Givosiran: Use in Pediatric Patients

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for GIVLAARI® (givosiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP.[1]
  - Per the ENVISION study protocol, patients ≥12 years of age were eligible to be included in the study and the youngest patient enrolled was 19 years of age.[1,2]
- The ELEVATE registry (NCT04883905) is a global, prospective, observational study designed to characterize the real-world long-term safety and efficacy of givosiran and to describe the natural history and management of patients with AHP.[3,4]
  - The youngest patient enrolled that received givosiran was 14 years of age.[4] Prospective data collection is ongoing.[3,4]
- Additional case reports on the use of givosiran in pediatric patients are provided below.

INDEX

CLINICAL DATA

ENVISION Study

The ENVISION study was a phase 3, 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 (n=48) or placebo (n=46) once a month for 6 months, followed by an optional 30-month OLE. The primary endpoint was the annualized rate of composite porphyria attacks among patients with AIP at 6 months.[1]

Per the ENVISION study protocol, patients ≥12 years of age were eligible to be included in the study.[2] The youngest patient enrolled in the study was 19 years of age, as shown in **Table 1**.[1]

Table 1. Age of Enrolled Patients at Baseline in ENVISION.[1]

	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)

ELEVATE Registry

The ELEVATE registry (NCT04883905) is a global, prospective, observational study designed to characterize the real-world long-term safety and efficacy of givosiran and to describe the natural history and management of patients with AHP. Patient demographic characteristics at enrollment are available for 166 patients, the youngest patient enrolled that received givosiran was 14 years of age.[3,4]

Prospective data collection is ongoing.[3,4] No additional data from clinical studies are available regarding the use of givosiran in pediatric patients.

CASE REPORTS

The following information provides an overview of published case reports of pediatric patients who received givosiran. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Rudnick SB, West NE, Fong K, Beaven SW, VanderVeen NT. Acute intermittent porphyria in an adolescent patient: Diagnostic and treatment challenges. *Cureus*. 2024;16(11):e74784. Published 2024 Nov 29. doi:10.7759/cureus.74784[5]

- A case report discussed a 17-year old previously heathy female patient with multiple presentations to the hospital for intense bouts of abdominal pain, nausea, vomiting, and seizure-like activity. On a later admission, porphyria tests were performed and a diagnosis of AIP was made. Genetic analysis confirmed a heterozygous mutation in the HMBS gene.
- The patient was started on IV hemin 3 mg/kg/day for 4 days, then increased to 4 mg/kg/day for 14 days due to suboptimal treatment response. Her nausea improved, but she experienced only mild improvement of abdominal pain despite normalization of her porphyria studies.
- Her course was complicated by diagnostic delays, language barrier, and challenges managing severe refractory pain requiring prolonged courses of hemin in addition to a multimodal pain plan.
- The patient was started on givosiran 2.5 mg/kg SC once monthly, and discharged home after her pain was adequately controlled and the porphyria flare was treated. She continued givosiran on an outpatient basis. A review of her medical records later showed that she remained asymptomatic since discharge and continued givosiran treatment, trigger avoidance, and laboratory monitoring.

Bujold KE, Kasher N, McKiernan C. Givosiran for the treatment of pediatric acute intermittent porphyria. *J Pediatr Hematol Oncol*.2024;46(7):e524-e527. doi:10.1097/MPH.0000000000002941[6]

- A case report discussed the use of givosiran in a 16-year old female patient with medical history of anorexia nervosa who was admitted to the hospital for 4 days of worsening generalized abdominal pain with bilateral radiation to the back, intermittent nonbloody nonbilious emesis, pleuritic chest pain, and constipation. Abdominal/pelvic CT and laboratory findings were unremarkable, and she was discharged home after her symptoms resolved.

- Three months later, the patient was admitted to the hospital with a similar presentation and a 6-kg weight loss. In addition to diffuse generalized abdominal pain, the patient was significant for tachycardia and hypertension on examination. The abdominal radiograph showed mild colonic ileus for which osmotic laxatives were given. On day 2, the patient reported paresthesias of her bilateral upper and lower extremities, which progressed to contractures of her hands. On hospital day 3, the patient had generalized tonic-clonic seizure and hyponatremia. Urine PBG, total plasma porphyrins, and urine PBG:creatinine ratio were elevated, consistent with AHP.
- She received IV carbohydrate loading and hemin infusions and was discharged after her pain was resolved, 4 days later. The pathogenic variant c.77G>A (p.Arg26His) of the HMBS gene was later identified with confirmatory genetic testing.
- Over the next 3 months, the patient was treated with 2 additional hemin infusions for AIP attacks and later started on givosiran due to the frequency and severity of her attacks. After 1 month of givosiran treatment, the patient developed hyperhomocystenemia, and vitamin B6 was initiated. There was an improvement of hyperhomocystenemia after 1 month of vitamin B6 supplementation. Creatinine levels ranged from 1.1 to 1.2 mg/dL after starting givosiran (before givosiran, the range was 0.6 to 1.0 mg/dL). Symptoms of diffuse abdominal and back pain resolved, and additional hemin was not required after starting givosiran.

Mazzoli M, et al. Recovery of chronic motor neuropathy due to acute intermittent porphyria after givosiran treatment in a young boy: A case report. *Eur Rev Med Pharmacol Sci*. 2024;28(8):3268-3274. doi:10.26355/eurrev_202404_36055[7]

- A case report detailed the treatment outcome of a 12-year-old patient with AIP and severe chronic porphyric neuropathy. The patient was diagnosed at 5 years of age after an acute porphyric attack, and genetic analysis confirmed a pathogenic mutation in the HMBS gene.
- The patient was initially treated with routine heme arginate infusions and continued to experience frequent porphyric attacks. The patient's neuropathy progressively worsened over time, necessitating the use of a wheelchair due to severe walking impairment. Later, the patient developed mild weakness of hand muscles and a chronic pain disorder. Givosiran treatment was initiated at 2.5 mg/kg monthly. Clinical assessments were performed at baseline and at 3, 6, 9, and 12 months after treatment initiation with givosiran. Neurophysiologic evaluations were performed at baseline and at 6 and 12 months after treatment initiation.
- During the 12 months of givosiran treatment, there were no acute porphyric attacks, and urinary ALA and PBG levels decreased. No SAEs were reported, and heme arginate infusions were discontinued at the beginning of treatment. Neurological scales demonstrated improvement in distal limb muscle strength, pain, disability, and QOL.

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The INDICATIONS AND USAGE section provides the following information[8]:

GIVLAARI is indicated for the treatment of adults with acute hepatic porphyria (AHP).

The USE IN SPECIFIC POPULATIONS section provides the following information[8]:

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ABBREVIATIONS

ADP = ALAD deficient porphyria; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ALA = aminolevulinic acid; CT = computed tomography; HCP = hereditary coproporphyria; HMBS = hydroxymethylbilane synthase; IV = intravenous; OLE = open-label extension; PBG = porphobilinogen; QOL = quality of life; SAE = serious adverse event; VP = variegate porphyria.

Updated 02 September 2025

REFERENCES

1. Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. *J Hepatol*. 2023;79(5):1150-1158. doi:10.1016/j.jhep.2023.06.013
2. Protocol for: Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med*. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1913147
3. Sardh E, Cassiman D, Gouya L, et al. Patient demographics and clinical characteristics at enrolment in ELEVATE, an international registry of acute hepatic porphyria. Presented at: International Congress of Porphyrins and Porphyrias (ICPP); September 21-25, 2024; Pamplona, Spain.
4. Wang B, Cassiman D, Gouya L, et al. Characteristics of patients treated with givosiran in ELEVATE, a global observational longitudinal registry of patients with acute hepatic porphyria. Presented at: American Association for the Study of Liver Diseases (AASLD) The Liver Meeting; November 10-14, 2023; Boston, MA, USA.
5. Rudnick SB, West NE, Fong K, Beaven SW, VanderVeen NT. Acute intermittent porphyria in an adolescent patient: Diagnostic and treatment challenges. *Cureus*. 2024. doi:10.7759/cureus.74784
6. Bujold KE, Kasher N, McKiernan C. Givosiran for the treatment of pediatric acute intermittent porphyria. *J Pediatr Hematol Oncol*. 2024;46(7):E524-E527. doi:10.1097/MPH.0000000000002941
7. Mazzoli M, Ricci A, Vaudano AE, et al. Recovery of chronic motor neuropathy due to acute intermittent porphyria after givosiran treatment in a young boy: a case report. *European review for medical and pharmacological sciences*. 2024;28(8):3268-3274. doi:10.26355/eurrev_202404_36055
8. GIVLAARI (givosiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.