Givosiran: ENVISION Study 36-Month Results

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SUMMARY

- The phase 3 ENVISION study included a 6-month DB period and a 30-month OLE period to evaluate the efficacy and safety of givosiran in patients with a documented diagnosis of AHP.[1]
- Long-term givosiran use demonstrated a durable response with efficacy across a wide range of clinical parameters during the OLE period. In the continuous givosiran and placebo crossover groups, 86% and 92% of patients, respectively, were attack-free during Months 33–36. A sustained reduction in AAR, ALA and PBG levels, hemin use, and further increases in physical functioning and QOL scores were observed through month 36.[1]
- AEs were reported in 97% (91/94) patients receiving givosiran. The majority of AEs were mild or moderate in severity, with the most common AEs (≥10%) being injection-site reactions, nausea, and fatigue. SAE's were reported in 37% (35/94) patients. SAEs were reported in 39% (37/94) patients. There was 1 death in the study, which was deemed unrelated to givosiran. Overall, 4 patients discontinued givosiran due to treatment-related AEs.[1]

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STUDY DESIGN

The phase 3 ENVISION study was a randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrolled patients were randomized on a 1:1 basis to receive subcutaneous injections of givosiran 2.5 mg/kg or placebo once a month for 6 months, followed by an optional 30-month OLE.[1]

The ENVISION study enrolled 94 patients at 36 study sites in 18 countries. All patients completed the 6-month DB period. Upon completion of dosing in the ENVISION DB period, all eligible patients (93/94) continued in the ENVISION OLE study, receiving monthly givosiran administration.[2] In the OLE, patients were initially assigned to givosiran 2.5 mg/kg monthly (N=56) or givosiran 1.25 mg/kg monthly (N=37). The lower dose was introduced in a protocol amendment to assess efficacy and safety. Those enrolled before the amendment received 2.5 mg/kg; therefore, dose allocation in the OLE was not balanced. Patients receiving 1.25 mg/kg who experienced inadequate disease control could revert to 2.5 mg/kg at or after the month 13 visit. A subsequent protocol amendment was enacted to increase the dose for all patients receiving the 1.25 mg/kg monthly dose to the 2.5 mg/kg monthly dose.[1]

The primary endpoint of the ENVISION 6-month DB period was AAR compared to placebo, defined as those requiring hospitalization, urgent healthcare visit, or IV hemin administration at home, in patients with AIP over the 6-month treatment period. Secondary endpoints evaluated the impact of givosiran treatment on the following outcome measures (all at 6 months unless noted otherwise)[2]:

- ALA levels at 3 and 6 months in AIP patients
- PBG levels at 6 months in AIP patients
- Annualized days of administered hemin doses in AIP patients
- AAR in patients with AHP (including AIP)
- Daily worst pain in AIP patients
- Daily worst fatigue in AIP patients
- Daily worst nausea in AIP patients
- The PCS of the SF-12 health survey (a 12-question measure capturing global quality of life and overall health status)[3] in AIP patients.

All of the above endpoints were considered exploratory endpoints in the OLE, and data from the 1.25 mg/kg monthly and 2.5 mg/kg monthly doses of givosiran have been pooled.[4]

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Overall patient demographics and baseline characteristics in ENVISION, including baseline disease characteristics and comorbidities, are found in **Table 1**. The majority of patients were female and had genetically confirmed AIP. Patients had a median, historical AAR of 8 (range, 0 to 46). Across both treatment groups at baseline, 40% of patients had received prior hemin prophylaxis and 52% of patients experienced chronic symptoms between attacks.[1] Common comorbidities included increased aminotransferase levels, iron overload, liver disease, hypertension, and renal impairment.[2]

Table 1. Patient Demographics and Baseline Characteristics in ENVISION.[1,2]

Baseline Characteristics	Placebo (N=46)	Givosiran (N=48)	Overall (N=94)
Age, years, median (range)	36.0 (20-60)	42.0 (19-65)	37.5 (19-65)
Female, n (%)	41 (89)	43 (90)	84 (89)
Body-mass index, mean ±SD	25.5±6.4	24.3±5.2	24.9±5.8
Race, n (%)			
White/Caucasian	34 (74)	39 (81)	73 (78)
Black	1 (2)	0	1 (1)
Asian	7 (15)	8 (17)	15 (16)
Other	4 (9)	1 (2)	5 (5)
AHP type, n (%)			
AIP with mutation in the HMBS gene	43 (93)	46 (96)	89 (95)
HCP	0	1 (2)	1 (1)
VP	1 (2)	1 (2)	2 (2)
AHP without identified mutation	2 (4)	0	2 (2)
Number of 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 therapy, n (%)	18 (39)	20 (42)	38 (40)
Historical AAR[a], n (%)			
High	21 (46)	24 (50)	45 (48)

Baseline Characteristics	Placebo (N=46)	Givosiran (N=48)	Overall (N=94)
Low	25 (54)	24 (50)	49 (52)
Median rate (range)	7 (0[b]–46)	8 (4–34)	8 (0[b]–46)
Chronic symptoms experienced daily or on most days between attacks, n (%)	26 (57)	23 (48)	49 (52)
Used opioids daily or most days in between attacks, n (%)	13 (28)	14 (29)	27 (29)
Baseline urinary ALA, mmol/mol Cr, median (range)[c]	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)[d]	39.3 (3.6–87.7)	39.6 (0.4–150.0)	39.6 (0.4–150.0)

Abbreviations: AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ALA = delta-aminolevulinic acid; Cr = creatinine, HCP = hereditary coproporphyria; HMBS = hydroxymethylbilane synthase; PBG = porphobilinogen; SD = standard deviation; VP = variegate porphyria.

[a]The historical AAR was calculated as the number of attacks resulting in a composite of hospitalization, a visit to a health care facility, or hemin use at home during the 6 months before randomization. For patients who were receiving hemin prophylaxis before the initiation of the trial, the attack rate was considered to be high if the historical AAR was 7 or more and low if AAR was less than 7 (attack rate of ≥12 and <12, respectively, for patients who were not receiving previous hemin prophylaxis).

[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 the 6 months prior to screening (patient had 2 attacks that were treated at home without IV hemin). This was identified as a protocol deviation.

[c]ULN, 1.47 mmol/mol Cr

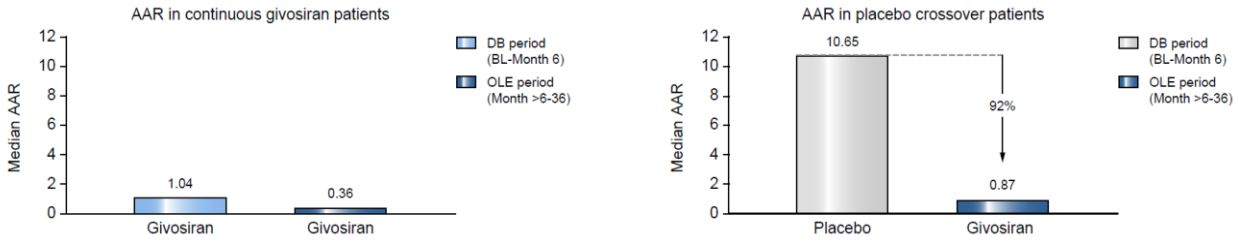
[d]ULN, 0.14 mmol/mol Cr

EFFICACY RESULTS

Attack Rate

Continued givosiran treatment during the OLE period led to a sustained reduction in AAR in patients (N=47) who initially received givosiran in the DB period (continuous givosiran group) and in patients (N=46) who received placebo in the DB period and crossed over to receive givosiran in the OLE period (placebo crossover group) (**Figure 1**). After the initial 6-month DB period, the median number of attacks during the OLE period (>6 months) was 0.36 and 0.87 in the continuous givosiran and placebo crossover groups, respectively.[1]

Figure 1. Median AAR for DB and OLE Study Periods: (Left) Continuous Givosiran and (Right) Placebo Crossover.[1,a,b]



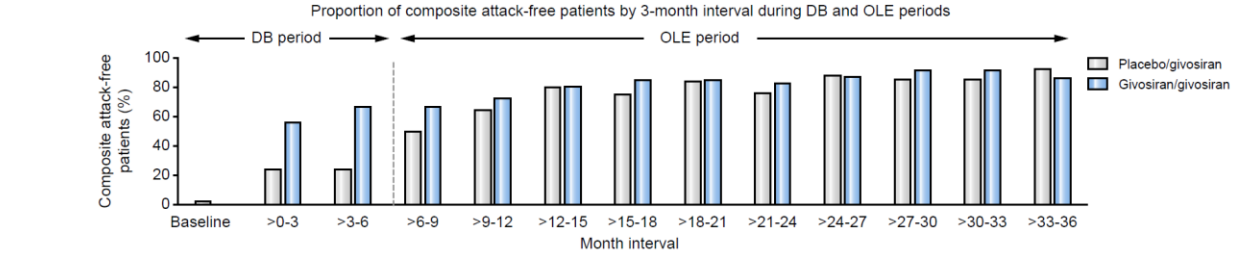
From Kuter et al[1]

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

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

The proportion of patients with no attacks by 3-month interval increased with givosiran treatment during the OLE period (**Figure 2**). Of the patients in the continuous givosiran group, 67% were attack free at >3–6 months, and 86% were attack-free at >33–36 months. Of the patients in the placebo crossover group, 24% were attack free at >3–6 months, and 92% were attack-free at >33–36 months.[1]

Figure 2. Proportion of Composite Attack-Free Patients by 3-Month Interval During DB and OLE Periods.[1,a,b]



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

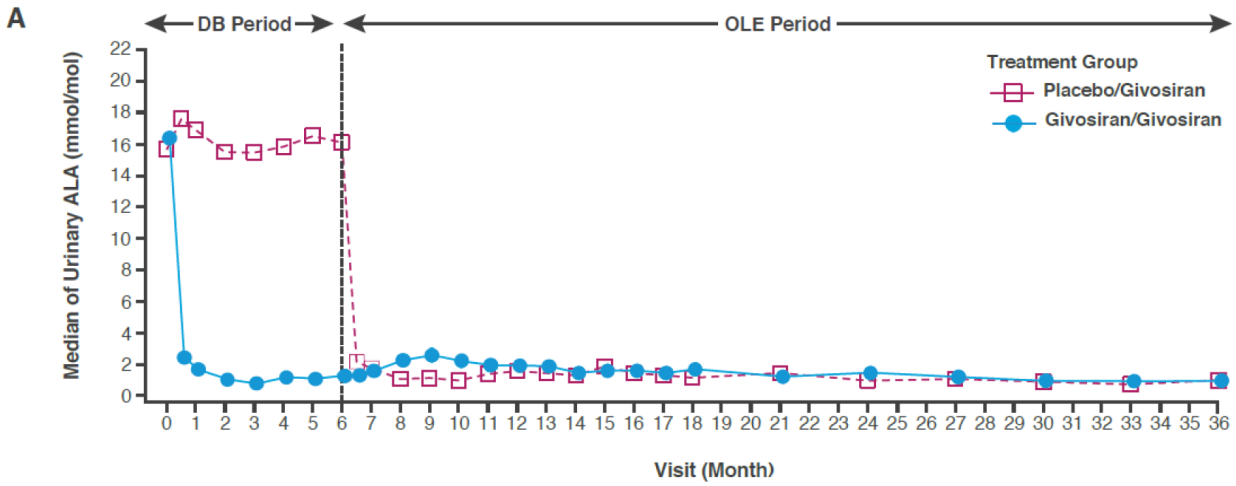
From Kuter et al[1]
Abbreviations: DB = double blind, OLE = open-label extension
[a]Composite attacks include porphyria attacks requiring hospitalization, urgent health care facility visit, or IV hemin administration at home; 1 month = 28 days, [b]Baseline represents 6 months before randomization.

In a post hoc analysis, the mean time from the start of givosiran treatment to when patients reached and remained below the historical AAR was 2.7 months and 3.7 months in the continuous givosiran and placebo crossover group, respectively. At 36 months, the proportion of patients with an AAR lower than historical AAR was 98% (40/41) and 100% (38/38) for the continuous givosiran and placebo crossover group, respectively.[1]

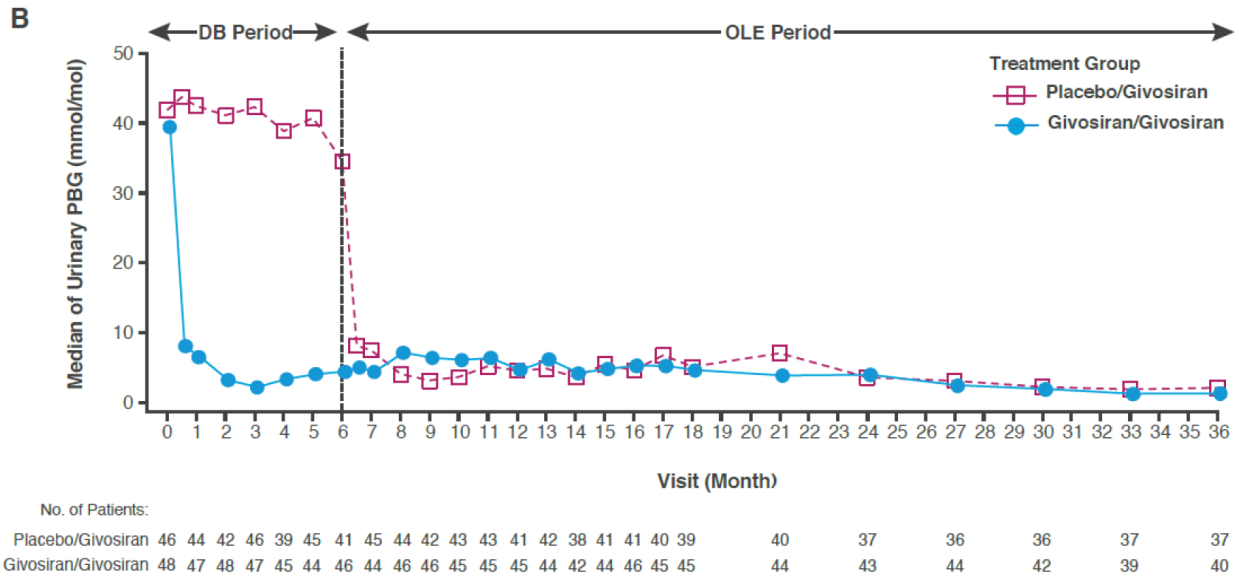
Urinary ALA and PBG

In the continuous givosiran and placebo crossover groups, givosiran treatment led to sustained lowering of median ALA levels to near normal and to lowering of PBG levels by >90% at Month 36 (**Figure 3**).[4]

Figure 3. Median Levels of (A) Urinary ALA and (B) PBG During DB and OLE Study Periods.[5,a]



No. of Patients:																									
Placebo/Givosiran	46	44	42	46	39	45	41	45	44	42	43	43	41	42	41	41	41	40	39	40	37	36	36	38	37
Givosiran/Givosiran	48	47	48	47	45	44	46	44	46	46	45	45	45	44	43	44	46	45	45	44	43	44	42	39	40

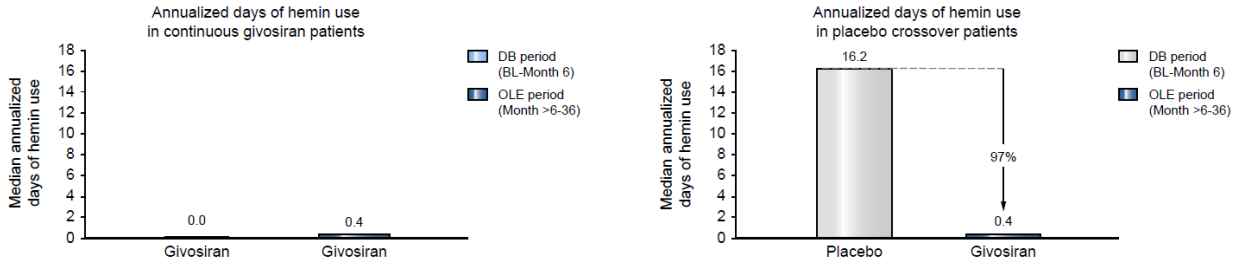


From Kuter et al[5]
Abbreviations: ALA = delta aminolevulinic acid; DB = double blind; OLE = open-label extension; PBG= porphobilinogen.
[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled. Reference ranges: ALA (ULN, 1.47 mmol/mol Cr), PBG (ULN, 0.137 mmol/mol Cr).[6]

Hemin Use

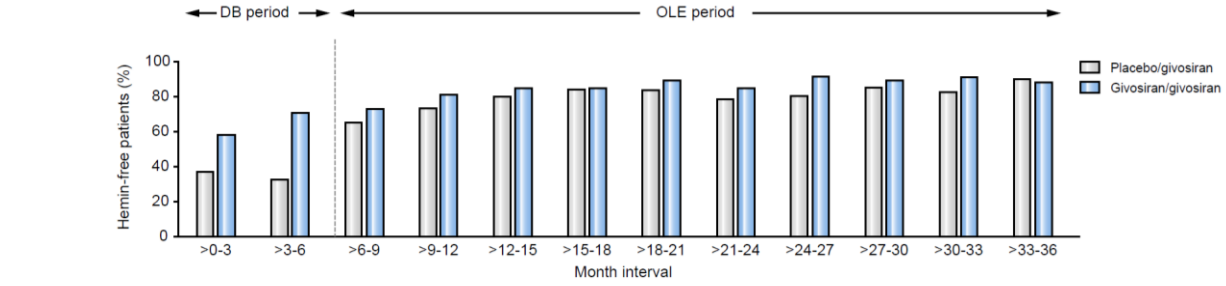
Median annualized days of hemin use remained low in the continuous givosiran group during the OLE period and decreased by 97% in the placebo crossover group during the OLE period (**Figure 4**). The proportion of patients with no days of hemin use increased over time in both the continuous givosiran and placebo crossover groups. Of the patients in the continuous givosiran group, 88% had no days of hemin use at >33–36 months. Of the patients in the placebo crossover group, 90% had no days of hemin use at >33–36 months (**Figure 5**).[1]

Figure 4. Median Annualized Days of Hemin Use: Continuous Givosiran (Left) and Placebo Crossover (Right).[1]



From Kuter et al.[1]
Abbreviations: DB = double blind, OLE = open-label extension

Figure 5. Proportion of Patients with 0 Days of Hemin Use by 3-Month Interval.[1]



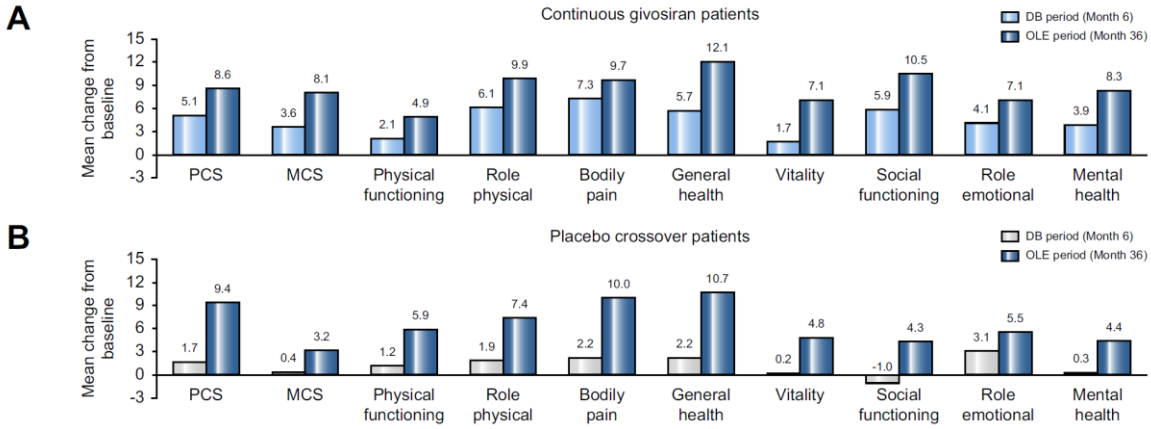
No. of patients												
Placebo/givosiran	46	46	46	45	45	44	43	42	41	40	40	39
Givosiran/givosiran	48	48	48	47	46	46	46	46	46	46	45	43

From Kuter et al.[1]
Abbreviations: DB = double blind, OLE = open-label extension

Patient-reported Efficacy Outcomes

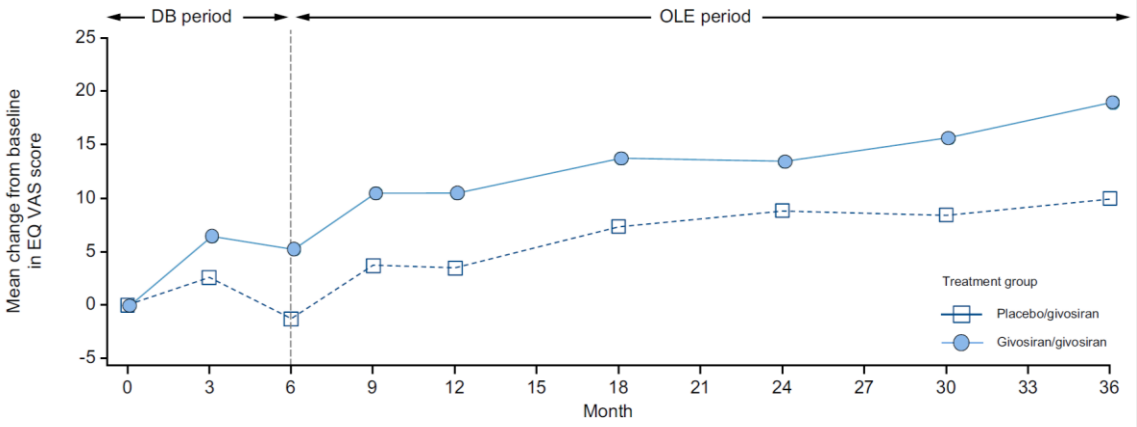
Patients in both the continuous givosiran group and the placebo crossover group experienced further increases in QOL scores, as assessed by the SF-12 PCS and MCS scores (including individual domain scores) (**Figure 6**) and the EQ-VAS scores (**Figure 7**). Increases in QOL scores were sustained from Month 6 to Month 36 in patients who continued givosiran treatment.[1]

Figure 6. Mean Changes in SF-12 PCS, MCS, and Individual Domain Scores from Baseline Through OLE Period.[1,a]



From Kuter et al.[1]
Abbreviations: DB = double blind, MCS = mental component summary; OLE = open-label extension; PCS = physical component summary; SF-12 = 12 item short-form health survey
[a]Higher scores represent improvement in that summary or domain; 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.[3,7]

Figure 7. Mean Change in EQ-VAS Scores from Baseline Through OLE Period.[1,a]

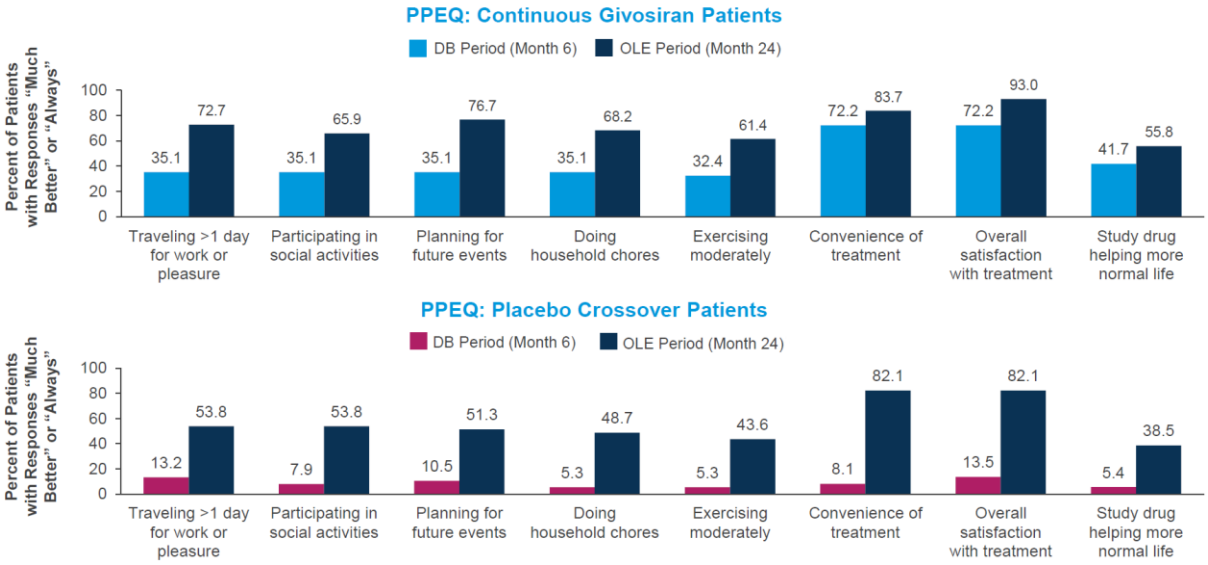


No. of patients									
Placebo/givosiran	46	45	46	44	42	41	39	36	36
Givosiran/givosiran	48	47	48	46	45	44	43	39	40

From Kuter et al.[1]
Abbreviations: EQ-VAS = EuroQol visual analog scale; OLE = open-label extension.
[a]Estimates for the clinically meaningful differs are ≥7 to 8 points for EQ-VAS, based on published data for other chronic diseases.[8,9]

Patients also reported changes in functioning, up to Month 24 per the protocol, using a custom questionnaire, the PPEQ. From the DB period through the Month 24 in the OLE, PPEQ results showed further increases across all domains, including activities of daily living, satisfaction with treatment, and living a more normal life, in the continuous givosiran group (**Figure 8**). Increases across all domains were also observed from the DB period through the OLE period in the placebo crossover group.[4]

Figure 8. Percentage of Patients Who Reported Ability Improvements ("Much Better" or "Always") on PPEQ.[4]



From Bonkovsky et al.[4]
Abbreviations: DB = double blind; OLE = open-label extension; PPEQ = Porphyria Patient Experience Questionnaire.

SAFETY RESULTS

The safety profile of givosiran was evaluated in all patients. Median (range) exposure to givosiran was 33.1 (2.7–34.1) months for the continuous givosiran group and 27.7 (1.8–28.3) months for the placebo crossover group. The maximum exposure time to givosiran was 34.1 months.[4]

The majority of AEs were mild or moderate in severity, and a summary of adverse events is shown in **Table 2**. The most common AEs included injection-site reactions (39%), nausea (37%), and fatigue (27%). Overall, 4 patients discontinued givosiran treatment due to treatment-related AEs (blood homocysteine increase with concomitant injection-site reaction, blood homocysteine increase with concomitant pancreatitis, abnormal liver function test, and drug hypersensitivity). SAEs considered related to givosiran included increased blood homocysteine, elevated transaminases, retinal vein occlusion, injection-site reaction, pancreatitis, worsening of chronic renal failure, pulmonary embolism, right iliac thrombophlebitis, and worsening of liver tests. There was 1 death due to aortic dissection during the OLE period that was determined to be unrelated to givosiran.[1]

Table 2. Summary of Patients with ≥1 Adverse Event.[1,a]

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

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a]Safety data from first dose of givosiran to completion of study, May 31, 2021

Hepatic Events

In the 6-month DB period, 1 patient (mentioned above) discontinued treatment with givosiran due to an SAE of abnormal liver-function testing (an ALT level of 9.9 × the upper limit of normal) which met a protocol-defined stopping rule. This event subsequently resolved.[2]

Hepatic AEs were reported in 9 patients (19%) in the continuous givosiran group and 9 patients (20%) in the placebo crossover group, all of which were mild to moderate in severity. The majority of hepatic AEs reported were elevations of serum aminotransferases. Of all patients who received givosiran, elevated ALT levels were reported in 10 patients (11%) and generally occurred 3–6 months after starting givosiran treatment and resolved over time; elevated AST levels were reported in 6 patients (6%).[1,4]

Renal Events

In the 6-month DB period, 2 patients experienced SAEs of CKD that were considered serious due to elective hospitalization for diagnostic evaluation; renal biopsies were performed and were consistent with the underlying disease. There was no indication of immune complex or other primary glomerular renal disorders.[2]

Renal AEs were reported in 12 patients (25%) in the continuous givosiran group and 9 patients (20%) in the placebo crossover group; the renal AEs were mostly characterized by increased serum creatinine and/or decreased eGFR. No renal AE led to discontinuation of study treatment. Small decreases in eGFR observed early in therapy stabilized over Months 12 to 26. In most patients, mean changes in eGFR remained stable during the OLE.[1]

ABBREVIATIONS

AAR = annualized attack rate; AE = adverse event; AHP = acute hepatic porphyria; ALA = delta aminolevulinic acid; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CKD = chronic kidney disease; DB = double blind; eGFR = estimated glomerular filtration rate; EQ-VAS = EuroQol visual analog scale; MCS = mental component summary; OLE = open-label extension; PBG = porphobilinogen; PPEQ = Porphyria Patient Experience Questionnaire; PCS = physical component summary; SAE = serious adverse event; QoL = quality of life; SF-12 = 12 item short-form health survey; ULN = upper limit of normal.

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