Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyria

24-Month Interim Analysis of the Phase 3 ENVISION Randomised Clinical Trial

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Disclosure of Conflicts of Interest for Herbert L. Bonkovsky, MD

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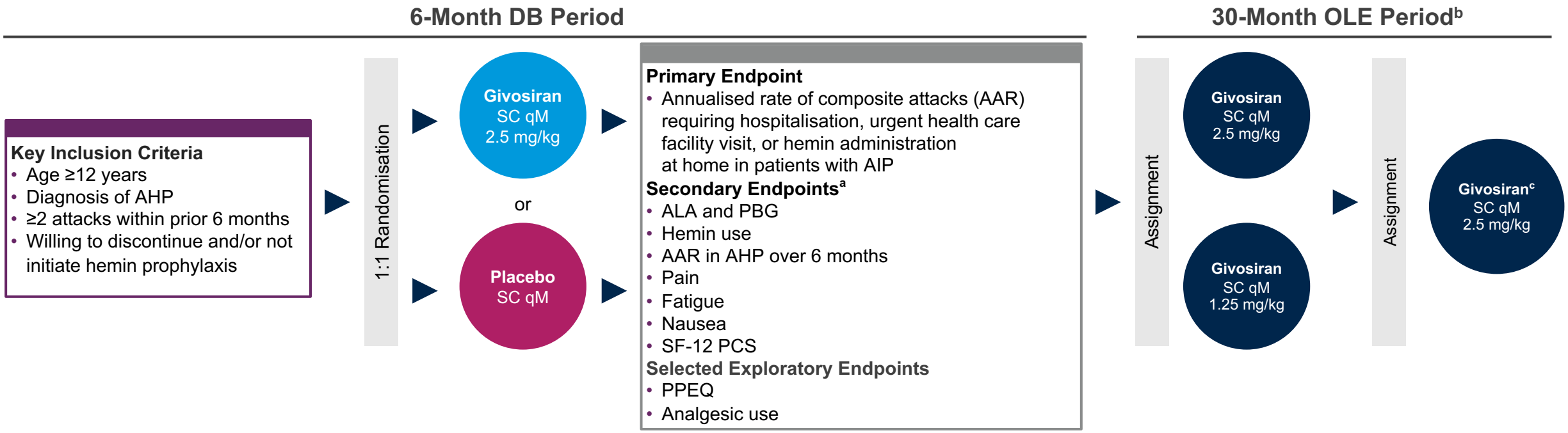
Introduction

- AHP is caused by hepatic heme biosynthesis defects leading to accumulation of neurotoxic heme intermediates, ALA and PBG, and/or porphyrins primarily in the liver.[1-3]
  - Characterised by acute disabling neurovisceral attacks, which can become recurrent in some patients,[4,5] and chronic symptoms, which diminish patients' functioning and QOL.[4,6]
  - Hypertension, chronic kidney disease, and liver disease are common in patients with AHP.[4,7-12]
- IV hemin is commonly used for treatment of acute attacks and for prophylaxis, but can result in acute (eg, phlebitis) and chronic (eg, iron overload, venous thrombosis/obliteration) complications.[4,5]
- Givosiran is a subcutaneously administered RNA interference therapeutic that specifically targets ALAS1 mRNA in the liver to reduce ALA and PBG.[13]
  - Approved for treatment of AHP in adults in the United States and adults and adolescents ≥12 years old in the European Union.[14,15]
- The 6-month DB period of ENVISION showed givosiran treatment was associated with reductions in AAR, ALA and PBG levels, hemin use, and daily pain scores versus placebo.[13] Here we report 24-month interim data from the ENVISION 30-month OLE period.

AAR, annualised attack rate; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; DB, double-blind; IV, intravenous; mRNA, messenger RNA; OLE, open-label extension; PBG, porphobilinogen; QOL, quality of life.

1. Puy H, et al. *Am J Hum Genet.* 1997;60(6):1373-1383. 2. Balwani M, Desnick RJ. *Blood.* 2012;120(23):4496-4504. 3. Bissell DM, et al. *Am J Med.* 2015;128(3):313-317. 4. Gouya L, et al. *Hepatology.* 2020;71(5):1546-1558. 5. Pischik E, Kauppinen R. *Appl Clin Genet.* 2015;8:201-214. 6. Simon A, et al. *Patient.* 2018;11(5):527-537. 7. Bonkovsky HL, et al. *Am J Med.* 2014;127(12):1233-1241. 8. Pallet N, et al. *Kidney Int.* 2015;88:386-395. 9. Willandt B, et al. *JIMD Rep.* 2016;25:77-81. 10. Sardh E, et al. *J Inherit Metab Dis.* 2013;36(6):1063-1071. 11. Innala E, Andersson C. *J Intern Med.* 2011;269(5):538-545. 12. Andant C, et al. *J Hepatol.* 2000;32(6):933-939. 13. Balwani M, et al. *N Engl J Med.* 2020;382(24):2289-2301. 14. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. 15. Givlaari [summary of product characteristics]. 2020. https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pd.

Methods: ENVISION Study Design



[a]Endpoints were evaluated in patients with genetically confirmed AIP (except where noted otherwise) at 6 months. [b]For the OLE period, all endpoints were exploratory.
[c]A protocol amendment increased the dose to 2.5 mg/kg monthly for all patients.

AAR, annualised attack rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire; qM, every month; QoL, quality of life; SC, subcutaneous; SF-12, Short Form (12-item) Health Survey.

Results: Patient Demographics and Characteristics at Baseline

All patients completed the 6-month DB period, and
all eligible patients (n=93) entered the 30-month OLE period

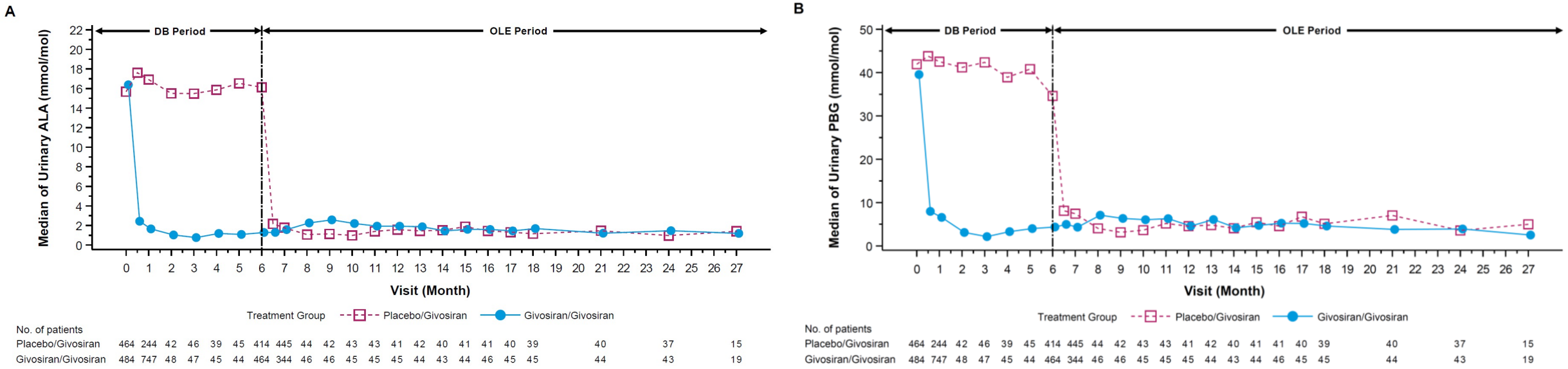
Demographic/Characteristic	Placebo–Givosiran Crossover (n=46)	Continuous Givosiran (n=48)	All Patients Who Received Givosiran (N=94)
Age at screening, y, median (range)	36 (20–60)	42 (19–65)	38 (19–65)
Female, n (%)	41 (89)	43 (90)	84 (89)
AIP with identified mutation, n (%)	43 (94)	46 (96)	89 (95)
Years since diagnosis, median (range)	6.5 (0.1–38.5)	7.0 (0.2–43.3)	6.6 (0.1–43.3)
Prior hemin prophylaxis, n (%)	18 (39)	20 (42)	38 (40)
Historical AAR,[a] median (range)	7.0 (0[b]–46)	8.0 (4–34)	8.0 (0[b]–46)
Chronic symptoms daily or most days between attacks, n (%)	26 (57)	23 (48)	49 (52)
Baseline urinary ALA, mmol/mol Cr, median (range)	16.4 (1.4–41.5)	16.4 (1.8–88.9)	16.4 (1.4–88.9)
Baseline urinary PBG, mmol/mol Cr, median (range)	39.3 (3.6–87.7)	39.6 (0.4–150.0)	39.6 (0.4–150.0)

[a]Composite porphyria attacks requiring hospitalisation, an urgent health care visit, or IV hemin treatment at home.
[b]One patient in the placebo group was enrolled in the study but did not meet an inclusion criterion (did not have requisite number of attacks within 6 months before randomisation).
Reference ranges: ALA (ULN, 1.47 mmol/mol Cr); PBG (ULN, 0.137 mmol/mol/Cr).

AAR, annualised attack rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; Cr, creatinine; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen.

Results: Urinary ALA and PBG Levels over Time

In the placebo-givosiran crossover and continuous givosiran groups, givosiran treatment led to sustained lowering of median ALA levels to near normal and to lowering of PBG levels by >75% through Month 24[a]

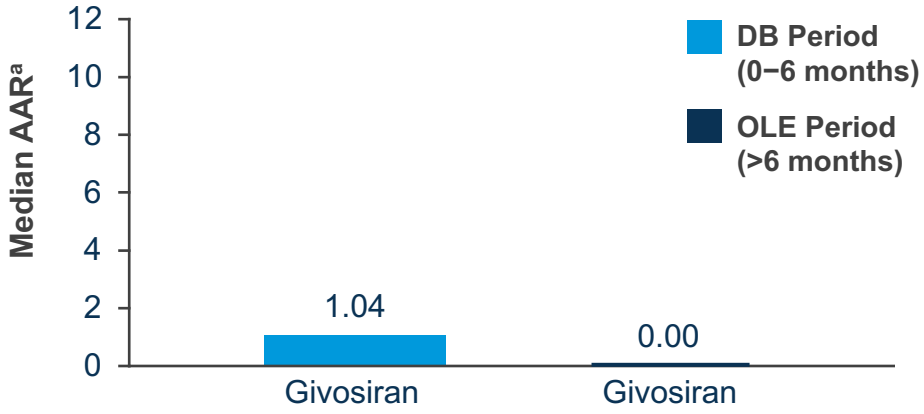


[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled. Reference ranges: ALA (ULN, 1.47 mmol/mol Cr); PBG (ULN, 0.137 mmol/mol/Cr).

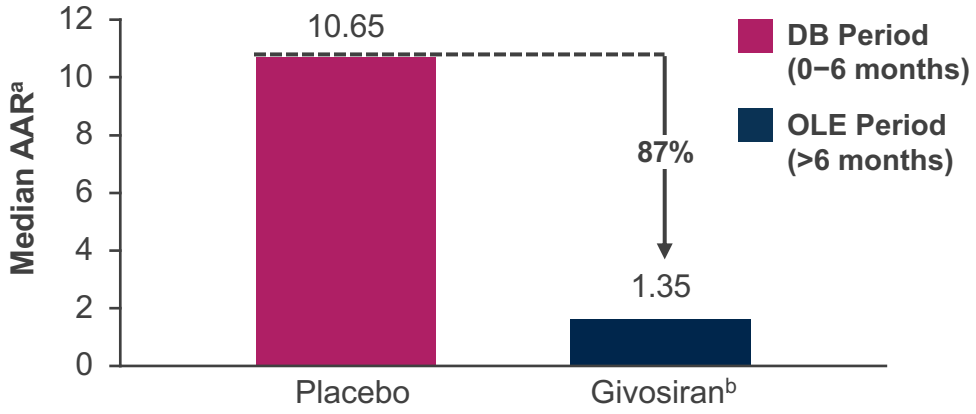
AAR, annualised attack rate; ALA, aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; DB, double-blind; Givo, givosiran; OLE, open-label extension; PBG, porphobilinogen; Pbo, placebo.

Results: AAR and Proportions of Attack-Free Patients

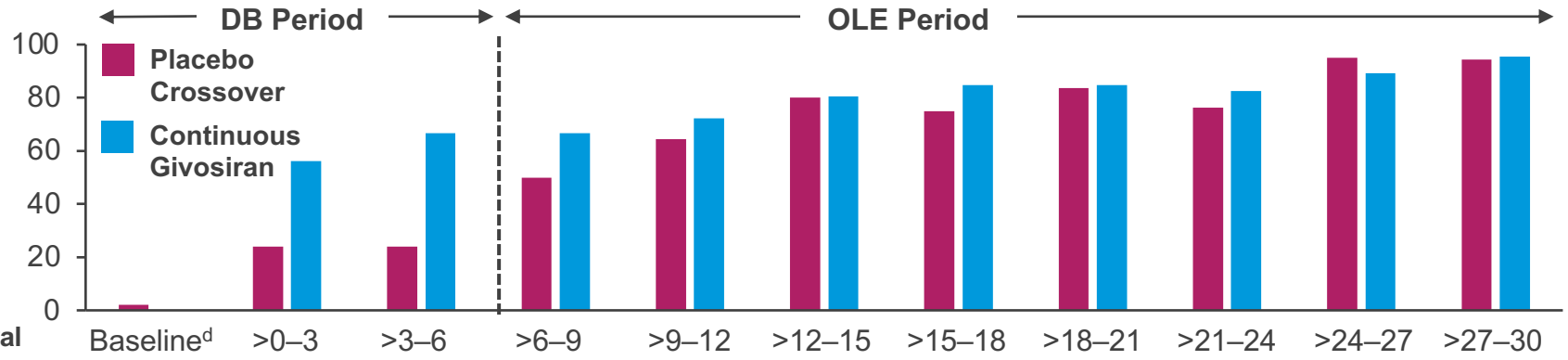
AAR in Continuous Givosiran Patients



AAR in Placebo Crossover Patients



Proportion of Composite Attack-Free Patients by 3-Month Interval during DB and OLE Periods[c]



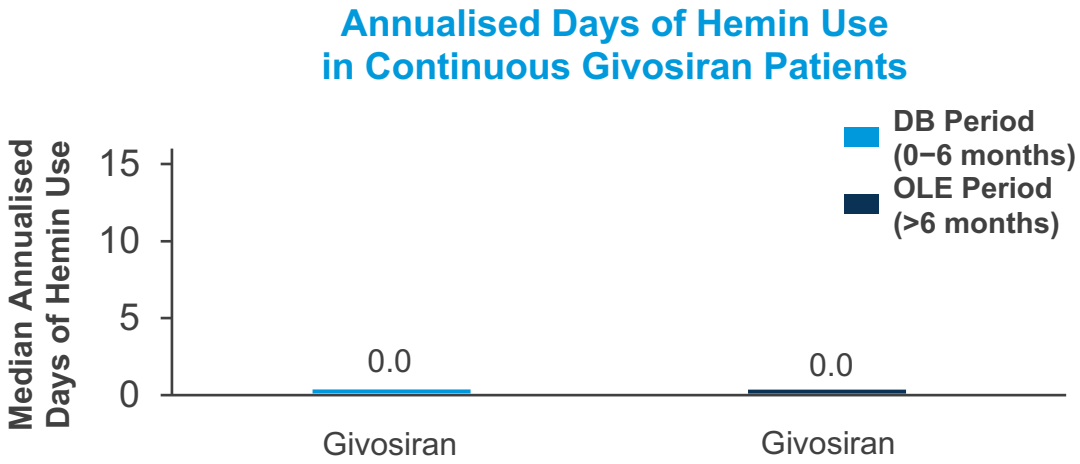
Month Interval	Baseline[d]	>0–3	>3–6	>6–9	>9–12	>12–15	>15–18	>18–21	>21–24	>24–27	>27–30
No. of patients											
Placebo/Givosiran	46	46	46	46	45	45	44	43	42	41	18
Givosiran/Givosiran	48	48	48	48	47	46	46	46	46	46	22

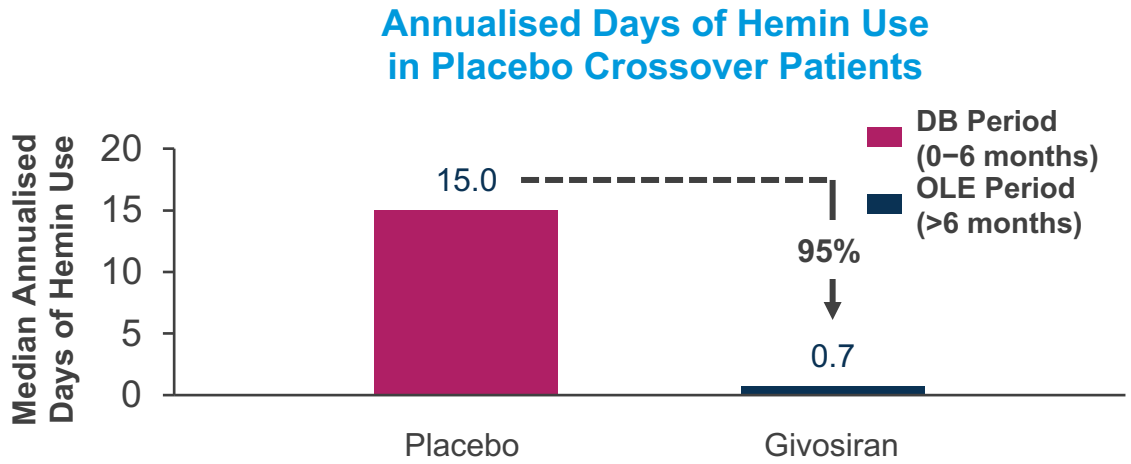
[a]Descriptive analysis. [b]Placebo crossover patients receiving givosiran 2.5 mg/kg (n=29) or 1.25 mg/kg (n=17). [c]Composite attacks include porphyria attacks requiring hospitalisation, urgent health care visit, or intravenous hemin administration at home; 1 month = 28 days. [d]Baseline represents 6 months before randomisation.

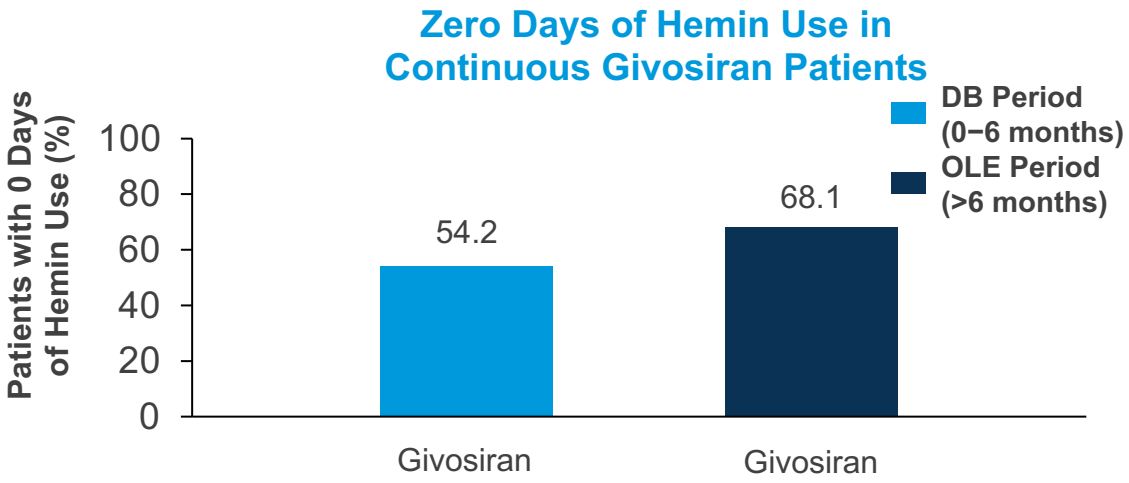
AAR, annualised attack rate; DB, double-blind; OLE, open-label extension.

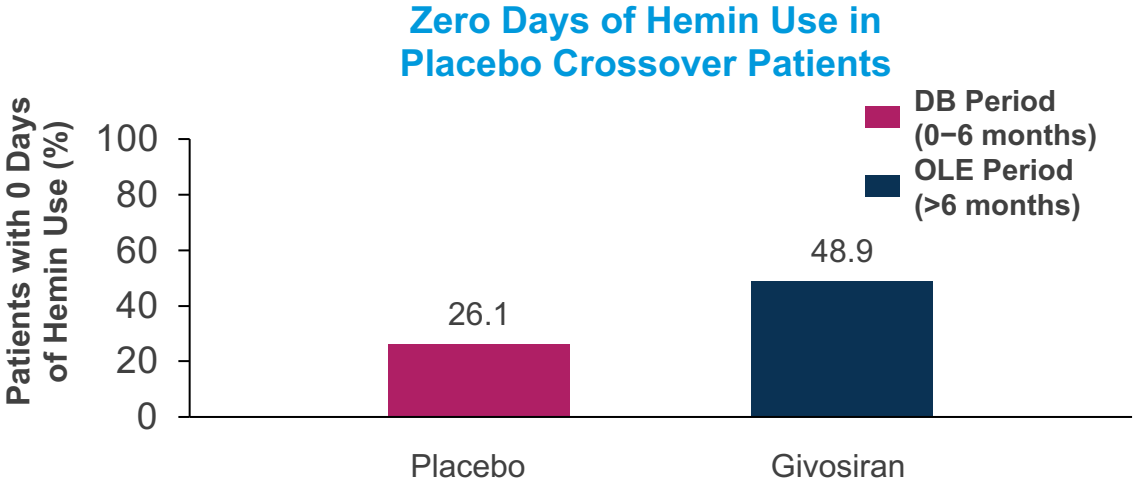
Results: Hemin Use

The proportion of patients with no days of hemin use increased during the OLE period versus the DB period







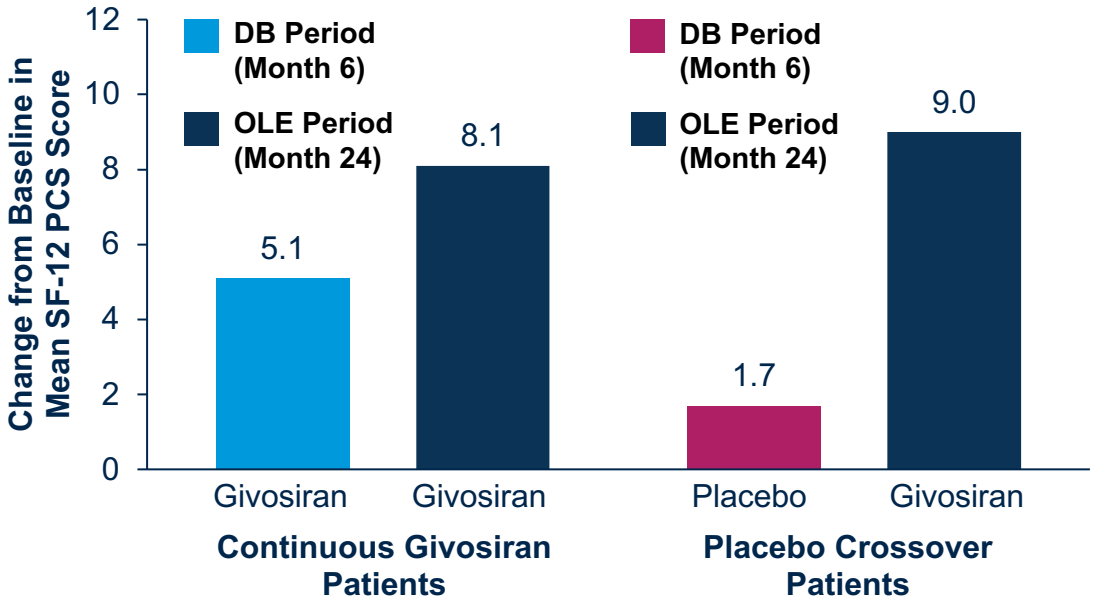


DB, double-blind; OLE, open-label extension.

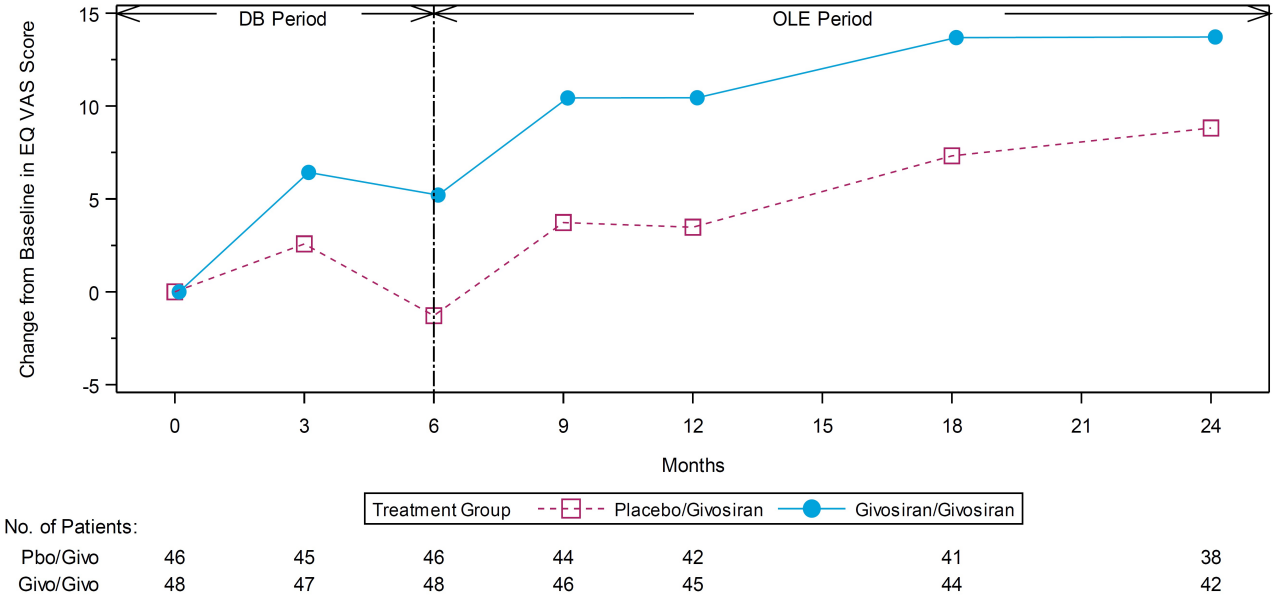
Results: Quality of Life

With givosiran, patients experienced improvements in QOL, as reflected in SF-12 PCS scores and EQ-VAS scores

Change in SF-12 PCS Scores from Baseline through OLE Period[a]



Change in EQ-VAS Scores from Baseline through OLE Period[b]



No. of Patients:							
Pbo/Givo	46	45	46	44	42	41	38
Givo/Givo	48	47	48	46	45	44	42

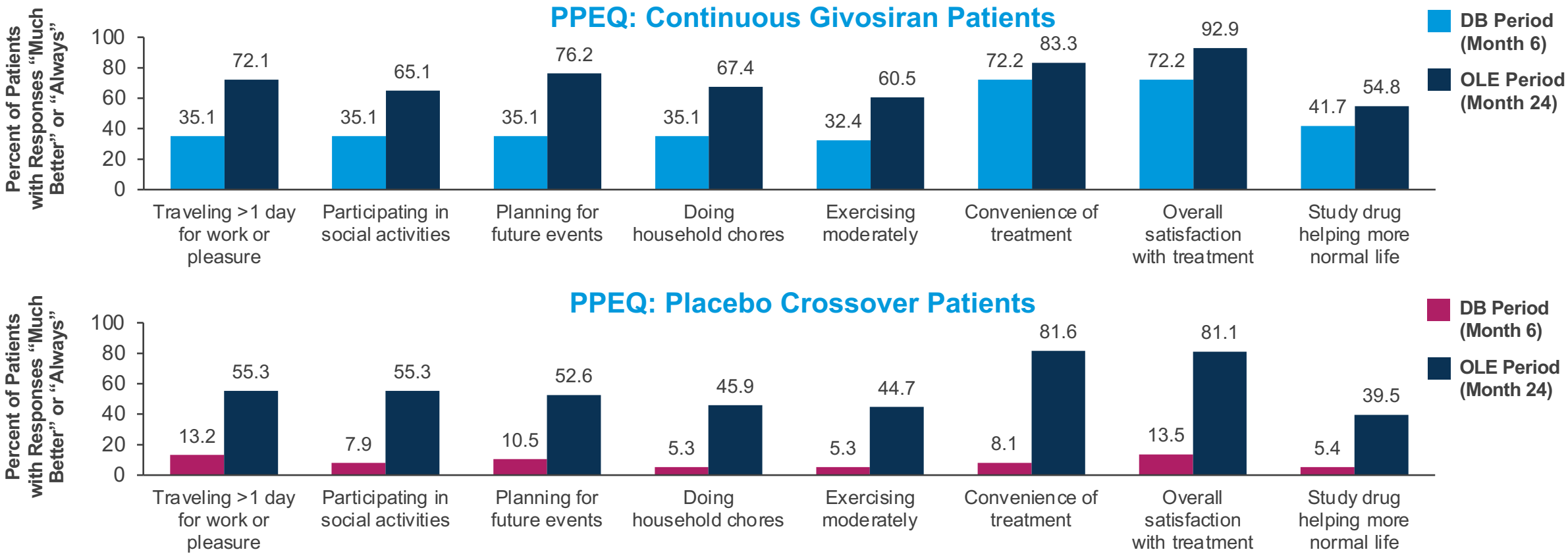
[a]Estimates for the clinically meaningful difference are ≥2 to 5 points for SF-12 PCS, based on published data for other chronic diseases.[1,2]
[b]Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS, based on published data for other chronic diseases.[3,4]

DB, double-blind; EQ-VAS, EuroQol-visual analogue scale; Givo, givosiran; OLE, open-label extension; Pbo, placebo; PCS, Physical Component Summary; QOL, quality of life; SF-12, Short Form (12-item) Health Survey.

1. Clement ND, et al. *Knee Surg Sports Traumatol Arthrosc.* 2014;22(8):1933-1939. 2. Parker SL, et al. *J Neurosurg Spine.* 2012;16(5):471-478.
3. Zanini A, et al. *Respir Care*. 2015;60(1):88-95. 4. Nolan CM, et al. *Thorax.* 2016;71(6):493-500.

Results: Patient-Reported Outcomes

From the DB period through the OLE period, PPEQ results showed further improvements across all domains, including patients who crossed over from placebo to givosiran



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

Results: Adverse Events[a]

≥1 Event, n (%)[b]	Placebo–Givosiran Crossover (n=46)	Continuous Givosiran (n=48)	All Patients Who Received Givosiran (N=94)
AE	43 (94)	47 (98)	90 (96)
SAE[c]	13 (28)	15 (31)	28 (30)
Severe AE	14 (30)	13 (27)	27 (29)
AE leading to treatment discontinuation	2 (4)	1 (2)	3 (3)
AE leading to study withdrawal	2 (4)	1 (2)	3 (3)
Death	0	0	0

- The most common treatment-related AEs were injection-site reactions (29% [27/94] patients), nausea (20% [19/94]), and fatigue (13% [12/94])
- SAEs reported in ≥2% of patients included blood homocysteine increased, CKD, device breakage, pyrexia, and UTI (each occurred in 2 patients)
- Hepatic AEs were reported in 17 (18%) patients; all were mild to moderate in severity
- Renal AEs (mostly increased blood creatinine and/or decreased eGFR) were reported in 21 (22%) patients; none led to treatment discontinuation
  - Small decreases in eGFR observed early in therapy stabilized over Months 12 to 24

[a]Safety data from first dose of givosiran to data cutoff date, June 24, 2020. [b]For calculating exposure, 1 month = 30.44 days.
[c]SAE of liver function test abnormal that led to treatment discontinuation during DB period was previously reported.[1]
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SAE, serious adverse event; UTI, urinary tract infection.

1. Balwani M, et al. *N Engl J Med.* 2020;382(24):2289-2301.

Conclusions

- The ENVISION 24-month interim analysis further confirms that long-term dosing with givosiran provides sustained and continuous benefit to patients with AHP.
- Long-term givosiran use demonstrated a durable response with efficacy across a wide range of clinical parameters during the OLE period.
- 83% and 76% of patients in the continuous givosiran and placebo crossover groups, respectively, continued to be attack-free during Months 21–24.
- The analysis showed a sustained reduction in AAR, ALA and PBG levels, and hemin use and further improvements in physical functioning and QOL.
- The safety profile of givosiran remained acceptable.

AAR, annualised attack rate; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; QOL, quality of life.