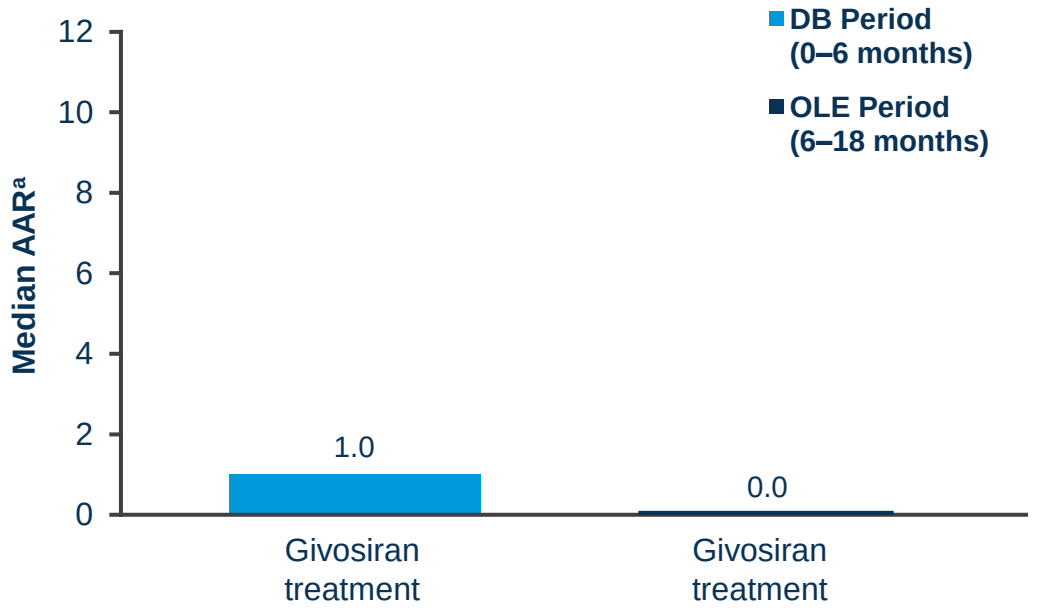
AHP, acute hepatic porphyria; ALA, δ-aminolevulinic acid; DB, double-blind; Givo, givosiran; OLE, open-label extension; PBG, porphobilinogen; PBO, placebo

1. Agarwal et al. *JIMD Reports* 2020; DOI:10.1002/jmd2.12173
Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

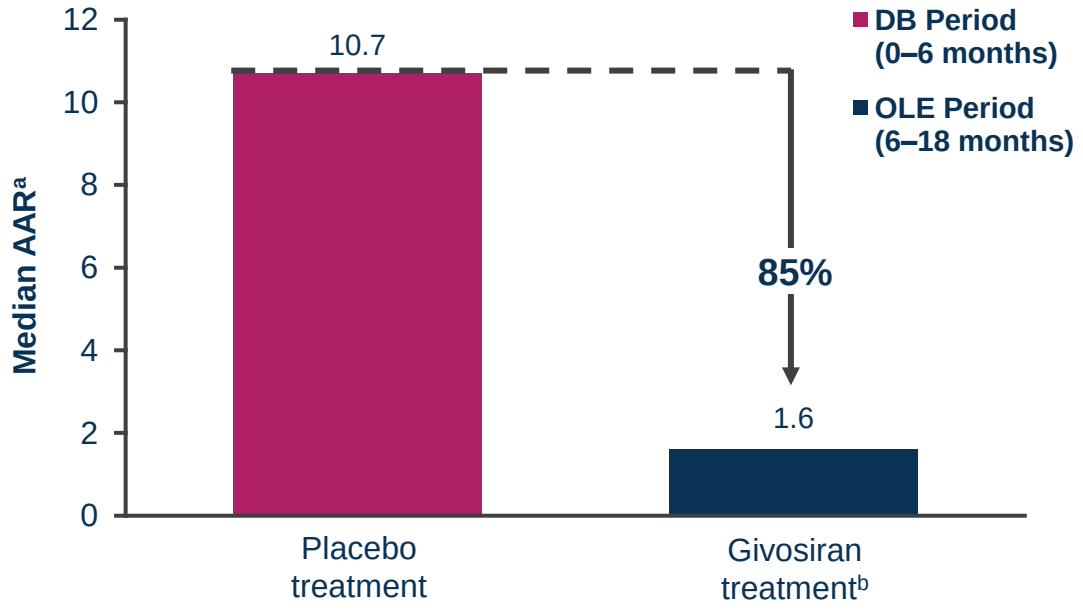
Long-Term Givosiran Dosing Led to Sustained Reduction of Attacks

- Continued givosiran treatment led to sustained reduction in attacks during the OLE period
  - Following initial 6 months of givosiran treatment in the OLE, placebo crossover patients continued to have a sustained reduction in attacks after 12 months of treatment (median AAR 1.8 vs 1.6, respectively)[1]

AAR in Continued Givosiran Patients



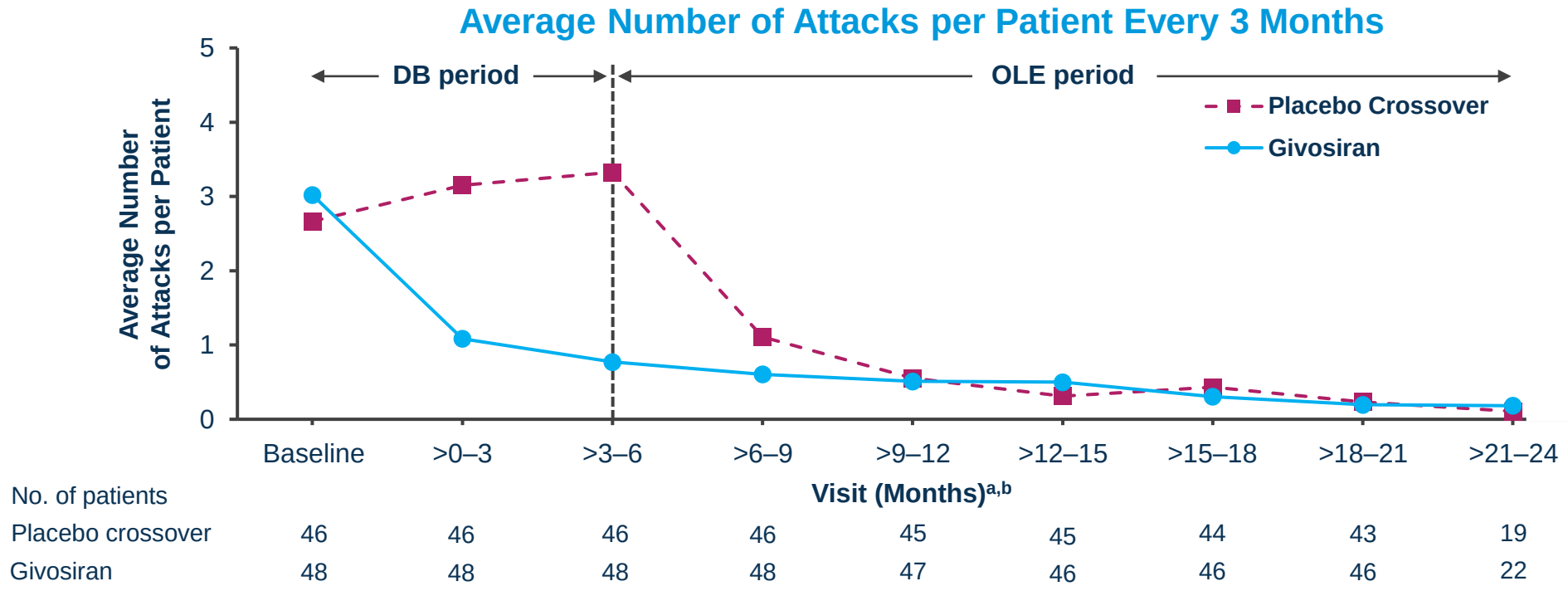
AAR in Placebo Crossover Patients



[a]Descriptive analysis. [b]Placebo crossover patients receiving givosiran 2.5 mg/kg (n=29) or 1.25 mg/kg (n=17)
AAR, annualized attack rate; DB, double-blind; OLE, open-label extension

1. Sardh et al. Presented at The Digital International Liver Congress 2020. Oral
Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

Long-Term Givosiran Dosing Led to Sustained Reduction of Attacks



No. of patients									
Placebo crossover	46	46	46	46	45	45	44	43	19
Givosiran	48	48	48	48	47	46	46	46	22

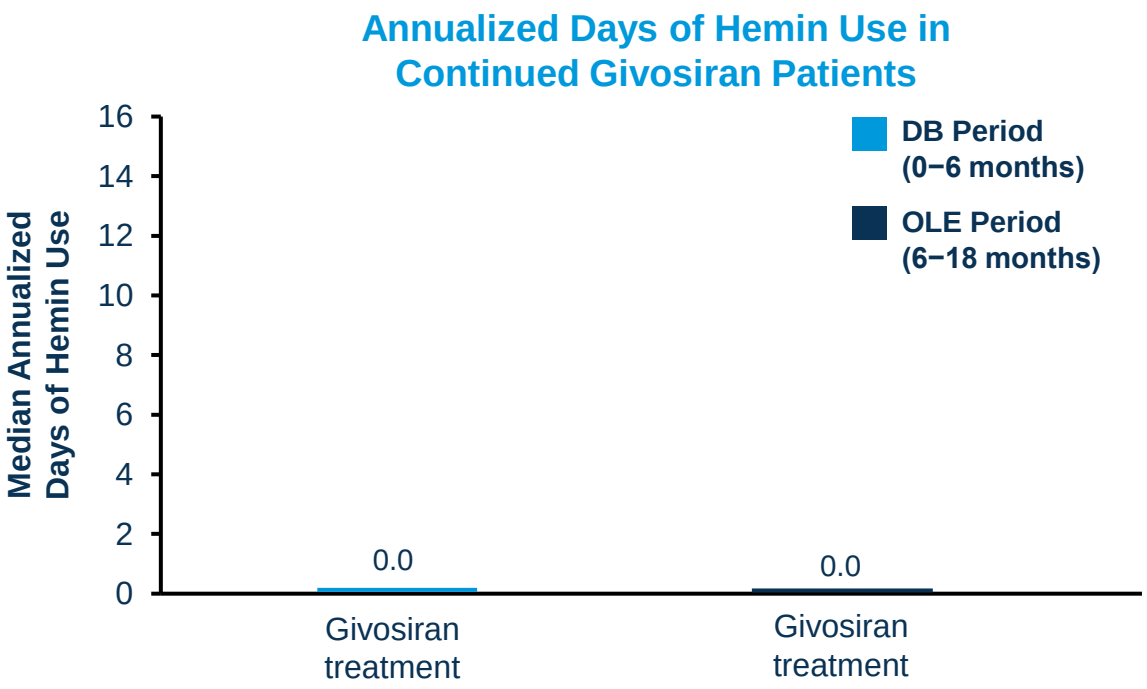
- With a further 6 months of givosiran treatment, proportion of patients with zero attacks during the OLE period was sustained
  - 61.7% vs 60.9% (Month 12 vs Month 18) for continued givosiran patients[1]
  - 42.2% vs 40.0% (Month 12 vs Month 18) for placebo crossover patients[1]

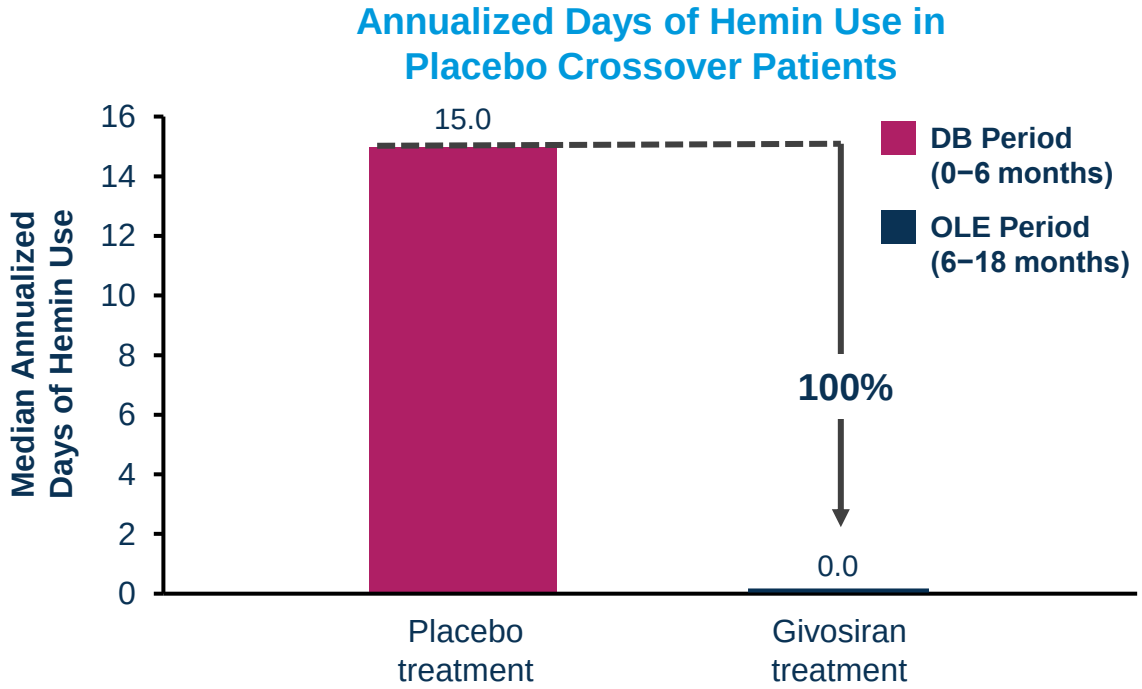
[a]The estimate for each 3-month interval is calculated as total number of attacks/total number of patients reached that 3 months. Three months=28 × 3 days. [b]OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled
DB, double-blind; OLE, open-label extension

1. Sardh et al. Presented at The Digital International Liver Congress 2020. Oral
Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

Sustained Reductions in Hemin Use with Long-Term Dosing

- Givosiran led to sustained reductions in hemin use, with median days of hemin use being 0.0 days for both groups during the OLE period, compared with 15.0 days for placebo patients during the DB period
  - Over half (51%) of placebo crossover patients had zero days of hemin use at Month 18 of the OLE period, compared with 26% in the DB period





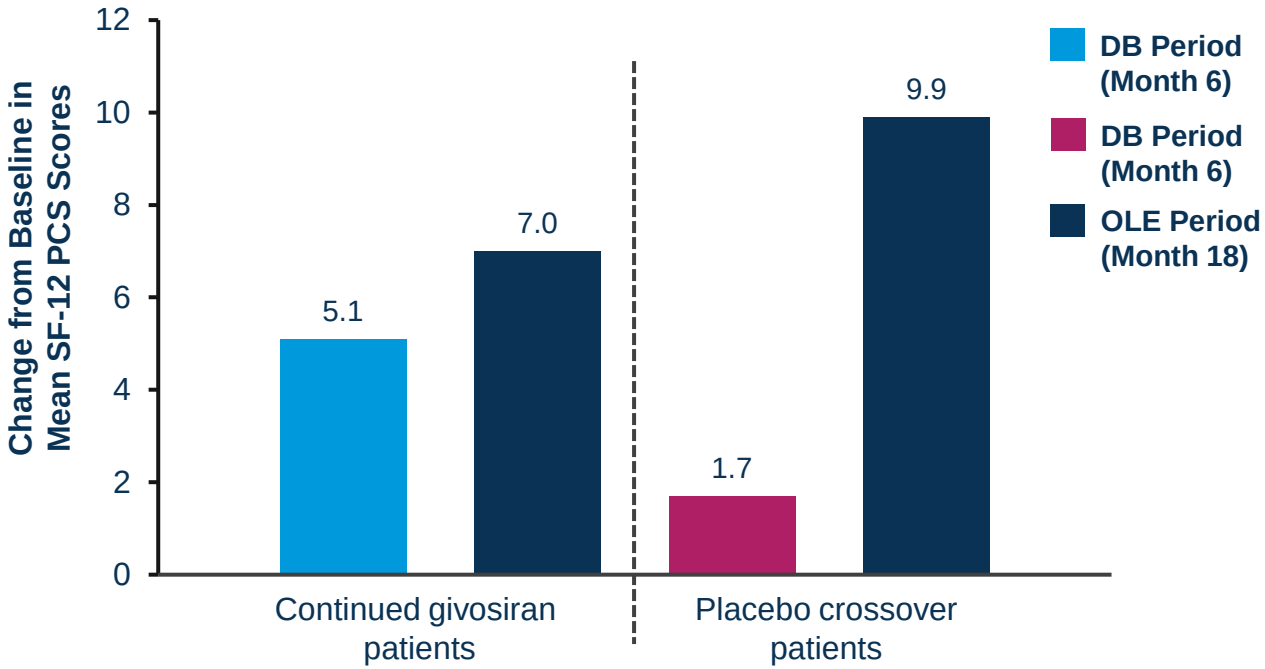
DB, double-blind; OLE, open-label extension

Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

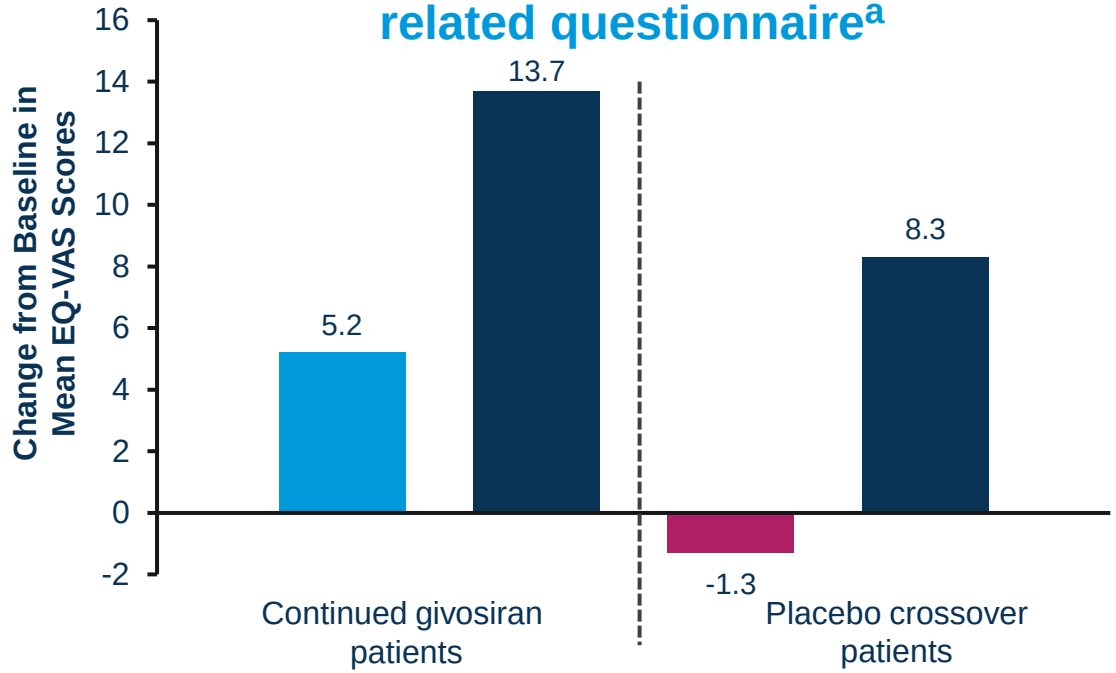
Further Improvement in QOL with Long-Term Dosing

- Patients experienced further improvements in QOL, as assessed by SF-12 Physical Component Summary[a] and EuroQol-visual analog scale health-related questionnaire scores, with givosiran treatment
  - Improvements in QOL scores were observed at Month 6 and Month 18 in patients continuing givosiran treatment, while placebo crossover patients had similar improvements at Month 18 to those seen in givosiran patients in the DB period

SF-12 Physical Component Summary[a]



EuroQol-visual analog scale health-related questionnaire[a]



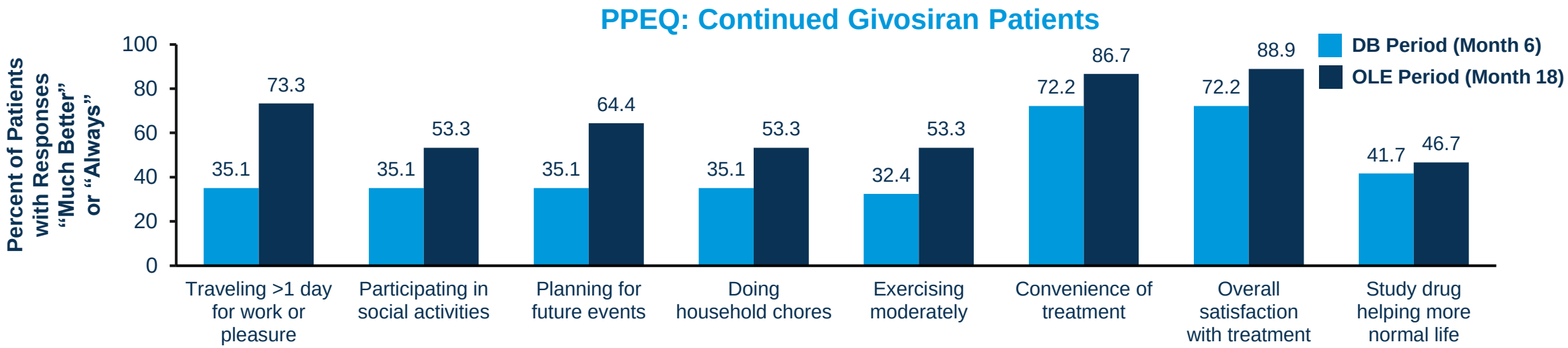
[a]Estimates for the clinically meaningful difference are ≥2−5 points for SF-12 PCS and 7–8 points for EQ-VAS, based on published data for other chronic diseases[1–4]

DB, double-blind; EQ-VAS, EuroQol-visual analog scale health-related questionnaire; PCS, Physical Component Summary; QOL, quality of life; SF-12, Short Form (12-item) Health Survey

1. Clement et al. Knee Surg Sports Traumatol Arthrosc 2014;22:1933–9; 2. Parker et al. J Neurosurg Spine 2012;16:471–8; 3. Zanini et al. Respir Care 2015;60:88–95; 4. Nolan et al. Thorax 2016;71:493–500
Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

Improvement in Patient-Reported Outcomes with Long-Term Dosing

- The PPEQ questionnaire observed further improvements across all domains in patients continuing givosiran treatment compared with the DB period[1]
  - Improvements across all domains were also observed in placebo crossover patients compared with the DB period



- Givosiran treatment led to a decrease in the number of work days missed due to porphyria in the past 4 weeks in both patient groups when compared with placebo crossover patients in the DB period[a]
  - Mean (SD) of 2.4 (6.8) days vs 1.8 (6.3) days (Month 6 vs Month 18) for continued givosiran patients[b]
  - Mean (SD) of 6.7 (7.8) days vs 2.5 (5.1) days (Month 6 vs Month 18) for placebo crossover patients[c]

[a]Including only those patients who have been employed in the past 4 weeks. [b]Patient numbers: n=17 at Month 6; n=20 at Month 18. [c]Patient numbers: n=20 at Month 6; n=23 at Month 18
DB, double-blind; OLE, open-label extension; PPEQ, Porphyria Patient Experience Questionnaire; SD, standard deviation

1. Balwani et al. *N Engl J Med* 2020;382:2289–301
Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

Safety Profile[a] of Givosiran Remained Acceptable with No New Safety Concerns

- Mean (SD) exposure was 18.9 (3.6) months for continued givosiran patients and 13.0 (3.6) months for placebo crossover patients, with maximum exposure of 25.1 months
- Majority of AEs continued to be mild or moderate in severity
- Most common related AEs (≥10%): ISRs, nausea, and fatigue[c]
- SAEs in ≥2%: UTI, CKD, and device breakage[d]
- There were no deaths

Safety Summary in Patients Receiving Givosiran[a]

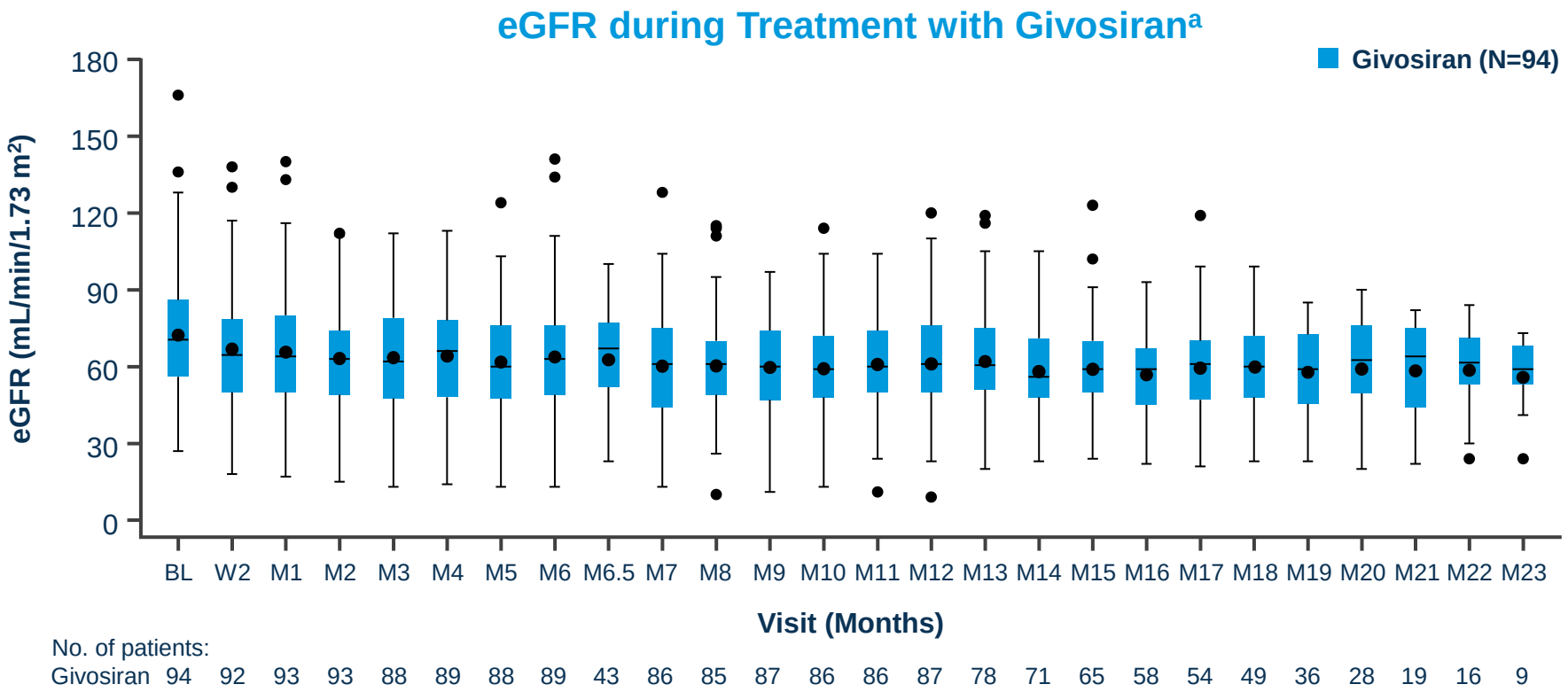
At Least 1 Event, n (%)[b]	Placebo Crossover (N=46)	Givosiran (N=48)	All Patients (N=94)
AEs	43 (94)	47 (98)	90 (96)
SAEs	9 (20)	15 (31)	24 (26)
Severe AEs	12 (26)	12 (25)	24 (26)
AEs leading to treatment discontinuation	1 (2)	1 (2)	2 (2)
AEs leading to study withdrawal	0	1 (2)	1 (1)
Deaths	0	0	0

- During interim period between data cuts at Months 12 and 18, there was one new AE of drug hypersensitivity which led to treatment discontinuation[e]
  - No new treatment-related SAEs or safety concerns regarding hepatic AEs

[a]Safety data from first dose of givosiran to data cut-off date (January 10, 2020). [b]For calculating exposure: 1 month=30.44 days. [c]ISRs occurred in 36% of patients (103 events), nausea in 30%, and fatigue in 23%.
[d]Each SAE occurred in 2 patients. [e]SAE of LFT abnormal that led to treatment discontinuation during the DB period previously reported
AE, adverse event; CKD, chronic kidney disease; ISR, injection-site reaction; LFT, liver function test; SAE, serious AE; SD, standard deviation; UTI, urinary tract infection
Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

Renal Events in Patients with AHP

- Renal AEs (mostly increased serum creatinine and/or decreased eGFR) occurred in 16 patients (17%)
  - None led to discontinuation of study treatment
- Small decreases in eGFR observed early in therapy which stabilized by Months 12 to 18



[a]The line and dot inside the box indicate the median and mean value respectively. The bottom and top edges of the box indicate interquartile range (IQR). The vertical lines represent the most extreme point within 1.5x IQR. Any value more extreme than this is marked with a dot.

AE, adverse event; AHP, acute hepatic porphyria; BL, baseline; eGFR, estimated glomerular filtration rate; IQR, interquartile range; M, month; W, week; Q1, lower quartile; Q3, upper quartile

Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

18-Month ENVISION OLE Summary

- Givosiran decreased ALA and PBG levels through Month 18
- Reductions in annualized rate of composite porphyria attacks in patients with AHP were sustained during the OLE period
  - Placebo crossover patients had an 85% reduction in AAR compared with the DB period
  - More than 60% of continued givosiran patients continued to have zero attacks during the OLE period
- Median annualized days of hemin use reduced from 15 to zero during OLE for placebo crossover patients
- Givosiran treatment led to improvements in multiple measures of QOL and reductions in work days missed due to porphyria
- The safety profile of givosiran remained acceptable and consistent with that previously observed
- In the ongoing ENVISION OLE, patients receiving long-term treatment with givosiran demonstrated a durable response in clinical efficacy across a wide range of clinical parameters

AAR, annualized attack rate; AHP, acute hepatic porphyria; ALA, δ-aminolevulinic acid; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; QOL, quality of life

Kuter et al. Presented at American Society of Hematology (ASH) Congress 2020

ELEVATE AHP Registry

An observational study in AHP patients

Commitment to Continued Evidence Generation

Objectives

- Primary
  - Characterize the long-term real-world safety of GIVLAARI in patients with all types of AHP
- Secondary
  - Characterize the long-term real-world effectiveness of GIVLAARI in patients with all types of AHP
  - Describe the natural history and real-world clinical management of patients diagnosed with AHP

Study Design

- Prospective, global, multicenter, longitudinal registry conducted to characterize the natural history and real-world clinical management of patients diagnosed with AHP
- Includes patients on GIVLAARI, other treatments, and untreated
- Patient data will be collected through electronic data capture
  - Data entered at enrollment and at least once every 12 months; sites can enter multiple follow-up visits if patients have more than one visit per year
- No visits or examinations, laboratory tests or procedures are mandated as part of this study

Data Overview

- AHP disease history (includes demographics, diagnosis, treatments, comorbidities)
- Effectiveness assessments (includes attack rates, signs and symptoms, patient-reported outcomes)
- Safety assessments (includes adverse events, hospitalizations, vital status, pregnancy and outcomes)

ClinicalTrials.gov Identifier: NCT04883905

Agenda

Welcome
- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction & GIVLAARI® (givosiran) Overview
- Akin Akinc, Ph.D. – Vice President & General Manager, Givosiran

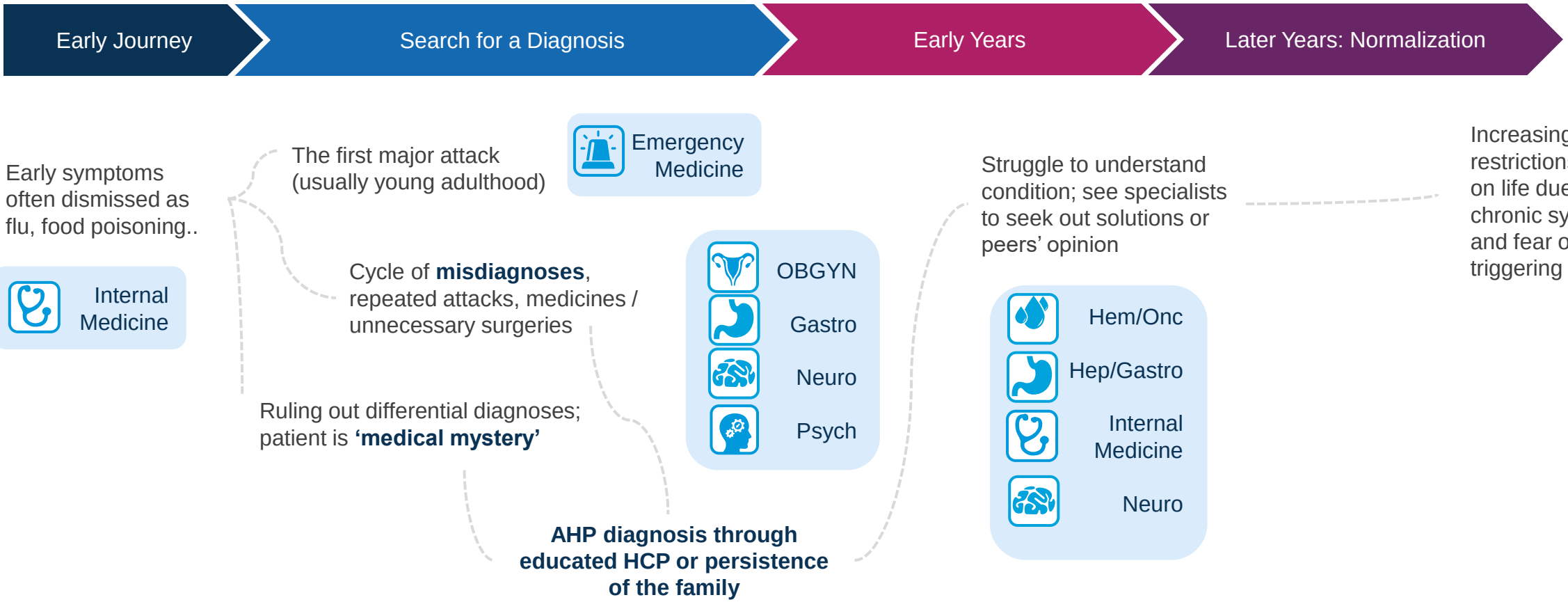
18-Month Interim Data from ENVISION Phase 3 Study
- Marianne Sweetser, M.D., Ph.D. – Senior Distinguished Fellow, Clinical Development

Disease Awareness, Patient Identification & Geographic Expansion
- Laurent Placidi, Ph.D., PharmD. – Senior Director, Global Marketing, Givosiran

Q&A Session

Often a Long, Frustrating Journey to Diagnosis

Many Opportunities Exist to Accelerate Awareness of AHP via HCP and Patient Education

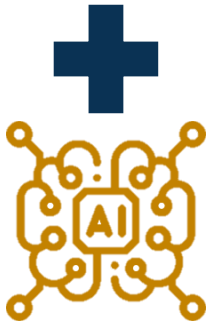


Looking back, patients identify symptoms they previously dismissed	Patients search for answers; online, social media. **Knowledge is power**: Educational initiatives result in patients and doctors being more aware of AHP	In the years following diagnosis, patients begin to feel isolated and their lives are disrupted as attacks continue. **Patients seek solutions**	**Patients feel that only they can understand what it is like;** some prefer to self-manage; others prefer to **seek new opinions and new treatment options**

Leveraging Combination of Innovative Data, Technology, and Digital Efforts to Support HCP Diagnosis and Educate Patients

Data & Scientific Exchange

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



Technology

- *Support improved visibility of AHP testing available in EMR*
- *Support holistic, longitudinal assessment and management of patients with AHPs*
- *Improve HCP-Patient communication about disease burden*

Digital

PORPHYRIA Diagnosis™

Pinpoint® AHP
Acute Hepatic Porphyria

Increase Awareness & Suspicion to Decrease Time to Diagnosis of Disease

Multifaceted Approaches to Reach Broader HCP Audiences

Disease Awareness

- HCP-focused campaign and disease education website

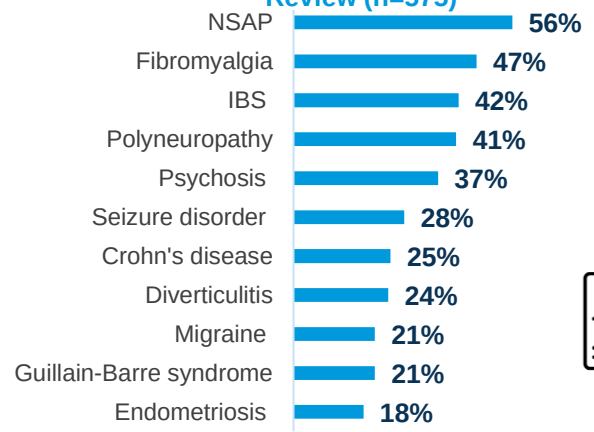
Languages:
English
German
Spanish
Italian
Brazilian
Japanese
French (soon)

  - >1.5 million website visits globally since campaign launch
  - >11,000 HCPs engaged YTD
  - US HCPs asking to connect with Field Teams has led to Dxs and Rxs for AHP patients (Launching in EU Q3)

Screening Studies

- Analyze claims data to understand potential mis-diagnoses or co-morbidities and to support or help improve diagnostic algorithms
- Support research collaborations and Investigator Initiated Studies
- Identify/test potential enrichment criteria

Top Misdiagnoses / Comorbidities – Global AHP Chart Review (n=575)



NSAP = nonspecific abdominal pain
Misdiagnoses of depression and stress excluded.

Increase Access & Ease of Testing

- Supported the development of a rapid, screening test for urine PBG that is now cleared by the FDA
- Facilitated panel of commercial laboratories and AHP clinical experts to develop recommendations for publication on biochemical diagnosis of AHP for PCPs[1]
- Provide independent third-party genetic testing and counseling in select geographies

[1] Biochemical Diagnosis of Acute Hepatic Porphyria: Updated Expert Recommendations for Primary Care Physicians. Anderson K et al. Am J Med Sci. 2021 Apr 16:S0002-9629(21)00093-8

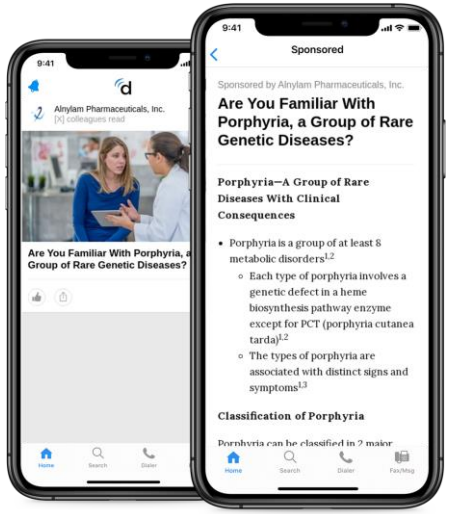
HCP Virtual Education

Pandemic Learnings – HCP Online Education

U.S.

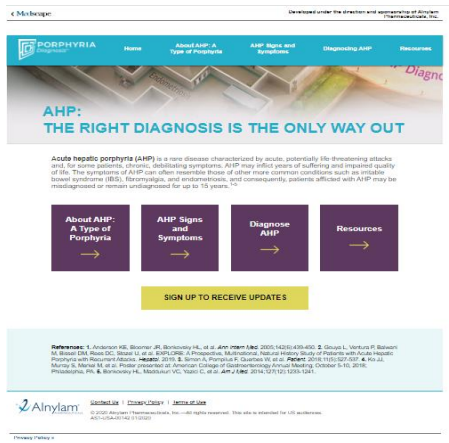
Medscape

- Medscape Infosite*
  - ~6,000 HCP Visits (50% OBGYNs, 25% GI)
  - >3,000 recontact emails sent



doximity

- >7,000 HCPs targeted*



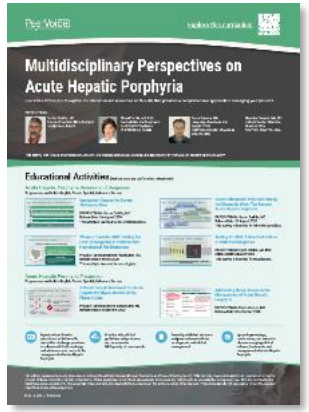
DMD Connecting Healthcare

- Triggered email program to ~34,000 HCPs^

EU

PeerVoice

- Multi-disciplinary perspectives targeting key specialties involved in diagnosis journey
- Launched in 2020, >35,000 HCP meaningful engagements
  - Gastroenterology
  - Neurology
  - Internal Medicine
  - OBGYN
  - Psychiatry



EMJ EUROPEAN MEDICAL JOURNAL

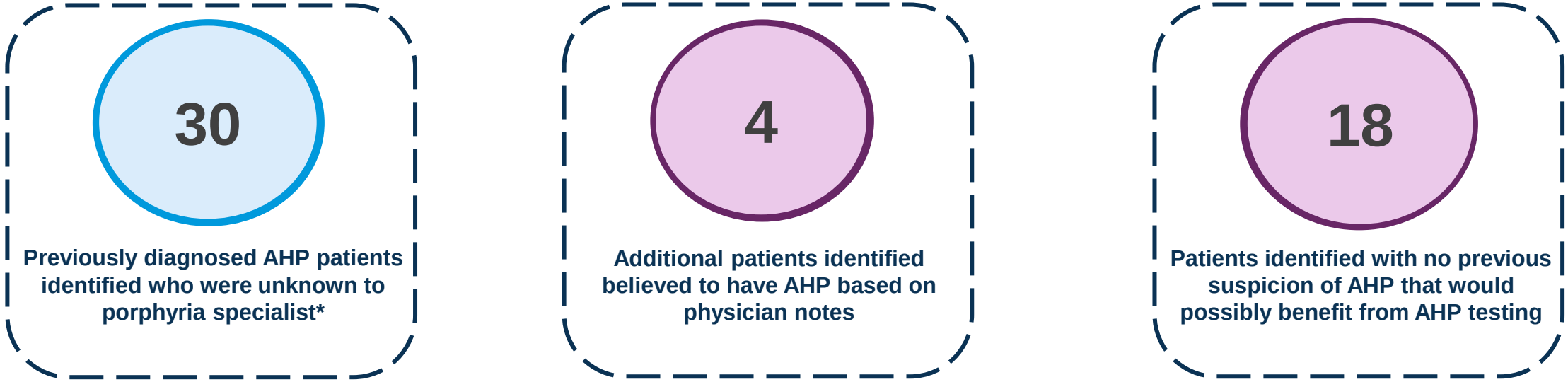
- Email sent via EMJ, with link to Alnylam AHP webinar replay
- 1,800 meaningful interactions since Q4 2020

*Provided Medscape and Doximity metrics current as of May 2021

^Provided DMD metrics current as of July 2021

HCP Identification of AHP Patients

- **Objective:**
  - Improve the ability to identify undiagnosed AHP patients using machine learning and knowledge engineering in electronic health record (EHR) data
- **Our approach:**
  - Analyze 200,000+ de-identified EHR patient charts and 30+ million text notes for both inpatient and outpatient encounters at Oregon Health & Science University (OHSU)
  - Use 30 diagnosed AHP patient profiles to create a positive data set of 146 machine trained features to create an AHP prediction score
  - As follow up to this study, an IRB-approved clinical validation study is being implemented
- **Output:**

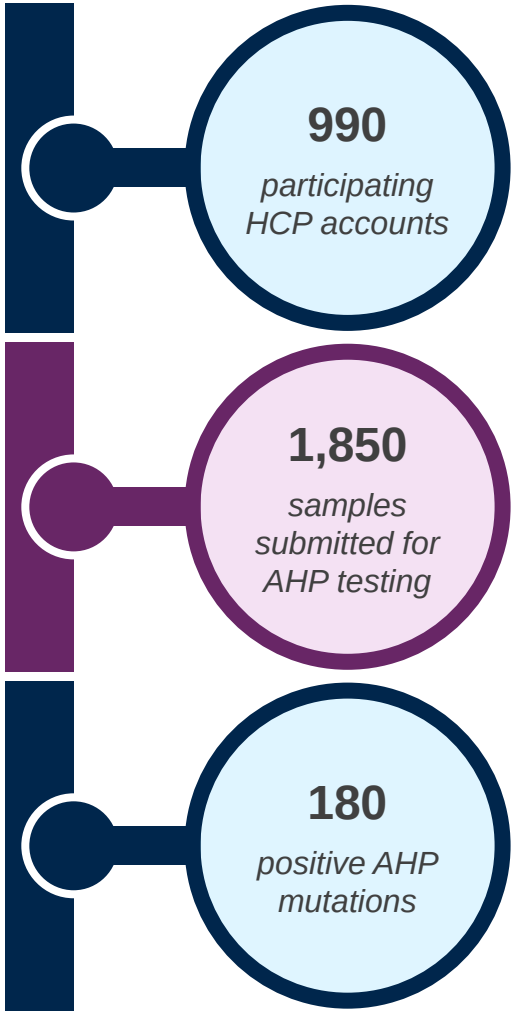


Detecting rare diseases in electronic health records using machine learning and knowledge engineering: Case study of acute hepatic porphyria. Cohen A et al. PLoS One. 2020 Jul 2;15(7):e0235574

*Previously diagnosed AHP patients identified in the OSHU network who were unknown to the porphyria specialist at OSHU

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 certain other countries (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**

Data as of July 2021

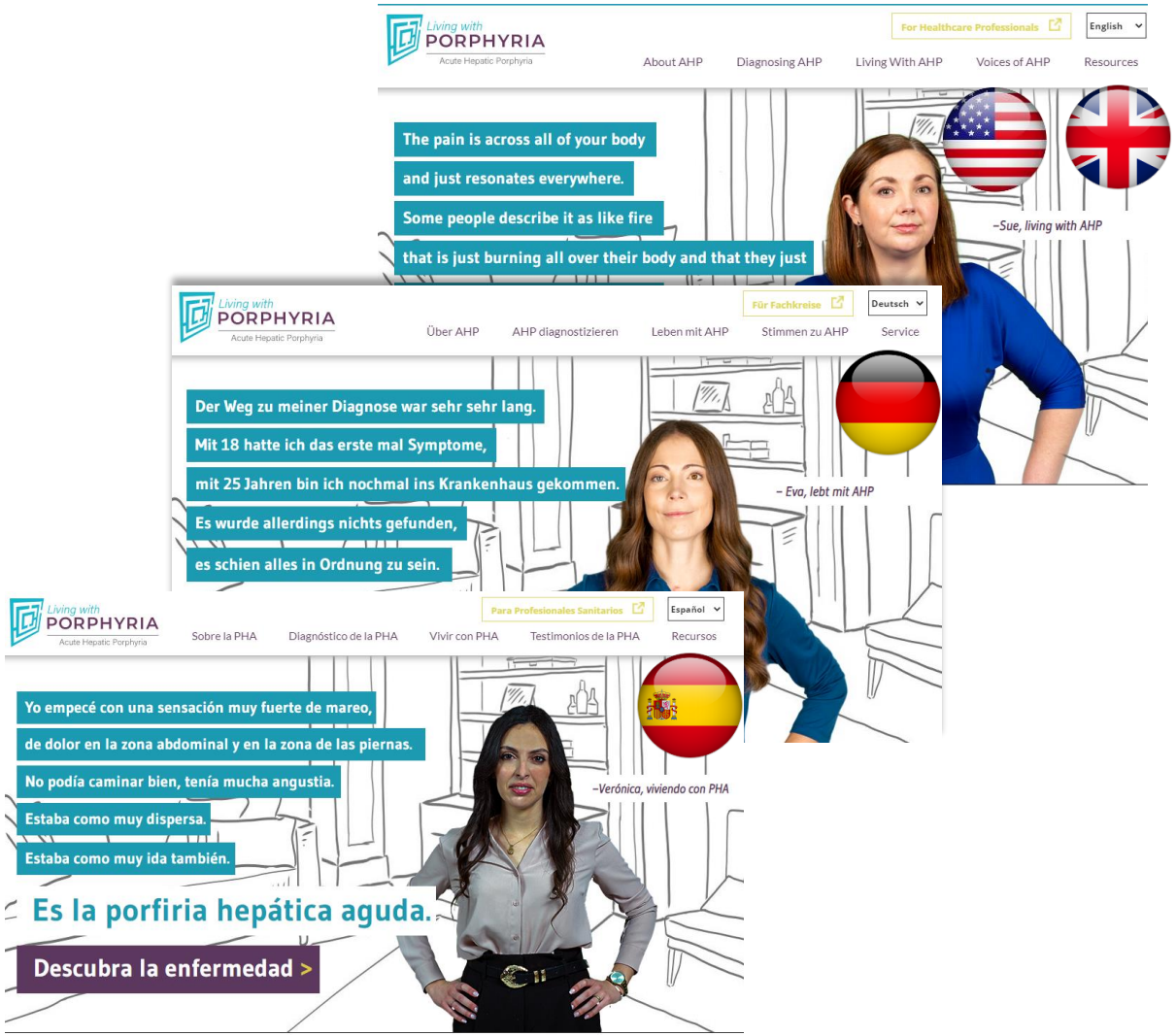
At no time does Alnylam receive patient-identifiable information. Alnylam receives contact information for healthcare professionals who use this program

Patient-Focused Disease Awareness Initiatives

Significant Engagement Throughout 2021

- Initiatives applied at a global scale, with patient-facing websites available in English, Spanish, French, German, Italian, Dutch, Swedish

- As of June 2021:
  - ~300,000 website visits across all patient-facing websites
    - >11,000 video views on websites
    - >4,000 PDF downloads on websites
  - Received >16,000 requests for more information across all web platforms
  - Social Media follow-ups: >60,000 engagements
  - In 2021, over 50 interested individuals connected with Alnylam Patient Education Liaisons (US only)



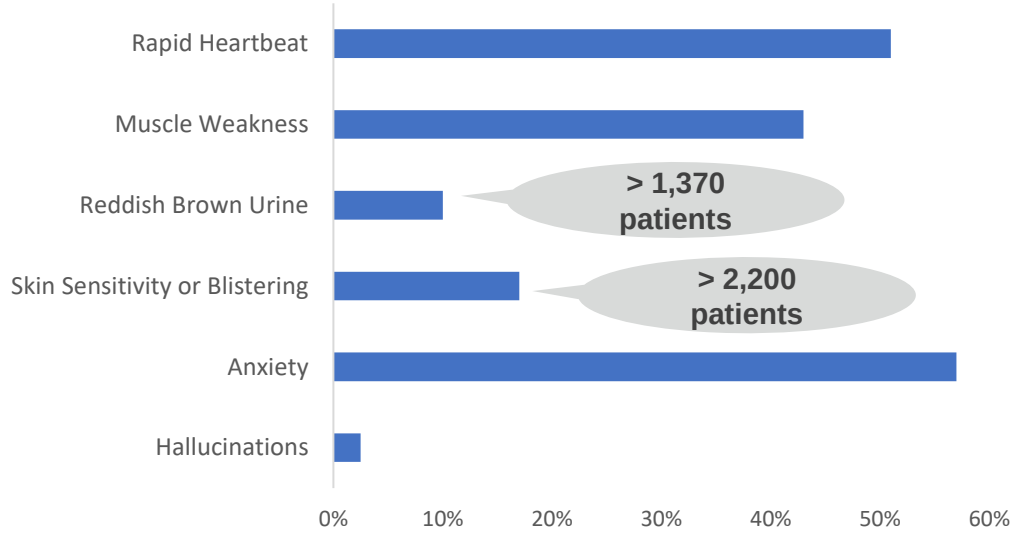
Social Media as a Way to Engage U.S. Patients Looking for Disease Information

Reaching an Enriched Audience via Facebook

Target Specific Facebook Communities	Enriched Audience	Users May Agree for Future Communications	Disease Education Delivered via CRM
• Target audience provided with information on FB • Clicks directed to online Health survey	• Responses to questionnaire identify potential patients and urge them to speak with their doctor	• Respondents may opt-in to share contact information and receive further information about AHP	• Information delivered via email or connection with website

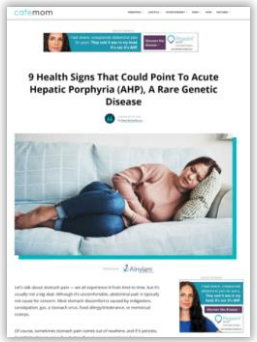
- Over 6 M reach
- >56,000 people took the survey
- Majority with intense abdominal pain

Q: Thinking about these episodes of abdominal pain, what other changes have you experienced before or during an episode (N=13,647)



Telling the AHP Story to Broad Audiences to Help Raise Awareness

- Alnylam and Wild Sky Media (WSM) entered a collaboration to develop and share two articles about AHP and GIVLAARI:
  - An article about AHP signs and symptoms
  - An article about GIVLAARI Patient Ambassador Donna that highlights her experience on treatment
  - The articles were published on two consumer outlets: LittleThings.com (38M unique monthly visitors) and CafeMom.com (25M unique monthly visitors)



little THINGS

cafemom

Over 720,000 article views

- Partnership with The Balancing Act to air a “Behind the Mystery” segment about AHP on Lifetime TV during International Porphyria Awareness Week 2021
  - Segment attracted 700K viewers on Lifetime TV, reaching 52% of U.S. households
  - Digital and social media promotion led to ~500,000 impressions and >20,000 engagements

The Balancing Act Presents BEHIND THE MYSTERY

Lifetime

700,000 viewers

Technology Can Also Be Used to Support Identification of Diagnosed Patients Who May Benefit from Treatment

- In the short term, goal is to develop symptoms tracking tool to:
  - Record current impact of AHP, both clinical and QOL
  - Improve HCP-Patient communication about burden of disease

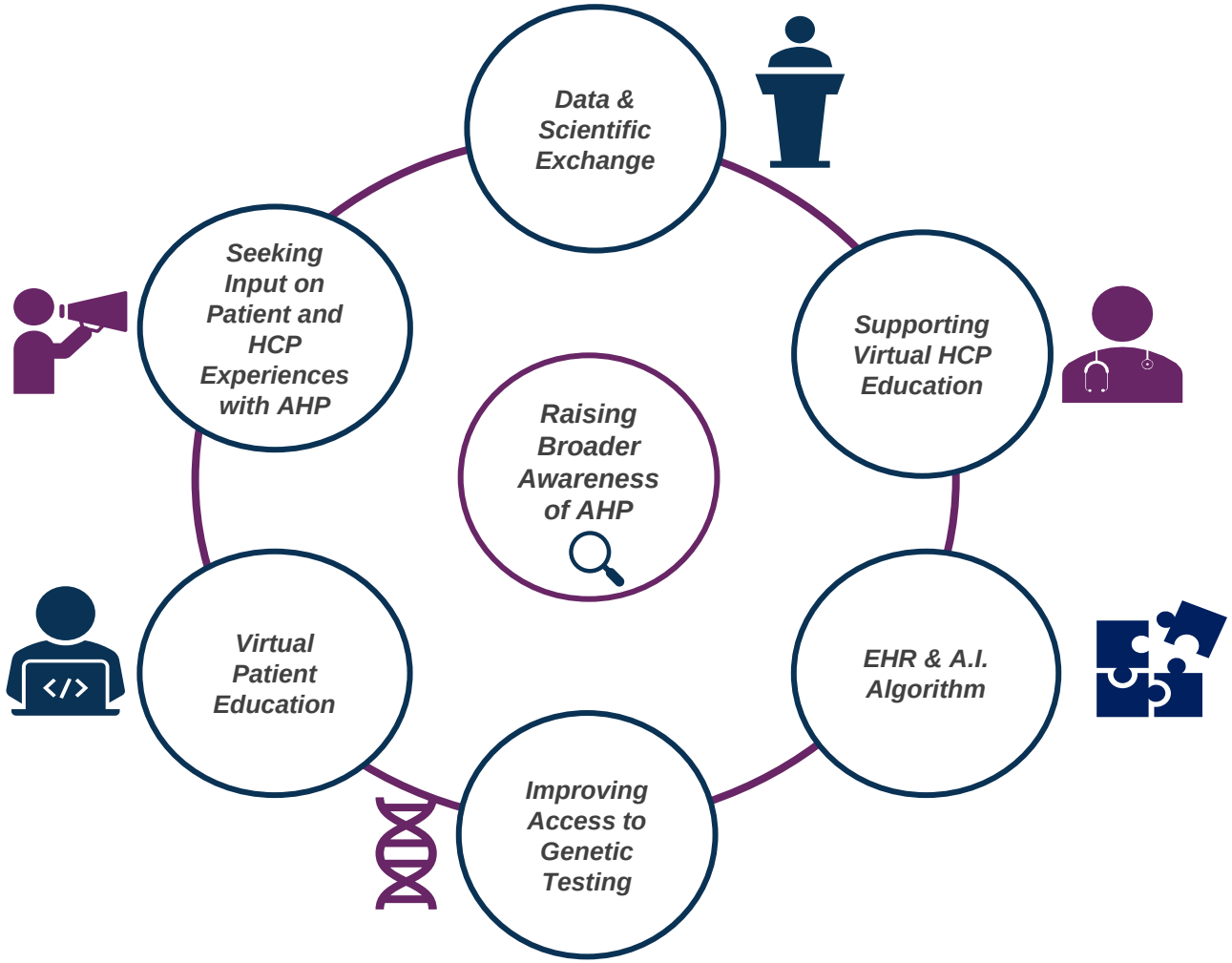
- In the long term, goal will be to support:
  - Improved understanding of disease presentation and progression
  - Identification of chronic symptomatology
  - Holistic, longitudinal assessment and management of patients with AHP, including GIVLAARI patients

- MyPorphyriApp to include:
  - Symptom tracker
  - Surveys/ePRO
  - Performance tests
  - Ability for patient to invite treating HCP to access data

- **Built with input from KOLs and PAGs**
- **Expect to launch pilot in Germany Q4 2021***

(*) MyPorphyriAPP is a symptom, lifestyle tracker – not a medical device

Understanding the Patient Journey Has Been Critical in our Disease Awareness Efforts



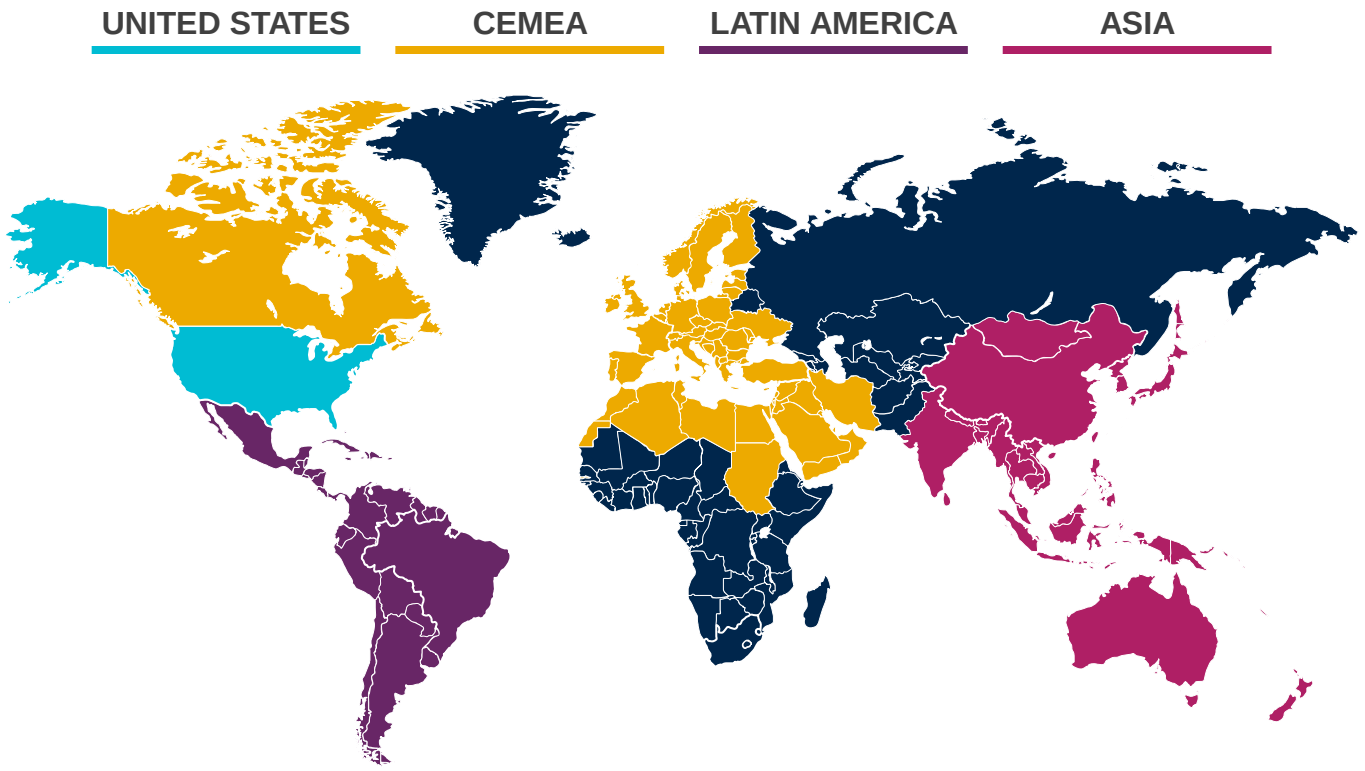
"After dealing with this my whole life and almost giving up on ever finding a doctor or diagnosis, your video is the only one that I have ever fully related to…without your video I would've given up and continued to suffer. Now I am in the process of getting a referral to a hematologist."

-AHP Patient

GIVLAARI Global Expansion

Ensuring GIVLAARI Availability Around the World Following Regulatory Approval

- Launched in the U.S.
- Launched in Germany and Italy, with additional EU launches this year
  - "Considerable added" benefit rating in Germany
  - "Innovation status" rated in Italy
- Named patient sales in France and other countries
  - ASMR II granted in France
- Recently approved in Japan; also approved in Canada, Switzerland, and Israel
- Continued global regulatory filings and launches planned across regions



GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

CEMEA: Canada, Europe, Middle East, North Africa

Bringing GIVLAARI to AHP Patients in Japan

Japan

- **Market Dynamics:**
  - Estimated 1,000 AHP patients with active disease
  - ALA and PBG biochemical test reimbursed; some academic centers offer genetic testing as well
  - Practice Guidelines for “Primary Care of Acute Abdomen” (2015) include differential diagnosis of AHP

- **Approval and Ongoing Disease Awareness Initiatives:**
  - JNDA approved June 2021 for the treatment of AHP in adults and adolescents aged 12 years and older
  - Analyzing claims database to identify additional “diagnosed” patients
  - HCP disease awareness website launched
  - Engagement with KOLs and patient association group (Sakura Friendship Association) to increase awareness and understanding of AHP

Summary

- GIVLAARI represents a treatment option for patients with AHP[1], a rare disease with significant burden
- 18-month ENVISION OLE data demonstrate GIVLAARI's long-term efficacy and safety profile
- Global, multi-channel initiatives underway to improve AHP disease awareness
  - Applying digital tools to promote education
  - Leveraging A.I. and data-driven approaches
  - Utilizing media platforms to ensure broad reach
- GIVLAARI launch ongoing in U.S. and selected EU countries
  - Value-based philosophy facilitates broad access
- Continued geographic expansion an important driver of growth
  - Japan represents a key new market

[1] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU, Israel, Japan, and Switzerland for the treatment of AHP in adults and adolescents aged 12 years and older

Agenda

Welcome
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Introduction & GIVLAARI® (givosiran) Overview
- Akin Akinc, Ph.D. – Vice President & General Manager, Givosiran

18-Month Interim Data from ENVISION Phase 3 Study
- Marianne Sweetser, M.D., Ph.D. – Senior Distinguished Fellow, Clinical Development

Disease Awareness, Patient Identification & Geographic Expansion
- Laurent Placidi, Ph.D., PharmD. – Senior Director, Global Marketing, Givosiran

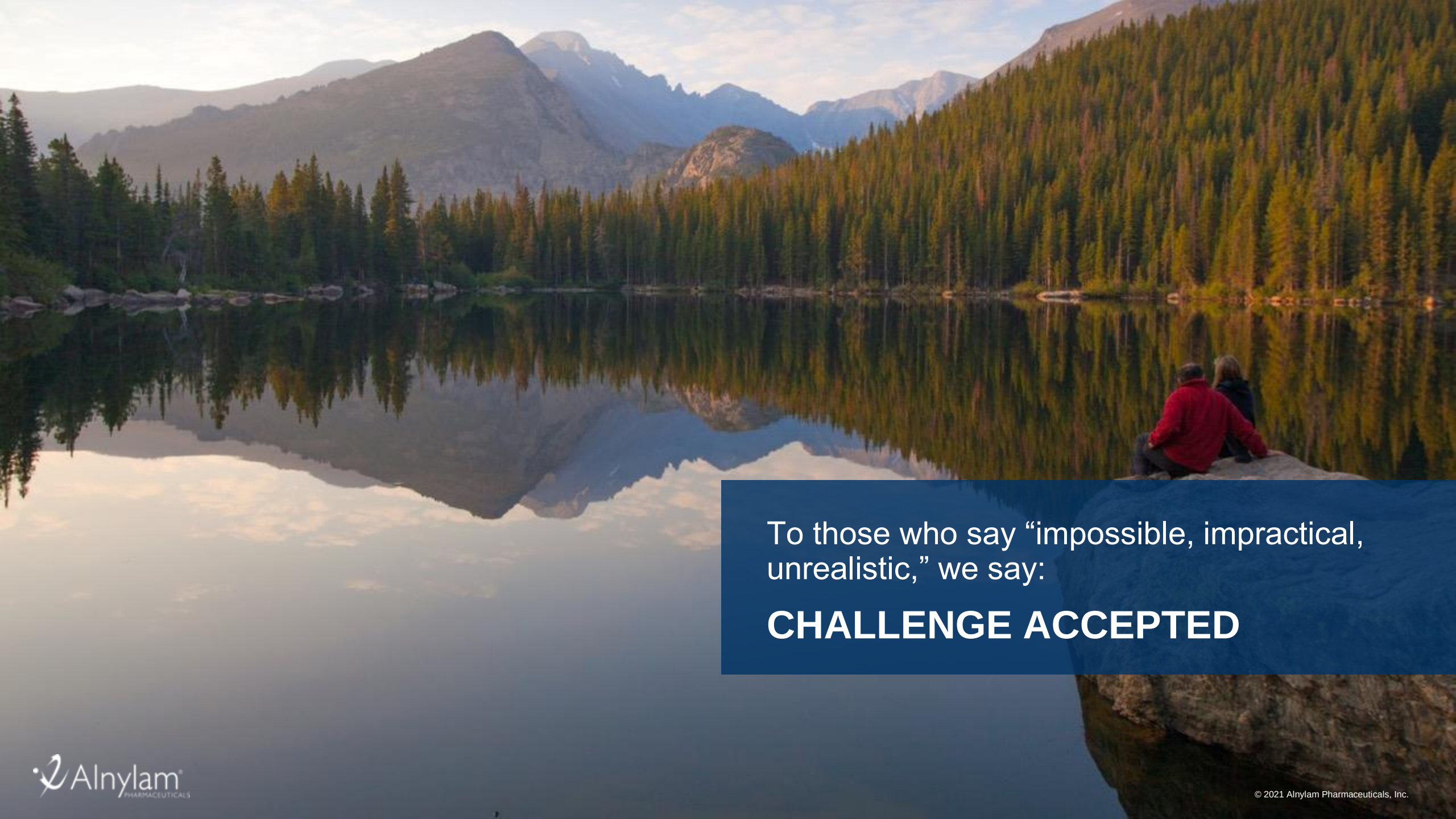
Q&A Session

Upcoming RNAi Roundtables

Lumasiran, for the Treatment of Primary Hyperoxaluria Type 1

- Thursday, August 19, 9:30 am ET

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



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