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

Gouya L[1], Sardh E[2], Balwani M[3], Ventura P[4] ,Rees DC[5], Stein P[5], Stölzel U[6], Aguilera Peiro P[7], Bissell DM[8], Bonkovsky HL[9], Keel S[10], Parker C[11], Phillips JD[11], Silver S[12], Windyga J[13], D'Avola D[14], Ross G[15], Stewart P[16], Ritchie B[17], Oh J[18], Harper P[2], Wang JD[19], Langendonk JG[20], Ivanova A[21], Horie, Y[22], Anderson KE[23], Cappellini MD[24], Vassiliou D[2], Monroy S[25], Petrides P[26], Adachi T[27], Kuter D[28], Scalera S[29], Penz C[29], Simon A[29], Kim J[29], Liu G[29], John Ko[29] , Garg P[29], Vaishnaw A[29], on behalf of the ENVISION investigators

[1]Centre Français des Porphyries, France.[2] Porphyria Centre Sweden, Centre for Inherited Metabolic Diseases, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden. [3]Icahn School of Medicine at Mount Sinai, New York, New York, USA. [4]Università degli Studi di Modena e Reggio Emilia, Modena, Italy. [5]King's College Hospital, United Kingdom. [6]Klinikum Chemnitz, Chemnitz, Germany. [7]Hospital Clinic Barcelona, Spain. [8]University of California, San Francisco, California, USA. [9]Wake Forest University, Winston-Salem, North Carolina, USA. [10]University of Washington, Seattle, Washington, USA. [11]University of Utah, Salt Lake City, Utah, USA. [12]University of Michigan, Ann Arbor, Michigan, USA. [13]Instytut Hematologii i Transfuzjologii, Warsaw, Poland. [14]Clinica Universidad de Navarra, Madrid, Spain. [15]Melbourne Health - Royal Melbourne Hospital, Melbourne, Australia. [16]Royal Prince Alfred Hospital, Sydney, Australia. [17]University of Alberta Hospital, Edmonton, Canada. [18]Konkuk University Hospital. Konkuk University Medical Center, Seoul, South Korea. [19]Taichung Veterans General Hospital, Center for Rare Disease and Hemophilia, Taipai, Taiwan. [20]Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands. [21]St. Ivan Rilski University Hospital, Sofia, Bulgaria. [22]Tottori University School of Medicine, Tottori, Japan. [23]University of Texas, Medical Branch, Galveston, Texas, USA. [24]University of Milan, Milan, Italy; [25]Instituto Nacional de Pediatría de Mexico, Mexico City, Mexico, [26]Praxis für Hämatologie und Onkologie am Isartor, Munich, Germany, [27]Tokyo Saiseikai Central Hospital, Tokyo, Japan; [28] Massachusetts General Hospital, Boston, Massachusetts, USA; [29]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA

10 September 2019 | ICPP | Milan, Italy

ENVISION

Agenda

- **Part 1: Key ENVISION Phase 3 Efficacy and Safety Data**
  Laurent Gouya

- **Part 2: ENVISION Patient Reported Outcomes and Patient Experience Data**
  Eliane Sardh

Key ENVISION Phase 3 Efficacy and Safety Data

Laurent Gouya

Acute Hepatic Porphyria (AHP)

Disease Overview[1,2]

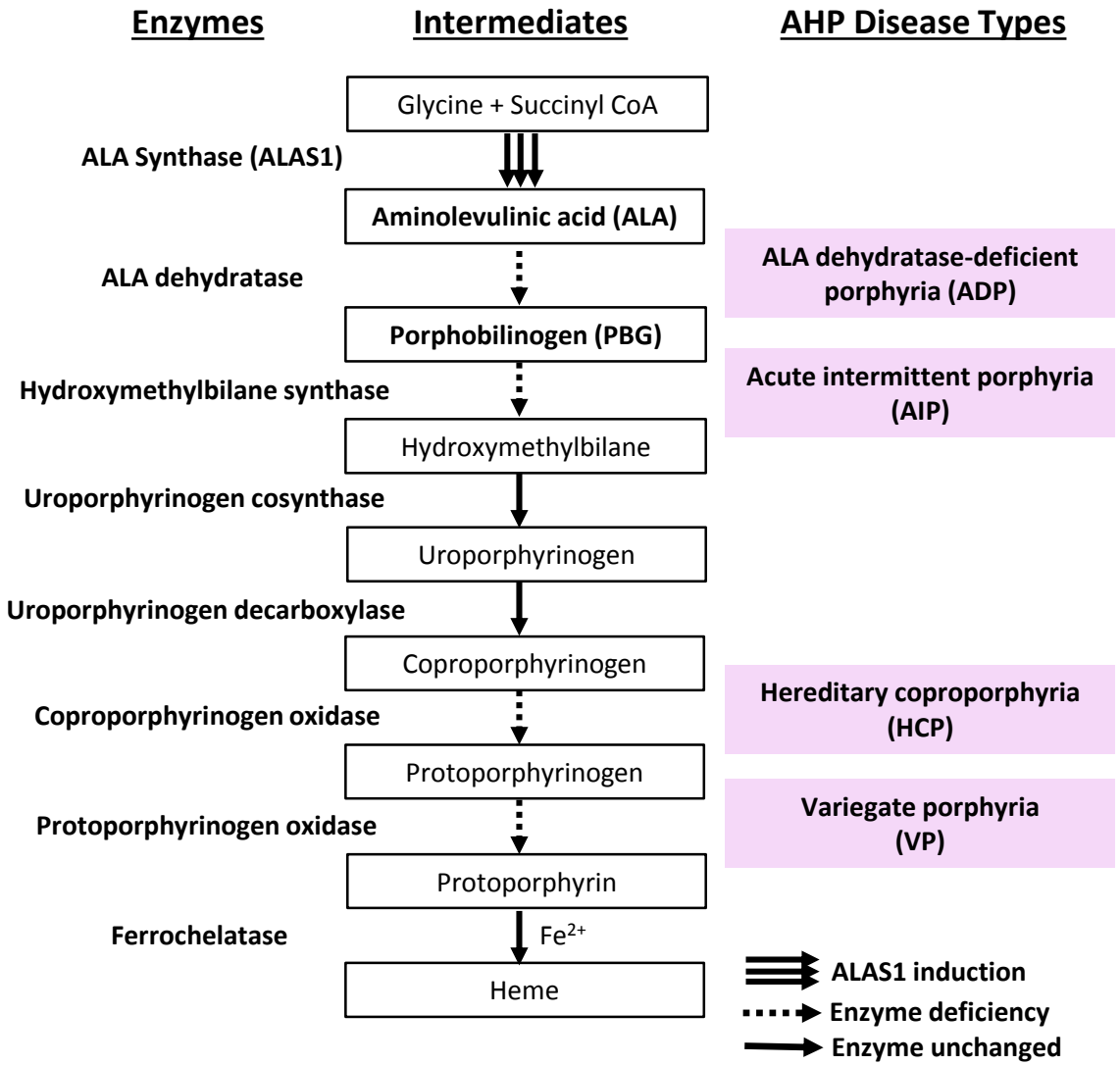
- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in liver
- Acute Intermittent Porphyria (AIP) most common, with mutation in hydroxymethylbilane synthase (HMBS)

Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA/PBG
- ALA believed to be primary toxic 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

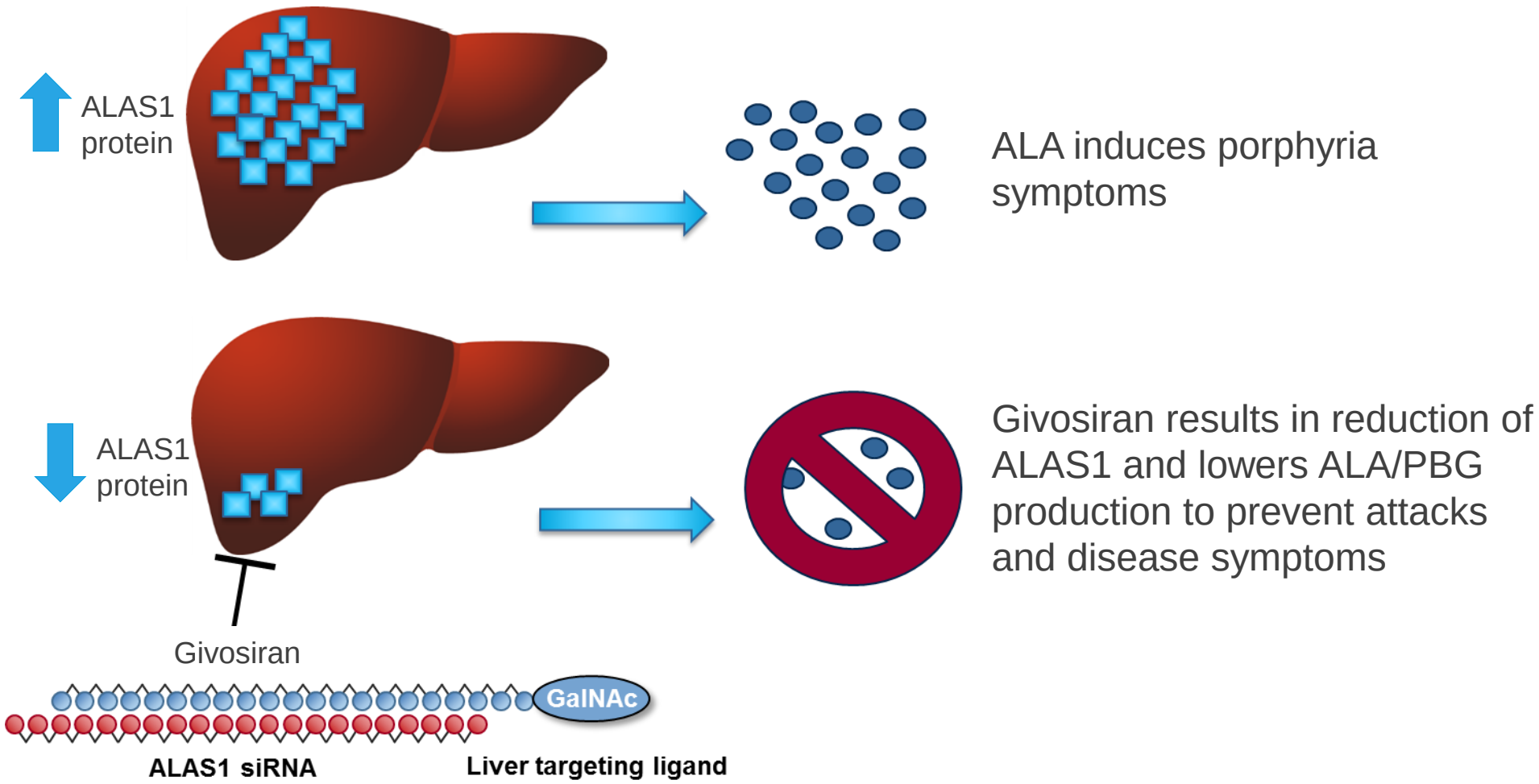


1. Bonkovsky, et al., Am J Med. 2014;127:1233-41; 2. Elder, et al., JIMD. 2013;36:849-57; 3 Pischik and Kauppinen. Appl Clin Genet. 2015;8:201-14. 4. Bonkovsky, et al., Poster. Presented at the American Association for the Study of Liver Diseases; November 9-13, 2018, San Francisco, CA, USA. 5. Stewart.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

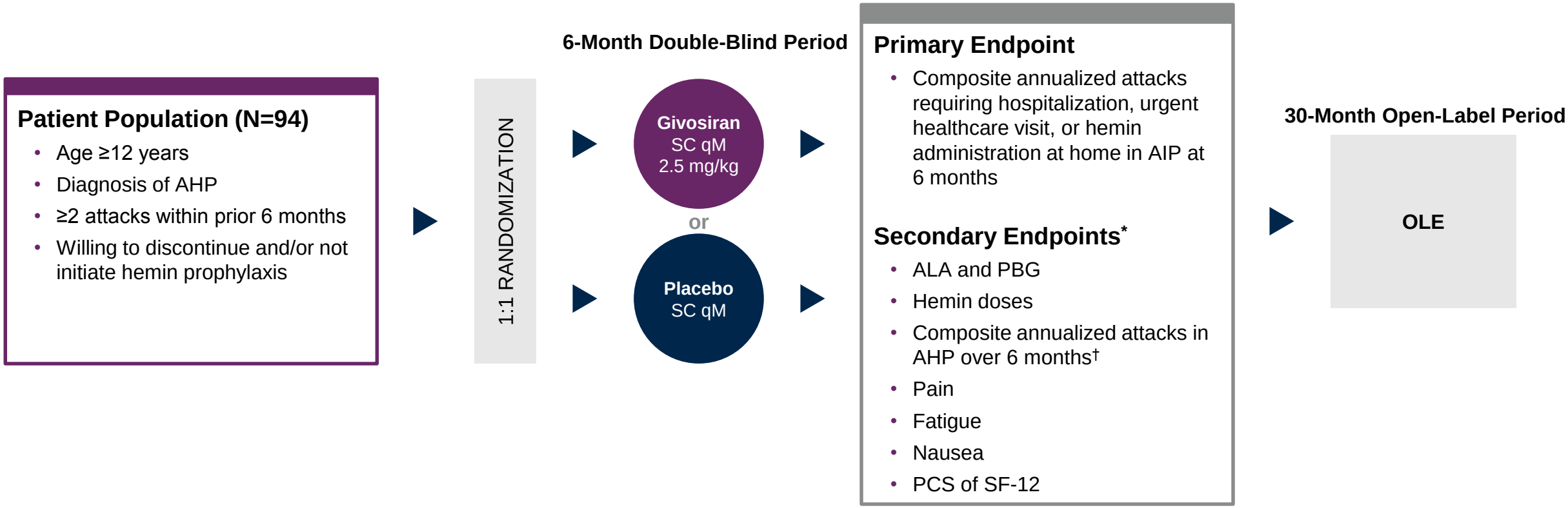


AHP, Acute Hepatic Porphyria; ALA, Aminolevulinic acid; ALAS1, ALA synthase 1; PBG, Porphobilinogen.

Givosiran ENVISION Phase 3 Study

Randomized, Double-Blind, Placebo-Controlled Study in 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.

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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%)

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

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)

[a]Protocol qualifying attacks: ≥2 attacks in past 6moniths requiring hospitalization, urgent healthcare visit, or IV hemin at home
[b]Worst study value of ALT or AST prior to dosing: >ULN and ≤3×ULN
GFR, Glomerular Filtration Rate; mL, ULN, Upper Limit of Normal,; ALT, alanine aminotransferase; AST, aspartate transaminase; ULN, upper limit of normal

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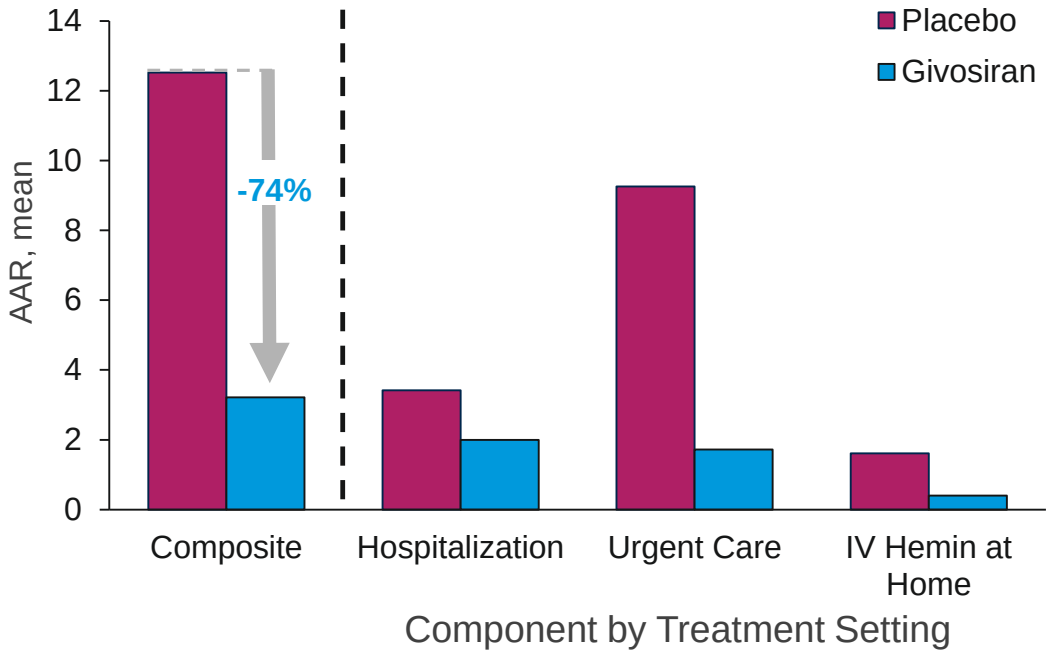
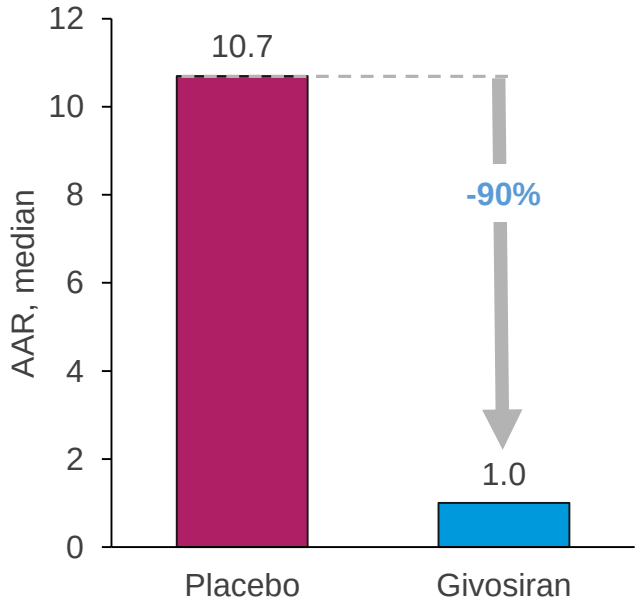
Primary Efficacy Endpoint: Annualized Attack Rate (AAR) in Patients with AIP

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}

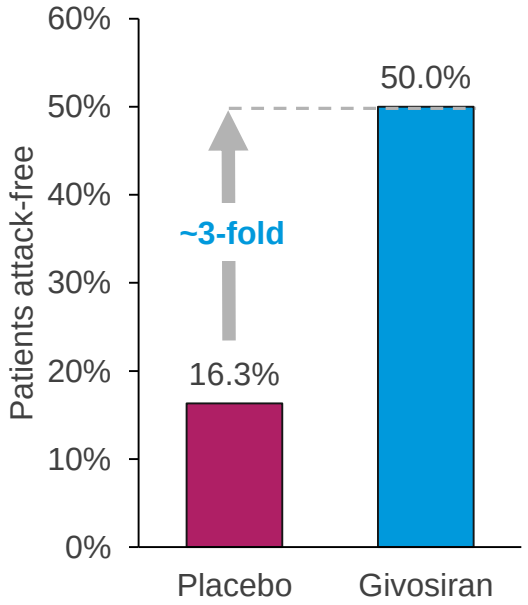
Composite and all endpoint components reduced



Reduction in median composite attack rate



Increase in patients attack-free



Mean AAR was derived using the negative binomial regression model; mean AAR for components was duration-weighted AAR; median AAR was calculated from the individual's patient's AAR

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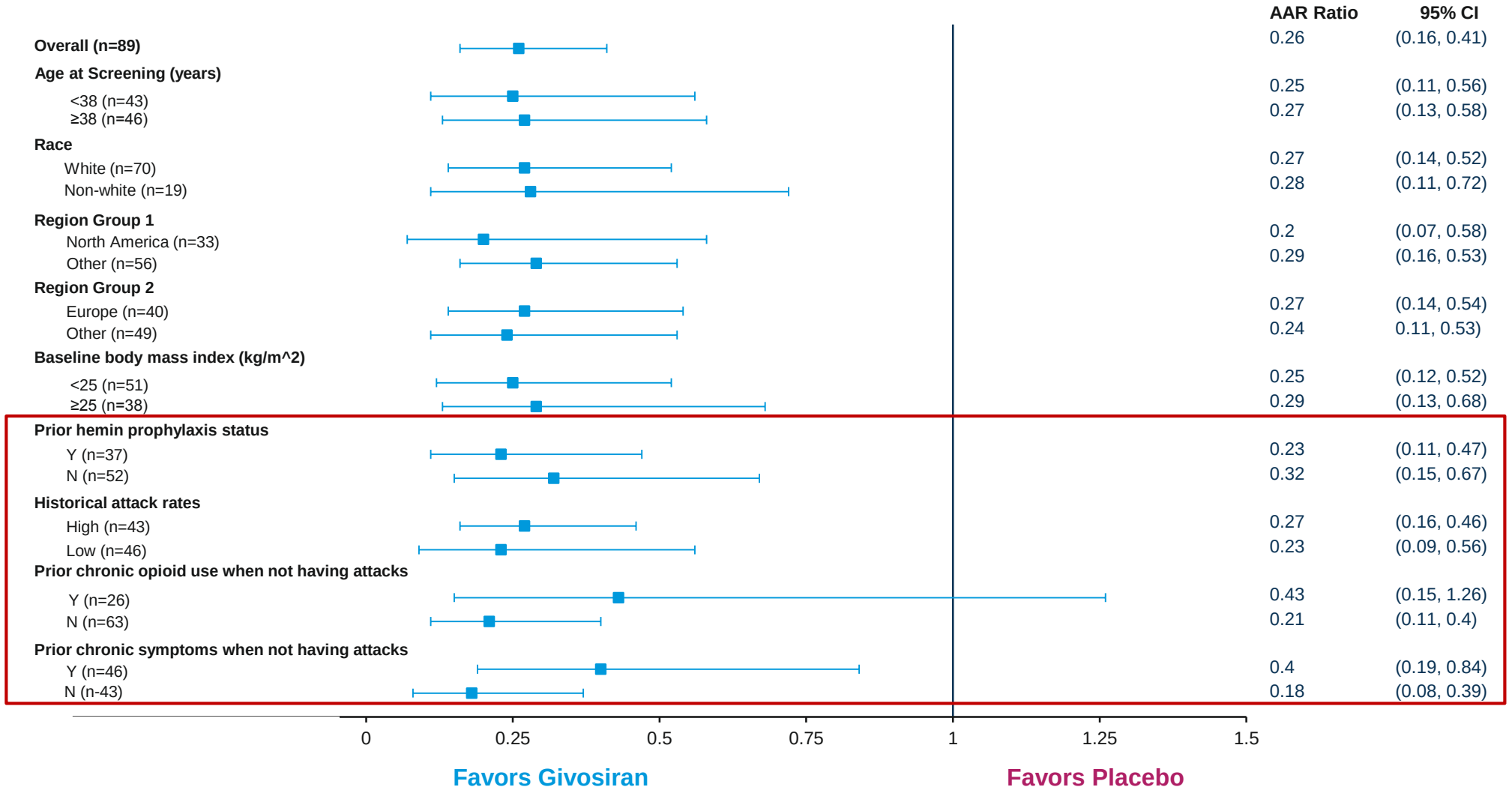
AAR in AIP Patients: Pre-Specified Subgroup Analysis

Treatment with givosiran was favored compared to placebo 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
LS Mean ALA in AIP at Month 3, mmol/mol Cr	19.96	1.75	-18 (-22.3, -14.2)	8.74×10^{-14}
LS Mean ALA in AIP at Month 6, mmol/mol Cr	23.15	4.01	-19 (-26.0, -12.2)	6.24×10^{-7}
LS Mean PBG in AIP at Month 6, mmol/mol Cr	49.11	12.9	-36 (-49.7, -22.7)	8.80×10^{-7}
Mean Annualized days on hemin in AIP	29.71	6.77	0.23 (0.11, 0.45)	2.36×10^{-5}
Mean Composite Attack Rate in AHP	12.26	3.35	0.27 (0.17, 0.43)	1.36×10^{-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.

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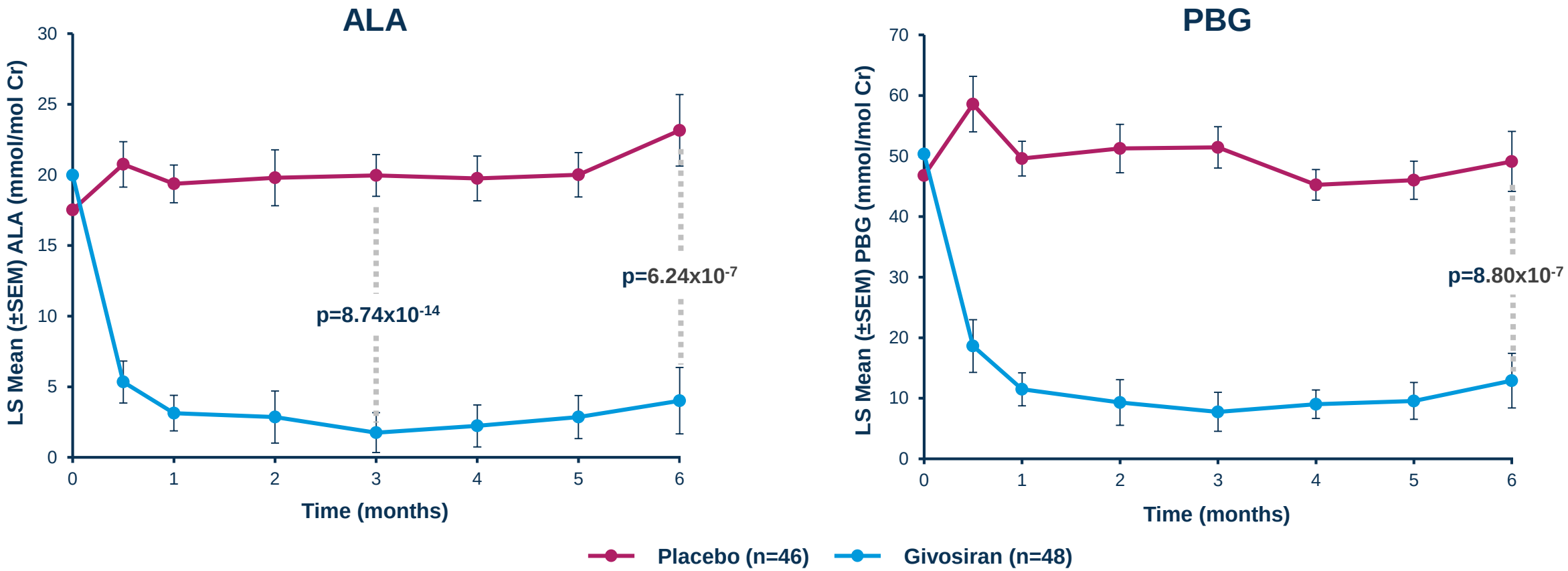
ALA and PBG Levels in AIP Patients

- 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



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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

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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

AE, Adverse Event; SAE, Serious Adverse Event

*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

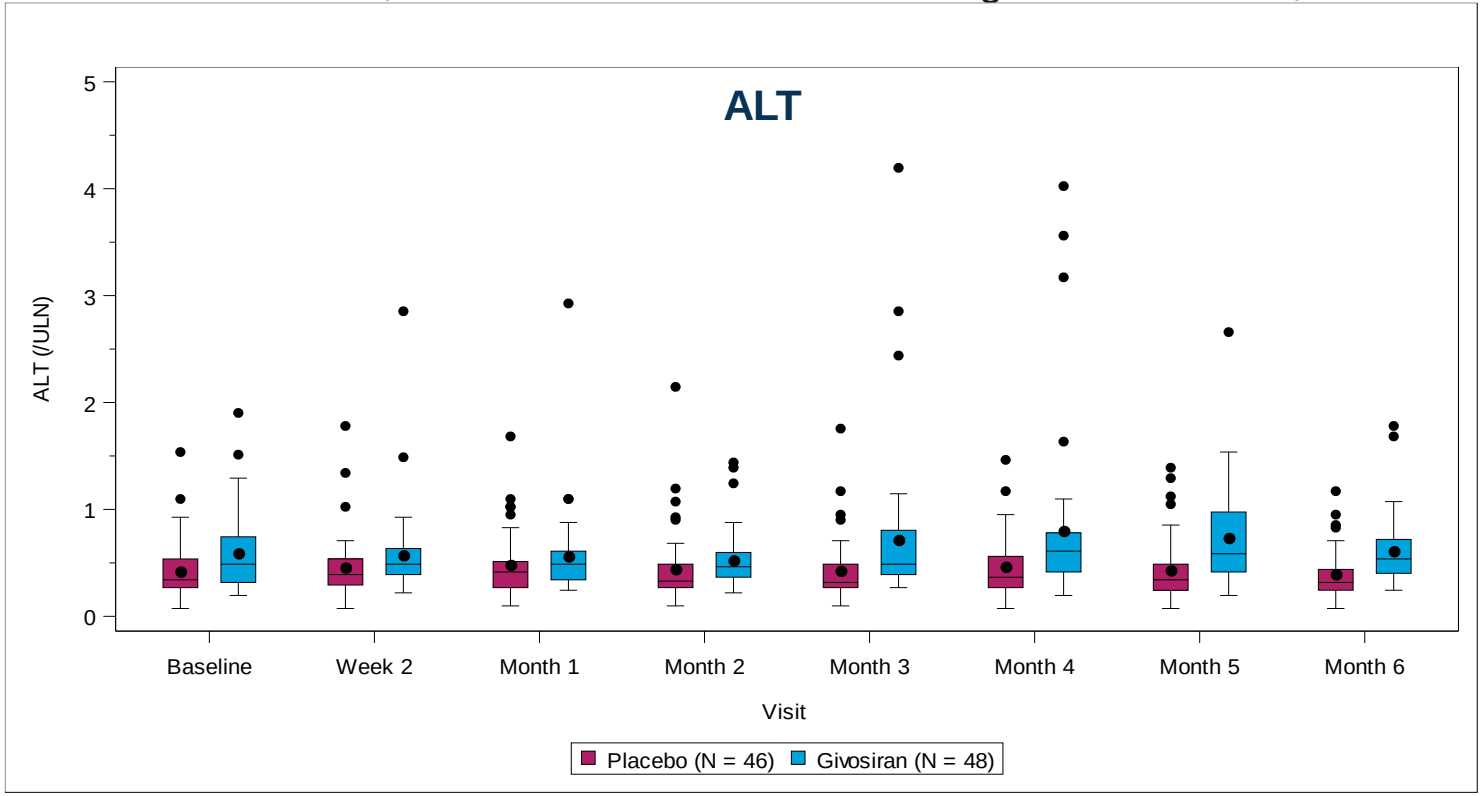
Common Adverse Events (≥5% difference in treatment groups)

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

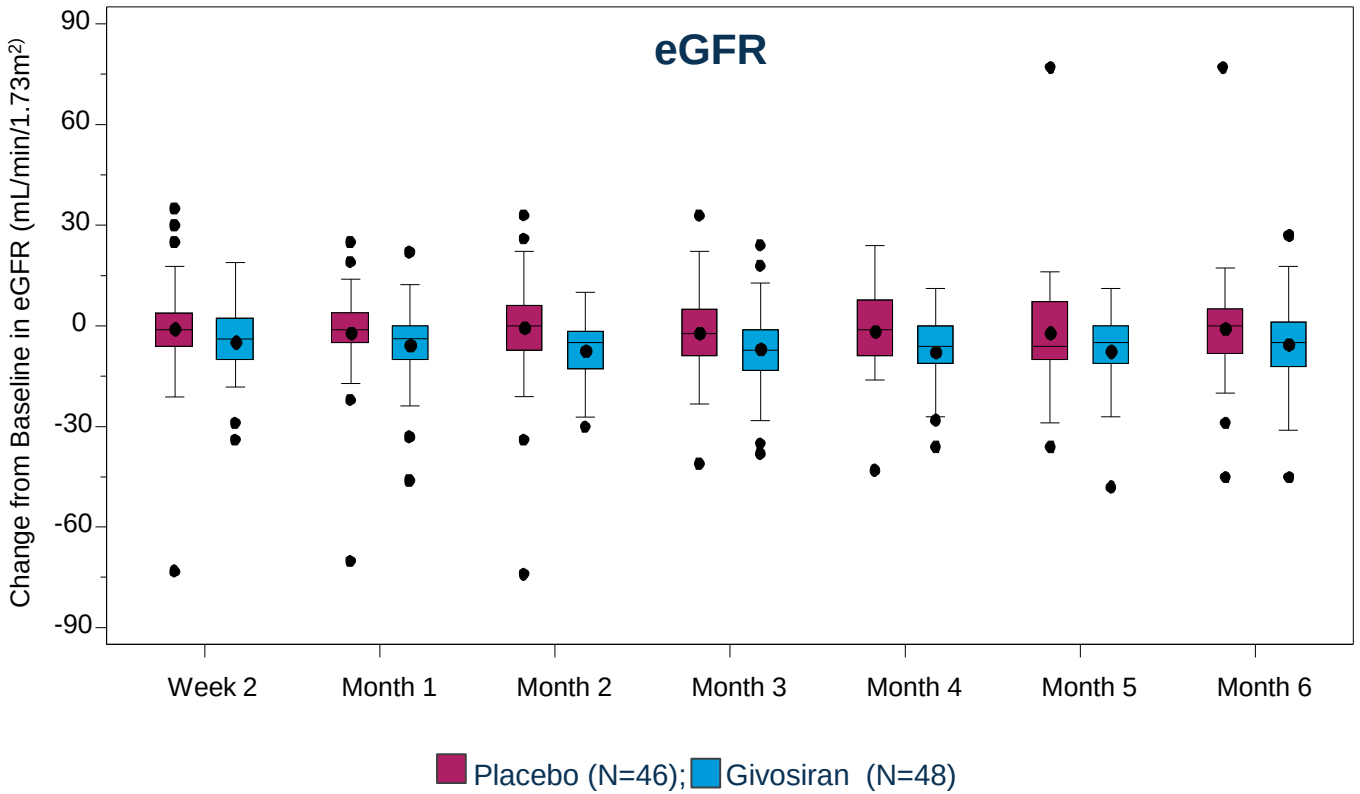
- ALT > 3x ULN in 7 (14.6%) givosiran patients and 1 (2.2%) placebo patient
  - 1 givosiran patient discontinued due to a protocol-defined stopping rule of ALT >8x ULN
  - 1 givosiran patient had dose interrupted due to a protocol-specified rule, with resumption at 1.25 mg/kg
  - 5 patients had resolution 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



ALT, alanine aminotransferase; ULN, Upper Limit of Normal

Impact of Givosiran on Renal Function

- 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

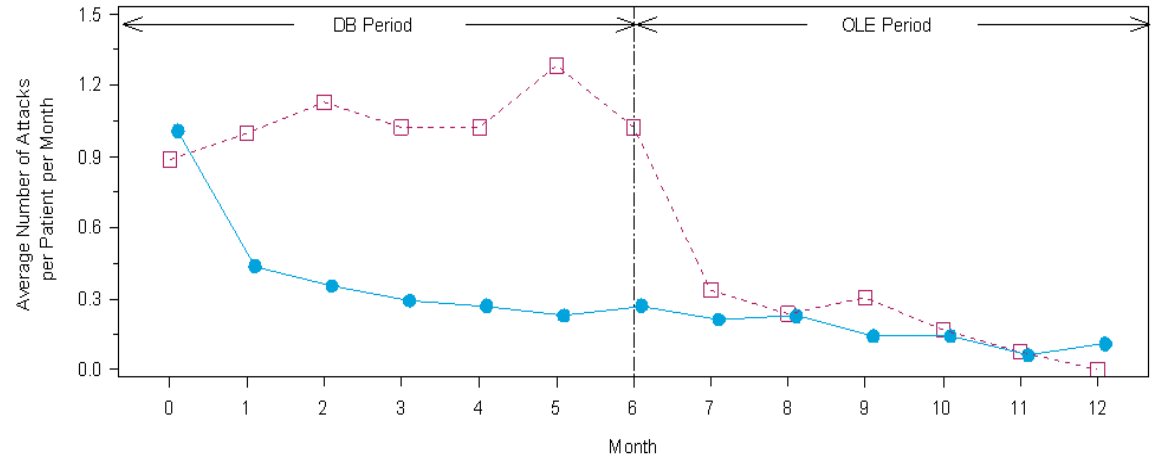


eGFR, Estimated Glomerular Filtration Rate ULN, Upper Limit of Normal

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

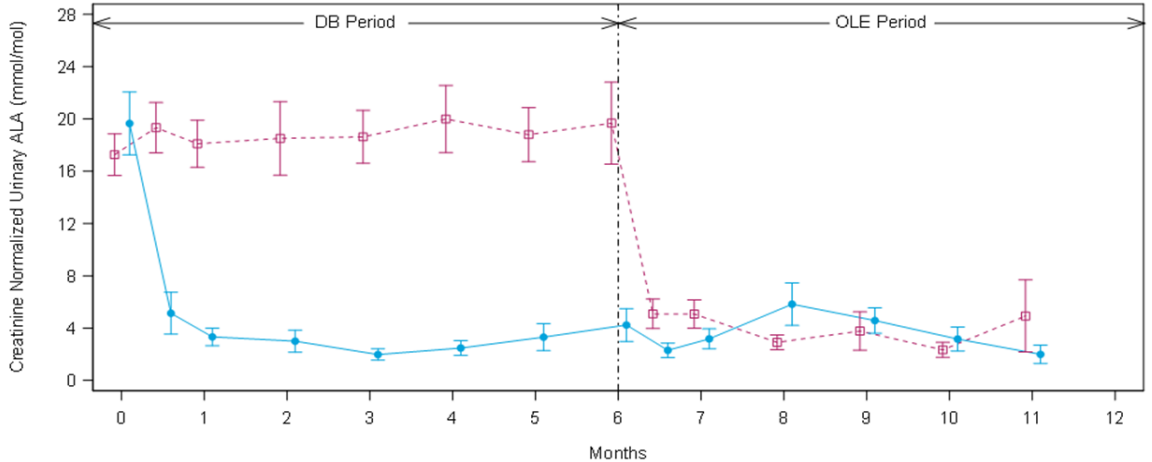
Monthly Attack Rate



No. of Patients:

Placebo	46	46	46	46	46	46	46	45	38	26	18	13	7
Givosiran	48	48	48	48	48	48	48	47	35	28	21	16	9

Urinary ALA



No. of Patients:

Placebo	46	42	44	42	45	39	44	41	40	36	26	19	13	6
Givosiran	48	47	47	48	47	45	44	46	33	33	27	20	13	8

Data cut 31 Jan 2019

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

ENVISION Patient Reported Outcomes and Patient Experience Data

Eliane Sardh

Patient-focused Approach to Endpoint Selection in ENVISION Study

Understanding AHP

- Literature Search
- Patient Interview Study; Qualitative
- FDA Voice of the Patient Meeting
- EXPLORE Natural History
- Phase 1/2 Studies

Treatment Benefit: Key Concepts

- Attacks
- IV hemin use
- Pain (cardinal symptom)❖
- Nausea❖
- Fatigue❖
- Impact on daily activities and global health

❖ Pain, nausea and fatigue measured during and between attacks

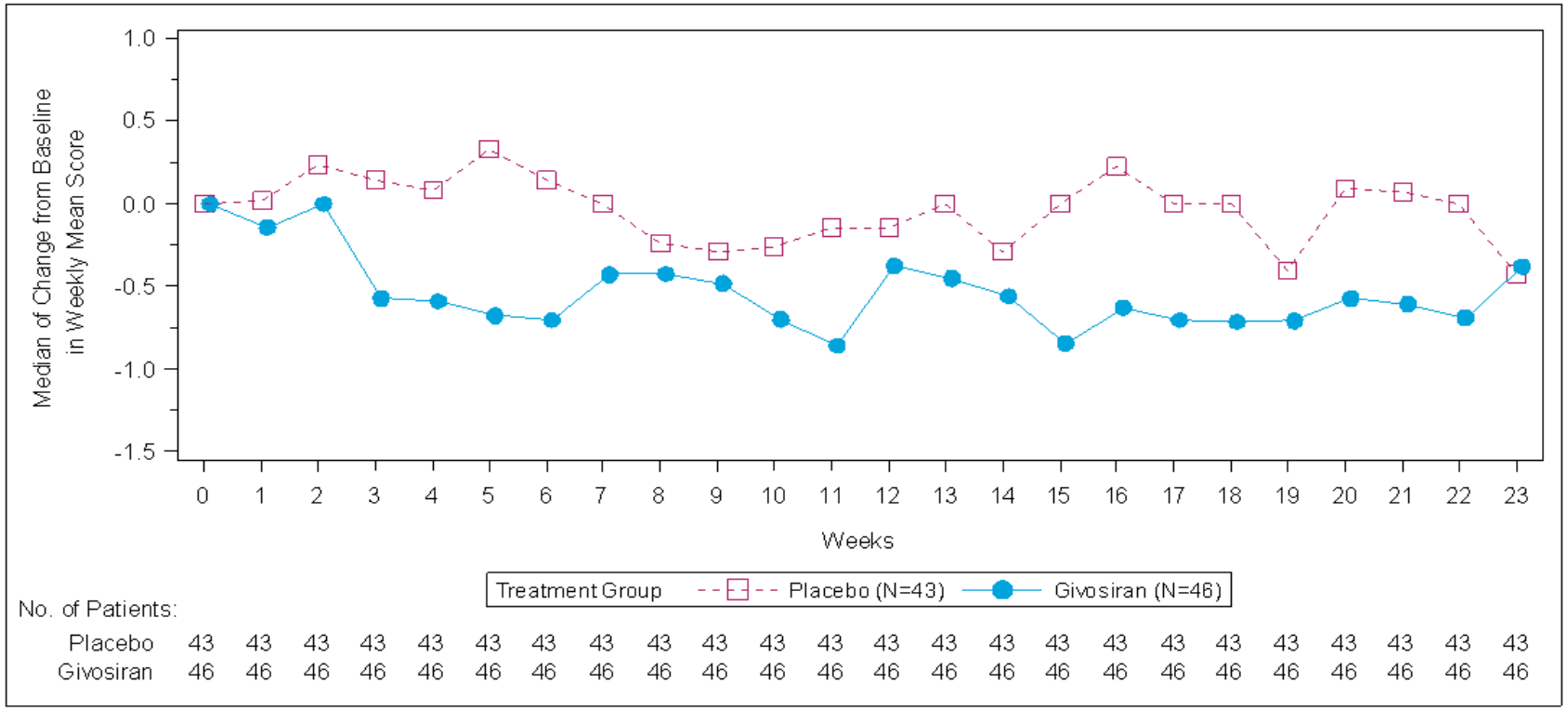
ENVISION Endpoints	Measure
Primary Endpoint	
Composite Porphyria Attacks*	Investigator-adjudicated events requiring healthcare utilization
Secondary Endpoints	
ALA/ PBG	LC-MS/MS
IV hemin doses	Concomitant Medications
Pain severity	Worst pain NRS* daily ediary
Nausea severity	Worst nausea NRS** daily ediary
Fatigue severity	Worst fatigue NRS***daily ediary
Global health/ physical impact	SF-12 PCS
Exploratory Endpoints	
Pain severity	Daily analgesic use
Global health/mental impact	SF-12 MCS^, SF-12 eight subscales
Impression of improvement or decline in in clinical status	PGIC^^^
Patient experience	PPEQ^^^^

*measured by Brief Pain Inventory – Short Form (BPI-SF) Item 3; **measured by Nausea Numeric rating scale (NRS); ***measured by Brief Fatigue Inventory – Short Form (BFI-SF) Item 3
^ SF-12, Short Form (12-item) Health Survey, Mental Component Summary; ^^ Patient Global Impression of Change; ^^^ Porphyria Patient Experience Questionnaire

Daily Worst Pain Score in AIP Patients

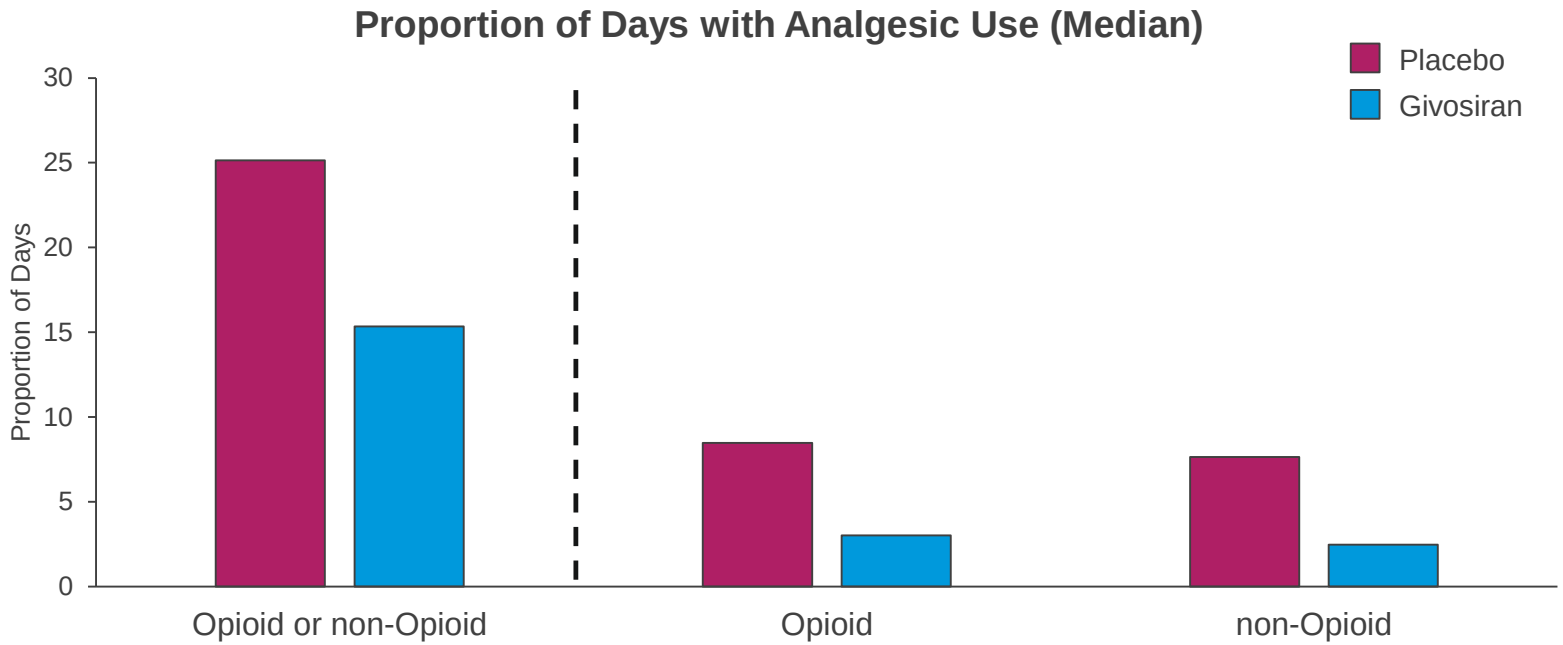
- Based on a numeric rating scale (NRS) of 0 to 10, where 0 equals no or lowest symptom level and 10 equals the highest or worst symptom level. Daily worst pain was captured by eDiary and averaged into a weekly (i.e., 7-day) score
- Patients on givosiran had greater reduction in daily worst pain throughout 6-month treatment than placebo

Median Change from Baseline in Worst Daily Pain Score During the 6-Month DB Period



Lower Daily Worst Pain Scores: Not Due to Higher Analgesic Use

- At Month 6, givosiran was associated with a lower proportion of days with analgesic use*, compared to placebo
  - At baseline, proportion of patients using opioids daily or most days in between attacks was similar between placebo (28%) and givosiran (29%)**

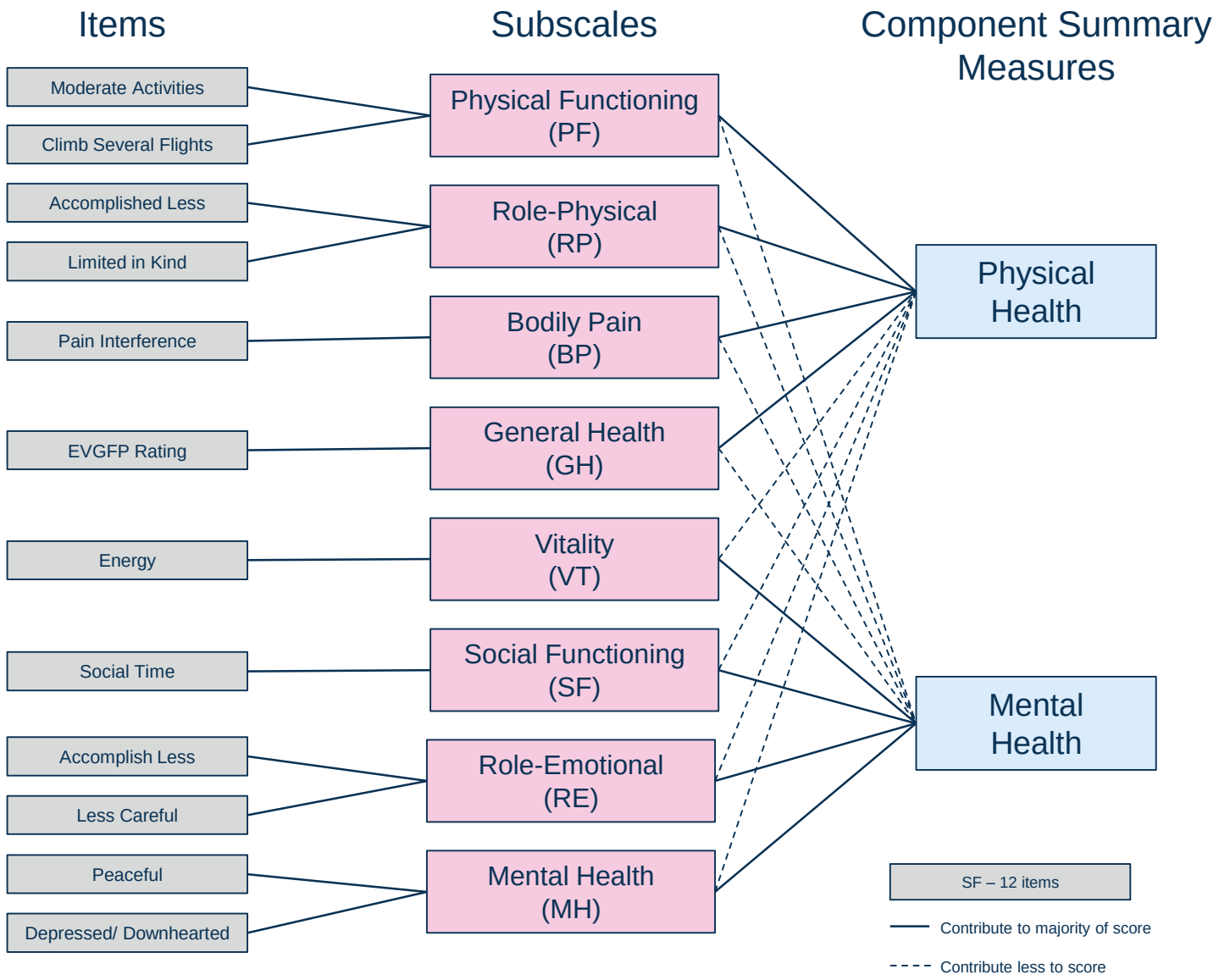


*Analgesic use is an exploratory endpoint

**Proportion of days with opioid use was not captured at baseline

SF-12 PCS, MCS, and 8 Subscales

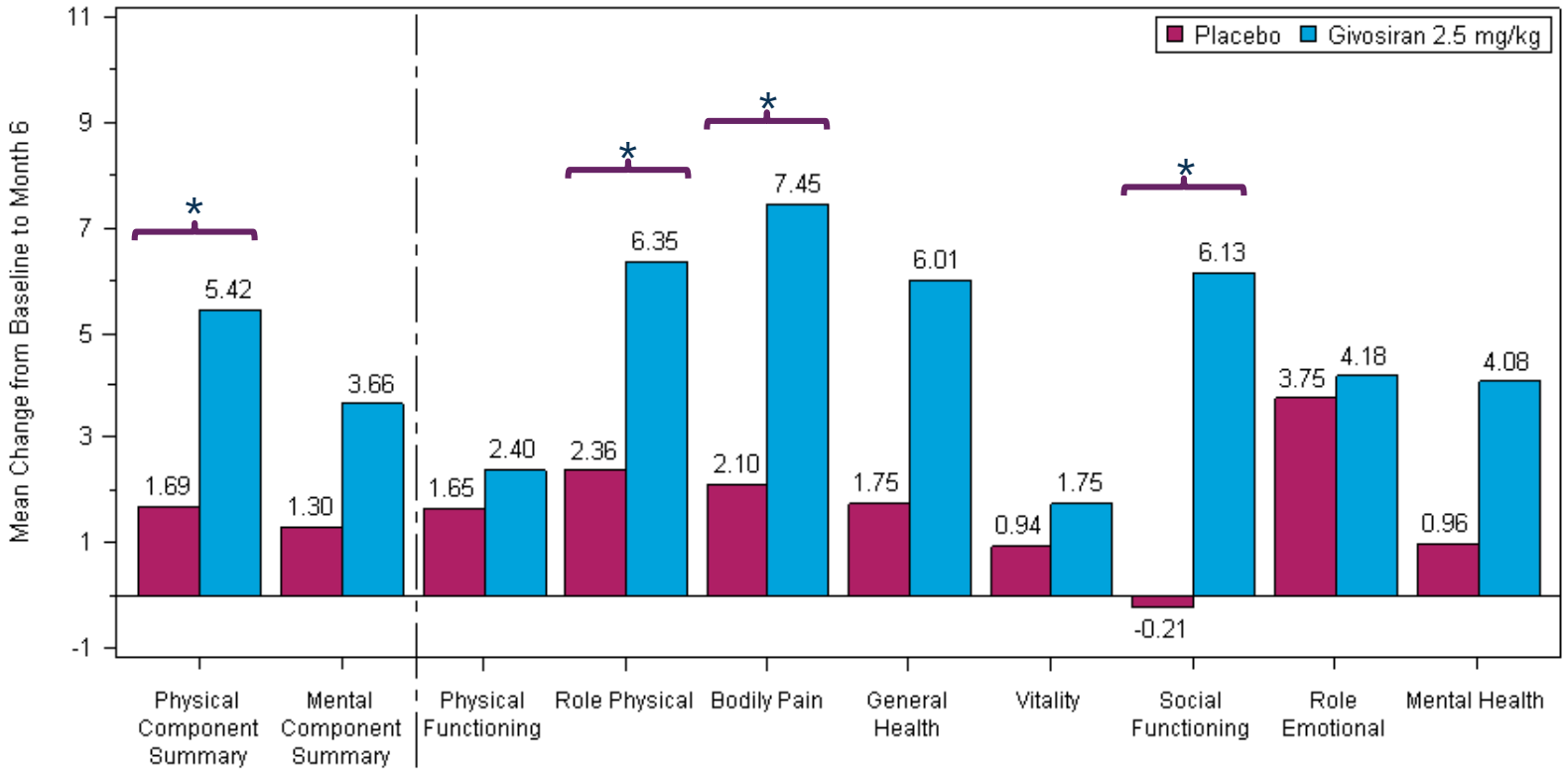
- 12 items and 8 subscales feed into both Component Summaries; solid lines indicate the domains contributing most to PCS* and MCS**; dashed lines indicate domains contributing less
- Domains and Component Summaries are not mutually exclusive
- Question answers are scored into quantitative values from a pre-specified psychometrically validated algorithm



*PCS is a secondary endpoint; MCS is an exploratory endpoint

SF-12 Assessment: Change from Baseline at Month 6 (AIP)

- Improvement in PCS of SF-12 (secondary endpoint) with givosiran compared to placebo
- Consistent evidence of effect favoring givosiran in the SF-12 domains of bodily pain, social functioning, and role-physical



Higher scores indicate greater improvement from baseline

*Indicates nominal statistical significance p<0.05

Patient Global Impression of Change (PGIC)

- PGIC measures the patient's belief about the efficacy of treatment on a single item using a 7-point global rating of change scale which is anchored to "since the start of the study"
- PGIC is a commonly used and well documented measure to assess clinically meaningful change in clinical trials

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is:

✔ *one box only:*

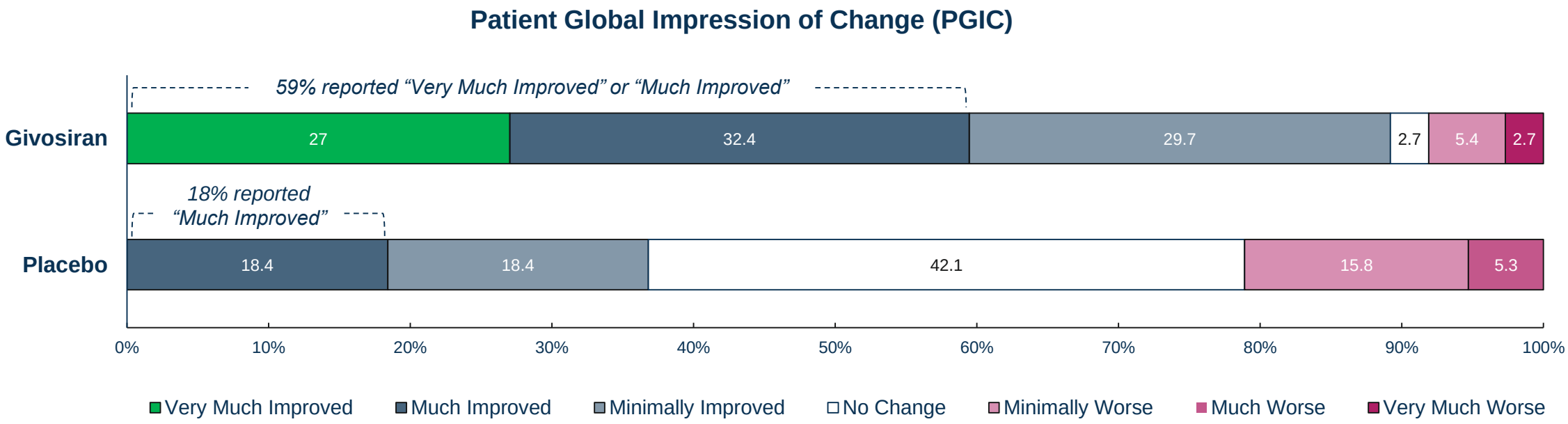
[1] ☐ Very Much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No Change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very Much Worse

(US/English)

Guy, W. *ECDEU Assessment Manual for Psychopharmacology Revised*. Rockville, MD: National Institute of Mental Health; 1976.

PGIC: AHP Patients at Month 6

- When given the PGIC at 6 months, 59% of givosiran patients reported their overall status since the beginning of the study was “very much improved” or “much improved” compared to 18% of placebo treated patients reporting “much improved”



Results displayed are among those who responded (38 out of the 46 placebo patients and 37 out of the 48 givosiran patients); only 1 non-AIP patient responded to the question

Porphyria Patient Experience Questionnaire (PPEQ)

- Porphyria Patient Experience Questionnaire (PPEQ) contains 8 items measuring impacts and treatment experience
- Concepts selected based on qualitative patient interviews and literature review

IMPACTS

Compared to before you started this study, how has your ability to do the following changed?

	Much better	Minimally better	No change	Minimally worse	Much worse	Not applicable
1. Traveling more than a day for work or pleasure	□	□	□	□	□	□
2. Participating in social activities, such as visiting friends	□	□	□	□	□	□
3. Planning future events, such as work or personal appointments	□	□	□	□	□	□
4. Doing household chores, such as meal preparation or cleaning	□	□	□	□	□	□
5. Exercising moderately, such as walking more than 20 minutes	□	□	□	□	□	□

TREATMENT EXPERIENCE

Compared to your porphyria treatment prior to the study, how has your current study drug changed your view on the following items?

	Much better	Minimally better	No change	Minimally worse	Much worse
6. Convenience of your current porphyria treatment	□	□	□	□	□
7. Your overall satisfaction with your porphyria treatment	□	□	□	□	□

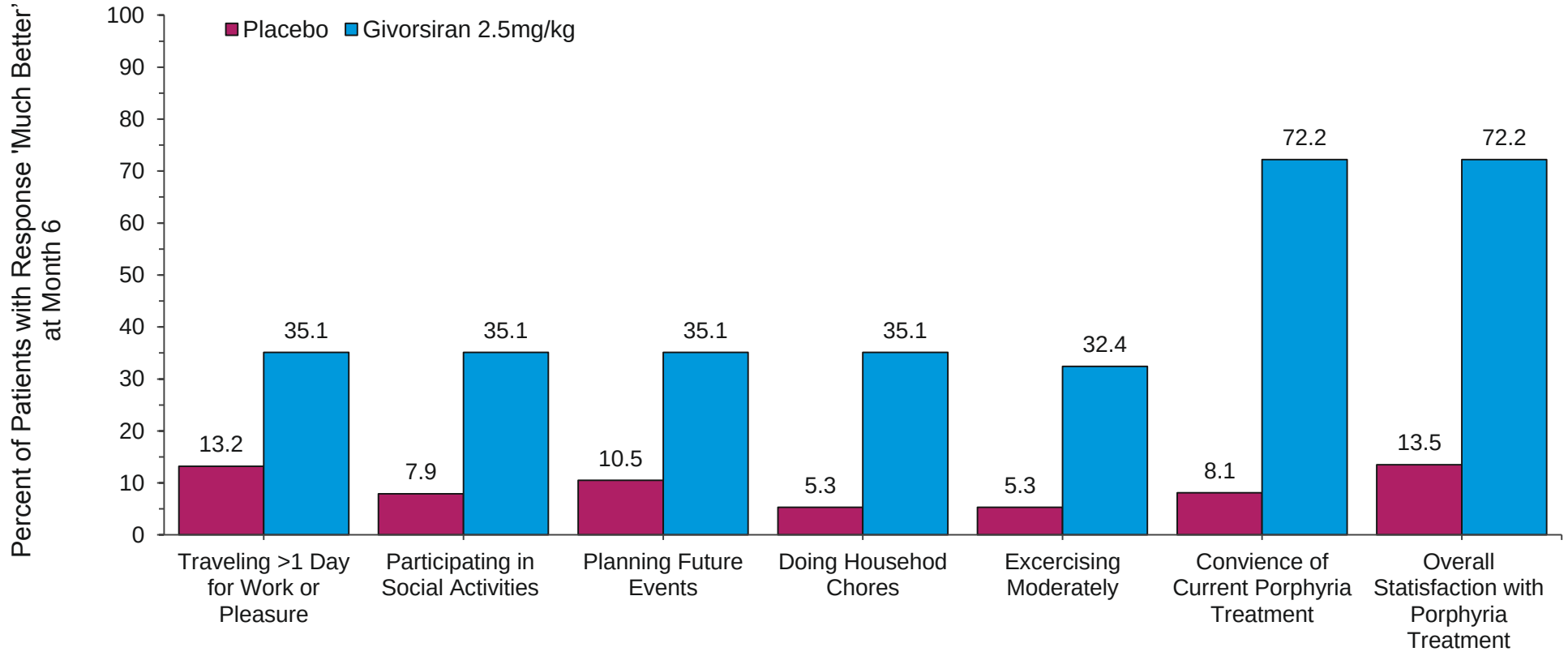
In general, in the last four weeks, how often did you feel:

	Always	Most of the time	Sometimes	Rarely	Never
8. That your study drug was helping you to return back to a more normal life?	□	□	□	□	□

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

PPEQ: AHP Patients at Month 6

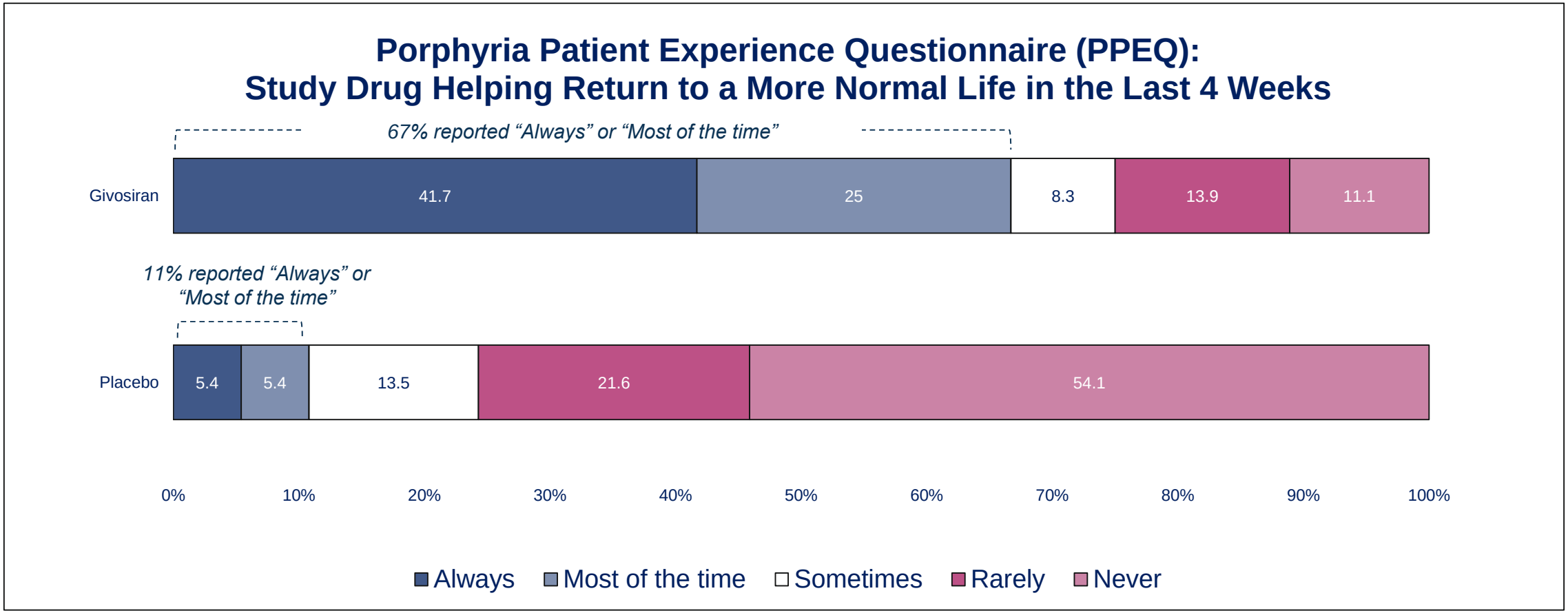
- A higher proportion of patients receiving givosiran reported improvements in activities of daily living and disease impacts on daily functioning, as well as satisfaction with treatment, compared to placebo



Note: The figure presents the percent of patients with response 'Much Better' (other options were “Minimally Better”, “No Change”, “Minimally Worse”, “Much Worse”)

PPEQ: AHP Patients at Month 6

- 67% of Givosiran patients reported “Always” or “Most of the time” to the question about the study drug helping return to a more normal life in the last four weeks, compared to 11% of patients receiving placebo



Results displayed are among those who responded (37 out of the 46 placebo patients and 36 out of the 48 givosiran patients)

ENVISION Patient Reported Outcome/Patient Experience Summary

- AIP patients on givosiran had greater reduction in daily worst pain (secondary endpoint) throughout 6-month treatment than placebo
- Givosiran treatment did not impact the secondary endpoints of daily worst fatigue or daily worst nausea at Month 6
  - Assessments will be repeated at Month 12 to determine if this result persists or changes with ongoing dosing
- Patients treated with givosiran had greater improvements in quality of life and ability to function, and greater treatment satisfaction than placebo at Month 6 as demonstrated by:
  - Consistent evidence in AIP patients of effect favoring givosiran in the SF-12 domains of bodily pain, social functioning, and role-physical (secondary endpoint)
  - A greater proportion of AHP patients noting improvement in their “overall status” since starting study (PGIC, exploratory endpoint)
  - A greater proportion of AHP patients with the ability to travel, participate in social activities, perform household chores, exercise moderately, as well as greater overall porphyria treatment satisfaction (PPEQ, exploratory endpoint)
  - A greater proportion of AHP patients reporting study drug helped them “return to a more normal life” when reflecting on the last four weeks (PPEQ, exploratory endpoint)

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