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

Balwani M[1], Gouya L[2], Rees DC[3], Stein P[3], Stölzel U[4], Aguilera Peiro P[5], Bissell DM[6], Bonkovsky HL[7], Keel S[8], Parker C[9], Phillips JD[9], Silver S[10], Windyga J[11], D'Avola D[12], Ross G[13], Stewart P[14], Ritchie B[15], Oh J[16], Harper P[17], Wang JD[18], Langendonk JG[19], Ivanova A[20], Horie, Y[21], Anderson KE[22], Ventura P[23], Chan A[24], Penz C[24], Simon A[24], Kim J[24], Dinh Q[24,] Liu G[24], Garg P[24], Vaishnaw A[24], and Sardh E[17] on behalf of the ENVISION investigators

[1]Icahn School of Medicine at Mount Sinai, New York, New York, USA. [2]Centre Français des Porphyries, France. [3]King's College Hospital, United Kingdom. [4]Klinikum Chemnitz, Chemnitz, Germany. [5]Hospital Clinic Barcelona, Spain. [6]University of California, San Francisco, California, USA. [7]Wake Forest University, Winston-Salem, North Carolina, USA. [8]University of Washington, Seattle, Washington, USA. [9]University of Utah, Salt Lake City, Utah, USA. [10]University of Michigan, Ann Arbor, Michigan, USA. [11]Instytut Hematologii i Transfuzjologii, Warsaw, Poland. [12]Clinica Universidad de Navarra, Madrid, Spain. [13]Melbourne Health - Royal Melbourne Hospital, Melbourne, Australia. [14]Royal Prince Alfred Hospital, Sydney, Australia. [15]University of Alberta Hospital, Edmonton, Canada. [16]Konkuk University Hospital. Konkuk University Medical Center, Seoul, South Korea. [17] Porphyria Centre Sweden, Centre for Inherited Metabolic Diseases, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden. [18] Taichung Veterans General Hospital, Center for Rare Disease and Hemophilia, Taipai, Taiwan. [19]Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands. [20]St. Ivan Rilski University Hospital, Sofia, Bulgaria. [21]Tottori University School of Medicine, Tottori, Japan. [22]University of Texas, Medical Branch, Galveston, Texas, USA. [23]Università degli Studi di Modena e Reggio Emilia, Modena, Italy. [24]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA.

13 April 2019 | EASL | Vienna, Austria

ENVISION

Acute Hepatic Porphyria (AHP)

Disease Overview[1,2]

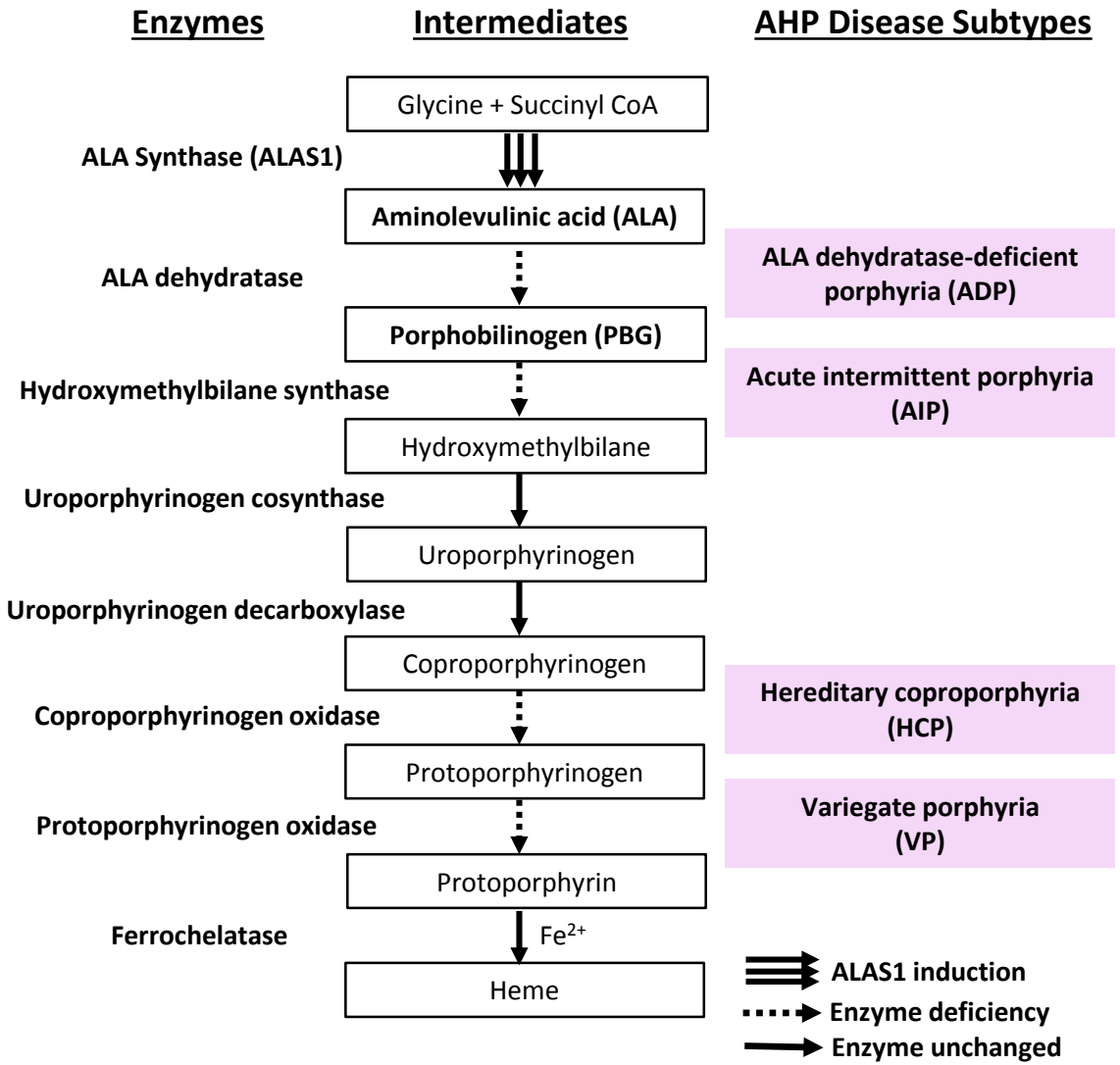
- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in liver
- Acute Intermittent Porphyria (AIP) most common, with mutation in hydroxymethylbilane synthase (HMBS)

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[3-7]

- 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

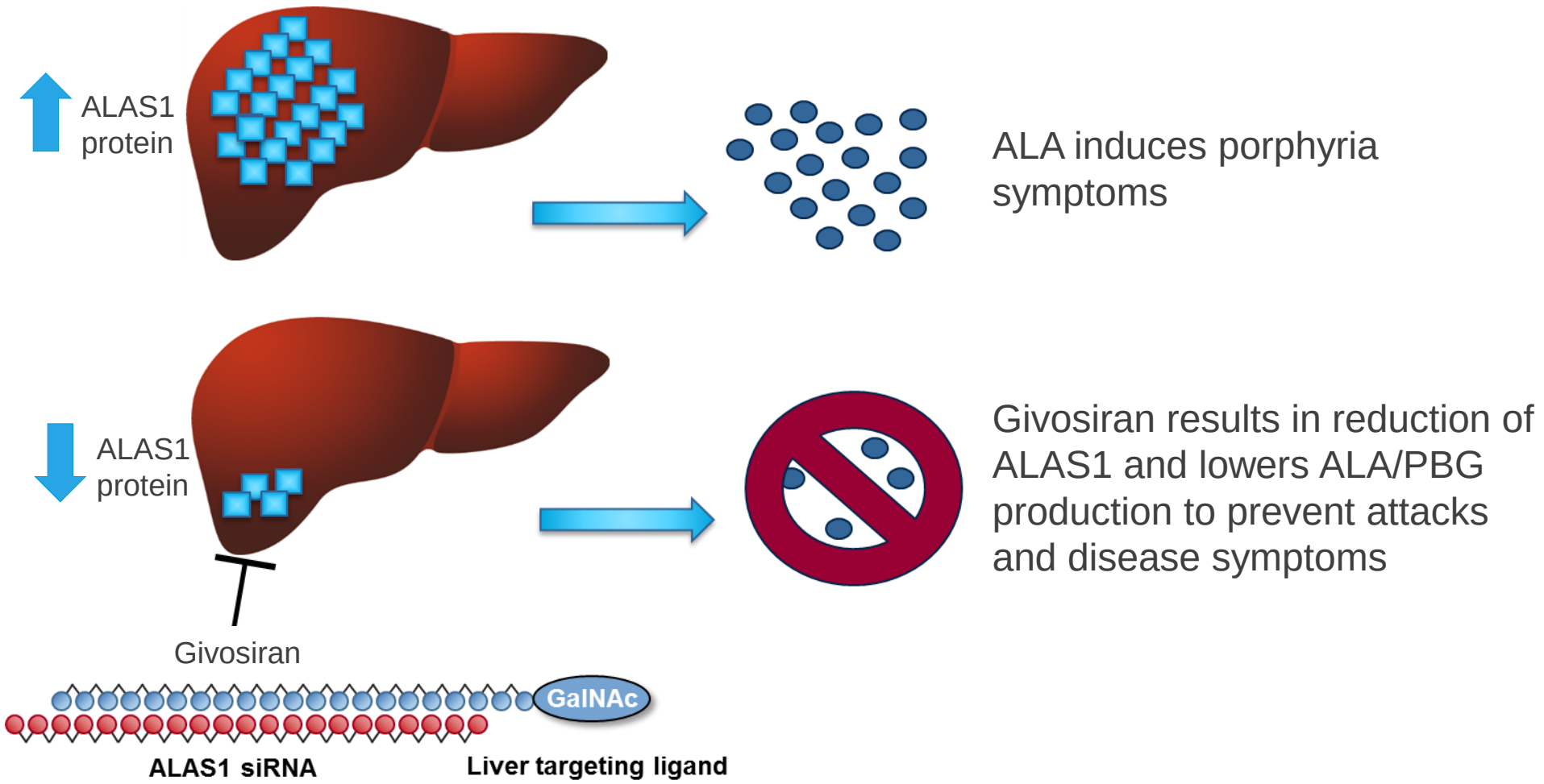


1. Bonkovsky, et al., Am J Med. 2014;127:1233-41; 2. Elder, et al., JIMD. 2013;36:849-57; 3 Pischik and Kauppinen. Appl Clin Genet. 2015;8:201-14. 4. Bonkovsky, et al., Poster. Presented at the American Association for the Study of Liver Diseases; November 9-13, 2018, San Francisco, CA, USA. 5. Stewart. 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

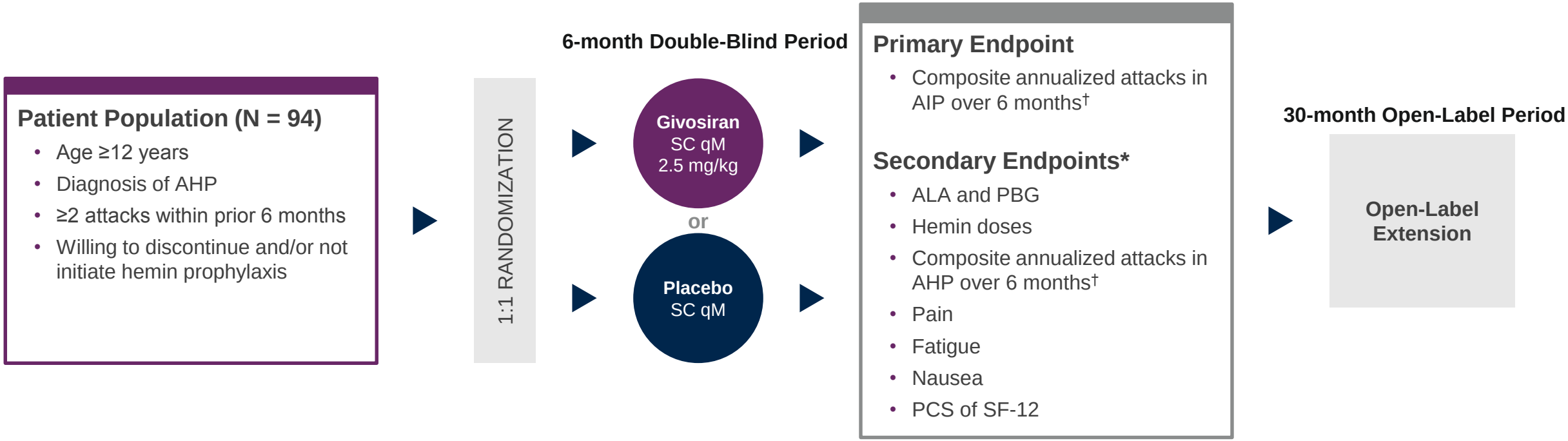


AHP, Acute Hepatic Porphyria; ALA, Aminolevulinic acid; ALAS1, ALA synthase 1; PBG, Porphobilinogen.

Givosiran ENVISION Phase 3 Study

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

94 patients enrolled at 36 sites in 18 countries



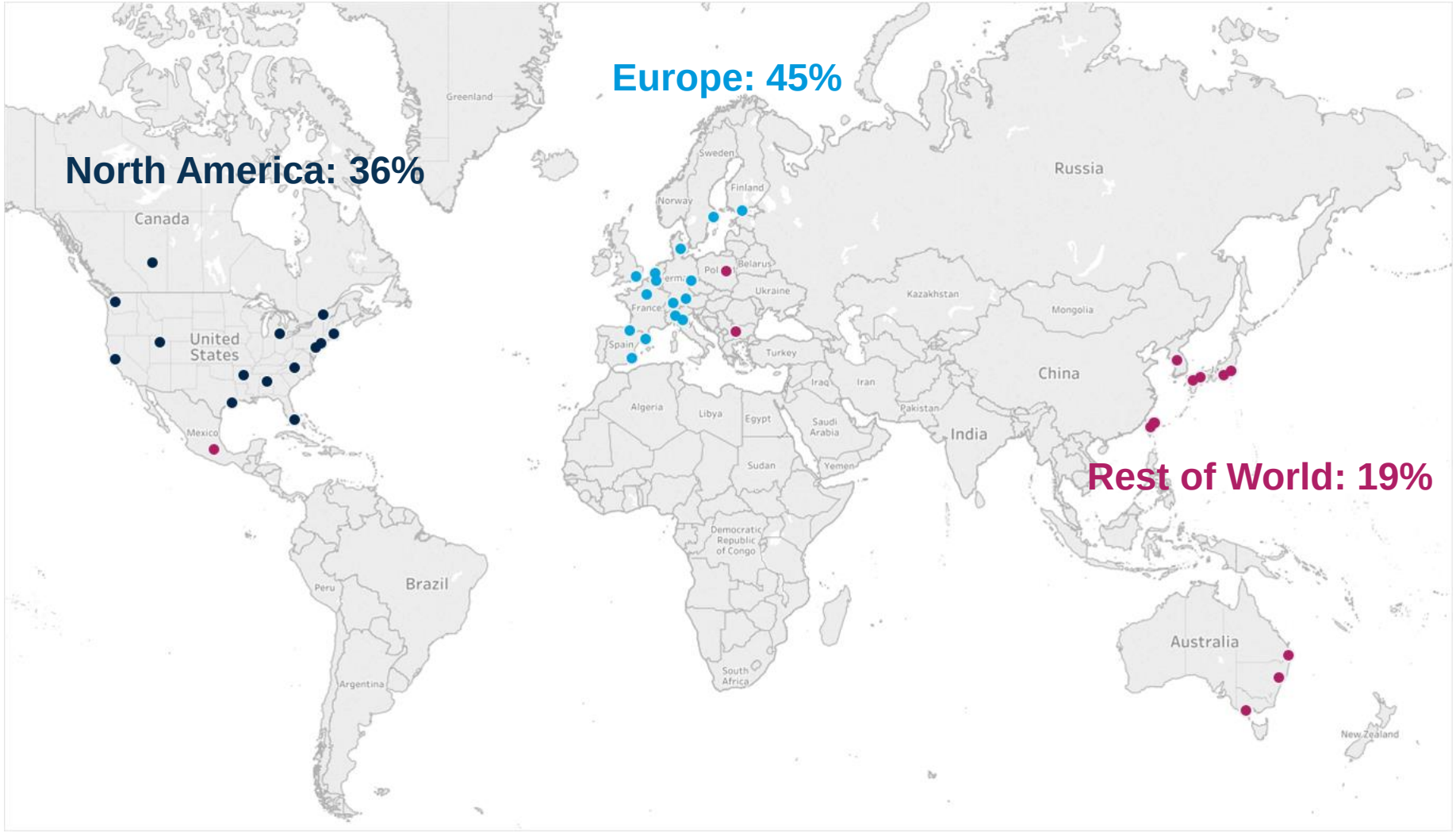
† Attacks requiring hospitalization, urgent healthcare visit, or hemin administration

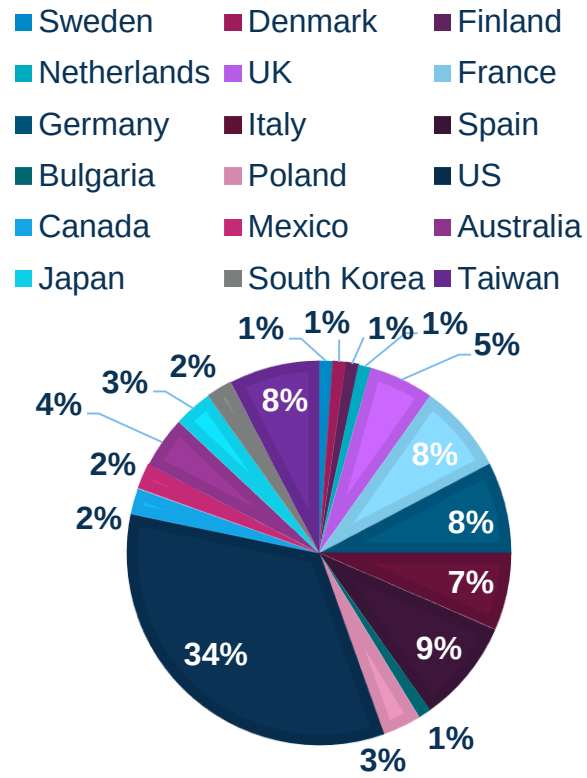
*Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted

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

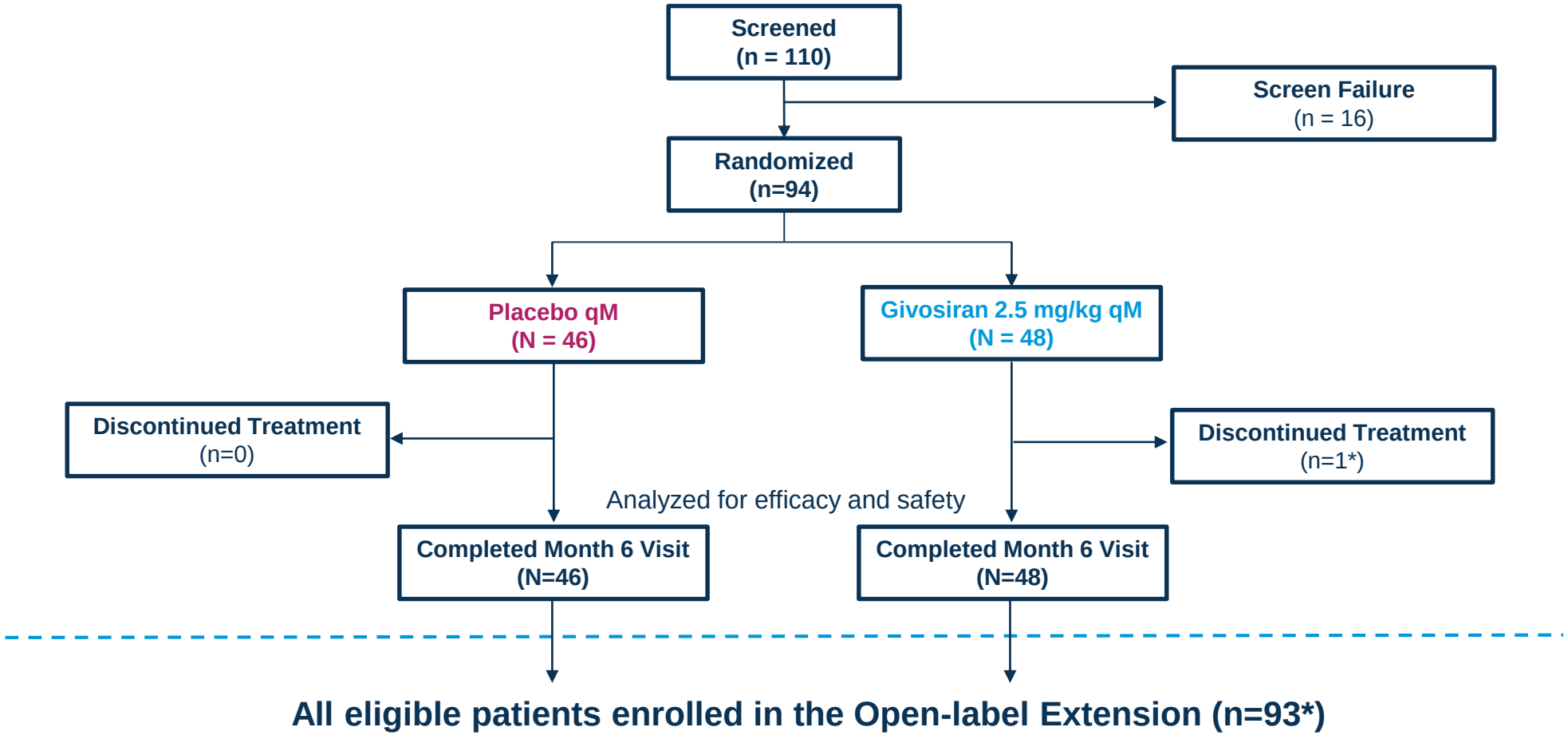
94 patients enrolled at 36 sites in 18 countries





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

AIP, Acute Intermittent Porphyria; HCP, Hereditary Coproporphyria; HMBS, hydroxymethylbilane synthase; VP, variegate porphyria

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

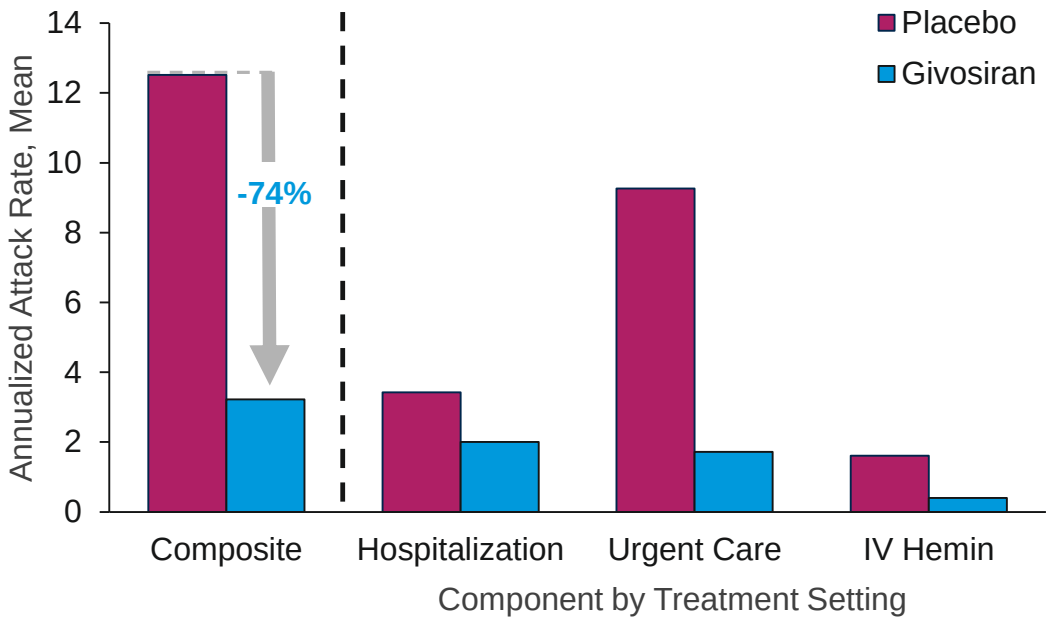
Baseline Disease Characteristics in AHP Patients	Placebo (N=46)	Givosiran (N=48)
Porphyria attacks* in past 6 months, median (range)	3.5 (0, 23)	4.0 (2, 17)
Prior hemin prophylaxis therapy, n (%)	18 (39)	20 (42)
Used opioids daily or most days in between attacks, n (%)	13 (28)	14 (29)
Daily chronic symptoms 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^2, 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.

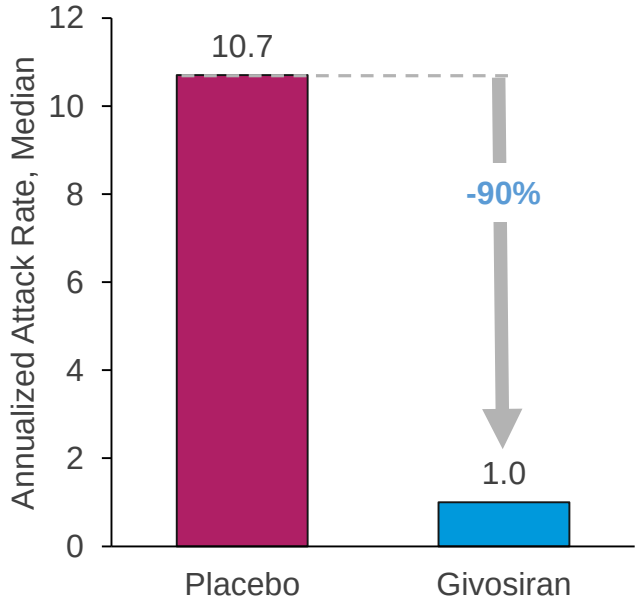
Primary Efficacy Endpoint: Annualized Attacks in AIP

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)	6.04×10^{-9}

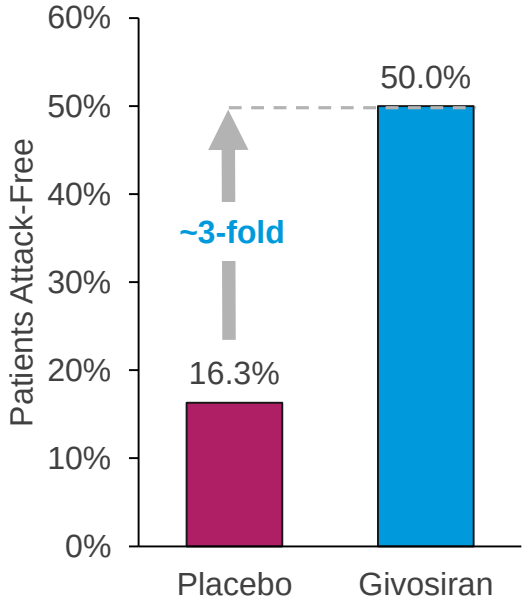
Composite and all endpoint components reduced



Reduction in median composite attack rate

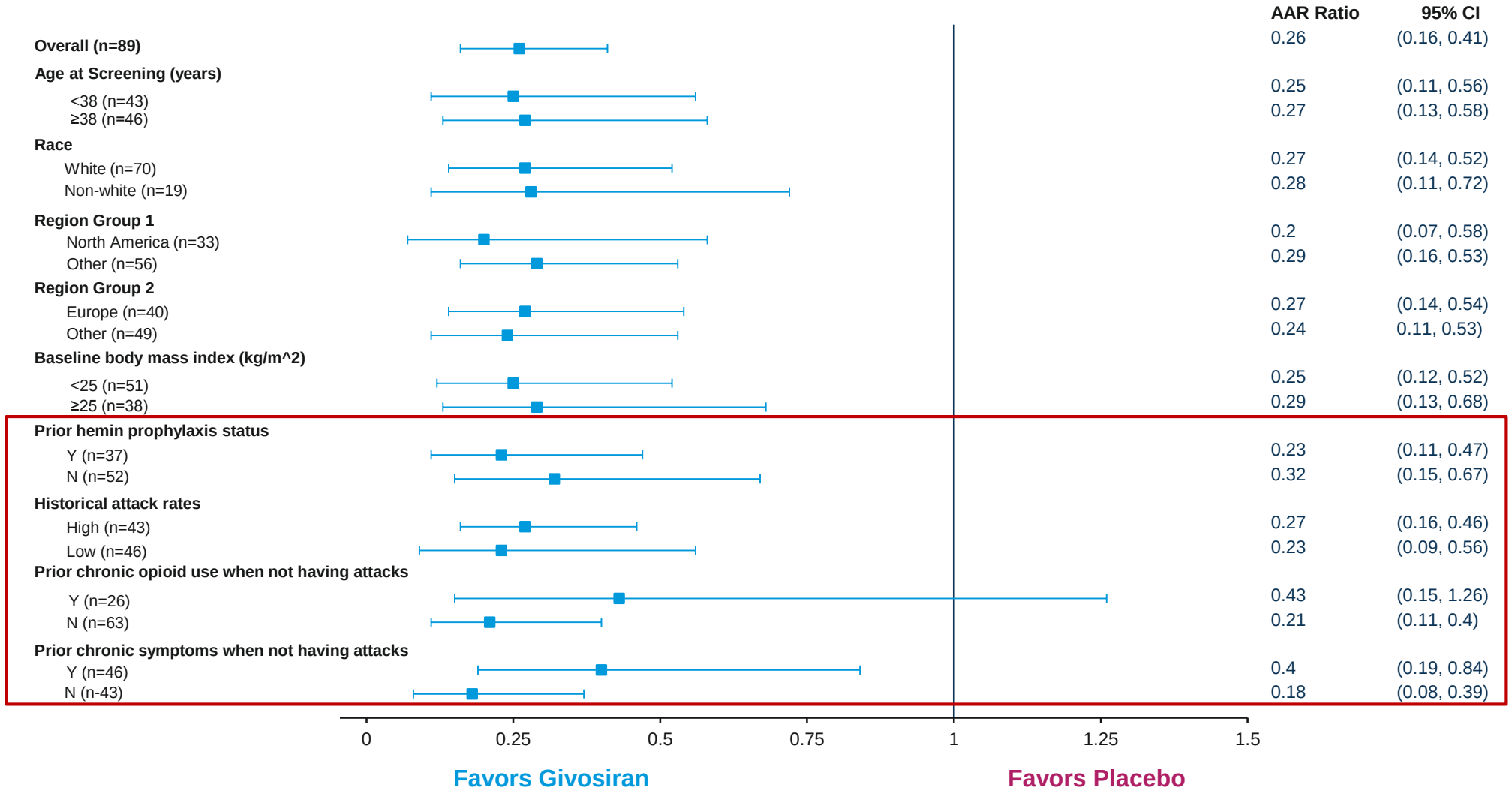


Increase in patients attack-free



Annualized Attacks in AIP Patients: Pre-Specified Subgroup Analysis

Treatment benefit for givosiran compared to placebo maintained across all subgroups



AIP, Acute Intermittent Porphyria.

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)	8.74×10^{-14}
ALA in AIP at Month 6, mmol/mol Cr	23	4	-19 (-26.0, -12.2)	6.24×10^{-7}
PBG in AIP at Month 6, mmol/mol Cr	49	13	-36 (-49.7, -22.7)	8.80×10^{-7}
Annualized days on hemin in AIP	29.71	6.77	0.23 (0.11, 0.45)	2.35×10^{-5}
Composite Attack Rate in AHP	12.26	3.35	0.27 (0.17, 0.43)	1.35×10^{-8}
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

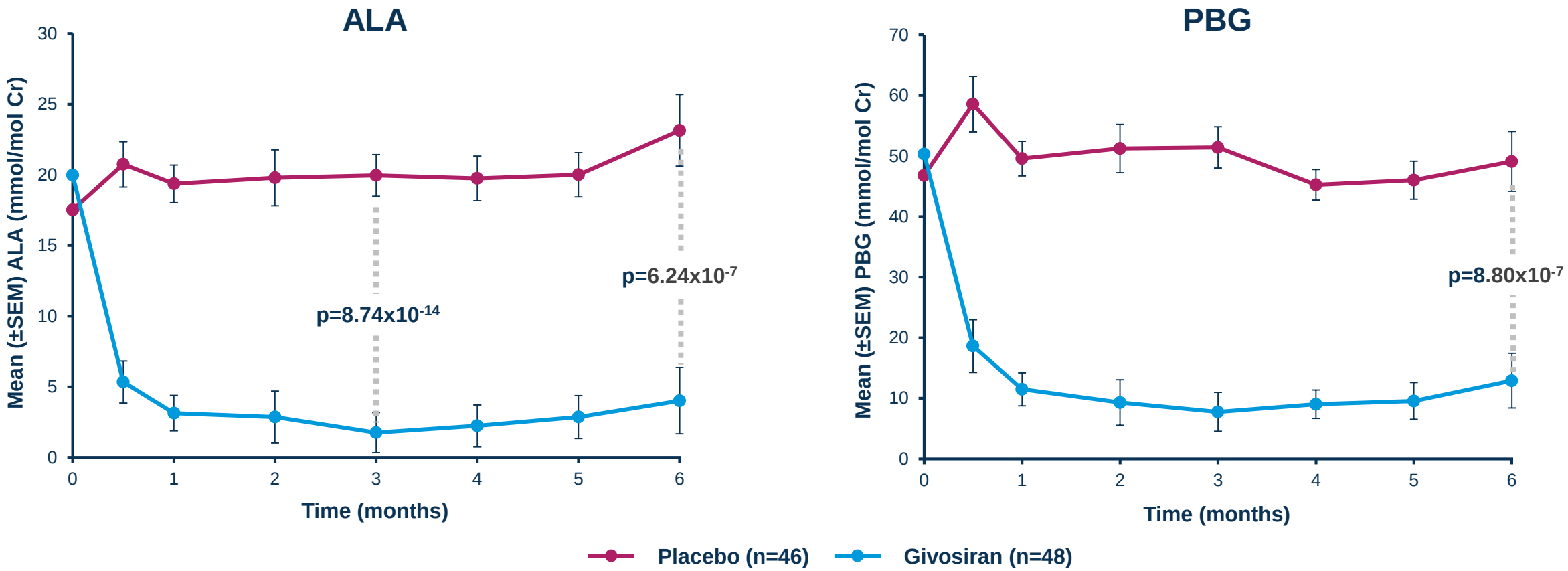
* Pain data not normally distributed; ANCOVA method not valid. Non-parametric WILCOXON method used (p=0.0455)

** 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

* If a patient experienced more than 1 event in a given category, that patient was counted only once in that category. A patient can contribute to multiple events. Adverse events listed by Preferred Term

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

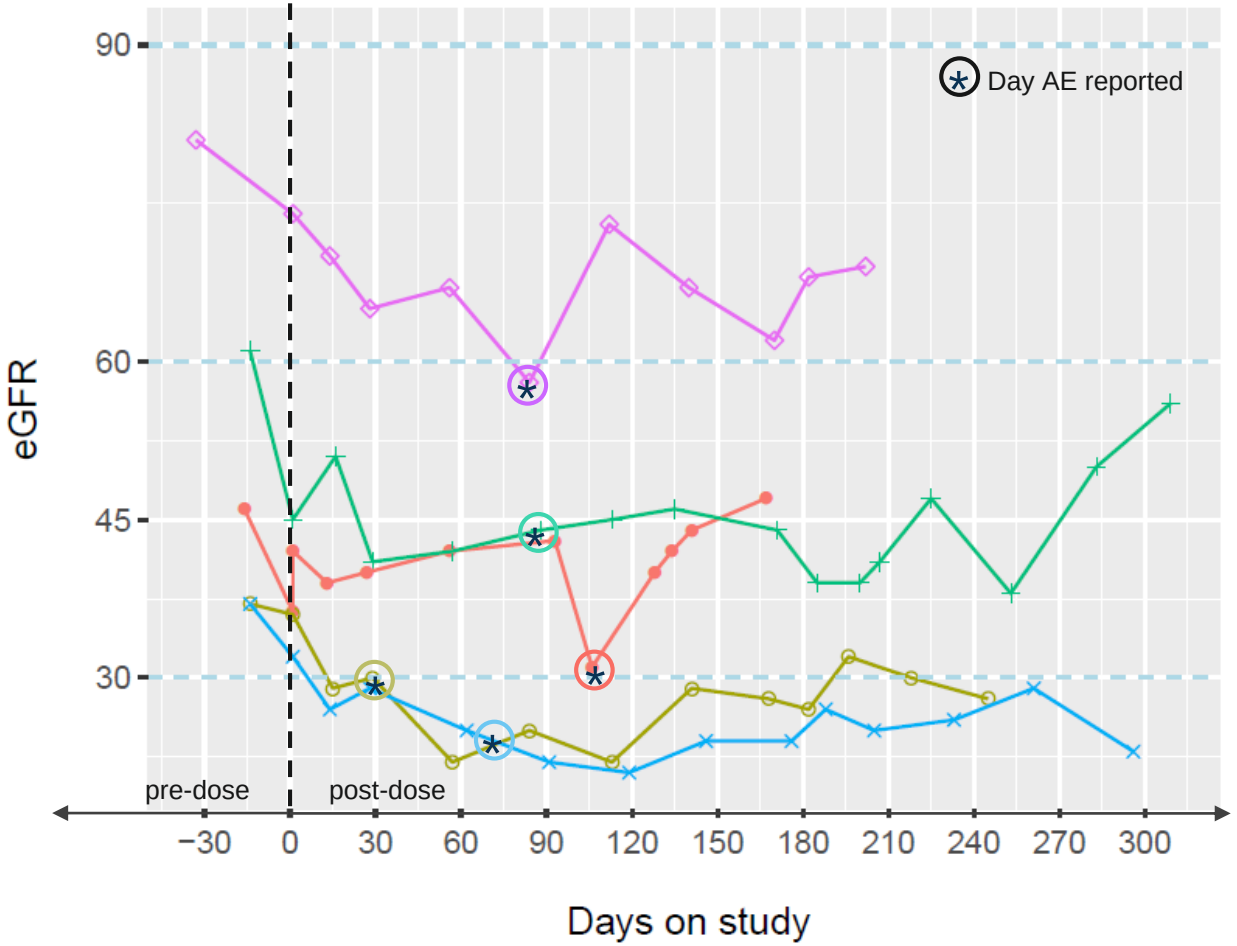
- ALT elevations > 3x ULN or baseline occurred in 7 (14.6%) givosiran patients compared to 1 (2.2%) placebo
  - Majority of ALT elevations mild to moderate in severity; occurred after the first 3 to 5 doses of givosiran
  - 6 patients continued dosing with givosiran with resolution of ALT elevation
    - 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

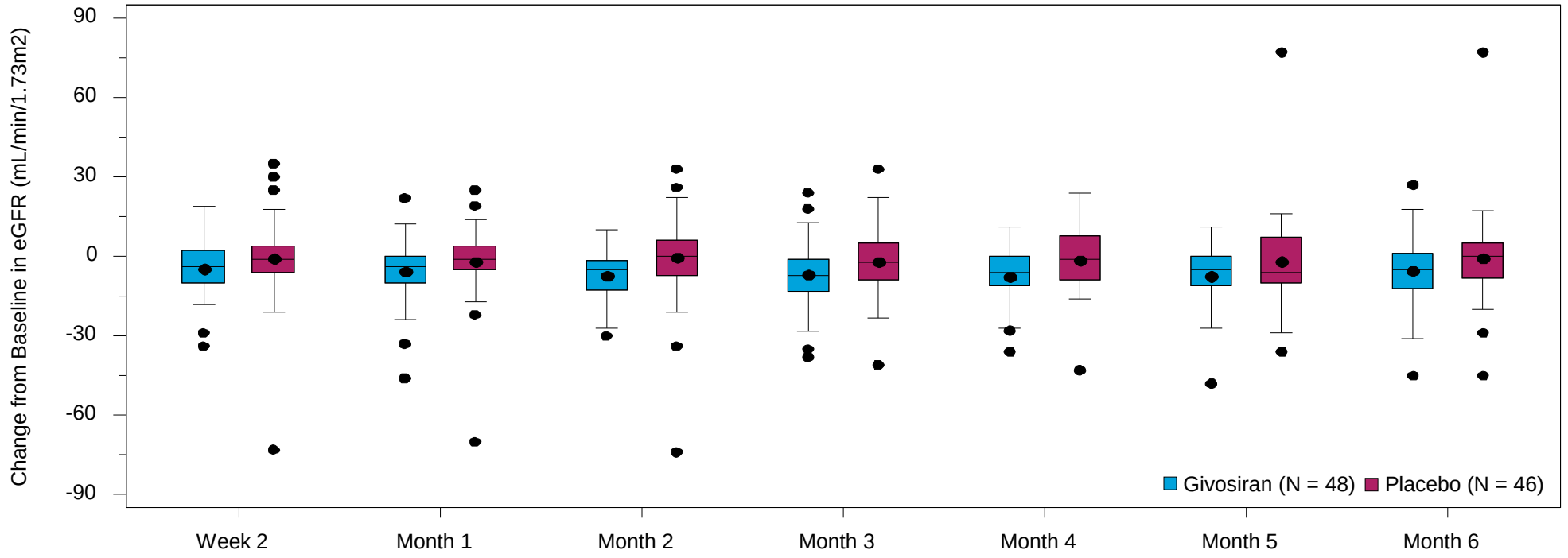


- 4 of 5 patients had prior history of CKD or a baseline estimated GFR (eGFR) < 60 mL/min/1.73m^2
- Verbatim terms for AEs coded as CKD included:
  - 3 patients with “worsening of chronic renal failure”
  - 1 patient with “worsening of chronic renal disease”
  - 1 patient with “chronic kidney disease”
- 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)

CKD, Chronic Kidney disease; eGFR, estimated Glomerular Filtration Rate; eGFR calculated based on MDRD

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

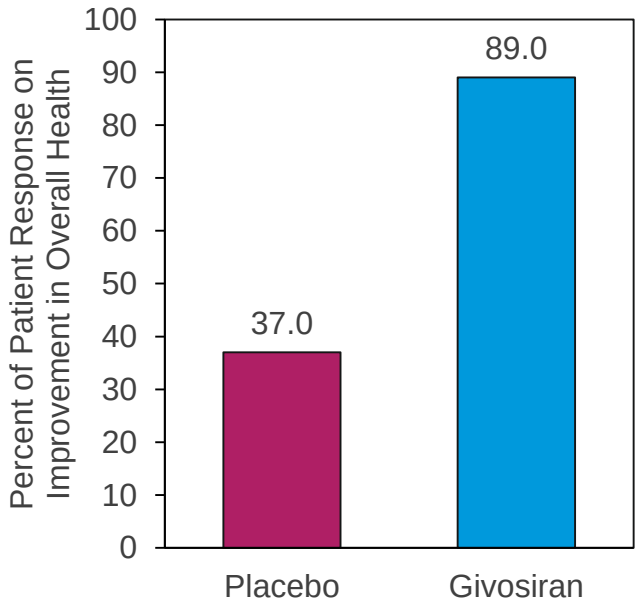


eGFR, estimated Glomerular Filtration Rate; eGFR calculated based on MDRD
ULN, Upper Limit of Normal

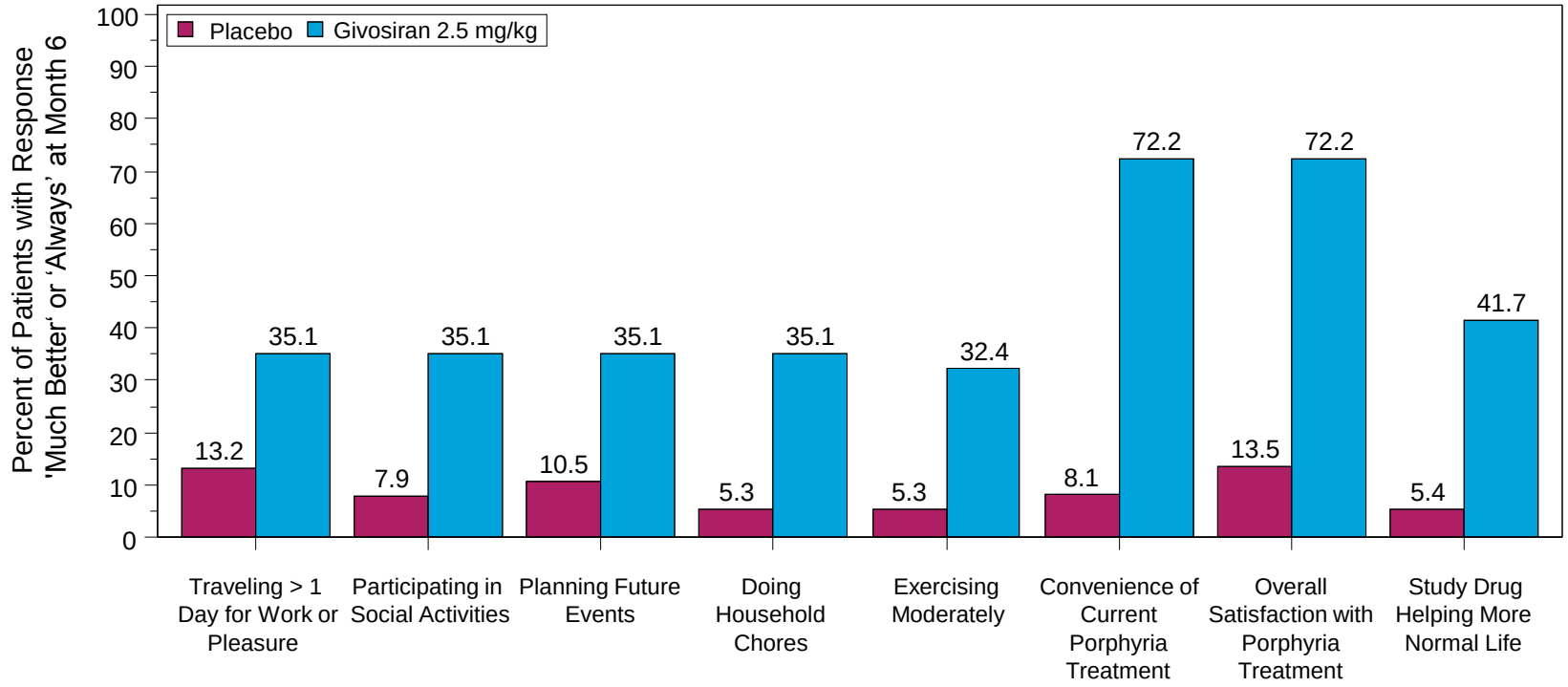
AHP Patient Perspectives at Month 6

- 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.

Custom questionnaires that used global rating of change, with questions asked once at month 6, looking back at entire study period.

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 ≥ 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

- Tomohide Adachi
- Paula Aguilera Peiro
- Karl Anderson
- Manisha Balwani
- Montgomery Bissell
- Herb Bonkovsky
- Maria Cappellini
- David Cassiman
- David Coman
- Delia D'Avola
- Yoshie Goto
- Laurent Gouya
- Encarna Guillén Navarro
- Pauline Harper
- Yutaka Horie
- Ole Hother-Nielsen
- Aneta Ivanova
- David Kuter
- Raili Kauppinen
- Sioban Keel
- Hung-Chou Kuo
- Janneke Langendonk
- Ming-Jen Lee
- Cynthia Levy
- Elisabeth Minder
- Susana Monroy
- Jeeyoung Oh
- Charles Parker
- Petro Petrides
- John Phillips
- David Rees
- Bruce Ritchie
- Gayle Ross
- Eliane Sardh
- Appalanaidu Sasapu
- Samuel Silver
- Penny Stein
- Peter Stewart
- Ulrich Stölzel
- Kei-ichiro Takase
- Manish Thapar
- Daphne Vassiliou
- Paolo Ventura
- Jiaan-Der Wang
- Bruce Wang
- Jerzy Windyga

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

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