Twelve-month Interim Analysis of Efficacy and Safety of Givosiran, an Investigational RNAi Therapeutic for AHP, in the ENVISION Open Label Extension

***Sardh E[1]**, Balwani M[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[1], Wang JD[17], Langendonk JG[18], Ivanova A[19], Horie, Y[20], Anderson KE[21], Ventura P[22], Cappellini MD[23], Vassiliou D[1], Monroy S[24], Petrides PE[25], Adachi T[26], Kuter D[27], Scalera S[28], Sweetser MT[28], Hua Z[28], Penz C[28], Liu S[28], Ko JJ[28], Simon A[28], Gouya L[29] on behalf of the ENVISION investigators*

[1]Porphyria Centre Sweden, Centre for Inherited Metabolic Diseases, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [2]Icahn School of Medicine at Mt. Sinai, New York, New York, USA; [3]King's College Hospital, United Kingdom; [4]Klinikum Chemnitz, Chemnitz, Germany; [5]Hospital Clinic Barcelona, Barcelona, Spain; [6]University of California, San Francisco, California, USA; [7]Wake Forest University NC Baptist Medical Center, 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]Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan; [18]Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [19]St. Ivan Rilski University Hospital, Sofia, Bulgaria; [20]Tottori University School of Medicine, Tottori, Japan; [21]University of Texas Medical Branch, Galveston, Texas, USA; [22]Università degli Studi di Modena e Reggio Emilia, Modena, Italy; [23]University of Milan, Milan, Italy; [24]Instituto Nacional de Pediatría de Mexico, Mexico City, Mexico; [25]Hematology Oncology Center and LM University Munich, Munich, Germany; [26]Tokyo Saiseikai Central Hospital, Tokyo, Japan; [27]Massachusetts General Hospital, Boston, Massachusetts, USA; [28]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA; [29]Centre Français des Porphyries, Paris, France

June 30, 2020 || Webcast

Meeting organized and funded by Alnylam Pharmaceuticals || MED-UK-AS1-2000028 || Date of Preparation: June 2020

Disclosure Slide

I have previously been engaged as a consultant by Alnylam Pharmaceuticals with fees paid to Karolinska Institutet.

I am also leading an investigator-initiated study for which Karolinska Institutet receives funding from Alnylam Pharmaceuticals

Acute Hepatic Porphyria (AHP)

Disease Overview

- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in the liver[1,2]
- AIP is the most common type, with mutation in *hydroxymethylbilane synthase* (*HMBS*) gene[3,4]

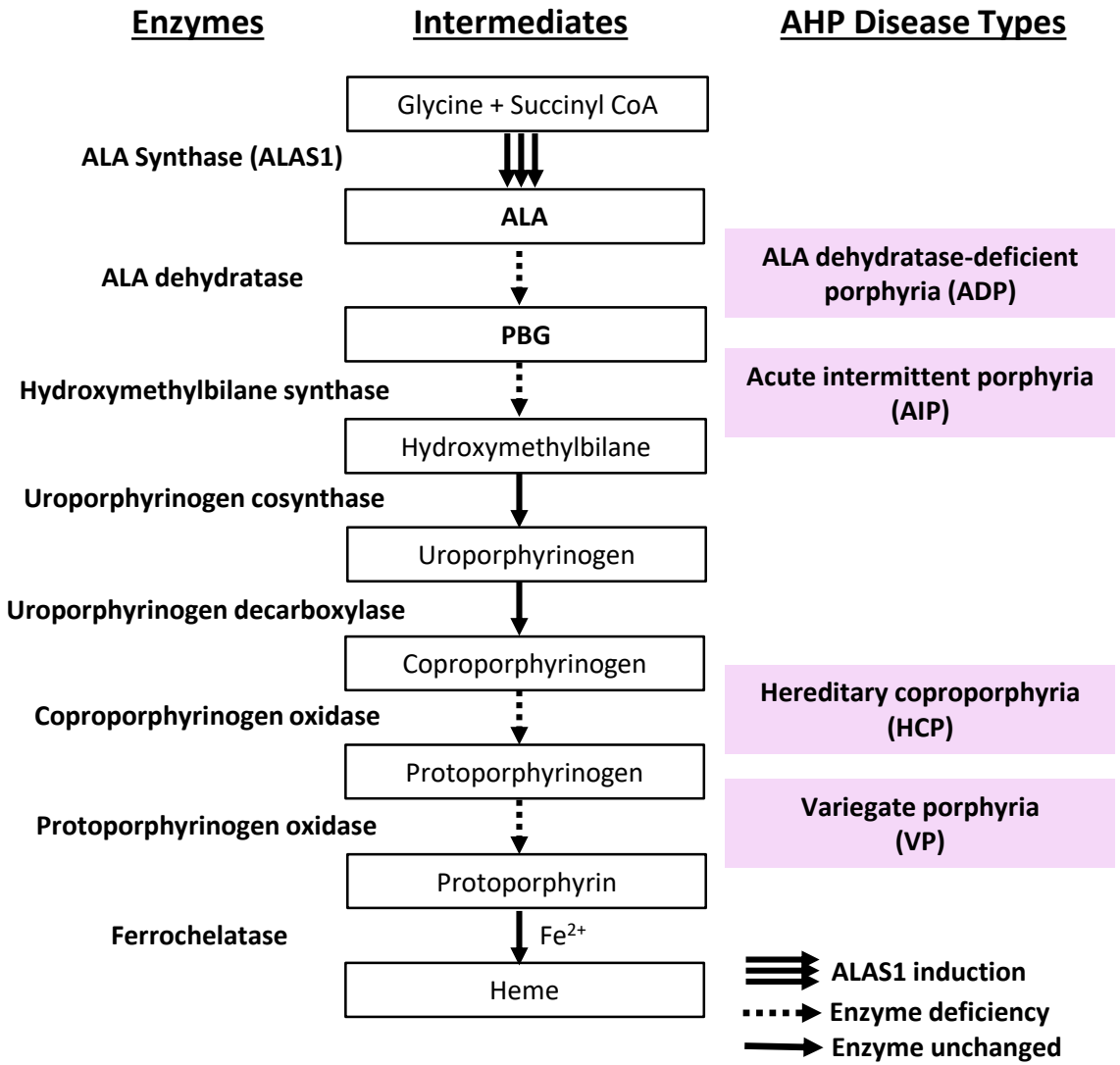
Disease Pathophysiology

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

Attacks, Chronic Manifestations, and Comorbidities

Patients can experience:

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



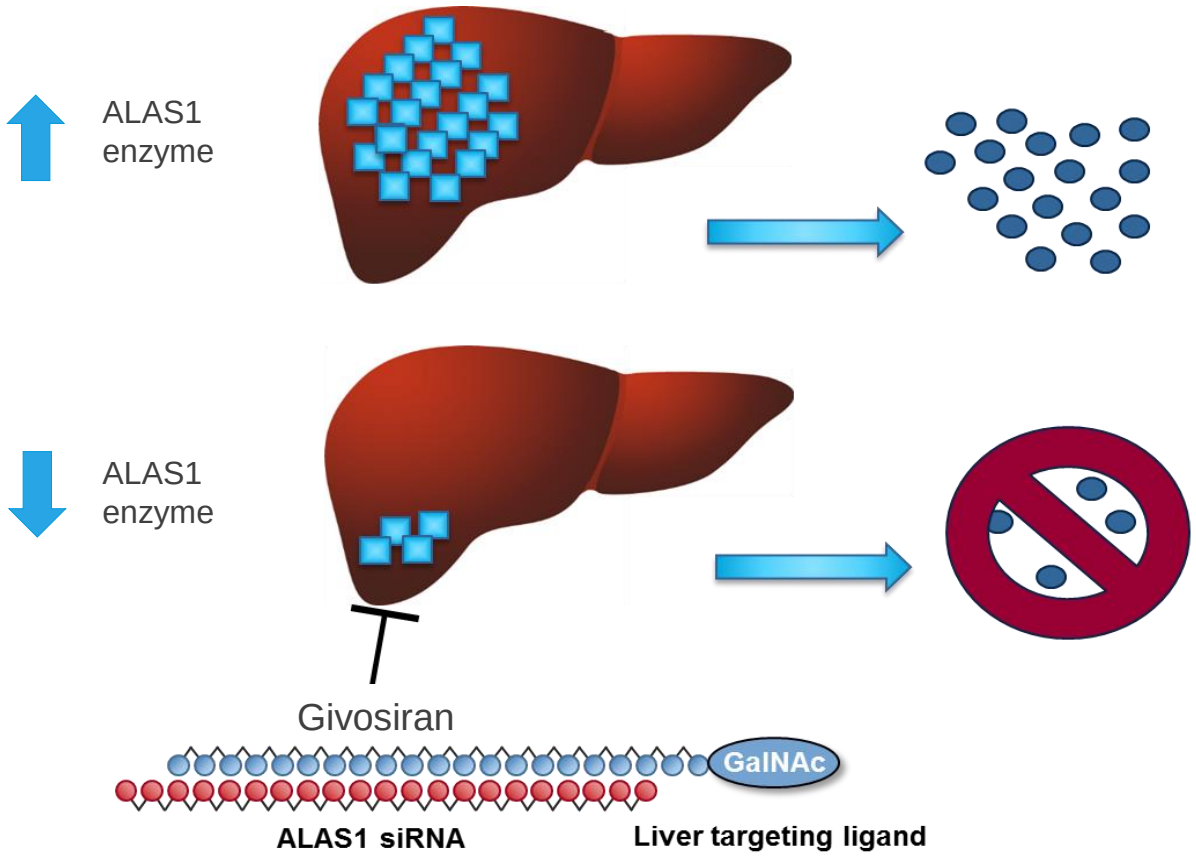
AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; CoA, coenzyme A; PBG; porphobilinogen

1. Puy et al. *Am J Hum Genet* 1997;60:1373–83 2. Balwani & Desnick. *Blood* 2012;120:4496–504 3. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 4. Elder et al. *JIMD* 2013;36:849–57; 5. Bissell et al. *Am J Med* 2015;128:313–7; 6. Gouya et al. *Hepatology* 2019; DOI:10.1002/hep.30936; 7. Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; 8. Simon et al. *Patient* 2018;11:527–37; 9. Stewart. *J Clin Pathol* 2012;65:976–80; 10. Pallet et al. *Kidney Int* 2015;88:386–95; 11. Andersson et al. *J Intern Med* 1996;240:195–201

Givosiran: An RNAi Therapeutic for AHP[1,2]

Therapeutic Hypothesis

- Reduction of Liver ALAS1 Enzyme to Lower ALA and PBG



ALA/PBG induces porphyria symptoms

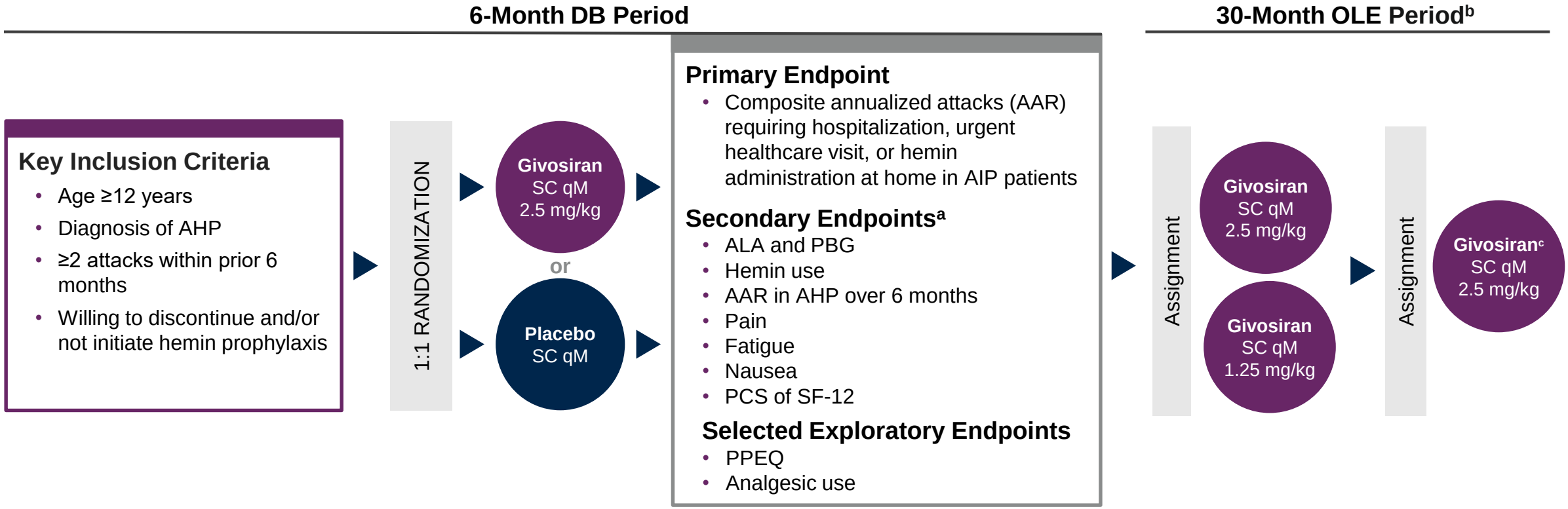
Givosiran results in reduction of ALAS1 mRNA and lowers ALA/PBG accumulation to prevent attacks and disease symptoms

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

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

ENVISION Phase 3 Study Design

- 94 patients with AHP enrolled in ENVISION at 36 sites in 18 countries
- All patients completed 6-month double-blind (DB) period; all eligible patients (n=93) entered 30-month open label extension (OLE) period



[a]Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted, at 6 months

[b]All endpoints listed above were considered exploratory in OLE period

[c]Amendment 5 increased the dose of all patients to 2.5 mg/kg monthly

ALA, delta-aminolevulinic acid; AAR, annualized rate of composite porphyria attacks, DB, double-blind; PBG; porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire qM, every month; SC, subcutaneous; SF-12, Short Form (12-item) Health Survey, OLE, Open Label Extension

Balwani et al. *International Liver Congress* 2019. Oral

Demographics and Baseline Characteristics of AHP Patients

- Baseline characteristics were generally balanced between groups

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

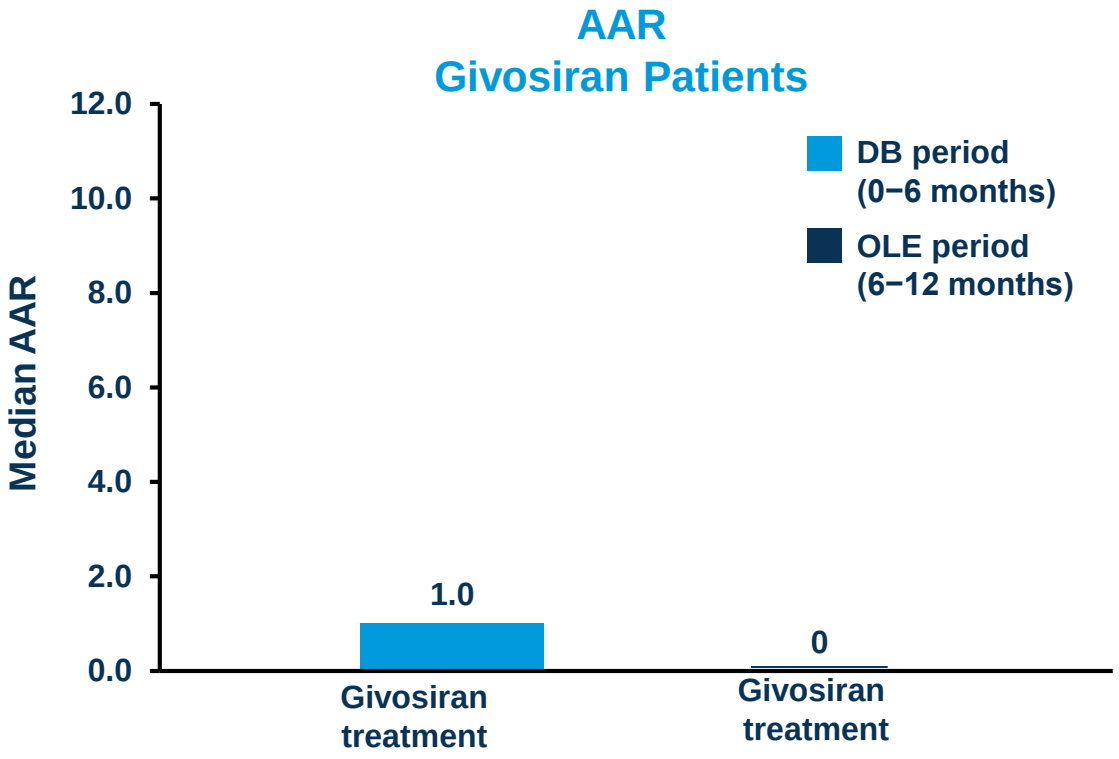
[a]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home

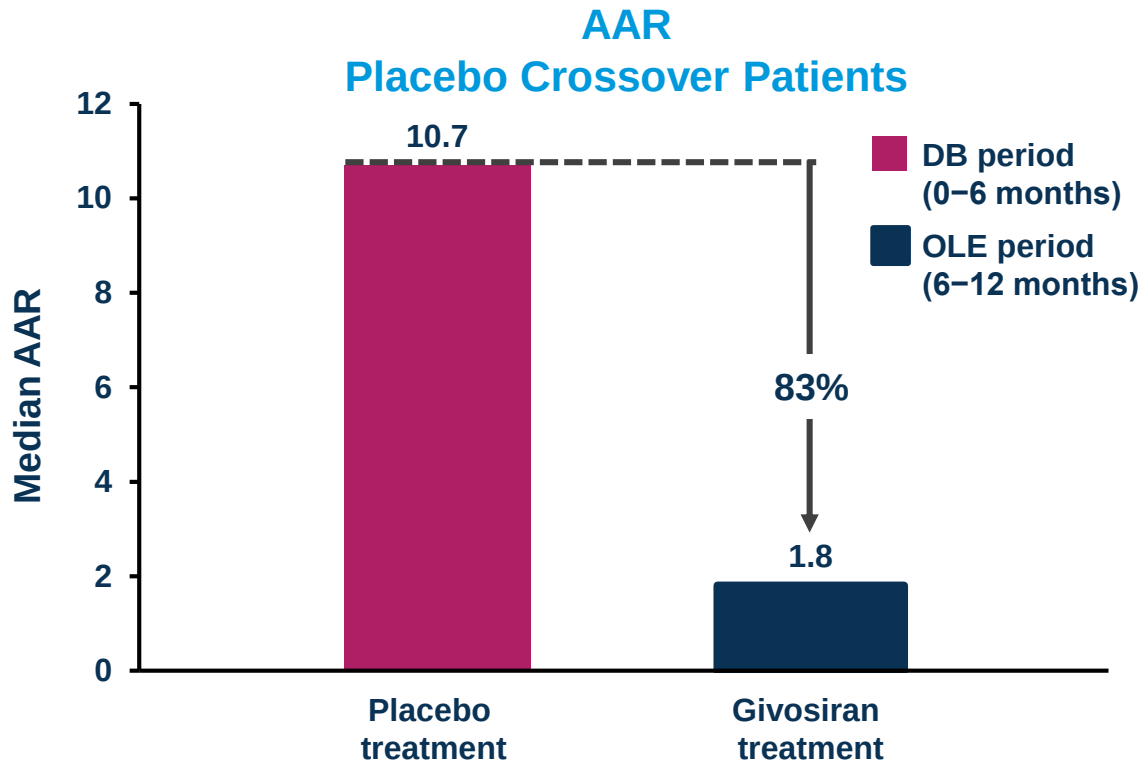
[b]One patient in the placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalization, urgent healthcare visit or intravenous hemin at home within 6 months prior to screening (patient had 2 attacks that were treated at home without intravenous hemin). This was identified as a protocol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

AAR, annualized rate of composite porphyria attacks; IV, intravenous

Sustained AAR Reduction with Long-Term Dosing

- Continued givosiran treatment led to sustained AAR reduction during the OLE
- Placebo crossover patients had similar AAR reduction in OLE period as givosiran patients in DB period[a]
  - Trend towards increased efficacy in placebo crossover patients for 2.5 mg/kg[b] dose compared to 1.25 mg/kg[c] dose (Intra-patient AAR reduction of 79% vs 67%, respectively)



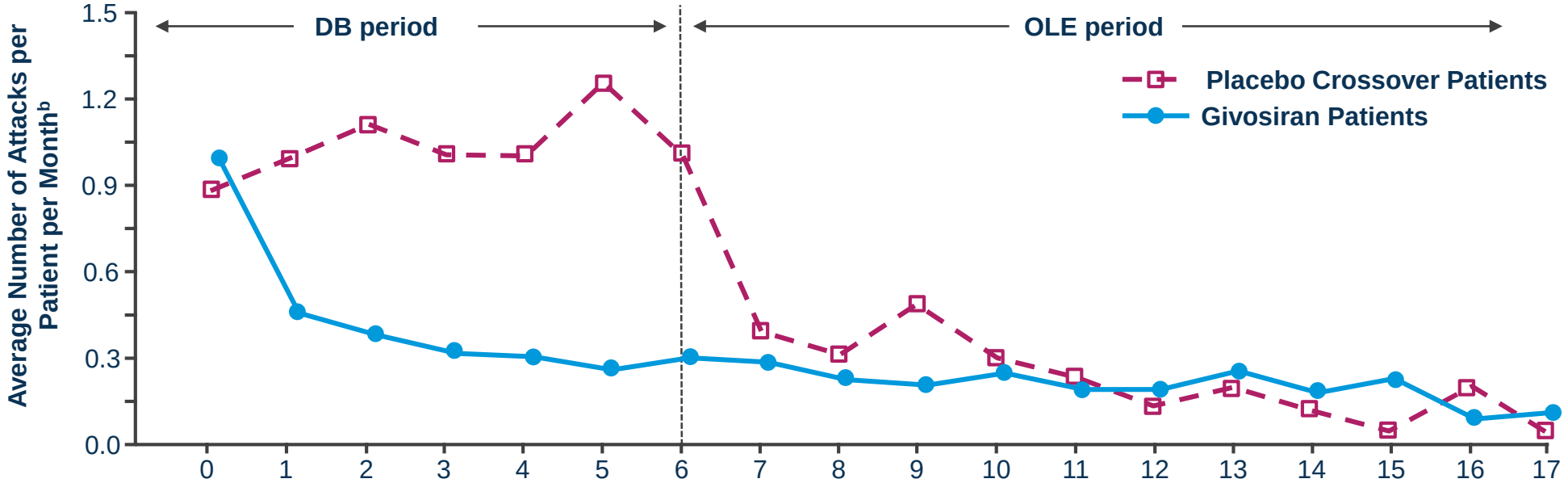


[a]Descriptive analysis
[b]Placebo cross over patients receiving 2.5mg/kg (n=29)
[c]Placebo cross over patient receiving 1.25mg/kg (n=17)
OLE, open label extension; AAR, annualized rate of composite porphyria attacks
Balwani et al. International Liver Congress 2019. Oral

Givosiran Treatment Led to Sustained and Rapid Reduction of Attacks Over Time

- Patients who continued givosiran treatment had sustained or enhanced reduction in attacks over time
- Placebo crossover patients had similar attack reduction during OLE period as givosiran patients in DB period

Average Number of Attacks Over Time



No. of patients:																				
Placebo Crossover	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9
Givosiran	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9

[a]Month = 28 days

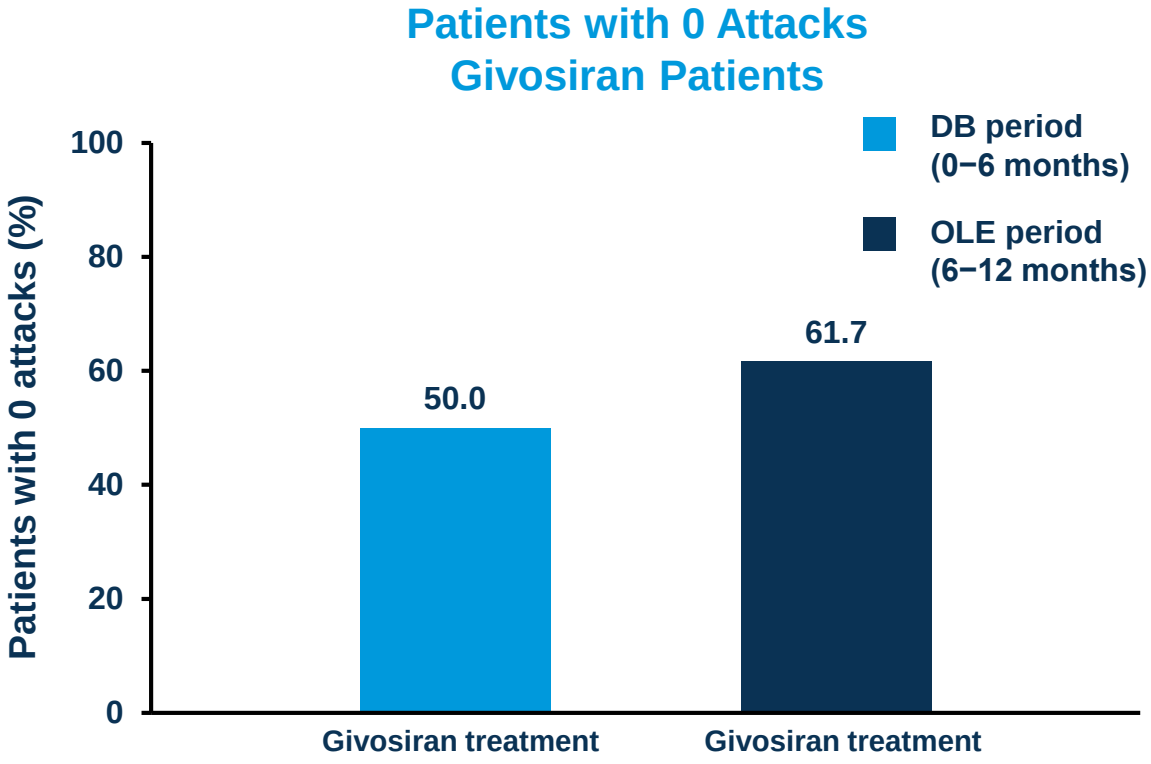
[b]OLE Data for 1.25mg/kg and 2.5mg/kg are pooled

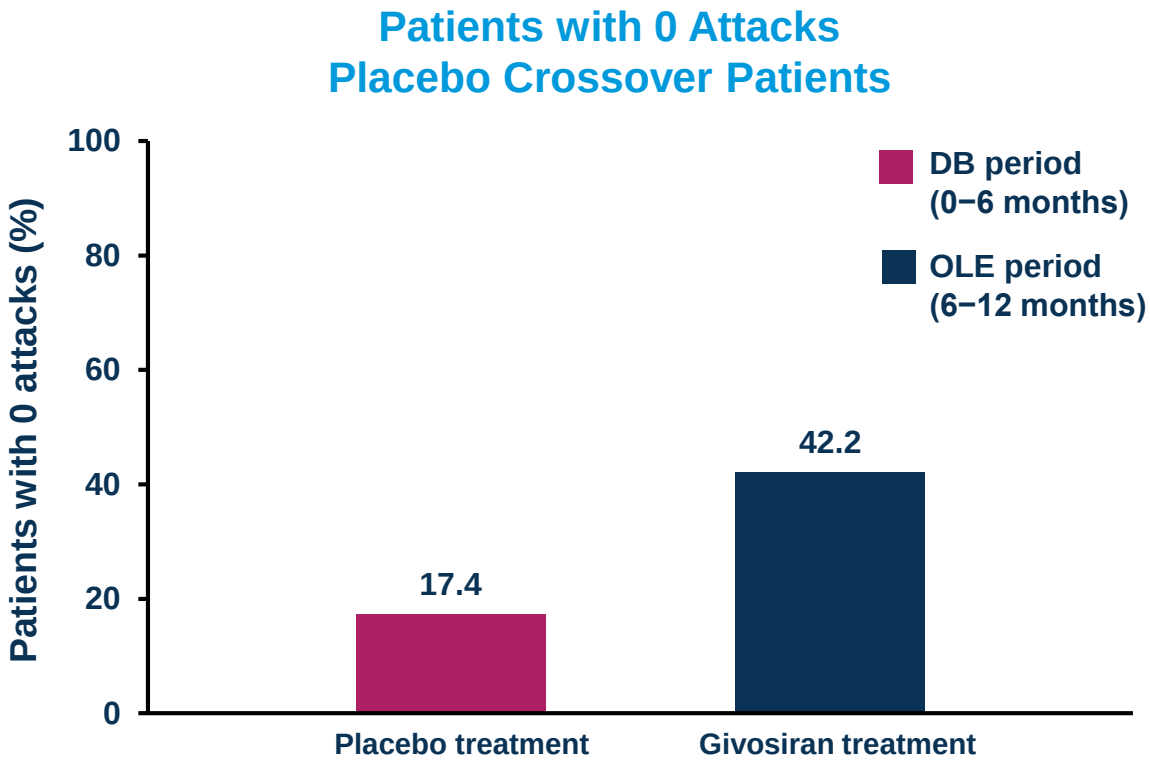
DB, double-blind; OLE, open label extension

Balwani et al. International Liver Congress 2019. Oral

Increased Number of Patients With Zero Attacks with Long-Term Dosing

- Proportion of patients with zero attacks (61.7%) increased with continued givosiran treatment
- Proportion of placebo crossover patients with zero attacks (42.2%) increased with givosiran treatment in OLE period



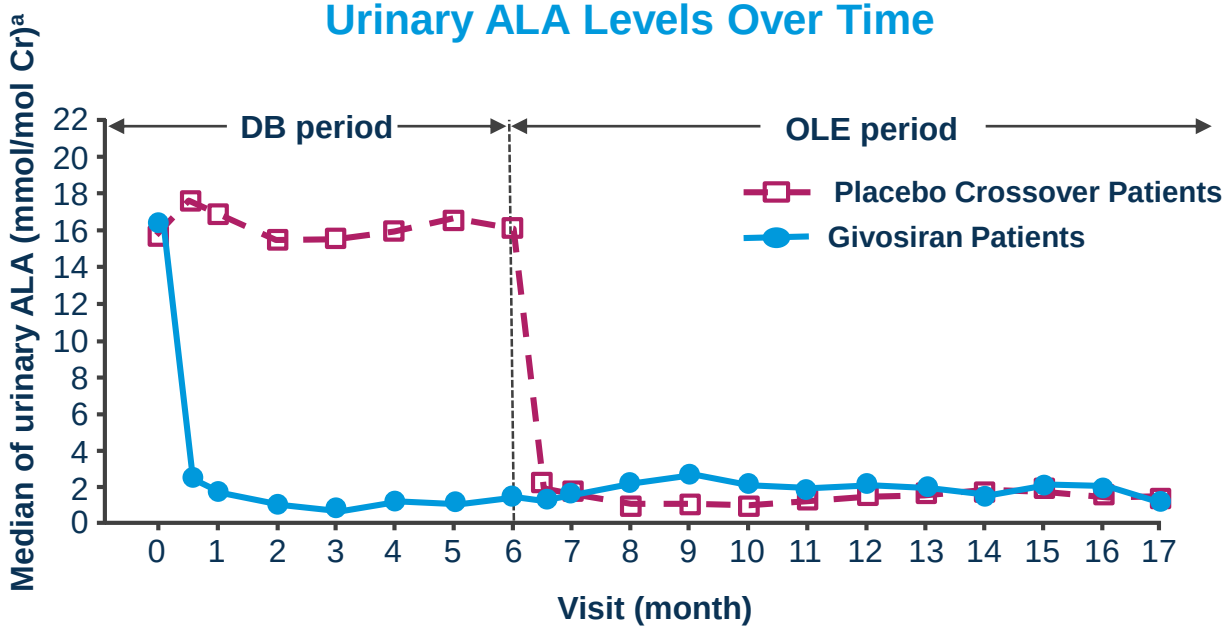


DB, double-blind; OLE, open label extension
Attacks are composite

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

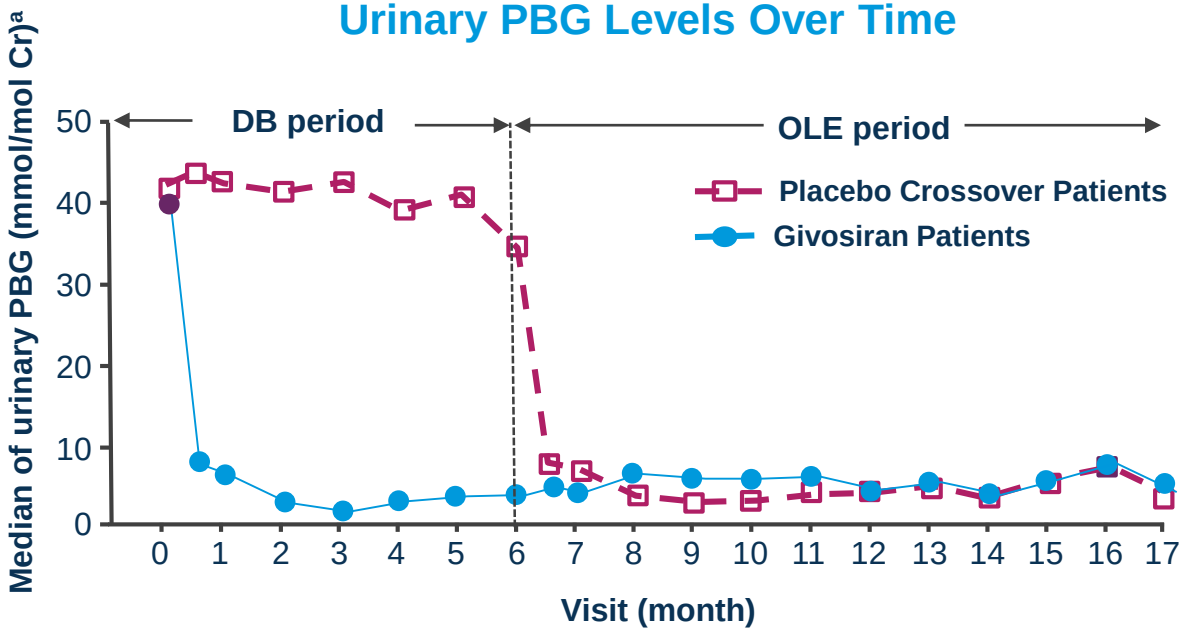
- Continued givosiran treatment led to sustained ALA and PBG reduction during OLE period
- Placebo crossover patients had >75% reduction in median ALA and PBG levels compared to baseline, consistent with data in givosiran patients during DB period[1]

Urinary ALA Levels Over Time



No. of patients:																				
PBO Crossover	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9
Givosiran	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9

Urinary PBG Levels Over Time



No. of patients:																				
PBO Crossover	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9
Givosiran	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9

[a]OLE Data for 1.25mg/kg and 2.5mg/kg are pooled

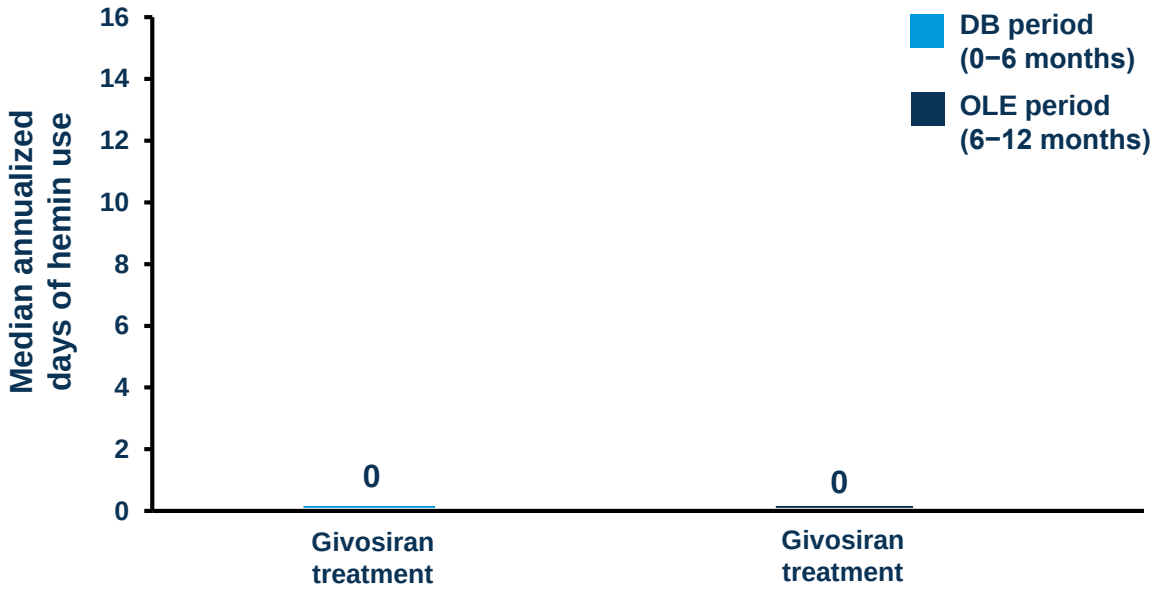
ALA, delta-aminolevulinic acid; DB, double-blind period; Cr, creatinine; No., number; OLE, open label extension; PBG; porphobilinogen; PBO, Placebo

1. Balwani et al. International Liver Congress 2019. Oral

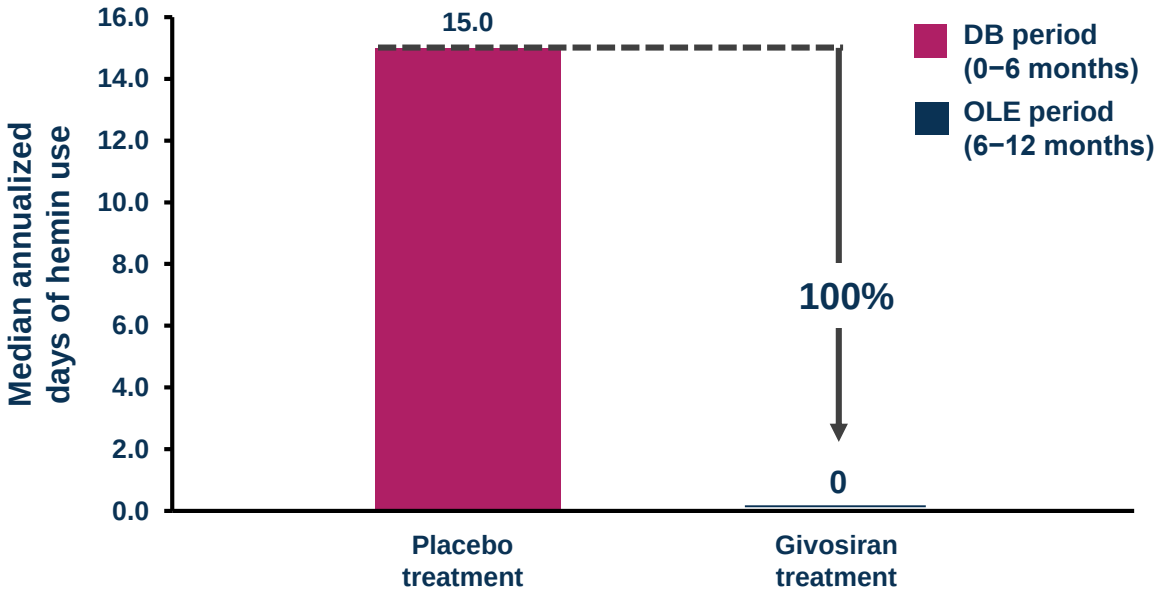
Sustained Reductions in Hemin Use with Long-Term Dosing

- Continued givosiran treatment led to sustained reductions in hemin use in OLE period, with 70% of patients requiring zero days of hemin
- Placebo crossover patients had 100% reduction in median annualized days of hemin use during OLE period, consistent with data in givosiran patients during DB period[1]
- Proportion of patients with 0 days of hemin use increased in OLE compared with DB period

Annualized Days of Hemin Use Givosiran Patients



Annualized Days of Hemin Use Placebo Crossover Patients



DB, double-blind; OLE, open label extension

1. Balwani et al. International Liver Congress 2019. Oral

Daily Worst Pain Decreased with Long-Term Dosing

- Continued givosiran treatment led to a further decrease in pain during the OLE period
- Placebo crossover patients had a decrease in pain and proportion of days with analgesics use, consistent with data in givosiran patients during DB period[1]

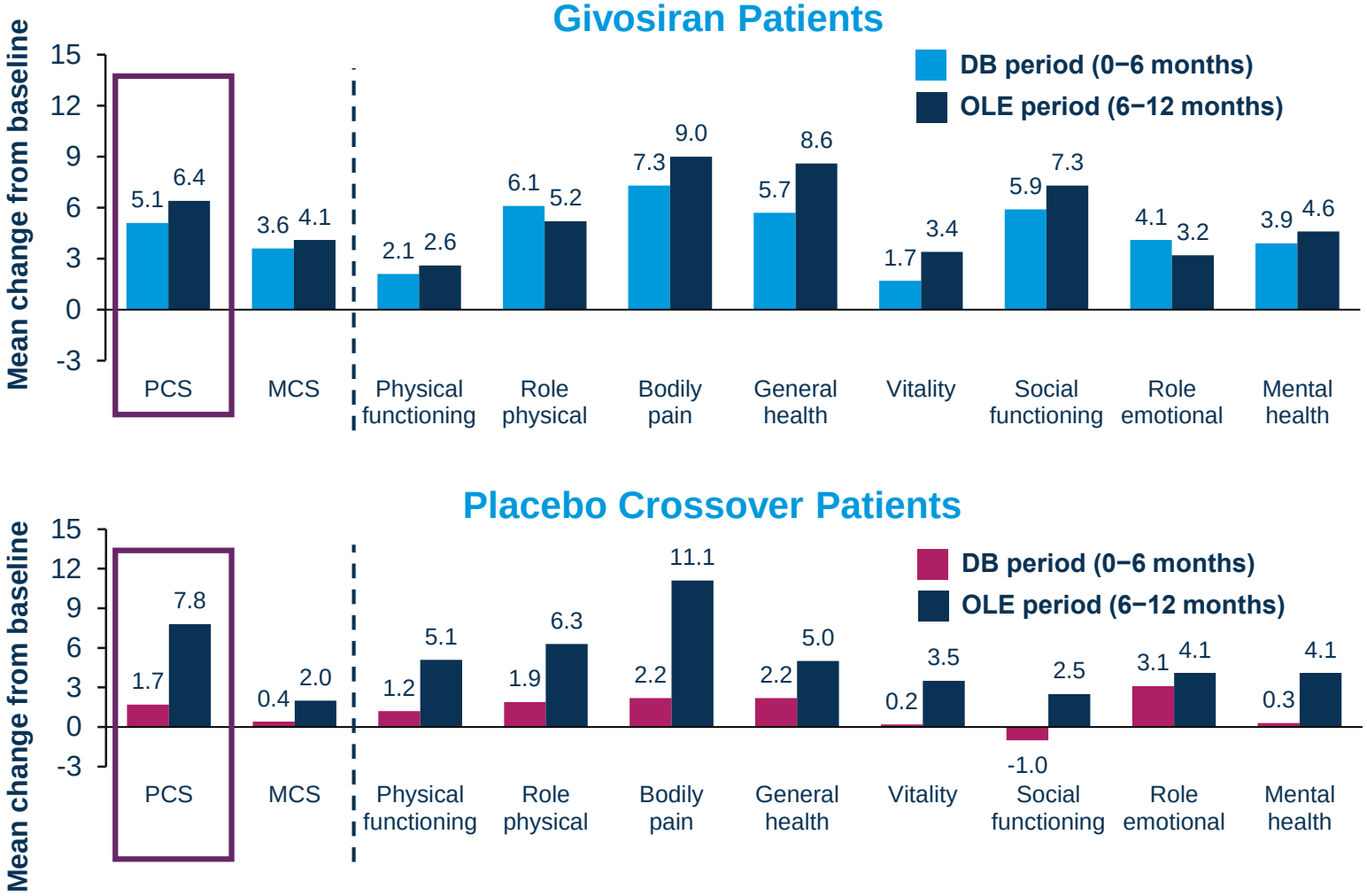
Period	Placebo Crossover Patients (N=46)	Givosiran Patients (N=48)
Baseline Pain score (NRS), median	3.50	2.29
DB period (0−6 months), median change from baseline	+0.10	−0.34
OLE period (6−12 months), median change from baseline	−0.54	−0.77

NRS, numerical rating scale for assessing pain intensity; OLE, open label extension

1. Balwani et al. *International Liver Congress* 2019. Oral

Improvement in Physical Health (SF-12) with Long-Term Dosing

- Continued givosiran treatment resulted in improvements in SF-12 scores, with most impact on role physical, bodily pain, general health and social functioning[a]
- Placebo crossover patients had improvement in SF-12 scores[a], consistent with givosiran treated patients during DB period[1]
- Research from chronic diseases suggests a 2–5 point increase in PCS scores represents a clinically meaningful difference[2,3]



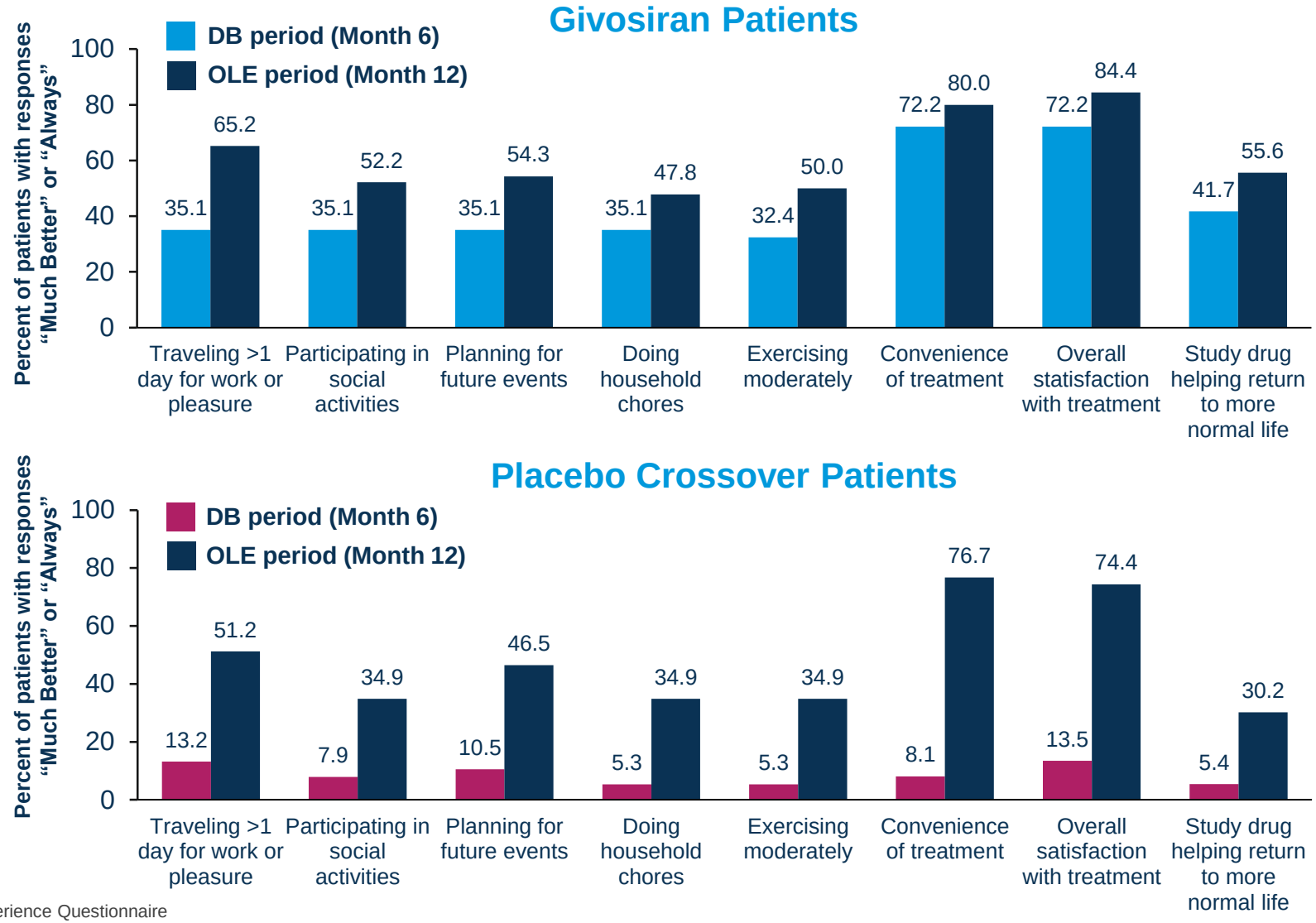
[a]Higher scores represent an improvement in that summary or domain

DB, double-bind; MCS, mental component summary; OLE, open label extension; PCS, physical component summary; SF-12, Short Form (12-item) Health Survey

1. Sardh et al. *International Congress on Porphyrins and Porphyrias* 2019. Oral; 2. Clement et al. *Knee Surg Sports Traumatol Arthrosc* 2014;22:1933–9; 3. Parker et al. *J Neurosurg Spine* 2012;16:471–8

Improvement in PPEQ with Long-Term Dosing

- Custom questionnaire that used global rating of change scale, with questions asked at month 6 and month 12, looking back at entire study period
- Continued givosiran treatment led to further improvements in every PPEQ category at Month 12[a]
- Placebo crossover patients had improvement in all PPEQ categories, consistent with data in givosiran patients during the DB period[a,1]



[a]Higher scores represent an improvement in that category

DB, double-blind; OLE, open label extension; PPEQ, Porphyria Patient Experience Questionnaire

1. Sardh et al. Presented at *International Congress on Porphyrins and Porphyrias* 2019. Oral

Safety in AHP Patients with Ongoing Dosing

Safety Profile of Givosiran Remained Acceptable with No New Safety Concerns

- Overall exposure: 11.22 months (median; range 1.8 to 19.5 months); cumulative exposure of 84.5 person-years[a]
  - 87 patients treated for ≥6 months, 36 patients treated for ≥12 months and 3 patients ≥18 months

Majority of AEs were mild or moderate in severity

- Most common related AEs (≥ 10%) were ISRs, nausea and fatigue
- ISRs in 33% of patients; 7.4% of injections
  - Erythema, pruritus, rash, pain, and swelling most common
- SAEs in ≥ 2% were CKD and urinary tract infection (2 patients each)
  - SAEs of CKD reported during the DB period
- 1 patient with SAE of LFT abnormal discontinued treatment during the DB period per protocol-specified rules
- No other treatment discontinuations due to AEs; no deaths

- Safety profile was acceptable at both 2.5 mg/kg and 1.25 mg/kg doses

Patients with at least 1 event, n (%)	Placebo Crossover Patients (N=46)	Givosiran Patients (N=48)	All Patients (N=94)
AEs	42 (91)	46 (96)	88 (94)
SAEs	6 (13)	14 (29)	20 (21)
Severe AEs	9 (20)	11 (23)	20 (21)
AE leading to treatment discontinuation	0	1 (2)	1 (1)
AE leading to study withdrawal	0	1 (2)	1 (1)
Deaths	0	0	0

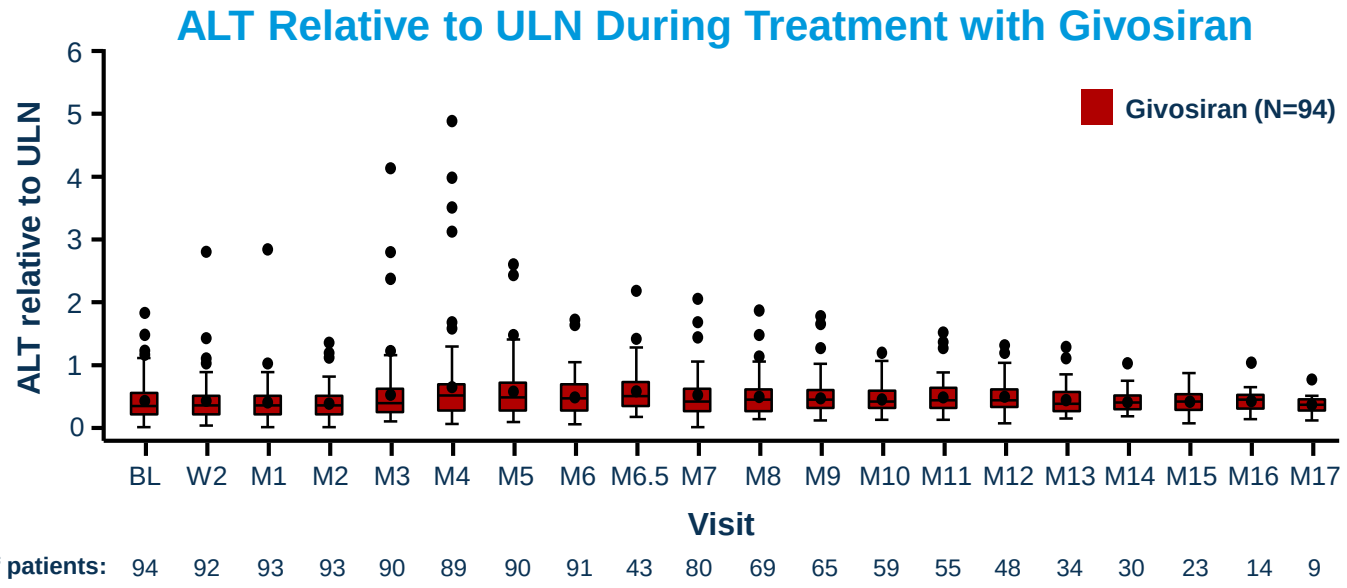
Safety data from first dose of givosiran to data cut-off date (23 July 2019)

[a]For calculating exposure: 1 Month=30.44 days

AE, adverse event; ALT, alanine aminotransaminase; CKD, chronic kidney disease; ISR, injection site reaction; LFT, liver function test; SAE, serious adverse event

Hepatic Events in AHP Patients

- Hepatic AEs were reported in 16 patients (17%)[a], all were mild or moderate in severity
  - Majority were elevations of serum aminotransferases
- ALT >3×ULN in 10 patients (10.6%), of whom 3 (3.2%) had ALT >5×ULN
  - 1 patient with ALT >8×ULN, discontinued treatment due to protocol-defined stopping rule in DB period
  - 2 patients with ALT of >5×ULN:
    - 1 patient on 2.5 mg/kg had dose interruption during DB period with resumption at 1.25 mg/kg
    - 1 patient on 1.25 mg/kg during OLE period had resolution during ongoing dosing
  - 7 patients with ALT >3×ULN: 6 patients with resolution during ongoing dosing and 1 patient with transient interruption
- ALT elevations generally occurred ~3 to 6 months after givosiran started and resolved

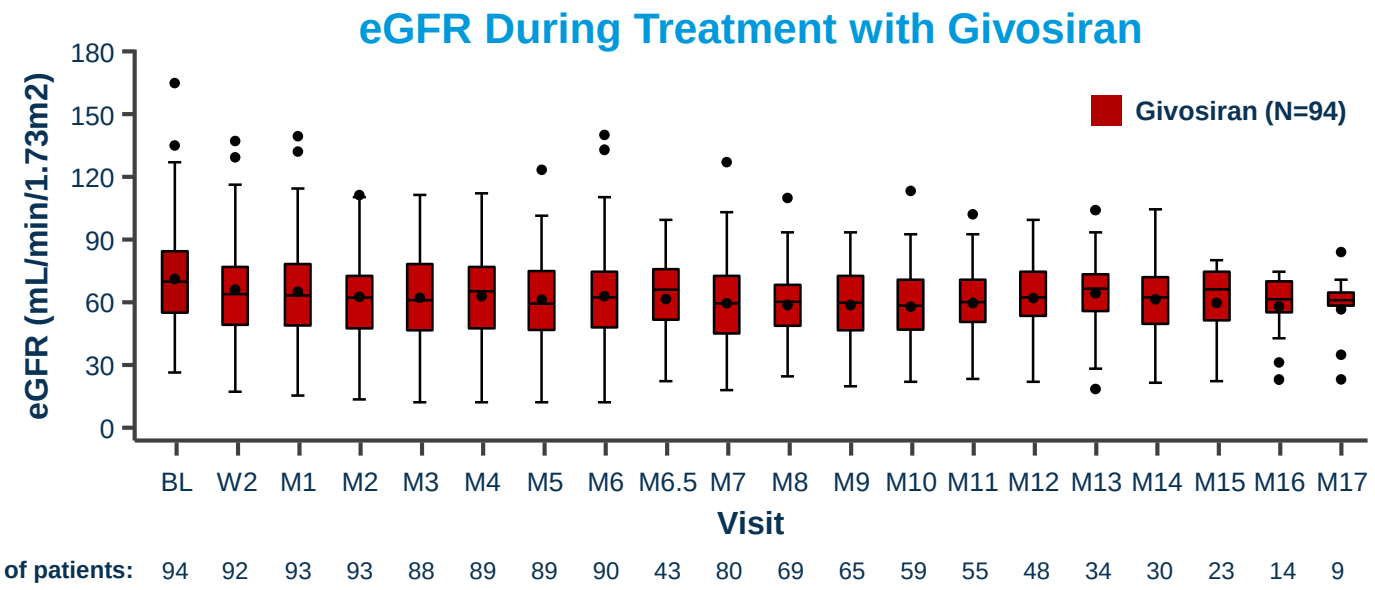


[a]Hepatic AEs included any AEs within the Drug-related hepatic disorders Standardized MedDRA query

AE, adverse events; ALT, alanine aminotransaminase; BL, baseline; M, median; ULN, upper limit of normal; W, week

Renal Events in AHP Patients

- 10 patients (11%) had renal AEs[a], characterized by increased serum creatinine and/or decreased eGFR
  - Majority of AEs mild or moderate in severity
  - None led to discontinuation of study treatment
- Small increases in serum creatinine were observed at Month 6 and 12
  - Median change 0.09 mg/dL at Month 6 and 0.11 mg/dL at Month 12
- Mean eGFR was generally stable over time
- A decrease in eGFR has been observed in some patients with pre-existing renal disease



[a]Renal AEs included custom search for any AEs of blood creatinine increased, glomerular filtration rate decreased, chronic kidney disease, nephropathy, renal impairment, renal failure

eGFR, estimated glomerular filtration rate

ENVISION 12-Month OLE Summary

- Reductions in annualized rate of composite porphyria attacks in patients with AHP were sustained or enhanced during the OLE
  - 61.7% of patients who continued on givosiran had zero attacks during the OLE period
- Givosiran treatment led to sustained lowering of ALA and PBG levels through month 12 in the OLE
- Reductions in the annualized days of hemin use in patients with AHP were sustained during the OLE
  - 70% of patients who continued on givosiran reported no hemin use during the OLE period
- Givosiran treatment led to reductions in daily worst pain and analgesic use, and improvements in quality of life compared to placebo according to PCS of the SF-12 and PPEQ measurements
- Safety profile of givosiran remained acceptable with no new safety findings identified

AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; OLE, open label extension; PBG; porphobilinogen; PCS, physical component score; PPEQ, Porphyria Patient Experience Questionnaire; QOL, quality of life; SF-12, Short Form (12-item) Health Survey

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 E 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