Final Results from a Phase 1/2, 48-Month, Open-Label Extension Study of Givosiran in Patients with Acute Intermittent Porphyria

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Introduction

- AHP is a multisystem disease characterized by chronic symptoms, long-term complications, and acute, disabling, and sometimes life-threatening neurovisceral attacks manifesting as severe abdominal pain that can become recurrent[1-3]
- Both acute and chronic symptoms of AHP can be debilitating and impact multiple domains of patient QoL[3]
- AIP is the most common AHP subtype[1]
- Givosiran, a subcutaneously delivered RNA interference therapeutic specifically targeting ALAS1 mRNA in the liver to reduce ALA and PBG,[4] is approved for treatment of AHP in adults and adolescents age ≥12 years in the European Union and adults in the United States[5,6]
- Once-monthly treatment with givosiran resulted in sustained reductions in ALA and PBG levels, and reduction in annualized rate of porphyria attacks and annualized days of hemin use compared to placebo in a phase 1 trial (NCT02452372)[7]
- Here we report results from the phase 1/2 OLE study (NCT02949830) assessing the safety and clinical activity of up to 48 months of givosiran treatment in adults with AIP

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; OLE, open-label extension; QoL, quality of life; PBG, porphobilinogen.

1. Wang B, et al. *Hepatol Commun.* 2019;3:193-206. 2. Elder G, et al. *J Inherit Metab Dis*. 2013;36:849-857. 3. Wheeden K, et al. *Adv Ther*. 2022;39:4330-4335. 4. Balwani M, et al. *N Engl J Med*. 2020;382(24):2289-2301. 5. Givlaari [summary of product characteristics]. 2021. https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf. 6. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2023. 7. Sardh E, et al. *N Engl J Med*. 2019;380:549-558.

Study Design and Methods

PATIENT POPULATION (N=16)[a]

- Age 18-65 years
- Diagnosed with AIP (confirmed *HMBS* mutation), with recurrent porphyria attacks[b]
- Not on scheduled hemin regimen at screening
- ALT <2 × ULN; total bilirubin <2 mg/dL; eGFR >30 mL/min/1.73m^2
- Completed randomized, placebo-controlled phase 1 parent study[1]
  - 3:1 randomization to SC givosiran 2.5 or 5.0 mg/kg vs placebo for 12 weeks, following run-in period (4–24 weeks)
  - Follow up for additional 12 weeks after last injection

GIVOSIRAN TREATMENT UP TO 48 MONTHS

Phase 1/2 OLE: All patients received givosiran

Givosiran dosing

- **Patients initially received either 2.5 mg/kg once monthly, 5.0 mg/kg once monthly, or 5.0 mg/kg once every 3 months (as per phase 1 study protocol)**
- **2.5 mg/kg once monthly starting August 2017[c]**

ENDPOINTS

- **Primary**
  - Incidence of AEs
- **Secondary**
  - Change in urinary ALA and PBG levels
  - Porphyria attack frequency and characteristics
  - Change in hemin administration

AE, adverse event; AIP, acute intermediate porphyria; ALA, delta-aminolevulinic acid; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HMBS, hydroxymethylbilane synthase; OLE, open-label extension; PBG, porphobilinogen; PK/PD, pharmacokinetic/pharmacodynamic; SC; subcutaneous; ULN, upper limit of normal. [a]Phase 1 parent study group: continuous givosiran (N=12); placebo crossover (N=4). [b]Recurrent porphyria attacks defined as ≥2 porphyria attacks during previous 6 months without hemin, or on scheduled hemin regimen to prevent porphyria attacks at start of phase 1 study run-in period. [c]Patients were transitioned to givosiran 2.5 mg/kg once monthly starting in August 2017 based on emerging safety, efficacy, and PK/PD modeling data from the phase 1 study and remained on this dose for the OLE study duration. 1. Sardh E et al. *N Engl J Med.* 2019;380:549-558.

Patient Demographics and Characteristics[a]

Demographic/Characteristic	Placebo–Givosiran Crossover (N=4)	Continuous Givosiran (N=12)	Total Givosiran (N=16)
Age at screening, years, median (range)	42 (27–60)	37.5 (21–59)	39.5 (21–60)
Female, n (%)	2 (50)	12 (100)	14 (87.5)
White, n (%)	4 (100)	9 (75)	13 (81)
Number of porphyria attacks[b] during 12 months before enrollment in phase 1 study, median (min, max)	10 (5, 50)	9.5 (0, 36)	10 (0, 50)
Any hemin use during an attack prior to phase 1 study enrollment, n (%)	4 (100)	12 (100)	16 (100)
Hemin use on scheduled basis just before phase 1 study enrollment, n (%)	2 (50)	6 (50)	8 (50)
Other prior treatment for porphyria, n (%)			
Hormone suppression therapy	0	4 (33)	4 (25)
High carbohydrate diet	2 (50)	5 (42)	7 (44)
Glucose infusion	2 (50)	8 (67)	10 (63)
Other treatment	0	4 (33)	4 (25)
Baseline urinary ALA, mmol/mol Cr, median (min, max)	16.7 (7.5, 33.9) (n=4)	15.4 (1.5, 50.5) (n=11)	15.8 (1.54, 50.5) (n=15)
Baseline urinary PBG, mmol/mol Cr, median (min, max)	46.3 (30.8, 51.8)	54.0 (3.2, 95.3)	48.0 (3.2, 95.3)

ALA, delta-aminolevulinic acid; Cr, creatinine; PBG, porphobilinogen. [a]Includes patients who received ≥1 dose of givosiran. [b]Represents all porphyria attacks, including attacks requiring hospitalization, urgent healthcare visit, or IV hemin treatment at home, and attacks treated at home without hemin.

Safety Summary

- Median (min, max) total administered givosiran doses were 43.5 (1, 49) doses; median total exposure duration was 48 (2.1, 49) months
- Seven (43.8%) patients experienced ≥1 SAE
  - One had an SAE of anaphylactic reaction considered related to givosiran; the event resolved and the patient withdrew from the study
  - The other 6 had SAEs that were not considered to be related to givosiran
- The most frequently reported AEs were abdominal pain (N=8, 50%), nasopharyngitis (N=8, 50%), nausea (N=8, 50%), fatigue (N=7, 44%), and injection-site reactions (N=7, 44%)
- The most common treatment-related AEs (>2 patients) were injection-site erythema (N=6, 38%) and injection-site pruritus (N=4, 25%)
  - Other injection-site reactions affecting ≥2 patients included rash, swelling, and discoloration
  - All injection-site reactions were mild to moderate in severity and did not lead to study withdrawal or treatment discontinuation
- One patient experienced mild elevation of blood homocysteine, which did not lead to change in givosiran treatment
- No patients interrupted treatment or discontinued givosiran due to hepatic or renal AEs
- No deaths occurred

AE, adverse event; SAE, serious adverse event.

Results: Most Common Adverse Events[a]

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)
Fatigue	1 (25)	6 (50)	7 (44)
Injection-site erythema	3 (75)	3 (25)	6 (37.5)
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)
Injection-site pruritus	2 (50)	2 (17)	4 (25)
INR 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)

AE, adverse event; INR, international normalized ratio. [a]AEs that occurred or worsened in severity on or after the first dose date/time of givosiran and within 28 days of the last dose are included. AEs that occurred in the placebo crossover group prior to givosiran are not included.

Results: AEs[a]

n (%)	Placebo–Givosiran Crossover (N=4)	Continuous Givosiran (N=12)	Total Givosiran (N=16)
Any serious AE	1 (25)	6 (50)	7 (44)
Serious AEs			
Abdominal pain	0	2 (17)	2 (13)
Anaphylactic reaction	0	1 (8)	1 (6)
Clostridium difficile colitis	0	1 (8)	1 (6)
Deep vein thrombosis	1 (25)	0	1 (6)
Dyspnea	0	1 (8)	1 (6)
Forearm fracture	1 (25)	0	1 (6)
Lower limb fracture	1 (25)	0	1 (6)
Mental status changes	0	1 (8)	1 (6)
Pyrexia	0	1 (8)	1 (6)
Respiratory tract infection	0	1 (8)	1 (6)
Sinusitis bacterial	0	1 (8)	1 (6)
Synovitis	0	1 (8)	1 (6)
Tonsilitis	0	1 (8)	1 (6)
Hepatic AEs[b]	3 (75)	4 (33)	7 (44)
Renal AEs[c]	1 (25)	4 (33)	5 (31)
Blood homocysteine increased[d]	1 (25)	0	1 (6)

- One patient discontinued treatment and withdrew from the study due to an SAE of anaphylactic reaction that was considered related to treatment

AE, adverse event; SAE, serious adverse event. [a]AEs that occurred or worsened in severity on or after the first dose date/time of givosiran and within 28 days of the last dose are included. AEs that occurred in the placebo crossover group prior to givosiran are not included. [b]Includes all AEs within SMQ *drug-related hepatic disorders*. [c]Includes all AEs within SMQ *acute renal failure*. [d]Considered treatment-related AE.

Individual Research Results

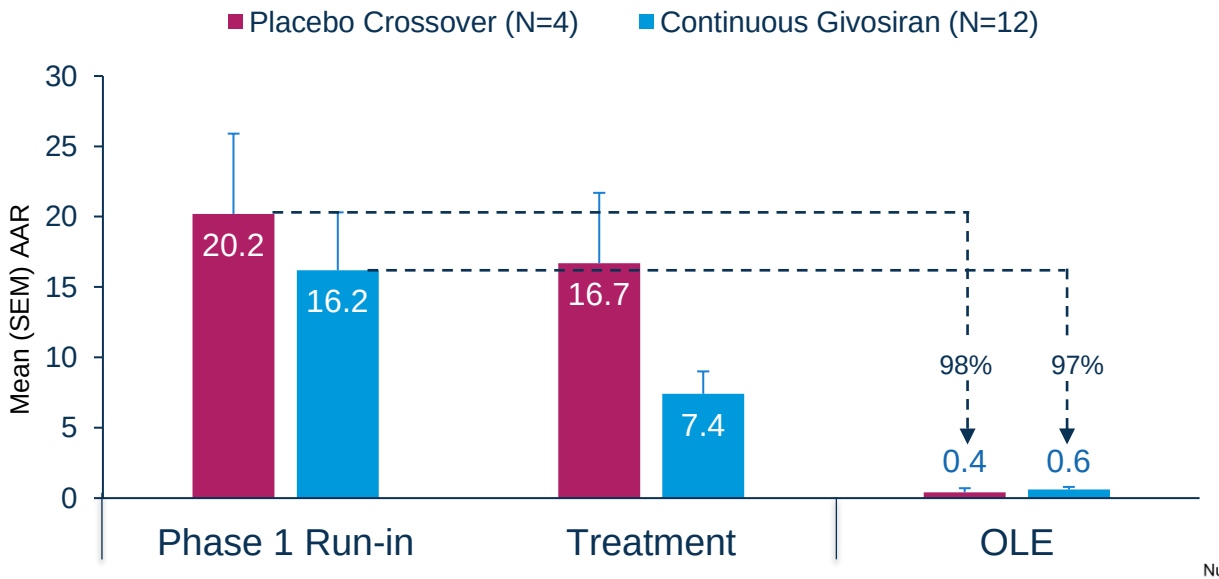
- No patients interrupted treatment or discontinued givosiran due to hepatic or renal AEs
- Seven patients had hepatic AEs
  - Hepatic events: INR increase (4 patients), GGT increase (3 patients), ALT increase and AST increase (2 patients each), and increases in bilirubin conjugated, blood bilirubin, liver function test, and transaminases (1 patient each)
  - No hepatic AEs were serious, and most were mild or moderate in severity; all hepatic AEs resolved with continued givosiran treatment
- Five patients had renal AEs
  - Renal events: GFR decreased (3 patients), renal impairment (2 patients; both with long-standing histories of renal impairment and hypertension), blood creatinine increased (2 patients), protein urine present (1 patient), and urine output decreased (1 patient)
  - No renal AEs were serious; all were mild or moderate in severity
- One patient had a mild elevation in blood homocysteine, deemed possibly related to givosiran

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; INR, international normalized ratio.

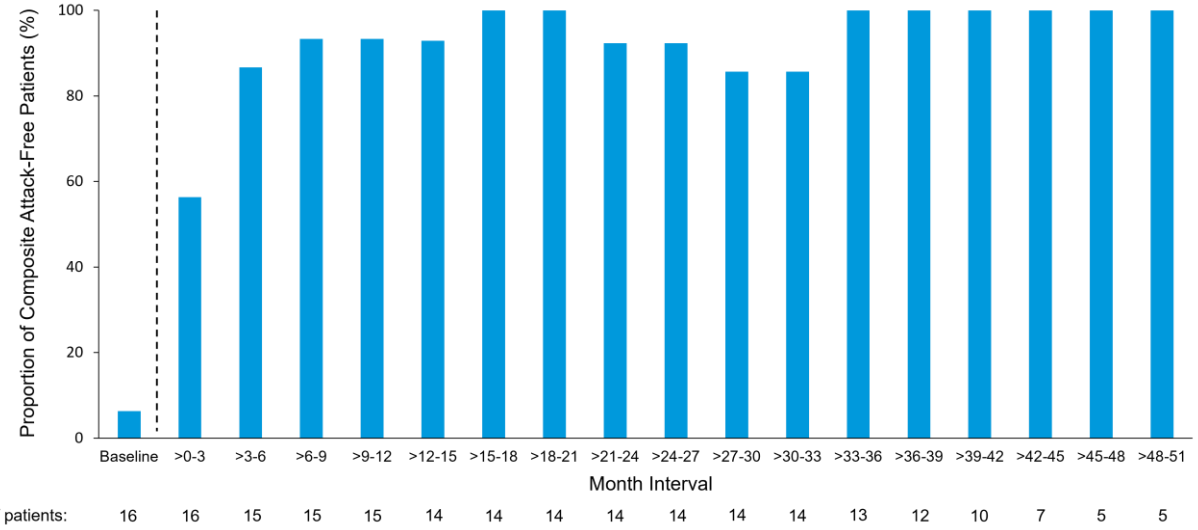
Results: Change in Annualized Attack Rate

- Long-term treatment with givosiran 2.5 mg/kg monthly reduced the overall mean composite AAR by 98% during the phase 1/2 OLE period relative to the phase 1 run-in period
- The attack-free proportion of patients increased over time and was sustained; all patients (100%) were free of attacks by the month >33-36 interval and continued free of attacks until the end of the study

Change in Composite AAR[a,b] by OLE Study Group



Proportion of Composite Attack[a]-Free Patients, by 3-Month Intervals During Treatment with Givosiran 2.5 mg/kg Once Monthly[c]



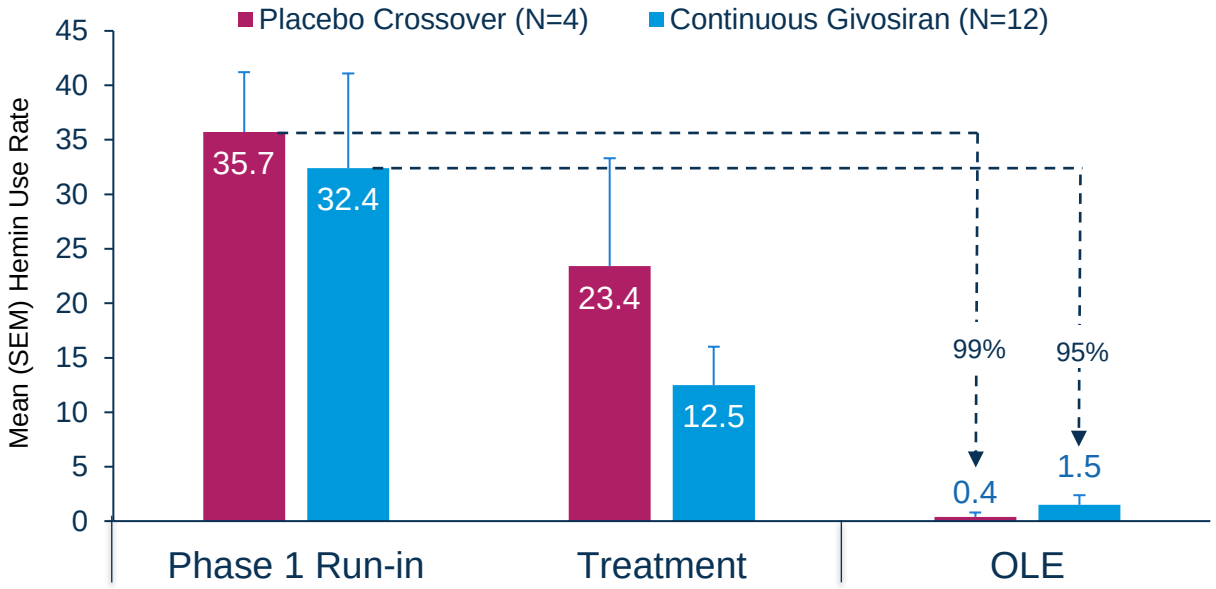
AAR, annualized attack rate; OLE, open-label extension; SEM, standard error of the mean. [a]Composite attacks include porphyria attacks requiring hospitalization, urgent health care facility visit, or IV hemin administration at home. [b]Data are aggregated across all dose groups. Mean time in phase 1 run-in and treatment periods of 103 days and 165 days, respectively; mean time in OLE period of 733 days. [c]The dashed line indicates the gap in time that existed between part C of the phase 1 study and the first visit in the current study (phase 1/2 OLE study).

Results: Change in Hemin Use

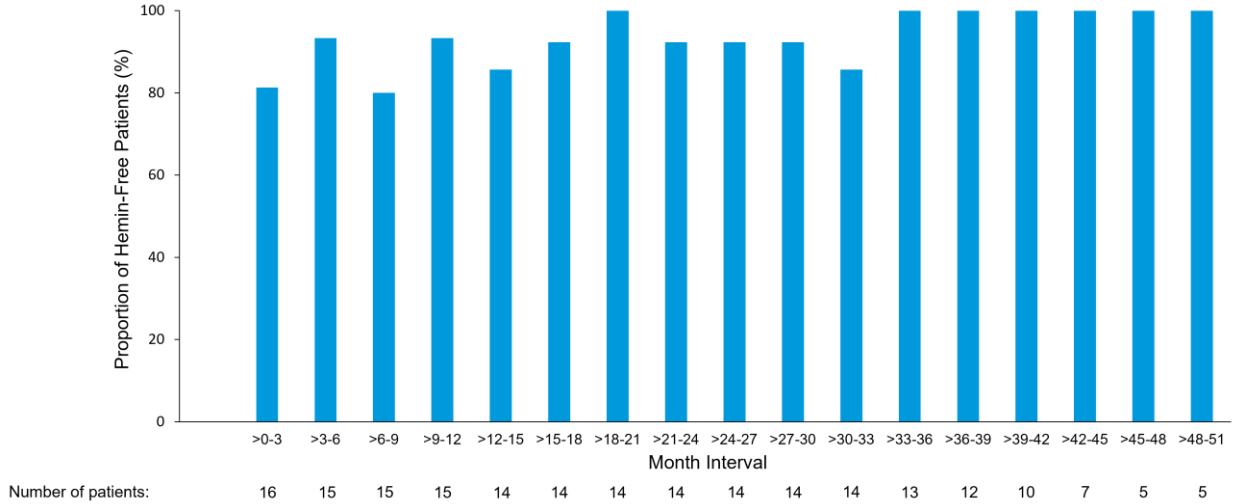
- Long-term treatment with givosiran 2.5 mg/kg monthly reduced the overall mean annualized days of hemin use by 97% during the phase 1/2 OLE period relative to the phase 1 run-in period

- The proportion of patients with 0 days of hemin use increased over time and was sustained; all patients (100%) were hemin-free by the month >33-36 interval and continued free of hemin use until the end of the study

Change in Hemin Use[a] by OLE Study Group



Proportion of Hemin-Free Patients, by 3-Month Intervals During Treatment with Givosiran 2.5 mg/kg Once Monthly[a]



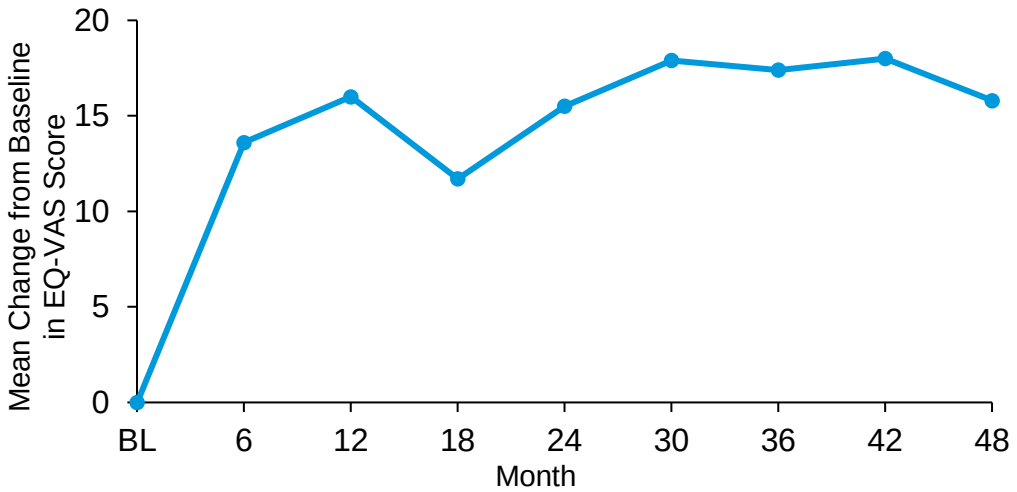
OLE, open-label extension; SEM, standard error of the mean. [a]Data are aggregated across all dose groups. Mean time in phase 1 run-in and treatment periods of 103 days and 165 days, respectively; mean time in OLE period of 733 days.

Results: QoL Evaluation

Treatment with givosiran resulted in QoL improvements, assessed by self-rated EQ-VAS and EQ-5D-5L index score

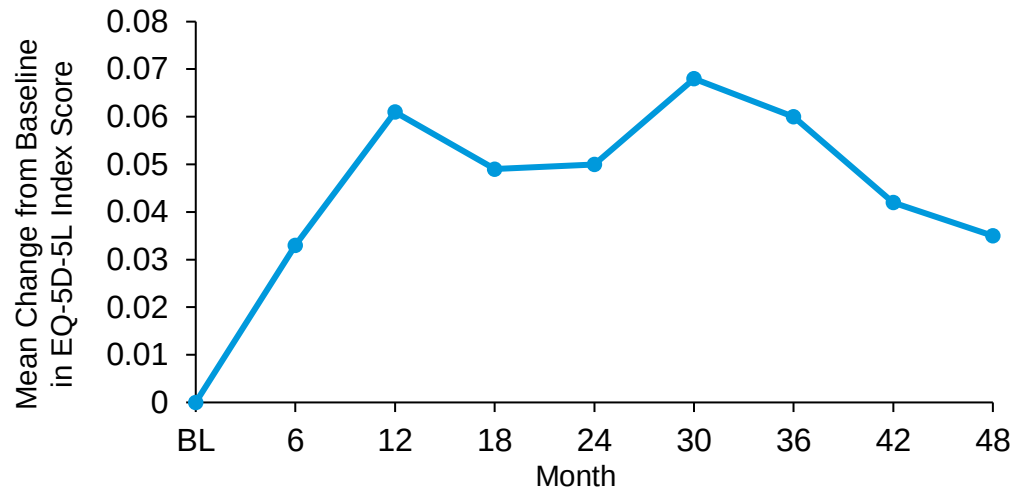
- Mean EQ-VAS score increased from 68.9 points at baseline to 84.4 points at month 48, a mean improvement of 30%
- Mean increase in EQ-VAS of 15.8 points exceeds the range of scores estimated to represent a minimal clinically important difference for the EQ-VAS in other chronic diseases (approximately 7–10 points)[1,2]

Change in EQ-VAS[a]



- Mean EQ-5D-5L index score increased from 0.81 points at baseline to 0.88 points at month 48, a mean improvement of 5%

Change in EQ-5D-5L[b]



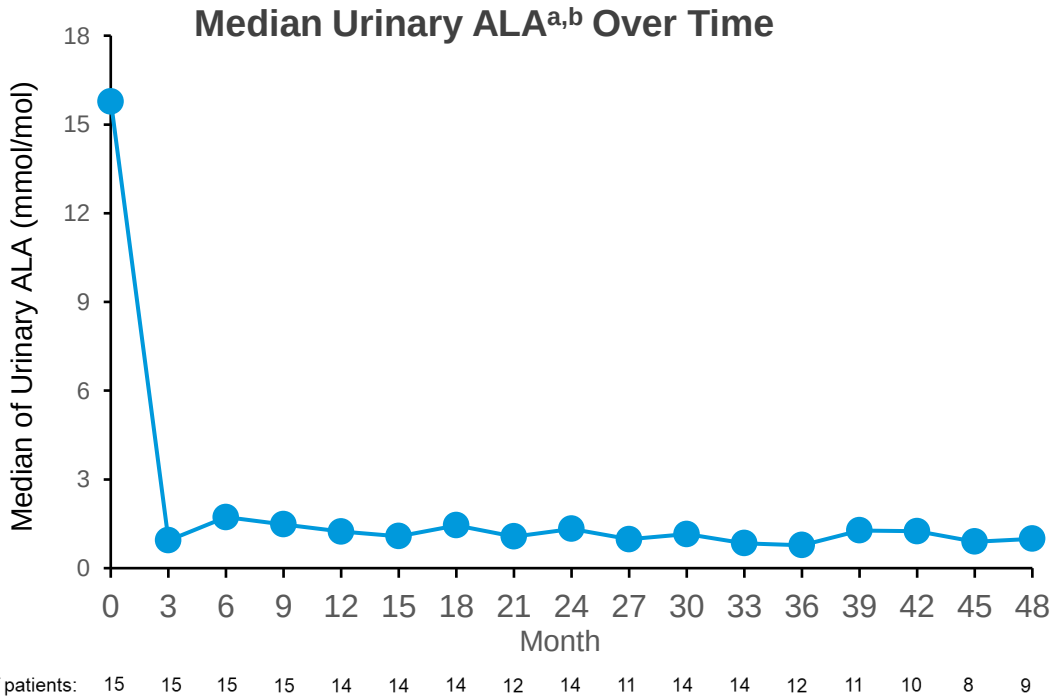
EQ-5D-5L, Euro Quality of Life Health State Profile Questionnaire; EQ-VAS, EuroQol visual analog scale; QoL, quality of life. [a]The EQ-VAS is a self-rated measure of global health status ranging from 0 (worst imaginable health) to 100 (best imaginable health). [b]The EQ-5D-5L summarizes measurements for each of 5 domains (mobility, self care, usual activities, pain/discomfort and anxiety/depression).

1. Zanini A et al. *Respir Care*. 2015;60:88-95. 2. Pickard AS et al. *Health Qual Life Outcomes.* 2007;5:70.

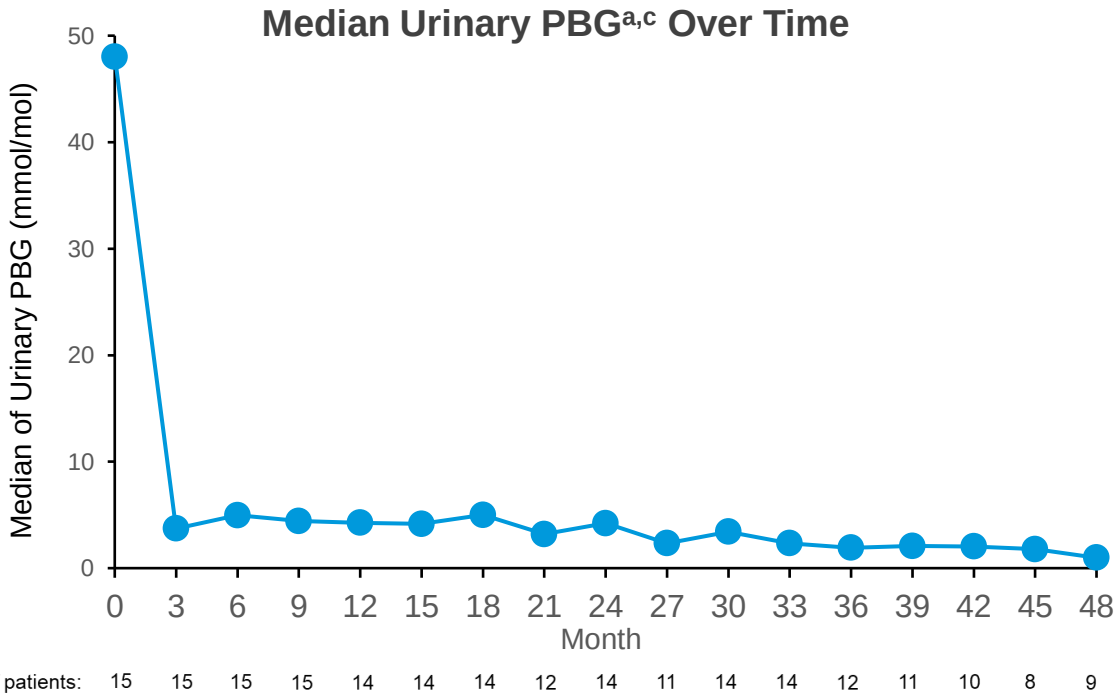
Results: ALA and PBG

Treatment with givosiran led to sustained reductions in urinary ALA and PBG levels

- Median urinary ALA levels decreased from 15.8 mmol/mol Cr at baseline to 1.0 mmol/mol Cr at month 48, a reduction of 95%



- Median urinary PBG levels decreased from 48.0 mmol/mol Cr at baseline to 1.0 mmol/mol Cr at month 48, a reduction of 98%



ALA, delta-aminolevulinic acid; Cr, creatinine; PBG, porphobilinogen; ULN, upper limit of normal. [a]Assessed using liquid chromatography-tandem mass spectrometry. [b]ULN for ALA: 1.47 mmol/mol Cr.[1] [c]ULN for PBG: 0.14 mmol/mol Cr.[1]

1. Agarwal S, et al. *JIMD Rep.* 2021;57:85-93.

Conclusions

- The final analysis of the givosiran phase 1/2 OLE study demonstrates that long-term givosiran dosing (up to 4 years) provides sustained and continuous benefit to patients with AIP
- Givosiran 2.5 mg/kg had an acceptable safety profile; most AEs were mild-to-moderate in severity
  - One patient with an SAE of anaphylactic reaction discontinued treatment and withdrew from the study
  - Injection-site reactions were mild or moderate in severity and did not lead to treatment discontinuation
  - The most common treatment-related AEs were injection-site erythema and injection-site pruritus
  - No patients interrupted or discontinued givosiran due to hepatic or renal AEs
- Long-term givosiran treatment improved clinical outcome measures, including porphyria attack rates, hemin use rates, and QoL measures
  - The annualized rate of porphyria attacks was reduced by 98%, and annualized days of hemin use by 97%
  - The proportion of patients free of porphyria attacks and hemin use increased over time and all evaluable patients had no attacks and hemin use on or after the month 33-36 interval
  - Mean EQ-VAS score increased by 15.8 points from baseline, representing a 30% improvement
- Long-term givosiran treatment demonstrated sustained reductions in ALA and PBG levels
- Safety and efficacy results of the phase 1/2 OLE study are consistent with the results of the ENVISION phase 3 study[1]

AE, adverse event; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; EQ-VAS, EuroQol visual analog scale; OLE, open-label extension; PBG, porphobilinogen; QoL, quality of life; SAE, serious adverse event.

1. Kuter DJ, et al. Poster presented at the Annual Meeting and Exposition of the American Society of Hematology, December 11-14, 2021; Atlanta, GA & Virtual.

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