



Givosiran, in Development for the Treatment of Acute Hepatic Porphyria

October 7, 2019



Agenda

Welcome

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

Introduction

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

Acute Hepatic Porphyria & Physician Perspective

- Srikanth Nagalla, M.D., M.S. – Associate Professor of Internal Medicine, Medical Director of Blood Disorders Clinic, Program Director of Hematology/Oncology Fellowship, UT Southwestern Medical Center

ENVISION Phase 3 Results

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

Opportunity in Acute Hepatic Porphyria & Disease/Diagnostic Education Efforts

- 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.anylam.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, including givosiran; pre-clinical and clinical results for our product candidates, including givosiran; actions or advice of regulatory agencies with respect to givosiran and the review of our NDA and MAA; delays, interruptions or failures in the manufacture and supply of our product candidates, including givosiran; 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 our products, including givosiran; 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, including our alliance with Ironwood; 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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Q&A Session

RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

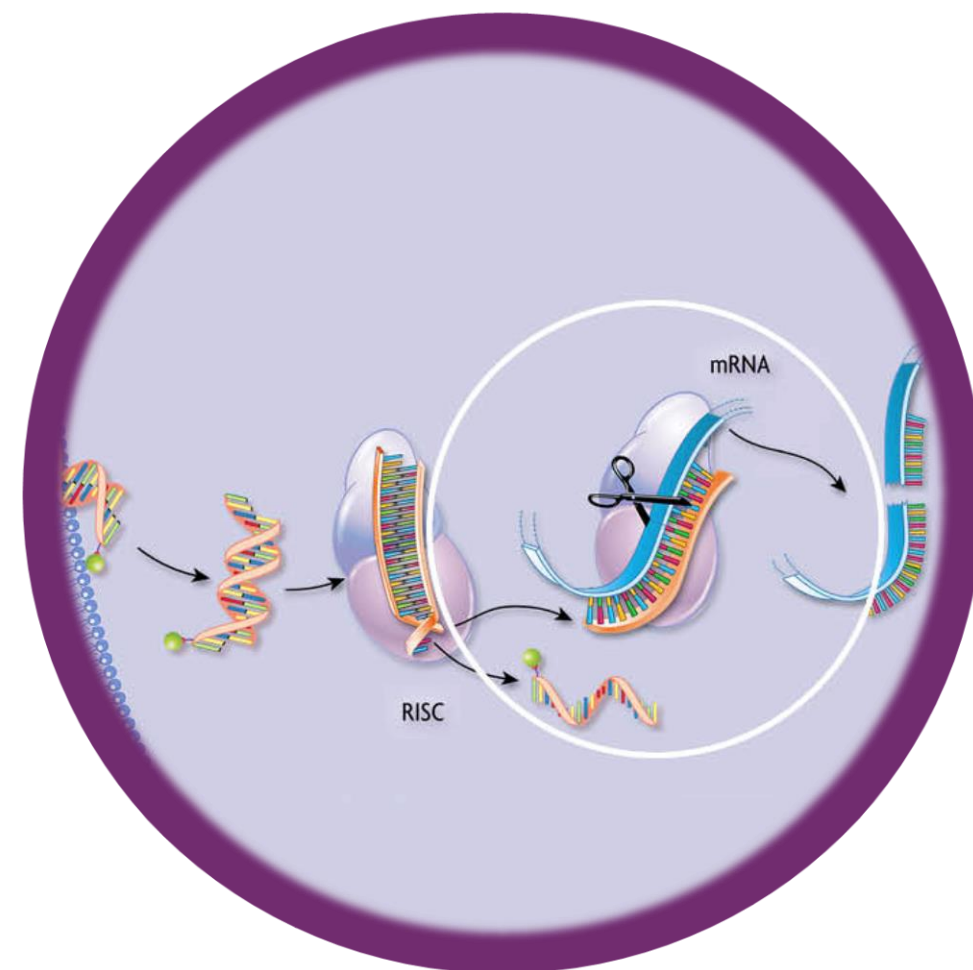
Nobel Prize-winning science

Silence any gene in genome

Potent and durable mechanism of action

Product engine for sustainable pipeline


Now commercial



Anylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArS):

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

		HUMAN POC ¹	BREAKTHROUGH DESIGNATION	EARLY STAGE <small>(IND or CTA Filed-Phase 2)</small>	LATE STAGE <small>(Phase 2-Phase 4)</small>	REGISTRATION/ COMMERCIAL ³	COMMERCIAL RIGHTS
 onpattro <small>(patisiran) liquid complex injection 10mg/5mL</small>	<i>hATTR Amyloidosis²</i>					●	Global
Givosiran	<i>Acute Hepatic Porphyria</i>					●	Global
Patisiran	<i>ATTR Amyloidosis Label Expansion</i>				●		Global
Fitusiran	<i>Hemophilia and Rare Bleeding Disorders</i>				●		15-30% royalties
Inclisiran	<i>Hypercholesterolemia</i>				●		Milestones & up to 20% royalties
Lumasiran	<i>Primary Hyperoxaluria Type 1</i>				●		Global
Vutrisiran	<i>ATTR Amyloidosis</i>				●		Global
Cemdisiran	<i>Complement-Mediated Diseases</i>			●			50-50
Cemdisiran/Pozelimab Combo⁴	<i>Complement-Mediated Diseases</i>			●			Milestone/Royalty
ALN-AAT02	<i>Alpha-1 Liver Disease</i>			●			Global
ALN-HBV02 (VIR-2218)	<i>Hepatitis B Virus Infection</i>			●			50-50 option rights post-Phase 2
ALN-AGT	<i>Hypertension</i>			●			Global

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

² Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU 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

³ Includes marketing application submissions

⁴ Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Anylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

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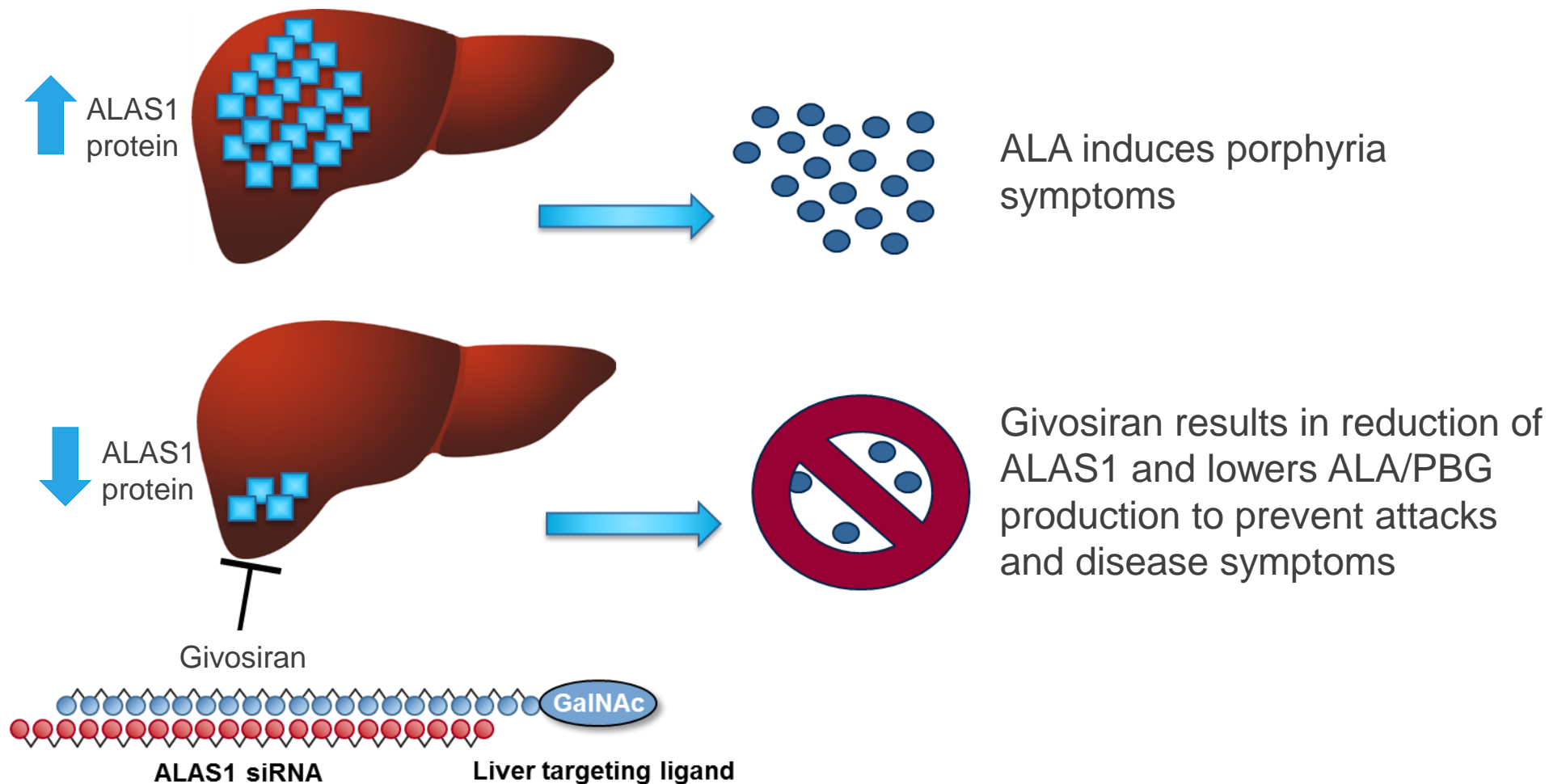
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Givosiran: Investigational RNAi Therapeutic for AHP

Therapeutic Hypothesis

- Reduction of Liver ALAS1 Protein to Lower ALA and PBG



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Q&A Session

Acute Hepatic Porphyrrias

Srikanth Nagalla, MD, MS

Associate Professor of Internal Medicine

Medical Director, Blood Disorders Clinic

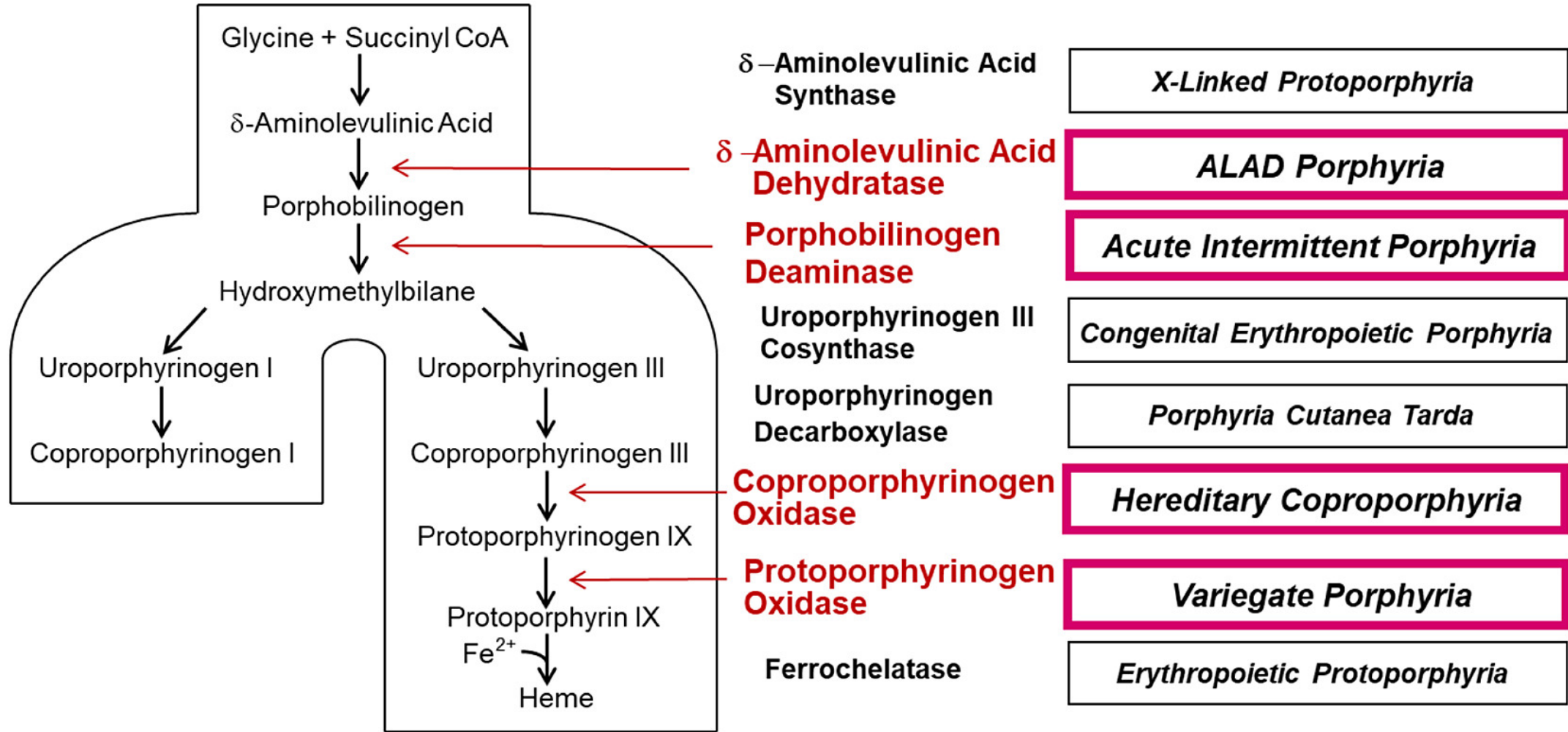
Program Director, Hematology/Oncology Fellowship

UT Southwestern Medical Center, Dallas, TX

Porphyrias

- Are a result of enzymatic defects in the heme synthetic pathway
- Challenging to diagnose due to non-specific symptoms and signs
- Could be classified as
 - Acute hepatic
 - Erythropoietic
- Will focus on acute hepatic porphyrias in this section
- Patients with acute hepatic porphyrias could present to a wide variety of specialists: Neurology, Gastroenterology, Hematology, Primary care, Emergency medicine, Psychiatry etc.

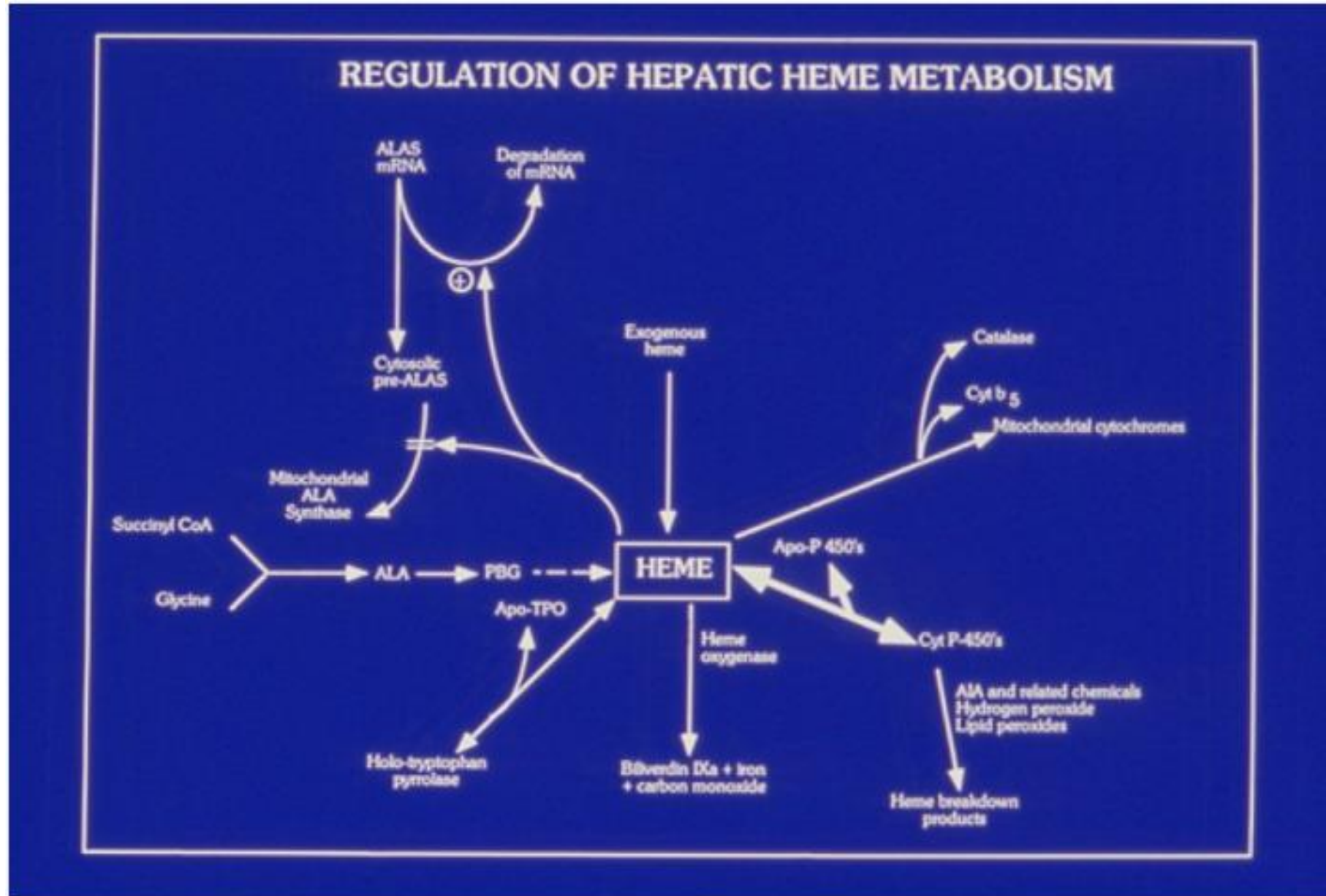
Heme synthetic pathway



Acute hepatic porphyrias

- There are four acute hepatic porphyrias
 - Acute intermittent porphyria
 - Hereditary coproporphyria
 - Variegate porphyria
 - ALA-dehydratase-deficient porphyria
- Heme synthesis ~85% Bone marrow and the rest in the Liver
- ALAS1 is the rate-limiting enzyme for heme synthesis in the liver
- Heme represses the synthesis of the ALA-synthase 1 messenger RNA
- Many drugs that induce hepatic ALA-synthase 1 also induce the CYP genes

Key role of heme in the regulation of hepatic ALAS-1 and heme metabolism



Clinical manifestations of an acute porphyria attack

Clinical features

Central

Hallucinations/anxiety

Seizures

Peripheral

Pain related to peripheral neuropathy

Respiratory weakness

Autonomic

Abdominal pain

Tachycardia/hypertension

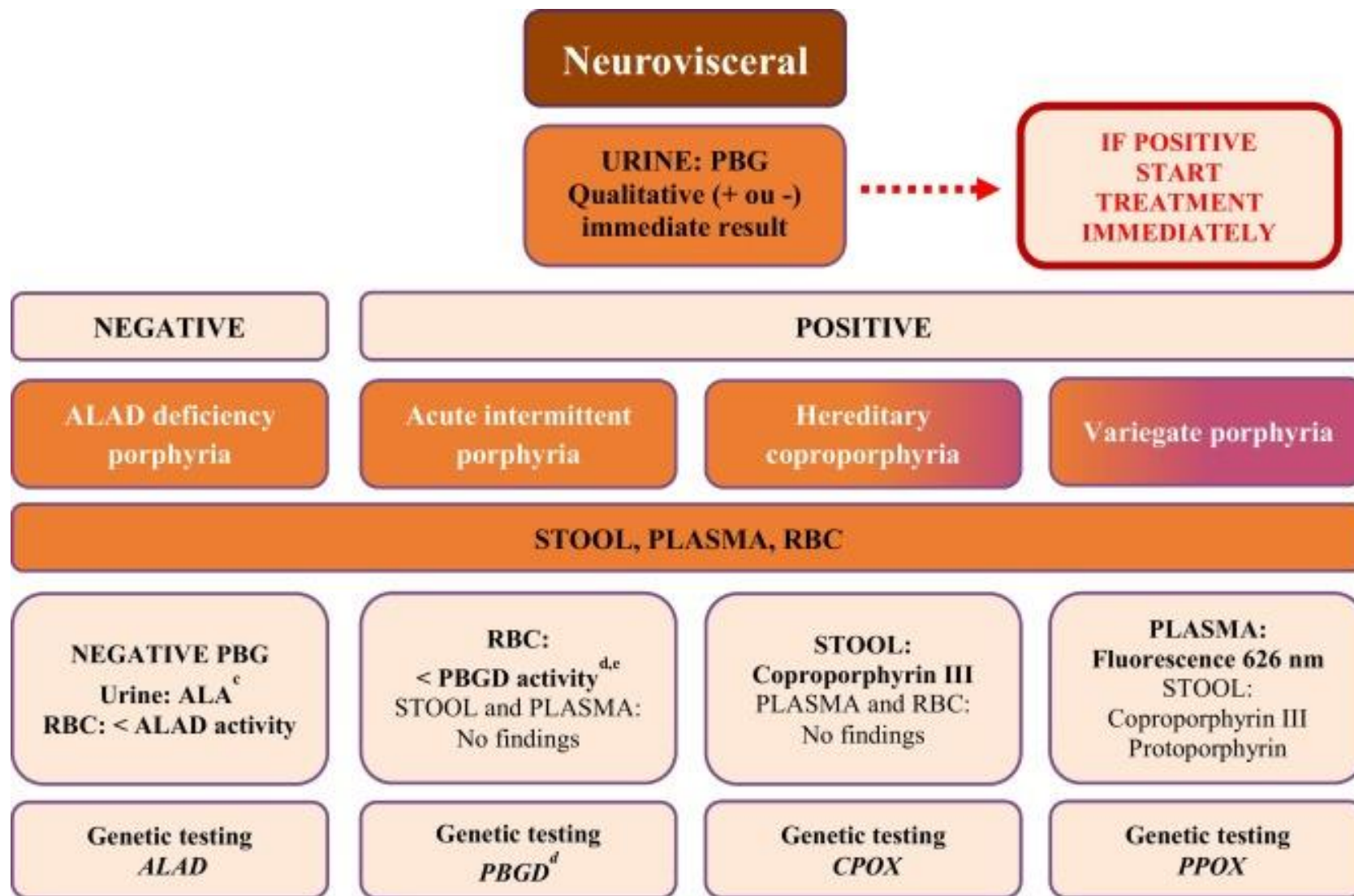
Constipation

Vomiting

Long term effects from Acute porphyrias

- Renal failure
- Hypertension
- Hepatocellular and cholangiocarcinoma
- Neurological damage
- Depression
- Suicide

Diagnostic algorithm for Acute hepatic (neurovisceral) porphyrias



ALA – delta-aminolevulinic acid; ALAD – delta-aminolevulinic acid dehydratase; CPOX – coproporphyrinogen oxidase; PBG – porphobilinogen; PBGD – porphobilinogen deaminase; PPOX – protoporphyrinogen oxidase

Biomarkers of disease activity

- In addition to diagnosis of acute porphyrias, ALA and PBG are useful as biomarkers of active disease
- Measuring ALAS1 mRNA might be useful in evaluating pathologic mRNA induction
- The biomarkers respond to treatment with hemin or givosiran

Treatment of acute attacks

- Discontinuation of a drug precipitating the attack
- Carbohydrate loading (represses hepatic ALAS1)
- Intravenous hemin (down-regulates hepatic ALAS1)
- Down regulation of ALAS1 is key to treatment of acute hepatic porphyrias

Current approaches for prevention or treatment of acute attacks

- Eliminate trigger factors
- Gonadotropin- releasing hormone analogues - for menstrual cycle related attacks
- Hemin prophylaxis- Weekly or twice weekly
- Liver transplantation- last resort
- Gene therapy- not effective at this time
- Gene silencing – ENVISION Phase 3 study of givosiran completed – regulatory reviews underway

Unmet need in AHP

- Current treatment options inadequate
- No currently approved prophylactic agents
- Therapies with long-lasting effect needed to ease patient burden
- Continued research is important for patients

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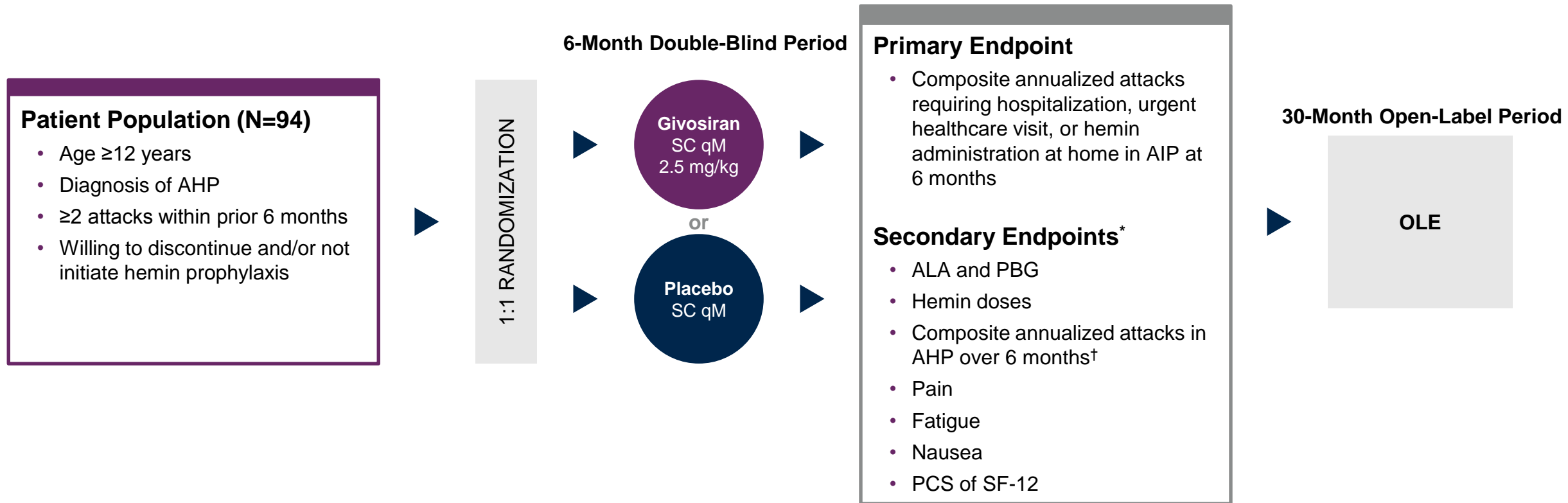
- Akin Akinc, Ph.D. – General Manager, Givosiran

Q&A Session

Givosiran ^{***}ENVISION Phase 3 Study

Randomized, Double-Blind, Placebo-Controlled Study in Patients with AHP

94 patients enrolled at 36 sites in 18 countries



*Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted

PCS, Physical Component Summary; qM, every month; SC, subcutaneous; SF-12, Short Form (12-item) Health Survey, OLE, Open Label Extension.

Demographics and Baseline Characteristics of AHP Patients

Characteristic	Placebo (N=46)	Givosiran (N=48)
Age, years, median (range)	36 (20, 60)	42 (19, 65)
Female, n (%)	41 (89%)	43 (90%)
Race, n (%)		
White/Caucasian	34 (74%)	39 (81%)
Asian	7 (15%)	8 (17%)
Other	5 (11%)	1 (2%)
Age at diagnosis, years, median (range)	29 (17, 51)	30 (5, 58)
AHP type		
AIP	43 (94%)	46 (96%)
HCP	0	1 (2%)
VP	1 (2%)	1 (2%)
AHP without identified mutation	2 (4%)	0
Region, n (%)		
North America	18 (39%)	16 (33%)
Europe	19 (41%)	23 (48%)
Other	9 (20%)	9 (19%)

Baseline Disease Characteristics and Comorbidities of AHP Patients

- Patients with median of 3 composite attacks during the 6 months prior to screening
- 40% of patients were on hemin prophylaxis prior to study
- ~50% of patients experienced chronic symptoms between attacks
- Comorbidities included liver disease, chronic kidney disease, neuropathy, and iron overload

Baseline Disease Characteristics in Patients with AHP	Placebo (N=46)	Givosiran (N=48)
Porphyria attacks ^a in past 6 months, median (range)	3 (0, 25)	4.0 (2, 24)
Prior hemin prophylaxis therapy, n (%)	18 (39)	20 (42)
Used opioids daily or most days in between attacks, n (%)	13 (28)	14 (29)
Daily chronic symptoms between attacks, n (%)	26 (57)	23 (48)
Current or prior central venous catheter, n (%)	32 (70)	35 (73)
Ever diagnosed with neuropathy, n (%)	16 (35)	20 (42)
Ever diagnosed with iron overload, n (%)	15 (33)	16 (33)
Liver transaminase elevation >ULN ^b , n (%)	3 (7)	13 (27)
eGFR <60 mL/min/1.73 m ² , n (%)	11 (24)	16 (33)

^aProtocol qualifying attacks: ≥2 attacks in past 6 months requiring hospitalization, urgent healthcare visit, or IV hemin at home

^bWorst study value of ALT or AST prior to dosing: >ULN and ≤3xULN

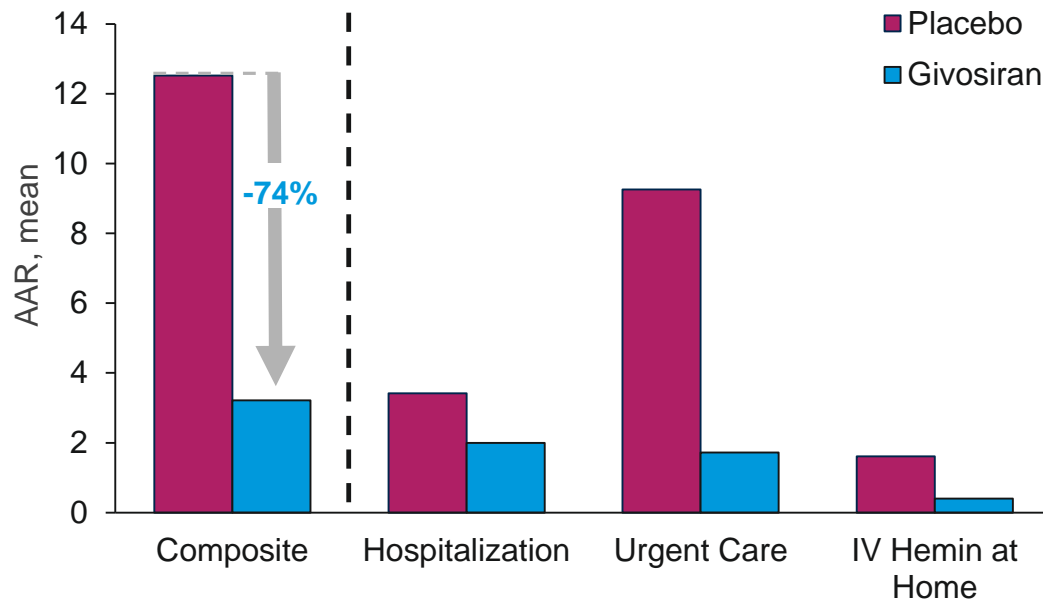
GFR, Glomerular Filtration Rate; mL, ULN, Upper Limit of Normal.; ALT, alanine aminotransferase; AST, aspartate transaminase; ULN, upper limit of normal

Balwani et al. Presented at the International Liver Congress, April 2019

Primary Efficacy Endpoint: Annualized Attack Rate (AAR) in Patients with AIP

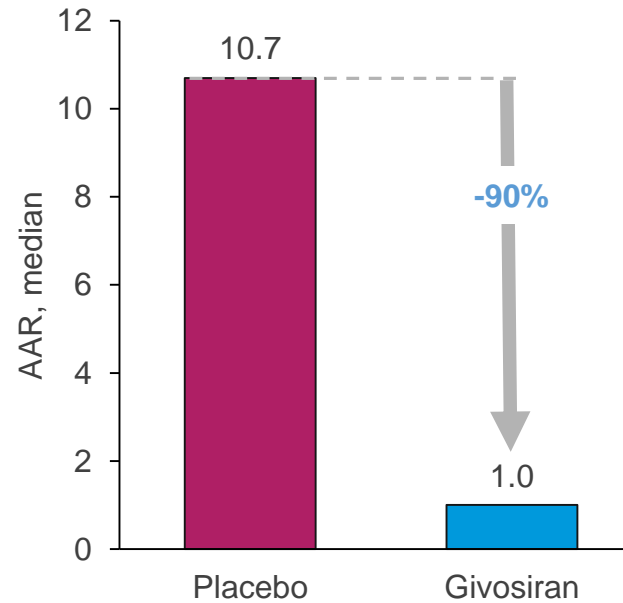
Primary Endpoint	Givosiran (N=46)	Placebo (N=43)	Rate Ratio (95% CI) (givosiran vs placebo)	P-Value
Composite AAR, mean (95% CI)	3.2 (2.25, 4.59)	12.5 (9.35, 16.76)	0.26 (0.16, 0.41)	6.04 × 10 ⁻⁹

Composite and all endpoint components reduced

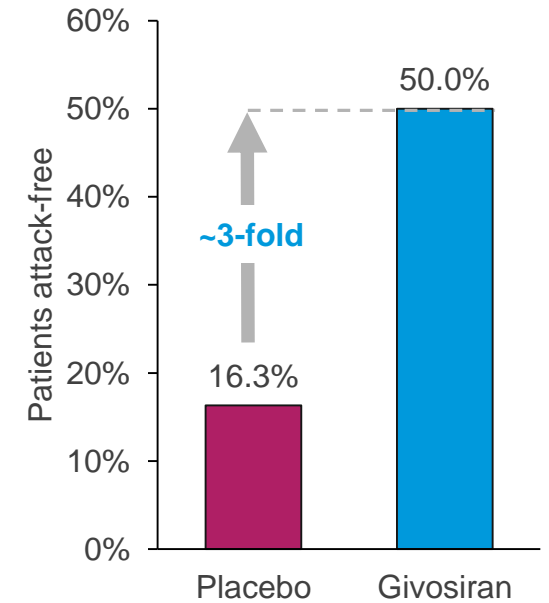


Component by Treatment Setting

Reduction in median composite attack rate

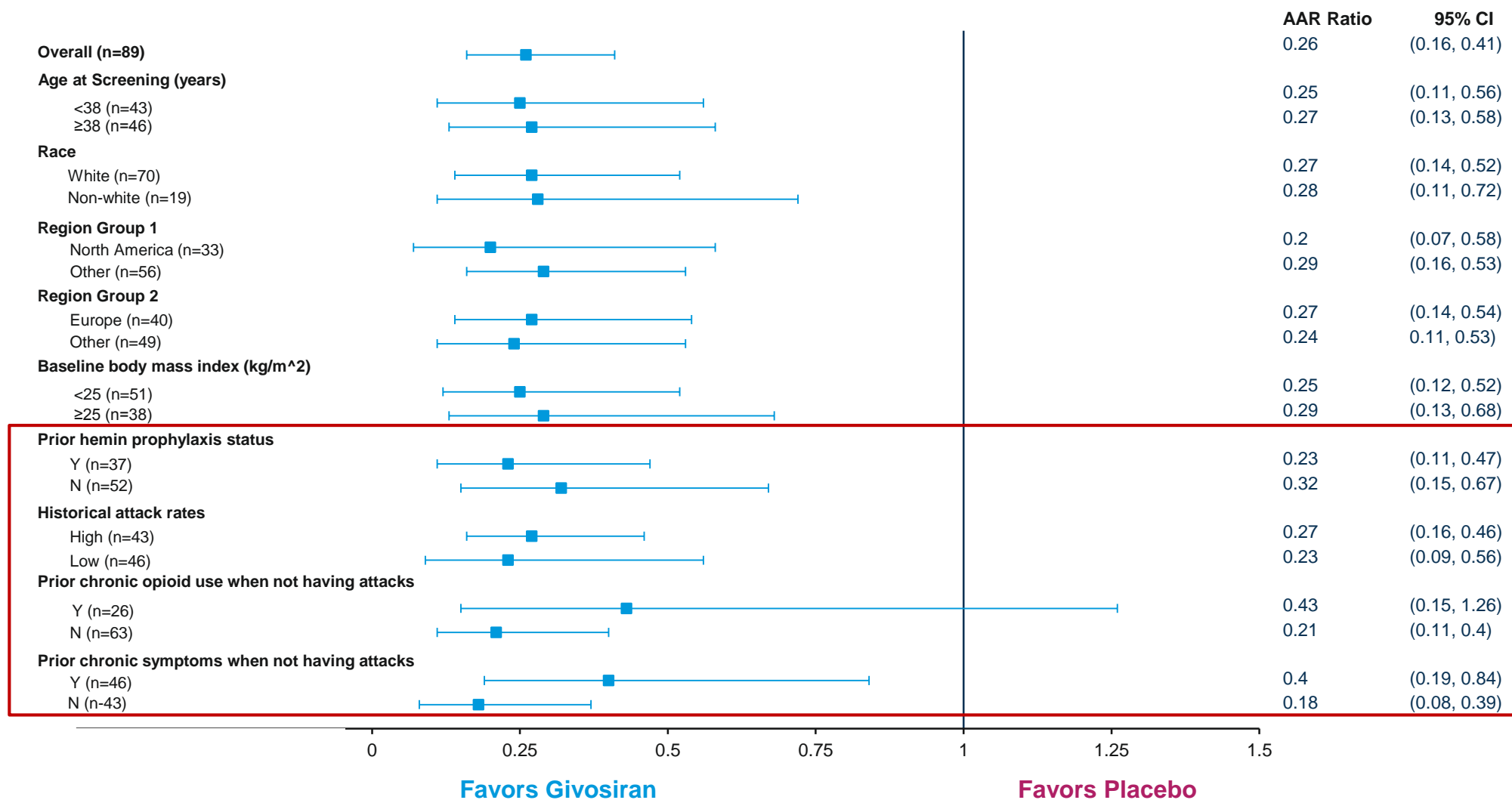


Increase in patients attack-free



AAR in AIP Patients: Pre-Specified Subgroup Analysis

Treatment with givosiran was favored compared to placebo across all subgroups



Secondary Efficacy Endpoints

Givosiran demonstrated statistically significant differences in multiple secondary endpoints

Secondary Endpoints [†]	Placebo (N = 43/46 [‡])	Givosiran (N = 46/48 [‡])	Treatment Difference (95% CI)	P-Value
LS Mean ALA in AIP at Month 3, mmol/mol Cr	19.96	1.75	-18 (-22.3, -14.2)	8.74 x 10 ⁻¹⁴
LS Mean ALA in AIP at Month 6, mmol/mol Cr	23.15	4.01	-19 (-26.0, -12.2)	6.24 x 10 ⁻⁷
LS Mean PBG in AIP at Month 6, mmol/mol Cr	49.11	12.9	-36 (-49.7, -22.7)	8.80 x 10 ⁻⁷
Mean Annualized days on hemin in AIP	29.71	6.77	0.23 (0.11, 0.45)	2.36 x 10 ⁻⁵
Mean Composite Attack Rate in AHP	12.26	3.35	0.27 (0.17, 0.43)	1.36 x 10 ⁻⁸
Daily worst pain in AIP (AUC of change from baseline)**	-0.196	-12.876	-12.680 (-25.526, 0.166)	0.0530 (ANCOVA)* 0.0455 (Wilcoxon)
Daily worst fatigue in AIP (AUC of change from baseline)**	-4.208	-11.148	-6.940 (-19.837, 5.957)	0.2876
Daily worst nausea in AIP (AUC of change from baseline)**	-4.011	1.481	5.492 (-4.000, 14.984)	0.2532
PCS of SF-12 change from baseline in AIP***	1.431	5.369	3.939 (0.592, 7.285)	0.0216

Statistical significance in pre-specified hierarchical testing met



[†] Treatment differences are based on estimated LS mean difference (givosiran – placebo) with the exception of annualized days on hemin and Composite Attack Rate endpoints, for which annualized rates are estimated and the treatment differences are measured by risk ratio (givosiran/placebo)

[‡] N=46 for placebo and N=48 for givosiran for Composite Attack Rate in AHP endpoint

* Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method

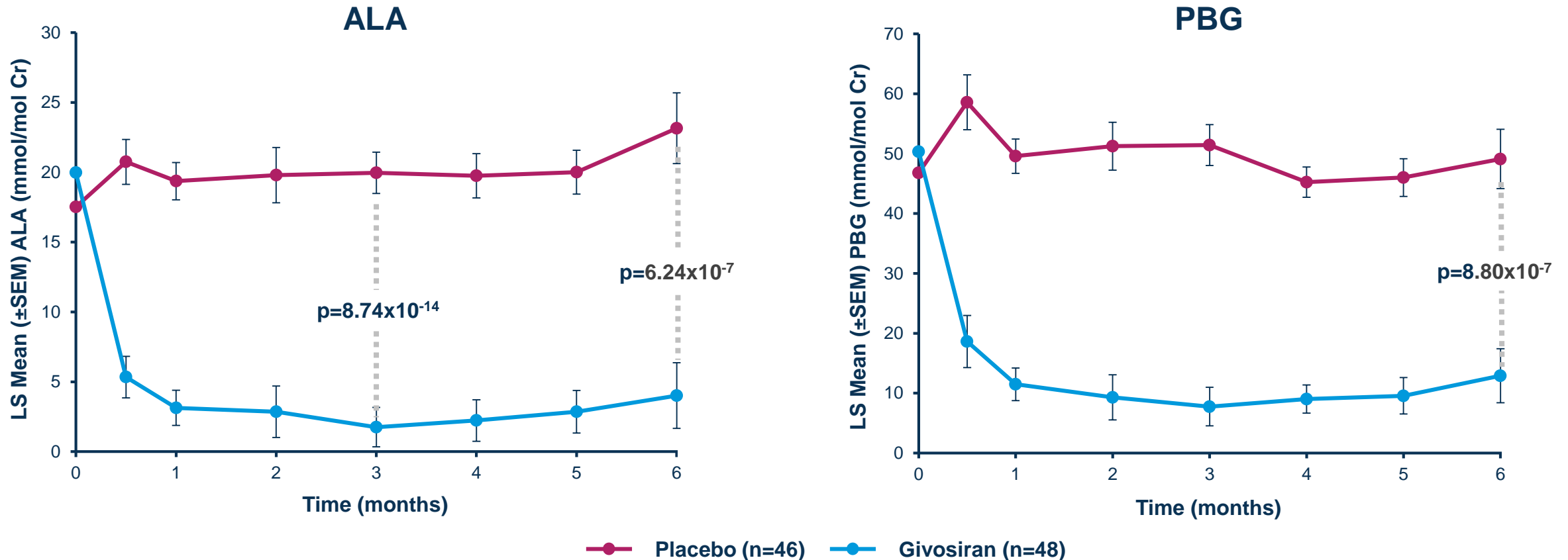
** A higher score indicates worse manifestation; *** A higher score indicates better physical health and functioning

Cr, creatinine; PCS, Physical Component Summary; SF-12, Short Form 12.

Balwani et al. Presented at the International Liver Congress, April 2019

ALA and PBG Levels in AIP Patients

- Givosiran showed rapid, robust, and sustained reductions in urinary ALA and PBG over six months
- Mean ALA and PBG were reduced by 77% and 76%, respectively, compared with baseline at 6 months
- Median ALA and PBG were reduced by 86% and 91%, respectively, compared with baseline at 6 months



Summary of Adverse Events in AHP Patients

Adverse Event, n of patients (%)	Placebo (N=46)	Givosiran (N=48)
At least 1 adverse event (AE)	37 (80.4)	43 (89.6)
At least 1 serious adverse event (SAE)	4 (8.7)	10 (20.8)
At least 1 severe AE	5 (10.9)	8 (16.7)
At least 1 AE leading to treatment discontinuation	0	1 (2.1)
Deaths	0	0

- All patients completed the 6-month double blind period
- 1 patient discontinued givosiran for an ALT elevation meeting protocol stopping rules

Serious Adverse Events in AHP Patients

Serious Adverse Event*, n of patients (%)	Placebo (N=46)	Givosiran (N=48)
Chronic kidney disease	0	2 (4.2)
Asthma	0	1 (2.1)
Device related infection	2 (4.3)	1 (2.1)
Gastroenteritis	0	1 (2.1)
Hypoglycaemia	0	1 (2.1)
Liver function test abnormal	0	1 (2.1)
Major depression	0	1 (2.1)
Pain management	0	1 (2.1)
Pyrexia	1 (2.2)	1 (2.1)
Escherichia urinary tract infection	1 (2.2)	0
Fractured sacrum	1 (2.2)	0
Sepsis	1 (2.2)	0
Septic shock	1 (2.2)	0

- Two SAEs in givosiran patients reported as study drug related: 1 abnormal liver function test, and 1 chronic kidney disease; no SAEs in placebo patients reported as study drug related
- Two chronic kidney disease AEs considered serious due to elective hospitalization for diagnostic evaluation; renal biopsies consistent with underlying disease. No signs of immune complex or primary glomerular renal disorders

Common Adverse Events ($\geq 5\%$ difference in treatment groups)

Category, n (%) / number events	Placebo (N=46)	Givosiran (N=48)
AEs with Higher Frequency in the Givosiran Group		
Injection site reaction	0	8 (16.7)/15
Nausea	5 (10.9)/6	13 (27.1)/15
Chronic kidney disease	0	5 (10.4)/5
Glomerular filtration rate decreased	0	3 (6.3)/3
Rash	0	3 (6.3)/3
Alanine aminotransferase increased	1 (2.2)/1	4 (8.3)/6
Fatigue	2 (4.3)/2	5 (10.4)/6
AEs with Higher Frequency in the Placebo Group		
Pyrexia	6 (13.0)/7	1 (2.1)/3
Hypoaesthesia	4 (8.7)/5	0
Dyspepsia	4 (8.7)/4	0
Vomiting	5 (10.9)/5	2 (4.2)/5
Urinary tract infection	6 (13.0)/6	3 (6.3)/4
Back pain	4 (8.7)/4	1 (2.1)/1

AE, Adverse Event

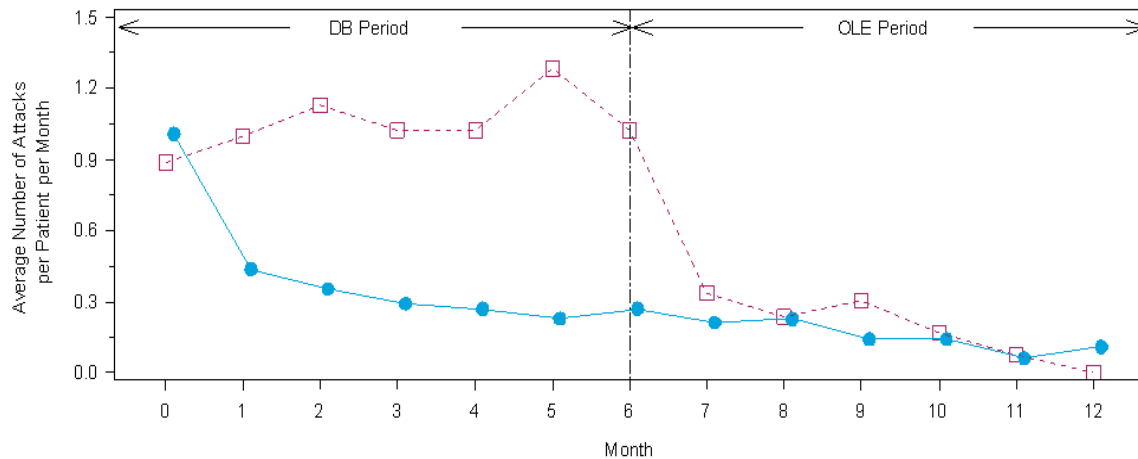
Impact of Givosiran on Transaminases and Renal Function

- ALT > 3x ULN in 7 (14.6%) givosiran patients and 1 (2.2%) placebo patient
 - 1 givosiran patient discontinued due to a protocol-defined stopping rule of ALT >8x ULN
 - 1 givosiran patient had dose interrupted due to a protocol-specified rule, with resumption at 1.25 mg/kg
 - 5 patients had resolution with ongoing givosiran dosing
 - No Hy's Law cases
- ALT elevations were mild to moderate, occurred ~3 to 5 months after givosiran started, and resolved or stabilized by Month 6
- 7 (15%) givosiran patients and 2 (4.3%) placebo patients had renal AEs of increased creatinine and/or decreased eGFR, including 5 AEs of CKD in givosiran patients
 - Most AEs were mild to moderate in severity and resolved without treatment interruption
- Generally small increases in serum creatinine (median change 0.07 mg/dL at Month 3) and decreases in eGFR with givosiran that resolved or stabilized by Month 6

Open-Label Extension (OLE) Period

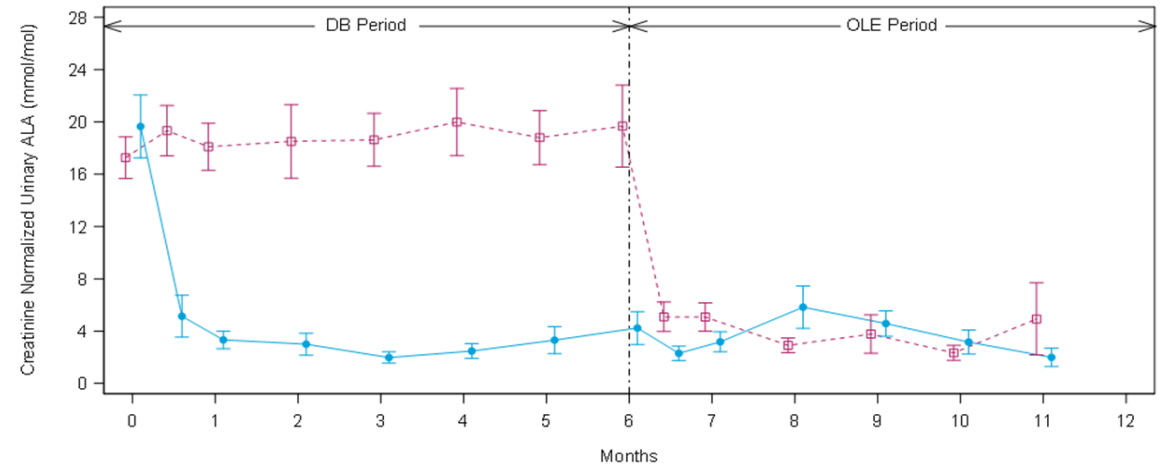
- Maintenance of reduction of composite porphyria attack rate and urinary ALA levels in AHP patients who continued on givosiran during OLE period (blue line)
- Rapid and sustained lowering of composite porphyria attack rate and ALA levels in placebo AHP patients who crossed over to givosiran in the OLE period (red line)
- Safety profile consistent with observed profile in DB period

Monthly Attack Rate



No. of Patients:	Placebo (N=46)						Givosiran (N=48)					
Placebo	46	46	46	46	46	46	48	48	48	48	48	48
Givosiran	46	46	46	46	46	46	47	38	26	18	13	7

Urinary ALA



No. of Patients:	Placebo (N=46)						Givosiran (N=48)					
Placebo	46	42	44	42	45	39	44	41	40	36	26	19
Givosiran	48	47	47	48	47	45	44	46	33	33	27	20

ENVISION Phase 3 Study Summary

- Givosiran resulted in a 74% mean reduction in annualized composite rate of porphyria attacks in AIP patients relative to placebo
 - Corresponding 90% reduction in median AAR, with 50% of patients on givosiran attack-free (16.3% for placebo)
 - All components of composite attacks reduced and all subgroup analyses favored givosiran
 - 73% reduction in mean AAR in patients with any AHP relative to placebo
- Givosiran resulted in a mean reduction in days of hemin use of 77% compared to placebo
- Givosiran led to sustained lowering from baseline of ALA (86%) and PBG (91%), the toxic heme intermediates causal for attacks and other AHP disease manifestations
- Overall safety and tolerability profile acceptable in AHP, a serious illness
 - Majority of ALT elevations were mild to moderate, occurred ~3 to 5 months after givosiran started, and resolved or stabilized by Month 6
 - ALT > 3x ULN in 7 (14.6%) givosiran patients and 1 (2.2%) placebo patient.
 - 7 (15%) givosiran patients and 2 (4.3%) placebo patients had renal AEs of increased creatinine and/or decreased eGFR, including 5 AEs of CKD in givosiran patients
 - Generally small increases in serum creatinine (median change 0.07 mg/dL at Month 3) and decreases in eGFR with givosiran that resolved or stabilized by Month 6
- OLE data to-date support maintenance of reduction in composite AAR and urinary ALA levels, with a consistent safety profile

Additional ENVISION Results

Patient Reported Outcomes and other Data Presented at ICPP 2019

- Gouya et al. – “ENVISION, a Phase 3 Study to Evaluate the Efficacy and Safety of Givosiran, an Investigational RNAi Therapeutic Targeting Aminolevulinic Acid Synthase 1, in Acute Hepatic Porphyria Patients”
- Sardh et al. – “Overall Health, Daily Functioning, and Quality of Life in Patients with Acute Hepatic Porphyria: ENVISION, a Phase 3 Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial”
- Balwani et al. – “Disease Characteristics of Patients with Acute Hepatic Porphyria Patients: ENVISION, a Phase 3 Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial”
- Bonkovsky et al. – “A Phase 1/2 Open-Label Extension Study of Givosiran, an Investigational RNAi Therapeutic, in Patients with Acute Intermittent Porphyria”
- Anderson et al. – “Acute Hepatic Porphyria (AHP) Disease Manifestations and Daily Life Impacts in EXPLORE International Prospective, Natural History Study”
- Gill et al. – “Burden of Illness in Acute Hepatic Porphyria (AHP): Insights from Patient and Caregiver Members of the British Porphyria Association”
- Gill et al. – “The Evolving Diagnosis and Care of Patients with Acute Hepatic Porphyria (AHP) in the UK: from 2006 to 2018”
- Vassiliou et al. – “A Drug-Drug Interaction Study to Investigate the Effect of Givosiran on the Activity of 5 Major Drug Metabolizing CYP450 Enzymes in Subjects with Acute Intermittent Porphyria (AIP) who are Chronic High Excretors (CHE)”

These results can be found on the Capella section of the Company’s website, www.alnylam.com/capella.

Agenda

Welcome

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

Introduction

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

Acute Hepatic Porphyria & Physician Perspective

- Srikanth Nagalla, M.D., M.S. – Associate Professor of Internal Medicine, Medical Director of Blood Disorders Clinic, Program Director of Hematology/Oncology Fellowship, UT Southwestern Medical Center

ENVISION Phase 3 Results

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

Opportunity in Acute Hepatic Porphyria & Disease/Diagnostic Education Efforts

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

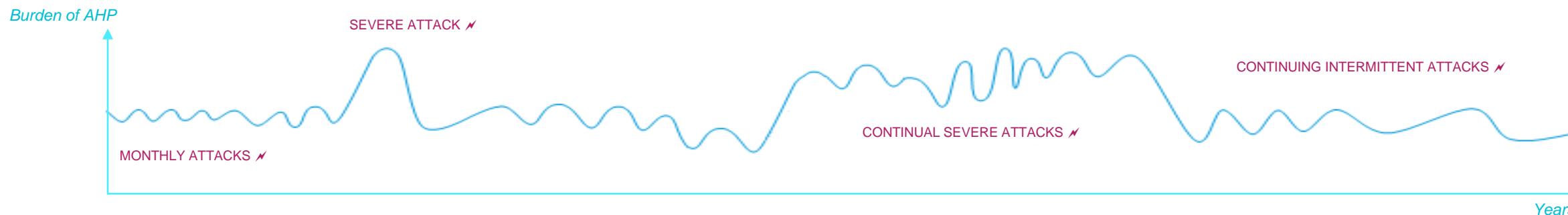
Q&A Session

Acute Hepatic Porphyrria

Unpredictable Nature of AHP Places Burden on Patients

- Patients are frequently misdiagnosed (e.g., non-specific abdominal pain, fibromyalgia, depression, endometriosis) and undergo potentially unnecessary surgeries (e.g., cholecystectomy, appendectomy, hysterectomy)^{1,2,5}
- Frequent healthcare utilization, reduced quality of life, and reduced employment all contribute to disease burden^{3,4}
- Unpredictable nature of attacks is a source of fear and anxiety for patients

Illustrative Patient Experience with AHP



- In the words of patients

“The pain is all consuming. I mean it's like someone is holding, squeezing, stabbing. You're not able to function. You can't do anything, you just want to die...”

-AHP Patient

“Before my first porphyria attack...I was active, dynamic, and cheerful...now, after the porphyria attack, the various attacks...I have unfortunately become tired, scared and lost.”

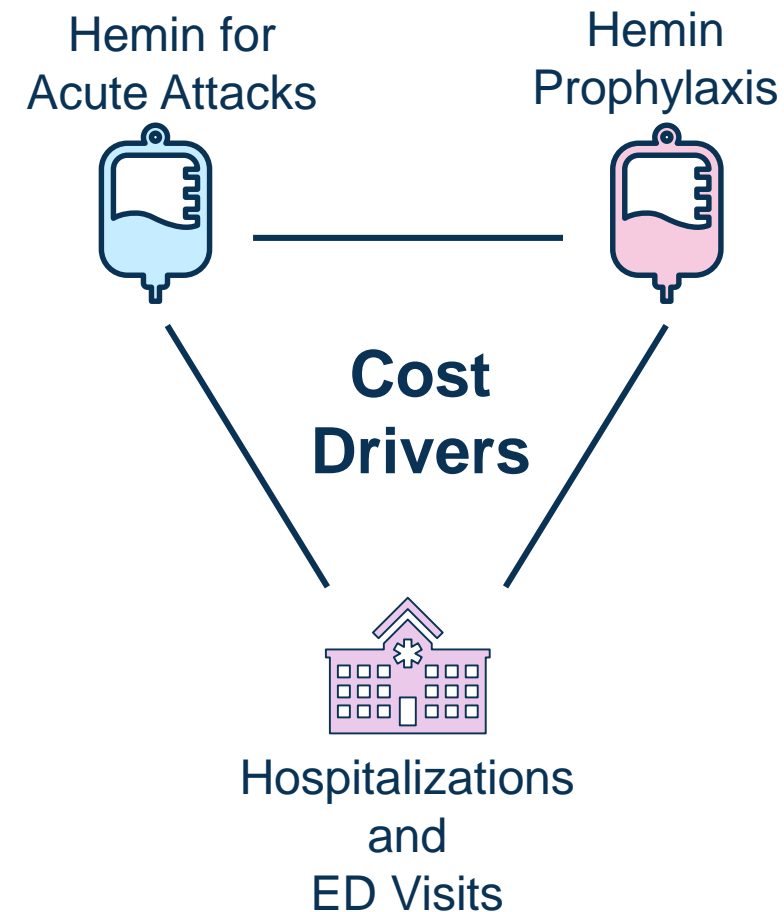
-AHP Patient

Healthcare Expenditure in EXPLORE Study

Patients with AHP Experiencing Attacks

Average Annual Healthcare Expenditure

Healthcare Category	Avg. Annual Cost Per Patient (\$)
PCP visits	443
Specialist visits	1,203
Hemin administration*	3,282
Hemin for acute attacks	141,738
Hemin prophylaxis (off-label) [†]	148,145
ED visits	3,753
Overnight Hospitalizations [‡]	100,078 (costs)/ 356,853 (charges)
Total with hospital costs, mean (95% CI)	398,463 (328,303–475,477)
Total with hospital charges, mean (95% CI)	655,418 (482,278–847,448)



*Hemin administration costs were calculated for both acute and prophylaxis administration

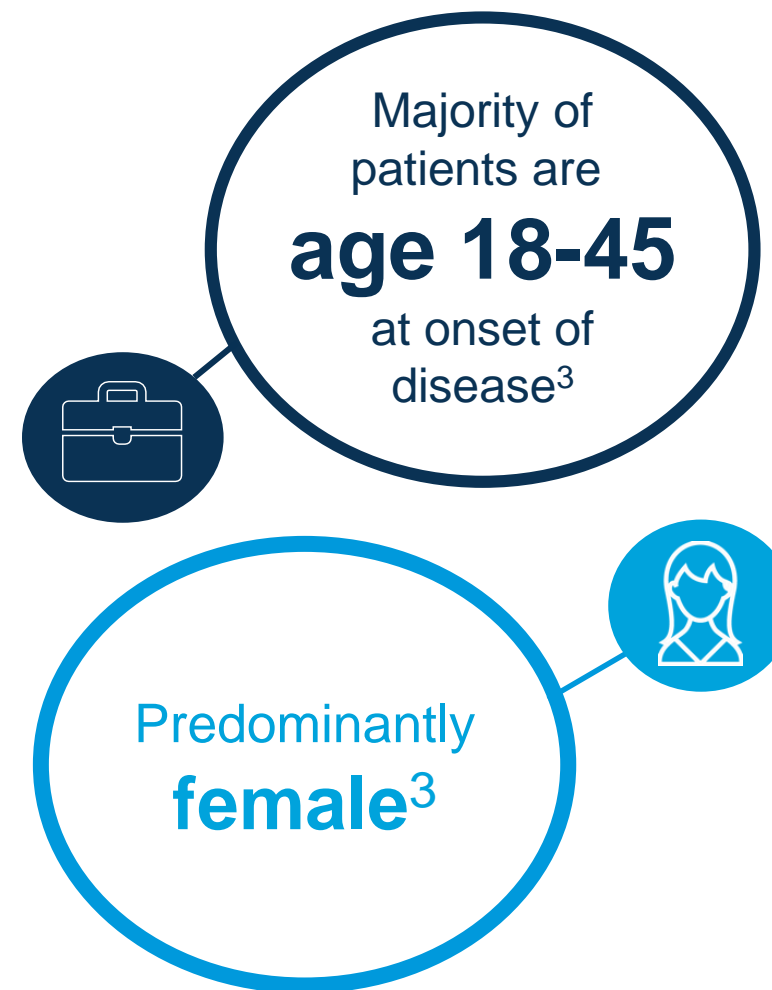
[†]Hemin prophylaxis was calculated as an average cost associated with hemin prophylaxis regimens observed in EXPLORE, inclusive of patients not receiving hemin prophylaxis

[‡]Hospitalization charges (amount billed) and costs (amount paid) from published data sources in the US

AHP Patient Population

Rare disease disproportionately impacting female patients of working and childbearing age

- Consensus estimated global prevalence of 2-5 per 100,000¹
- Estimated ~1,000 severely affected patients with recurrent attacks in US/EU²
- Many more estimated to have sporadic attacks (~5,000 patients in US/EU²) and yet additional patients may have chronic symptoms and impaired quality of life
- AHP are challenging to diagnose, and most patients with active disease currently remain undiagnosed
 - Internal estimates of ~3,000 patients with active disease currently diagnosed in US/EU, with ~1,000 in urgent need with frequent attacks



1. Anderson KE, Metabolic & Molecular Bases of Inherited Disease, 2001

2. ORPHANET; The Porphyria Consortium

3. Bissell DM et al. N Engl J Med. 2017;377:862-872

Often a Long, Frustrating Journey to Diagnosis

Patients May Remain Undiagnosed for up to 15 Years



**Multiple
Hospitalizations**



Unnecessary Surgeries



Misdiagnoses

Increasing AHP Awareness

Education Initiatives Tailored to Physician and Patient Communities

Porphyria Diagnosis

ABOUT AHPs SYMPTOMS OF AHPs DIAGNOSING AHPs TESTING FOR AHPs

Acute Hepatic Porphyrias (AHPs): Guide Your Patients to a Clear Diagnosis

AHPs often feature chronic, debilitating symptoms punctuated by acute, potentially life-threatening exacerbations. They may inflict years of suffering and impaired quality of life. The symptoms of AHPs can often resemble those of other more common conditions such as irritable bowel syndrome (IBS), fibromyalgia, and endometriosis, and consequently, patients afflicted with AHPs are often misdiagnosed or remain undiagnosed for an average of 15 years.

Guide your patients to a clear AHPs diagnosis by learning to detect the signs and symptoms below.

Pinpoint™ AHP Acute Hepatic Porphyria

For Healthcare Professionals Sign Up

About AHP Diagnosing AHP Living With AHP Resources

It started with nausea, vomiting, and fainting.

I was treated for ulcerative colitis.

Then endometriosis and depression.

They said it was all in my head.

It's not.

COULD IT BE ACUTE HEPATIC PORPHYRIA (AHP)?

Alnylam Act[®] - Acute Hepatic Porphyria

No-Charge, Third-Party Genetic Testing and Counseling Program

305

*participating
HCP accounts*

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

519

*samples
submitted*

Tests and services are performed by independent third parties

55

*positive AHP
mutations*

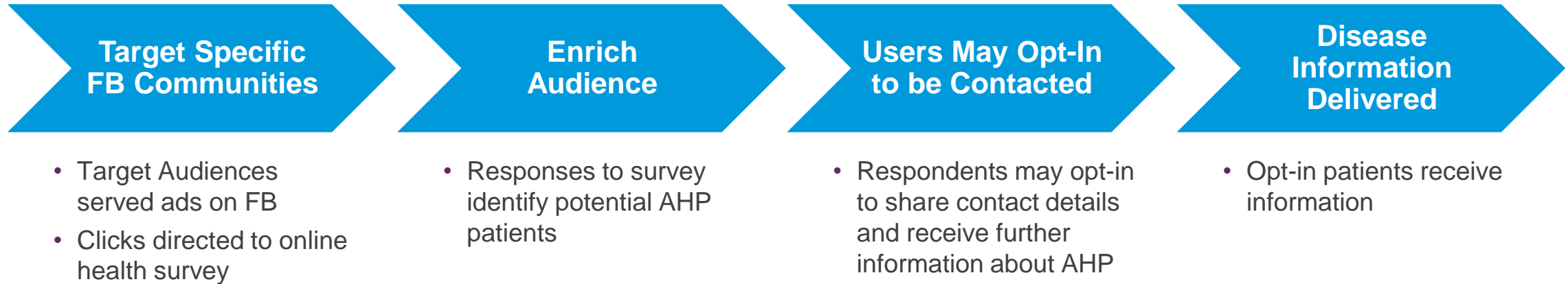
Available in U.S. and Canada (genetic counseling service available in U.S.)

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

Reaching an Enriched Audience via Social Media

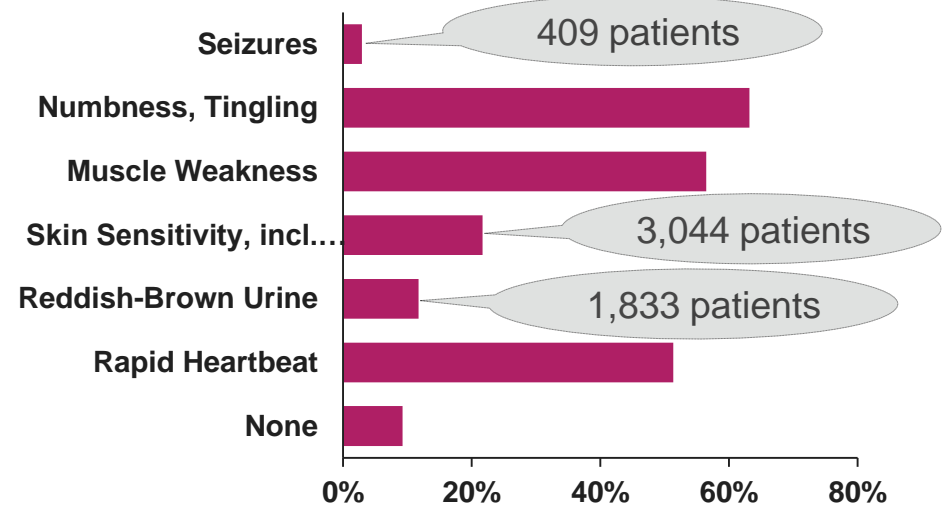
Effort with Facebook Communities Ongoing



Roughly 17,000 individuals have completed the survey*

- 70% have had intense abdominal pain that required them to seek emergency or urgent medical care
 - 90% mention it reoccurred without proper diagnosis or treatment
 - 82% with constipation, 66% with nausea, 29% with vomiting

What other physical changes have you experienced since being exposed to this excruciating abdominal pain? (n=15,489)



Collaboration With Ironwood[®]

US Gastroenterologist Disease Awareness and Promotional Agreement

Rationale

- Gastroenterologists are one of the most frequently seen specialty group due to GI manifestations of AHP*
 - ~20% of AHP patients receive diagnosis from a gastroenterologist
 - Diagnosed patients typically see > 3 gastroenterologists during their journey
 - ~40% of AHP patients have received a prior diagnosis of IBS

Overview

- Ironwood will provide disease education to gastroenterologists to support accurate diagnosis of AHP patients
- If givosiran is approved, Ironwood clinical sales specialists will begin promotional efforts

Terms

- Ironwood receives fixed payments and, subject to regulatory approval of givosiran, royalties on net sales generated from prescriptions or referrals from certain HCPs related to Ironwood's promotional efforts
- Alnylam retains responsibility for all other aspects of givosiran, including global development and commercial rights

Status and Path Forward



Givosiran New Drug Application and Marketing Authorisation Application accepted for filing by FDA and EMA



Granted Priority Review by FDA

- Currently no plan to hold advisory committee meeting to discuss application



PDUFA date set for February 4, 2020 (US)



Potential additional approvals: in 2020 (EU) and in 2021+ (Japan and ROW)

THANK YOU!!



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Q&A Session

Upcoming RNAi Roundtables

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

- Thursday, October 10, 11:30am EST

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

SAVE THE DATE

Anylam R&D Day

Friday, November 22, 2019

Westin Times Square

New York City



CHALLENGE ACCEPTED



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

CHALLENGE ACCEPTED