Eighteen-Month Interim Analysis of Efficacy and Safety of Givosiran, an RNAi Therapeutic for Acute Hepatic Porphyria, in the ENVISION Open-Label Extension

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ENVISION

Background and Rationale

Acute Hepatic Porphyria (AHP)

- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in the liver[1,2]
- Acute intermittent porphyria (AIP) is the most common type of AHP[3,4]
- Delta-aminolevulinic acid synthase 1 (ALAS1) induction leads to accumulation of toxic intermediates δ-aminolevulinic acid (ALA) and porphobilinogen (PBG), thought to cause AHP manifestations[1,2,5]

Attacks, Chronic Manifestations, and Comorbidities

- Acute neurovisceral attacks commonly manifest as severe abdominal pain and can be life-threatening[6,7]
- Chronic debilitating symptoms can negatively impact daily functioning and QOL (quality of life)[6–8]
- Comorbidities include hypertension, chronic kidney disease, and liver disease[3,6,9–11]

Unmet need for therapies to prevent attacks and chronic disease manifestations

Hemin

- Hemin used to treat acute attacks and sometimes as off-label treatment to prevent attacks[7]
  - Chronic hemin use often requires an indwelling central venous catheter, and can lead to iron overload[7,12]

Givosiran

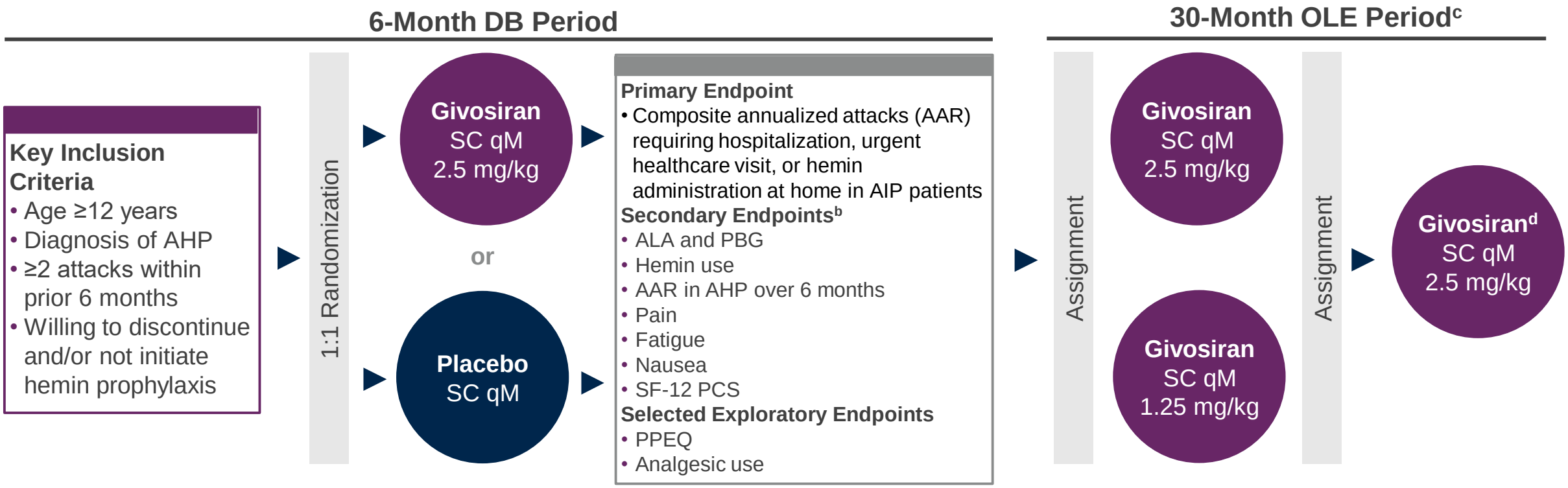
- Subcutaneously administered RNAi therapeutic that specifically targets ALAS1 messenger RNA in the liver to reduce disease-causing neurotoxic intermediates ALA and PBG
- Approved for treatment of AHP in adults in the US and adults and adolescents aged 12 years or older in the EU[13,14]

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; ALAS1, δ-aminolevulinic acid synthase 1; PBG, porphobilinogen; QOL, quality of life; RNA, ribonucleic acid; RNAi, RNA interference

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 Gen*et 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; 12. Wang et al. *Hepatol Commun* 2018;3:193–206; 13. GIVLAARI US Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf (accessed October 23, 2020); 14. GIVLAARI EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (accessed October 23, 2020)

ENVISION Study Design

- 94 patients with AHP enrolled in ENVISION at 36 sites in 18 countries
- All patients completed the 6-month double-blind (DB) period; all eligible patients (n=93) entered the 30-month open-label extension (OLE) period; here we present results from an 18-month interim analysis[a]



[a]Data from the timepoint after which all patients had completed at least their Month 18 visit (January 10, 2020). [b]Endpoints evaluated in patients with genetically confirmed AIP, unless otherwise noted, at 6 months. [c]All endpoints listed above were considered exploratory in the OLE period. [d]A protocol amendment increased the dose of all patients to 2.5 mg/kg monthly

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

Baseline Characteristics Generally Balanced Between Groups

Baseline Demographics and Disease Characteristics of Patients in ENVISION

Characteristic	Placebo Crossover (N=46)	Givosiran (N=48)	All Patients (N=94)
Age at screening, years, 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)	6.46 (0.1, 38.5)	6.98 (0.2, 43.3)	6.55 (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)
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)

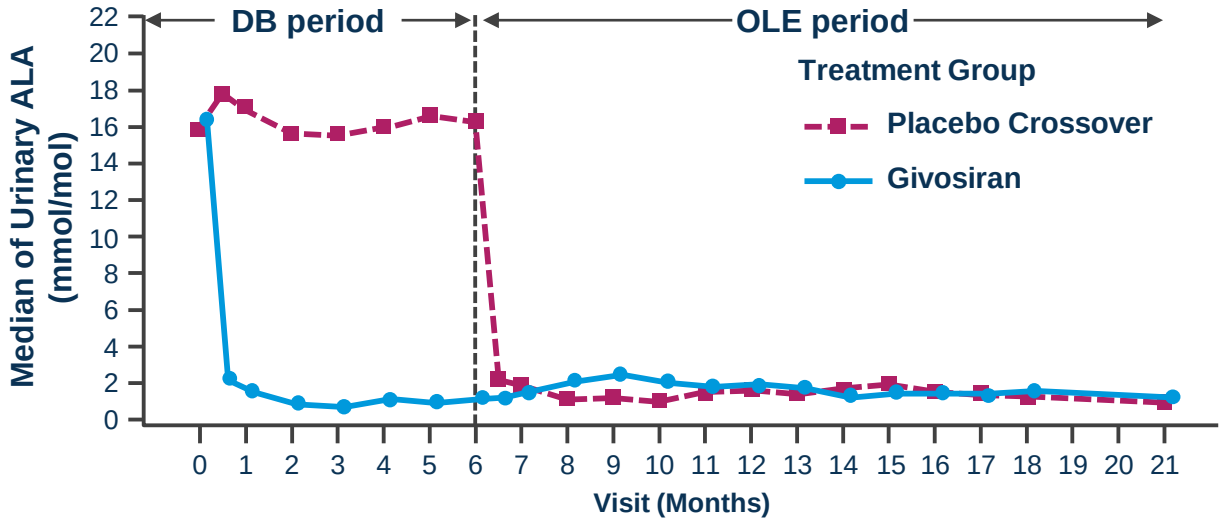
[a]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home. [b]One patient in the placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home within 6 months prior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

AAR, annualized attack rate; ALA, δ-aminolevulinic acid, Cr, creatinine; IV, intravenous; PBG, porphobilinogen

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

- During the OLE, givosiran treatment led to sustained reductions in ALA and PBG levels through Month 18
- Patients with AHP achieved near normalization or normalization of ALA and PBG levels with givosiran treatment[1]

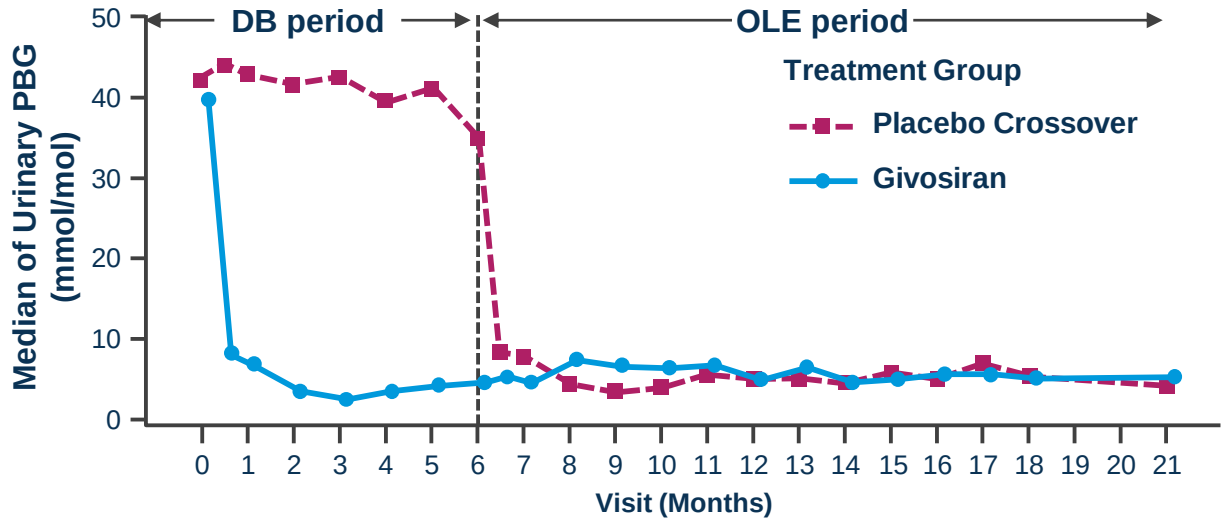
Median Urinary ALA Levels over Time[a]



No. of patients:

PBO/Givo	46	42	44	42	46	39	45	41	44	45	44	42	43	43	41	42	40	41	41	40	39		19
Givo/Givo	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	44	43	44	46	45	45		19

Median Urinary PBG Levels over Time[a]



No. of patients:

PBO/Givo	46	42	44	42	46	39	45	41	44	45	44	42	43	43	41	42	40	41	41	40	39		19
Givo/Givo	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	44	43	44	46	45	45		19

[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled

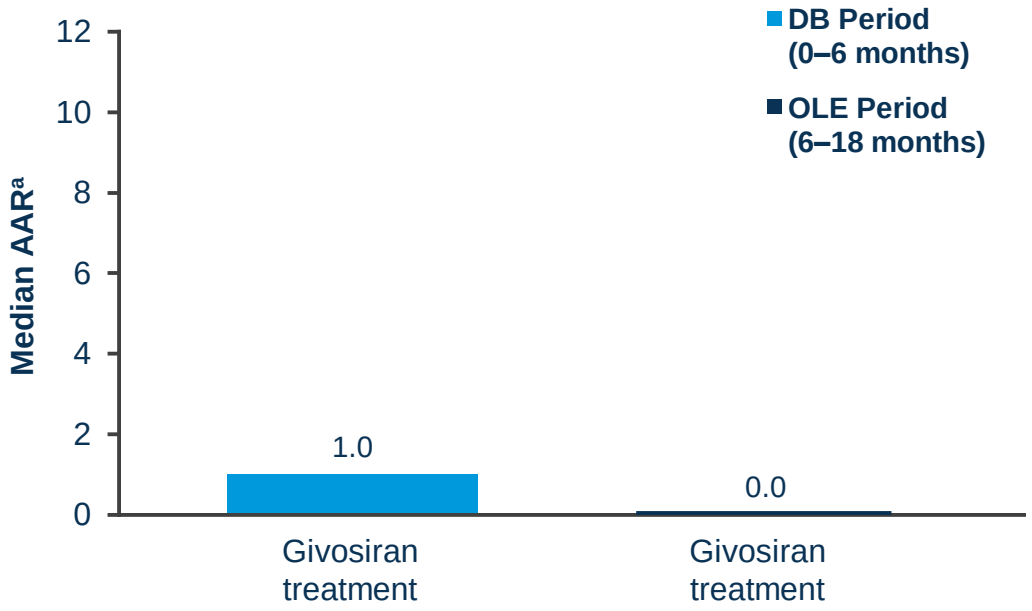
AHP, acute hepatic porphyria; ALA, δ-aminolevulinic acid; DB, double-blind; Givo, givosiran; OLE, open-label extension; PBG, porphobilinogen; PBO, placebo

1. Agarwal et al. *JIMD Reports* 2020; DOI:10.1002/jmd2.12173

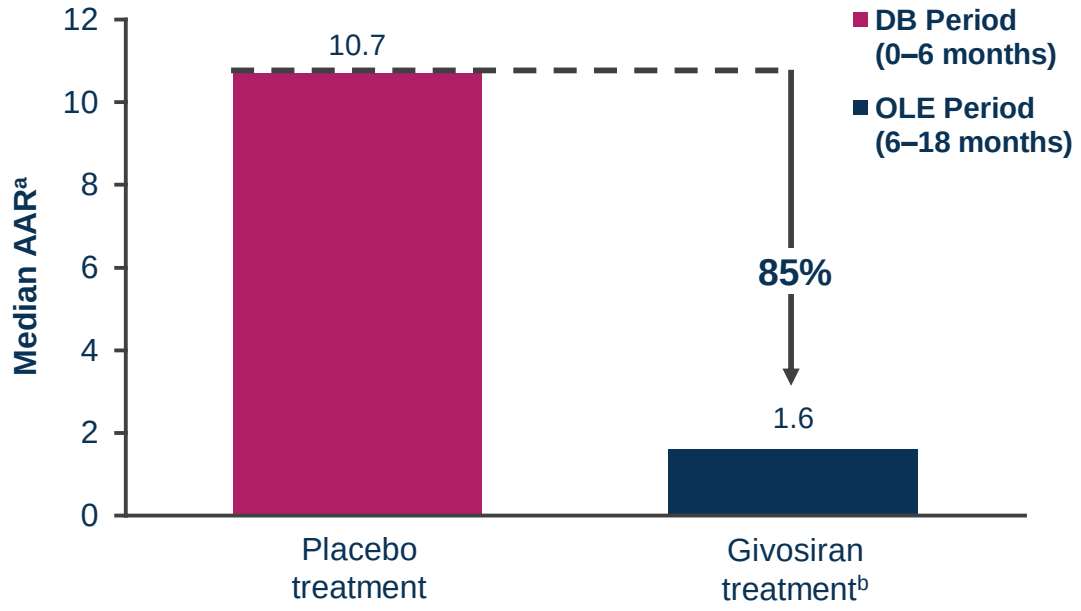
Long-Term Givosiran Dosing Led to Sustained Reduction of Attacks

- Continued givosiran treatment led to sustained reduction in attacks during the OLE period
  - Following initial 6 months of givosiran treatment in the OLE, placebo crossover patients continued to have a sustained reduction in attacks after 12 months of treatment (median AAR 1.8 vs 1.6, respectively)[1]

AAR in Continued Givosiran Patients



AAR in Placebo Crossover Patients

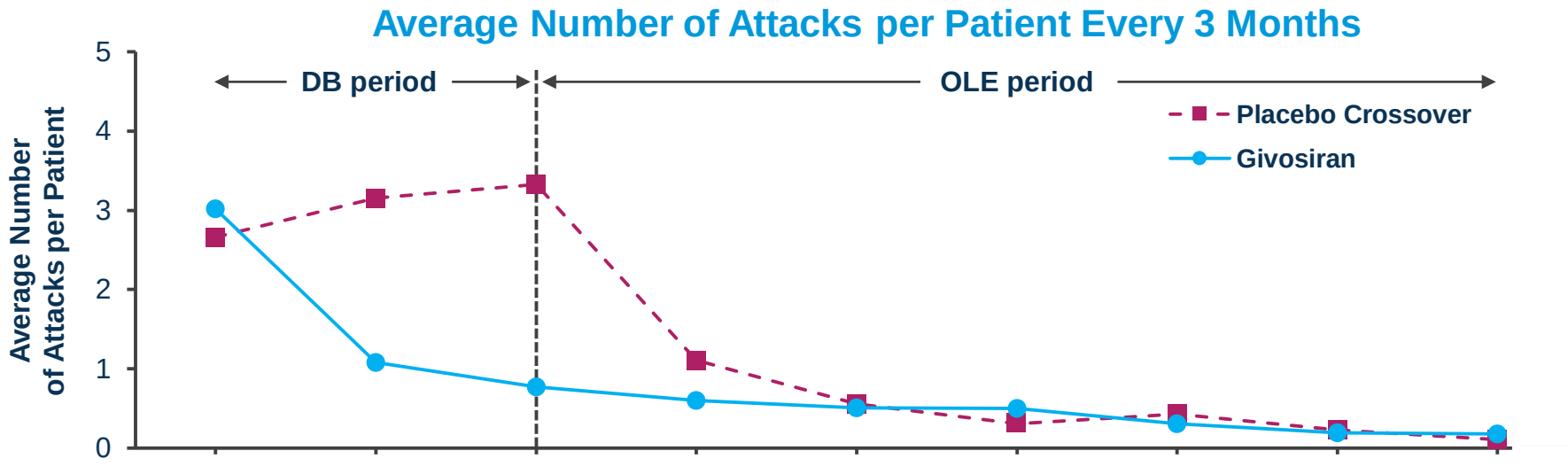


[a]Descriptive analysis. [b]Placebo crossover patients receiving givosiran 2.5 mg/kg (n=29) or 1.25 mg/kg (n=17)

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

1. Sardh et al. Presented at *The Digital International Liver Congress* 2020. Oral

Long-Term Givosiran Dosing Led to Sustained Reduction of Attacks



No. of patients									
Placebo crossover	46	46	46	46	45	45	44	43	19
Givosiran	48	48	48	48	47	46	46	46	22

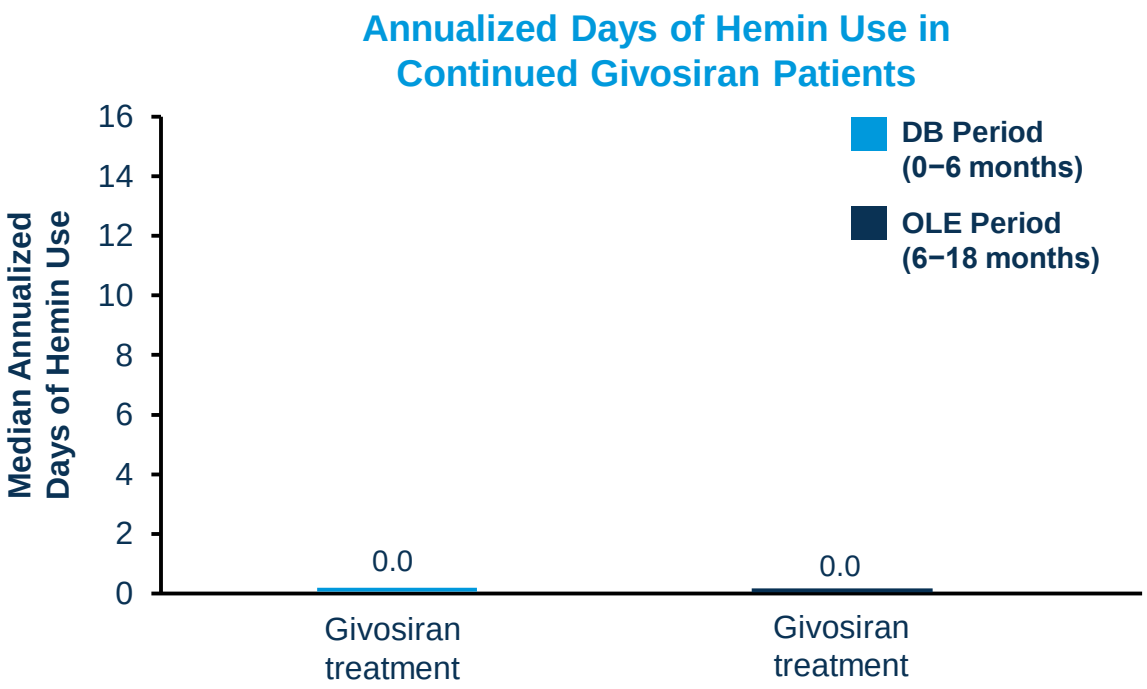
- With a further 6 months of givosiran treatment, proportion of patients with zero attacks during the OLE period was sustained
  - 61.7% vs 60.9% (Month 12 vs Month 18) for continued givosiran patients[1]
  - 42.2% vs 40.0% (Month 12 vs Month 18) for placebo crossover patients[1]

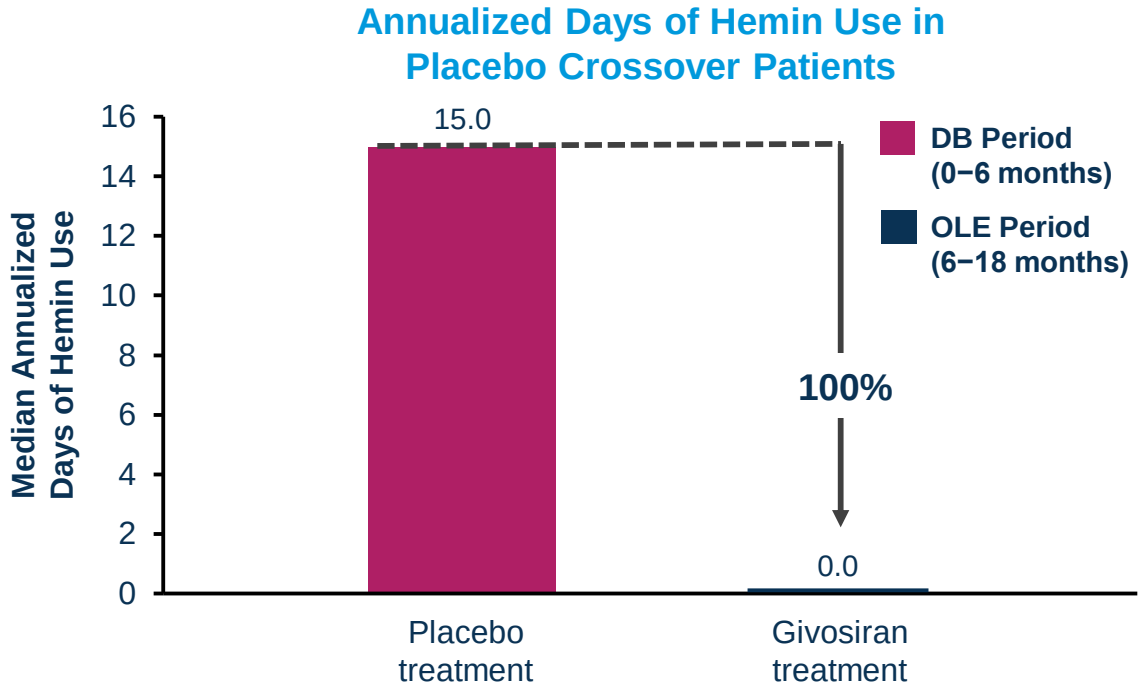
[a]The estimate for each 3-month interval is calculated as total number of attacks/total number of patients reached that 3 months. Three months=28 × 3 days. [b]OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled
DB, double-blind; OLE, open-label extension

1. Sardh et al. Presented at *The Digital International Liver Congress* 2020. Oral

Sustained Reductions in Hemin Use with Long-Term Dosing

- Givosiran led to sustained reductions in hemin use, with median days of hemin use being 0.0 days for both groups during the OLE period, compared with 15.0 days for placebo patients during the DB period
  - Over half (51%) of placebo crossover patients had zero days of hemin use at Month 18 of the OLE period, compared with 26% in the DB period



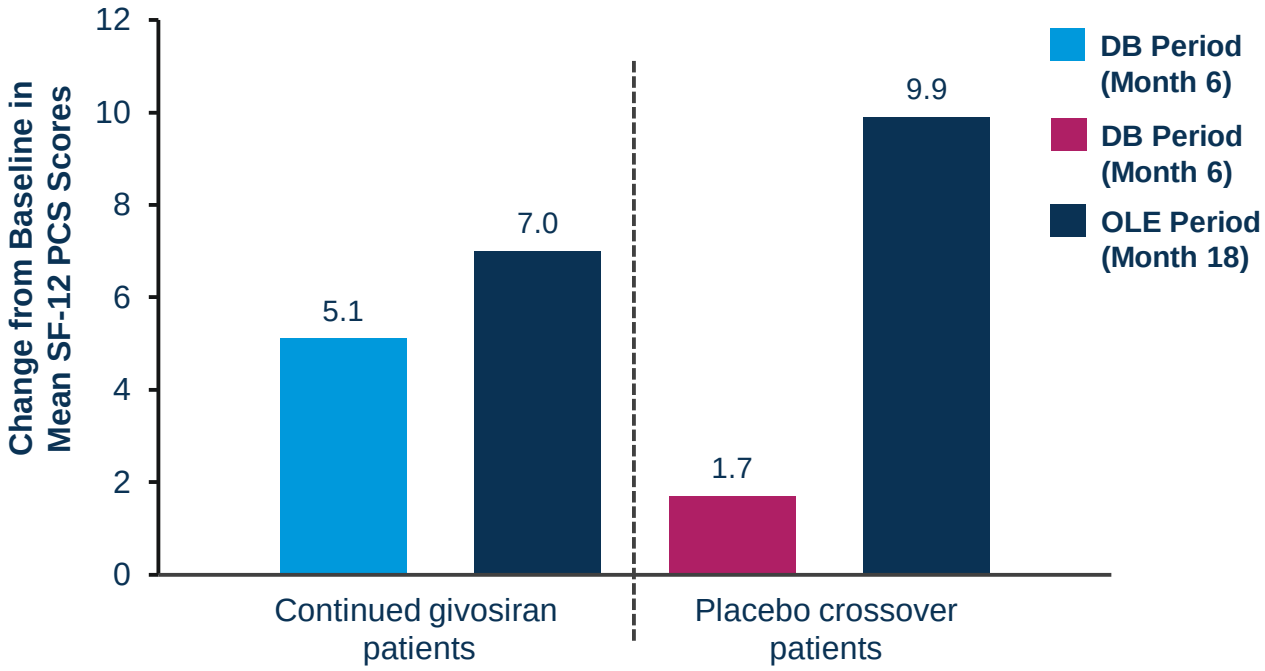


DB, double-blind; OLE, open-label extension

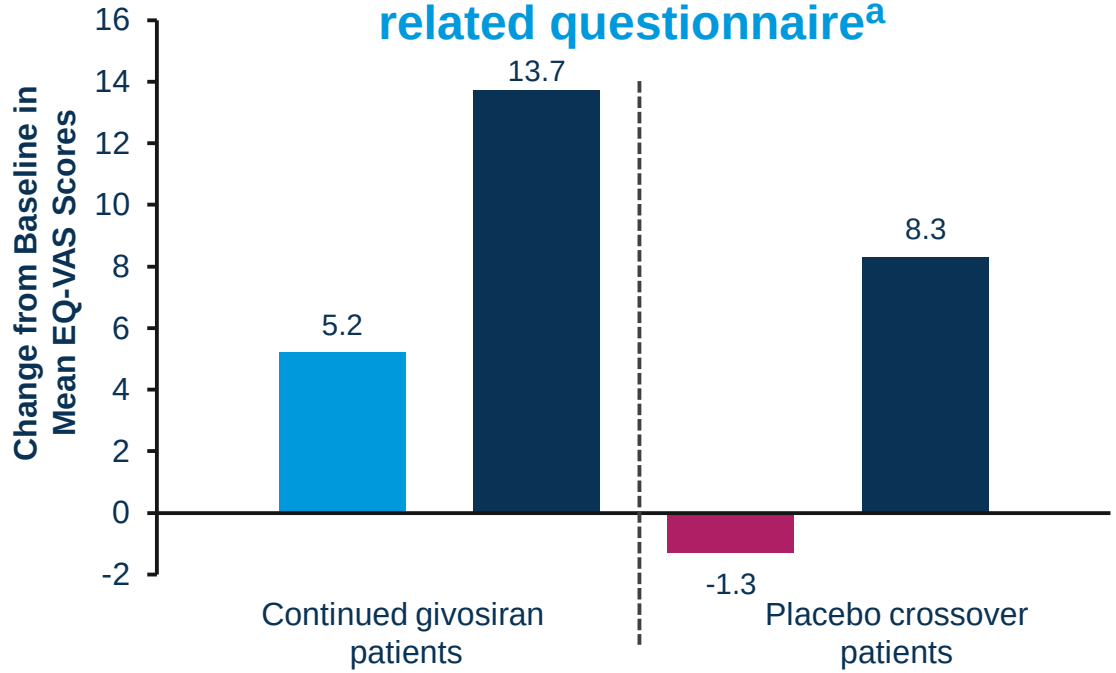
Further Improvement in QOL with Long-Term Dosing

- Patients experienced further improvements in QOL, as assessed by SF-12 Physical Component Summary[a] and EuroQol-visual analog scale health-related questionnaire scores, with givosiran treatment
  - Improvements in QOL scores were observed at Month 6 and Month 18 in patients continuing givosiran treatment, while placebo crossover patients had similar improvements at Month 18 to those seen in givosiran patients in the DB period

SF-12 Physical Component Summary[a]



EuroQol-visual analog scale health-related questionnaire[a]



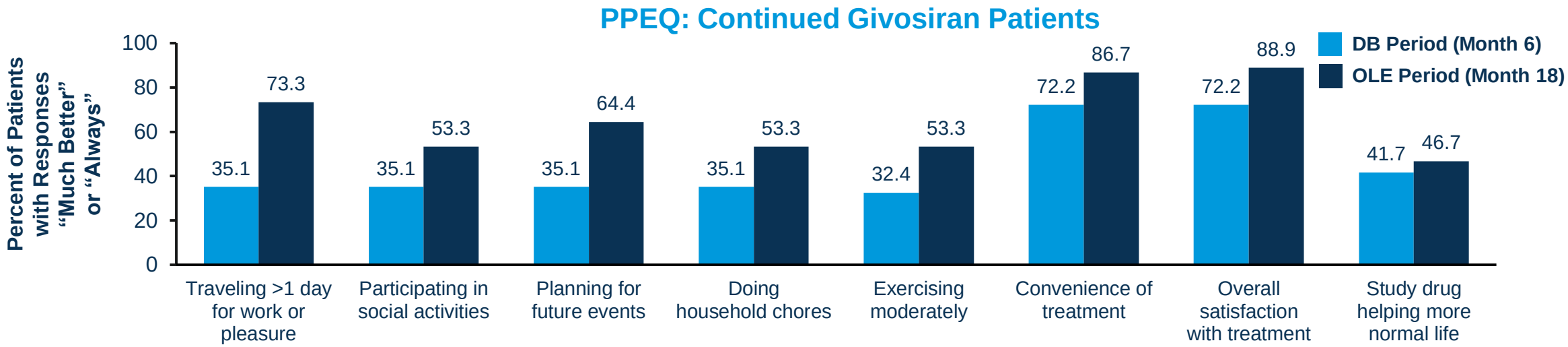
[a]Estimates for the clinically meaningful difference are ≥2−5 points for SF-12 PCS and 7–8 points for EQ-VAS, based on published data for other chronic diseases[1–4]

DB, double-blind; EQ-VAS, EuroQol-visual analog scale health-related questionnaire; PCS, Physical Component Summary; QOL, quality of life; SF-12, Short Form (12-item) Health Survey

1. Clement et al. *Knee Surg Sports Traumatol Arthrosc* 2014;22:1933–9; 2. Parker et al. *J Neurosurg Spine* 2012;16:471–8; 3. Zanini et al. *Respir Care* 2015;60:88–95; 4. Nolan et al. *Thorax* 2016;71:493–500

Improvement in Patient-Reported Outcomes with Long-Term Dosing

- The PPEQ questionnaire observed further improvements across all domains in patients continuing givosiran treatment compared with the DB period[1]
  - Improvements across all domains were also observed in placebo crossover patients compared with the DB period



- Givosiran treatment led to a decrease in the number of work days missed due to porphyria in the past 4 weeks in both patient groups when compared with placebo crossover patients in the DB period[a]
  - Mean (SD) of 2.4 (6.8) days vs 1.8 (6.3) days (Month 6 vs Month 18) for continued givosiran patients[b]
  - Mean (SD) of 6.7 (7.8) days vs 2.5 (5.1) days (Month 6 vs Month 18) for placebo crossover patients[c]

[a]Including only those patients who have been employed in the past 4 weeks. [b]Patient numbers: n=17 at Month 6; n=20 at Month 18. [c]Patient numbers: n=20 at Month 6; n=23 at Month 18
DB, double-blind; OLE, open-label extension; PPEQ, Porphyria Patient Experience Questionnaire; SD, standard deviation

1. Balwani et al. *N Engl J Med* 2020;382:2289–301

Safety Profile[a] of Givosiran Remained Acceptable with No New Safety Concerns

- Mean (SD) exposure was 18.9 (3.6) months for continued givosiran patients and 13.0 (3.6) months for placebo crossover patients, with maximum exposure of 25.1 months
- Majority of AEs continued to be mild or moderate in severity
- Most common related AEs (≥10%): ISRs, nausea, and fatigue[c]
- SAEs in ≥2%: UTI, CKD, and device breakage[d]
- There were no deaths

Safety Summary in Patients Receiving Givosiran[a]

At Least 1 Event, n (%)[b]	Placebo Crossover (N=46)	Givosiran (N=48)	All Patients (N=94)
AEs	43 (94)	47 (98)	90 (96)
SAEs	9 (20)	15 (31)	24 (26)
Severe AEs	12 (26)	12 (25)	24 (26)
AEs leading to treatment discontinuation	1 (2)	1 (2)	2 (2)
AEs leading to study withdrawal	0	1 (2)	1 (1)
Deaths	0	0	0

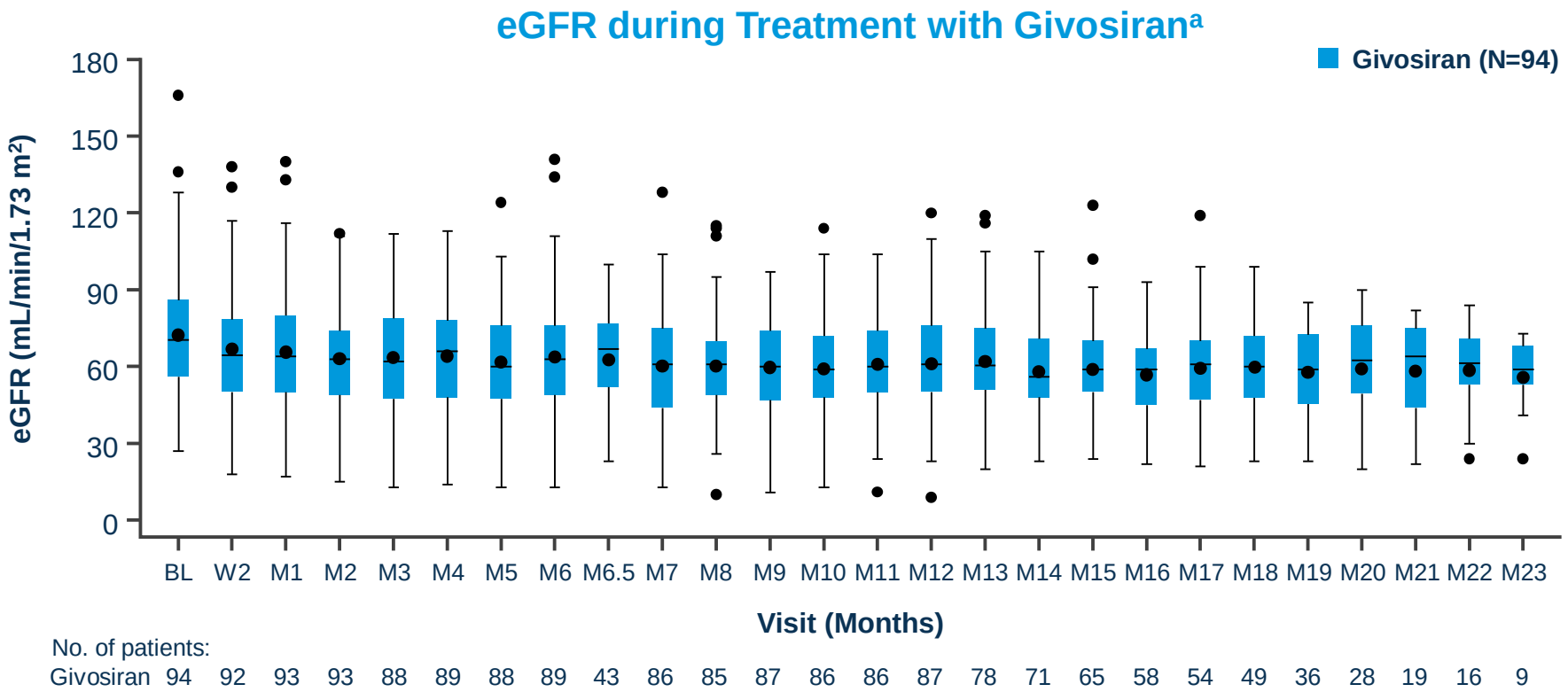
- During interim period between data cuts at Months 12 and 18, there was one new AE of drug hypersensitivity which led to treatment discontinuation[e]
  - No new treatment-related SAEs or safety concerns regarding hepatic AEs

[a]Safety data from first dose of givosiran to data cut-off date (January 10, 2020). [b]For calculating exposure: 1 month=30.44 days. [c]ISRs occurred in 36% of patients (103 events), nausea in 30%, and fatigue in 23%. [d]Each SAE occurred in 2 patients. [e]SAE of LFT abnormal that led to treatment discontinuation during the DB period previously reported

AE, adverse event; CKD, chronic kidney disease; ISR, injection-site reaction; LFT, liver function test; SAE, serious AE; SD, standard deviation; UTI, urinary tract infection

Renal Events in Patients with AHP

- Renal AEs (mostly increased serum creatinine and/or decreased eGFR) occurred in 16 patients (17%)
  - None led to discontinuation of study treatment
- Small decreases in eGFR observed early in therapy which stabilized by Months 12 to 18



[a]The line and dot inside the box indicate the median and mean value respectively. The bottom and top edges of the box indicate interquartile range (IQR). The vertical lines represent the most extreme point within 1.5x IQR. Any value more extreme than this is marked with a dot.

AE, adverse event; AHP, acute hepatic porphyria; BL, baseline; eGFR, estimated glomerular filtration rate; IQR, interquartile range; M, month; W, week; Q1, lower quartile; Q3, upper quartile

18-Month ENVISION OLE Summary

- Givosiran decreased ALA and PBG levels through Month 18
- Reductions in annualized rate of composite porphyria attacks in patients with AHP were sustained during the OLE period
  - Placebo crossover patients had an 85% reduction in AAR compared with the DB period
  - More than 60% of continued givosiran patients continued to have zero attacks during the OLE period
- Median annualized days of hemin use reduced from 15 to zero during OLE for placebo crossover patients
- Givosiran treatment led to improvements in multiple measures of QOL and reductions in work days missed due to porphyria
- The safety profile of givosiran remained acceptable and consistent with that previously observed
- In the ongoing ENVISION OLE, patients receiving long-term treatment with givosiran demonstrated a durable response in clinical efficacy across a wide range of clinical parameters

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