

# 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

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# Acute Hepatic Porphyria (AHP)

## Disease Overview<sup>1,2</sup>

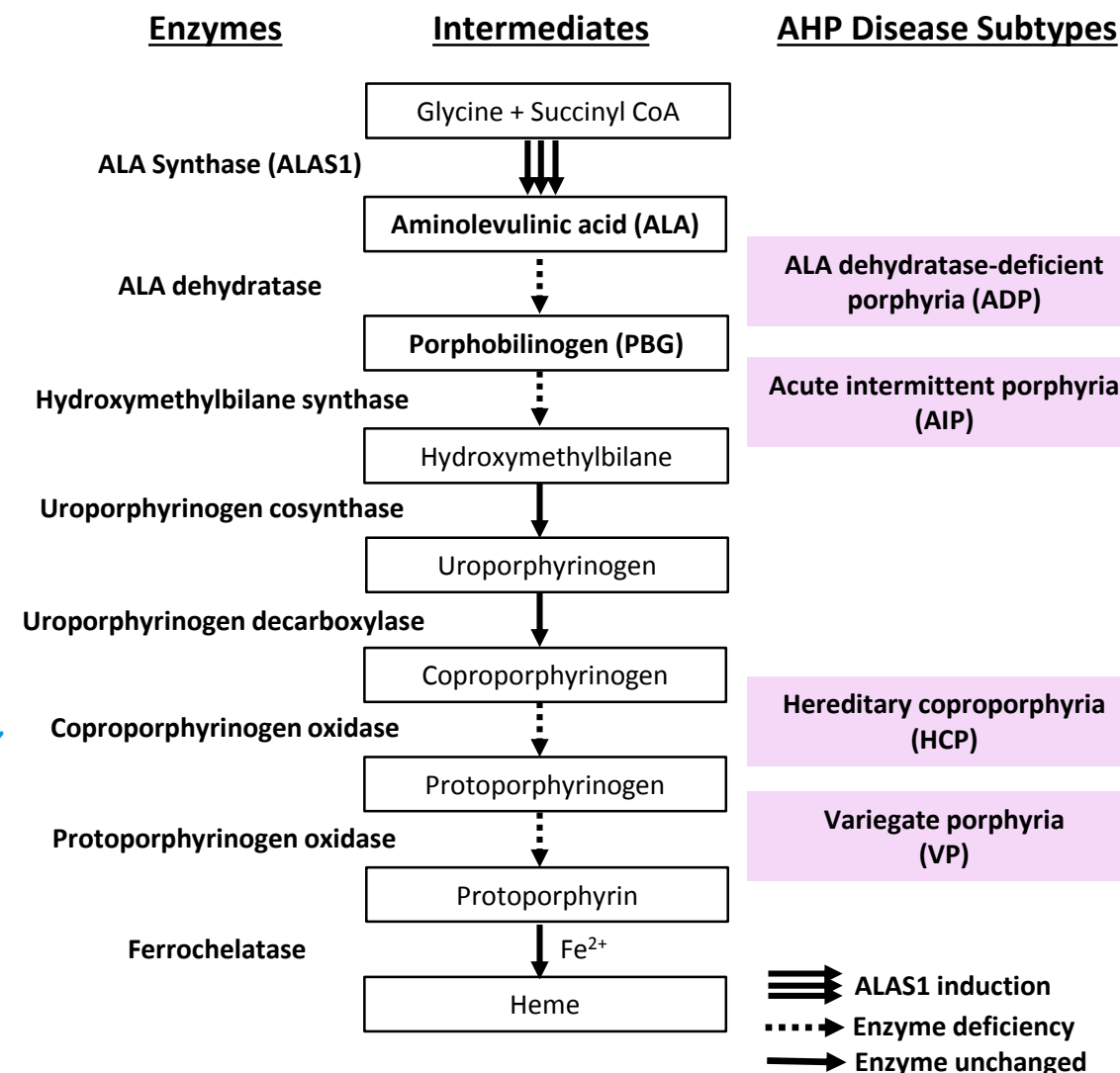
- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in liver
- Acute Intermittent Porphyria (AIP) most common, with mutation in hydroxymethylbilane synthase (HMBS)

## Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of neurotoxic heme intermediates ALA/PBG
- ALA believed to be primary neurotoxic intermediate that causes disease manifestations

## Attacks, Chronic Manifestations, and Comorbidities<sup>3-7</sup>

- Acute neurovisceral attacks can be life-threatening
- Chronic pain, fatigue, nausea, and anxiety
- Hypertension, chronic kidney disease and liver disease
- Disability and social isolation common

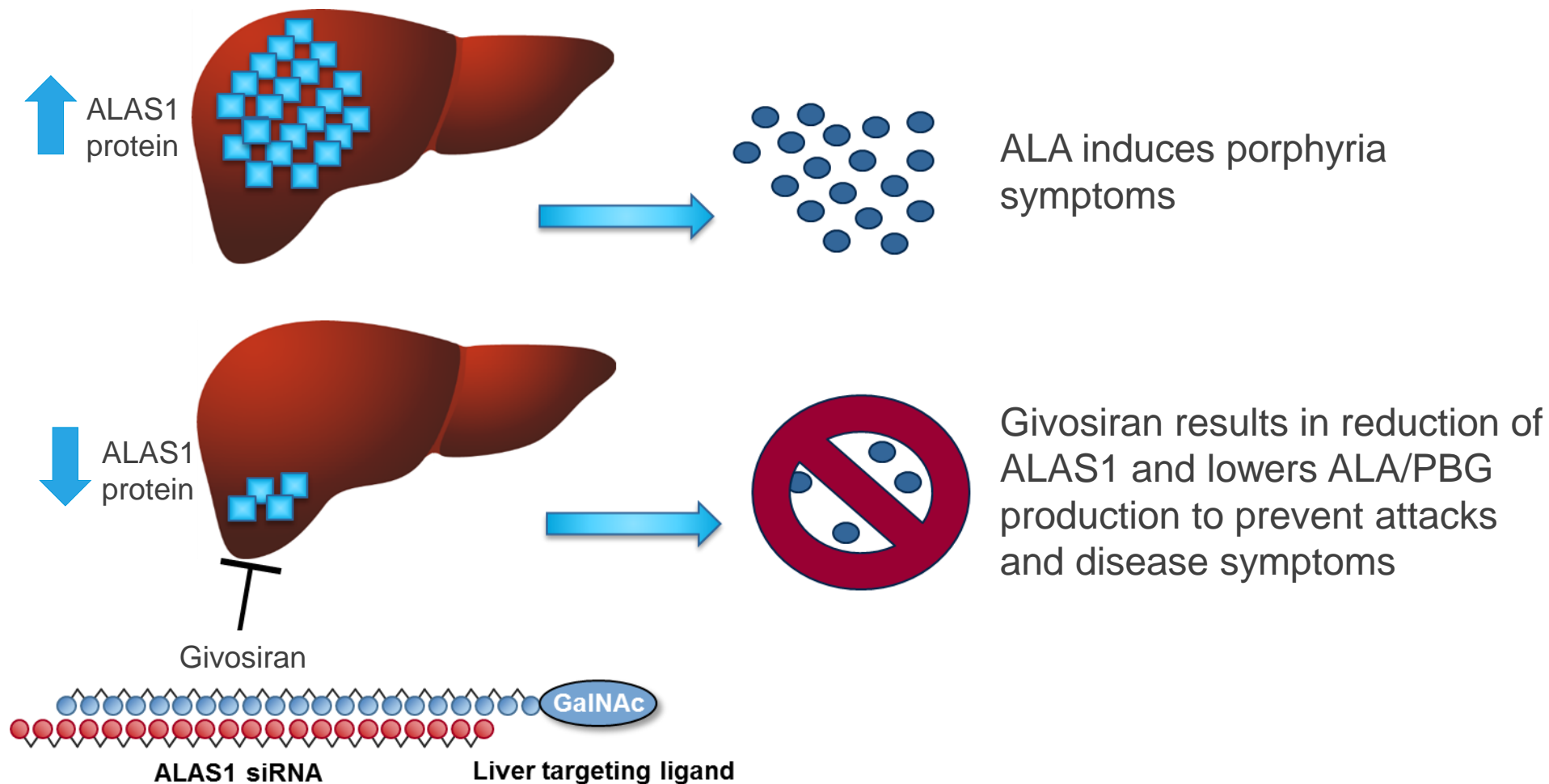


1. Bonkovsky, et al., Am J Med. 2014;127:1233-41; 2. Elder, et al., JIMD. 2013;36:849-57; 3 Pischik and Kauppinen. Appl Clin Genet. 2015;8:201-14. 4. Bonkovsky, et al., Poster. Presented at the American Association for the Study of Liver Diseases; November 9-13, 2018, San Francisco, CA, USA. 5. Stewart. J Clin Pathol. 2012;65:976-80. 6. Simon, et al., Patient. 2018;11:527-37. 7. Naik, et al., Mol Genet Metab. 2016;119:278-83.

# Givosiran: Investigational RNAi Therapeutic for AHP

## Therapeutic Hypothesis

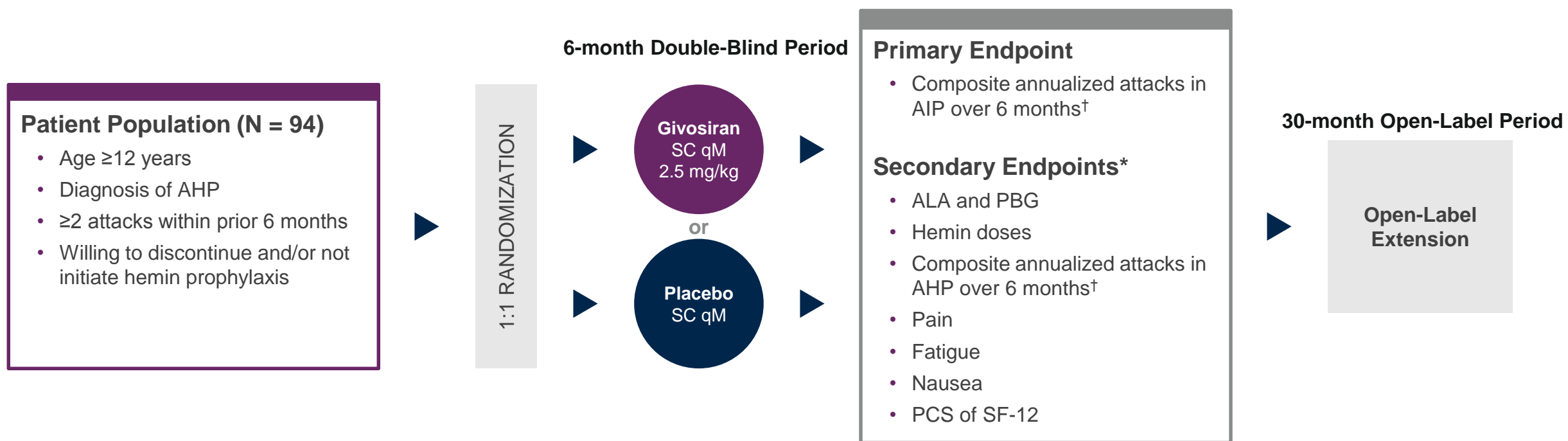
- Reduction of Liver ALAS1 Protein to Lower ALA and PBG



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

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

94 patients enrolled at 36 sites in 18 countries



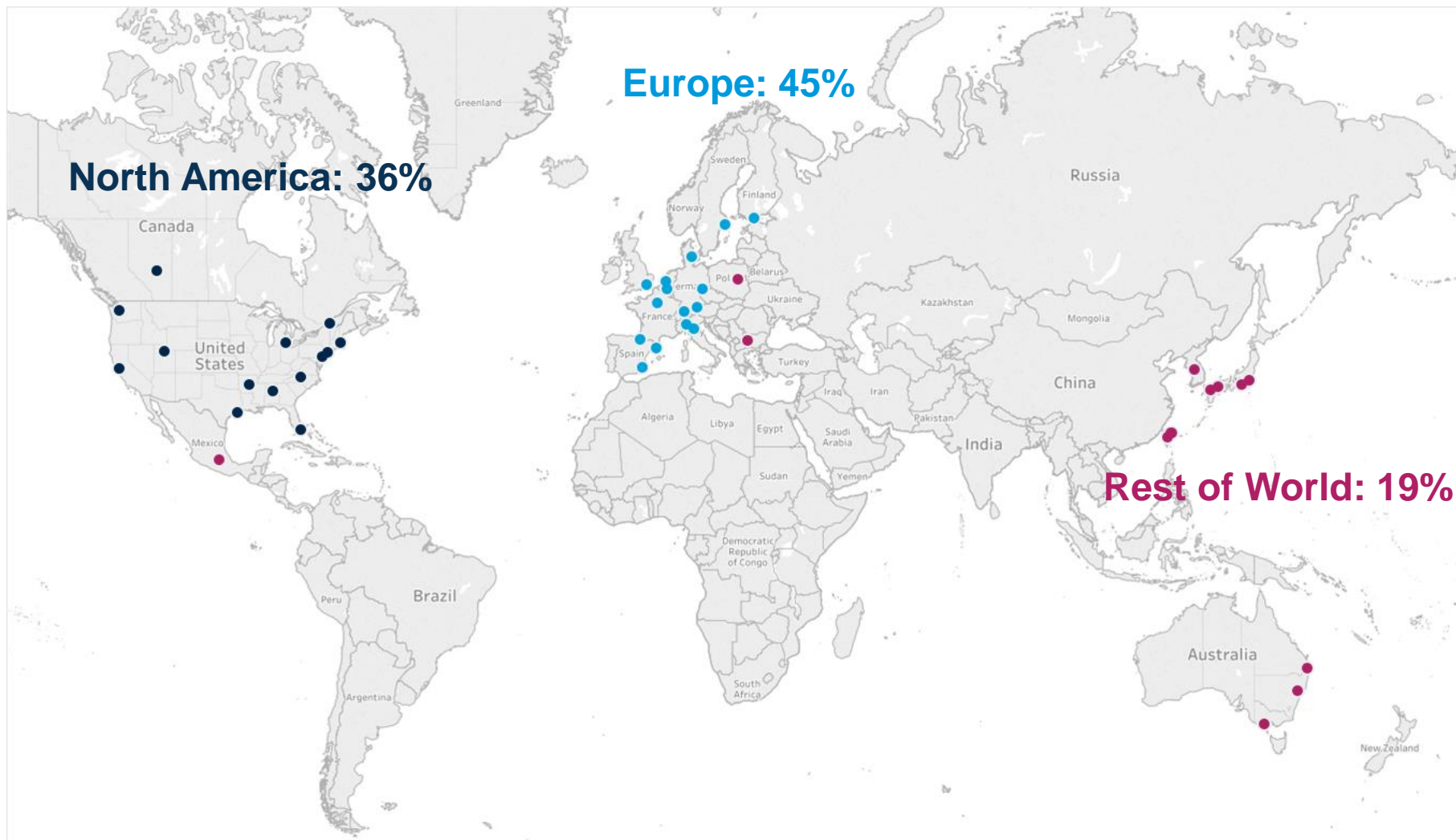
<sup>†</sup> Attacks requiring hospitalization, urgent healthcare visit, or hemin administration

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

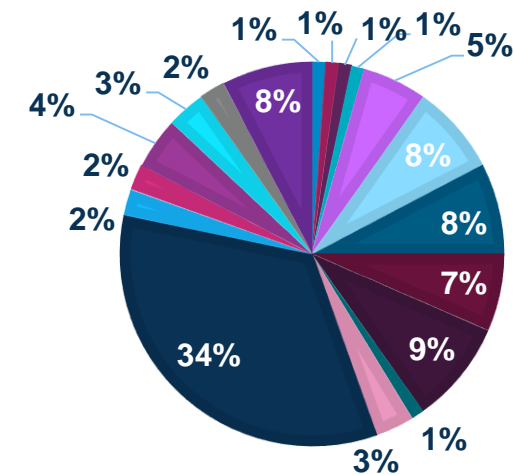
AHP, Acute Hepatic Porphyria; ALA, Aminolevulinic acid; kg, kilogram; mg, milligram; PBG, Porphobilinogen; PCS, Physical Component Summary; qM, every month; SC, subcutaneous; SF-12, Short Form 12.

# Study Enrollment

94 patients enrolled at 36 sites in 18 countries

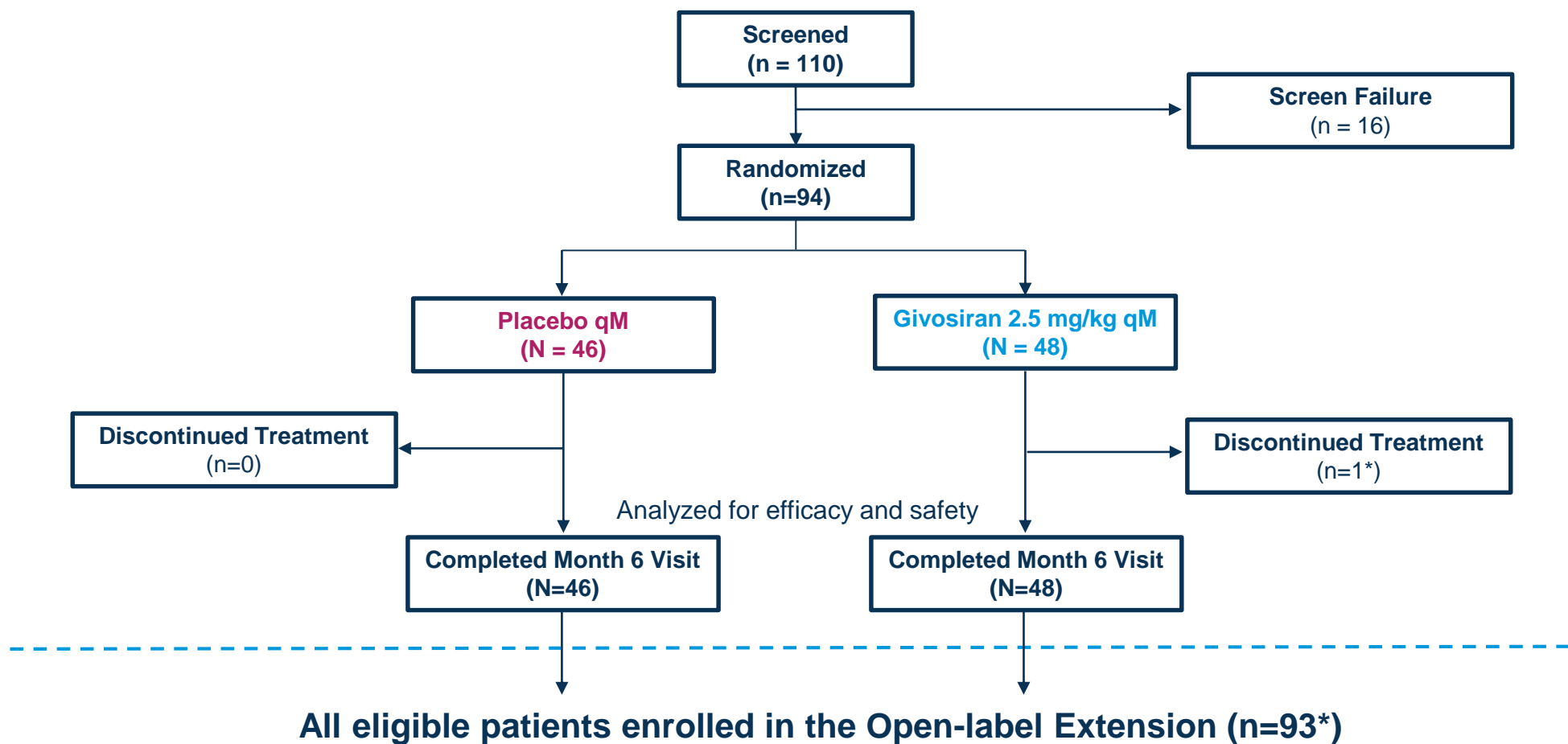


- Sweden
- Netherlands
- Germany
- Bulgaria
- Canada
- Japan
- Denmark
- UK
- Italy
- Poland
- Mexico
- Finland
- France
- Spain
- US
- Australia
- South Korea
- Taiwan



# Patient Disposition

## 6-Month Double-Blind Period



\*1 patient discontinued treatment due to ALT elevation (protocol stopping rule) but completed 6M DB visit

# Demographics and Baseline Characteristics

- Majority of patients were female and had AIP

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%)
Years since diagnosis, median (range)	6.11 (0.1, 38.5)	6.98 (0.2, 43.3)
AHP type		
AIP with mutation in the HMBS gene	43 (94%)	46 (96%)
HCP	0	1 (2%)
VP	1 (2%)	1 (2%)
AIP without identified mutation	2 (4%)	0

# Baseline Disease Characteristics and Comorbidities

- Patients with median of 4 composite attacks during the 6 months prior to randomization
- 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 AHP Patients	Placebo (N=46)	Givosiran (N=48)
Porphyria attacks* in past 6 months, median (range)	3.5 (0, 23)	4.0 (2, 17)
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), n (%)	3 (6.5)	13 (27)
Estimated GFR < 60 mL/min/1.73 m <sup>2</sup> , n (%)	11 (24)	16 (33)

\*Protocol qualifying attacks: ≥ 2 attacks in past 6mo requiring hospitalization, urgent healthcare visit or IV hemin at home

\*\*Worst study value prior to dosing of ALT or AST

GFR, Glomerular Filtration Rate; mL, ULN, Upper Limit of Normal.



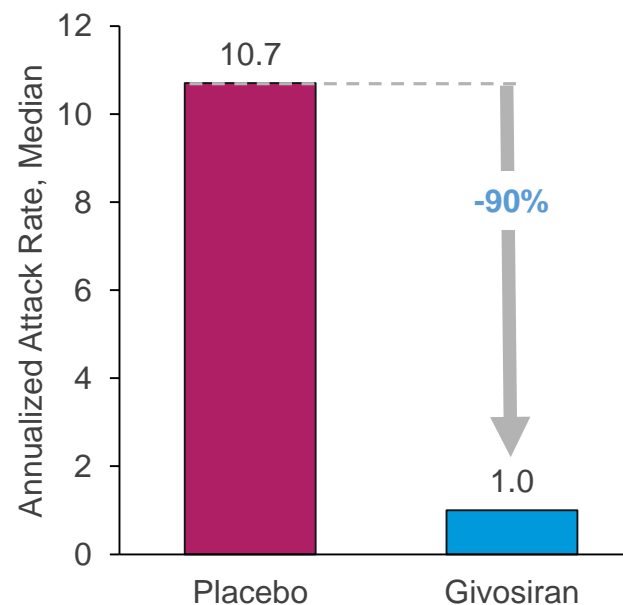
# Primary Efficacy Endpoint: Annualized Attacks in AIP

Primary Endpoint	Givosiran (N=46)	Placebo (N=43)	Rate Ratio (95% CI) (givosiran vs placebo)	P-Value
Composite Annualized Attack Rate, Mean	3.2 (2.25, 4.59)	12.5 (9.35, 16.76)	0.26 (0.16, 0.41)	6.04 x 10 <sup>-9</sup>

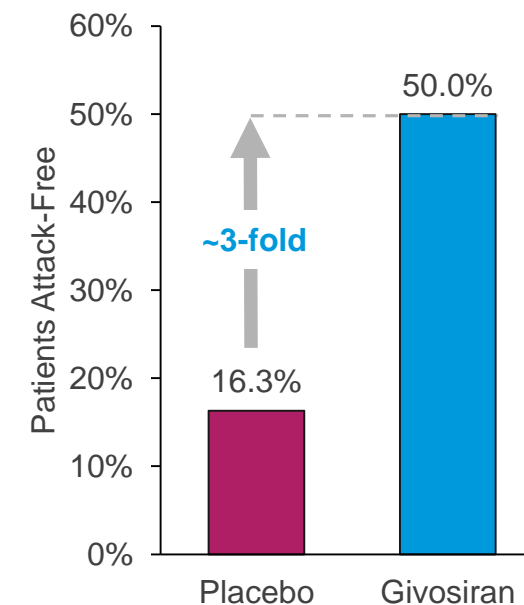
Composite and all endpoint components reduced



Reduction in median composite attack rate

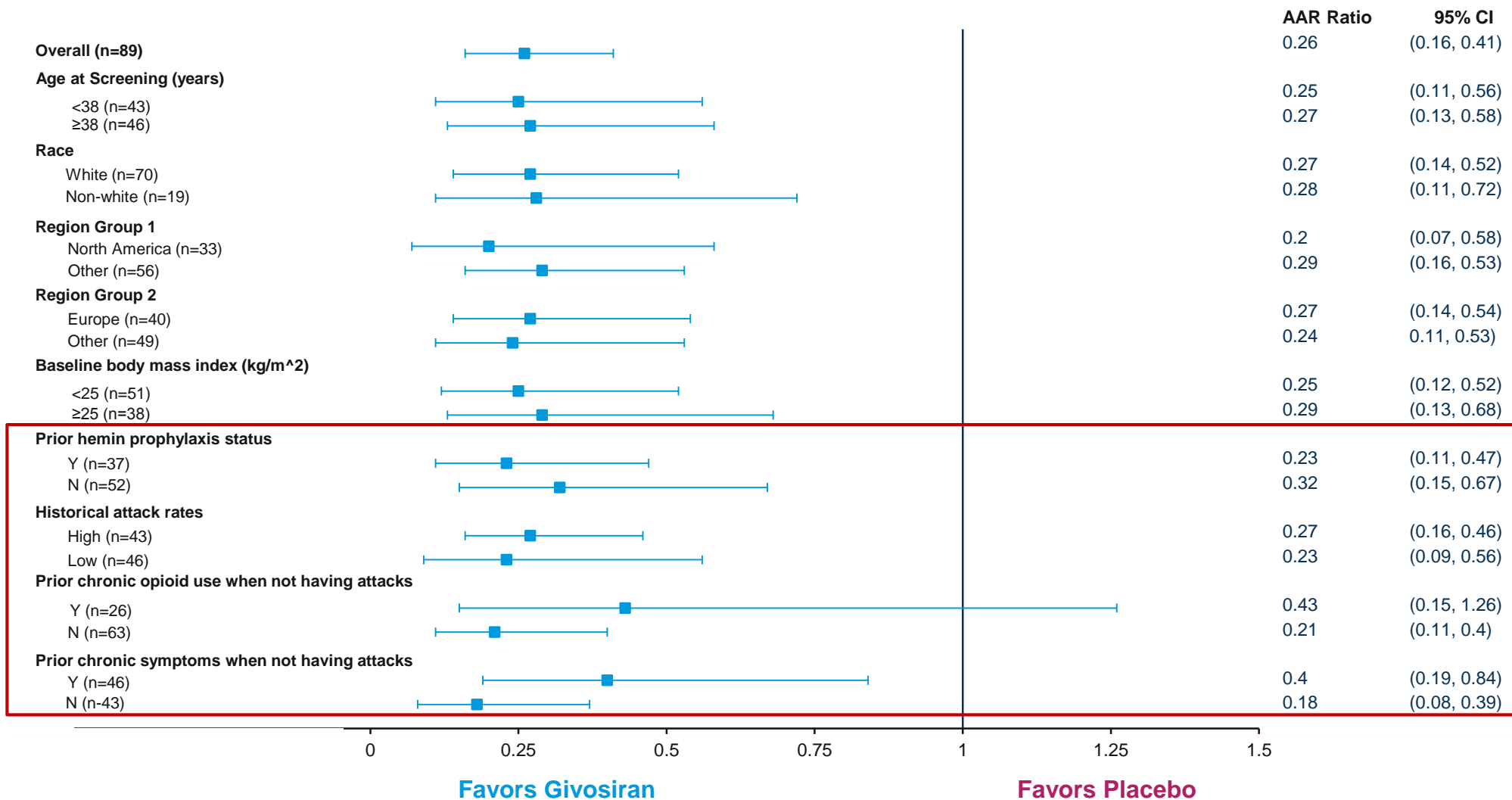


Increase in patients attack-free



# Annualized Attacks in AIP Patients: Pre-Specified Subgroup Analysis

Treatment benefit for givosiran compared to placebo maintained 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
ALA in AIP at Month 3, mmol/mol Cr	20	1.8	-18 (-22.3, -14.2)	8.74 x 10 <sup>-14</sup>
ALA in AIP at Month 6, mmol/mol Cr	23	4	-19 (-26.0, -12.2)	6.24 x 10 <sup>-7</sup>
PBG in AIP at Month 6, mmol/mol Cr	49	13	-36 (-49.7, -22.7)	8.80 x 10 <sup>-7</sup>
Annualized days on hemin in AIP	29.71	6.77	0.23 (0.11, 0.45)	2.35 x 10 <sup>-5</sup>
Composite Attack Rate in AHP	12.26	3.35	0.27 (0.17, 0.43)	1.35 x 10 <sup>-8</sup>
Daily worst pain in AIP (AUC of change from baseline)**	-0.196	-12.876	-12.680 (-25.526, 0.166)	0.0530*
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 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

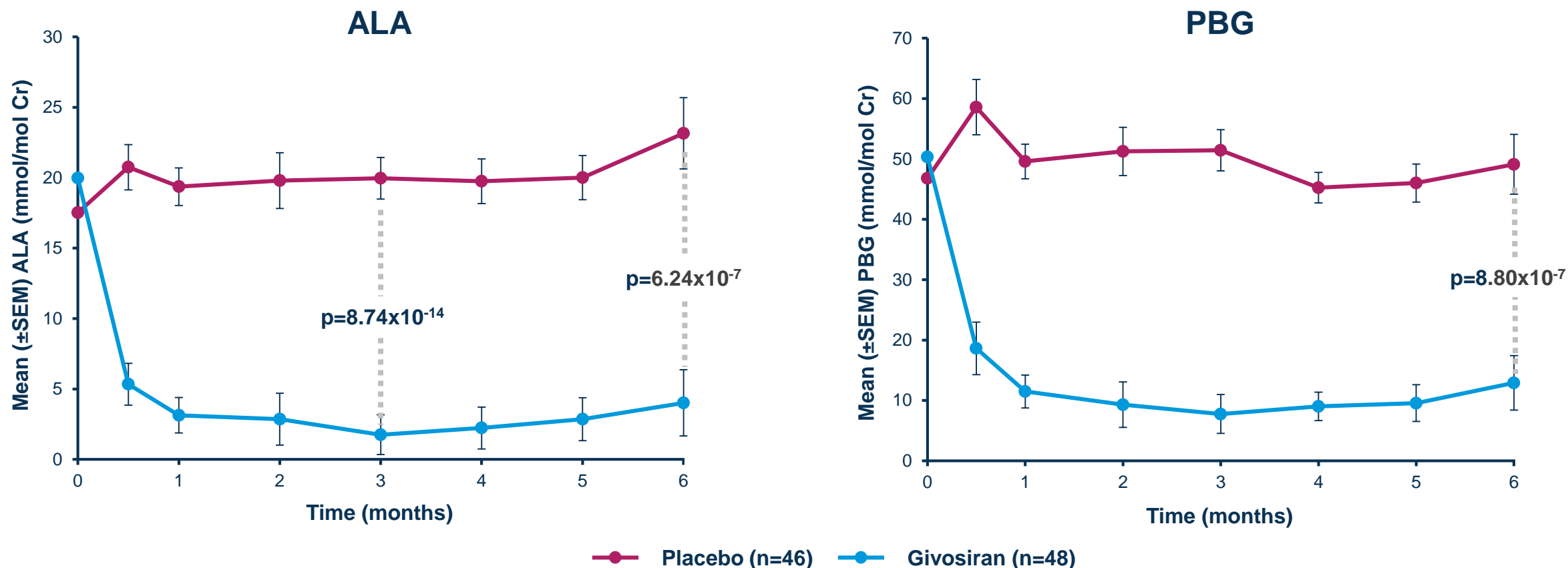
\* Pain data not normally distributed; ANCOVA method not valid. Non-parametric WILCOXON method used (p=0.0455)

\*\* 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.

# ALA and PBG Levels in AIP Patients

- Givosiran showed rapid, robust, and sustained reductions in urinary ALA and PBG over six months
- Median ALA and PBG reduced by 92% and 89%, respectively, compared to 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

# Serious Adverse Events in AHP Patients

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

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

# Common Adverse Events and Key Laboratory Investigations

AEs Reported in ≥ 5 Patients in any Treatment Group, n (%)	Placebo (N=46)	Givosiran (N=48)
Nausea	5 (10.9)	13 (27.1)
Injection Site Reaction*	0 (0)	8 (16.7)**
Headache	7 (15.2)	6 (12.5)
Fatigue	2 (4.3)	5 (10.4)
Chronic Kidney Disease	0 (0)	5 (10.4)
Urinary tract infection	6 (13.0)	3 (6.3)
Vomiting	5 (10.9)	2 (4.2)
Pyrexia	6 (13.0)	1 (2.1)

## Laboratory Investigations

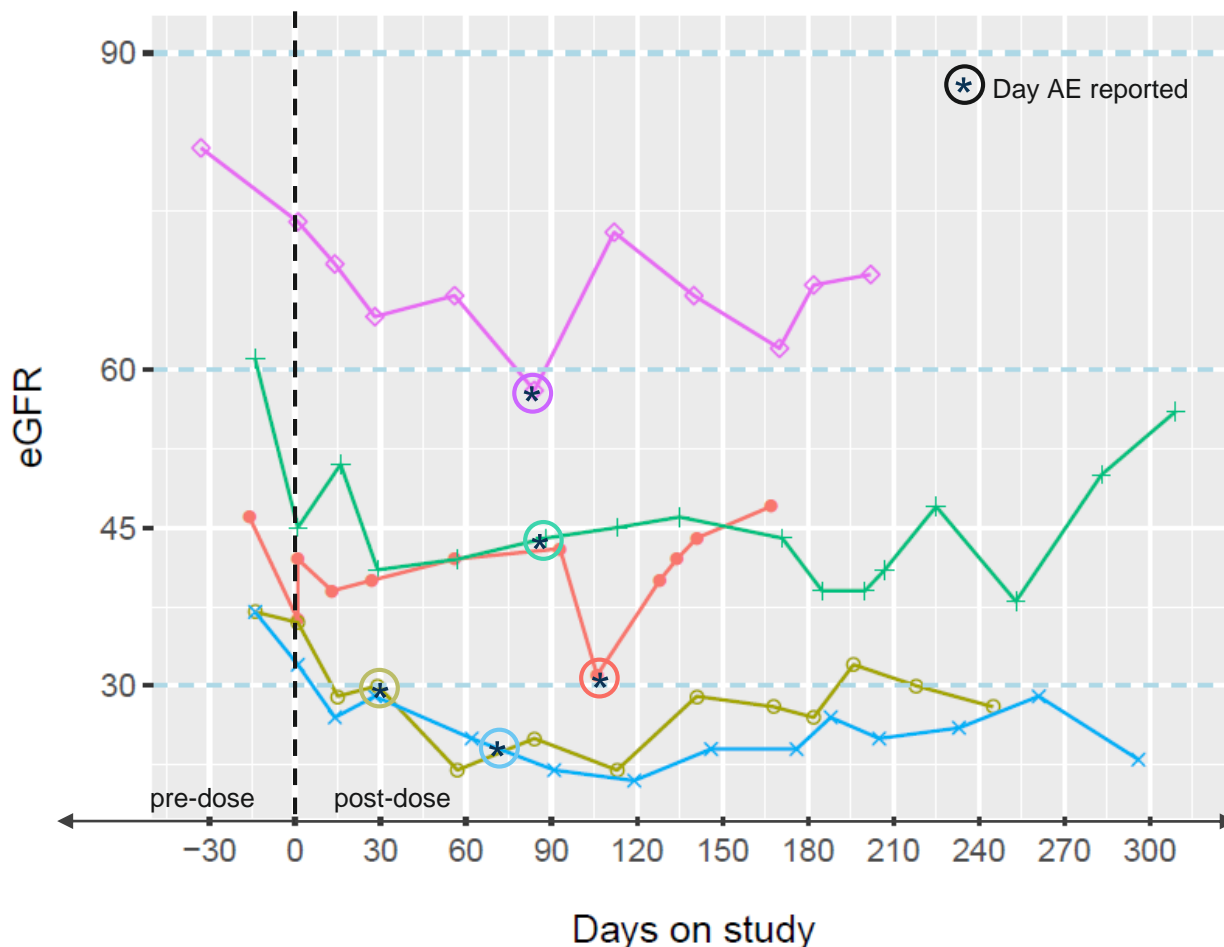
- ALT elevations > 3x ULN or baseline occurred in 7 (14.6%) givosiran patients compared to 1 (2.2%) placebo
  - Majority of ALT elevations mild to moderate in severity; occurred after the first 3 to 5 doses of givosiran
  - 6 patients continued dosing with givosiran with resolution of ALT elevation
    - 1 patient had givosiran held (ALT > 5x ULN) per protocol, and resumed dosing at 1.25 mg/kg without ALT elevation
  - 1 patient had givosiran permanently discontinued (ALT > 8x ULN) per protocol, with ALT resolution (reported previously)
  - No Hy's Law cases

\* ISRs mostly mild, with one moderate, and none required dose discontinuation

\*\* AEs mapping to High-Level Term (HLT) "Injection Site Reaction" in 12 (25%) of patients on givosiran

ALT, alanine aminotransferase; ULN, Upper Limit of Normal

# Renal Parameters in 5 Cases Reported as CKD

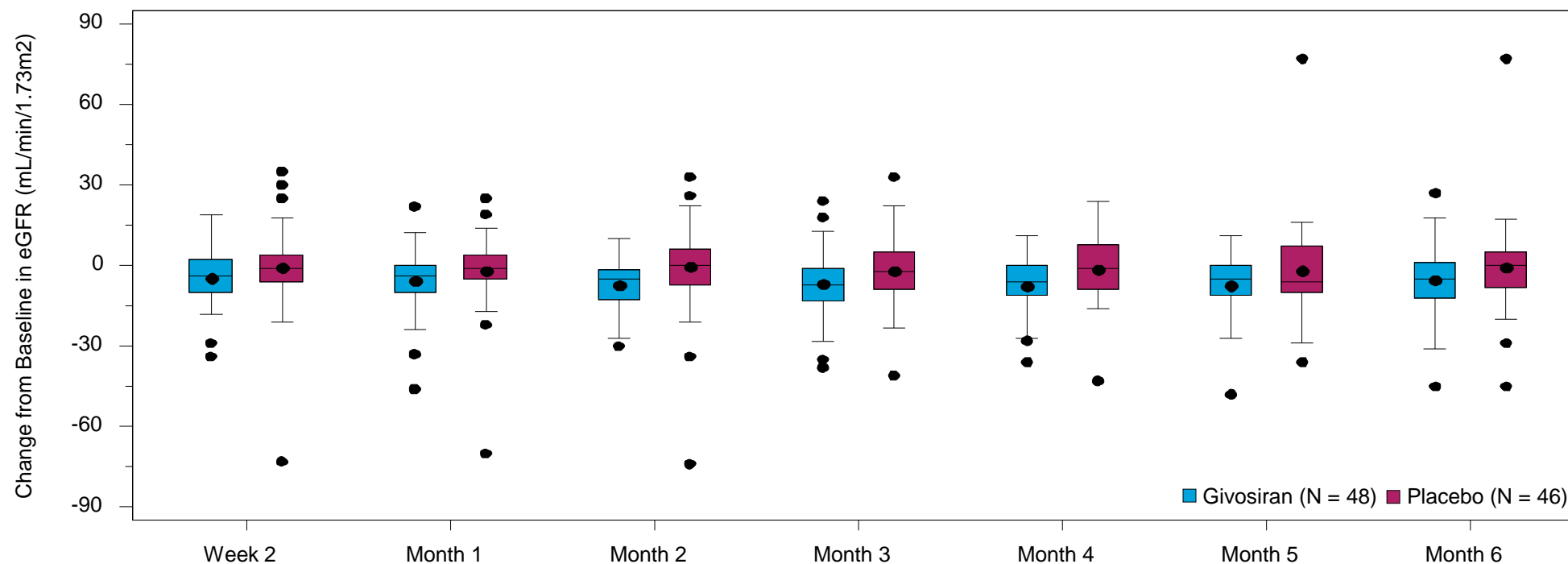


- 4 of 5 patients had prior history of CKD or a baseline estimated GFR (eGFR) < 60 mL/min/1.73m<sup>2</sup>
- Verbatim terms for AEs coded as CKD included:
  - 3 patients with “worsening of chronic renal failure”
  - 1 patient with “worsening of chronic renal disease”
  - 1 patient with “chronic kidney disease”
- Reductions in eGFR were early, asymptomatic and with evidence of reversibility
- No patients had clinically significant proteinuria
- No discontinuations due to renal AEs
  - 1 patient discontinued treatment (Day 106) due to ALT increase (previously described)



# Renal Parameters in Overall Study Population

- eGFR in givosiran-treated patients stable with ongoing dosing
- No increase in proteinuria in givosiran-treated patients compared to placebo



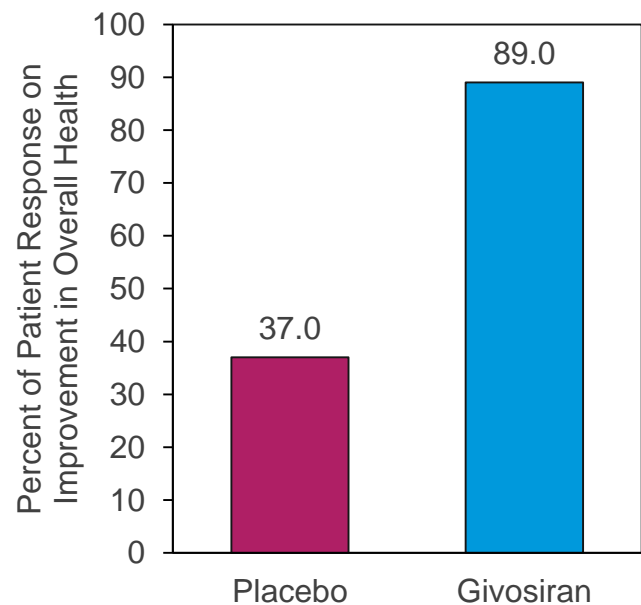
eGFR, estimated Glomerular Filtration Rate; eGFR calculated based on MDRD

ULN, Upper Limit of Normal

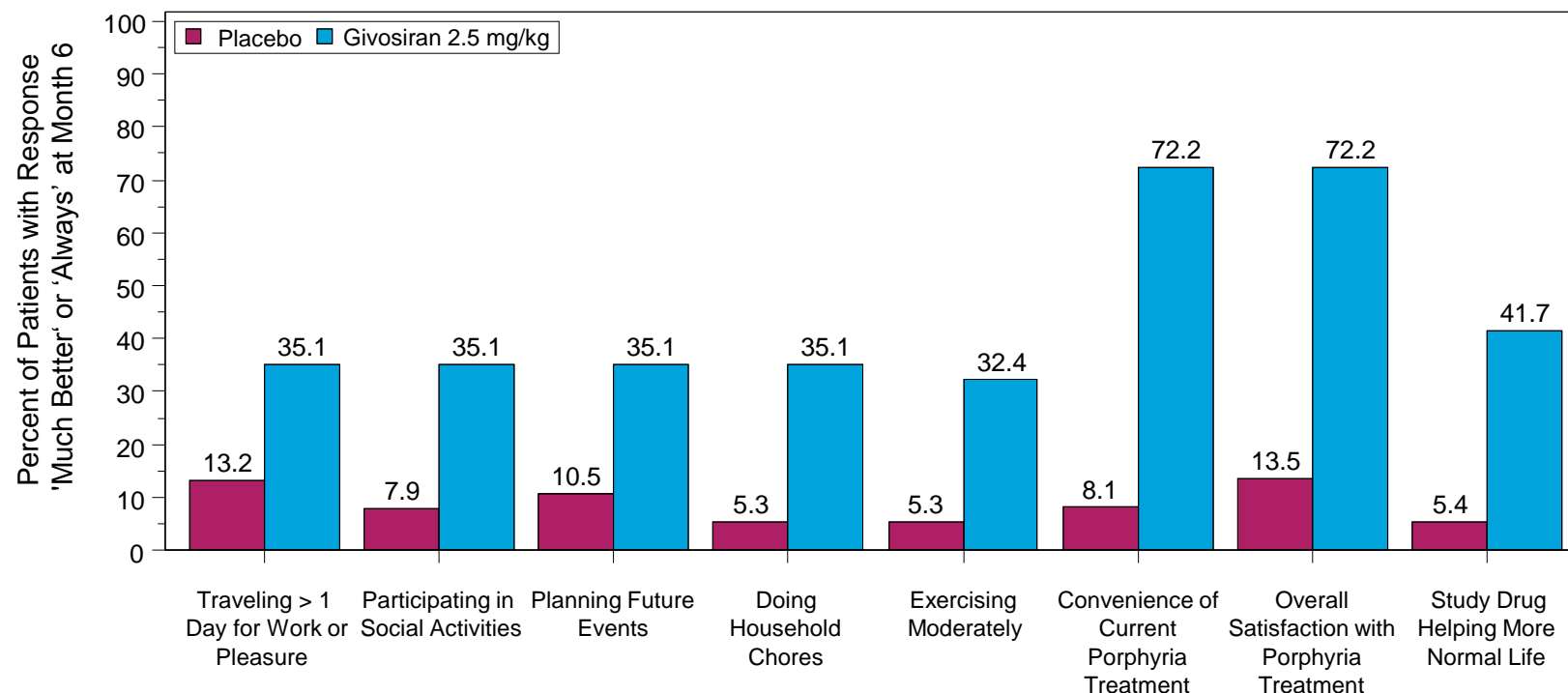
# AHP Patient Perspectives at Month 6

- Greater improvements in overall health status reported by givosiran patients (89%) compared to placebo (37%) as measured by Patient Global Impression of Change (PGIC) Questionnaire
- Givosiran patients report increased ability to perform daily activities and higher overall treatment satisfaction (72%) than placebo (14%) as measured by Porphyria Patient Experience Questionnaire (PPEQ)

**PGIC**



**PPEQ**



Note: The figure presents the percent of patients with response 'Much Better' for Q1 to Q7 or with response 'Always' for Q8 at Month 6.

# 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 were reduced and all subgroup analyses showed givosiran treatment benefit
  - 73% reduction in mean AAR in patients with any AHP relative to placebo
- Givosiran resulted in a reduction in days of hemin use of 77% compared to placebo
- Givosiran led to sustained ~90% lowering from baseline of ALA and PBG, the neurotoxic liver heme intermediates causal for attacks and other AHP disease manifestations
- Overall safety and tolerability profile encouraging in AHP, a serious illness
  - ALT elevations occurred more frequently in givosiran patients than placebo after 3 to 5 doses
    - 6 of 7 patients with ALT  $\geq$  3x ULN have continued givosiran dosing
  - Mild and mostly reversible increases in creatinine and decreases in eGFR were seen more commonly in givosiran than placebo; none led to study drug discontinuation
- All eligible patients (93/94) continued in the open-label extension period of the study
- A greater proportion of patients on givosiran reported improvements in their overall health, daily functioning, and treatment satisfaction, compared to placebo

# Acknowledgements

## ENVISION Investigators

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We also wish to thank the study site staff, the patient organizations, and most importantly, the patients for participating



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

**CHALLENGE ACCEPTED**