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Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial

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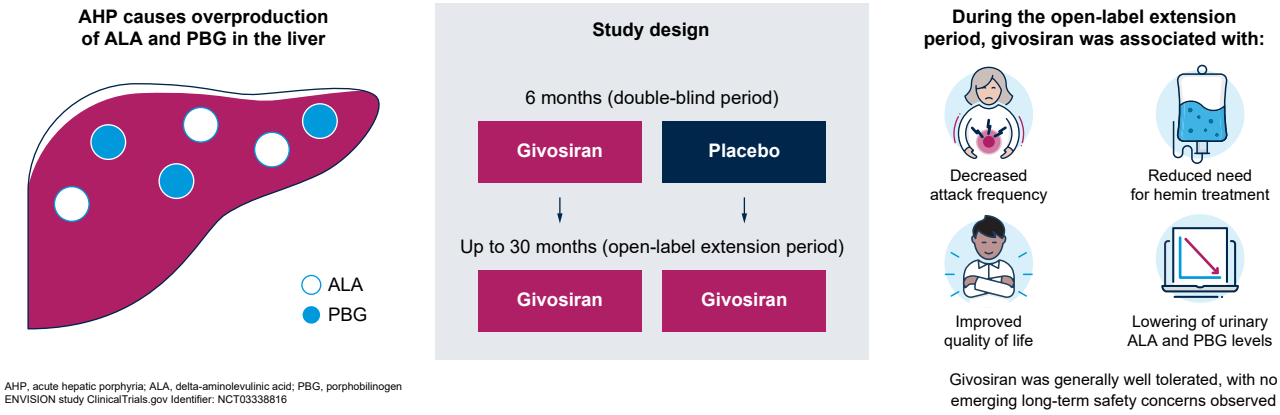
Graphical abstract



AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; PBG, porphobilinogen
ENVISION study ClinicalTrials.gov Identifier: NCT03338816

Highlights

- Givosiran treatment (≤36 months) resulted in sustained improvement in symptoms of AHP.
- Median annualized attack rate during givosiran treatment (through Month 36) was 0.4.
- Proportions of patients with 0 attacks or 0 days of hemin use increased over time.
- Patients showed continued improvement in physical/mental health and quality of life.
- Givosiran had an acceptable safety profile.

Impact and implications

Acute hepatic porphyria (AHP) is a group of rare, chronic, multisystem disorders associated with overproduction and accumulation of neurotoxic heme intermediates (delta-aminolevulinic acid and porphobilinogen), sometimes resulting in recurrent acute attacks and long-term complications. Givosiran, a small-interfering RNA that prevents accumulation of delta-aminolevulinic acid and porphobilinogen, is approved for the treatment of AHP. These final 36-month results of ENVISION, a phase III study of givosiran in patients with AHP and recurrent attacks, show that long-term monthly treatment with givosiran leads to continuous and sustained reductions in annualized attack rate and use of hemin over time, as well as improved quality of life, with an acceptable safety profile. These results are important for physicians, patients, families, and caregivers who are grappling with this debilitating and potentially life-threatening disease with few effective and tolerable treatment options.

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Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial

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Background & Aims: Acute hepatic porphyria (AHP) is caused by defects in hepatic heme biosynthesis, leading to disabling acute neurovisceral attacks and chronic symptoms. In ENVISION (NCT03338816), givosiran treatment for 6 months reduced attacks and other disease manifestations, compared with placebo. Herein, we report data from the 36-month final analysis of ENVISION.
Methods: Ninety-four patients with AHP (age ≥12 years) and recurrent attacks were randomized 1:1 to monthly double-blind subcutaneous givosiran 2.5 mg/kg (n = 48) or placebo (n = 46) for 6 months. In the open-label extension (OLE) period, 93 patients received givosiran 2.5 or 1.25 mg/kg for 6 months or more before transitioning to 2.5 mg/kg. Endpoints were exploratory unless otherwise noted.
Results: During givosiran treatment, the median annualized attack rate (AAR) was 0.4. Through Month 36, annualized days of hemin use remained low in the continuous givosiran group (median, 0.0 to 0.4) and decreased in the placebo crossover group (16.2 to 0.4). At end of OLE, in the continuous givosiran and placebo crossover groups, 86% and 92%, respectively, had 0 attacks. AAR was lower than historical AAR in 98% and 100%, respectively (*post hoc* analysis), and there were 0 days of hemin use in 88% and 90%, respectively. The 12-item short-form health survey physical and mental component summary scores increased by 8.6 and 8.1, respectively (continuous givosiran) and 9.4 and 3.2, respectively (placebo crossover). EQ-5D health-related questionnaire scores increased by 18.9 (continuous givosiran) and 9.9 (placebo crossover). Lower urinary delta-aminolevulinic acid and porphobilinogen levels were sustained. Safety findings demonstrated a continued positive risk/benefit profile for givosiran.
Conclusions: Long-term monthly givosiran treatment provides sustained and continued improvement in clinical manifestations of AHP.
ClinicalTrials.gov identifier: NCT03338816.
EudraCT number: 2017-002432-17.

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Introduction

Acute hepatic porphyria (AHP) is a group of rare, chronic, multisystem disorders characterized by acute attacks, progressive elements, and long-term complications requiring proactive management and treatment.[1–3] AHP is comprised of four types of porphyria: acute intermittent porphyria (AIP; the most common), variegate porphyria (VP), hereditary coproporphyria (HCP), and delta-aminolevulinic acid (ALA) dehydratase-deficiency porphyria.[2] Each type of AHP results from a genetic defect that leads to a deficiency in one of the enzymes involved in heme biosynthesis in the liver,[4] resulting in depletion of the hepatic free heme pool and induction of ALA synthase 1 (ALAS1; the rate-controlling enzyme of the heme biosynthetic pathway).[5,6] Induction of ALAS1 leads to overproduction and accumulation of heme intermediates (ALA and porphobilinogen [PBG]), which are neurotoxic and thought to cause injury to the nervous system and other organs, such as the liver and kidneys.[6,7] Diagnosis of AHP can be established if a patient presents with substantial urinary PBG elevation (>3x the upper limit of normal [ULN]).[3,8] PBG elevations of this magnitude do not result from medical conditions other than AIP, VP, and HCP; this high degree of specificity enables prompt recognition of AHP.[3,8]

Patients with AHP can experience potentially life-threatening acute attacks (characterized by symptoms including severe abdominal pain, nausea, vomiting, tachycardia, hypertension, hyponatremia, mental status changes, and muscle weakness) and chronic manifestations (*e.g.*, pain, fatigue, nausea between

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attacks), which impact daily functioning and quality of life (QOL).[1,9–15] Patients with AHP with chronic pain may require frequent pain medication, putting them at risk of opioid dependence.[4]

Treatment options for patients with AHP were limited before the approval of givosiran. Previously, management of AHP attacks included avoidance of attack triggers and use of intravenous glucose or hemin.[16,17] For patients experiencing recurrent attacks, treatment options include prophylactic hemin, carbohydrate loading, gonadotropin-releasing hormone analogs, and, rarely and as a last resort, liver transplantation.[16,17] Management with prophylactic hemin is highly individualized with variable regimen frequencies (monthly, bimonthly, or weekly).[4] Adverse events (AEs) associated with repeated and prophylactic use of hemin include venous damage and thrombophlebitis, coagulation abnormalities, and secondary iron overload.[2,9]

Givosiran is approved for the treatment of AHP in adults (United States, Brazil, Canada) and adults and adolescents age ≥12 years (European Economic Area, Switzerland, Japan).[18–23] Givosiran lowers ALAS1 expression in the liver, thereby preventing accumulation of ALA and PBG.[24–27] In the phase III ENVISION study (NCT03338816), patients with AHP and a history of acute attacks were randomized to double-blind givosiran or placebo for 6 months, followed by a 30-month open-label extension (OLE) period in which all patients received givosiran. During the double-blind period, givosiran treatment led to significant reductions in annualized attack rate (AAR), hemin use, and ALA and PBG levels, and improvements in daily worst pain, compared with placebo.[24] Here we report final results from the ENVISION study, and compare patients assigned to givosiran at study entry (the continuous givosiran group) with patients who received placebo for 6 months during the double-blind period and givosiran during the OLE (the placebo crossover group).

Patients and methods

Study design and patients

Details of the design (Fig. S1) and methodology of ENVISION have been reported previously.[24,28] Briefly, eligible patients were aged ≥12 years and had a documented diagnosis of AHP, confirmed AHP genetic mutation or biochemical and clinical criteria consistent with AHP, and ≥2 porphyria attacks (requiring hospitalization, urgent healthcare visit, or treatment with intravenous hemin at home) within 6 months before study entry. Patients agreed to discontinue prophylactic hemin (hemin was permitted for acute attacks). During the OLE, patients received subcutaneous givosiran 2.5 or 1.25 mg/kg monthly. The dose could be increased from 1.25 mg/kg to 2.5 mg/kg monthly at or after Month 13 in those who experienced inadequate disease control on the 1.25 mg/kg dose, as described in the supplementary information. Per a subsequent protocol amendment, the 1.25 mg/kg dose was increased to 2.5 mg/kg monthly in the remaining patients.

The study was approved by central and local institutional review boards or ethics committees and was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.[29,30] All patients provided written informed consent.

Outcome measures and safety assessments in the OLE period

Efficacy assessments included AAR of composite porphyria attacks (defined as attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home), annualized days of hemin use, proportion of attack-free and hemin-free patients at 3-month intervals, and urinary ALA and PBG levels. Patient-reported outcomes included opioid use and changes from baseline in 12-item short-form health survey (SF-12)[31] and EQ-5D.[32] Safety assessments included monitoring of AEs and clinical laboratory measures. AEs were coded according to the Medical Dictionary for Regulatory Activities Version 23.0. All efficacy endpoints in the OLE were exploratory.

Post hoc analyses

Post hoc analyses examined duration of AAR suppression, treatment effects by patients' prior hemin prophylaxis status, QOL assessments, and opioid use (additional details are provided in the supplementary information).

Statistical analysis

This final, 36-month analysis was based on the study completion date of May 31, 2021. Efficacy and patient-reported outcomes were analyzed according to treatment assignment (continuous givosiran, placebo crossover, and all-givosiran groups; Fig. S1). The continuous givosiran group (givosiran–givosiran) included patients who received givosiran from the start of the double-blind period and during the OLE. The placebo crossover group (placebo–givosiran) included patients who received placebo during the double-blind period and givosiran during the OLE (Months 7–36). The all-givosiran group included all patients who received givosiran during either the double-blind period or the OLE. Patients who received at least one dose of givosiran were included in the safety population. Descriptive statistics for clinical laboratory tests and efficacy parameters are reported as actual values and changes from baseline.

Results

Patient disposition

Ninety-four patients were enrolled in the double-blind period, including 89 with AIP, two with VP, one with HCP, and two with AHP without identified mutations. Ninety-three patients entered the OLE period, including 47 in the continuous givosiran group and 46 in the placebo crossover group. Seventy-nine patients completed the OLE, and 14 discontinued during the OLE (Fig. S2).

Patient demographics and clinical characteristics at baseline were similar between the continuous givosiran and placebo crossover groups and by prior hemin prophylaxis history (Table 1 and Table S1). At the end of the study, overall median exposure to givosiran was 28.1 months (range, 1.8–34.1 months); cumulative exposure was 219.6 person-years. In total, 89, 87, 85, 84, and 41 patients received givosiran for ≥6, ≥12, ≥18, ≥24, and ≥30 months, respectively, including 42, 41, 39, 38, and 0 patients in the placebo crossover group and 47, 46,

Table 1. Baseline demographic and clinical characteristics.

Characteristic	Placebo crossover (n = 46)	Continuous givosiran (n = 48)	All givosiran (N = 94)
Age at screening, years, median (range)	36.0 (20–60)	42.0 (19–65)	37.5 (19–65)
Female, n (%)	41 (89)	43 (90)	84 (89)
Race, n (%)			
White	34 (74)	39 (81)	73 (78)
Black/African American	1 (2)	0 (0)	1 (1)
Asian	7 (15)	8 (17)	15 (16)
Other	4 (9)	1 (2)	5 (5)
AIP, n (%)	43 (93)	46 (96)	89 (95)
Non-AIP,[a] n (%)	3 (7)	2 (4)	5 (5)
Hereditary coproporphyria	0 (0)	1 (2)	1 (1)
Variegate porphyria	1 (2)	1 (2)	2 (2)
AHP without identified mutation[b]	2 (4)	0 (0)	2 (2)
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,[c] median (range)	7.0 (0 [d]–46)	8.0 (4–34)	8.0 (0 [d]–46)
Prior chronic symptoms,[e] n (%)	26 (57)	23 (48)	49 (52)
Prior chronic opioid use,[f] n (%)	13 (28)	14 (29)	27 (29)
Baseline urinary ALA (mmol/mol Cr), median (range)[g]	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)[h]	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; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; Cr, creatinine; HCP, hereditary coproporphyria; PBG, porphobilinogen; ULN, upper limit of normal; VP, variegate porphyria.
[a]Porphyria subtypes other than AIP include HCP, VP, ALA dehydratase-deficiency porphyria with an identified mutation, and AHP without an identified mutation. No patients with ALA dehydratase-deficiency porphyria were enrolled in this trial.
[b]The two patients with AHP without an identified mutation were considered by trial investigator to have AIP on the basis of biochemical analysis.
[c]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or intravenous hemin treatment at home during the 6 months before randomization.
[d]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).
[e]Symptoms were chronic if patients experienced symptoms daily or on most days when not having an attack and were reported by investigators.
[f]Opioid use was defined as chronic if patients reported taking opioids for porphyria daily or most days when not having an attack.
[g]ALA reference range (ULN, 1.47 mmol/mol Cr).[47]
[h]PBG reference range (ULN, 0.14 mmol/mol Cr).[47]

46, 46, and 41 patients in the continuous givosiran group. Overall treatment adherence was high (described in the supplementary information).

Efficacy

Attacks

Long-term monthly treatment with givosiran was associated with continued AAR reduction (Fig. 1A). Patients in the continuous givosiran group had a median AAR of 1.0 in the 6-month double-blind period and a median AAR of 0.4 during the OLE. In the placebo crossover group, median AAR decreased from 10.7 in the double-blind period to 0.9 in the OLE. In all patients, during givosiran treatment (*i.e.*, across both the double-blind period and the OLE in the continuous givosiran group and during the OLE in the placebo crossover group), median AAR was 0.4.

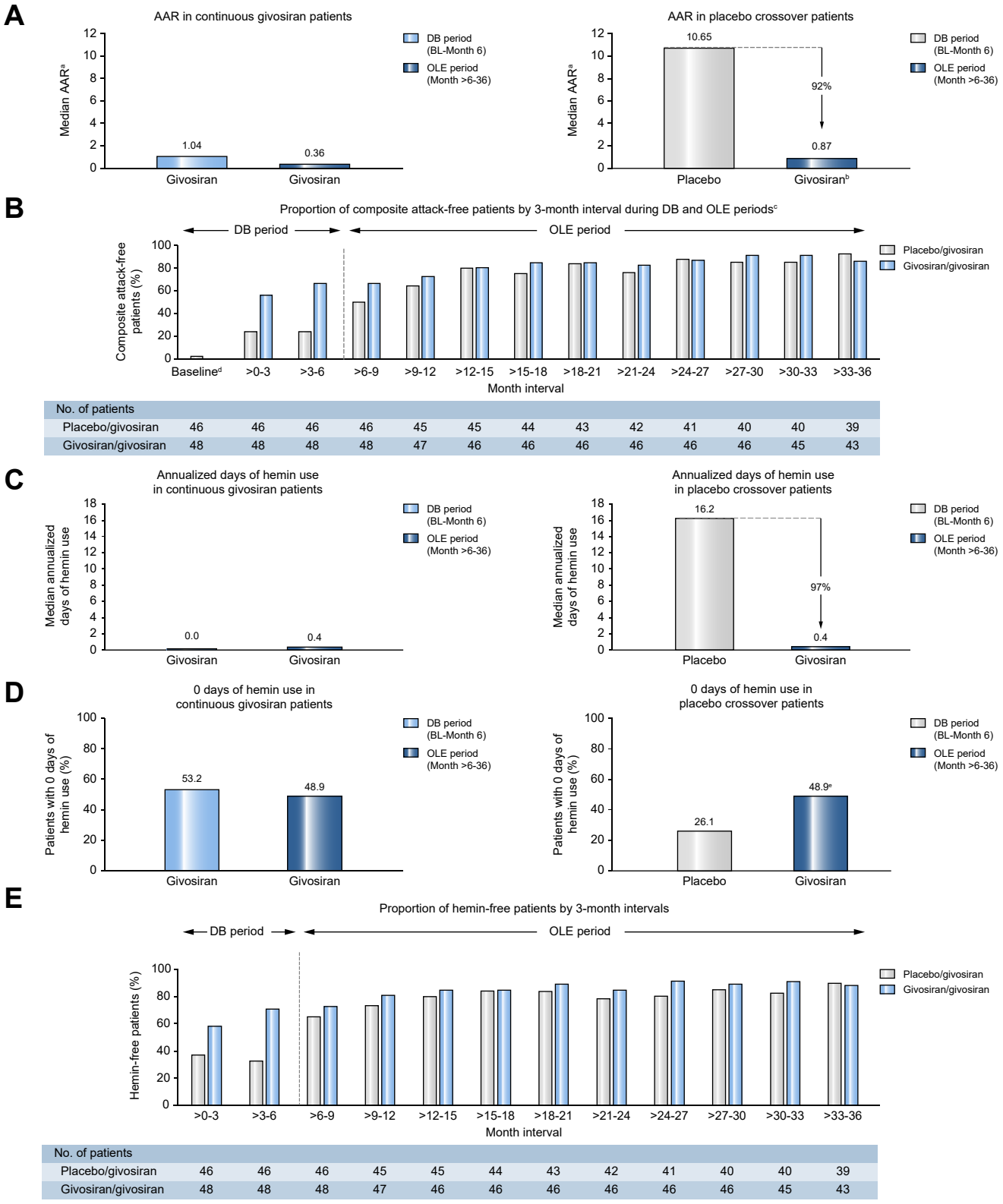
The proportion of patients with 0 attacks (per 3-month interval) increased over the course of the study (Fig. 1B). In the continuous givosiran group, 67% of patients were attack-free at Months >3 to 6, and 86% were attack-free at Months >33 to 36. In the placebo crossover group, 24% of patients were attack-free at Months >3 to 6, and 92% were attack-free at Months >33 to 36. Characteristics of patients who were not attack free during Months >3 to 6 and Months >33 to 36 are presented in the supplementary information.

In a *post hoc* analysis, the mean time from start of givosiran treatment until patients reached and remained at an AAR lower than the historical AAR was 2.7 months in the continuous givosiran group and 3.7 months in the placebo crossover group. The proportion of patients who had at least one attack after their first 6 months of givosiran treatment was 36% (17/47) in the continuous givosiran group (during Months 7–36) and 41% (19/46) in the placebo crossover group (during Months 13–36) (Table S2). The proportion of patients with an AAR that was lower than historical AAR (and that remained lower through end of study) by 3-month interval was higher with givosiran (81%, 39/48) *vs*. placebo (37%, 17/46) during the double-blind period, but the proportions were similar and increased through the end of the OLE (continuous givosiran, 98%, 40/41; placebo crossover, 100%, 38/38) (Fig. S3A). Results were similar in patients with and without a history of hemin prophylaxis (Fig. S3B).

Fig. S4 shows the results of a *post hoc* analysis on the proportions of attacks requiring treatment with opioids over time. Estimated median time to first attack is shown in Fig. S5.

Hemin use

Continuous givosiran treatment was associated with a sustained reduction in hemin use. From the double-blind period to the OLE period, median annualized days of hemin use remained low in the continuous givosiran group (0 to 0.4) and decreased by 97% in the placebo crossover group (16.2 to 0.4; Fig. 1C). The proportion of patients with 0 days of hemin use during the OLE was 49% in both treatment groups (continuous givosiran, 23/47; placebo crossover, 22/45; Fig. 1D). The proportion of patients with 0 days of hemin use by 3-month interval increased from the end of the double-blind period (Months >3 to 6) to the end of the OLE (Months >33 to 36) in both the continuous givosiran group (71% to 88%) and the placebo crossover group (33% to 90%; Fig. 1E). In a *post hoc* analysis, the proportion of attacks not requiring hemin use at the end of the double-blind period was 24% (12/49) in the continuous givosiran group and 7% (11/164) in the placebo crossover group and varied thereafter in both groups during the OLE



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

No. of patients												
Placebo/givosiran	46	46	46	45	45	44	43	42	41	40	40	39
Givosiran/givosiran	48	48	48	47	46	46	46	46	46	46	45	43

Fig. 1. Attack frequency and hemin use. (A) Median AAR. (B) Proportion of patients with 0 attacks by 3-month interval. (C) Median annualized days of hemin use. (D) Proportion of patients with 0 days of hemin use. (E) Proportion of patients with 0 days of hemin use by 3-month interval. [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 hospitalization, urgent healthcare visit, or intravenous hemin administration at home. 1 month = 28 days. [d]Baseline represents 6 months before randomization. [e]Excluding one patient with <85 days of follow-up. AAR, annualized attack rate; DB, double-blind; OLE, open-label extension.

(continuous givosiran, 8–42%; placebo crossover, 7–43%). There was no strong correlation between historical AAR and number of attacks requiring hemin use during givosiran treatment (Pearson correlation coefficient, 0.192; $p = 0.066$).

Patient-reported QOL outcome assessments

Patients receiving long-term givosiran treatment reported further improvement in physical and mental health, as assessed by the SF-12 physical and mental component summary (PCS and MCS) and individual domain scores (Fig. 2A,B). From baseline to Month 6 and Month 36, respectively, PCS scores in the continuous givosiran group improved by 5.1 and 8.6 points and MCS scores improved by 3.6 and 8.1 points. In the placebo crossover group, PCS scores improved by 1.7 and 9.4 points and MCS scores improved by 0.4 and 3.2 points. In *post hoc* analyses, improvements were generally seen in SF-12 PCS and MCS scores regardless of prior hemin prophylaxis treatment (Fig. S6).

Continuing improvements with givosiran treatment were also seen in mean scores for the visual analog scale element of the EQ-5D health-related questionnaire (EQ-VAS; Fig. 3). Mean changes from baseline at Month 6 and Month 36 were 5.2 and 18.9, respectively, in the continuous givosiran group, and −1.3 and 9.9, respectively, in the placebo crossover group.

Urinary ALA and PBG levels

Continuous givosiran treatment led to sustained lowering of median urinary ALA and PBG levels (Fig. S7).

Efficacy of givosiran 1.25 mg/kg and 2.5 mg/kg monthly

The ENVISION study was not designed to determine the efficacy of the 1.25 mg/kg dose of givosiran *vs*. the 2.5 mg/kg dose. Nevertheless, in placebo crossover patients who received givosiran in the OLE period, there was a trend of increased efficacy with givosiran 2.5 mg/kg compared with 1.25 mg/kg (additional details in the supplementary information).

Safety

AEs were reported in 97% (91/94) of patients, and the majority were mild or moderate in severity; 37% (35/94) of patients reported severe AEs (Table 2). The most frequently reported AEs were injection-site reactions and nausea. Thirty-nine percent (37/94) of patients experienced at least one injection-site reaction, and in all but one of these patients, the reactions were mild or moderate in severity. Of the total injections, 5% (142/2,820) were associated with injection-site reactions; the most common symptoms included erythema, pain, pruritus, rash, and swelling at the injection site.

Serious AEs were reported in 39% (37/94) of patients (Table 2). Serious AEs considered related to givosiran included increased blood homocysteine (2 patients) and elevated transaminases, retinal vein occlusion, injection-site reaction, pancreatitis, worsening of chronic renal failure, pulmonary embolism, right iliac thrombophlebitis, and worsening of liver tests (one patient each). Four patients discontinued study treatment because of treatment-related AEs (increased blood homocysteine and injection-site reaction, one patient; increased blood homocysteine and pancreatitis, one patient; drug hypersensitivity, one patient; abnormal liver tests, one patient). During the OLE, there was one death resulting from aortic dissection, which was considered not related to study drug.

Hepatic AEs were reported in 19% (9/48) of patients in the continuous givosiran group and 20% (9/46) of patients in the placebo crossover group. Overall, 11% (10/94) of patients had alanine aminotransferase (ALT) levels >3x ULN and 3% (3/94) had ALT levels >5x ULN. ALT elevations generally occurred ~3 to 6 months after givosiran treatment was started and resolved over time (Fig. S8).

Renal AEs were reported in 25% (12/48) of patients in the continuous givosiran group and 20% (9/46) of patients in the placebo crossover group. No renal AEs led to treatment discontinuation. The small decreases in estimated glomerular filtration rate observed soon after initiation of givosiran stabilized by Months 12 to 26 (Fig. S9), and mean changes in

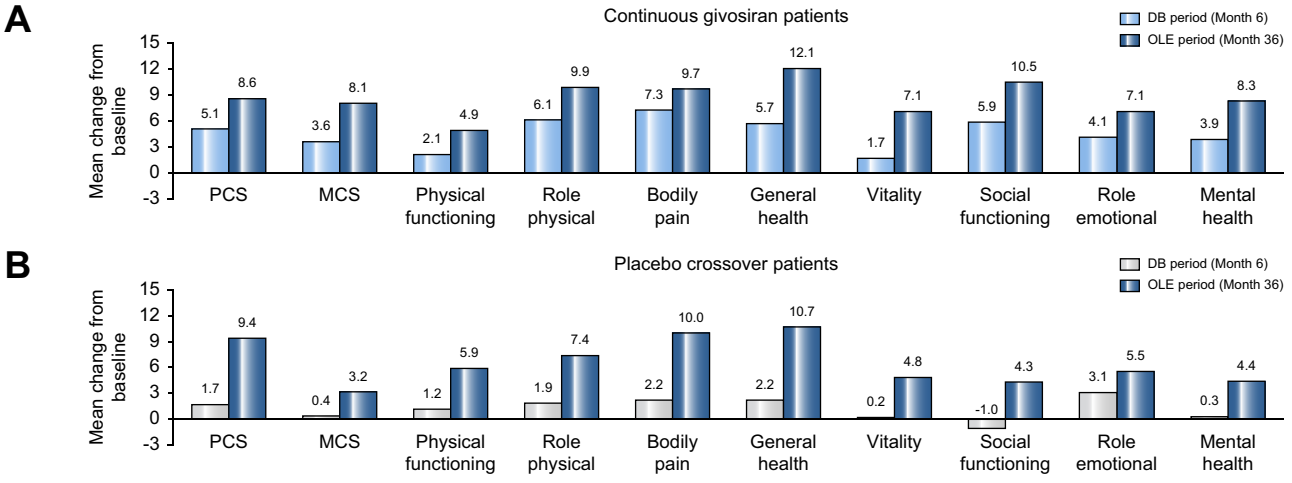


Fig. 2. Mean change from baseline in SF-12 summaries (PCS, MCS) and all SF-12 domains[a] by treatment group. (A) Continuous givosiran. (B) Placebo crossover. Higher scores represent improvement in that summary or domain. [a]Scores on the PCS range from 0 (worst functioning) to 100 (best functioning), with 2 to 5 points representing a clinically meaningful difference, according to published data for other chronic diseases.[38,39] DB, double-blind; MCS, mental component summary; OLE, open-label extension; PCS, physical component summary; SF-12, 12-item short-form health survey.

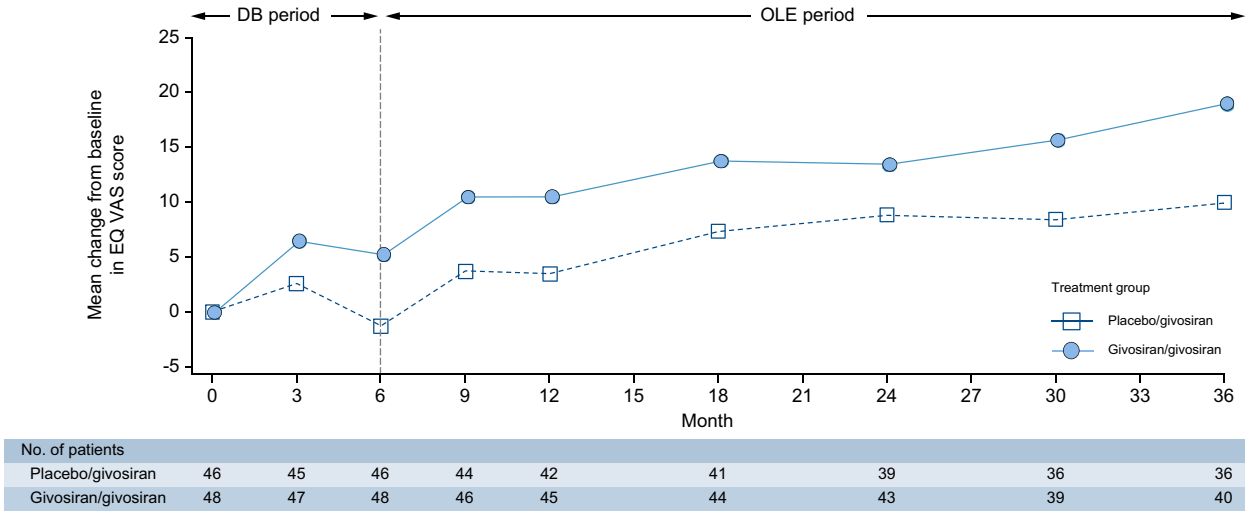


Fig. 3. Mean change in EQ-VAS score from baseline through OLE period[a]. [a]Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS, based on published data for other chronic diseases.[41,48] DB, double-blind; EQ-VAS, EuroQol visual analog scale; OLE, open-label extension.

Table 2. Safety overview in patients with AHP during givosiran treatment.

n (%)	Placebo crossover (n = 46)	Continuous givosiran (n = 48)	All givosiran (N = 94)
Any AE	44 (96)	47 (98)	91 (97)
AE occurring in ≥10% of patients			
Injection-site reactions[a]	17 (37)	20 (42)	37 (39)
Nausea	13 (28)	22 (46)	35 (37)
Fatigue	13 (28)	12 (25)	25 (27)
Nasopharyngitis	11 (24)	14 (29)	25 (27)
Headache	7 (15)	13 (27)	20 (21)
Urinary tract infection	10 (22)	10 (21)	20 (21)
Upper respiratory tract infection	12 (26)	7 (15)	19 (20)
Vomiting	9 (20)	7 (15)	16 (17)
Abdominal pain	8 (17)	7 (15)	15 (16)
Diarrhea	7 (15)	8 (17)	15 (16)
Back pain	6 (13)	7 (15)	13 (14)
Lipase increased	6 (13)	7 (15)	13 (14)
Pyrexia	6 (13)	6 (13)	12 (13)
Asthenia	5 (11)	5 (10)	10 (11)
Constipation	4 (9)	6 (13)	10 (11)
Influenza	5 (11)	5 (10)	10 (11)
AEs of interest			
Hepatic AEs[b]	9 (20)	9 (19)	18 (19)
Renal AEs[c]	9 (20)	12 (25)	21 (22)
Increased blood homocysteine[d]	9 (20)	6 (13)	15 (16)
Any serious AE[e,f]	17 (37)	20 (42)	37 (39)
Pulmonary embolism	1 (2)	3 (6)	4 (4)
Increased blood homocysteine	2 (4)	0 (0)	2 (2)
COVID-19 pneumonia	1 (2)	1 (2)	2 (2)
Chronic kidney disease	0 (0)	2 (4)	2 (2)
Device breakage	1 (2)	1 (2)	2 (2)
Urinary tract infection	1 (2)	1 (2)	2 (2)
Any severe AE	18 (39)	17 (35)	35 (37)
Any AE leading to treatment discontinuation	4 (9)	2 (4)	6 (6)
Any AE leading to study withdrawal	2 (4)	2 (4)	4 (4)
Death	0	1 (2)	1 (1)

AE, adverse event; AHP, acute hepatic porphyria; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.
Safety data from first dose of givosiran to completion of study (May 31, 2021).
[a]Included all AEs under term *high-level injection-site reactions* in MedDRA.
[b]Included all AEs within SMQ drug-related hepatic disorders.
[c]Included all AEs mapping to SMQ chronic kidney disease.
[d]Included AEs of increased blood homocysteine or hyperhomocysteinemia.
[e]SAE of liver function test abnormality that led to treatment discontinuation during double-blind period was previously reported.
[f]Ten SAEs were reported as possibly or definitely related to givosiran: elevated liver transaminases, retinal vein occlusion, increased blood homocysteine (two patients), injection-site reaction, pancreatitis, worsening of chronic renal failure, pulmonary embolism, right iliac thrombophlebitis, worsening of liver function test.

estimated glomerular filtration rate remained stable in most patients during the OLE.

Fifteen patients (out of 93) experienced AEs of increased blood homocysteine; in two of these patients, the homocysteine increases were considered related to study treatment. At a population level, givosiran treatment led to an increase in plasma homocysteine levels, without a progressive rise in plasma homocysteine over time.[33]

No patients tested positive for treatment-emergent antidrug antibodies (ADAs) during the double-blind period. In the OLE, 3% (3/94) of patients had treatment-emergent ADAs that were of low titer (1:50) and positive at a single time point. The presence of ADAs had no impact on the safety or efficacy of givosiran.

Discussion

Patients with AHP have debilitating, potentially life-threatening acute attacks, chronic symptoms, and a high disease burden (beyond attacks) that affect their physical, emotional, social, and financial well-being.[8,9,11,13–15,17] Consistent with the results from the ENVISION primary analysis,[24] these final 36-month results of ENVISION show that long-term monthly treatment with givosiran leads to continuous and sustained reductions in AAR and use of hemin over time in patients with AHP and recurrent attacks. Patients receiving long-term monthly treatment with givosiran reported improved patient QOL assessment scores, including assessments of physical functioning, activities of daily living, and overall health status.

During the 6-month double-blind period, attack frequency decreased dramatically with givosiran compared with placebo, assessed as mean composite AAR (primary endpoint; 74% decrease, p <0.001) and median AAR (90% decrease).[24] Final results from ENVISION demonstrated a meaningful reduction in attack frequency that was sustained until the end of the study with long-term givosiran treatment. Furthermore, the proportion of patients with 0 attacks in each 3-month interval increased in both groups throughout the OLE period. In the final 3-month interval of the OLE, >85% of patients in both groups reported 0 attacks – a notable improvement from baseline. The proportion of patients with an AAR lower than the historical AAR remained high throughout the OLE (≥83%, continuous givosiran; >67%, placebo crossover), and, by the end of the study, nearly all patients (>98%) had an AAR lower than their historical AAR. Thirty-six percent (17/47) of patients in the continuous givosiran group and 41% (19/46) in the placebo crossover group reported at least one attack after their first 6 months of givosiran treatment, suggesting that >6 months of treatment may be required for some patients to achieve their optimal response.

Estimated time to first attack over the entire trial (including its double-blind period) was shorter overall in the subgroup with prior hemin prophylaxis compared with the subgroup without; however, both subgroups demonstrated a similar beneficial effect of givosiran (*i.e.*, prolonged time to first attack). Moreover, time to first attack was similar in patients with and without prior prophylactic hemin who received continuous givosiran. Hence, patients who discontinued prophylactic hemin before initiating givosiran treatment generally achieved outcomes similar to those in patients with no history of hemin prophylaxis, despite evidence of more severe disease.[34]

The proportion of attacks that did not require hemin treatment by 3-month interval was variable; however, the proportion of attacks that required opioid treatment decreased considerably over the course of the study. The reduction in opioid-treated attacks became evident after ∼12 months of givosiran treatment, which may suggest a decrease in pain.

Intravenous hemin is indicated to treat acute attacks.[35] During the double-blind period of ENVISION, annualized days of hemin use (a secondary outcome) were reduced by 77% with givosiran compared with placebo (p <0.001).[24] Results from the OLE show that this effect, similar to the reduction in attack frequency, was sustained.

Despite its potential side effects, hemin is also used prophylactically to reduce the frequency of recurrent attacks in patients with AHP;[33] however, such use is associated with poorer perceived health-related QOL and three times more emergency department visits, compared with patients not receiving prophylactic treatment.[13] In a previous *post hoc* analysis of ENVISION data,[34] patients with prior hemin prophylaxis (40% of the total population) were more likely to have used opioids chronically (37%) compared with patients with no prior hemin prophylaxis (23%), and had higher historical AAR and lower SF-12 PCS scores at baseline, on average. However, during the OLE, patients who discontinued prophylactic hemin before initiating givosiran treatment generally achieved outcomes (including SF-12 and proportion of attack-free patients) similar to those in patients with no history of hemin prophylaxis.[34]

As there is no validated instrument for QOL assessment in patients with AHP, ENVISION used the SF-12 to capture patient perspectives on QOL and health status. The SF-12, a shortened version of the SF-36 health survey, has been widely used across a range of populations and disease states.[31] General US population norms for the SF-12 PCS and MCS were computed to have means of 50 and standard deviations of 10 (on a scale of 1–100).[31] In ENVISION, mean baseline SF-12 PCS scores were similar between the placebo and givosiran groups (38.4 and 39.4, respectively[24]) and in the range of scores observed in patients with other chronic diseases, such as cancer and coronary heart disease.[36,37] Increases in mean SF-12 PCS scores in the continuous givosiran and placebo crossover groups (8.6 and 9.4 points, respectively) were substantially above the ≥2- to 5-point increase threshold that is considered a clinically meaningful improvement for other chronic diseases,[38,39] although this threshold has not been validated in AHP. ENVISION also used the EQ-5D, a patient-reported outcome that includes a VAS to rate health.[32] The general US population norm for the EQ-5D VAS was computed to have a mean of 80.0 (interquartile range, 73–91) on a scale of 0 (worst imaginable health state) to 100 (best imaginable health state).[40] Increases from baseline in EQ-VAS scores at Month 36 in the continuous givosiran and placebo crossover groups (18.9 and 9.9, respectively) were within or above the range of scores estimated to represent a minimal clinically important difference for the EQ-VAS (approximately 7–10 points), although this threshold has not been validated in AHP.[41,42] These data further underscore the physical, emotional, and social burden of AHP, and suggest the sustained beneficial effect of appropriate long-term treatment on chronic manifestations of the disease that are often underappreciated because of the relative severity of attacks.

The safety profile of givosiran observed in this final analysis was consistent with that of previous interim analyses of ENVISION,[28,43] with no additional emerging long-term safety concerns observed. Patients with AHP may have plasma homocysteine elevation,[44] including some patients treated with givosiran.[45,46] A recently published exploratory analysis of the ENVISION trial data demonstrated that on a population level, givosiran increased homocysteine with wide interpatient variations and without correlation between hyperhomocysteinemia and changes in the efficacy or safety of givosiran.[33] The long-term consequences of homocysteine elevations in patients with AHP are still unknown, and the authors recommended supplementing with pyridoxine/vitamin B6.[33] Providers should refer to their local product label for guidance.

The study is limited by the relatively small number of patients in the study population, as expected for a rare disease. However, ENVISION is the largest interventional study in AHP to date.

In conclusion, the final results from the phase III ENVISION study confirm that long-term monthly dosing with givosiran is well tolerated and provides sustained and continuous benefit to patients with AHP.

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Abbreviations

AAR, annualized attack rate; ADA, antidrug antibody; AE, adverse event; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; ALT, alanine aminotransferase; EQ-VAS, EQ-5D health-related questionnaire visual analog scale; HCP, hereditary coproporphyria; MCS, mental component summary; OLE, open-label extension; PBG, porphobilinogen; PCS, physical component summary; QOL, quality of life; SF-12, 12-item short-form health survey; ULN, upper limit of normal; VP, variegate porphyria.

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Conflict of interest

Dr. Kuter received 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. Dr. Bonkovsky received grant support and financial support, paid to Wake Forest University School of Medicine, from Alnylam Pharmaceuticals, Gilead Sciences, and Mitsubishi Tanabe, NA, and consulting fees from Alnylam Pharmaceuticals, Disc Medicine, Eiger Biopharmaceuticals, Protagonist Therapeutics, and Recordati Rare Diseases. Dr. Monroy received advisory board and speaker fees from Alnylam Pharmaceuticals. Drs. Ross, Cappellini, and Hother-Nielsen reported having nothing to disclose. Dr. Guillén-Navarro received grants/research support, paid to the Fundación para la Formación e Investigación Biosanitaria-FFIS, from Alnylam Pharmaceuticals and consulting fees from BioMarin, UCB, and Alnylam Pharmaceuticals. Dr. Minder received an unrestricted research grant from Clinuvel Pharmaceuticals and financial support for a porphyria nurse, paid to Stiftung für wissenschaftliche Forschung Stadtspital Zürich, from Alnylam Pharmaceuticals. Dr. Ventura received consultancy fees and honoraria from Alnylam Pharmaceuticals and Recordati Rare Diseases. Drs. Jia and Sweetser are employed by and own stock and stock options in Alnylam Pharmaceuticals. Dr. Thapar is a consultant and speaker for Alnylam Pharmaceuticals and has served as a consultant for Disc Medicine, Mitsubishi Tanabe, and Recordati Rare Diseases.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study design: Herbert L. Bonkovsky. Study investigator: David J. Kuter, Herbert L. Bonkovsky, Susana Monroy, Encarna Guillén-Navarro, Anna-Elisabeth Minder, Manish Thapar. Enrolled patients: David J. Kuter, Herbert L. Bonkovsky, Susana Monroy, Encarna Guillén-Navarro, Manish Thapar. Collection and assembly of data: David J. Kuter, Herbert L. Bonkovsky. Data interpretation: All authors. Manuscript preparation: David J. Kuter, Herbert L. Bonkovsky. Manuscript review and revisions: All authors. Final approval of manuscript: All authors.

Data availability statement

Anonymized individual participant data that support these results would be made available in a secure-access environment 12 months after study completion and when the product and indication have been approved for no less than 12 months in the US and/or the EU. Access will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement. Requests for access to data can be submitted via the website www.vivli.org.

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Supplementary data

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Supplemental information

Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial

David J. Kuter, Herbert L. Bonkovsky, Susana Monroy, Gayle Ross, Encarna Guillén-Navarro, Maria Domenica Cappellini, Anna-Elisabeth Minder, Ole Hother-Nielsen, Paolo Ventura, Gang Jia, Marianne T. Sweetser, Manish Thapar, and for the ENVISION Investigators

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Givosiran dose escalation from 1.25 mg/kg to 2.5 mg/kg monthly

As per a protocol amendment, patients assigned to the once monthly 1.25-mg/kg treatment group were allowed to have their monthly dose increased to 2.5 mg/kg starting at Month 13 (when 6 months of open-label givosiran dosing were completed at 1.25 mg/kg). Dose escalation was considered if the following criteria were met: (1) tolerability to givosiran at 1.25 mg/kg once monthly had been demonstrated based on no dose interruptions due to liver function test elevations (ie, ALT levels >5 × ULN, when the patient was asymptomatic and there was no alternative cause; dosing was discontinued for ALT levels >8 × ULN) at the 1.25 mg/kg once monthly dose level and no significant safety concerns due to other AEs that precluded the patient from receiving a higher dose of givosiran, as judged by the Investigator and Sponsor; (2) urine ALA levels were not stably maintained at or below ULN or were inducible; (3) the patient had inadequate clinical response (eg, breakthrough attacks or ongoing chronic symptoms), according to the Investigator's judgment. Upon implementation of a subsequent protocol amendment, all patients receiving 1.25 mg/kg givosiran once monthly who did not have ongoing clinically relevant transaminase elevations had their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity.

Post hoc statistical analyses

Post hoc analyses were conducted to examine the timing of attacks, including mean time from initiation of givosiran treatment until patients reached and remained at an AAR lower than the historical AAR (ie, attacks during the 6 months prior to randomization, divided by 2), and proportion of patients with at least 1 attack after 6

months of givosiran treatment. Additional post hoc analyses compared outcomes between the placebo crossover group and the continuous givosiran group, and within subgroups of patients with and without prior hemin prophylaxis. Outcomes of interest included mean change from baseline in SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, the proportion of patients with an AAR lower than the historical AAR, and time to first attack (Kaplan-Meier estimate). The proportion of attacks requiring opioid treatment (as recorded by the investigator) was compared between treatment groups.

Treatment adherence

During the study, overall treatment adherence was high. Eighty-four patients (89.4%) had ≤1 missing dose during givosiran treatment; percentages of patients with 0, 1, 2, 3, or ≥4 missing doses were 78%, 12%, 6%, 3%, and 1%, respectively. The majority of missed doses were due to missed visits or AEs.

At the start of the COVID-19 pandemic, all patients had completed the primary analysis period and Month 12. Study visits from Month 15 through Month 36 were impacted by the pandemic. The participation of 54 (57%) patients in the All Givosiran group was affected, including missed, delayed, or partially completed visits (45 patients [48%]); visit location change (eg, phone visits; 46 patients [49%]); and missed/delayed study drug doses (15 patients [16%]). The majority of impacted visits were completed (51%) or partially completed (37%) rather than missed or delayed, and visit location changes were mostly home visits. Based on the 79 patients who completed the study, 21 (27%) patients had their final Month 36 study visit impacted by the COVID-19 pandemic, all of

whom had a location change and either partially (n=13; 62%) or fully (n=8; 38%) completed the study visit. There were no study treatment discontinuations or study withdrawals due to COVID-19.

Patients who were not attack free

Patients who experienced 1 or more attacks during Months >3 to 6 (placebo, 35/46 [76%]; givosiran, 16/48 [33%]) and patients who experienced 1 or more attacks during Months >33 to 36 (placebo crossover, 3/39 [8%]; continuous givosiran, 6/43 [14%]) were generally similar to the overall population in terms of disease duration (median [range] years since diagnosis: 7.1 [0.1–38.5] and 6.2 [0.2–27.3] vs 6.6 [0.1–43.3]), but their historical AAR (median [range]: 10.0 [4–46] and 12.0 [6–28] vs 8.0 [0–46]) and rate of prior hemin prophylaxis (24/51 [47.1%] and 6/9 [67%] vs 38/94 [40%] are suggestive of increased disease severity (**Table S3; Table 1**). Nevertheless, in these patients, givosiran treatment was associated with rapid and sustained reductions in urinary levels of ALA (**Supplementary Figure S10**) and PBG (**Supplementary Figure S11**), similar to the overall population (**Supplementary Figure S7**).

Efficacy of givosiran 1.25 mg/kg and 2.5 mg/kg monthly

The ENVISION study OLE period was not designed or powered to formally compare the clinical efficacy of givosiran 1.25 mg/kg monthly to 2.5 mg/kg monthly. In the OLE, patients were assigned to receive either 1.25 or 2.5 mg/kg givosiran once monthly based solely on their time of entry into the OLE period. They were not re-randomized. Patients assigned to givosiran 2.5 mg/kg monthly had characteristics consistent with

greater disease severity at baseline with respect to years since diagnosis, prior hemin prophylaxis at entry into the ENVISION study, historical AAR, and renal comorbidities than patients assigned to 1.25 mg/kg givosiran monthly (**Table S4**). Additionally, starting at the Month 13 study visit, patients assigned to the givosiran 1.25 mg/kg treatment group who experienced inadequate disease control were allowed to have their monthly dose increased to givosiran 2.5 mg/kg monthly. Eleven (30%) of the 37 patients assigned to givosiran 1.25 mg/kg monthly (placebo crossover, 5/17 [29%]; continuous givosiran, 6/20 [30%]) had their dose escalated to 2.5 mg/kg givosiran once monthly at or after the Month 13 study visit.

To evaluate the potential clinical efficacy of the givosiran 1.25 mg/kg monthly dosing regimen, an intrapatient analysis in the placebo crossover group was performed comparing AAR during the DB period (while receiving placebo) and AAR during the OLE period (while receiving givosiran). In this analysis, patients in the placebo/givosiran 1.25 mg/kg group who dose escalated to 2.5 mg/kg because of inadequate disease control are counted in the treatment group according to the dose assigned at the beginning of the OLE period (1.25 mg/kg). Overall, patients in the placebo crossover group had a reduction in mean AAR of 87%; patients in the placebo crossover group who received givosiran 2.5 mg/kg had a greater reduction in mean AAR compared with patients who received givosiran 1.25 mg/kg (90% vs 81%; **Table S5**). In addition, in patients who crossed over from placebo to givosiran 2.5 mg/kg, the percentage with 0 attacks increased from 10% during the double-blind period to 43% during the OLE period, whereas in patients who crossed over from placebo to givosiran 1.25 mg/kg, the

percentage with 0 attacks was 29% during the double-blind period and 35% during the OLE period.

Intrapatient comparisons in the placebo crossover groups demonstrated reductions in urinary ALA and PBG levels during givosiran treatment compared with placebo treatment, with patients who received givosiran 2.5 mg/kg having greater median reductions than patients who received givosiran 1.25 mg/kg in both ALA (−13.49 vs −12.90 mmol/mol Cr) and PBG (−35.76 vs −30.59 mmol/mol Cr). After 12 months of treatment in the OLE, median reductions from baseline in urinary ALA levels were 88.0% in the placebo/givosiran 2.5 mg/kg group and 88.2% in the placebo/givosiran 1.25 mg/kg group, and median reductions from baseline in urinary PBG levels were 87.3% in the placebo/givosiran 2.5 mg/kg group and 74.9% in the placebo/givosiran 1.25 mg/kg group.

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Supplementary figures

Fig. S1. ENVISION study design

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; qM, once monthly; SC, subcutaneous; SF-12, 12-item Short Form Health Survey. [a]Endpoints were evaluated in patients with genetically confirmed acute intermittent porphyria (except where noted otherwise) at 6 months. [b]For the OLE period, all endpoints were exploratory. [c]A protocol amendment (February 12, 2020) increased the dose to 2.5 mg/kg monthly for all patients.

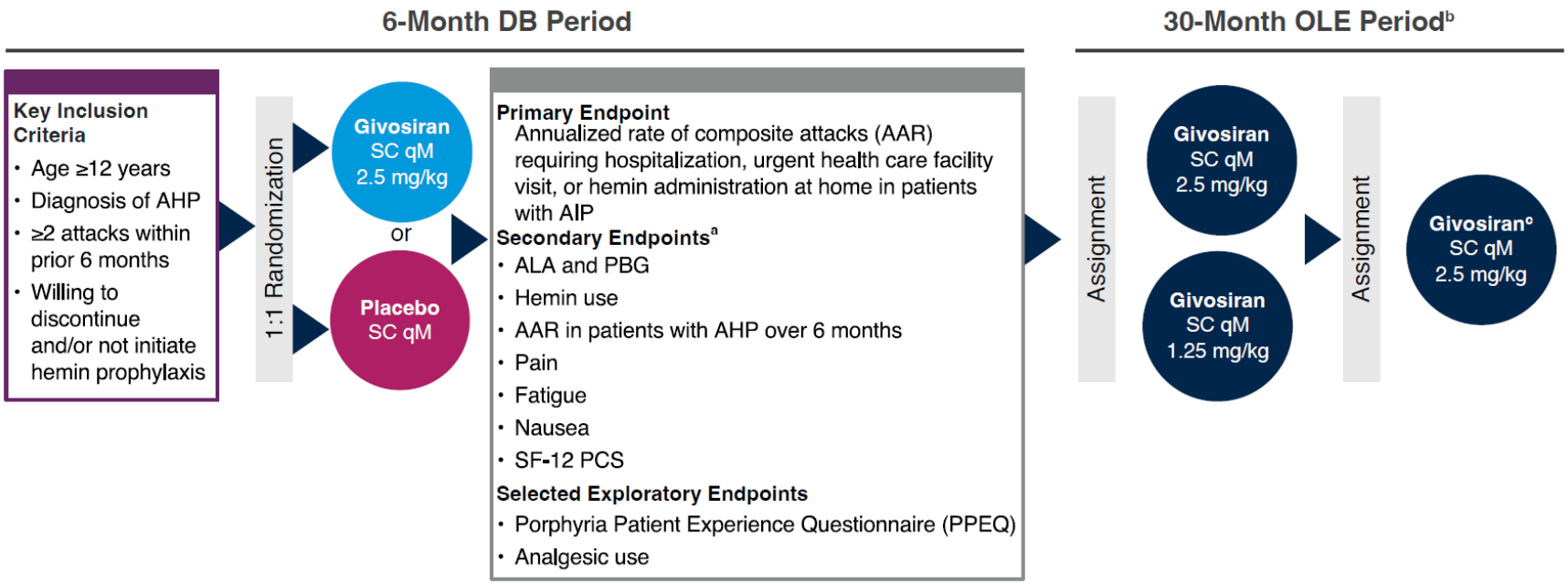


Fig. S2. Patient disposition at ENVISION OLE data cutoff

AHP, acute hepatic porphyria; DB, double-blind; OLE, open-label extension; qM, once monthly.
[a]Patients assigned to 1.25 mg/kg who experienced inadequate disease control and/or had no clinically relevant transaminase elevations were allowed to have their monthly dose increased to 2.5 mg/kg starting at the Month 13 study visit. Eleven patients (5 in the placebo/givosiran group and 6 in the givosiran/givosiran group) assigned to 1.25 mg/kg in the OLE had their dose increased to 2.5 mg/kg due to inadequate disease control at the Month 13–15 visits.

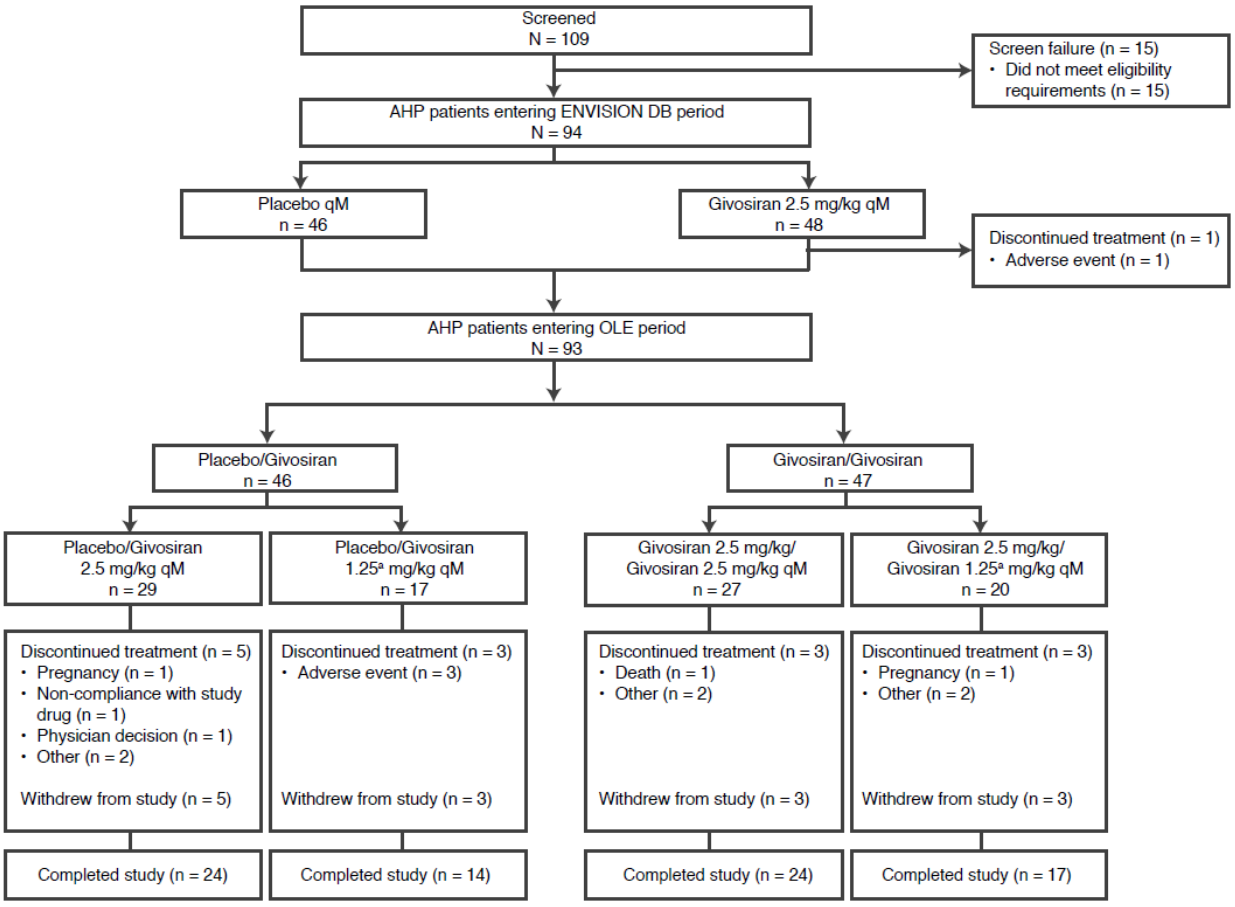
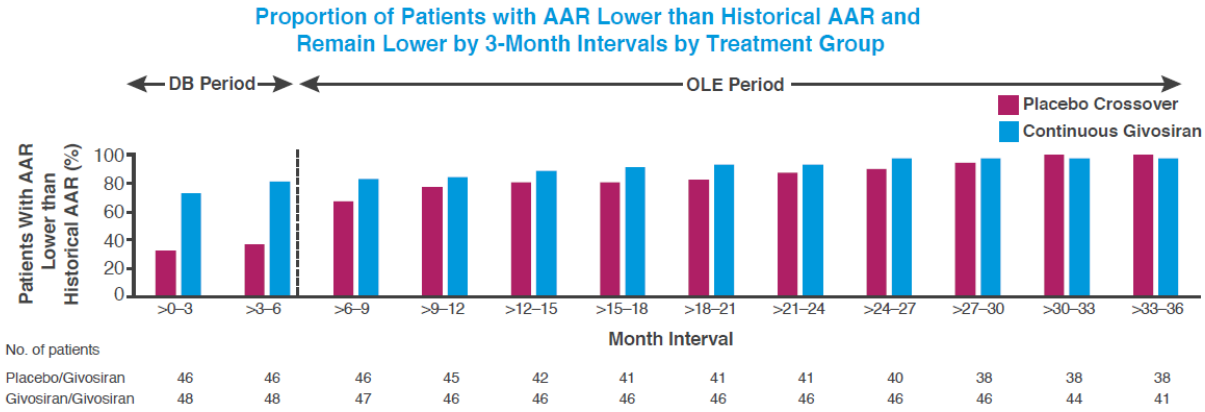


Fig. S3. Proportion of patients with an AAR lower than the historical AAR and remain lower by 3-month interval

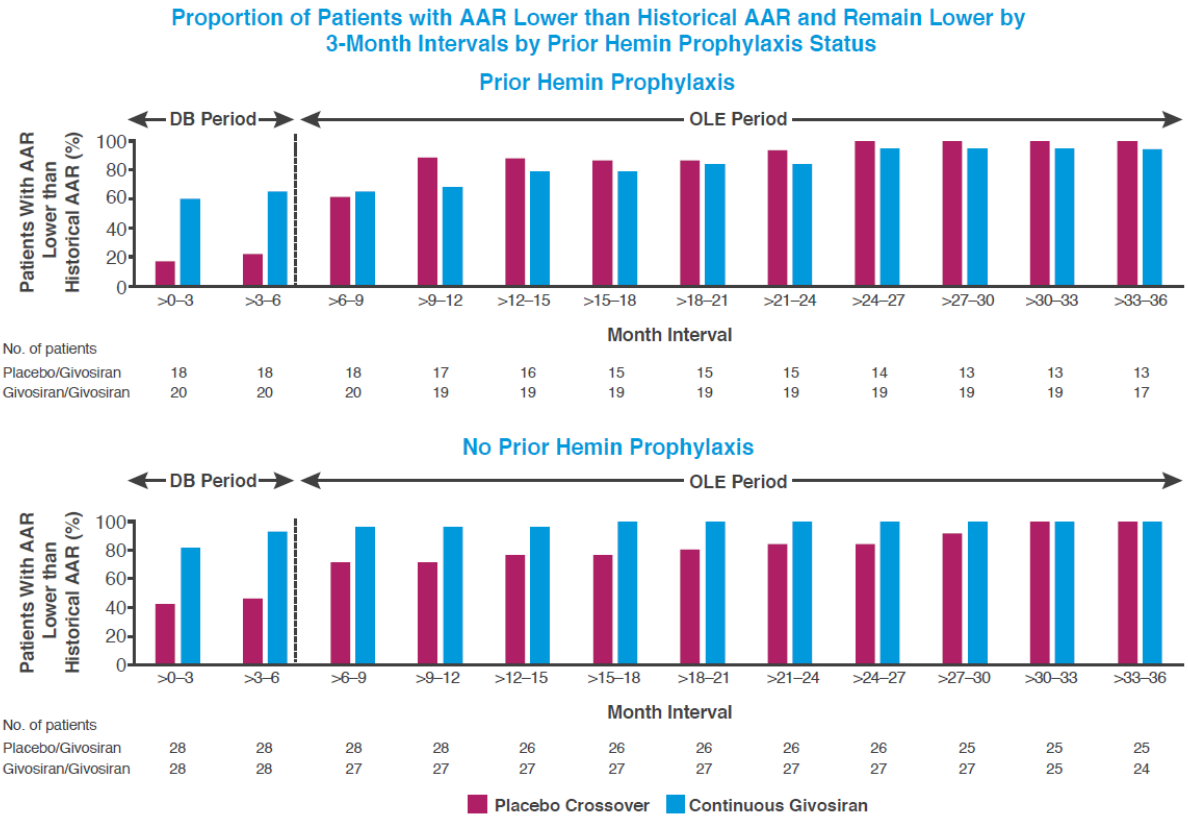
A. By treatment group. B. By treatment group and prior hemin prophylaxis status.
AAR, annualized attack rate; DB, double-blind; OLE, open-label extension.

A



No. of patients												
Placebo/Givosiran	46	46	46	45	42	41	41	41	40	38	38	38
Givosiran/Givosiran	48	48	47	46	46	46	46	46	46	46	44	41

B



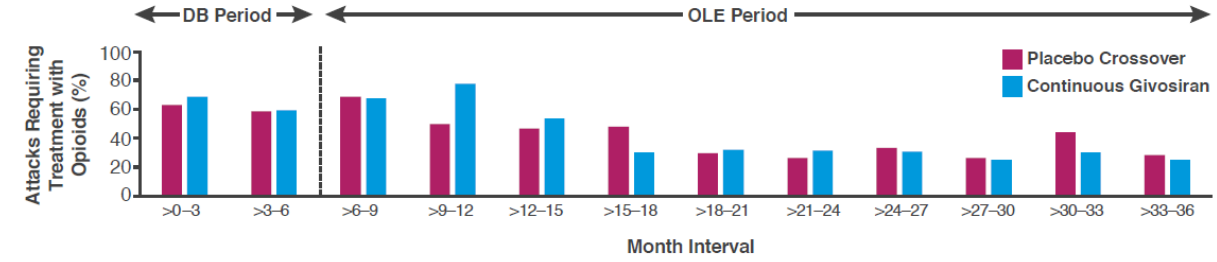
No. of patients												
Placebo/Givosiran	18	18	18	17	16	15	15	15	14	13	13	13
Givosiran/Givosiran	20	20	20	19	19	19	19	19	19	19	19	17

No. of patients												
Placebo/Givosiran	28	28	28	28	26	26	26	26	26	25	25	25
Givosiran/Givosiran	28	28	27	27	27	27	27	27	27	27	25	24

Fig. S4. Proportion of attacks requiring treatment with opioids[a] by 3-month intervals

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

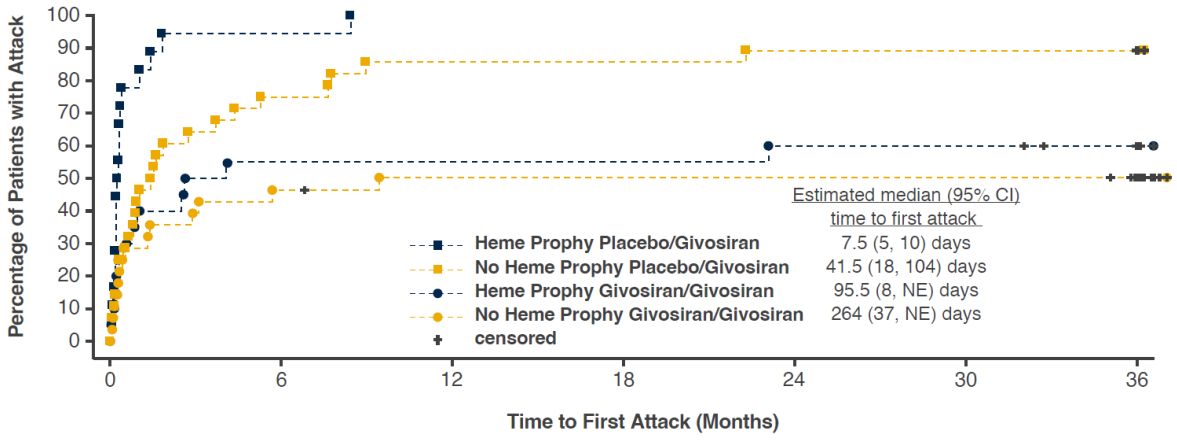
[a]Defined as opioid use reported by investigator (Months 0–36) and by patient e-diaries (Months 0–12), from Days 0–3 of a porphyria attack.



No. of attacks												
Placebo/Givosiran	154	164	58	30	15	21	17	23	12	15	9	7
Givosiran/Givosiran	58	49	37	27	28	23	22	19	13	12	10	12

Fig. S5. Time to first attack

1 month = 28 days.
CI, confidence interval; NE, not estimated.



Patients At Risk							
Heme Prophy Placebo/Givosiran	18	1	0				
Heme Prophy Givosiran/Givosiran	20	9	9	9	8	8	5
No Heme Prophy Placebo/Givosiran	28	7	4	4	3	3	2
No Heme Prophy Givosiran/Givosiran	28	15	13	13	13	13	10

Fig. S6. Mean change from baseline in SF-12 summaries (PCS, MCS)[a] by prior hemin prophylaxis status

A, Continuous givosiran, prior hemin prophylaxis. B. Continuous givosiran, no prior hemin prophylaxis. C. Placebo crossover, prior hemin prophylaxis. D. Placebo crossover, no prior hemin prophylaxis.
Higher scores represent improvement in that summary or domain.
DB, double-blind; MCS, Mental Component Summary; OLE, open-label extension; PCS, Physical Component Summary; SF-12, 12-item Short Form Health Survey.
[a]Scores on the PCS range from 0 (worst functioning) to 100 (best functioning), with 2 to 5 points representing a clinically meaningful difference, according to published data for other chronic diseases.[38,39]

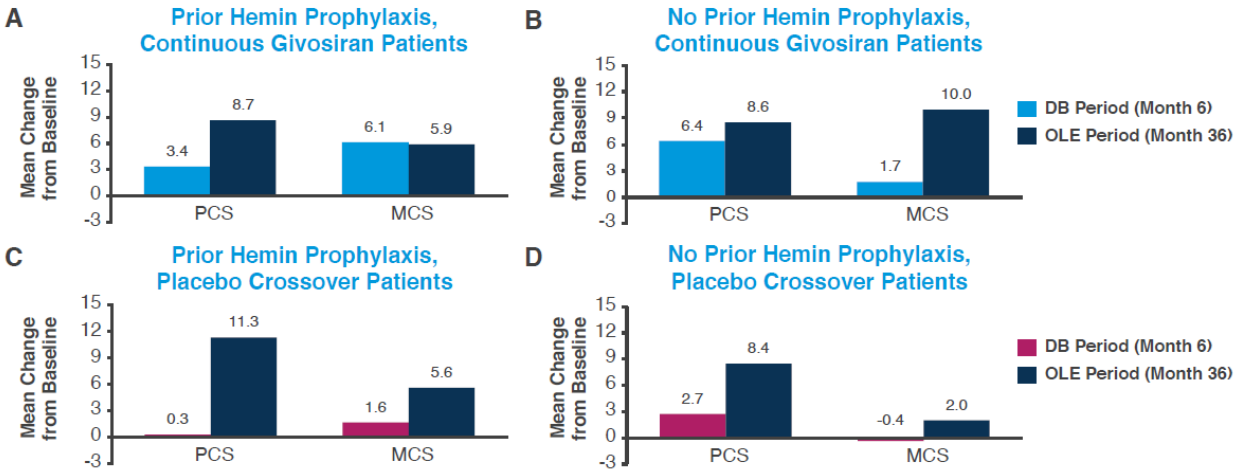
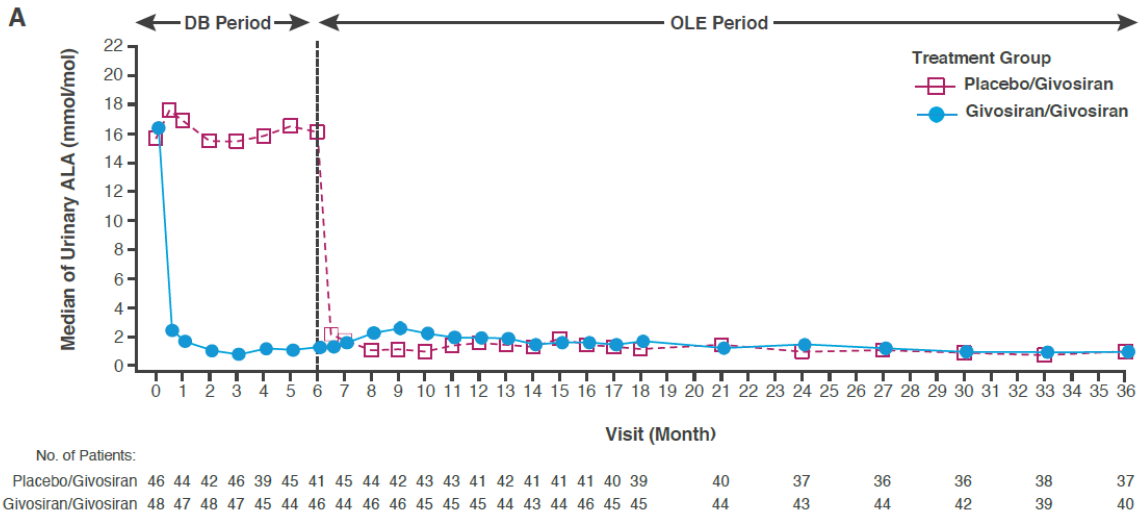


Fig. S7. Urinary ALA and PBG levels

A, Median ALA levels over time. B, Median PBG levels over time. OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled. Reference ranges: ALA (ULN, 1.47 mmol/mol Cr), PBG (ULN, 0.14 mmol/mol Cr).[47]
ALA, delta-aminolevulinic acid; Cr, creatinine; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; ULN, upper limit of normal.



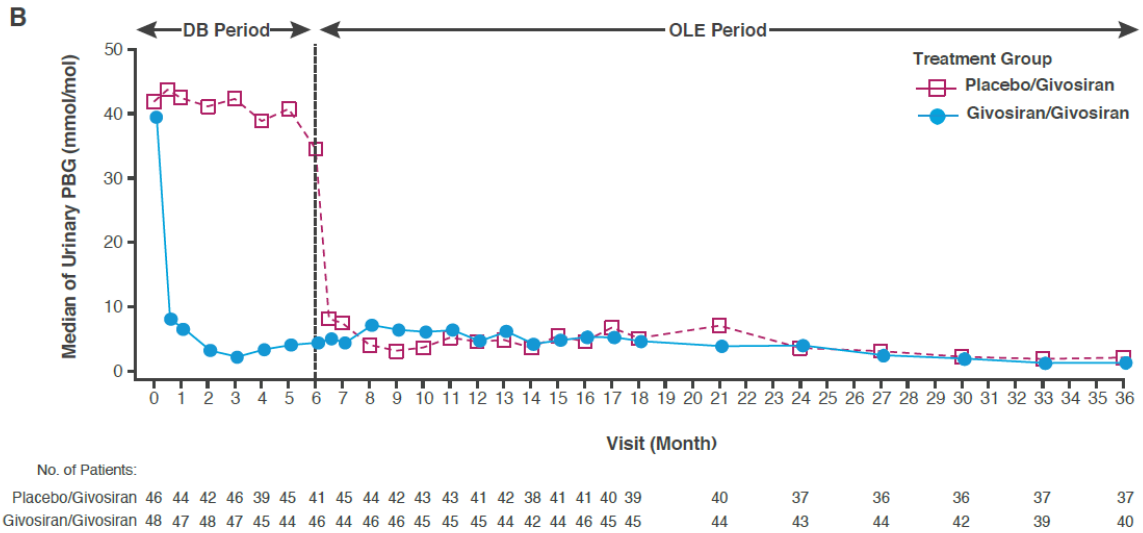
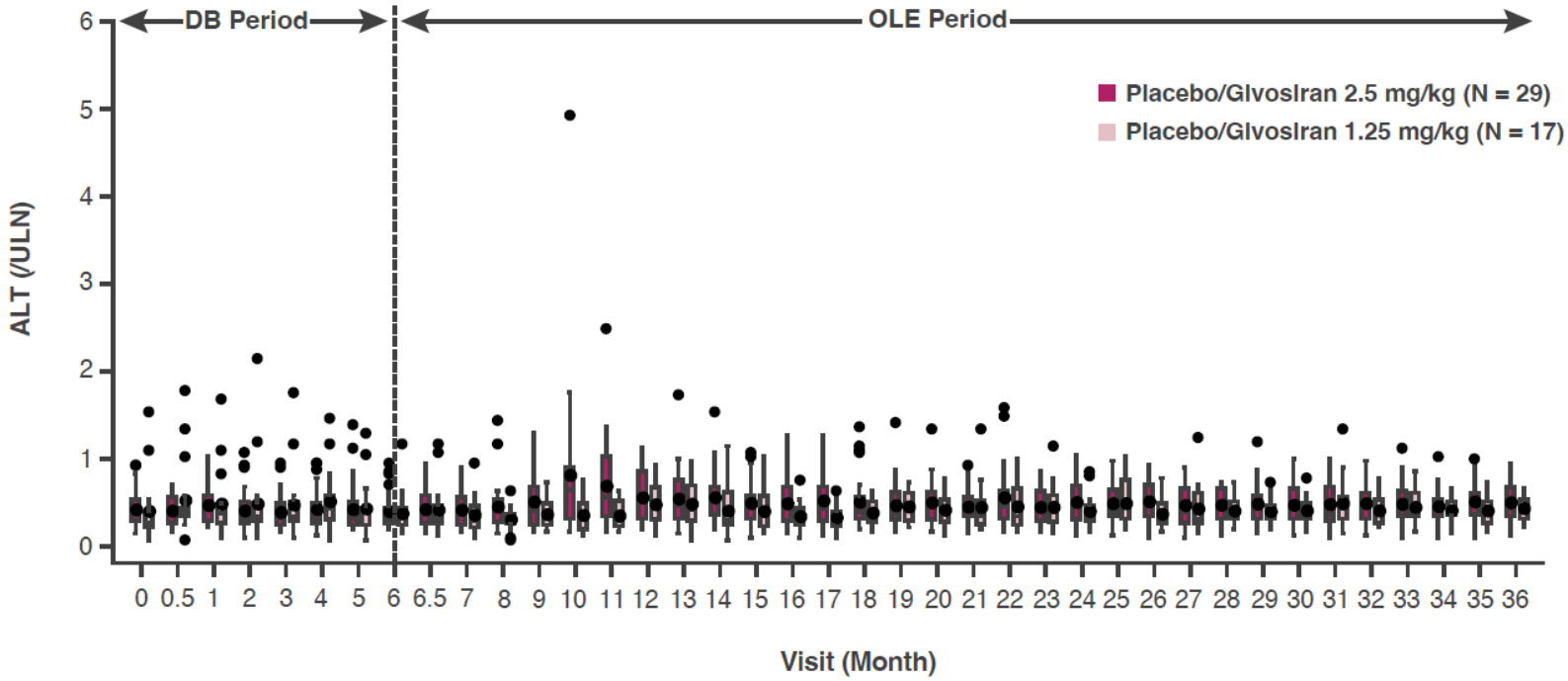


Fig. S8. ALT levels relative to ULN during treatment with givosiran

ALT, alanine aminotransaminase; DB, double-blind; OLE, open-label extension; ULN, upper limit of normal.

Boxplots present median (horizontal line), interquartile range (top and bottom edges of box), and range with outliers excluded (whiskers; third quartile + 1.5 * interquartile range). Outliers are represented as single data points.

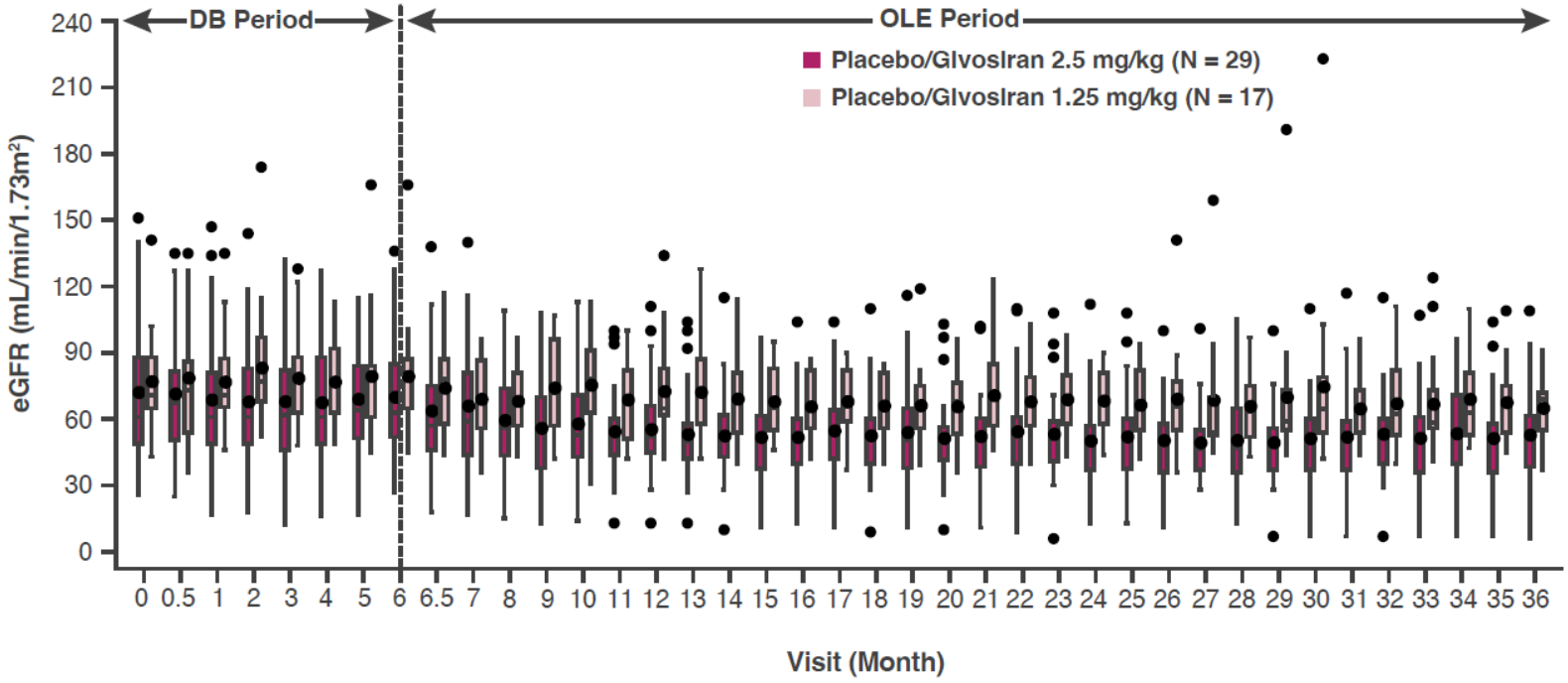


No. of Patients:																																				
Placebo/Givosiran 2.5	29	28	29	29	29	25	28	29	29	29	28	26	26	27	27	27	22	25	26	25	25	24	24	25	25	23	24	24	23	23	23	23	23	23	22	24	22	22	24
Givosiran/Givosiran 1.25	17	17	16	17	17	16	17	17	16	17	17	17	17	16	16	16	16	16	16	16	16	15	16	16	15	16	15	15	14	14	14	14	14	14	14	14	14	14	14

Fig. S9. eGFR during treatment with givosiran

DB, double-blind; eGFR, estimated glomerular filtration rate; OLE, open-label extension.

Boxplots present median (horizontal line), interquartile range (top and bottom edges of box), and range with outliers excluded (whiskers; third quartile + 1.5 * interquartile range). Outliers are represented as single data points.



No. of Patients:

Placebo/Givosiran 2.5	29	28	29	29	29	25	28	29	29	29	28	25	25	25	25	25	21	24	24	23	24	24	24	24	25	23	23	24	23	22	23	23	23	23	22	24	22	22	24
Givosiran/Givosiran 1.25	17	17	16	17	17	16	17	17	15	16	16	15	15	14	14	14	14	14	14	14	15	16	14	15	16	13	15	14	13	14	14	14	14	14	14	14	14	14	14

Fig. S10. Urinary ALA levels in patients who experienced 1 or more attacks during months >3 to 6 or months >33 to 36

A, Patients who experienced ≥1 attack during months >3 to 6. B, Patients who experienced ≥1 attack during months >33 to 36. OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled. ULN for ALA: 1.47 mmol/mol Cr).[47]
ALA, delta-aminolevulinic acid; Cr, creatinine; DB, double-blind; OLE, open-label extension; ULN, upper limit of normal.

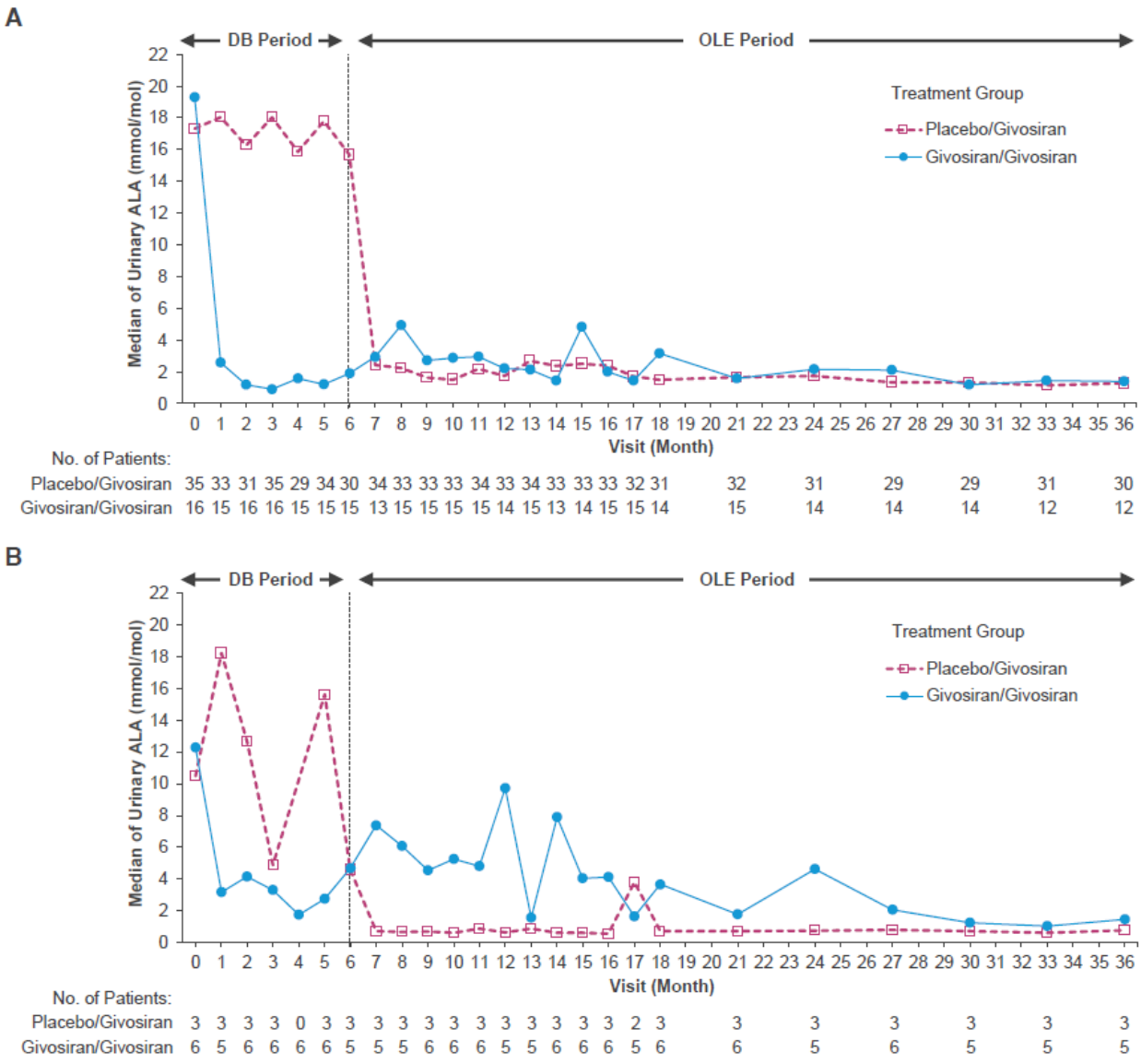
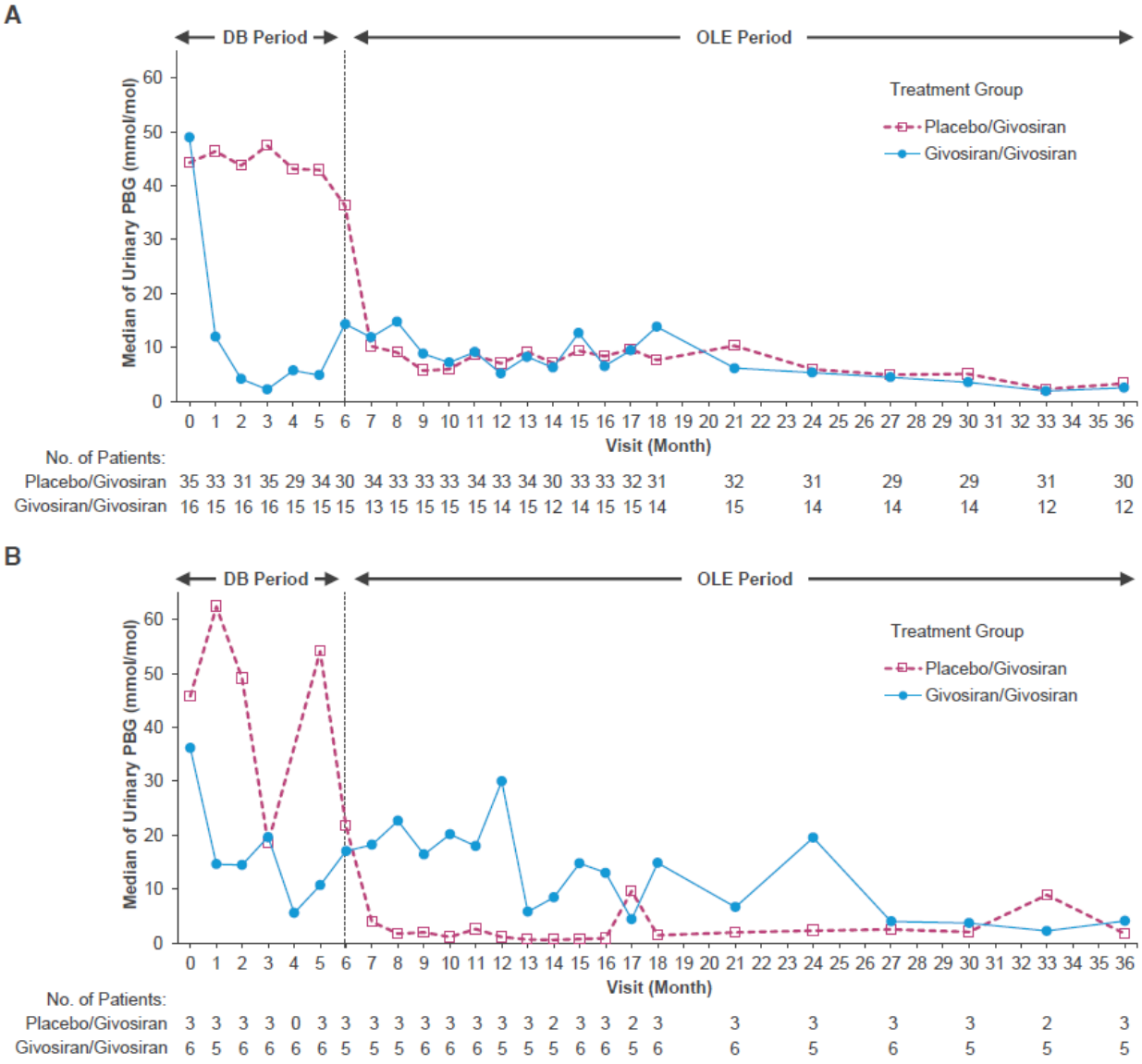


Fig. S11. Urinary PBG levels in patients who experienced 1 or more attacks during months >3 to 6 or months >33 to 36

A, Patients who experienced ≥1 attack during months >3 to 6. B, Patients who experienced ≥1 attack during months >33 to 36. OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled. ULN for PBG: 0.14 mmol/mol Cr.[47]
Cr, creatinine; DB, double-blind; OLE, open-label extension; PBG, porphobilinogen; ULN, upper limit of normal.



Supplementary tables

Table S1. Baseline demographic and clinical characteristics by prior hemin prophylaxis status

	Prior Hemin Prophylaxis			No Prior Hemin Prophylaxis		
Characteristic	**Placebo (n=18)**	**Givosiran (n=20)**	**Overall (N=38)**	**Placebo (n=28)**	**Givosiran (n=28)**	**Overall (N=56)**
Age at diagnosis, years, median (range)	29.6 (17–44)	32.4 (16–48)	30.6 (16–48)	28.0 (18–51)	28.1 (5–58)	28.1 (5–58)
Years since diagnosis, median (range)	7.08 (0.7–38.5)	6.56 (0.2–35.3)	6.81 (0.2–38.5)	4.06 (0.1–25.0)	7.20 (0.4–43.3)	5.68 (0.1–43.3)
Historical AAR,[a] median (range)	9.0 (4–38)	9.0 (4–32)	9.0 (4–38)	6.0 (0–46)	8.0 (4–34)	7.0 (0–46)
Prior chronic symptoms,[b] n (%)	9 (50)	7 (35)	16 (42)	17 (61)	16 (57)	33 (59)
Prior chronic opioid use,[c] n (%)	6 (33)	8 (40)	14 (37)	7 (25)	6 (21)	13 (23)
Baseline urinary ALA (mmol/mol Cr), median (range)[d]	17.6 (4.1–36.8)	14.8 (1.8–88.9)	16.1 (1.8–88.9)	14.9 (0.7–42.7)	17.2 (2.8–37.3)	15.7 (0.7–42.7)
Baseline urinary PBG (mmol/mol Cr), median (range)[e]	54.5 (7.9–96.1)	37.3 (3.0–150.0)	40.7 (3.0–150.0)	32.6 (0.4–106.5)	45.6 (0.4–143.6)	40.3 (0.4–143.6)

AAR, annualized attack rate; ALA, delta-aminolevulinic acid; Cr, creatinine; IV, intravenous; PBG, porphobilinogen; ULN, upper limit of normal.

[a]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare 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 most days when not having an attack.

[d]ALA reference range (ULN, 1.47 mmol/mol Cr).[47]

[e]PBG reference range (ULN, 0.14 mmol/mol Cr).[47]

Table S2. Composite porphyria attacks[a] following initiation of givosiran treatment

	Placebo Crossover (n=46)	Continuous Givosiran (n=48)	All Givosiran (N=94)
Time from initiation of givosiran to patients' reaching/remaining at an AAR lower than the historical AAR, months, mean (range)	3.7 (0–24)	2.7 (0–24)	3.2 (0–24)
Patients with ≥1 attack after 6 months of givosiran treatment, n (%)	19 (41)	17 (36)[b]	36 (39)[b]

AAR, annualized attack rate; IV, intravenous.
[a]Attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home during the 6 months before randomization.
[b]One patient who discontinued during the double-blind period was excluded.

Table S3. Baseline demographic and clinical characteristics of patients who experienced 1 or more attacks during months >3 to 6 or >33 to 36

Characteristic	Experienced ≥1 Attack During Months >3 to 6 in the DB period			Experienced ≥1 Attack During Months >33 to 36 in the OLE		
	Placebo (n=35)	Continuous (n=16)	Overall (N=51)	Placebo Crossover (n=3)	Continuous Givosiran (n=6)	Overall (N=9)
Age at diagnosis, years, median (range)	27.5 (16.9–47.2)	27.5 (6.3–46.1)	27.5 (6.3–47.2)	27.2 (16.9–35.2)	24.6 (17.0–30.4)	25.3 (16.9–35.2)
Years since diagnosis, median (range)	6.64 (0.1–38.5)	8.07 (0.2–31.3)	7.05 (0.1–38.5)	4.26 (0.4–6.7)	7.82 (0.2–27.3)	6.19 (0.2–27.3)
Prior hemin prophylaxis, n (%)	16 (46)	8 (50)	24 (47)	1 (33)	5 (83)	6 (67)
Number of attacks during the 6 months prior to screening, median (range)[a]	4.0 (2–25)	6.0 (2–17)	4.0 (2–25)	2.0 (2–4)	6.0 (2–16)	4.0 (2–16)
Number of attacks during the 6 months prior to randomization, median (range)[a]	5.0 (2–23)	6.0 (2, 17)	5.0 (2–23)	4.0 (3–7)	7.0 (3–14)	6.0 (3–14)
Historical AAR,[a] median (range)	10.0 (4–46)	12.0 (4–34)	10.0 (4–46)	8.0 (6–14)	14.0 (6–28)	12.0 (6–28)
Prior chronic symptoms,[b] n (%)	18 (51)	11 (69)	29 (57)	2 (67)	2 (33)	4 (44)
Prior chronic opioid use,[c] n (%)	9 (26)	5 (31)	14 (28)	0 (0)	2 (33)	2 (22)
Baseline creatinine normalized urinary	17.4 (1.4–41.5)	19.3 (2.8–88.9)	17.5 (1.4–88.9)	17.8 (3.6–19.5)	12.3 (3.3–88.9)	15.2 (3.3–88.9)

ALA (mmol/mol Cr), median (range)[d]						
Baseline creatinine normalized urinary PBG (mmol/mol Cr), median (range)[e]	43.3 (4.5– 87.7)	49.0 (0.4–150.0)	44.1 (0.4–150.0)	61.6 (3.6–66.1)	36.2 (0.4–150.0)	38.8 (0.4–150.0)

AAR, annualized attack rate; 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 are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home.

[b]Symptoms were chronic if patients experienced symptoms daily or on most days prior to the study.

[c]Opioid use was defined as chronic if patients reported taking opioids for porphyria daily or most days when not having an attack.

[d]ALA reference range (ULN, 1.47 mmol/mol Cr).[47]

[e]PBG reference range (ULN, 0.14 mmol/mol Cr).[47]

Table S4. Baseline Disease Characteristics and Comorbidities in Placebo/Givosiran Patients treated with 1.25 mg/kg vs 2.5 mg/kg Givosiran

Characteristic	Placebo/ Givosiran 2.5 mg/kg (n=29)	Placebo/ Givosiran 1.25 mg/kg (n=17)	All Placebo/ Givosiran (n=46)
Years since diagnosis, median (range)	8.31 (0.2–30.3)	2.39 (0.1–38.5)	6.46 (0.1–38.5)
Prior hemin prophylaxis, n (%)	14 (48.3)	4 (23.5)	18 (39.1)
Historical AAR,[a] median (range)	8.0 (0–46)	6.0 (2–38)	7.0 (0–46)
Prior chronic symptoms, n (%)	14 (48.3)	12 (70.6)	26 (56.5)
Comorbidities			
Transaminases increased, n (%)	11 (37.9)	7 (41.2)	18 (39.1)
Renal failure and impairment HLT,[b] n (%)	11 (37.9)	3 (17.6)	14 (30.4)
Chronic kidney disease, n (%)	8 (27.6)	1 (5.9)	9 (19.6)

AAR, annualized attack rate; HLT, high level term.
[a]Historical AAR was calculated by annualizing the number of attacks requiring hospitalization, urgent healthcare facility visit, or hemin use at home during the 6 months prior to randomization.
[b]Includes acute kidney injury, chronic kidney disease, renal failure, renal impairment, and renal injury.

Table S5. Intrapatient comparison of composite porphyria attacks[a] during placebo and givosiran treatment

	Placebo/Givosiran 2.5 mg/kg (n=29)		Placebo/Givosiran 1.25 mg/kg (n=17[b])		All Placebo/Givosiran (n=46)	
	DB Period	OLE Period[c]	DB Period	OLE Period	DB Period	OLE Period[c]
Total number of attacks, mean	206	83	91	84	297	167
Total follow-up time, years	13.4	58.0	7.9	35.8	21.2	93.8
AAR rate ratio[d] (OLE vs DB), 95% CI	0.10 (0.06, 0.17)		0.19 (0.11, 0.31)		0.13 (0.09, 0.19)	

AAR, annualized attack rate; CI, confidence interval; DB, double-blind; OLE, open-label extension.
Note: Patients in the placebo/givosiran 1.25 mg/kg treatment group who dose escalated because of inadequate disease control during the OLE at or after the Month 13 visit are counted in the treatment group according to the dose assigned at the beginning of the OLE period.
[a]Attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home.
[b]Fifteen (88%) of the 17 patients in the placebo/givosiran 1.25 mg/kg cohort had their dose escalated to givosiran 2.5 mg/kg at the Month 13 study visit.
[c]One patient whose follow-up duration after taking givosiran <85 days was excluded from the descriptive summaries.
[d]The rate ratio and corresponding 95% CI for comparing AAR during DB period and AAR during OLE period using the negative binomial regression model with period as a fixed effect and patient as a random effect with exchangeable working correlation matrix, and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favorable outcome for OLE period.