Givosiran: Phase 1/2 Open-Label Extension

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SUMMARY

- The Phase 1/2 OLE study was an extension of the Phase 1 clinical study to evaluate the long-term safety and tolerability of givosiran in patients with AIP for up to 48 months.[1]
- The primary endpoint was the incident of AEs, which were reported in all 16 patients (100%), and the majority of AEs were mild or moderate in severity. The most frequently reported AEs were abdominal pain, nasopharyngitis, nausea, fatigue, and ISRs. The most common treatment-related AE was ISRs, all of which were mild or moderate in severity and did not lead to treatment discontinuation or study withdrawal.[1]
- The AAR decreased during long-term monthly treatment with givosiran. Annualized hemin use decreased during givosiran treatment in both the placebo-givosiran crossover and continuous givosiran treatment groups. Once-monthly treatment with givosiran led to sustained reductions in urinary ALA and PBG levels through Month 48.[1]
- The mean (SD) EQ-VAS score increased from 68.9 (20.9) at Phase 1 study baseline to 84.4 (22.4) at OLE Month 48, representing a mean (SD) improvement of 15.8 (13.7) points, indicating a mean improvement of 30%.[1]

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STUDY DESIGN

The Phase 1/2 OLE study was an extension of the Phase 1 clinical study to evaluate the long-term safety and tolerability of givosiran in patients with AIP for up to 48 months. Upon study entry into the OLE, patients received givosiran 2.5 mg/kg once monthly or 5.0 mg/kg once monthly or every 3 months. All patients enrolled in the OLE (N=16) were transitioned to receive subcutaneous injections of givosiran 2.5 mg/kg once a month.[1]

Endpoints

The primary endpoint was the incidence of AEs. Key secondary endpoints were changes in urine ALA and PBG levels and clinical activity of givosiran as assessed by the frequency and characteristics of porphyria attacks (attacks leading to hospitalization, urgent health care visits, or use of IV hemin at home) and change in the number of hemin doses administered. Exploratory endpoints include changes in health-related QoL.[1]

Safety assessments consisted of monitoring AEs, vital signs, results from physical examinations, EKG measurements, and clinical laboratory assessments.[1]

Inclusion and Exclusion Criteria

Inclusion criteria included patients ages 18-65 diagnosed with AIP, pathogenic variant in *HMBS* gene, recurrent attacks (2 or more attacks within the 6 months prior to Phase 1 study run-in or received scheduled hemin prophylaxis at the start of Phase 1 study run-in), and completed part C of the Phase 1 study (to qualify for part C, patients were either not scheduled on a scheduled prophylactic hemin therapy regimen or agreed to discontinue any scheduled hemin prophylaxis during the 4-24 week run-in and up to 12-week treatment period). Exclusion criteria included ALT ≥2x ULN, total bilirubin ≥2 mg/dL, or eGFR ≤30 mL/min/1.73m^2.[1]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Of the 16 patients enrolled in the Phase 1/2 OLE study, 14 (88%) completed the study. Twelve patients (75%) received givosiran in both the Phase 1 study and the Phase 2 OLE (continuous givosiran), and the remaining 4 patients (25%) received placebo in the Phase 1 study and switched to givosiran during the Phase 2 OLE (placebo-givosiran crossover) (**Table 1**). The median (range) duration of drug exposure was 48.0 (2.1–49.0) months (cumulative exposure, 53.9 PY). Most patients (14/16; 88%) in the Phase 1/2 OLE received givosiran for ≥36 months; and 50% (8/16) received givosiran for ≥48 months. Across all patients, the total observation time was 4.24 person-years during the Phase 1 run-in period and 53.6 PY during the OLE study.[1]

Table 1. Baseline Demographics and Disease Characteristics.[1]

Statistic	Placebo–Givosiran Crossover (*N* = 4)	Continuous Givosiran (*N* = 12)	Total Givosiran (*N* = 16)
Age at screening, years, median (range)	42.0 (27–60)	37.5 (21–59)	39.5 (21–60)
Female, n (%)	2 (50)	12 (100)	14 (88)
Weight, kg, mean (SD)	91.4 (20.8)	70.7 (15.1)	75.8 (18.5)
BMI, kg/m^2, mean (SD)	31.1 (4.6)	26.6 (5.8))	27.7 (5.7)
Race, n (%)			
White	4 (100)	9 (75)	13 (81)
Black or African American	0	2 (17)	2 (13)
Asian	0	1 (8)	1 (6)
Ethnicity, n (%)			
Not Hispanic or Latino	4 (100%)	11 (92)	15 (94)
Not reported	0	1 (8)	1 (6)

Statistic	Placebo–Givosiran Crossover (*N* = 4)	Continuous Givosiran (*N* = 12)	Total Givosiran (*N* = 16)
Region, n (%)			
North America	1 (25)	8 (67)	9 (56)
Europe[b]	3 (75)	4 (33)	7 (44)
Patients with porphyria attack[a] in 12 months before enrollment in parent study, n (%)	4 (100)	11 (92)	15 (94)
Required hospitalization	2 (50)	6 (50)	8 (50)
Treated at outpatient clinic or infusion center	4 (100)	5 (42)	9 (56)
Treated at home	0	5 (42)	5 (31)
Number of porphyria attacks[a] in 12 months before enrollment in parent study, median (range)	10.0 (5–50)	9.5 (0–36)	10.0 (0–50)
Ever given hemin during an attack before enrollment in parent study, n (%)	4 (100)	12 (100)	16 (100)
Taking hemin on scheduled basis just before enrollment in parent study, n (%)	2 (50)	6 (50)	8 (50)
Other treatment for porphyria before enrollment in parent study, n (%)			
Hormone suppression therapy	0	4 (33)	4 (25)
High carbohydrate diet)	2 (50)	5 (42)	7 (44)
Glucose infusions	2 (50)	8 (67)	10 (63)
Others	0	4 (33)	4 (25)
Self-treated at home before enrollment in parent study, n (%)			
Sugar water	0	2 (17)	2 (13)
High carbohydrates	2 (50)	7 (58)	9 (56)
Opioid analgesic medications	2 (50)	7 (58)	9 (56)
Other	1 (25)	8 (67)	9 (56)
Urinary ALA, creatinine normalized, mmol/mol			
N	4	11	15
Median (range)	16.7 (7.5–33.9)	15.4 (1.5–50.5)	15.8 (1.5–50.5)
Urinary PBG, creatinine normalized, mmol/mol			
N	4	11	15
Median (range)	46.3 (30.8–51.8)	54.0 (3.2–95.3)	48.0 (3.2–95.3)

Abbreviations: ALA = 5-aminolevulinic acid; BMI = body mass index; PBG = porphobilinogen; SD = standard deviation.
[a]Represents all porphyria attacks, including attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin treatment at home and attacks treated without hemin at home.
[b]Europe includes Sweden and Great Britain.

PRIMARY ENDPOINT

Safety

AEs were reported in all 16 patients (100%), and the majority of AEs were mild or moderate in severity. A summary of AEs is provided in **Table 2**. The most frequently reported AEs were abdominal pain, nasopharyngitis, nausea, fatigue, and ISRs. The most common treatment-related AE was ISRs, all of which were mild or moderate in severity and did not lead to treatment discontinuation or study withdrawal. The most common symptoms included erythema, pruritus, rash, swelling, and

discoloration at or near the injection site. One patient had an AE of increased blood homocysteine that was mild in severity and considered possibly related to givosiran.[1]

Seven patients (44%) experienced serious AEs. The only serious AE occurring in >1 patient was abdominal pain (n=2). One patient (6%) with a medical history of allergic asthma and asthma experienced a SAE of anaphylaxis considered to be related to treatment.[1]

Seven patients (44%) reported hepatic AEs, most of which were mild or moderate in severity, and all resolved during treatment with givosiran. None of the hepatic AEs were serious, and there were no dose interruptions, changes in dose, or treatment discontinuation.[1]

Five patients (31%) reported kidney AEs, all of which were mild or moderate in severity. None of the kidney AEs were serious or resulted in treatment interruption or discontinuation.[1]

Four patients (25%) had transient increase in lipase levels, with no reported sign or symptoms of pancreatitis. All instances of lipase increase were of moderate severity and resolve during continued treatment with givosiran.[1]

Table 2. AEs by Parent Study Treatment Group.[1]

n (%)	Placebo-Givosiran Crossover (N=4)	Continuous Givosiran (N=12)	Total Givosiran (N = 16)
Any AE	4 (100)	12 (100)	16 (100)
AEs occurring in ≥25% of patients			
Abdominal pain	1 (25)	7 (58)	8 (50)
Nasopharyngitis	2 (50)	6 (50)	8 (50)
Nausea	2 (50)	6 (50)	8 (50)
ISR[a]	4 (100)	3 (25)	7 (44)
Fatigue	1 (25)	6 (50)	7 (44)
Back pain	2 (50)	3 (25)	5 (31)
Headache	0	5 (42)	5 (31)
Myalgia	2 (50)	3 (25)	5 (31)
Diarrhea	2 (50)	2 (17)	4 (25)
Gastroenteritis	2 (50)	2 (17)	4 (25)
Hypertension	1 (25)	3 (25)	4 (25)
International normalized ratio increased	3 (75)	1 (8)	4 (25)
Lipase increased	1 (25)	3 (25)	4 (25)
Migraine	1 (25)	3 (25)	4 (25)
Oropharyngeal pain	1 (25)	3 (25)	4 (25)
Pain in extremity	2 (50)	2 (17)	4 (25)
Vomiting	1 (25)	3 (25)	4 (25)
AEs of interest			
Hepatic AEs[b]	3 (75)	4 (33)	7 (44)
Kidney AEs[c]	1 (25)	4 (33)	5 (31)
Blood homocysteine increased	1 (25)	0	1 (6)
Any serious AE	1 (25)	6 (50)	7 (44)
Any severe AE	3 (75)	4 (33)	7 (44)
Any AE leading to treatment discontinuation	0	1 (8)	1 (6)
Any AE leading to study withdrawal	0	1 (8)	1 (6)

n (%)	Placebo-Givosiran Crossover (N=4)	Continuous Givosiran (N=12)	Total Givosiran (N = 16)
Death	0	0	0

Abbreviations: AE = adverse event; ISR = injection-site reaction; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query.

[a]Includes all AEs within the MedDRA high-level term of ISR.

[b]Includes all AEs within SMQ *drug-related hepatic disorders*.

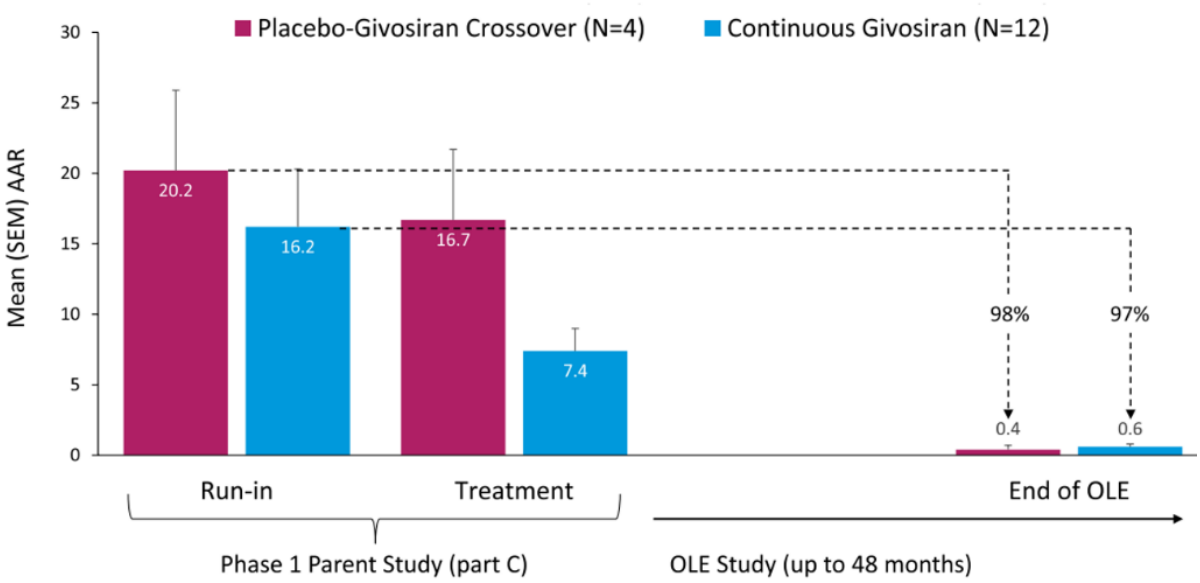
[c]Includes all AEs mapping to SMQ *acute renal failure*.

SECONDARY ENDPOINTS

Clinical Activity

The AAR decreased during long-term monthly treatment with givosiran (**Figure 1**). Across all patients in the Phase 1/2 OLE, a 97% reduction in the mean (SEM) composite AAR was observed from the run-in period of the Phase 1 study (17.0 [3.5]) to the once-monthly givosiran 2.5 mg/kg treatment period in the OLE (0.5 [0.2]). The proportion of patients who were attack-free (by 3-month intervals) increased, and this increase was sustained over time; all patients (100%) were attack-free by the month >33–36 interval and continued to be attack-free until the end of the study (**Figure 2**).[1]

Figure 1. Changes in Composite AAR by Study Group[a,b].[1]



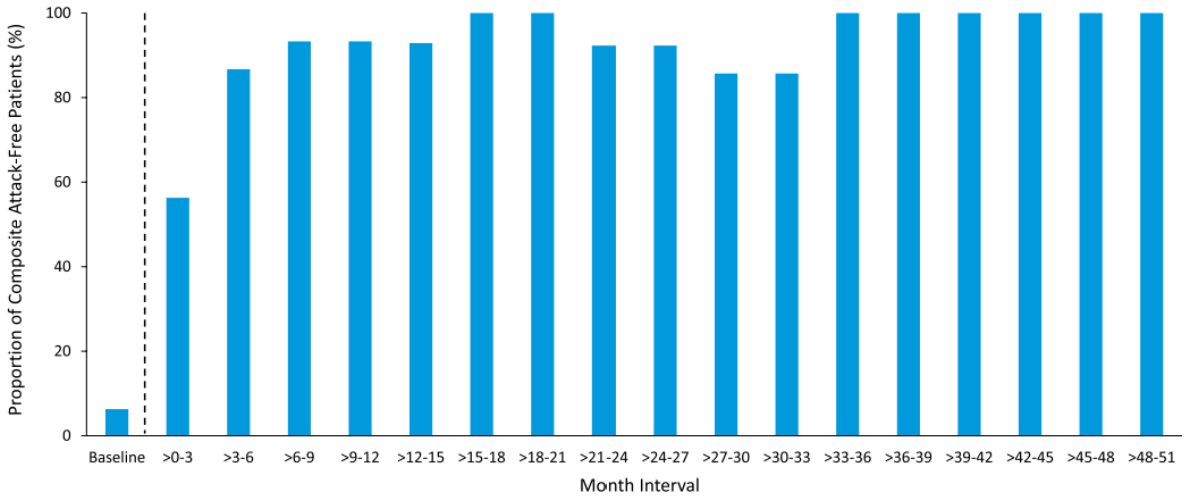
Abbreviations: AAR = annualized attack rate; IV = intravenous; OLE = open-label extension; PY = person-years; SEM = standard error of the mean.

[a]Composite attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home.

[b]Data are aggregated across all dose groups, based on an observation time 4.24 PY in the Phase 1 study run-in period and 53.6 PY during the OLE treatment period.

From Sardh et al.[1]

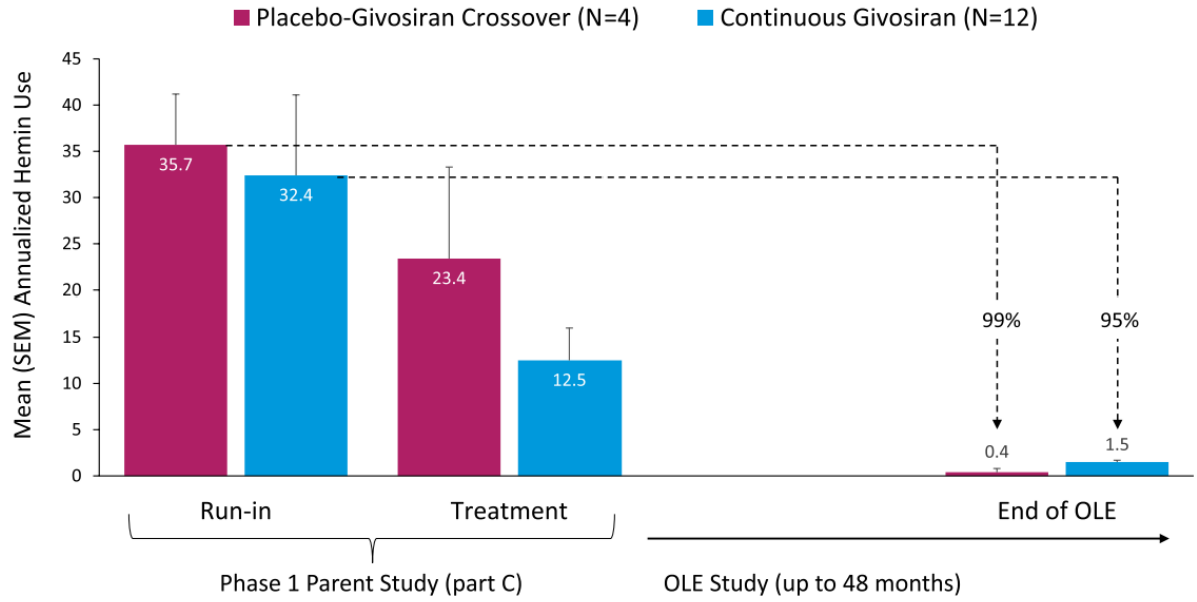
Figure 2. Proportions of Composite Attack-Free Patients by 3-Month Intervals with Givosiran 2.5 mg/kg Once Monthly Treatment[a,b].[1]



Abbreviations: IV = intravenous; OLE = open-label extension; PY = person-years.
[a]Composite attacks included porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.
[b]The dashed line indicates the gap in time between baseline of the Phase 1 study and the first visit in the OLE study. Baseline is defined as the derived baseline value in the Phase 1 study. Data are based on an observation time of 4.24 PY in the Phase 1 study run-in period and 53.6 PY during the OLE treatment period.
From Sardh et al.[1]

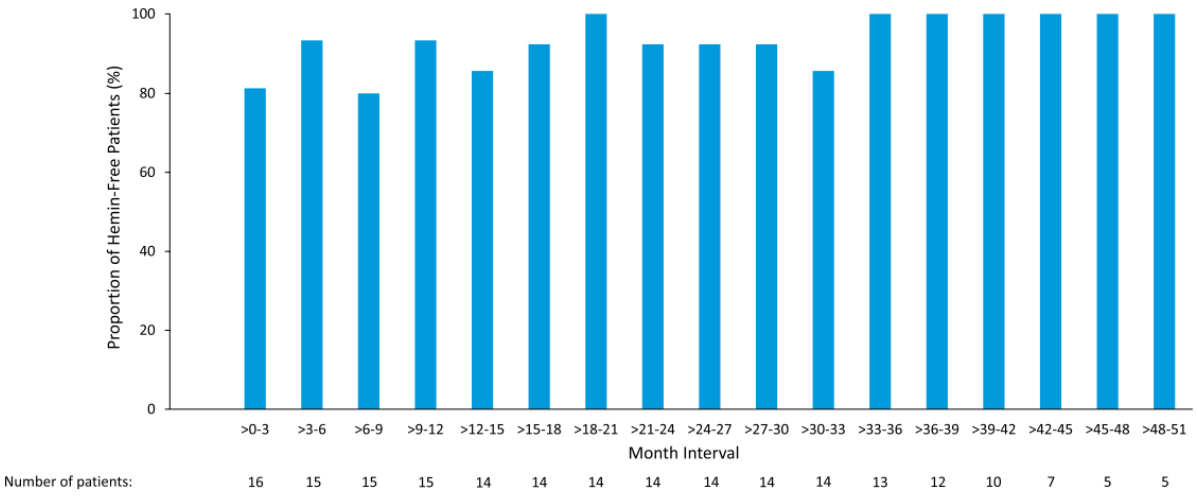
Annualized hemin use substantially decreased during givosiran treatment in both the placebo-givosiran crossover and continuous givosiran treatment groups (**Figure 3**). Across all patients in the Phase 1/2 OLE study, mean (SEM) annualized hemin use decreased from 33.1 (7.0) days during the run-in period in the parent study to 1.2 (0.7) days during treatment with givosiran 2.5 mg/kg once-monthly in the Phase 1/2 OLE, indicating a 96% reduction. Assessment of hemin in 3-month intervals demonstrated that the proportion of patients with 0 days of hemin use increased with time. This increase was sustained, and by months >33 to 36, all patients were hemin-free and remained hemin-free until the end of the Phase 1/2 OLE study (**Figure 4**).[1]

Figure 3. Changes in Annualized Hemin Use[a] by Study Group.[1]



Abbreviations: OLE = open-label extension; PY = person-years; SEM = standard error of the mean.
[a]Data are aggregated across all dose groups, based on an observation time of 4.24 PY in the Phase 1 study run-in period and 53.6 PY during the OLE treatment period treatment period.
From Sardh et al.[1]

Figure 4. Proportions of Hemin-Free Patients by 3-Month Intervals with Givosiran 2.5 mg/kg Once Monthly Treatment[a].[1]

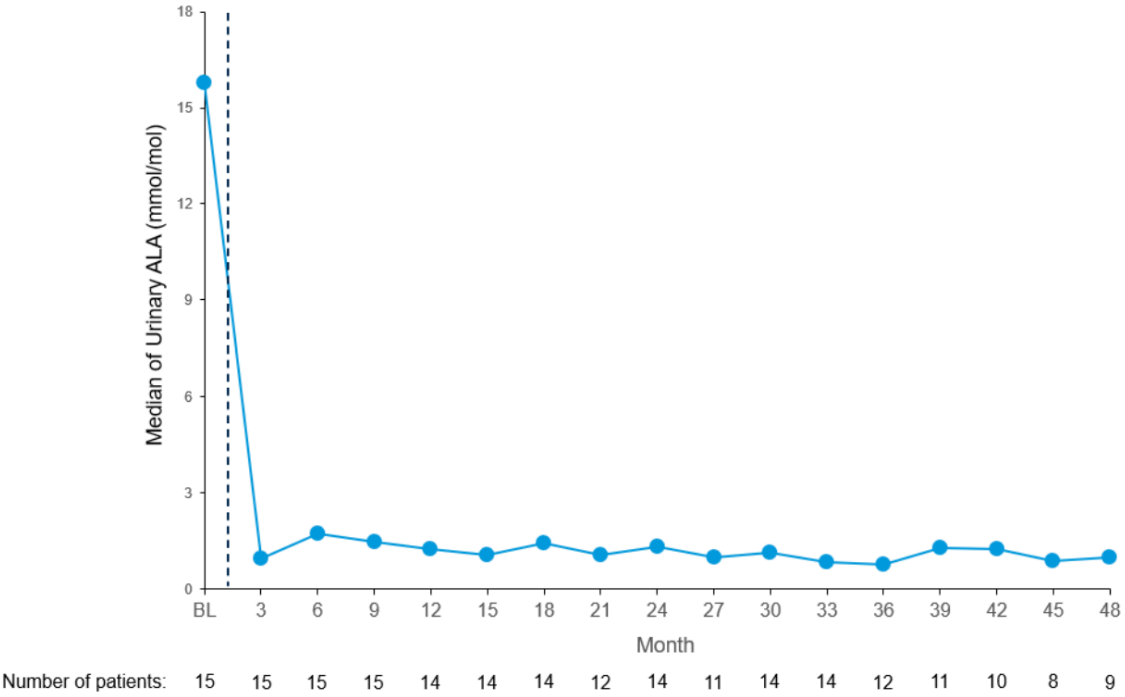


Abbreviations: OLE = open-label extension; PY = person-years.
[a]Data are aggregated across all dose groups, based on an observation time of 4.24 PY in the Phase 1 study run-in period and 53.6 PY during the OLE treatment period.
From Sardh et al.[1]

Urinary ALA, PBG, and *ALAS1* mRNA

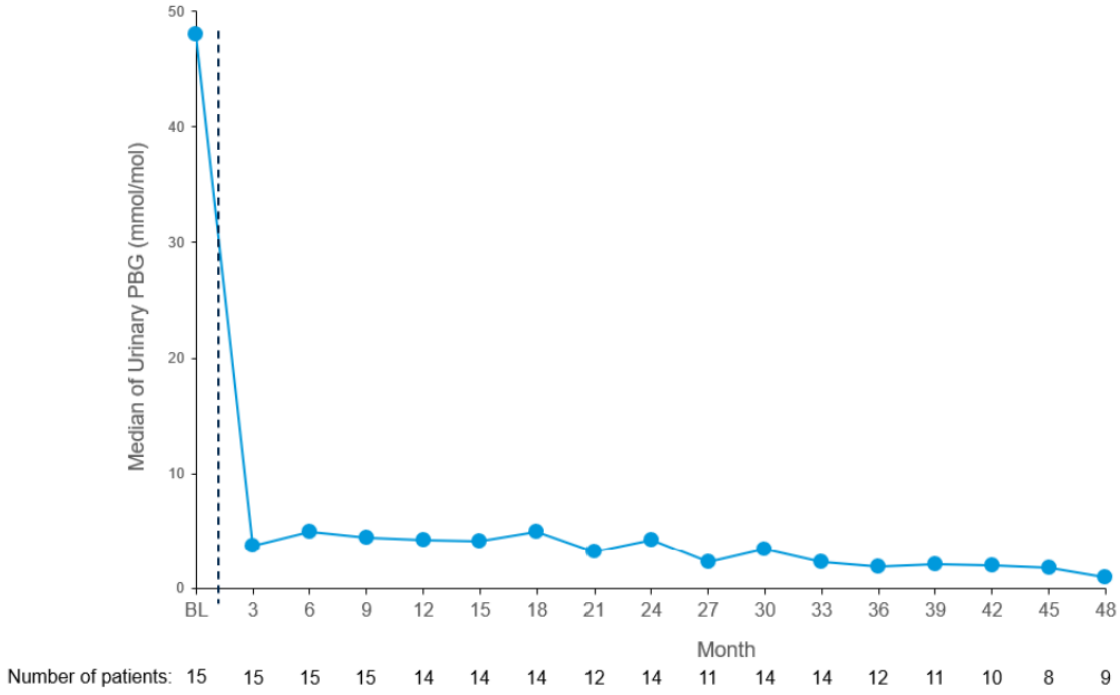
Once-monthly treatment with givosiran led to sustained reductions in urinary ALA and PBG levels through Month 48. Median urinary ALA levels decreased from 15.8 mmol/mol Cr at Phase 1 study baseline to 1.0 mmol/mol Cr at OLE Month 48, representing a median reduction of 95% (ULN for ALA, 1.47 mmol/mol Cr) (**Figure 5**). Median urinary PBG levels decreased from 48.0 mmol/mol Cr at Phase 1 study baseline to 1.0 mmol/mol Cr at OLE Month 48, indicating a median reduction of 98% (ULN for PBG, 0.14 mmol/mol Cr) (**Figure 6**). Circulating hepatic urinary *ALAS1* mRNA levels were assessed through OLE Month 18; samples taken during a porphyria attack were excluded from analysis to reduce potential confounding due to hemin administration. Mean urinary *ALAS1* mRNA level was 3.51 at baseline of the Phase 1 study, which decreased to 1.54 at OLE Month 12, a mean reduction of 58% (**Figure 7**). At OLE Month 18, the *ALAS1* mRNA level was 2.09.[1]

Figure 5. Median Urinary ALA Levels[a,b] (mmol/mol Cr).[2]



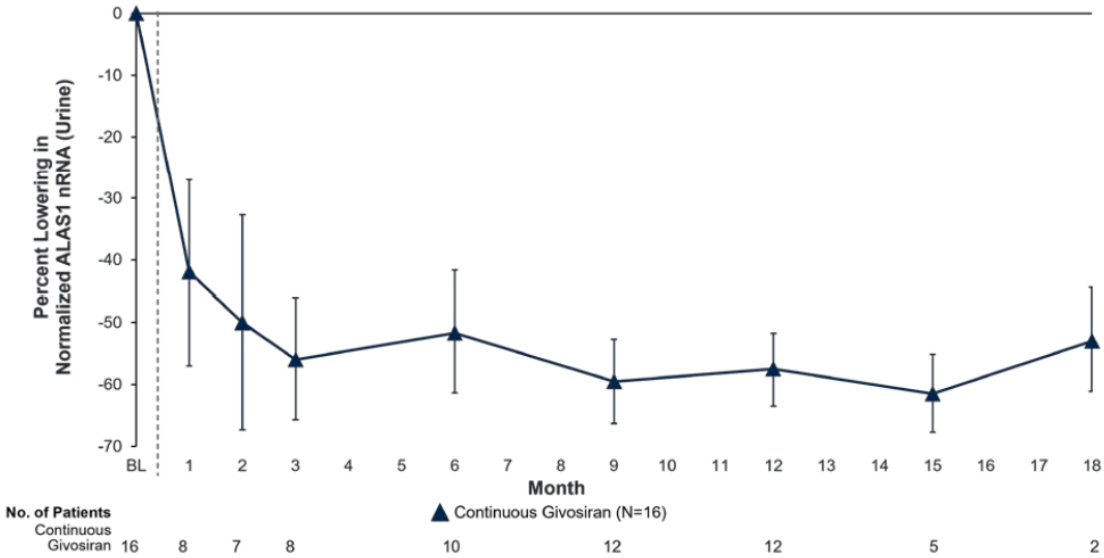
Abbreviations: ALA = 5-aminolevulinic acid; Cr = creatinine; OLE = open-label extension; ULN = upper limit of normal.
[a]Assessed using liquid chromatography-tandem mass spectrometry.
[b]ULN for ALA: 1.47 mmol/mol Cr.
Baseline is defined as the derived baseline value in the Phase 1 study. The dotted line indicates the gap in time between baseline of the Phase 1 study and the first visit in the OLE study.
From Sardh et al.[2]

Figure 6. Median Urinary PBG Levels[a,b] (mmol/mol Cr).[2]



Abbreviations: Cr = creatinine; OLE = open-label extension; PBG = porphobilinogen; ULN = upper limit of normal.
[a]Assessed using liquid chromatography-tandem mass spectrometry.
[b]ULN for PBG: 0.14 mmol/mol Cr.
Baseline is defined as the derived baseline value in the Phase 1 study. The dotted line indicates the gap in time between baseline of the Phase 1 study and the first visit in the OLE study.
From Sardh et al.[2]

Figure 7. Mean (SEM) Percent Lowering of Normalized Urinary Circulating Hepatic *ALAS1* mRNA.[2]



Abbreviations: *ALAS1* = aminolevulinate synthase 1; mRNA = messenger RNA; OLE = open-label extension.
Baseline is defined as the derived baseline value in the Phase 1 study. The dotted line indicates the gap in time between baseline of the Phase 1 study and the first visit in the OLE study.
From Sardh et al.[2]

EXPLORATORY ENDPOINT

The mean (SD) EQ-VAS score increased from 68.9 (20.9) at Phase 1 study baseline to 84.4 (22.4) at OLE Month 48, representing a mean (SD) improvement of 15.8 (13.7) points, indicating a mean improvement of 30%. The mean increase in EQ-VAS of 15.8 points exceeded the EQ-VAS score range estimated to indicate a minimal clinically important difference (~7–10 points) in other chronic disease states. A similar trend was observed in mean (SD) EQ-5D-5L score, which increased from 0.81 (0.11) at Phase 1 study baseline to 0.88 (0.11) at OLE Month 48, representing a mean (SD) improvement of 0.04 (0.09) point (mean improvement of 4.5% from baseline).[1]

ABBREVIATIONS

AAR = annualized attack rate; AE = adverse event; AIP = acute intermittent porphyria; ALA = 5-aminolevulinic acid; *ALAS1* = aminolevulinate synthase 1; ALT = alanine aminotransferase; BMI = body mass index; Cr = creatinine; eGFR = estimated glomerular filtration rate; EKG = electrocardiogram; EQ-5D-5L = Euro Quality of Life Health State Profile Questionnaire; EQ-VAS = EuroQoL visual analogue scale; *HMBS* = hydroxymethylbilane synthase; ISR = injection-site reaction; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; mRNA = messenger RNA; OLE = open-label extension; PBG = Porphobilinogen; PY = patient-years; QoL = quality of life; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SMQ = Standardized MedDRA Query; ULN = upper limit of normal.

Updated 14 August 2025

REFERENCES

1. Sardh E, Balwani M, Rees DC, et al. Long-term follow-up of givosiran treatment in patients with acute intermittent porphyria from a phase 1/2, 48-month open-label extension study. *Orphanet J Rare Dis*. 2024;19(1). doi:10.1186/s13023-024-03284-w
2. Supplement to: Sardh E, Balwani M, Rees DC, et al. Long-term follow-up of givosiran treatment in patients with acute intermittent porphyria from a phase 1/2, 48-month open-label extension study. *Orphanet J Rare Dis*. 2024;19(1). doi:10.1186/s13023-024-03284-w.