

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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Disclosure of Conflicts of Interest for David J. Kuter, MD

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

- 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
- 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

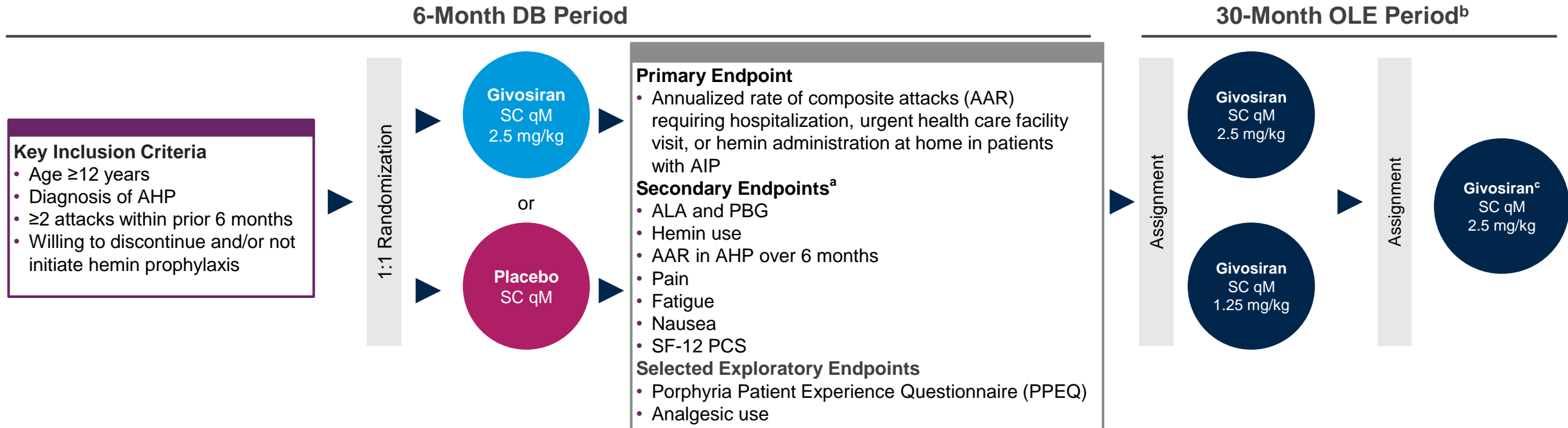
Introduction

- AHP is caused by hepatic heme biosynthesis defects leading to accumulation of neurotoxic heme intermediates, ALA and PBG, and/or porphyrins primarily in the liver¹⁻³
 - Characterized by acute disabling and sometimes life-threatening neurovisceral attacks manifesting as severe abdominal pain, which can become recurrent in some patients^{4,5}
- Givosiran is a subcutaneously administered RNA interference therapeutic that specifically targets ALAS1 mRNA in the liver to reduce ALA and PBG⁶
 - Approved for treatment of AHP in adults in the United States and adults and adolescents age ≥ 12 years in the European Union^{7,8}
- 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 placebo⁶
- Here we report data from the 36-month (6-month DB and 30-month OLE) analysis of the ENVISION trial

AAR, annualized attack rate; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; DB, double-blind; 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. Balwani M, et al. *N Engl J Med.* 2020;382(24):2289-2301. 7. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. 8. Givlaari [summary of product characteristics]. 2020. https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf.

Methods: ENVISION Study Design



^aEndpoints were evaluated in patients with genetically confirmed AIP (except where noted otherwise) at 6 months. ^bFor the OLE period, all endpoints were exploratory.

^cA protocol amendment increased the dose to 2.5 mg/kg monthly for all patients.

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

Results: Patient Demographics and Characteristics at Baseline

All patients (N=94) 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 (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)

^aComposite porphyria attacks requiring hospitalization, an urgent health care visit, or intravenous hemin treatment at home during the 6 months prior to randomization.

^bOne 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).

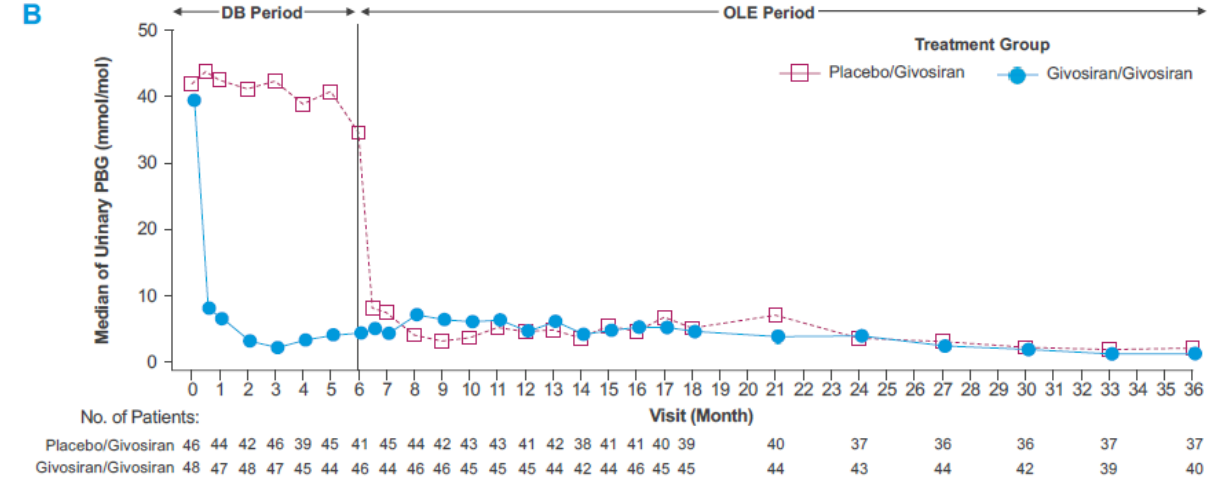
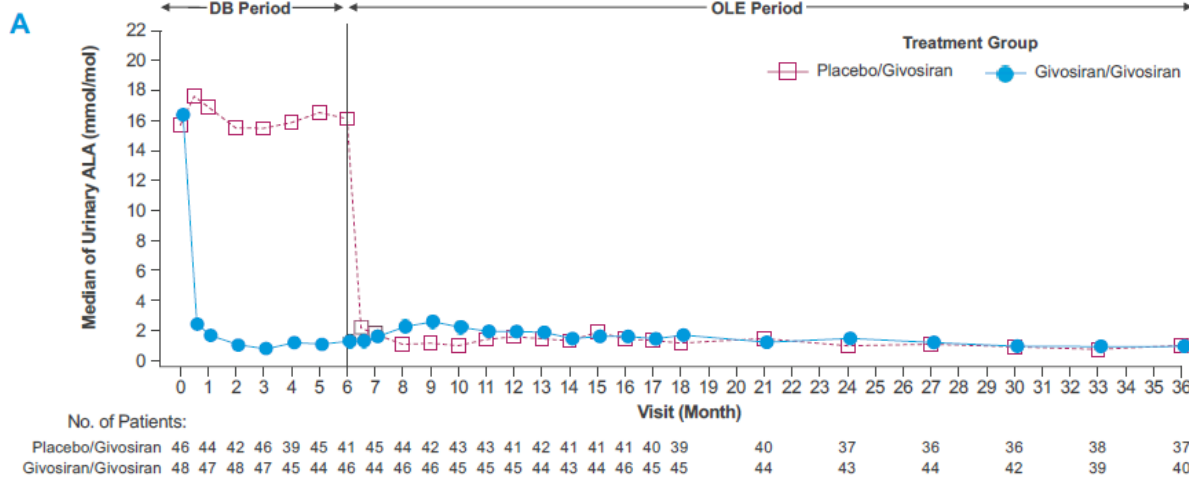
Reference ranges: ALA (ULN, 1.47 mmol/mol Cr); PBG (ULN, 0.137 mmol/mol Cr).¹

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

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

Results: Urinary ALA and PBG Levels over Time

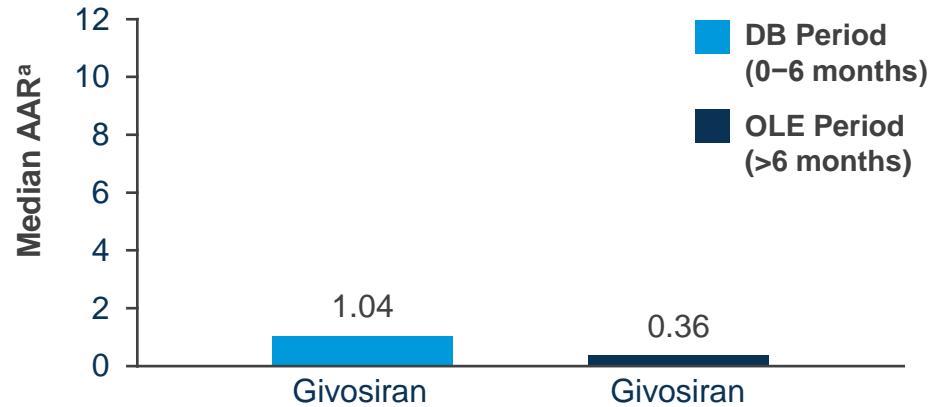
In the placebo–givosiran crossover and continuous givosiran groups, givosiran treatment led to sustained lowering of median ALA levels to near normal and to lowering of PBG levels by >90% at Month 36^a



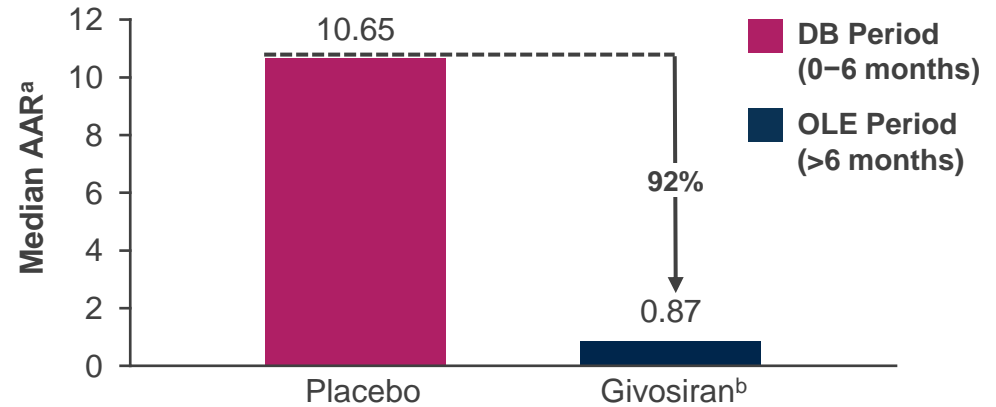
^aOLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled. Reference ranges: ALA (ULN, 1.47 mmol/mol Cr); PBG (ULN, 0.137 mmol/mol/Cr).

Results: AAR and Proportions of Attack-Free Patients

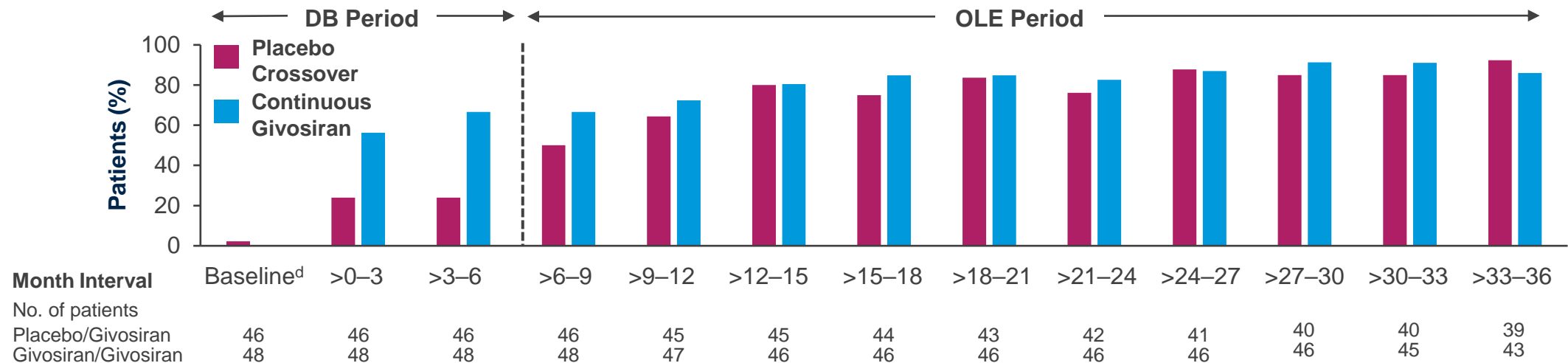
AAR in Continuous Givosiran Patients



AAR in Placebo Crossover Patients



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

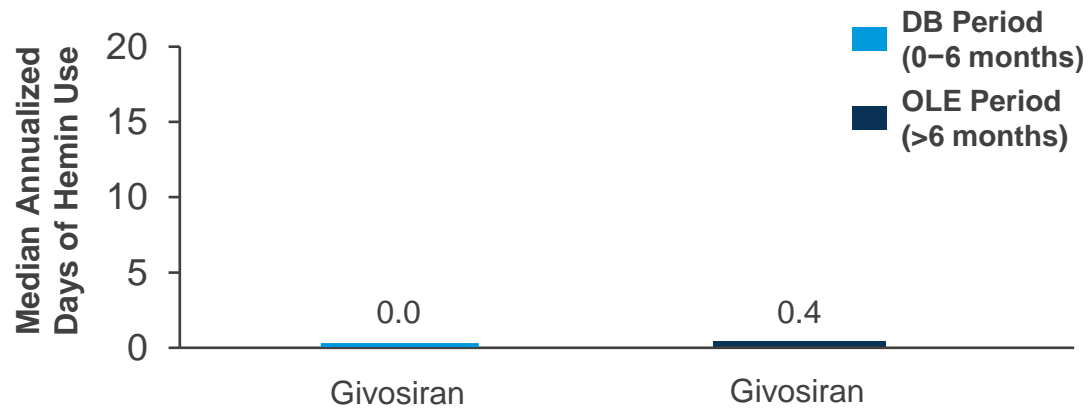


^aDescriptive analysis. ^bPlacebo crossover patients receiving givosiran 2.5 mg/kg (n=29) or 1.25 mg/kg (n=17). ^cComposite attacks include porphyria attacks requiring hospitalization, urgent health care visit, or intravenous hemin administration at home; 1 month = 28 days. ^dBaseline represents 6 months before randomization.

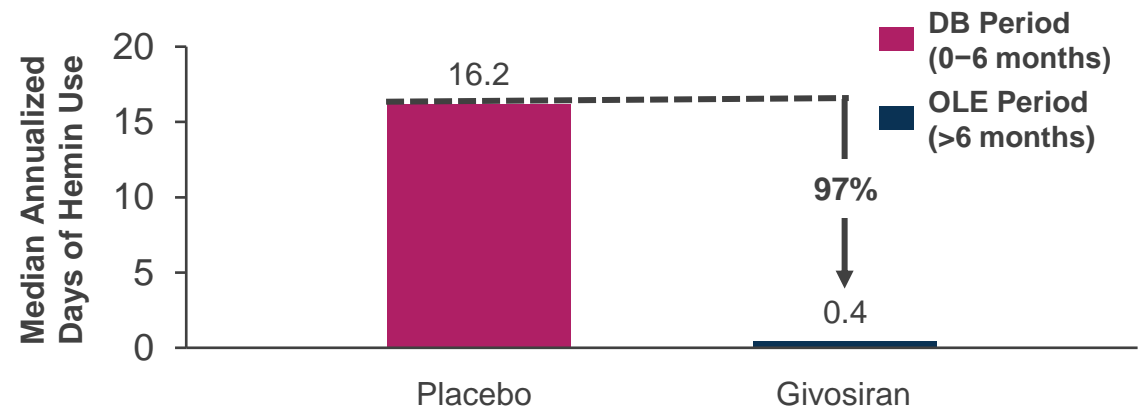
Results: Hemin Use

The proportion of patients with no days of hemin use increased over time in the continuous givosiran group and placebo crossover group

Annualized Days of Hemin Use in Continuous Givosiran Patients



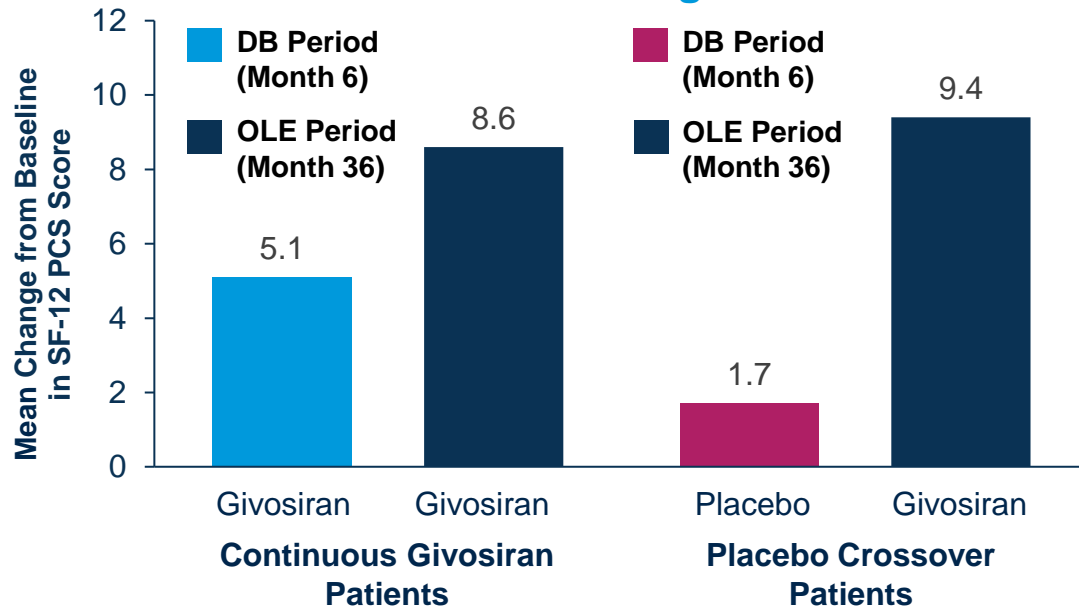
Annualized Days of Hemin Use in Placebo Crossover Patients



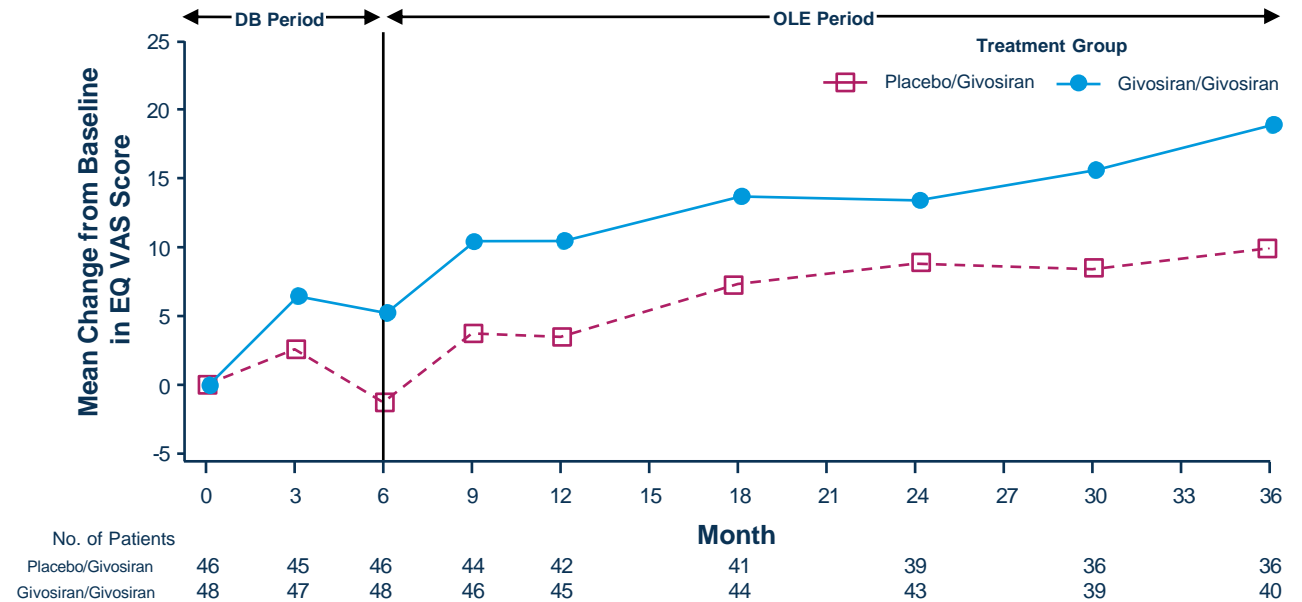
Results: Quality of Life

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

Mean Change in SF-12 PCS Scores from Baseline through OLE Period^a



Mean Change in EQ-VAS Scores from Baseline through OLE Period^b



^aEstimates for the clinically meaningful difference are ≥ 2 to 5 points for SF-12 PCS, based on published data for other chronic diseases.^{1,2}

^bEstimates 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 analog scale; OLE, open-label extension; 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: Adverse Events^a

Patients with ≥1 Event, n (%) ^b	Placebo–Givosiran Crossover (n=46)	Continuous Givosiran (n=48)	All Patients Who Received Givosiran (N=94)
AE	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)

- The most common treatment-related AEs were injection-site reactions (32% [30/94] patients), nausea (21% [20/94]), and fatigue (14% [13/94])
- SAEs reported in ≥2% of patients included pulmonary embolism, blood homocysteine increased, COVID-19 pneumonia, CKD, device breakage, and UTI (each occurred in 2 patients, except for pulmonary embolism, which occurred in 4 patients)
- Hepatic AEs were reported in 18 (19%) 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

^aSafety data from first dose of givosiran to completion of study, May 31, 2021. ^bFor calculating exposure, 1 month = 30.44 days.

^cSAE of liver function test abnormal that led to treatment discontinuation during DB period was previously reported.¹

AE, adverse event; 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 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 ($\geq 10\%$) were injection-site reactions, nausea, and fatigue