Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyria: 36-Month Results of the Phase 3 ENVISION Randomized Clinical Trial

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Data previously disclosed at ASH 2021 Annual Meeting, December 11–14, 2021

Disclosures

Manish Thapar reported being a consultant and speaker for Alnylam Pharmaceuticals. **Herbert L. Bonkovsky** reported being an independent contractor for Alnylam Pharmaceuticals and Disc Medicine, and receiving grant support and financial support, paid to Wake Forest University School of Medicine, from Alnylam Pharmaceuticals, Gilead Sciences, and Mitsubishi Tanabe, NA; consulting fees from Alnylam Pharmaceuticals, Disc Medicine, Eiger Biopharma, and Protagonist Pharma. **Susana Monroy** reported receiving advisory board fees from Alnylam Pharmaceuticals and Speaker/teaching fees from Ultragenyx Pharmaceutical Inc. **Gayle Ross** reported having nothing to disclose. **Encarna Guillén-Navarro** reported receiving grants/research support, paid to the Fundación para la Formación e Investigación Biosanitaria-FFIS, from Alnylam Pharmaceuticals; consulting fees from Alnylam Pharmaceuticals, BioMarin, and UCB. **Maria Domenica Cappellini** reported receiving consultancy, research funding, and honoraria from Novartis; research funding and consultancy from Celgene; consultancy from Vifor; research funding from La Jolla; research funding from Protagonist Therapeutics; consultancy from IONIS Pharmaceuticals; and research funding from CRISPR Therapeutics. **Anna-Elisabeth Minder** reported receiving Speaker/teaching fees from Alnylam Pharmaceuticals and an unrestricted research grant from Clinuvel Pharmaceuticals. **Shangbin Liu** and **Marianne T. Sweetser** reported being employed by and owning stock and stock options in Alnylam Pharmaceuticals. **David J. Kuter** reported receiving grant support and consulting fees from Actelion (Syntimmune), Agios, Alnylam Pharmaceuticals, Amgen, Argenx, Bristol Myers Squibb, Protalix, Rigel, and Takeda (Bioverativ); grant support from Kezar and Principia; and consulting fees from Caremark, Daiichi Sankyo, Dova, Kyowa-Kirin, Merck Sharp & Dohme, Momenta, Novartis, Pfizer, Platelet Disorder Support Association, Principia, Protalix, Sanofi Genzyme, Shionogi, Shire, UCB, Up-To-Date, and Zafgen

Data previously disclosed at ASH 2021 Annual Meeting, December 11–14, 2021

Acute Hepatic Porphyria (AHP) and Givosiran

- Acute hepatic porphyria (AHP) is caused by hepatic heme biosynthesis defects, sometimes leading to up-regulation of delta-aminolevulinic acid (ALA) synthase 1, the first and rate-controlling enzyme in the pathway, and accumulation of neurotoxic heme intermediates, ALA and porphobilinogen (PBG), and/or porphyrins[1-3]
- Although clinical penetrance of AHP is low (~2%), some patients experience acute disabling and sometimes life-threatening neurovisceral attacks, especially severe abdominal pain, which can become recurrent in some patients[4-7]
- During the 6-month, double-blind (DB) phase of the ENVISION study (NCT03338816), givosiran treatment reduced the annualized attack rate (AAR) by 74% and reduced ALA and PBG levels, hemin use, and daily pain versus placebo[8]
- Here we report results from the 36-month (6-month DB and 30-month open-label extension [OLE]) analysis of the ENVISION trial

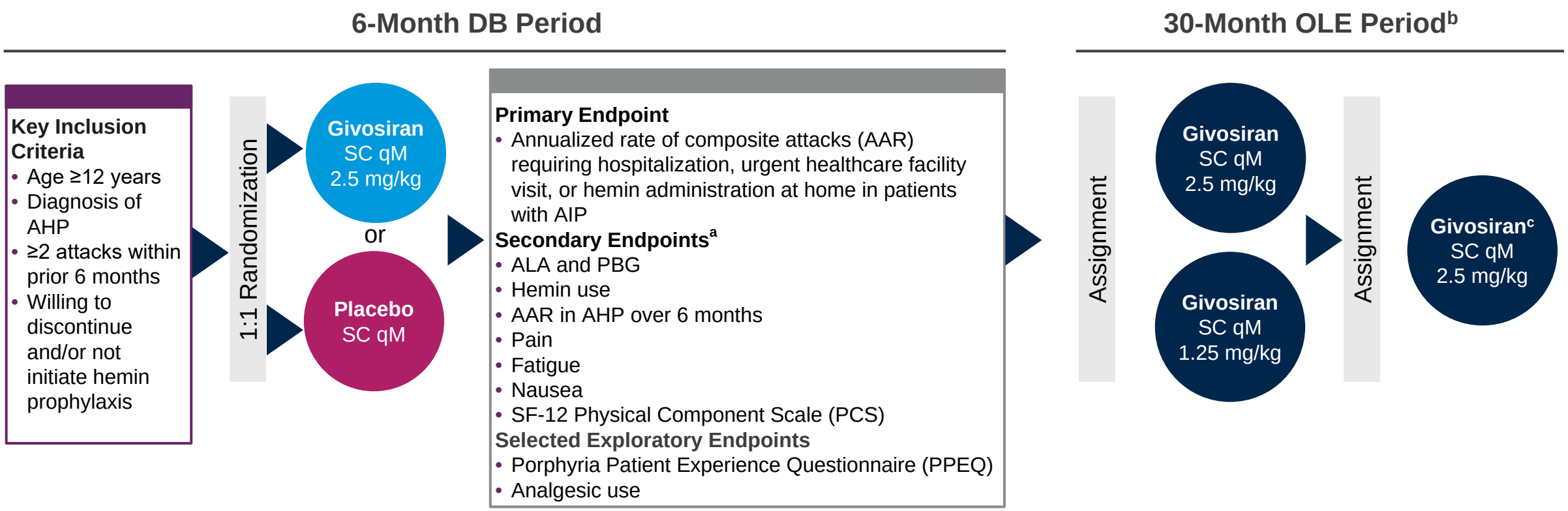
Givosiran

- A subcutaneously administered RNA interference therapeutic approved for treatment of AHP in adults (18+ y) in the United States and adults and adolescents (12+ y) in the European Union[9,10]
- Givosiran specifically down-regulates ALA synthase 1 mRNA in the liver to reduce ALA and PBG[8]

AAR, annualized attack rate; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; DB, double-blind; mRNA, messenger ribonucleic acid; OLE, open-label extension; PBG, porphobilinogen

1. Puy H, et al. Am J Hum Genet. 1997;60(6):1373–83. 2. Balwani M, Desnick RJ. Blood. 2012;120(23):4496–504. 3. Bissell DM, et al. Am J Med. 2015;128(3):313–7. 4. Gouya L, et al. Hepatology. 2020;71(5):1546–58. 5. Pischik E, Kauppinen R. Appl Clin Genet. 2015;8:201–14. 6. Wang B, et al. Hepatol Commun. 2018;3(2):193–206. 7. Bonkovsky H, et al. Mol Genet Metab. 2019;128(3):213–8. 8. Balwani M, et al. N Engl J Med. 2020;382(24):2289–301. 9. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. 10. Givlaari [summary of product characteristics]. 2021. https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf

ENVISION Study Design (ClinicalTrials.gov: NCT03338816)



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

[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

Baseline Demographics and Disease Characteristics

- Ninety-four patients with AHP were enrolled at 36 sites in 18 countries
- All patients completed the 6-month DB period, and all eligible patients (n=93) entered the 30-month OLE period
- Baseline characteristics were generally balanced between groups

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)
AHP with identified mutation, n (%)	43 (93)	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)
Chronic opioid use daily or most days between attacks, n (%)	13 (28)	14 (29)	27 (29)
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)

AAR, annualized attack rate; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; Cr, creatinine; DB, double-blind; IV, intravenous; OLE, open-label extension; PBG, porphobilinogen; ULN, upper limit of normal

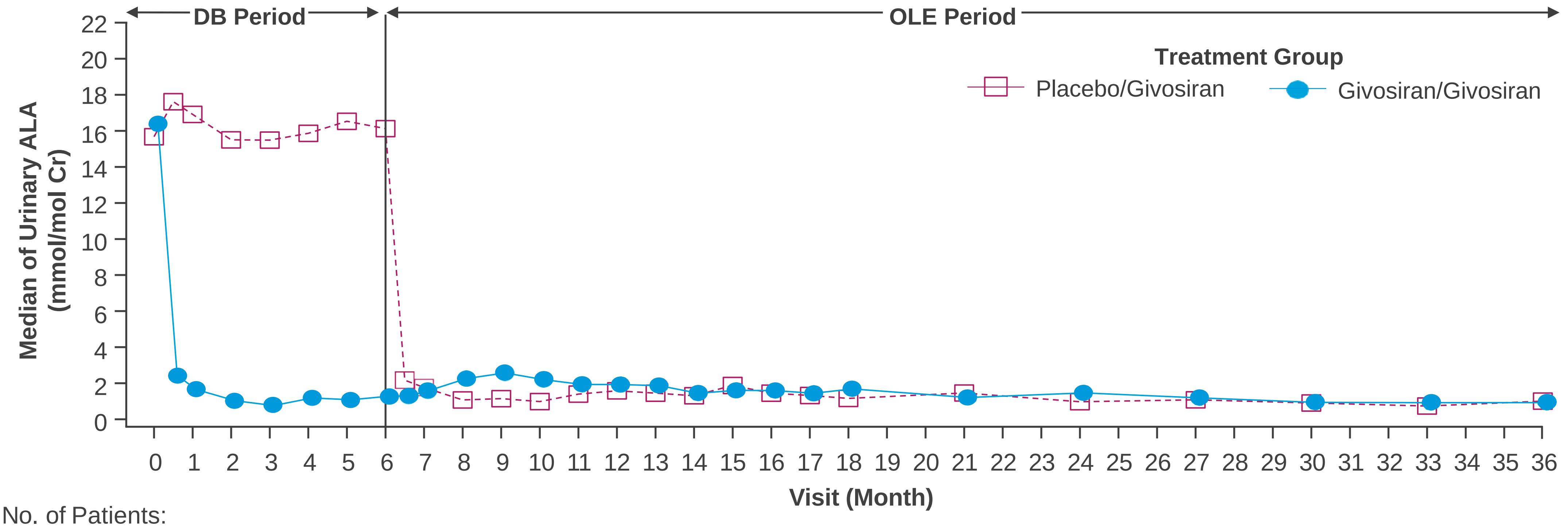
[a]Composite porphyria attacks requiring hospitalization, an urgent healthcare facility visit, or IV hemin treatment at home during the 6 months prior to randomization

[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 randomization). Reference ranges: ALA (ULN, 1.47 mmol/mol Cr), PBG (ULN, 0.137 mmol/mol Cr)[1]

1. Agarwal S, et al. JIMD Rep. 2021;57(1):85–93

ALA Levels

Median Levels of Urinary ALA during DB and OLE Study Periods[a]



No. of Patients:

Placebo/Givosiran	46	44	42	46	39	45	41	45	44	42	43	43	41	42	41	41	41	40	39	40	37	36	36	38	37
Givosiran/Givosiran	48	47	48	47	45	44	46	44	46	46	45	45	45	44	43	44	46	45	45	44	43	44	42	39	40

- In the placebo–givosiran crossover and continuous givosiran groups, givosiran treatment led to sustained lowering of median ALA levels to near normal, sustained through Month 36

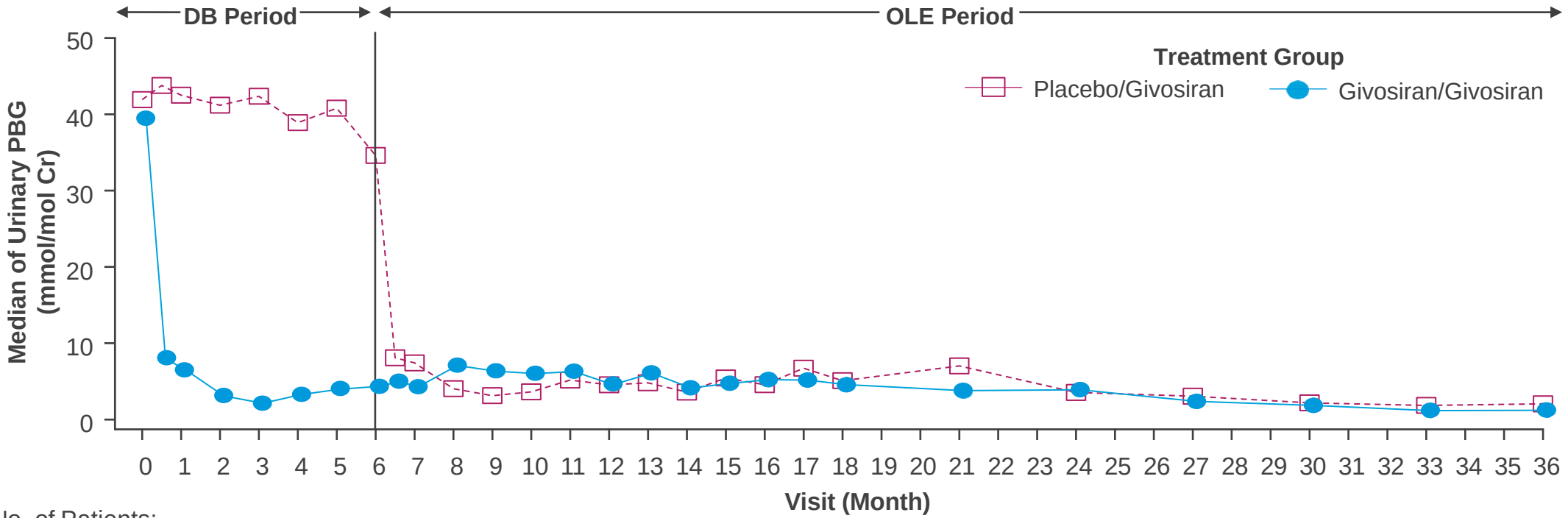
ALA, delta-aminolevulinic acid; Cr, creatinine; DB, double-blind; OLE, open-label extension; ULN, upper limit of normal

[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled. Reference range: ALA (ULN, 1.47 mmol/mol Cr)[1]

1. Agarwal S, et al. JIMD Rep. 2021;57(1):85–93

PBG Levels

Median Levels of Urinary PBG During DB and OLE Study Periods[a]



No. of Patients:

Placebo/Givosiran	46	44	42	46	39	45	41	45	44	42	43	43	41	42	38	41	41	40	39		40		37		36		36		37		37		
Givosiran/Givosiran	48	47	48	47	45	44	46	44	46	46	45	45	45	44	42	44	46	45	45		44		43		44		42		39		40		

- In the placebo–givosiran crossover and continuous givosiran groups, givosiran treatment led to sustained lowering of PBG levels by >90% at Month 36

Cr, creatinine; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; ULN, upper limit of normal

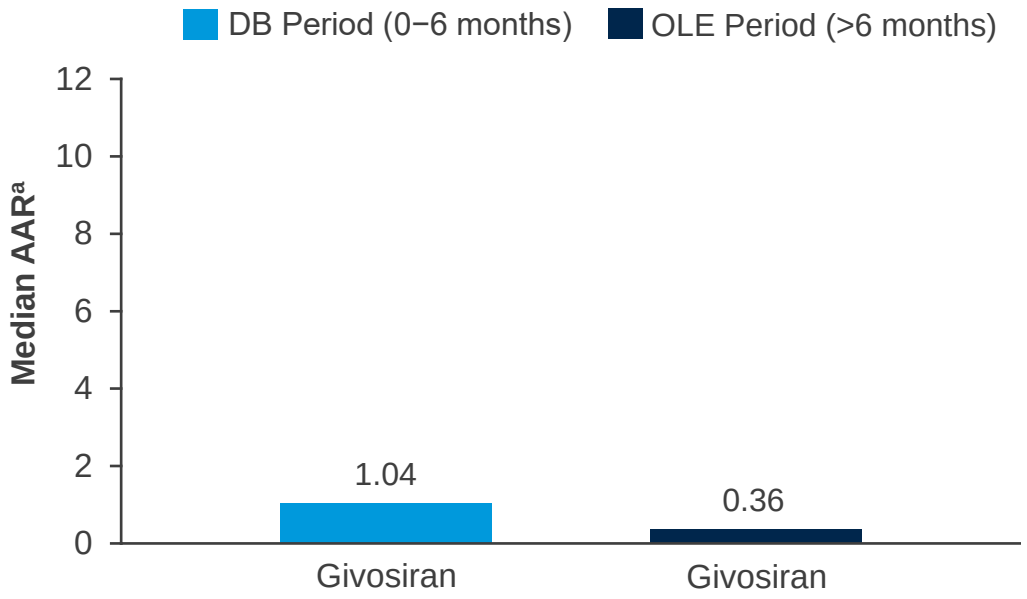
[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled. Reference range: PBG (ULN, 0.137 mmol/mol Cr)[1]

1. Agarwal S, et al. JIMD Rep. 2021;57(1):85–93

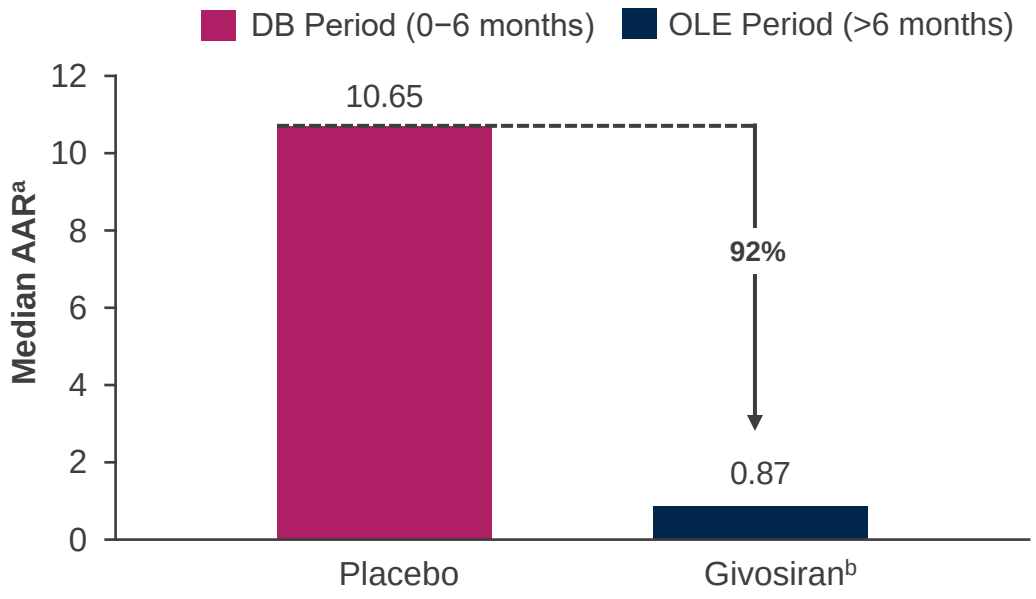
Annualized Attack Rate

Median AAR for DB and OLE Study Periods

AAR in Continuous Givosiran Patients



AAR in Placebo Crossover Patients



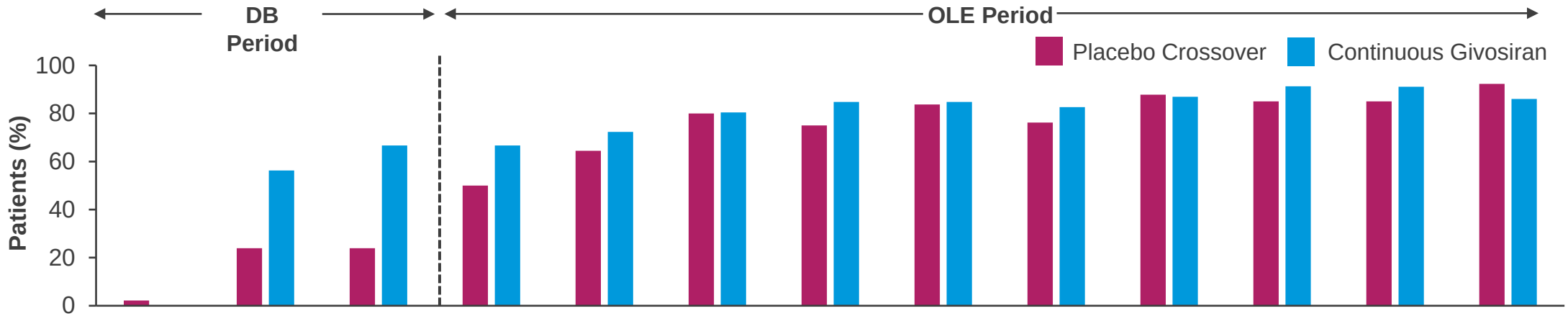
- Continued givosiran treatment during the OLE period led to a sustained reduction in AAR
  - After the initial 6-month DB period, the median number of attacks during the OLE period (>6 months) was 0.36 and 0.87 in the continuous givosiran and placebo crossover groups, respectively

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

[a]Descriptive analysis. [b]Placebo crossover patients receiving givosiran 2.5 mg/kg (n=29) or 1.25 mg/kg (n=17)

Attack-Free Patients

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



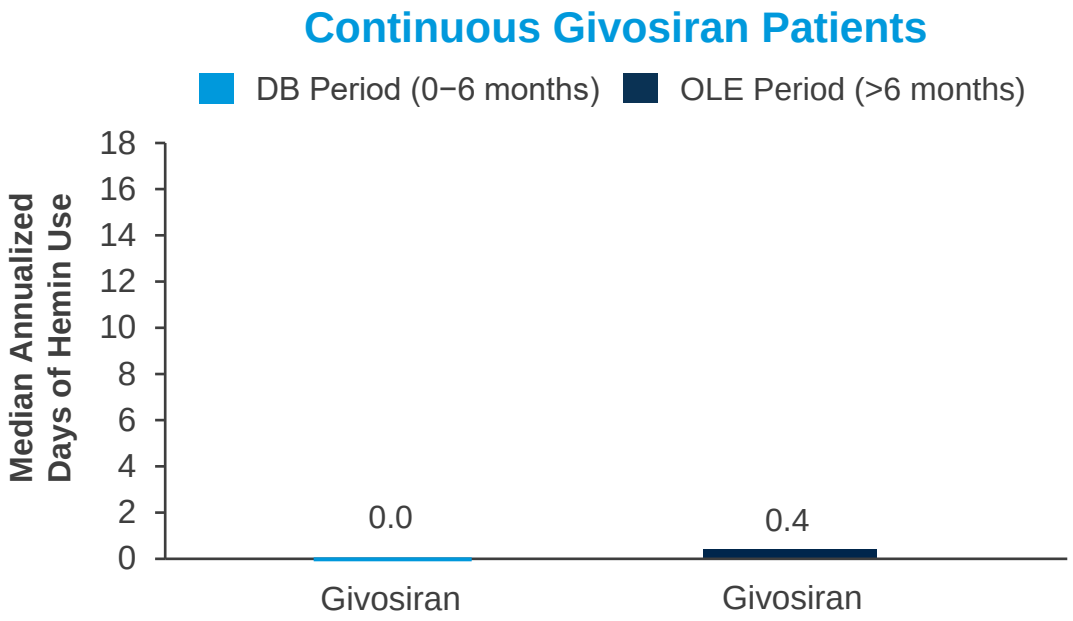
Month Interval	Baseline[b]	>0–3	>3–6	>6–9	>9–12	>12–15	>15–18	>18–21	>21–24	>24–27	>27–30	>30–33	>33–36
No. of Patients:													
Placebo/Givosiran	46	46	46	46	45	45	44	43	42	41	40	40	39
Givosiran/Givosiran	48	48	48	48	47	46	46	46	46	46	46	45	43

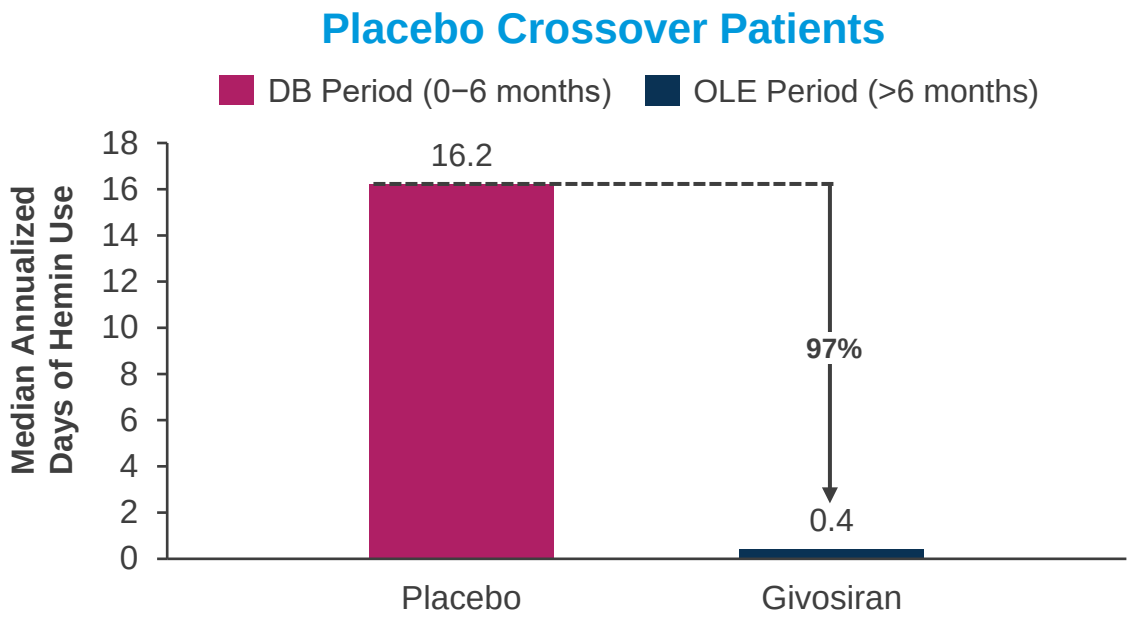
- The proportion of patients with no attacks by 3-month interval improved with continued givosiran treatment during the OLE period
  - 86% of patients who continued givosiran treatment were attack-free[a] at >33−36 months
  - 92% of patients who crossed over from placebo to givosiran were attack-free[a] at >33−36 months
    - In comparison, 24% of those who received placebo were attack-free[a] at >3−6 months of the DB period

DB, double-blind; IV, intravenous; OLE, open-label extension

[a]Composite attacks include porphyria attacks requiring hospitalization, urgent healthcare facility visit, or IV hemin administration at home; 1 month = 28 days. [b]Baseline represents 6 months before randomization

Median Annualized Days of Hemin Use



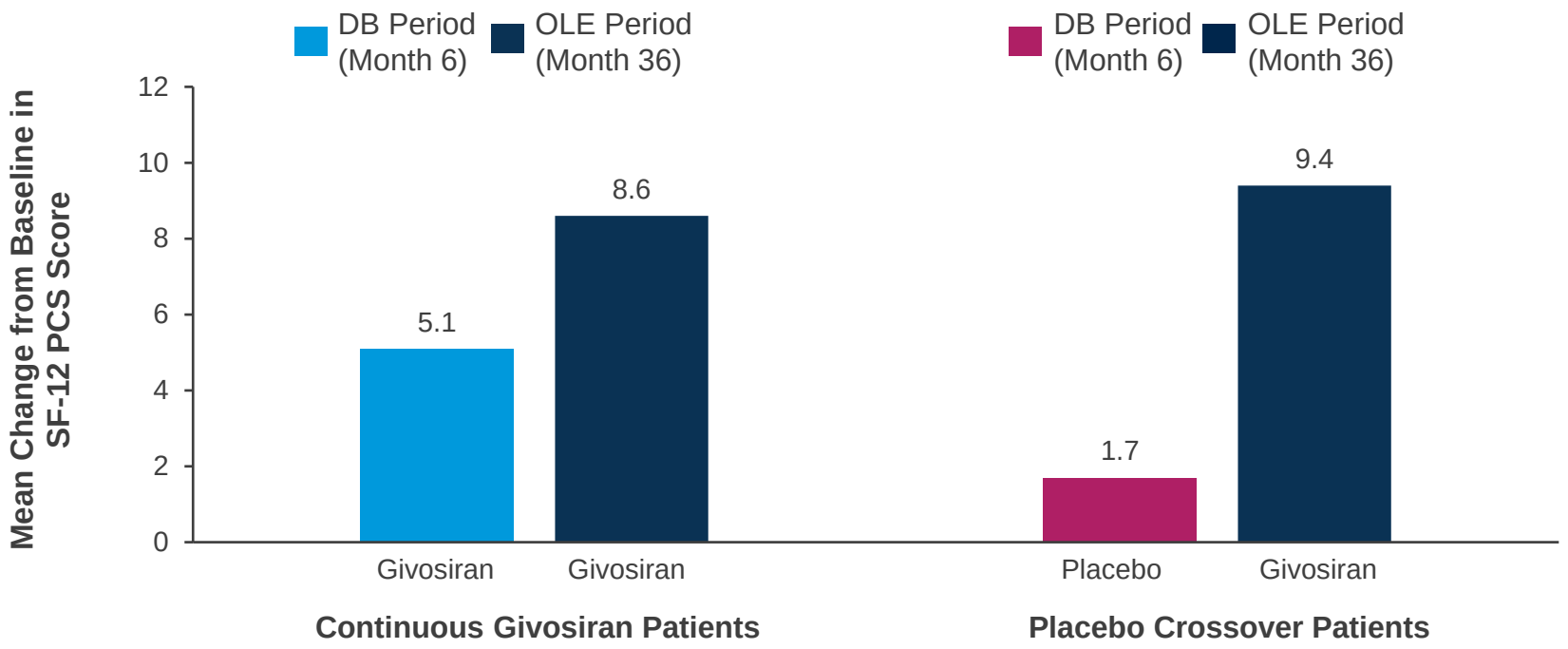


- Median annualized days of hemin use remained low in the continuous givosiran group during the OLE period and decreased by 97% in the placebo crossover group during the OLE period
- The proportion of patients with no days of hemin use increased over time in the continuous givosiran group and placebo crossover group
  - 88% of patients in the continuous givosiran group had no days of hemin use at >33−36 months
  - 90% of patients in the placebo crossover group had no days of hemin use at >33−36 months

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

QOL: SF-12 Physical Component Summary (PCS)

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



- With givosiran, patients experienced further improvements in QOL, as assessed with SF-12 PCS scores
- Improvements were sustained from Month 6 to Month 36 in patients who continued givosiran treatment

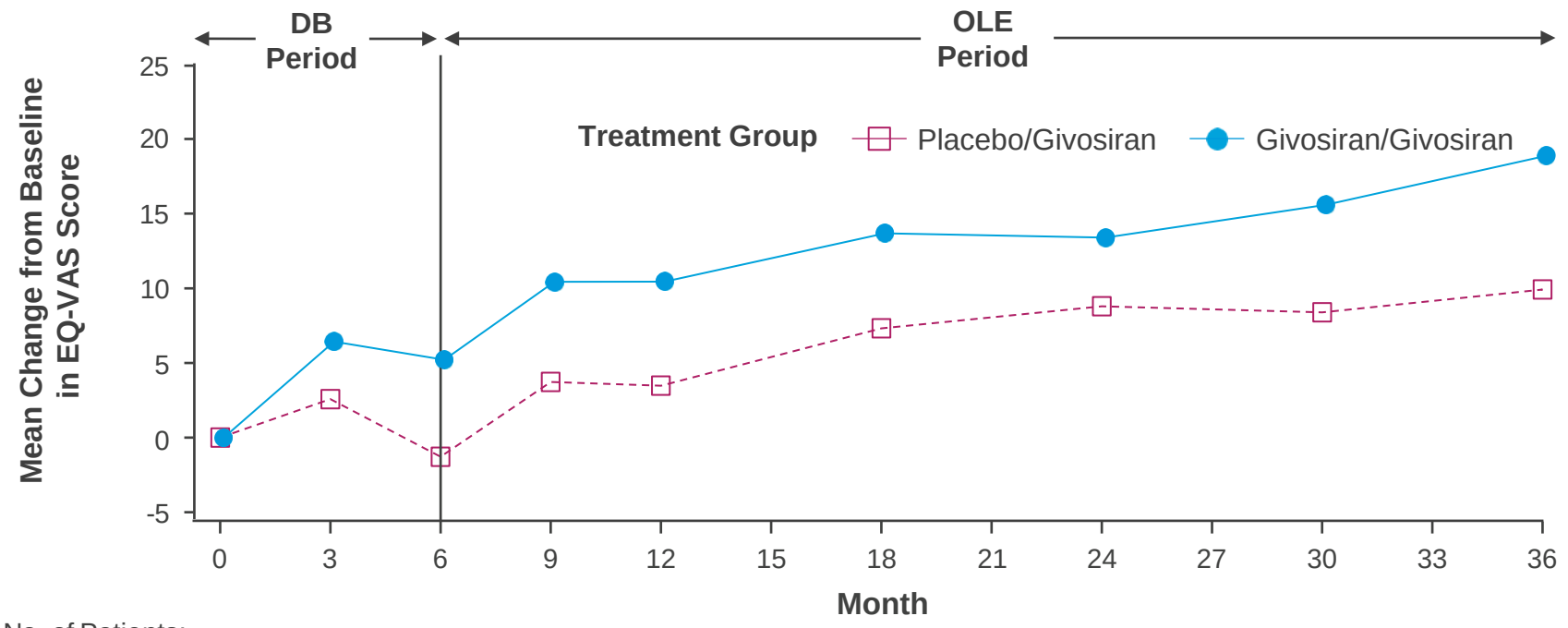
DB, double-blind; OLE, open-label extension; PCS, Physical Component Summary; QOL, quality of life; SF-12, Short Form (12-item) Health Survey

[a]Estimates for the clinically meaningful difference are ≥2 to 5 points for SF-12 PCS, based on published data for other chronic dases[1,2]

1. Clement ND, et al. Knee Surg Sports Traumatol Arthrosc. 2014;22(8):1933–9. 2. Parker SL, et al. J Neurosurg Spine. 2012;16(5):471–8

QOL: EuroQol Visual Analog Scale (EQ-VAS)

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



No. of Patients:									
Placebo/Givosiran	46	45	46	44	42	41	39	36	36
Givosiran/Givosiran	48	47	48	46	45	44	43	39	40

- With givosiran, patients experienced further improvements in QOL, as assessed with EQ-VAS scores
- Improvements were sustained from Month 6 to Month 36 in patients who continued givosiran treatment

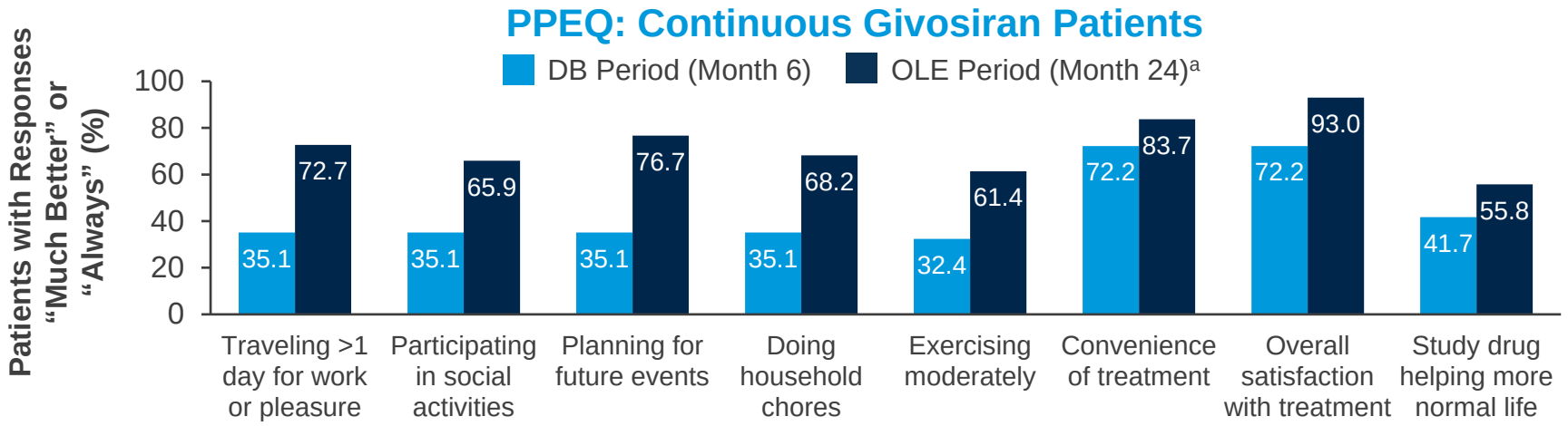
DB, double-blind; EQ-VAS, EuroQol visual analog scale; OLE, open-label extension; QOL, quality of life

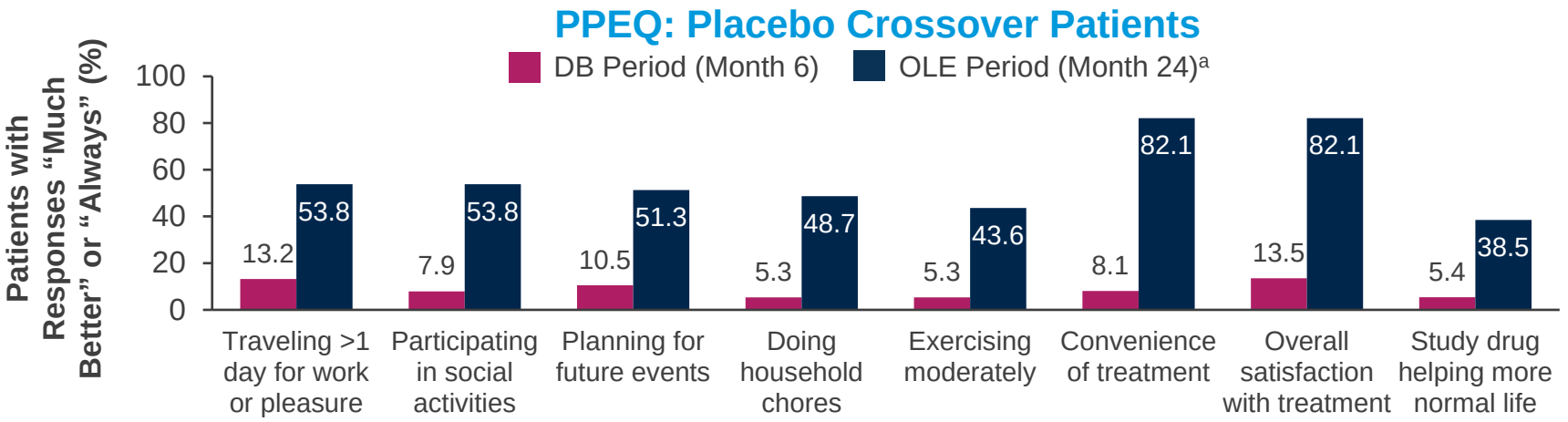
[a]Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS, based on published data for other chronic dases[1,2]

1. Zanini A, et al. Respir Care. 2015;60(1):88-95. 2. Nolan CM, et al. Thorax. 2016;71(6):493–500

Patient-Reported Outcomes

Percentage of Patients Who Reported Ability Improvements ("Much Better" or "Always") on PPEQ





- From the DB period through the OLE period, Porphyria Patient Experience Questionnaire (PPEQ) results showed further improvements across all domains, including activities of daily living, satisfaction with treatment, and living a more normal life, in patients who continued givosiran
- Improvements across all domains were also observed from the DB period through the OLE period in patients who crossed over from placebo to givosiran

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

[a]PPEQ was collected up to Month 24 per the protocol

Safety[a]

Patients with ≥1 Event, n (%)[b]	Placebo–Givosiran Crossover (n=46)	Continuous Givosiran (n=48)	All Patients Who Received Givosiran (N=94)
Adverse events (AEs)	44 (96)	47 (98)	91 (97)
SAE[c]	17 (37)	20 (42)	37 (39)
Severe AE	18 (39)	17 (35)	35 (37)
AE leading to treatment discontinuation	4 (9)	2 (4)	6 (6)
AE leading to study withdrawal	2 (4)	2 (4)	4 (4)
Death	0	1 (2)	1 (1)

AE, adverse event; SAE, serious adverse event

[a]Safety data from first dose of givosiran to completion of study, May 31, 2021. [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]

1. Balwani M, et al. N Engl J Med. 2020;382(24):2289–301

Safety[a]

- Median (range) exposure to givosiran was 33.1 (2.7–34.1) months[b] for the continuous givosiran group and 27.7 (1.8–28.3) months for the placebo crossover group, with maximal exposure of 34.1 months
- Most AEs continued to be mild or moderate in severity
- The most common treatment-related AEs (≥10% of patients) were injection-site reactions (32% [30/94] patients), nausea (21% [20/94]), and fatigue (14% [13/94])
  - Overall, the most common AEs (≥20% of patients) were injection-site reactions (39% [37/94] of patients), nausea (37% [35/94]), and fatigue (27% [25/94])
  - Four patients discontinued study drug due to treatment-related AEs (blood homocysteine increase with concomitant injection-site reaction, n=1; blood homocysteine increase with concomitant pancreatitis, n=1; abnormal liver tests, n=1; drug hypersensitivity, n=1)
- SAEs that occurred in ≥2% of patients included pulmonary embolism, blood homocysteine increased, COVID-19 pneumonia, chronic kidney disease, device breakage, and urinary tract infection (each occurred in 2 patients, except for pulmonary embolism, which occurred in 4 patients)
- One death due to aortic dissection during OLE was assessed as likely unrelated to study drug
- Hepatic AEs were reported in 18 (19%) patients; all were mild to moderate in severity
  - ALT elevations were reported in 10 (11%) patients and AST elevations in 6 (6%) patients
  - ALT elevations generally occurred 3−6 months after starting givosiran treatment and resolved over time even with ongoing givosiran
- Renal AEs (mostly increased blood creatinine and/or decreased eGFR) were reported in 21 (22%) patients; none led to discontinuation of treatment

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; OLE, open-label extension; SAE, serious adverse event

[a]Safety data from first dose of givosiran to completion of study, May 31, 2021. [b]For calculating exposure, 1 month = 30.44 days

Conclusions

- The ENVISION 36-month 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
  - 86% and 92% of patients in the continuous givosiran and placebo crossover groups, respectively, were attack-free during Months 33–36
  - The analysis showed a sustained reduction in AAR, ALA, and PBG levels and hemin use, and further improvements in physical functioning and QOL
- The majority of AEs were mild or moderate in severity
  - The most common treatment-related AEs (≥10%) were injection-site reactions, nausea, and fatigue

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AAR, annualized attack rate; AE, adverse event; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; OLE, open-label extension; PBG, porphobilinogen; QOL, quality of life