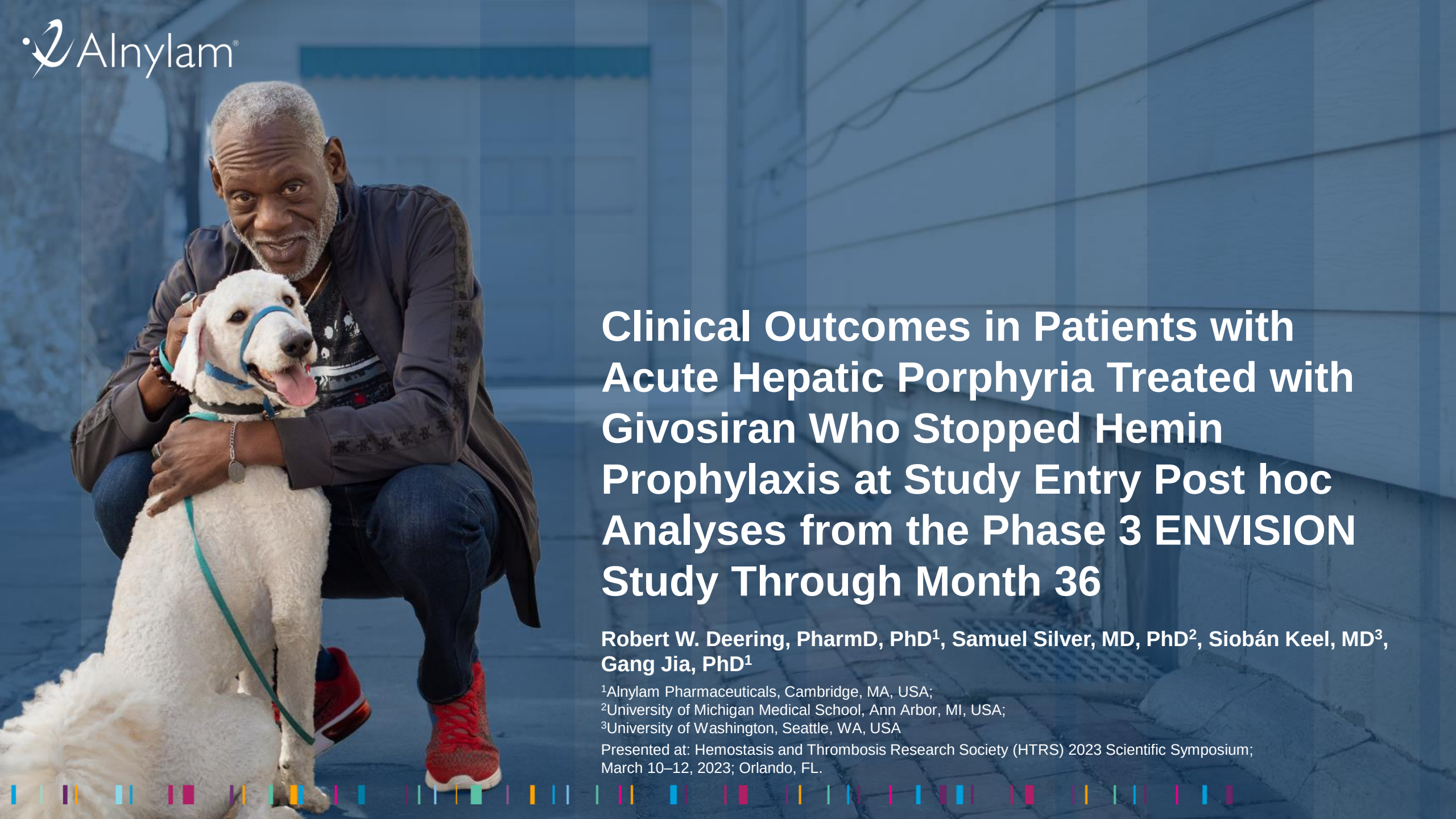

# Clinical Outcomes in Patients with Acute Hepatic Porphyria Treated with Givosiran Who Stopped Hemin Prophylaxis at Study Entry Post hoc Analyses from the Phase 3 ENVISION Study Through Month 36

**Robert W. Deering, PharmD, PhD[1], Samuel Silver, MD, PhD[2], Siobán Keel, MD[3], Gang Jia, PhD[1]**

[1]Alnylam Pharmaceuticals, Cambridge, MA, USA;
[2]University of Michigan Medical School, Ann Arbor, MI, USA;
[3]University of Washington, Seattle, WA, USA

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# Background

- AHP is a genetic disorder caused by hepatic heme biosynthesis defects, sometimes leading to accumulation of the neurotoxic heme intermediates ALA and PBG[1,2]
- Patients with AHP suffer from acute, disabling, and sometimes life-threatening neurovisceral attacks, which in a subset of patients are recurrent[3,4]
- IV hemin is approved to treat acute attacks and is used off-label prophylactically[5–7]
- Givosiran is a subcutaneously administered small interfering RNA against ALAS1 that is taken up by hepatocytes and reduces urinary exosome *ALAS1* mRNA as a surrogate to hepatic *ALAS1* mRNA
- Givosiran is approved for the treatment of AHP in adults in the United States and in adults and adolescents age ≥12 years in the European Union[8,9]
- During the 6-month DB period of the Phase 3, randomized, placebo-controlled ENVISION study (NCT03338816) in people with AHP, givosiran treatment reduced the AAR by 74%, reduced ALA and PBG levels and hemin use, and improved patient-reported QOL assessment scores, compared with placebo[10]
- Continued givosiran treatment in the OLE period of ENVISION led to sustained improvement in these measures for up to 36 months[11]

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

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# Objective

- To evaluate outcomes in patients with and without prior hemin prophylaxis who were treated with givosiran for up to 36 months in the ENVISION study



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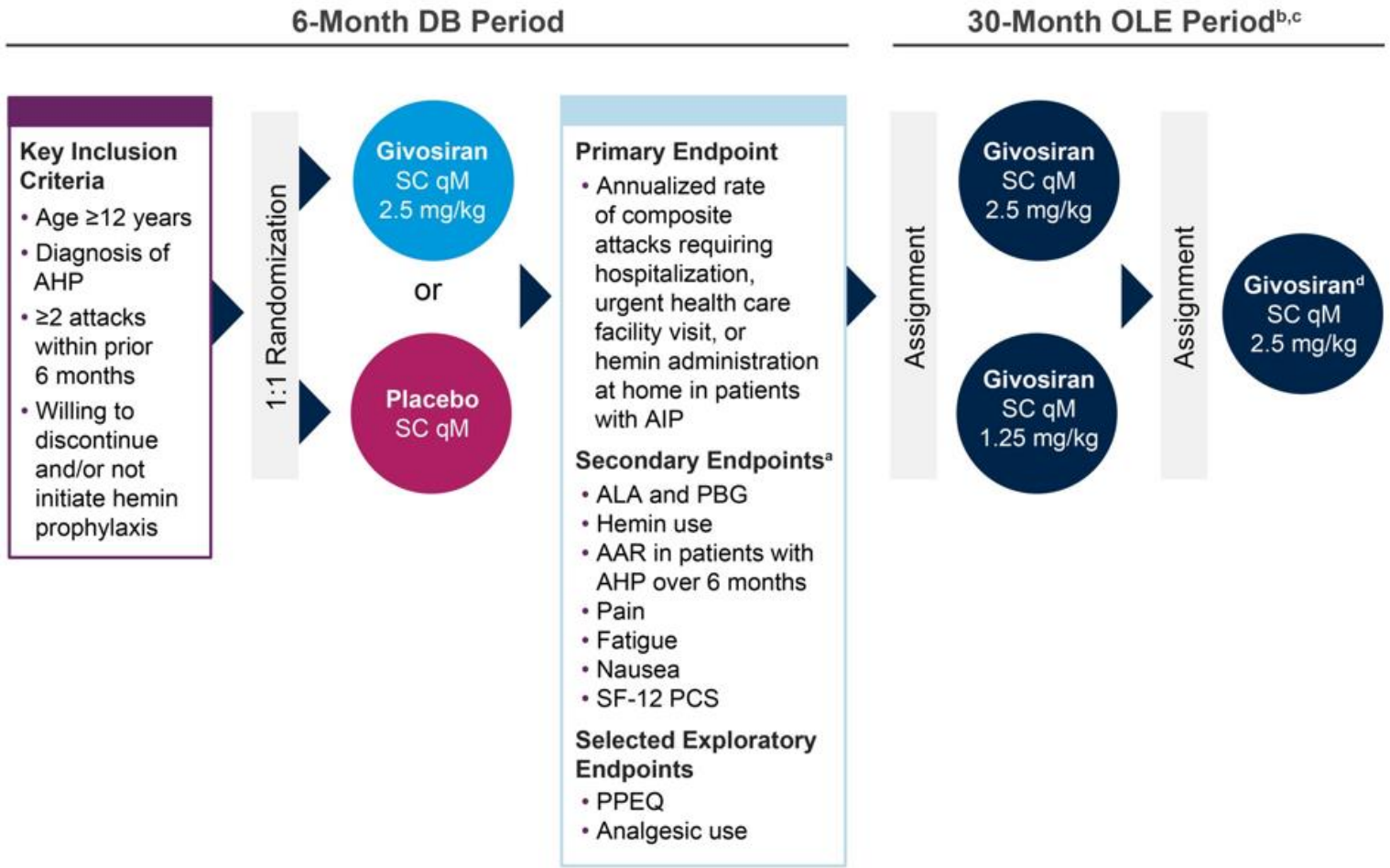
# Methods

## Figure 1. ENVISION Study Design

- The ENVISION study design is shown in **Figure 1**




[a]Endpoints in the primary study were evaluated in patients with genetically confirmed AIP (except where noted otherwise) at 6 months; the current post hoc analysis includes study patients with AHP.
[b]For the OLE period, all endpoints were exploratory.
[c]Data for 1.25 and 2.5 mg/kg doses are pooled in all analyses.
[d]A protocol amendment (February 12, 2020) 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; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; PCS, physical component summary; PPEQ, Porphyria Patient Experience Questionnaire; qM, once a month; SC, subcutaneous; SF-12, 12-item Short Form Health Survey.

# Results

## Demographics

- Ninety-four patients with AHP were enrolled at 36 sites in 18 countries
- Ninety-three patients completed the DB period and entered the OLE period
- Median (range) duration of historical hemin use was 5.0 (1–33) years
- Baseline characteristics were generally balanced between groups **(Table 1)**

**Table 1. Baseline Demographics and Clinical Characteristics of Patients with AHP in ENVISION**

| Characteristic | Prior Hemin Prophylaxis | | No Prior Hemin Prophylaxis | |
|---|---|---|---|---|
| | Placebo (n=18) | Givosiran (n=20) | Placebo (n=28) | Givosiran (n=28) |
| **Age at diagnosis, years, median (range)** | 29.6 (17–44) | 32.4 (16–48) | 28.0 (18–51) | 28.1 (5–58) |
| **Region, n (%)**<br>Europe<br>North America<br>Other | <br>8 (44)<br>8 (44)<br>2 (11) | <br>7 (35)<br>9 (45)<br>4 (20) | <br>11 (39)<br>10 (28)<br>7 (25) | <br>16 (57)<br>7 (28)<br>5 (28) |
| **Years since diagnosis, median (range)** | 7.08 (0.7–38.5) | 6.56 (0.2–35.3) | 4.06 (0.1–25.0) | 7.20 (0.4–43.3) |
| **Historical AAR,[a] median (range)** | 9.0 (4–38) | 9.0 (4–32) | 6.0 (0–46) | 8.0 (4–34) |
| **Prior chronic symptoms,[b] n (%)** | 9 (50) | 7 (35) | 17 (61) | 16 (57) |
| **Prior chronic opioid use,[c] n (%)** | 6 (33) | 8 (40) | 7 (25) | 6 (21) |
| **Historical hemin prophylaxis,[d] years, median (range)** | 4.5 (1–14) | 5.0 (1–33) | 0 (NA) | 0 (NA) |
| **Current or prior central venous catheter use, n (%)** | 16 (89) | 17 (85) | 16 (57) | 18 (64) |
| **Complications related to central venous access, n (%)** | 8 (44) | 7 (35) | 8 (29) | 8 (29) |
| **Diagnosed iron overload, n (%)** | 11 (61) | 10 (50) | 4 (14) | 6 (21) |

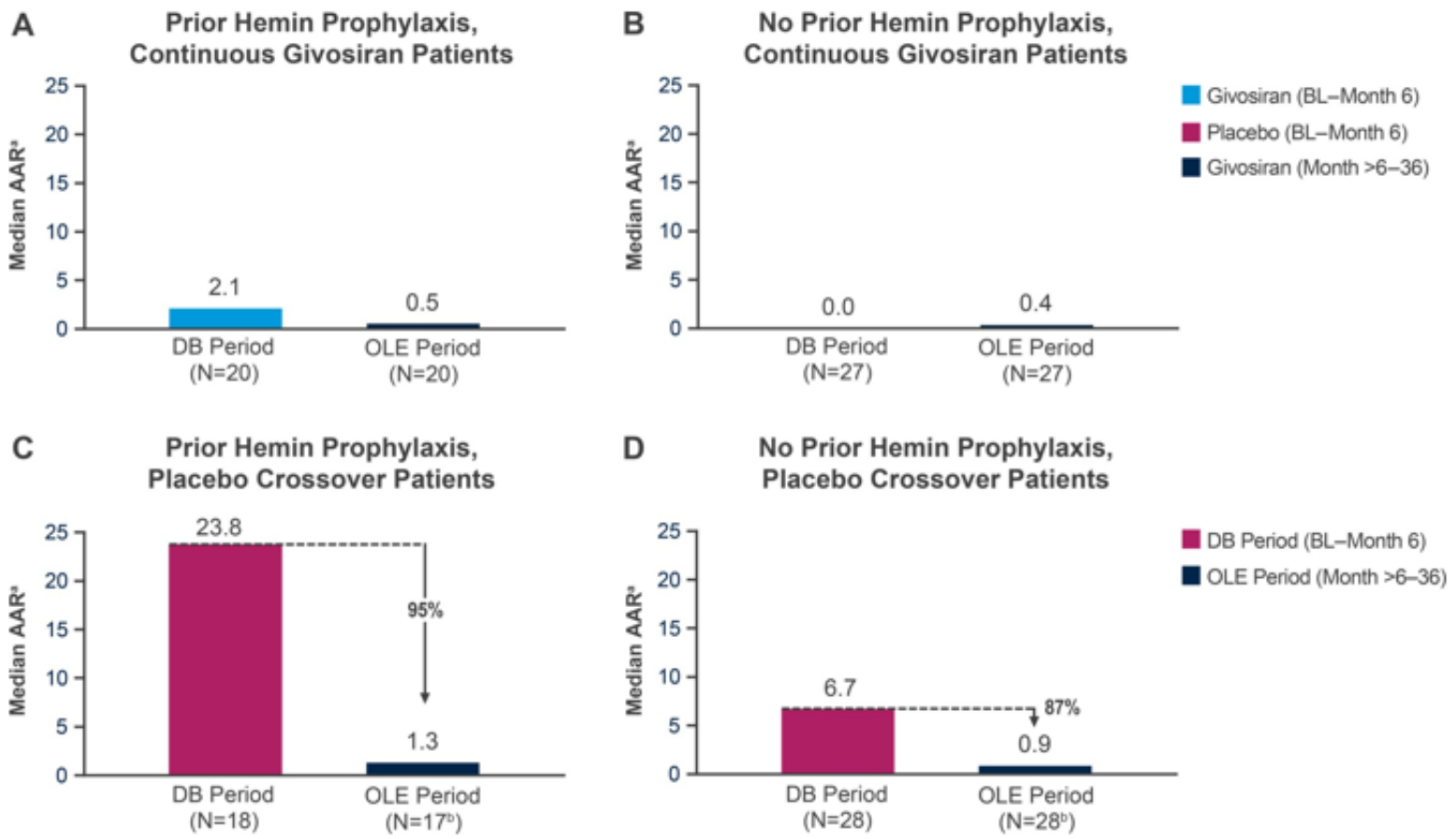
[a]Composite porphyria attacks are attacks requiring hospitalization, an urgent health care facility visit, or IV hemin treatment at home during the 6 months before randomization.
[b]Symptoms were chronic if patients experienced symptoms daily or on most days when not having an attack and were reported by investigators.
[c]Opioid use was defined as chronic if patients reported taking opioids for porphyria daily or on most days when not having an attack.
[d]Yes/no; hemin prophylaxis regimen not specified.
AAR, annualized attack rate; AHP, acute hepatic porphyria; DB, double-blind; NA, not applicable; OLE, open-label extension.

# Results

## Attacks

- During the OLE period, continued givosiran treatment led to a sustained reduction in median AAR in the continuous givosiran group, regardless of prior hemin prophylaxis status **(Figure 2A, 2B)**
- In the placebo crossover group as well, median AAR decreased during the OLE period, regardless of prior hemin prophylaxis status **(Figure 2C, 2D)**

**Figure 2. Median AAR for DB and OLE Periods, by Treatment and Prior Hemin Prophylaxis Status**



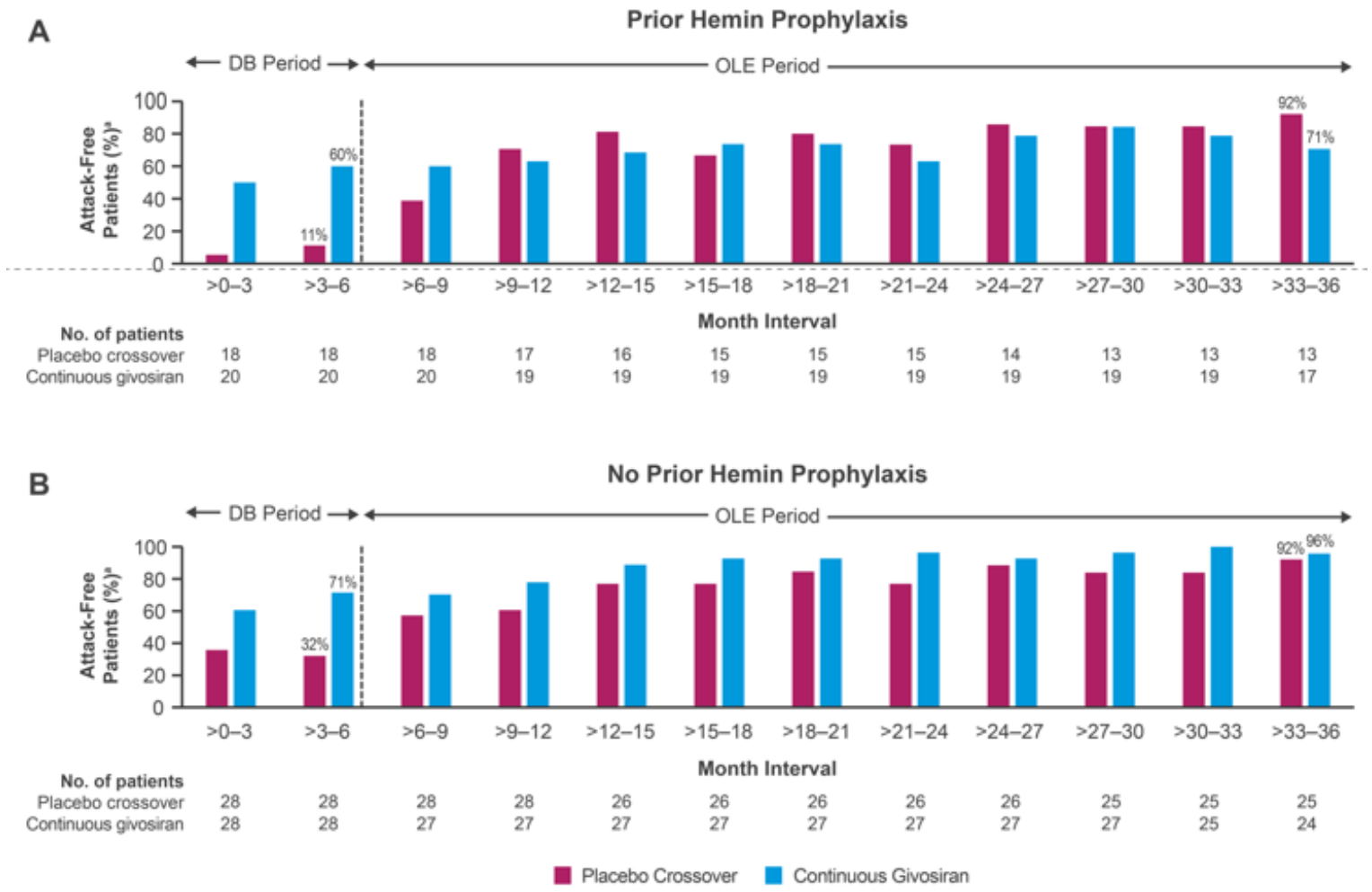

[a]Descriptive analysis.
[b]One patient with <85 days' follow-up after taking givosiran was excluded from descriptive summaries.
AAR, annualized attack rate; BL, baseline; DB, double-blind; OLE, open-label extension.

# Results

## Attacks

- The proportion of attack-free patients increased from the DB period through the OLE period, regardless of prior hemin prophylaxis status **(Figure 3)**

### Figure 3. Proportion of Attack-Free Patients, by 3-Month Interval, Treatment, and Prior Hemin Prophylaxis Status



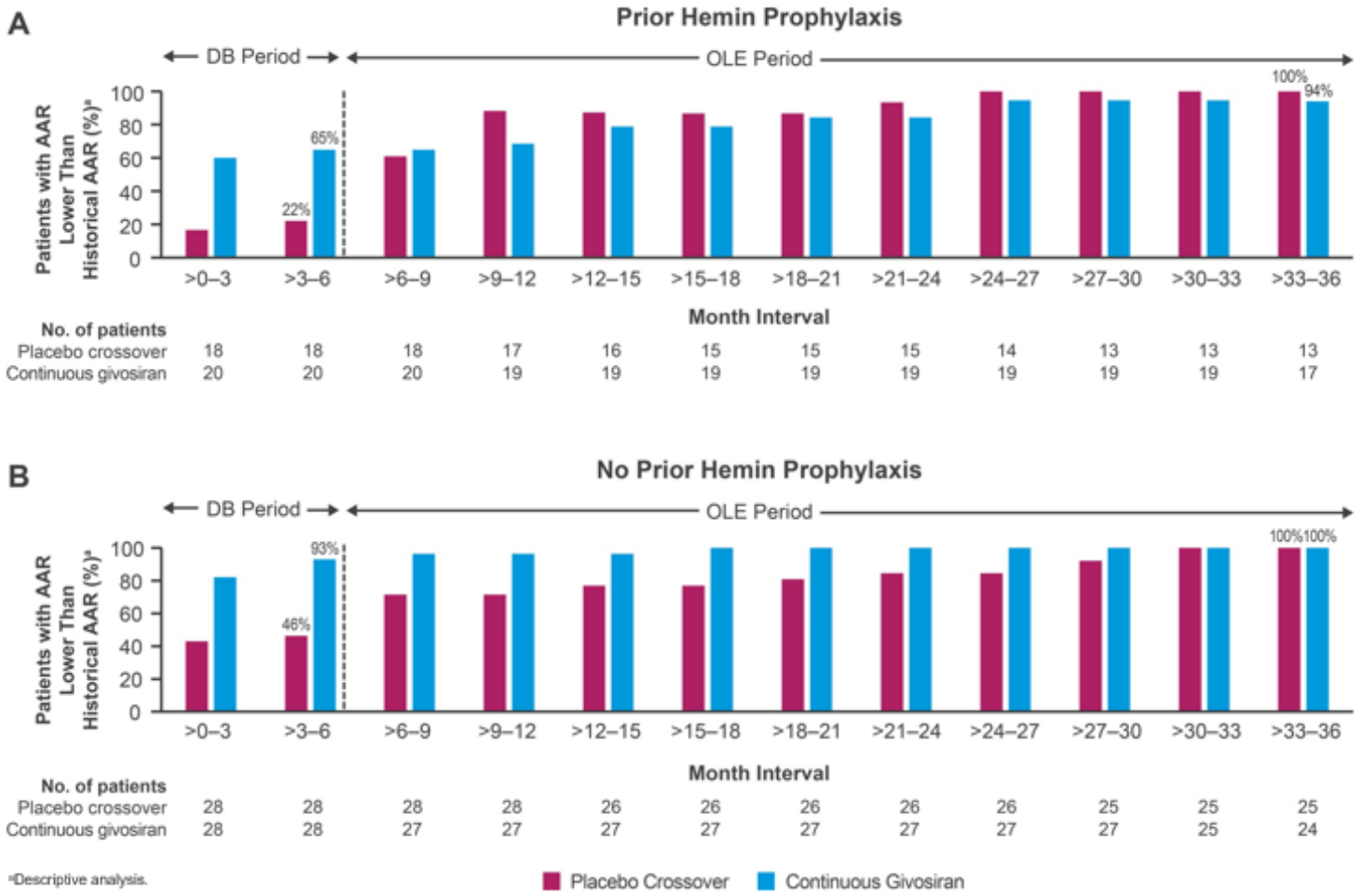

[a]Descriptive analysis.
DB, double-blind; OLE, open-label extension.

# Results

## Attacks

- The proportion of patients whose AAR was lower than the historical AAR and remained lower increased from the DB period through the OLE period, regardless of prior hemin prophylaxis status **(Figure 4)**

### Figure 4. Proportion of Patients with an AAR That Was Lower Than the Historical AAR and Remained Lower, by 3-Month Interval, Treatment, and Prior Hemin Prophylaxis Status



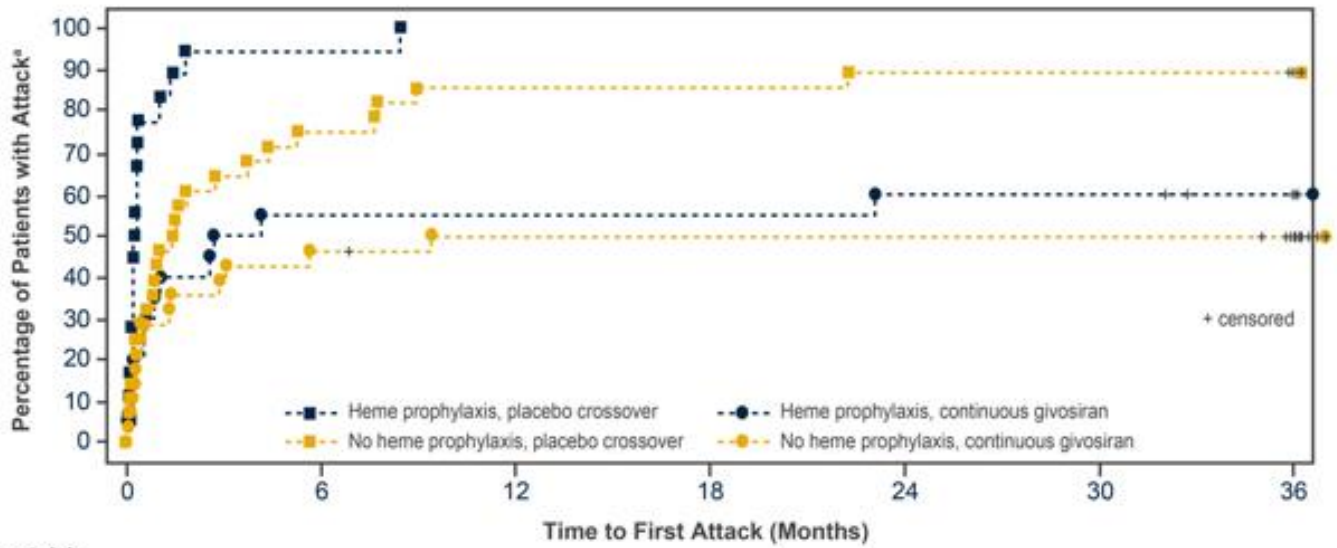

[a]Descriptive analysis.
AAR, annualized attack rate; DB, double-blind; OLE, open-label extension.

# Results

## Attacks

- Estimated median (95% CI) time to first attack (50% quartile; **Figure 5**) was:
  - Prior hemin prophylaxis, placebo crossover: 7.5 (5, 10) days
  - Prior hemin prophylaxis, continuous givosiran: 95.5 (8, NE) days
  - No prior hemin prophylaxis, placebo crossover: 41.5 (18, 104) days
  - No prior hemin prophylaxis, continuous givosiran: 264 (37, NE) days

**Figure 5. Time to First Attack, by Treatment and Prior Hemin Prophylaxis Status**




| Patients at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Heme prophylaxis, placebo crossover | 18 | 1 | 0 | | | | |
| Heme prophylaxis, continuous givosiran | 20 | 9 | 9 | 9 | 8 | 8 | 5 |
| No heme prophylaxis, placebo crossover | 28 | 7 | 4 | 4 | 3 | 3 | 2 |
| No heme prophylaxis, continuous givosiran | 28 | 15 | 13 | 13 | 13 | 13 | 10 |

*Descriptive analysis

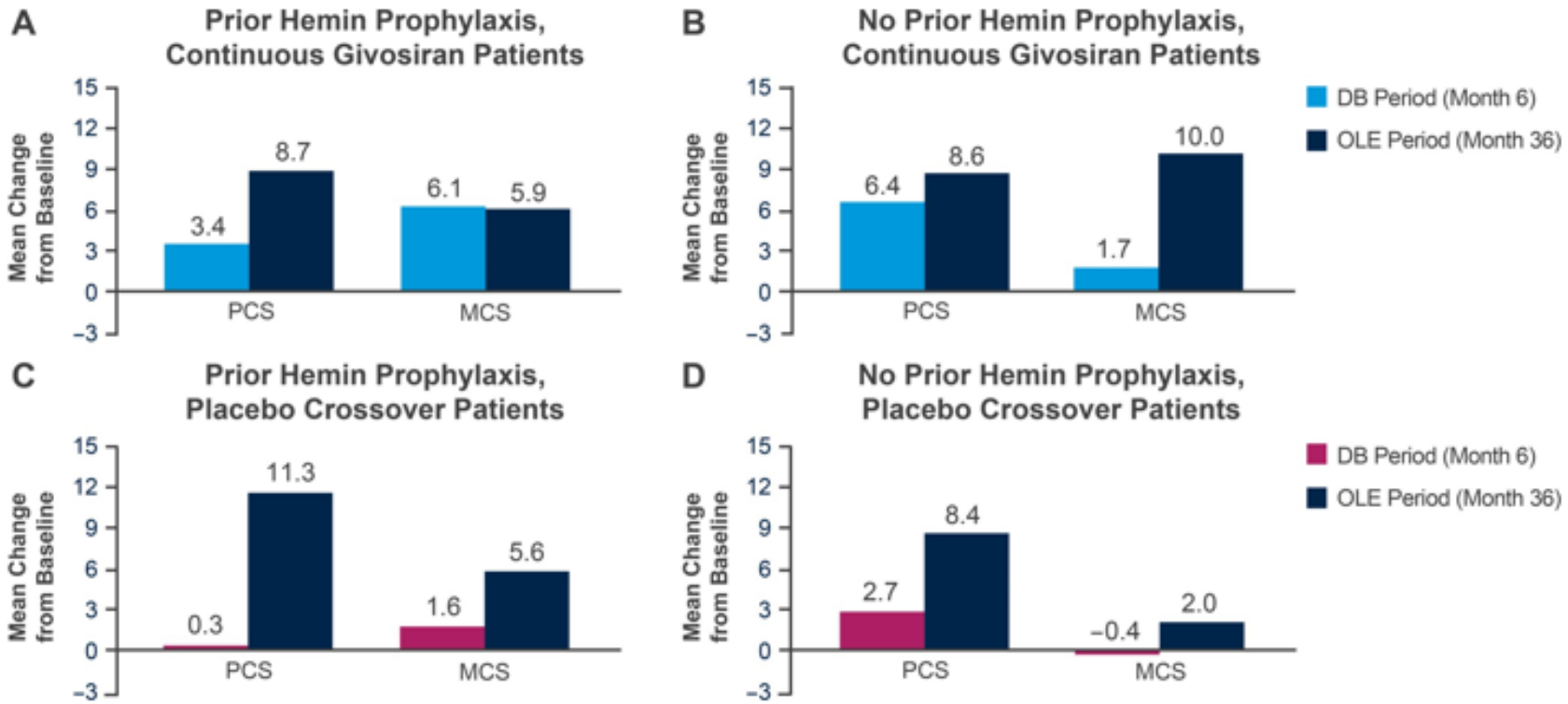
CI, confidence interval; NE, not estimated.

# Results

## Quality of life

- Improvements were seen in mean SF-12 component summary (PCS and MCS) scores from baseline to the end of the DB period (Month 6) and the end of the OLE period (Month 36), in both treatment groups, regardless of prior hemin prophylaxis status **(Figure 6)**

**Figure 6. Mean Change from Baseline in SF-12 Summaries (PCS, MCS), by Treatment and Prior Hemin Prophylaxis Status**






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

# Results

## Safety

- AEs were reported by 97% of patients overall **(Table 2)**
- The most common treatment-related AEs (>10%) during givosiran treatment were injection-site reactions (32%), nausea (21%), and fatigue (14%)

**Table 2. Safety Overview in Patients with AHP During Givosiran Treatment[a]**

| Patients with ≥1 event, n (%) | Placebo crossover (n=46) | Continuous Givosiran (n=48) | All Givosiran (N=94) |
|---|---|---|---|
| AE | 44 (96) | 47 (98) | 91 (97) |
| SAE[b] | 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 withdrawal | 2 (4) | 2 (4) | 4 (4) |
| Death | 0 | 1 (2) | 1 (1) |

[a]Safety data from first dose of givosiran to completion of study (May 31, 2021).
[b]A continuous givosiran patient's SAE of abnormal liver function test, which led to treatment discontinuation during the DB period, was previously reported.
AE, adverse event; AHP, acute hepatic porphyria; DB, double-blind; SAE, serious adverse event.

# Conclusions

- Givosiran treatment led to substantial reductions in AAR and time to first attack, and to improvement in QOL, in patients with AHP who experience frequent acute attacks, regardless of prior hemin prophylaxis status
- These effects were sustained with ongoing dosing with givosiran through the end of the study
- The most common treatment-related AEs during givosiran treatment were injection-site reactions, nausea, and fatigue



AAR, annualized attack rate; AE, adverse event; AHP, acute hepatic porphyria; QOL, quality of life.

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