Acute hepatic porphyria (AHP) can cause debilitating, potentially life-threatening attacks[1,2]

GIVLAARI® (givosiran)

SIGNIFICANTLY REDUCED ATTACKS

IN ADULTS WITH AHP[3]

During the 6-month double-blind period of the ENVISION trial, patients with AHP experienced 70% fewer attacks on average with GIVLAARI vs placebo[3]

Average number of porphyria attacks: 1.9 (95% CI: 1.3, 2.8) with GIVLAARI vs 6.5 (95% CI: 4.5, 9.3) with placebo; attack rate ratio: 0.3 (95% CI: 0.2, 0.4; *P*<0.0001)[3]

Attacks were defined as those requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.[3]

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.

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

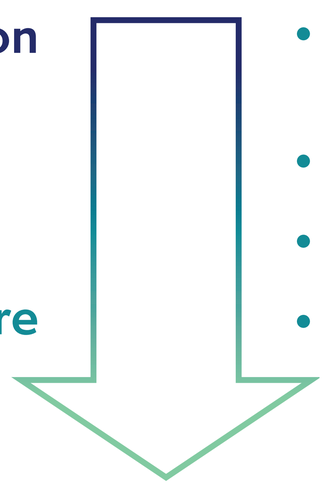
Please see Important Safety Information on page 21 and full Prescribing Information.

AHP is a rare, genetic disease characterized by debilitating, potentially life-threatening attacks[1,2]

There are 4 types of AHP[1,4]

Most common

Extremely rare



- **Acute Intermittent Porphyria (AIP)**
  - ~80% of all AHP cases are AIP
- **Variegate Porphyria (VP)**
- **Hereditary Coproporphyria (HCP)**
- **ALAD-Deficiency Porphyria (ADP)**

AHP attacks can be unpredictable, severe, and progressive

- AHP is most commonly seen in women of childbearing age[5]
- Attacks generally last 3 to 7 days, but recovery can take longer[1]
- Severe attacks may progress to respiratory failure or paralysis, leading to temporary or permanent disability[1,2]
- Some patients with recurrent attacks report chronic symptoms and long-term complications and describe how chronic symptoms have contributed to their burden of disease[1,6]

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

Common signs and symptoms of an AHP attack[1,2]

CARDINAL SYMPTOM

SEVERE, DIFFUSE ABDOMINAL PAIN[1,4]

+

1 OR MORE ADDITIONAL FINDINGS[4]

AUTONOMIC Nervous System[4,6]	CENTRAL Nervous System[4,6]	PERIPHERAL Nervous System[4,6]	CUTANEOUS[4*]
• Nausea/Vomiting • Constipation • Tachycardia	• Seizures • Anxiety • Mental status changes	• Limb weakness or pain	• Skin lesions on sun-exposed areas

*Cutaneous symptoms only occur in HCP and VP.[4]

AHP=acute hepatic porphyria; HCP=hereditary coproporphyria; VP=variegate porphyria.

>90% of patients report abdominal pain during AHP attacks.[4]

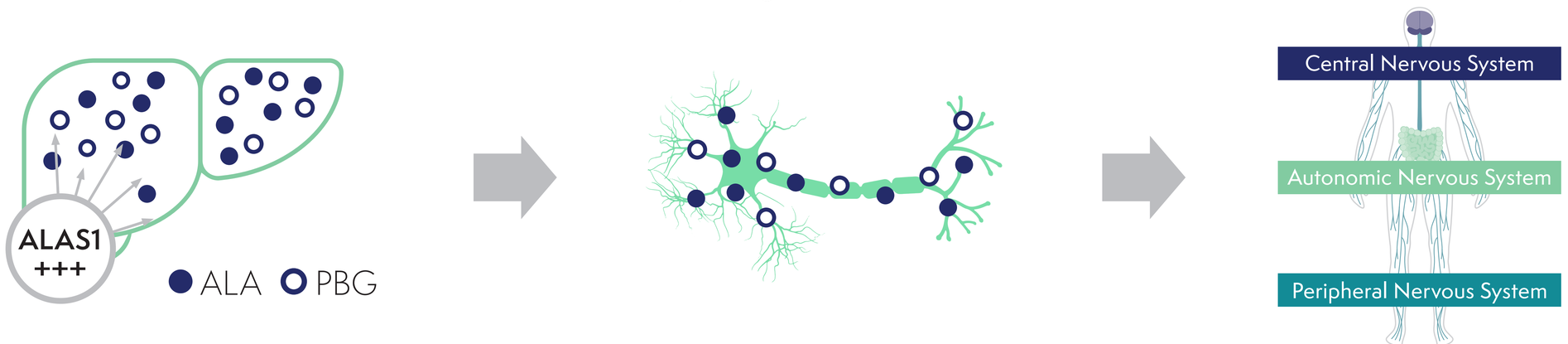
Patients with AHP have an enzyme deficiency in the heme biosynthesis pathway[7]

ALAS1 upregulation leads to accumulation of neurotoxic intermediates that can cause damage across the body[6]

Disease triggers, such as infections or certain medications, can induce ALAS1 and lead to overproduction of the neurotoxic intermediates ALA and PBG[6,7]

ALA and PBG accumulate in the liver, and are further released into circulation, thereby causing neurotoxic effects[5,6,8]

Neurotoxic effects lead to acute attacks[6]



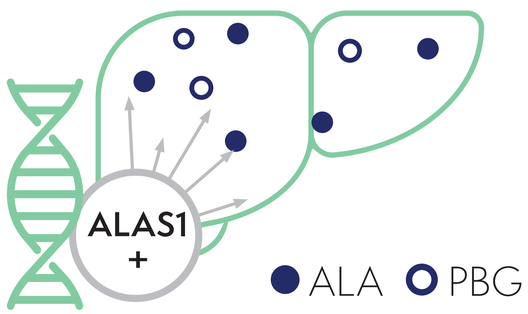
AHP=acute hepatic porphyria; ALA=delta-aminolevulinic acid; ALAS1=delta-aminolevulinic acid synthase 1; mRNA=messenger RNA; PBG=porphobilinogen.

Neurotoxic intermediates ALA and PBG are factors associated with AHP attacks and other disease manifestations.[3,9]

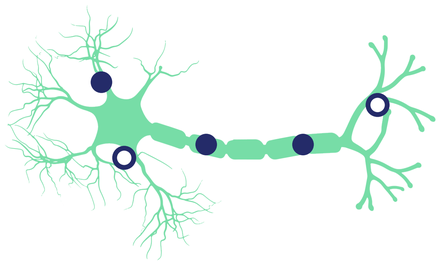
GIVLAARI® (givosiran) specifically targets ALAS1, key to the pathophysiology of AHP[3]

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[3,9]

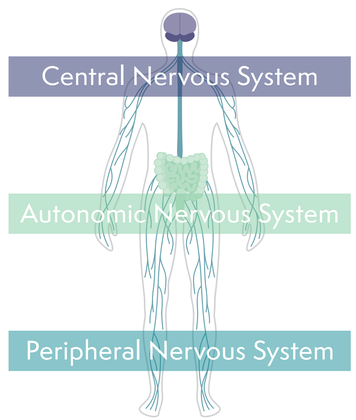
GIVLAARI targets ALAS1 mRNA for degradation, thereby reducing the production of the neurotoxic intermediates ALA and PBG[3,9]



Less ALA and PBG are released into circulation[5,9]



Reductions of ALA and PBG have been associated with fewer attacks[9]



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

IMPORTANT SAFETY INFORMATION

Anaphylactic Reaction

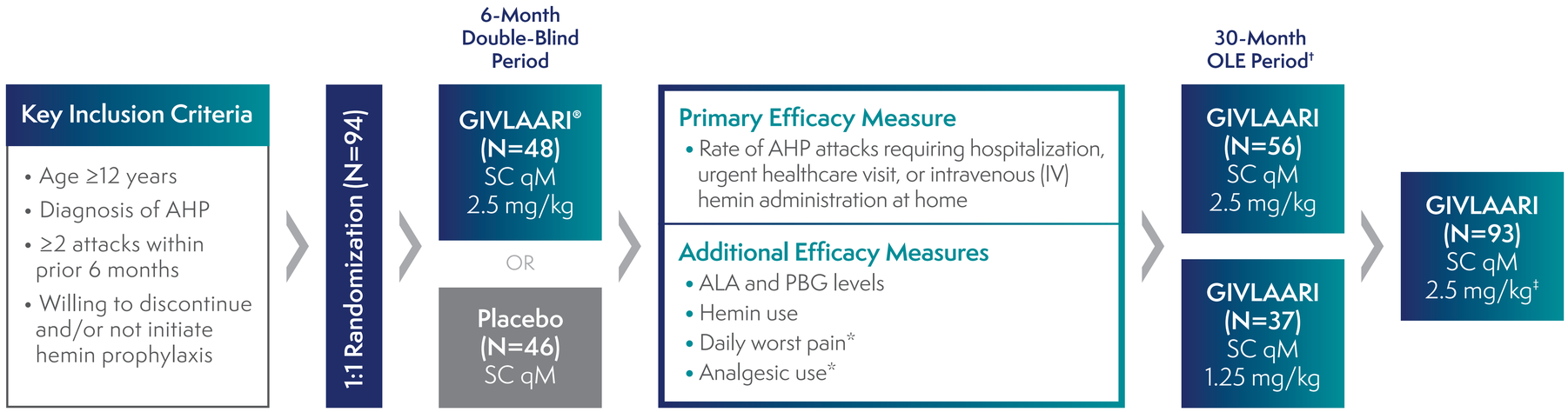
Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration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

ENVISION is 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)[3,10-12]



- Patients who experienced an AHP attack were treated according to the local standard of care, which could include IV hemin[3,10]

*These measures were in AIP patients 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.

AHP=acute hepatic porphyria; ALA=delta-aminolevulinic acid; PBG=porphobilinogen; qM=once monthly; SC=subcutaneous.

ENVISION is the largest interventional study in AHP.[3]

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.

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

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

ENVISION study patient population[3,10,12]

Baseline Demographic and Clinical Characteristics of Patients With AHP			
	GIVLAARI® (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)**
Attacks* in past 6 months, median (range)	4 (2, 24)	3 (0, 25)	**3 (0, 25)**
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)**

*Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.
†Use of opioids was defined as chronic if patients reported taking them for porphyria daily, or on most days, when not having an attack.
‡Symptoms were chronic if patients experienced symptoms of porphyria daily, or on most days, when not having an attack.

AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; HCP=hereditary coproporphyria; VP=variegate porphyria.

All eligible patients (93 of 94) enrolled in the open-label extension.[10]

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

Treatment with GIVLAARI® (givosiran) resulted in robust and sustained reductions in ALA and PBG[3]

Reductions through the ENVISION 6-month double-blind period[3,11,12]

- 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 ongoing ENVISION open-label extension period[11,12]

- In the first 6 months of the OLE period, 56 patients received GIVLAARI 2.5 mg/kg once monthly and 37 patients received GIVLAARI 1.25 mg/kg once monthly*†
- All endpoints were considered exploratory in the OLE period (a total of 6 months of treatment with GIVLAARI)
- In patients who continued treatment with GIVLAARI in the OLE period, reductions in urinary ALA and PBG were sustained through Month 12
  - 87% median reduction (Q1, Q3: 93%, 72%) and 91% median reduction (Q1, Q3: 96%, 72%) from baseline in urinary ALA and PBG, respectively
- In patients who crossed over from placebo to GIVLAARI in the OLE period (a total of 6 months of treatment with GIVLAARI)
  - 86% median reduction (Q1, Q3: 92%, 72%) and 87% median reduction (Q1, Q3: 93%, 72%) from baseline in urinary ALA and PBG, respectively, at Month 12

*Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg have been pooled.
†Protocol amendment increased the dose for all patients to 2.5 mg/kg once monthly.

ALA=delta-aminolevulinic acid; OLE=open-label extension; PBG=porphobilinogen.

Continued treatment with GIVLAARI resulted in robust and sustained reductions in ALA and PBG over 12 months.[11]

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.

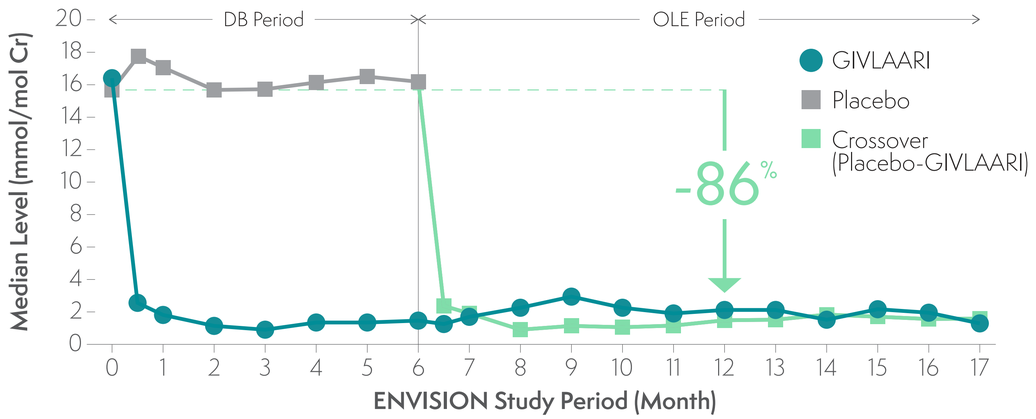
Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have 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.

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

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

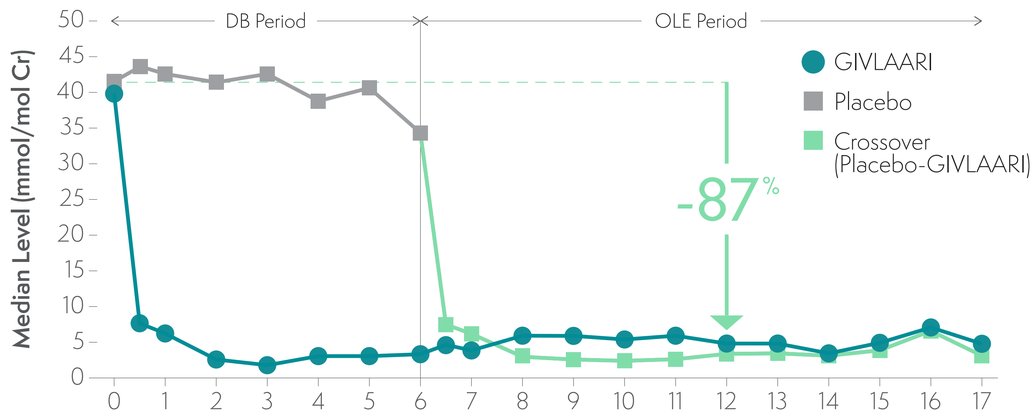
Treatment with GIVLAARI® (givosiran) resulted in robust and sustained reductions in ALA and PBG (cont'd)[3]

Urinary ALA levels[11,12]



GIVLAARI (N)	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9
Crossover (Placebo-GIVLAARI) (N)	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9

Urinary PBG levels[11,12]



GIVLAARI (N)	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9
Crossover (Placebo-GIVLAARI) (N)	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9

- In the first 6 months of the ENVISION OLE period, 56 patients received GIVLAARI 2.5 mg/kg once monthly and 37 patients received GIVLAARI 1.25 mg/kg once monthly[11,12*†]
- In patients who continued treatment with GIVLAARI in the OLE period, reductions in urinary ALA and PBG were sustained through Month 12[12]
  - 87% median reduction (Q1, Q3: 93%, 72%) and 91% median reduction (Q1, Q3: 96%, 72%) from baseline in urinary ALA and PBG, respectively
- In patients who crossed over from placebo to GIVLAARI in the OLE period (a total of 6 months of treatment with GIVLAARI)[12]
  - 86% median reduction (Q1, Q3: 92%, 72%) and 87% median reduction (Q1, Q3: 93%, 72%) from baseline in urinary ALA and PBG, respectively, at Month 12

*Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg have been pooled.
†Protocol amendment increased the dose for all patients to 2.5 mg/kg once monthly.

ALA=delta-aminolevulinic acid; DB=double-blind; OLE=open-label extension; PBG=porphobilinogen.

IMPORTANT SAFETY INFORMATION

Injection Site Reactions

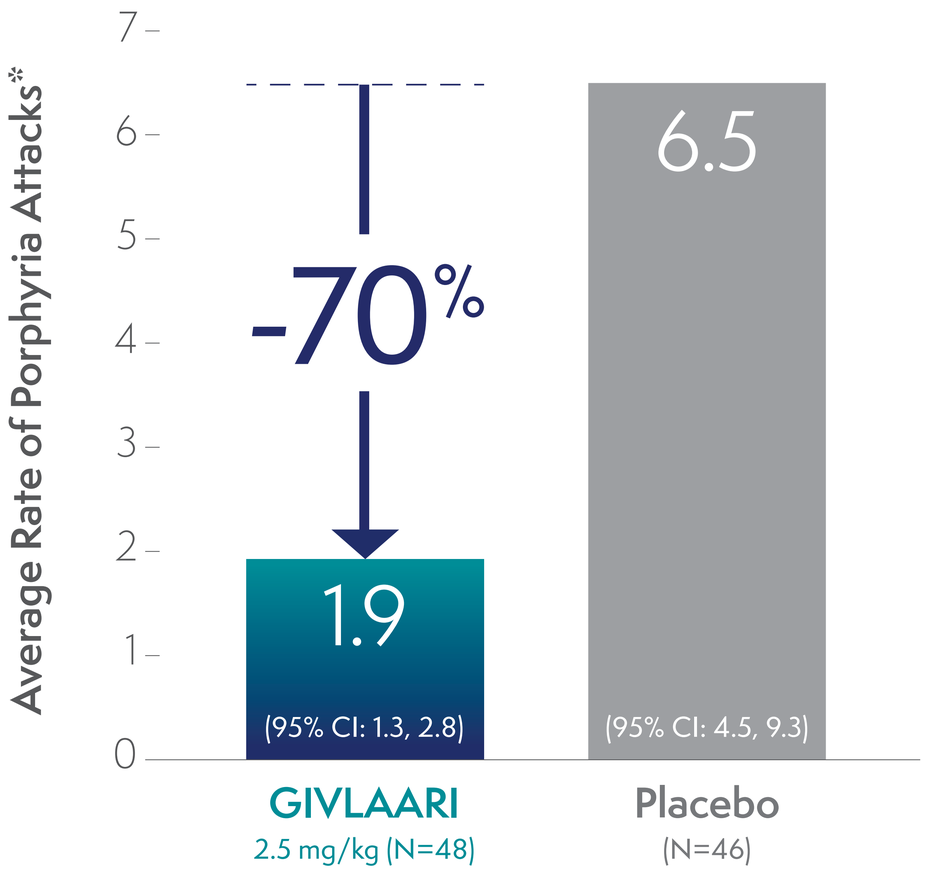
Injection site reactions were reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior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

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

Treatment with GIVLAARI® (givosiran) led to a significant reduction in porphyria attacks[3]*



70% fewer attacks* on average with GIVLAARI vs placebo[3]

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

*Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

AHP=acute hepatic porphyria.

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.

Adverse Reactions

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

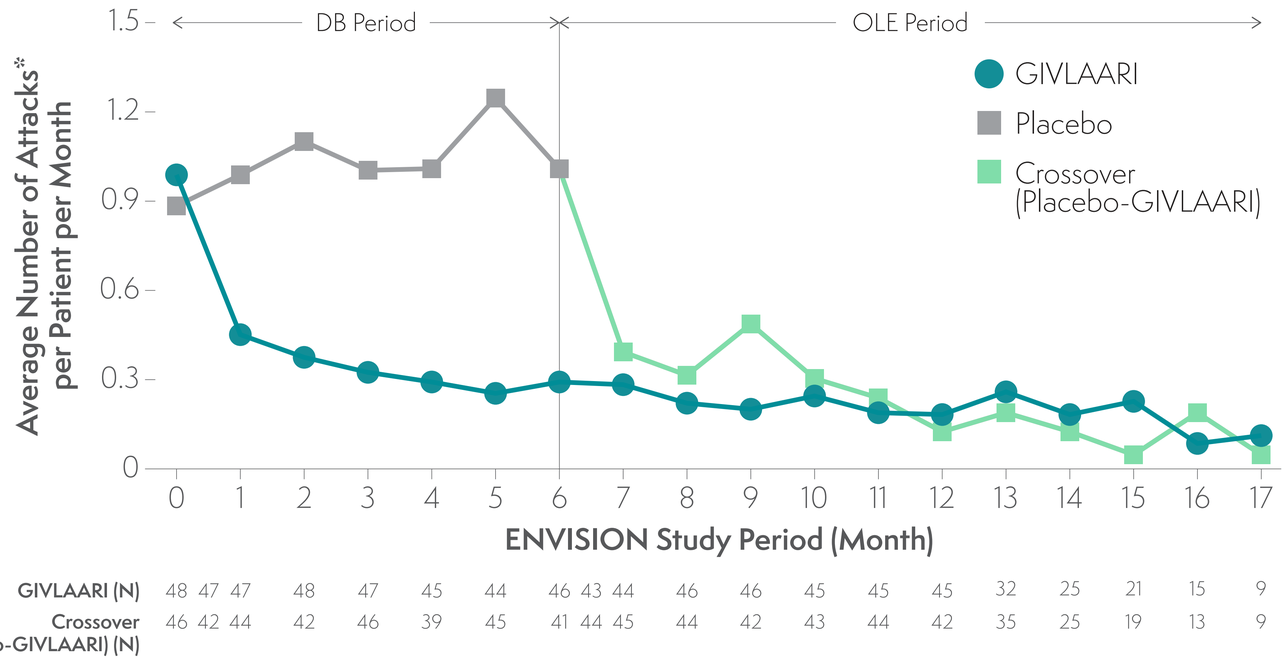
Please see Important Safety Information on page 21 and full Prescribing Information.

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

In a 12-month interim analysis of patients with AHP in the ENVISION OLE

Patients continuing treatment with GIVLAARI® (givosiran) had sustained attack* reduction[11,12]

Average number of attacks* over time



GIVLAARI (N)	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	32	25	21	15	9
Crossover (Placebo-GIVLAARI) (N)	46	42	44	42	46	39	45	41	44	45	44	42	43	44	42	35	25	19	13	9

- Attack* reduction was sustained in patients continuing treatment with GIVLAARI® during the ENVISION OLE period[11]
- Patients who crossed over from placebo to GIVLAARI had attack* reduction in the OLE period (for a total of 6 months of treatment) similar to that seen in GIVLAARI patients in the double-blind period†
- Endpoints in the OLE period are exploratory

*Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

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

AHP=acute hepatic porphyria; DB=double-blind; OLE=open-label extension.

IMPORTANT SAFETY INFORMATION

Contraindications

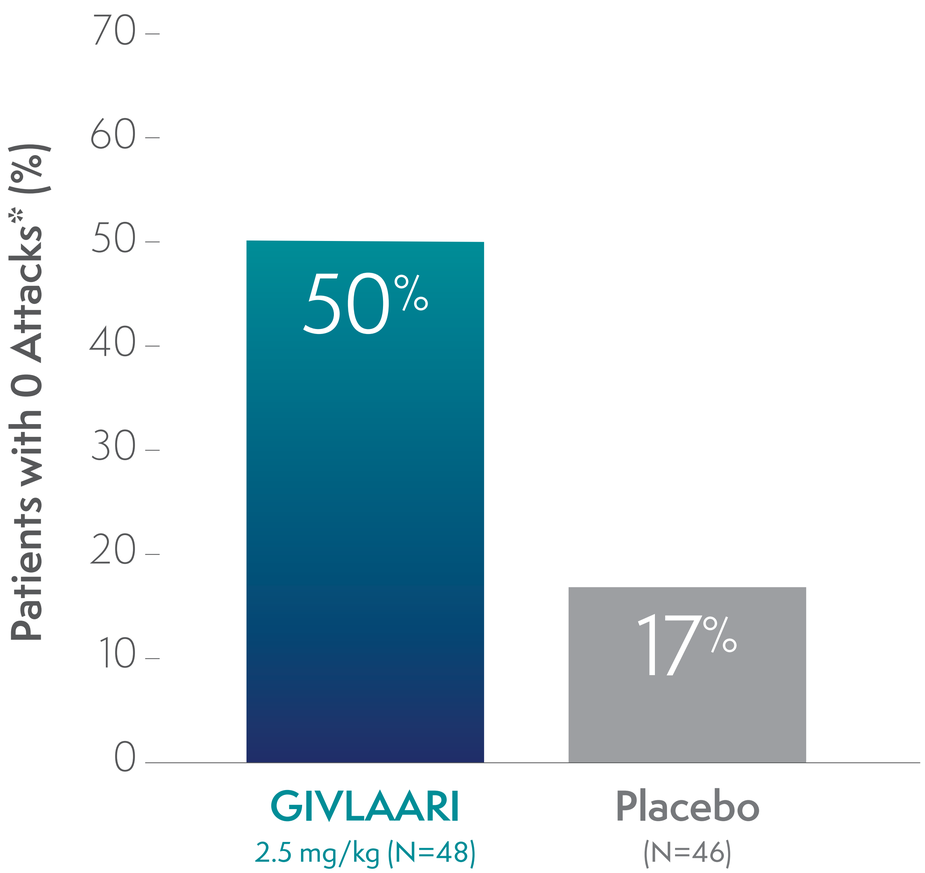
GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis.

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

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

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

A greater number of patients treated with GIVLAARI® (givosiran) had zero attacks vs placebo[10]*



50% of patients receiving GIVLAARI had zero attacks* in the 6-month DB period vs 17% of placebo patients

*Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

AHP=acute hepatic porphyria; DB=double-blind.

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.

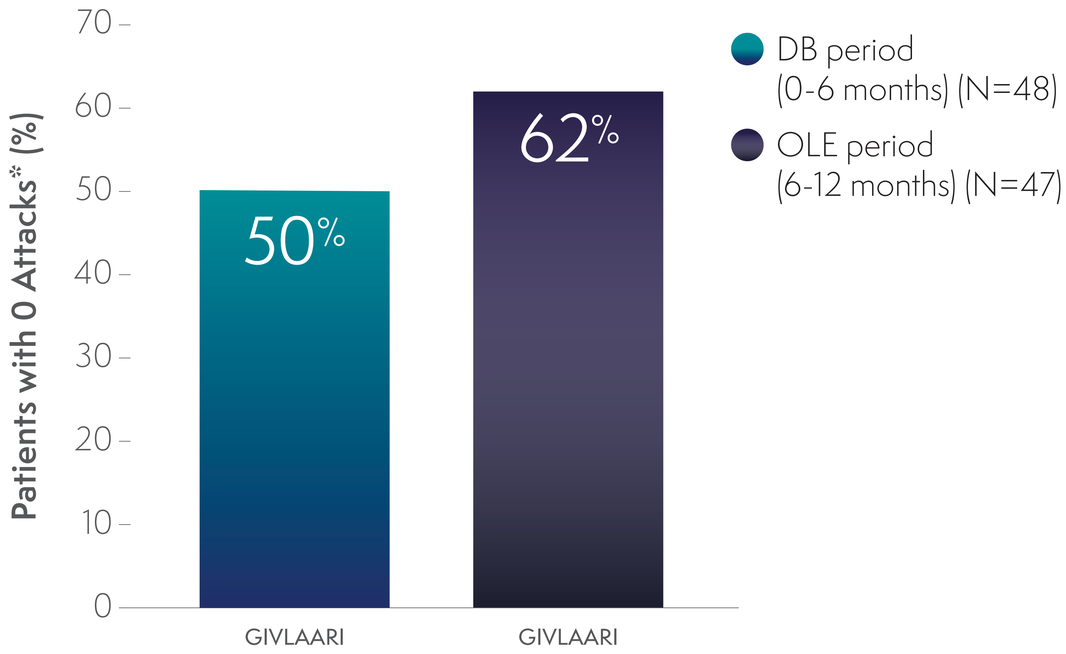
Please see Important Safety Information on page 21 and full Prescribing Information.

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

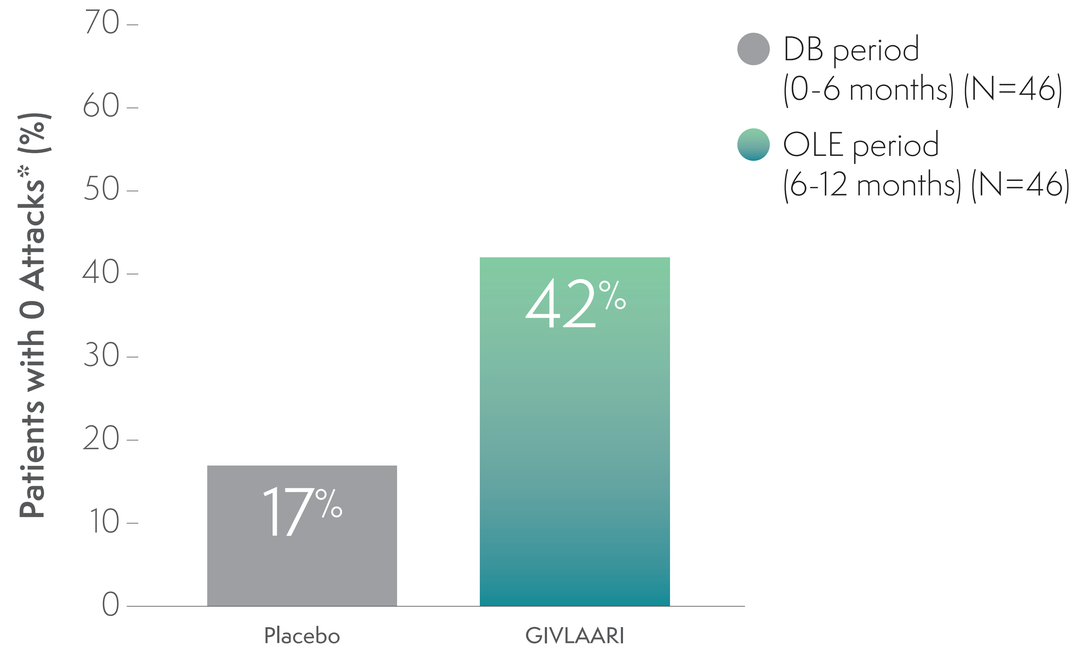
In a 12-month interim analysis of patients with AHP in the ENVISION OLE

The number of patients with zero attacks* increased with continued treatment with GIVLAARI® (givosiran)[11,12†]

The number of patients with zero attacks* increased with continued treatment with GIVLAARI®[11,12†]



In the patients who crossed over from placebo to GIVLAARI, more had zero attacks* after starting GIVLAARI[11,12†]



*Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

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

AHP=acute hepatic porphyria; DB=double-blind; OLE=open-label extension.

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.

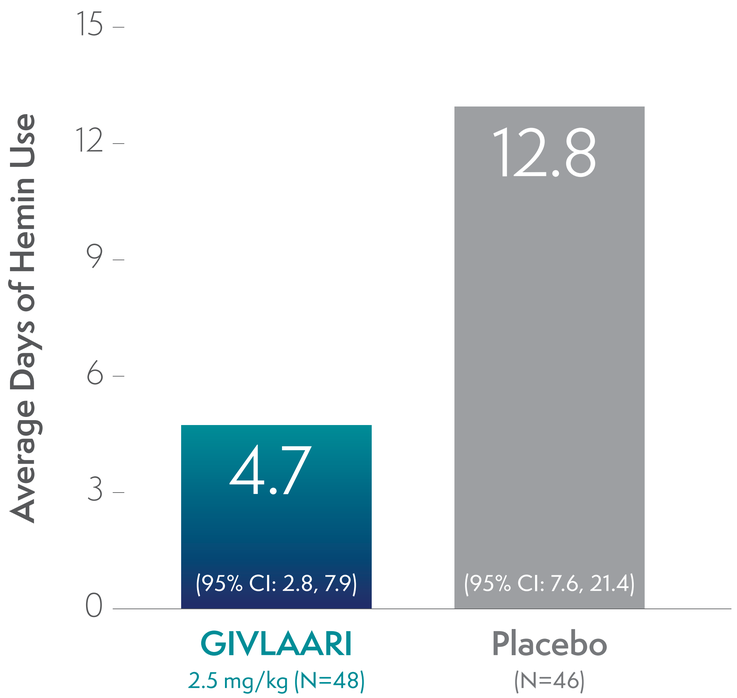
Please see Important Safety Information on page 21 and full Prescribing Information.

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

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

Significantly less hemin was used by patients treated with GIVLAARI® (givosiran)[3]

70% reduction in average days of hemin use with GIVLAARI vs placebo[3]



In the ENVISION 6-month DB period, 54% of AIP patients (N=25/46) treated with GIVLAARI had zero days of hemin compared with 23% of patients (N=10/43) receiving placebo.[3]

- Ratio of average days of hemin use (GIVLAARI:placebo): 0.3 (95% CI: 0.1, 0.5; *P*=0.0002)[3]

AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; DB=double-blind.

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 a 12-month interim analysis of patients with AHP in the ENVISION OLE

Days of hemin use decreased with continued treatment with GIVLAARI® (givosiran)[11,12]

70% of patients who continued treatment with GIVLAARI® (N=33/47) required zero days of hemin[11,12*]

- Patients who crossed over from placebo to GIVLAARI had hemin use reduction in the ENVISION OLE period (for a total of 6 months of treatment with GIVLAARI) similar to that seen in patients receiving GIVLAARI in the double-blind period*

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

AHP=acute hepatic porphyria; DB=double-blind; OLE=open-label extension.

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.

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

Daily worst pain in the ENVISION 6-month double-blind period

Daily worst pain score in AIP patients was a secondary endpoint[13]

- Pain was measured using patient-reported daily worst pain scores based on a numeric rating scale (NRS)[13]
- A statistical analysis of the change from baseline in daily worst pain score for GIVLAARI® vs placebo was conducted[13]
- A positive score represents a worsening in daily worst pain from baseline; a negative score represents an improvement from baseline[13]
- GIVLAARI did not meet statistical significance for this endpoint based on the prespecified statistical method[13]
- The daily worst pain scores were lower with GIVLAARI compared with placebo[13]

Daily worst pain scores in AIP patients (AUC of mean change from baseline)[13]

GIVLAARI (N=46) (95% CI)	Placebo (N=43) (95% CI)	Treatment difference (95% CI)
-12.876 (-21.776, -3.976)	-0.196 (-9.468, 9.077)	-12.680 (-25.526, 0.166)

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

IMPORTANT SAFETY INFORMATION

Drug Interactions

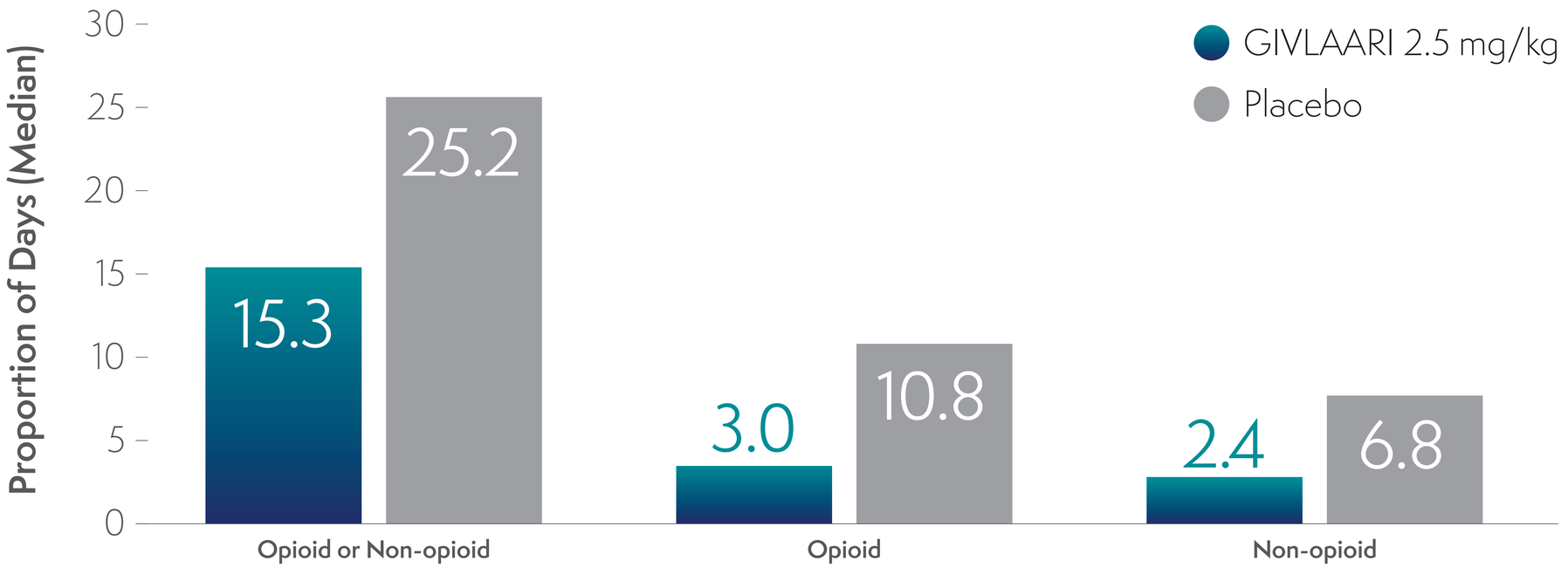
Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GIVLAARI with CYP1A2 or CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. 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

Analgesic use in AIP patients in the ENVISION 6-month double-blind period[12,13]

Analgesic use in AIP patients was a prespecified exploratory endpoint[13]



- Through Month 6, the proportion of days with opioid and non-opioid analgesic use was lower in patients treated with GIVLAARI® compared to placebo[13]
- An evaluation compared to baseline analgesic use cannot be conducted because the proportion of days with analgesic use was not captured at baseline[12]

AIP=acute intermittent porphyria.

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

Safety profile of GIVLAARI® (givosiran) in the ENVISION study[3]

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 period[3]

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[3]
  - No additional discontinuations due to adverse events in the ENVISION OLE period[12]
- The most frequently occurring (≥20%) adverse reactions reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%)[3]
- The safety profile of GIVLAARI in the OLE period was similar to that observed in the 6-month double-blind period[11]

eGFR=estimated glomerular filtration rate; OLE=open-label extension.

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.

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)[3]

The recommended dose of GIVLAARI is 2.5 mg/kg administered via subcutaneous injection once monthly. Dosing is based on actual body weight.

Missed dose

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

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
- 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

GIVLAARI is administered via subcutaneous injection by a healthcare professional only

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

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.

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

Alnylam Assist® provides personalized support for patients

Alnylam Assist® is here to help your patients:

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

*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.

Alnylam ASSIST®

Monday–Friday, 8AM–6PM ET

: 1-833-256-2748 | : 1-833-256-2747

To learn more, visit www.AlnylamAssist.com.

How to get started:

1 **Complete Start Form**

2 **Case Manager Reaches Out**

3 **Patient Assistance Offered**

After discussing GIVLAARI with your patient, begin the enrollment process by completing the GIVLAARI Start Form. Upon receipt of the Start Form, an **Alnylam Case Manager dedicated to your patient's needs** will reach out to you and your patient within 1-2 business days.

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.

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.

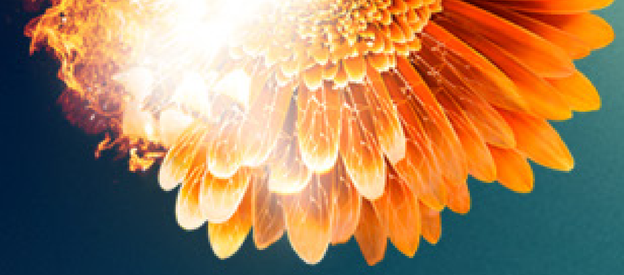
Adverse Reactions

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

References: 1. Simon A, Pompilus F, Querbes W, et al. *Patient*. 2018;11(5):527-537. doi:10.1007/s40271-018-0319-3. **2.** Neeleman RA, Wagenmakers MAEM, Koole-Lesuis RH, et al. *J Inherit Metab Dis*. 2018;41(5):809-817. doi:10.1007/s10545-018-0178-z. **3.** GIVLAARI [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; 2019. **4.** Ventura P, Cappellini MD, Biolcati G, Guida CC, Rocchi E; Gruppo Italiano Porfiria (GrIP). *Eur J Intern Med*. 2014;25(6):497-505. **5.** Bissell DM, Anderson KE, Bonkovsky HL. *N Engl J Med*. 2017;377(21):862-872. **6.** Puy H, Gouya L, Deybach JC. *Lancet*. 2010;375(9718):924-937. **7.** Balwani M, Wang B, Anderson KE, et al; Porphyrias Consortium of the Rare Diseases Clinical Research Network. *Hepatology*. 2017;66(4):1314-1322. **8.** Bonkovsky HL, Dixon N, Rudnick S. *Mol Genet Metab*. 2019;128(3):213-218. doi:10.1016/j.ymgme.2019.03.002. **9.** Sardh E, Harper P, Balwani M, et al. *N Engl J Med*. 2019;380(6):549-558. **10.** Sardh E, Balwani M, Rees DC, et al. *J Hepatology*. To be published August, 2020; Accessed at: https://ilc-congress.eu/programme-dilc-2020/. **11.** Balwani M, Sardh E, Ventura P, et al; ENVISION Investigators. *N Engl J Med*. 2020;382(24):2289-2301. **12.** Data on file. Alnylam Pharmaceuticals, Inc. **13.** Gouya L, Sardh E, Balwani M, et al; ENVISION investigators. Poster presented at: International Congress on Porphyrins and Porphyrias; September 10, 2019; Milan, Italy.

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

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



GIVLAARI® (givosiran) significantly reduced attacks* in adults with acute hepatic porphyria (AHP)[3]

- 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[3,9]

Efficacy findings from the ENVISION 6-month DB period and ongoing OLE period

- 70% fewer porphyria attacks* on average with GIVLAARI vs placebo in the 6-month double-blind period of ENVISION[3]
  - **Average number of porphyria attacks:** 1.9 (95% CI: 1.3, 2.8) with GIVLAARI vs 6.5 (95% CI: 4.5, 9.3) with placebo; attack rate ratio: 0.3 (95% CI: 0.2, 0.4; *P*<0.0001)[3]
- Attack* reduction was sustained for patients continuing to receive GIVLAARI through Month 12 of the OLE period[11,12]

***Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.**

Safety findings from the ENVISION 6-month DB period and ongoing OLE period

- Permanent discontinuation of GIVLAARI occurred in 1 patient (2.1%) due to elevated transaminases per protocol-defined stopping rules[3]
- Most common adverse reactions (≥20%) reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%) in the 6-month double-blind period[3]
- The safety profile of GIVLAARI in the OLE period was similar to that observed in the 6-month DB period[11]

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 administer 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.

Drug Interactions: Avoid concomitant use with CYP1A2 and CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities.

See additional Important Safety Information on page 21 and full Prescribing Information.

Alnylam® PHARMACEUTICALS

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