GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

For adults with acute hepatic porphyria (AHP), including **acute intermittent porphyria (AIP)**,

GIVLAARI® (givosiran) SIGNIFICANTLY REDUCED ATTACKS[1,2]

70% fewer attacks

on average with GIVLAARI vs placebo[1]*

Attacks were defined as those requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.[1]

*Based on results during the 6-month double-blind period of the ENVISION trial in patients with AHP.[1]

For more information about the ENVISION trial, please see page 6.

INDICATION

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

IMPORTANT SAFETY INFORMATION

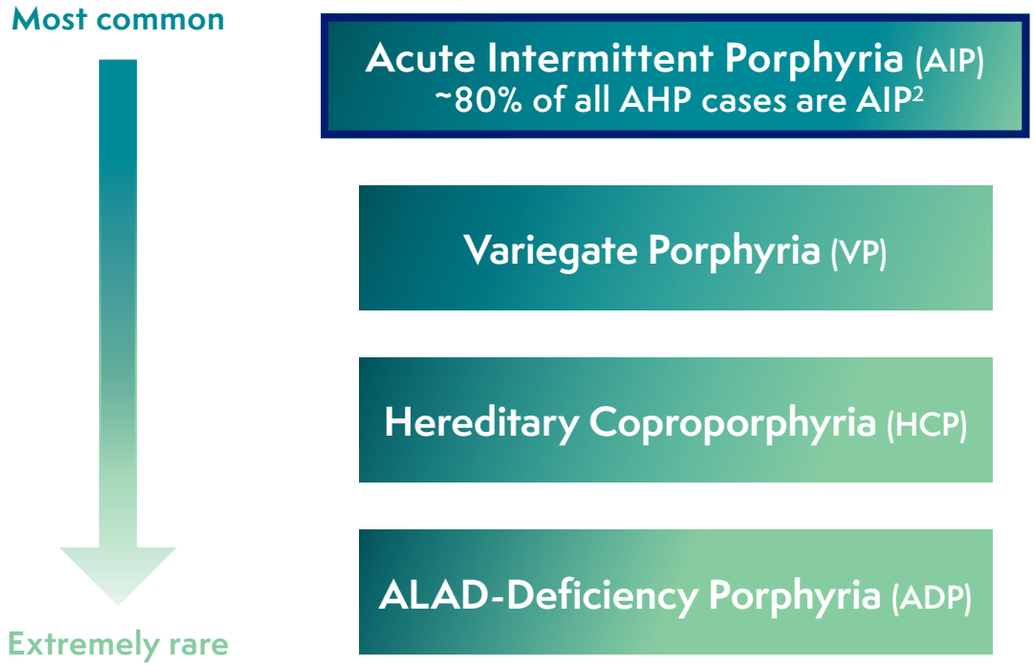
Contraindications

GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis.

Please see Important Safety Information on page 21 and full Prescribing Information.

AHP is a rare, genetic disease characterized by debilitating, potentially life-threatening attacks[2,3]

There are 4 types of acute hepatic porphyria (AHP)[2,4]



AHP attacks can be unpredictable, severe, and progressive[2]

- AHP is most commonly seen in women of childbearing age[4]
- Attacks generally last 3 to 7 days, but recovery can take longer[2,5]
- Severe attacks may progress to respiratory failure or paralysis, leading to temporary or permanent disability[3,5]
- In one study, patients with recurrent attacks averaged 5 hospitalizations in a 12-month period[6*]
- Some patients with AHP may develop long-term complications, such as hypertension, chronic kidney disease (CKD), and hepatocellular carcinoma (HCC)[5]

"The first thing I think when I hear porphyria is, debilitating."
—Lina, a real patient with AIP

*Results from EXPLORE, a 12-month prospective natural history study of 112 patients who experienced recurrent AHP attacks (≥3 attacks/year) or received prophylactic treatment. Attacks were defined as those requiring increased pain medication or carbohydrate intake, hemin administration, and/or hospitalization for signs and symptoms of AHP.[6]

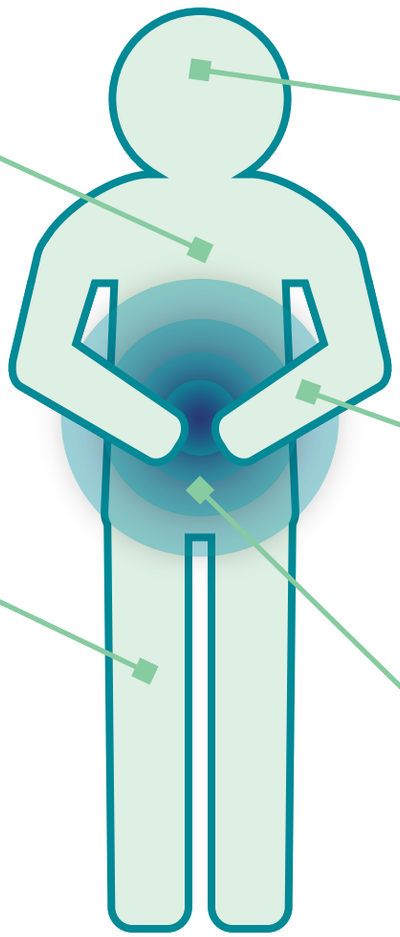
AHP=acute hepatic porphyria; ALAD=delta-aminolevulinic acid dehydratase.

Common signs and symptoms of an AHP attack[3,7,8]

Severe, diffuse abdominal pain[7,8†]

+

1 or more of the following



AUTONOMIC
Nervous System[7,8]

- Nausea/vomiting
- Constipation
- Tachycardia
- Systemic arterial hypertension

CENTRAL
Nervous System[3,7,8]

- Seizures
- Anxiety
- Mental status changes

CUTANEOUS[8]

- Skin lesions on sun-exposed areas
- (Cutaneous symptoms primarily occur in HCP and VP.)

PERIPHERAL
Nervous System[7,8]

- Limb weakness or pain
- Peripheral neuropathy

OTHER
Common AHP Symptoms[8,9]

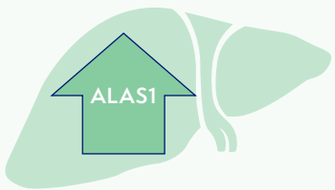
- Hyponatremia
- Dark, reddish urine

>90% of patients report abdominal pain during AHP attacks[7]

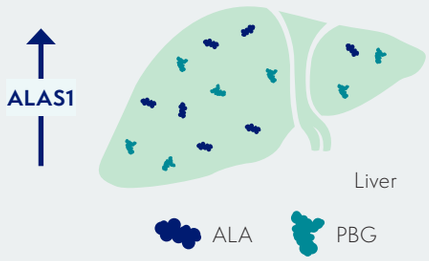
†These are not all the possible signs and symptoms of an AHP attack.

Patients with AHP have an enzyme deficiency in the heme biosynthesis pathway[9]

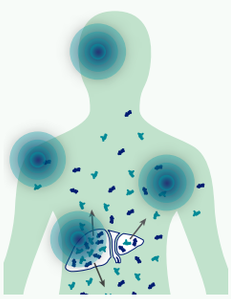
ALAS1 upregulation leads to accumulation of neurotoxic intermediates that can cause damage across the body[3,10]



Disease triggers, such as infections or certain medications, can induce upregulation of ALAS1 in the liver[9]



Upregulation of ALAS1 leads to the accumulation of neurotoxic intermediates ALA and PBG in the liver[3,11]



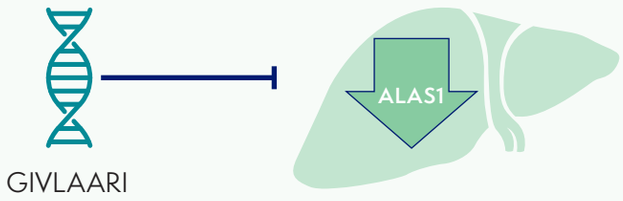
ALA and PBG are released into circulation, thereby causing neurotoxic effects[3,11]

Neurotoxic effects of ALA and PBG are associated with AHP attacks and other disease manifestations[10,12]

AHP=acute hepatic porphyria; ALA=delta-aminolevulinic acid; ALAS1=delta-aminolevulinic acid synthase 1; PBG=porphobilinogen.

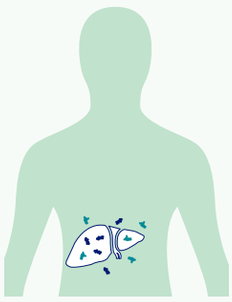
GIVLAARI® (givosiran) specifically targets ALAS1, key to the pathophysiology of AHP[1]

GIVLAARI is a double-stranded, small interfering RNA (siRNA) therapeutic specifically targeting ALAS1 mRNA, reducing ALAS1 mRNA levels and leading to reductions in urinary ALA and PBG[1]



GIVLAARI targets ALAS1 mRNA for degradation in the liver[1,9]

ALAS1 mRNA degradation reduces the production of the neurotoxic intermediates ALA and PBG[1,11]



Less ALA and PBG are released into circulation. Reductions of ALA and PBG have been associated with fewer AHP attacks[1,11,13]

mRNA=messenger RNA.

IMPORTANT SAFETY INFORMATION

Anaphylactic Reaction

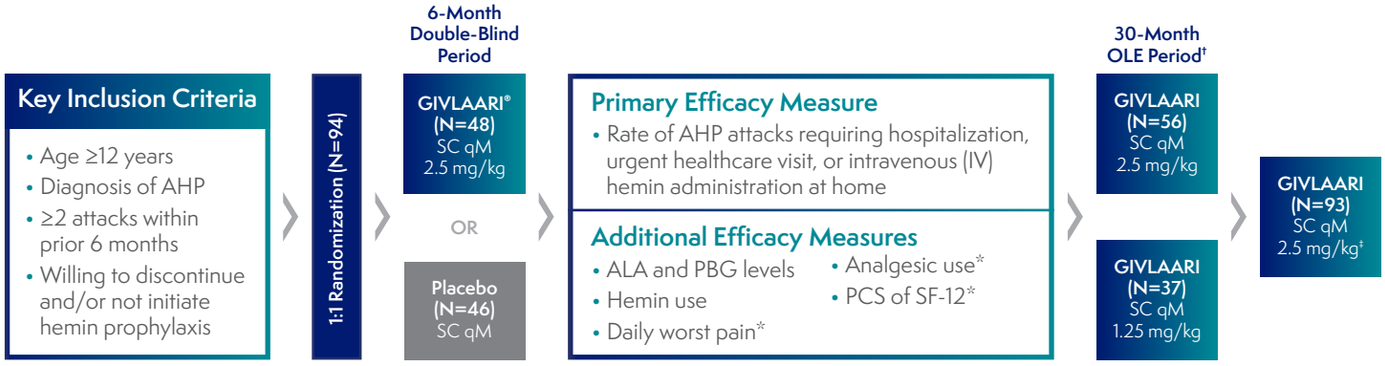
Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.

Please see Important Safety Information on page 21 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

ENVISION: The largest interventional study in AHP[1,14]

ENVISION was a randomized, double-blind, placebo-controlled, multinational phase 3 study in adult patients with AHP (N=94), with a 30-month open-label extension (OLE) period (N=93)[1,14,15]



*These measures were in patients with AIP only.
†All endpoints were considered exploratory in the ENVISION OLE period.
‡A protocol amendment increased the dose for all patients to 2.5 mg/kg once monthly.

- Patients who experienced an AHP attack were treated according to the local standard of care, which could include IV hemin[15]

All eligible patients (93 of 94) enrolled in the open-label extension[14]

AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; ALA=delta-aminolevulinic acid; PBG=porphobilinogen; PCS=Physical Component Summary; qM=once monthly; SC=subcutaneous; SF-12=12-Item Short-Form Health Survey, version 2.

IMPORTANT SAFETY INFORMATION

Hepatic Toxicity

Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients receiving GIVLAARI in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment.

Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

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GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

ENVISION study patient population[1,15]

Baseline Demographic and Clinical Characteristics of Patients With AHP[15]			
	GIVLAARI® (givosiran) (N=48)	Placebo (N=46)	Overall (N=94)
Median age, years (range)	42 (19, 65)	36 (20, 60)	37.5 (19, 65)
Female, n (%)	43 (90)	41 (89)	84 (89)
Caucasian, n (%)	39 (81)	34 (74)	73 (78)
AHP type, n (%)			
– AIP	46 (96)	43 (93)	89 (95)
– HCP	1 (2)	0 (0)	1 (1)
– VP	1 (2)	1 (2)	2 (2)
– No identified mutation	0 (0)	2 (4)	2 (2)
Historical annualized attack rate, median (IQR)	8 (4-18)	7 (4-14)	8 (4-16)
Prior hemin prophylaxis, n (%)	20 (42)	18 (39)	38 (40)
Prior chronic opioid use, n (%)[§]	14 (29)	13 (28)	27 (29)
Prior chronic symptoms, n (%)[‖]	23 (48)	26 (57)	49 (52)

[§]Use of opioids was defined as chronic if patients reported taking them for porphyria daily, or on most days, when not having an attack.[14]
[‖]Symptoms were chronic if patients experienced symptoms of porphyria daily, or on most days, when not having an attack.[14]

The historical annualized attack rate was calculated as the number of attacks resulting in a composite of hospitalization, a visit to a healthcare facility, or hemin use at home during the 6 months before randomization.[15]

HCP=hereditary coproporphyria; IQR=interquartile range; VP=variegate porphyria.

IMPORTANT SAFETY INFORMATION

Renal Toxicity

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI. In the placebo-controlled study, 15% of patients receiving GIVLAARI experienced a renally-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment with GIVLAARI as clinically indicated.

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GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

In a 36-month analysis of patients with AHP,

Treatment with once-monthly subcutaneous GIVLAARI® (givosiran) resulted in rapid and sustained reductions in ALA and PBG[1]

Reductions through the ENVISION 6-month double-blind period[1,15]

- Reductions in urinary ALA and PBG were seen with GIVLAARI 2.5 mg/kg at Day 14, the first time point measured
  - 14 days after the first dose of GIVLAARI, **median reductions from baseline in urinary ALA and PBG were 84% and 75%**, respectively
- **Maximal reductions in ALA and PBG levels were achieved around Month 3** with GIVLAARI 2.5 mg/kg, with median reductions from baseline of 94% for ALA and 95% for PBG, and were sustained thereafter with repeated once-monthly dosing

Reductions in the ENVISION open-label extension (OLE) period[16]

- In patients who continued treatment with GIVLAARI in the OLE period, **reductions in urinary ALA and PBG were sustained through Month 36**
  - 92.6% median reduction (Q1, Q3: 96.0%, 88.3%) and 95.9% median reduction (Q1, Q3: 99.2%, 90.7%) from baseline in urinary ALA and PBG, respectively
- In patients who crossed over from placebo to GIVLAARI in the OLE period (a total of 30 months of treatment with GIVLAARI):
  - 92.0% median reduction (Q1, Q3: 94.9%, 86.9%) and 94.2% median reduction (Q1, Q3: 98.1%, 85.1%) from baseline in urinary ALA and PBG, respectively, were observed at Month 36

Elevated levels of ALA and PBG are associated with AHP attacks[10,12]

ALA=delta-aminolevulinic acid; PBG=porphobilinogen.

IMPORTANT SAFETY INFORMATION

Injection Site Reactions

Injection site reactions were reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration.

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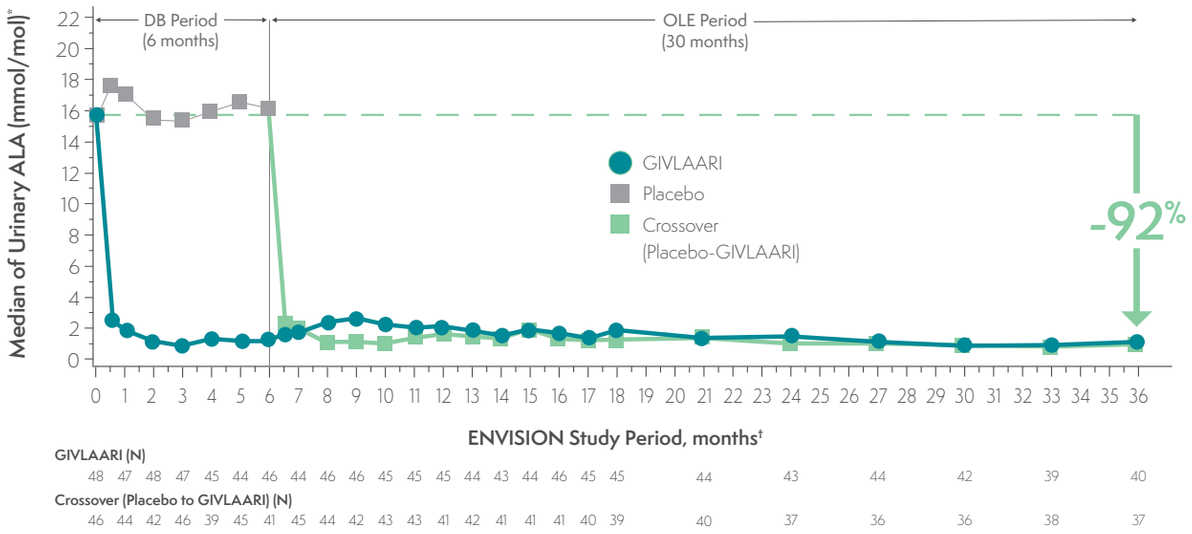
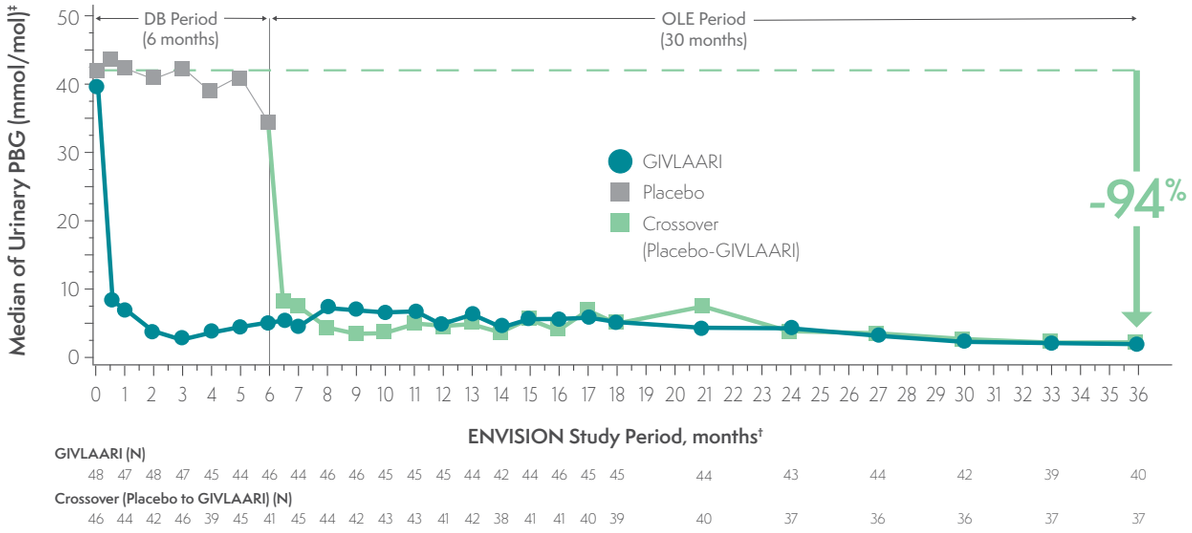
In a 36-month analysis of patients with AHP,

Long-term GIVLAARI® (givosiran) treatment reduced ALA and PBG by over 90%[17]

Urinary ALA levels[17]



Urinary PBG levels[17]



*The determination of the upper limit of normal (ULN) for ALA (1.5 mmol/mol of creatinine) was based on samples obtained from 150 healthy persons.
†Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg in the OLE period were pooled.
‡The determination of the ULN for PBG (0.14 mmol/mol of creatinine) was based on samples obtained from 150 healthy persons.
AHP=acute hepatic porphyria; DB=double-blind; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION

Blood Homocysteine Increased

Increases in blood homocysteine levels have occurred in patients receiving GIVLAARI. In the ENVISION study, during the open label extension, adverse reactions of blood homocysteine increased were reported in 15 of 93 (16%) patients treated with GIVLAARI. Measure blood homocysteine levels prior to initiating treatment and monitor for changes during treatment with GIVLAARI. In patients with elevated blood homocysteine levels, assess folate, vitamins B12 and B6. Consider treatment with a supplement containing vitamin B6 (as monotherapy or a multivitamin preparation).

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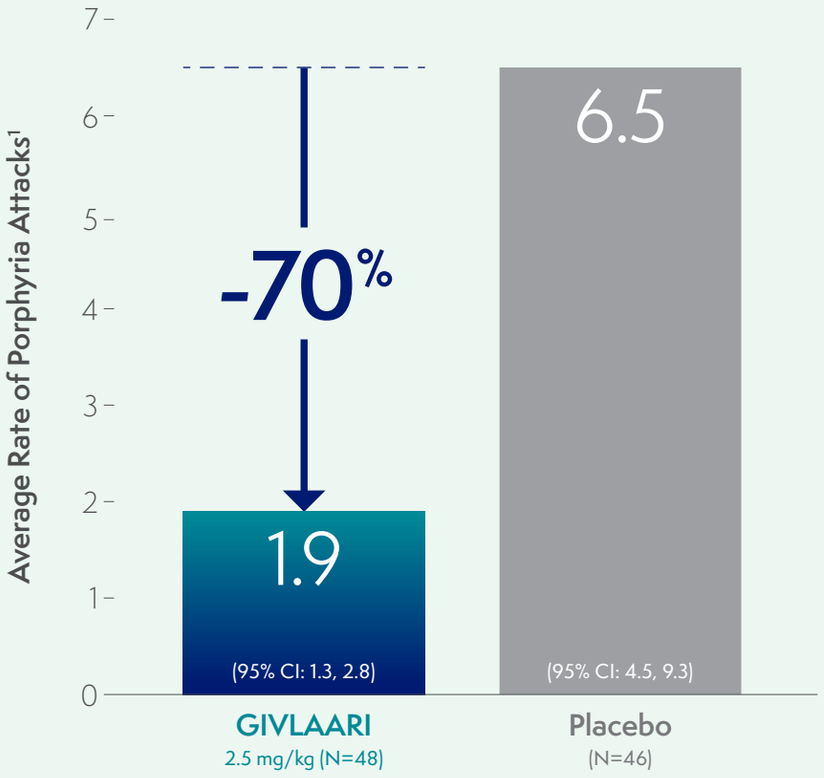
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

In patients with AHP in the ENVISION 6-month double-blind period,

GIVLAARI® (givosiran) led to a significant reduction in porphyria attacks[1]

Average rate of porphyria attacks in the 6-month double-blind period[1]



70% fewer attacks

on average vs placebo[1]

- Attack rate ratio of GIVLAARI vs placebo: 0.3 (95% CI: 0.2, 0.4; *P*<0.0001)[1]

Attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.[1]

"AIP used to be the most significant thing in my life. Not anymore. I do still have a debilitating condition, but I'm experiencing fewer attacks."

—Lina, an Alnylam Patient Ambassador on GIVLAARI

AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; CI=confidence interval.

IMPORTANT SAFETY INFORMATION

Drug Interactions

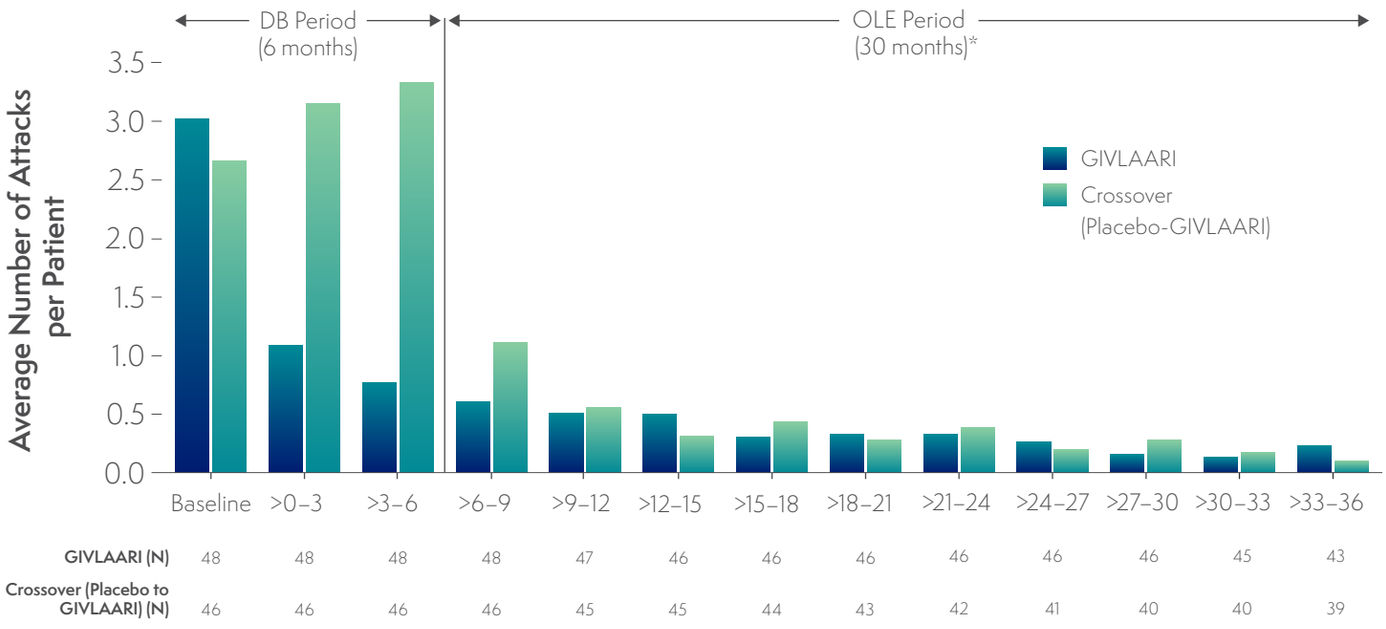
Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GIVLAARI with CYP1A2 or CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP1A2 or CYP2D6 substrate dosage in accordance with approved product labeling.

Please see Important Safety Information on page 21 and full Prescribing Information.

In a 36-month analysis of patients with AHP,

Long-term GIVLAARI® (givosiran) treatment demonstrated sustained attack reduction[16]

Average number of attacks per 3-month interval[16]



	Baseline	>0–3	>3–6	>6–9	>9–12	>12–15	>15–18	>18–21	>21–24	>24–27	>27–30	>30–33	>33–36
GIVLAARI (N)	48	48	48	48	47	46	46	46	46	46	46	45	43
Crossover (Placebo to GIVLAARI) (N)	46	46	46	46	45	45	44	43	42	41	40	40	39

*Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg in the OLE period were pooled.[14]

Attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.[14]

- Attack reduction was sustained in patients continuing or crossing over to GIVLAARI treatment during the ENVISION OLE period[16]
- Endpoints in the OLE period are exploratory[18]

The average number of attacks per patient in the final 3-month interval of the OLE period was 0.233 and 0.103 *in the GIVLAARI and crossover groups, respectively*[16]

Sustained GIVLAARI treatment reduced the number of attacks for patients with AHP[16]

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

IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common adverse reactions that occurred in patients receiving GIVLAARI were nausea (27%) and injection site reactions (25%).

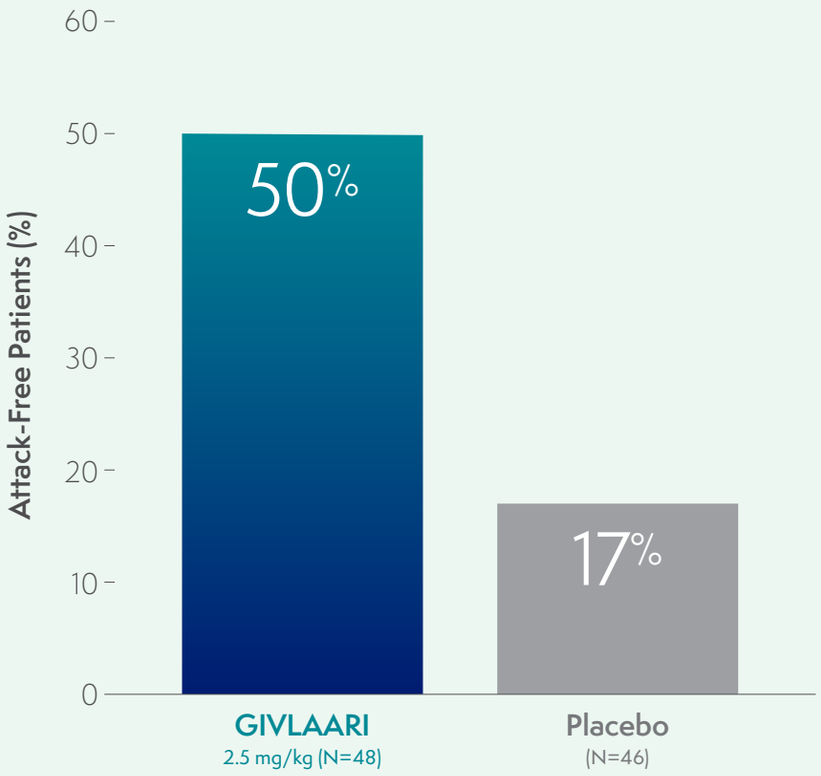
Please see Important Safety Information on page 21 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

In patients with AHP in the ENVISION 6-month double-blind period,

50% were attack-free with GIVLAARI® (givosiran) treatment[15]

Percentage of patients who were attack-free in the 6-month double-blind period[15]



50% of patients taking GIVLAARI were attack-free
vs 17% of placebo patients[15]

Attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.[1]

AHP=acute hepatic porphyria.

IMPORTANT SAFETY INFORMATION

Contraindications

GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis.

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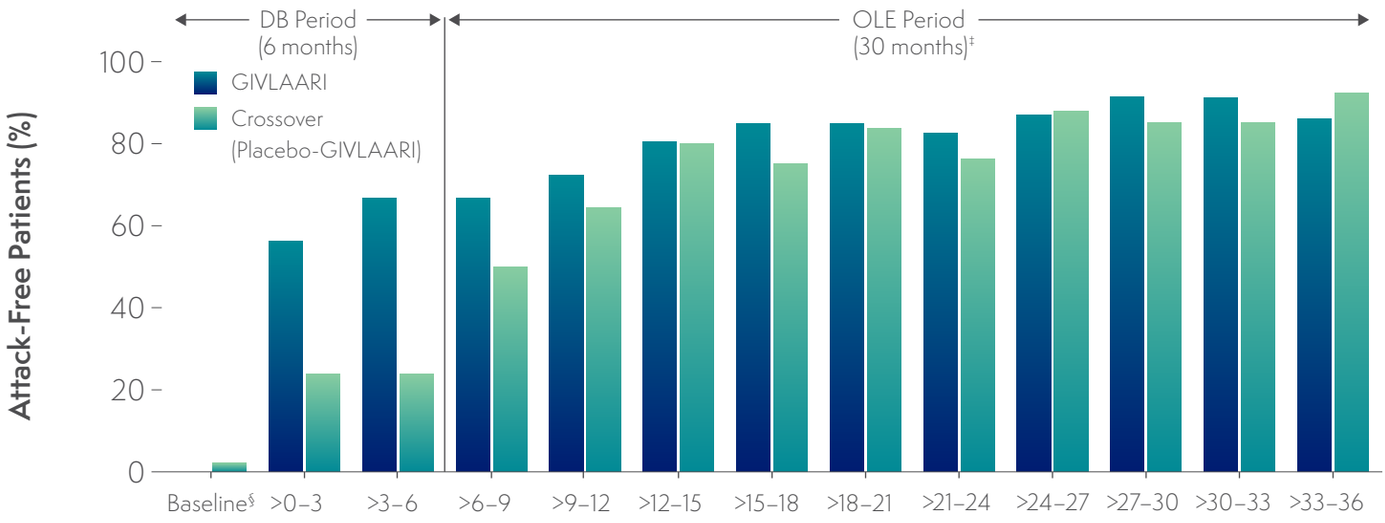
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

In a 36-month analysis of patients with AHP,

The number of attack-free patients increased with GIVLAARI® (givosiran) treatment[17]

Percentage of patients who were attack-free* per 3-month† interval[17]



	Baseline§	>0–3	>3–6	>6–9	>9–12	>12–15	>15–18	>18–21	>21–24	>24–27	>27–30	>30–33	>33–36
GIVLAARI (N)	48	48	48	48	47	46	46	46	46	46	46	45	43
Crossover (Placebo to GIVLAARI) (N)	46	46	46	46	45	45	44	43	42	41	40	40	39

*Attacks were defined as those that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.[14]
†1 month = 28 days.[14]
‡Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg in the OLE period were pooled.[14]
§Baseline represents 6 months before randomization.[14]

- Endpoints in the OLE period are exploratory[18]

In the final 3-month interval of the OLE period, 86% and 92% of patients were attack-free
in the GIVLAARI and crossover groups, respectively[17]

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

IMPORTANT SAFETY INFORMATION

Anaphylactic Reaction

Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.

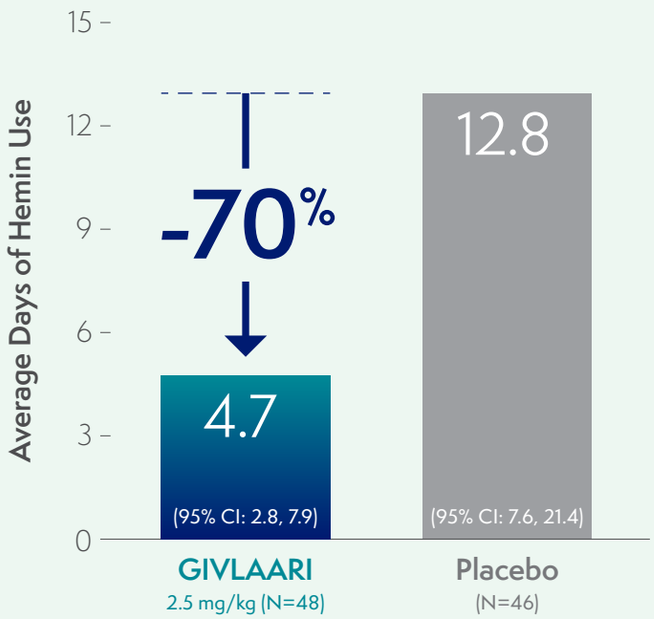
Please see Important Safety Information on page 21 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

In patients with AHP in the ENVISION 6-month double-blind period,

GIVLAARI® (givosiran) reduced the average days of hemin use by 70%[1]

Average days of hemin use during the 6-month double-blind period[1]



70% reduction in average days of **hemin use** with GIVLAARI vs placebo[1]

- Ratio of average days of hemin use (GIVLAARI:placebo): 0.3 (95% CI: 0.1, 0.5; *P*=0.0002)[1]
- In the ENVISION 6-month DB period, 54% of patients with AIP (n=25/46) treated with GIVLAARI had zero days of hemin use compared with 23% of patients (n=10/43) receiving placebo[15]

AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; CI=confidence interval.

IMPORTANT SAFETY INFORMATION

Hepatic Toxicity

Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients receiving GIVLAARI in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment.

Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

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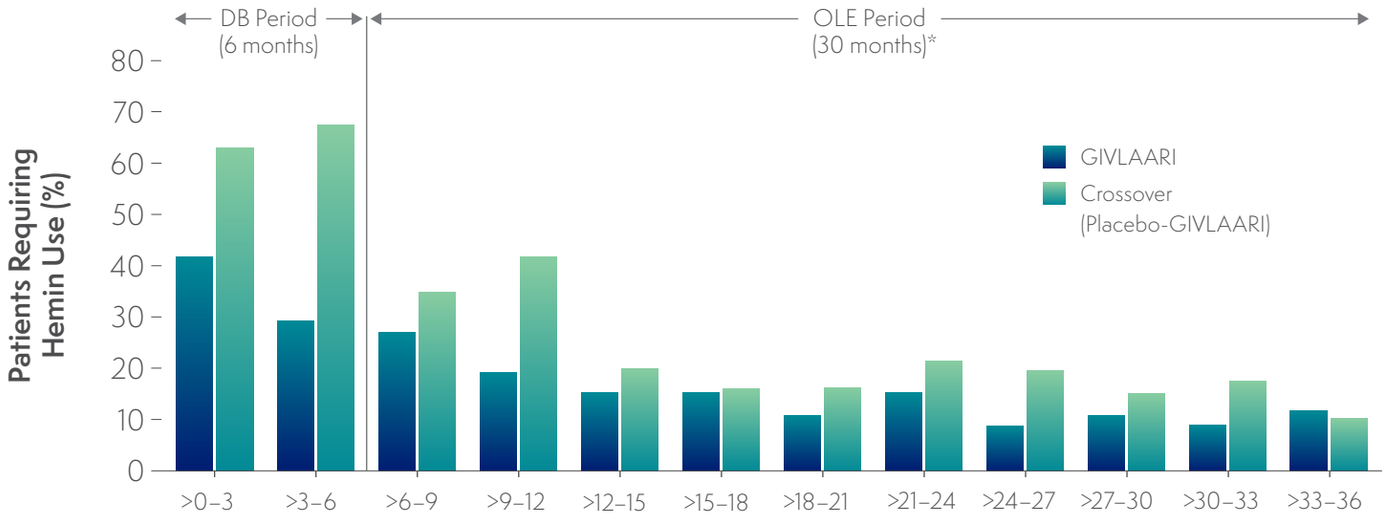
In a 36-month analysis of patients with AHP,

Long-term GIVLAARI® (givosiran) treatment led to sustained reductions in hemin use[16]

Percentage of patients requiring hemin in 3-month intervals[16]



	>0–3	>3–6	>6–9	>9–12	>12–15	>15–18	>18–21	>21–24	>24–27	>27–30	>30–33	>33–36
GIVLAARI (N)	48	48	48	47	46	46	46	46	46	46	45	43
Crossover (Placebo to GIVLAARI) (N)	46	46	46	45	45	44	43	42	41	40	40	39

*Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg in the OLE period were pooled.

- Patients were required to discontinue or not initiate prophylactic hemin during the trial[15]
  - 40% of patients with AHP had prior hemin prophylaxis[15]
  - Patients experiencing an AHP attack were treated according to the local standard of care, which could include IV hemin to treat an acute attack[15]
- Endpoints in the OLE period are exploratory[18]

In the final 3-month interval of the OLE period,
hemin treatment was not required by 88% and 90% of patients
in the GIVLAARI and crossover groups, respectively[17]

OLE=open-label extension.

IMPORTANT SAFETY INFORMATION

Renal Toxicity

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI. In the placebo-controlled study, 15% of patients receiving GIVLAARI experienced a renally-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment with GIVLAARI as clinically indicated.

Please see Important Safety Information on page 21 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

In patients with AIP in the ENVISION 6-month double-blind period,

Daily worst pain scores and analgesic use with GIVLAARI® (givosiran) and placebo[15]

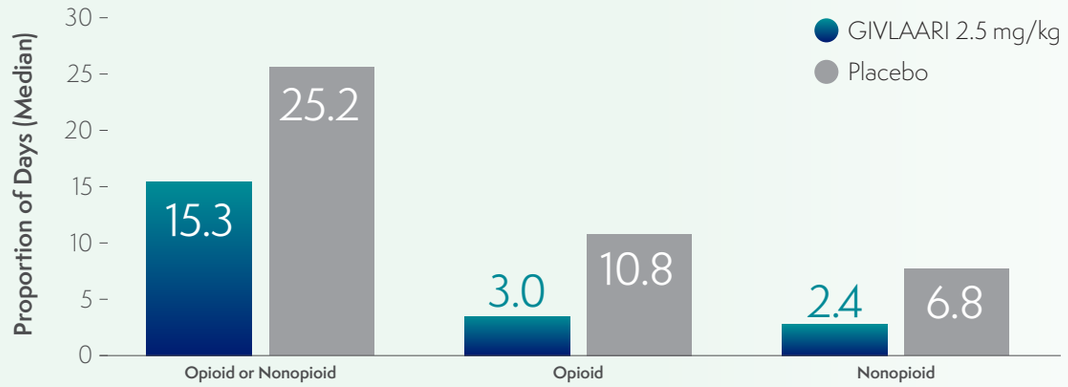
Daily worst pain score in patients with AIP was a secondary endpoint[15]

- Pain was measured using patient-reported daily worst pain scores based on a numeric rating scale (NRS)[15]
- A statistical analysis of the change from baseline in daily worst pain score for GIVLAARI vs placebo was conducted[15]
- A positive score represents a worsening in daily worst pain from baseline; a negative score represents an improvement from baseline[15]
- GIVLAARI did not meet statistical significance for this endpoint based on the prespecified statistical method[19]
- The daily worst pain scores were lower with GIVLAARI compared with placebo[15]

Daily worst pain scores in patients with AIP (AUC of mean change from baseline)[19]

GIVLAARI (N=46)	Placebo (N=43)	Treatment difference (95% CI)
-12.876	-0.196	**-12.680 (-25.526, 0.166)**

Analgesic use in patients with AIP was a prespecified exploratory endpoint[15,16]



- Through Month 6 in the double-blind period, the proportion of days with opioid and nonopioid analgesic use was lower in patients treated with GIVLAARI compared with placebo[15]
- An evaluation compared with baseline analgesic use cannot be conducted because the proportion of days with analgesic use was not captured at baseline[15]

AIP=acute intermittent porphyria; AUC=area under the curve; CI=confidence interval.

IMPORTANT SAFETY INFORMATION

Injection Site Reactions

Injection site reactions were reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration.

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In patients with AIP in the ENVISION 6-month double-blind period,

PCS of the SF-12 was evaluated[15]

The Physical Component Summary (PCS) of the 12-Item Short Form Health Survey (SF-12) was a planned secondary endpoint[15]

- Patient-reported quality of life (QoL) was measured by the SF-12, a 12-question measure capturing global QoL and overall health status[18]
  - Scores on the PCS range from 0 (worst functioning) to 100 (best functioning), with published literature in other chronic diseases suggesting that a change of 2 to 5 points represents a clinically meaningful difference[15]
- The PCS of the SF-12 was a planned secondary endpoint. The PCS of the SF-12 was not tested due to not meeting the conditions of the prespecified hierarchical order of statistical testing. As such, the PCS of SF-12 change from baseline in AIP is viewed as exploratory[15,19]

The results have limitations due to the following considerations:

- PCS score included concepts that may not be relevant for the target population (ie, general health, moderate activities, climbing stairs)[15]
- The domains of bodily pain, social functioning, role limitations due to physical problems, and general health contributed more to the total PCS score[15]
- The 6-month double-blind period may not have been long enough to observe a meaningful treatment effect[15]

- PCS scores were higher with GIVLAARI® (givosiran) compared to placebo[15]

Observed values in PCS of the SF-12 scores in patients with AIP (least-squares [LS] mean of change from baseline)[15]

Endpoint	GIVLAARI (N=46)	Placebo (N=43)	Treatment difference
PCS of SF-12 LS mean of change from baseline at Month 6 (95% CI)	5.4	1.4	**3.9 (95% CI: 0.6, 7.3)**

CI=confidence interval; LS=least squares; PCS=Physical Component Summary; QoL=quality of life; SF-12=12-Item Short-Form Health Survey, version 2.

IMPORTANT SAFETY INFORMATION

Blood Homocysteine Increased

Increases in blood homocysteine levels have occurred in patients receiving GIVLAARI. In the ENVISION study, during the open label extension, adverse reactions of blood homocysteine increased were reported in 15 of 93 (16%) patients treated with GIVLAARI. Measure blood homocysteine levels prior to initiating treatment and monitor for changes during treatment with GIVLAARI. In patients with elevated blood homocysteine levels, assess folate, vitamins B12 and B6. Consider treatment with a supplement containing vitamin B6 (as monotherapy or a multivitamin preparation).

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Safety profile of GIVLAARI® (givosiran) in the ENVISION study[1]

Safety during the 6-month DB period

Adverse reactions that occurred at least 5% more frequently in patients treated with GIVLAARI compared with patients receiving placebo in the 6-month double-blind (DB) period[1]		
Adverse Reaction	GIVLAARI (N=48) n (%)	Placebo (N=46) n (%)
Nausea	13 (27)	5 (11)
Injection site reactions	12 (25)	0
Rash*	8 (17)	2 (4)
Serum creatinine increase†	7 (15)	2 (4)
Transaminase elevations	6 (13)	1 (2)
Fatigue	5 (10)	2 (4)

*Grouped term includes pruritus, eczema, erythema, rash, rash pruritic, urticaria.
†Grouped term includes blood creatinine increased, glomerular filtration rate decreased, chronic kidney disease (decreased eGFR).

- Permanent discontinuation of GIVLAARI occurred in 1 patient (2.1%) due to elevated transaminases, in adherence with prespecified protocol-defined stopping rules[1]
- The most frequently occurring (≥20% incidence) adverse reactions reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%)[1]

Safety through the open-label extension (OLE) period

- The most common treatment-related adverse events (AEs) (≥10%) were injection site reactions (32% [30/94] patients), nausea (21% [20/94]), and fatigue (14% [13/94])[17]
- Treatment-related serious adverse events were reported in 7 patients (7% of patients). Related SAEs reported in 2 or more patients were blood homocysteine increased (2 patients) and SAEs related to elevated LFTs (transaminases increased and LFT abnormal in 1 patient each)[16,17]
- There was 1 death due to aortic dissection during the OLE that was determined to be unrelated to givosiran treatment[17]
- Three patients (3.2%) discontinued treatment due to treatment-related AEs in the OLE period. One patient discontinued treatment due to an AE of hypersensitivity, and 2 patients discontinued due to SAEs of increased blood homocysteine[16]
- Increased blood homocysteine was reported in 15 of 93 (16%) patients treated with GIVLAARI[1]

AE=adverse event; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; LFT=liver function test; SAE=serious adverse event.

IMPORTANT SAFETY INFORMATION

Drug Interactions

Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GIVLAARI with CYP1A2 or CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP1A2 or CYP2D6 substrate dosage in accordance with approved product labeling.

Please see Important Safety Information on page 21 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Once-monthly dosing with GIVLAARI® (givosiran)[1]

The recommended dose of GIVLAARI is 2.5 mg/kg administered via subcutaneous injection once monthly by a healthcare professional.
Dosing is based on actual body weight.[1]

Missed dose

- Administer GIVLAARI as soon as possible after a missed dose. Resume dosing at monthly intervals following administration of the missed dose[1]

Dose modifications for adverse reactions

- In patients with severe or clinically significant transaminase elevations, who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly[1]
- In patients who resume dosing at 1.25 mg/kg once monthly without recurrence of severe or clinically significant transaminase elevations, the dose may be increased to the recommended 2.5 mg/kg once monthly[1]

GIVLAARI is administered via subcutaneous injection by a healthcare professional only[1]

- Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI[1]

For detailed instructions on the administration of GIVLAARI, see the full Prescribing Information

IMPORTANT SAFETY INFORMATION

Injection Site Reactions

Injection site reactions were reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration.

Please see Important Safety Information on page 21 and full Prescribing Information.

Alnylam Assist™ provides support services for patients prescribed GIVLAARI® (givosiran)

Alnylam Assist™ is committed to helping patients access GIVLAARI:

- Get started on treatment with GIVLAARI
- Understand their benefits, coverage, and financial assistance options for eligible patients*
- Learn more about acute hepatic porphyria and treatment with GIVLAARI

Alnylam ASSIST®

Monday-Friday, 8 AM–6 PM

1-833-256-2748

1-833-256-2747

To learn more, visit
www.AlnylamAssist.com

How to get started:

1. **Complete Start Form**
2. **Alnylam Case Manager Reaches Out**
3. **Patient Assistance Offered**

After prescribing your patient GIVLAARI, begin the enrollment process by completing the GIVLAARI Start Form. Upon receipt of the Start Form, an **Alnylam Case Manager** will reach out to you and your patient within 2 business days.

99% of U.S. lives have confirmed access to GIVLAARI across commercial, Medicare, Medicaid, and other government payer categories†

*Patients must meet specified eligibility criteria to qualify for assistance. Alnylam reserves the right to make eligibility determinations and to modify or discontinue the program at any time.

†Coverage may vary from individual and plan. Data as of August 2022.

Please see Important Safety Information on page 21 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Indication and Important Safety Information

INDICATION

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

IMPORTANT SAFETY INFORMATION

Contraindications

GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis.

Anaphylactic Reaction

Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.

Hepatic Toxicity

Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients receiving GIVLAARI in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment.

Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

Renal Toxicity

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI. In the placebo-controlled study, 15% of patients receiving GIVLAARI experienced a renally-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment with GIVLAARI as clinically indicated.

Injection Site Reactions

Injection site reactions were reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration.

Blood Homocysteine Increased

Increases in blood homocysteine levels have occurred in patients receiving GIVLAARI. In the ENVISION study, during the open label extension, adverse reactions of blood homocysteine increased were reported in 15 of 93 (16%) patients treated with GIVLAARI. Measure blood homocysteine levels prior to initiating treatment and monitor for changes during treatment with GIVLAARI. In patients with elevated blood homocysteine levels, assess folate, vitamins B12 and B6. Consider treatment with a supplement containing vitamin B6 (as monotherapy or a multivitamin preparation).

Drug Interactions

Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GIVLAARI with CYP1A2 or CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP1A2 or CYP2D6 substrate dosage in accordance with approved product labeling.

Adverse Reactions

The most common adverse reactions that occurred in patients receiving GIVLAARI were nausea (27%) and injection site reactions (25%).

For additional information about GIVLAARI, please see full Prescribing Information.

References: 1. GIVLAARI [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc. **2.** Simon A, Pompilus F, Querbes W, et al. *Patient*. 2018;11(5):527-537. **3.** Puy H, Gouya L, Deybach JC. *Lancet*. 2010;375(9718):924-937. **4.** Bissell DM, Anderson KE, Bonkovsky HL. *N Engl J Med*. 2017;377(9):862-872. **5.** Neeleman RA, Wagenmakers MAEM, Koole-Lesuis RH, et al. *J Inherit Metab Dis*. 2018;41(5):809-817. **6.** Gouya L, Ventura P, Balwani M, et al. *Hepatology*. 2020;71(5):1546-1558. **7.** Ventura P, Cappellini MD, Biolcati G, Guida CC, Rocchi E; Gruppo Italiano Porfiria (GrIP). *Eur J Intern Med*. 2014;25(6):497-505. **8.** Anderson KE, Bloomer JR, Bonkovsky HL, et al. *Ann Intern Med*. 2005;142(6):439-450. **9.** Balwani M, Wang B, Anderson KE, et al; Porphyrias Consortium of the Rare Diseases Clinical Research Network. *Hepatology*. 2017;66(4):1314-1322. **10.** Szlendak U, Bykowska K, Lipniacka A. *Adv Clin Exp Med*. 2016;25(2):361-368. **11.** Pischik E, Kauppinen R. *Appl Clin Genet*. 2015;8:201-214. **12.** Kuo H-C, Huang C-C, Chu C-C, et al. *Eur Neurol*. 2011;66(5):247-252. **13.** Sardh E, Harper P, Balwani M, et al. *N Engl J Med*. 2019;380(6):549-558. **14.** Ventura P, Bonkovsky HL, Gouya L, et al. *Liver Int*. 2021;00:1-12. **15.** Balwani M, Sardh E, Ventura P, et al; ENVISION Investigators. *N Engl J Med*. 2020;382(24):2289-2301. **16.** Data on file. Alnylam Pharmaceuticals, Inc. **17.** Kuter DJ, Bonkovsky HL, Monroy S, et al. Presented at: American Society of Hematology (ASH) 2021 Annual Meeting; December 11-14, 2021. **18.** Balwani M, Sardh E, Ventura P, et al; ENVISION Investigators Protocol. *N Engl J Med*. 2020;382:2289-2301. **19.** Balwani M, Gouya L, Rees DC, et al; ENVISION Investigators. Presented at: EASL International Liver Congress; April 13, 2019; Vienna, Austria.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

GIVLAARI® (givosiran)

SIGNIFICANTLY REDUCED ATTACKS

in adults with acute hepatic porphyria (AHP)[1]

GIVLAARI is an RNA interference (RNAi) therapeutic that targets ALAS1 mRNA in the liver, leading to reductions in levels of ALA and PBG, factors associated with AHP attacks and other disease manifestations[1,12]

Selected efficacy findings from the ENVISION 6-month DB period and OLE period

- **70% fewer porphyria attacks** on average with GIVLAARI vs placebo in the 6-month DB period of ENVISION[1]
- **Attack reduction was sustained** for patients continuing to receive GIVLAARI through Month 36 of the OLE period[16]

Attacks were defined as those requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.[1]

Selected safety findings from the ENVISION 6-month DB period and OLE period

- During the 6-month DB period, permanent discontinuation of GIVLAARI occurred in 1 patient (2.1%) due to elevated transaminases, in adherence with prespecified protocol-defined stopping rules[1]
- The most common adverse reactions (≥20%) reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%) in the 6-month DB period[1]
- Three patients (3.2%) discontinued treatment due to adverse events in the OLE period. One patient discontinued treatment due to an AE of hypersensitivity, and 2 patients discontinued due to SAEs of increased blood homocysteine[16]
- The most common treatment-related adverse events (AEs) (≥10%) were injection site reactions (32% [30/94] patients), nausea (21% [20/94]), and fatigue (14% [13/94]) in the OLE period[17]
- In the OLE period of the ENVISION study, increased blood homocysteine was reported in 15 of 93 (16%) patients treated with GIVLAARI[1]

AE=adverse event; ALA=delta-aminolevulinic acid; ALAS1=delta-aminolevulinic acid synthase 1; DB=double-blind; mRNA=messenger RNA; OLE=open-label extension; PBG=porphobilinogen.

INDICATION

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

SELECTED IMPORTANT SAFETY INFORMATION

Contraindications: GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis.

Anaphylactic Reaction: Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms. If anaphylaxis occurs, discontinue GIVLAARI and institute appropriate medical treatment.

Hepatic Toxicity: Measure liver function at baseline and periodically during treatment with GIVLAARI. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations.

Renal Toxicity: Monitor renal function during treatment with GIVLAARI as clinically indicated.

Injection Site Reactions: May occur, including recall reactions. Monitor for reactions and manage clinically as needed.

Blood Homocysteine Increased: Measure blood homocysteine at baseline and monitor for changes during treatment with GIVLAARI. In patients with elevated blood homocysteine, consider supplementation with vitamin B6 (as monotherapy or multivitamin).

Please see Important Safety Information on page 21 and full Prescribing Information.

Alnylam® PHARMACEUTICALS

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL