

My GIVLAARI® (givosiran) Journal

Get the most out
of your treatment



Amalia, an Alnylam Patient Ambassador on GIVLAARI

Individual results may vary

What is GIVLAARI?

GIVLAARI is a prescription medicine used to treat acute hepatic porphyria (AHP) in adults.

IMPORTANT SAFETY INFORMATION

Do not use GIVLAARI if you have ever had a severe allergic reaction to GIVLAARI.

Please see Important Safety Information on page 9 and full Prescribing Information.

START TRACKING YOUR TREATMENT JOURNEY

It's important to prepare and stay organized for your GIVLAARI® (givosiran) treatment over time.

In a 6-month study, 48 people with acute hepatic porphyria (AHP) received GIVLAARI, while 46 received placebo (an injection that did not contain any medicine), once monthly.



GIVLAARI reduced AHP attacks* by 70% and resulted in 70% fewer days of hemin use compared with placebo during the 6-month period, with sustained attack reduction observed through 36 months



The most common side effects in patients treated with GIVLAARI compared to those taking placebo in the first 6 months of the study were nausea, injection site reactions, rash, changes in kidney function, changes in liver function, and fatigue



The most frequently reported side effects occurring in $\geq 20\%$ of patients through 36 months of the study were injection site reactions, nausea, fatigue, nasopharyngitis, headache, urinary tract infection, and upper respiratory tract infection. Increased blood homocysteine was reported in 15 of 93 (16%) patients treated with GIVLAARI

* Attacks were defined as those that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin at home.

***"Your pain is real;
it is valid, and you don't
have to go through
it alone."***

Amalia, Alnylam Patient
Ambassador on GIVLAARI



Please see [Important Safety Information](#) on page 9 and full [Prescribing Information](#).

WHAT TO EXPECT: PREPARING FOR POSSIBLE SIDE EFFECTS

Ask your doctor about ways that may help manage some of the following most common treatment-related side effects observed with GIVLAARI[†]:

NAUSEA

Anti-nausea medication may be an option.

INJECTION SITE REACTIONS

Numbing the injection site prior to treatment may reduce discomfort, and rotating where you get your injection (abdomen, thighs, or the side or back of the upper arms) may help reduce injection site reactions (like redness, pain, itchiness, rash, discoloration, or swelling around the injection site).

RASH

There are topical treatments for skin rash that may be an option.

CHANGES IN KIDNEY FUNCTION

Kidney function changes may occur. Your doctor will monitor your level of kidney function while you are using GIVLAARI.

CHANGES IN LIVER FUNCTION

Liver enzymes may increase after starting GIVLAARI. Your doctor will check your liver function before and during the first 6 months of treatment with GIVLAARI, and when they think it is needed.

FATIGUE

Take it easy. Rest as much as you can. You might feel tired after receiving your injection and may want to ask a caretaker, friends, or family for support.

[†]These are not all the possible side effects you may experience with GIVLAARI.

Reach out to your Alnylam Patient Engagement Liaison (PEL), who can answer questions and provide education about treatment with GIVLAARI.[‡]

GIVLAARI is a once-a-month injection given subcutaneously (under the skin) by a healthcare professional. If a dose is missed, a healthcare professional should administer GIVLAARI as soon as possible.

IT'S IMPORTANT TO TRACK YOUR PROGRESS

Keep track of how you're feeling from month to month, injections, and side effects to discuss progress with your doctor.

MONTH 1

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 2

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 3

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 4

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 5

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 6

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



BE PROUD OF YOUR JOURNEY

Look back at how you felt before starting treatment, and compare it with how you feel at 6 months.

IT'S IMPORTANT TO TRACK YOUR PROGRESS

Keep track of how you're feeling from month to month, injections, and side effects to discuss progress with your doctor.

MONTH 7

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 8

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 9

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 10

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 11

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



MONTH 12

Date and location of injection _____

Side effects _____

Notes _____

How are you feeling?



THINK OF HOW FAR YOU'VE COME

Reflect on how you felt before treatment and at month 6, and compare it to how you feel after 12 months.

NOTES

GOALS FOR GIVLAARI® (givosiran) TREATMENT

QUESTIONS TO ASK YOUR DOCTOR

OTHER THOUGHTS WHILE ON TREATMENT

IMPORTANT SAFETY INFORMATION

Do not use GIVLAARI® (givosiran) if you have ever had a severe allergic reaction to GIVLAARI.

GIVLAARI can cause:

- **Severe allergic reaction**

Tell your doctor or nurse right away if you experience any of the following signs or symptoms of a severe allergic reaction during treatment:

- Swelling – mainly of the lips, tongue or throat which makes it difficult to swallow or breathe
- Breathing problems or wheezing
- Feeling dizzy or fainting
- Rash or hives
- Itching

If you have a severe allergic reaction, your doctor or nurse will stop GIVLAARI treatment right away and you may need to take other medicines to control the symptoms.

- **Liver problems**

Your doctor will check your liver function by doing blood tests:

- Before you start using GIVLAARI
- Once a month for the first 6 months of treatment
- And when they think it is needed

If these tests show abnormal results, your doctor or nurse will decide whether to temporarily interrupt or stop treatment with GIVLAARI.

- **Kidney problems**

Your doctor will check how your kidneys are working while you are using GIVLAARI.

- **Injection site reactions**

GIVLAARI is given as an injection under the skin (called a “subcutaneous injection”). Reactions to this injection may happen during treatment with GIVLAARI.

Tell your doctor or nurse right away if you experience any of the following symptoms of an injection site reaction during treatment: redness, pain, itchiness, rash, discoloration, or swelling around the injection site.

- **Increased blood homocysteine levels**

GIVLAARI may cause increased levels of homocysteine (a type of amino acid) in your blood. Your doctor will check your homocysteine levels before and during treatment by doing blood tests. If your levels are increased, your doctor may check your folate, vitamins B12 and B6, and tell you to take a vitamin B6 supplement.

- **Inflammation of the pancreas (pancreatitis)**

Cases of acute pancreatitis including some that were severe, have been reported in patients receiving GIVLAARI. If you have a severe case of acute pancreatitis your doctor or nurse will decide whether to temporarily interrupt or stop treatment with GIVLAARI.

What are the common side effects of GIVLAARI?

The most common side effects of GIVLAARI are nausea and injection site reactions. These are not all the possible side effects of GIVLAARI. Talk to your doctor about side effects that you experience. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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

THE ALNYLAM ASSIST® PROGRAM OFFERS YOU SUPPORT THROUGHOUT YOUR TREATMENT WITH GIVLAARI® (givosiran).

Your Alnylam Case Manager is experienced in:

- ✓ Helping you get started on treatment
- ✓ Navigating your insurance benefits
- ✓ Determining your eligibility for financial assistance
- ✓ Providing you with product support throughout your treatment

Name _____

Phone Number _____

Your Alnylam Patient Education Liaison (PEL) can help you in a variety of ways, such as:

- ✓ Supporting you with disease education
- ✓ Connecting you to additional resources
- ✓ Answering questions about treatment with GIVLAARI
- ✓ Providing you with product education

Name _____

Phone Number _____

Reach out to **Alnylam Assist®** team members whenever you need them.



**CONNECT WITH
YOUR PEL**

*The purpose of Alnylam PELs is to provide education to patients, their families, and caregivers. PELs are employees of Alnylam Pharmaceuticals. They are not acting as healthcare providers and are not part of your healthcare team. PELs do not provide medical care or advice. All diagnosis and treatment decisions should be made by you and your doctor.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GIVLAARI® safely and effectively. See full prescribing information for GIVLAARI.

GIVLAARI (givosiran) injection, for subcutaneous use
Initial U.S. Approval: 2019

-----**RECENT MAJOR CHANGES**-----
Warnings and Precautions, Pancreatitis (5.6) 4/2024

-----**INDICATIONS AND USAGE**-----
GIVLAARI is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria (AHP). (1)

-----**DOSAGE AND ADMINISTRATION**-----
The recommended dose of GIVLAARI is 2.5 mg/kg once monthly by subcutaneous injection. (2.1)

-----**DOSAGE FORMS AND STRENGTHS**-----
Injection: 189 mg/mL in a single-dose vial. (3)

-----**CONTRAINDICATIONS**-----
Severe hypersensitivity to givosiran. (4)

- WARNINGS AND PRECAUTIONS**-----
- 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. (5.1)
 - 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. (2.1, 5.2)
- Renal Toxicity: Monitor renal function during treatment with GIVLAARI as clinically indicated. (5.3)
- Injection Site Reactions: May occur, including recall reactions. Monitor for reactions and manage clinically as needed. (5.4)
- 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). (5.5)
- Pancreatitis: Consider acute pancreatitis as a potential diagnosis in GIVLAARI-treated patients with acute upper abdominal pain, clinically significant elevation of pancreatic enzymes and/or imaging findings of acute pancreatitis, to ensure appropriate management. (5.6)

-----**ADVERSE REACTIONS**-----
The most common adverse reactions (≥20% of patients) included nausea and injection site reactions. (6.1)

To report **SUSPECTED ADVERSE REACTIONS**, contact Alnylam Pharmaceuticals at 1-877-256-9526 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----
Sensitive CYP1A2 and CYP2D6 Substrates: Avoid concomitant use with CYP1A2 and CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. (7.1)

See 17 for **PATIENT COUNSELING INFORMATION**.

Revised: 4/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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 Modification 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 [see *Warnings and Precautions* (5.2)]. 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 dose of 2.5 mg/kg once monthly.

2.2 Administration Instructions

Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI [see *Warnings and Precautions* (5.1)].

GIVLAARI is intended for subcutaneous use by a healthcare professional only.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. GIVLAARI is a sterile, preservative-free, clear, colorless-to-yellow solution. It is supplied in a single-dose vial, as a ready-to-use solution that does not require additional reconstitution or dilution prior to administration.

Use aseptic technique.

- Calculate the required volume of GIVLAARI based on the recommended weight-based dosage [see *Dosage and Administration* (2.1)].
- Withdraw the indicated injection volume of GIVLAARI using a 21-gauge or larger needle.
 - Divide doses requiring volumes greater than 1.5 mL equally into multiple syringes.
- Replace the 21-gauge or larger needle with either a 25-gauge or 27-gauge needle with 1/2" or 5/8" needle length.
- Avoid having GIVLAARI on the needle tip until the needle is in the subcutaneous space.
- Administer injection into the abdomen, the back or side of the upper arms, or the thighs. Rotate injection sites. An injection should never be given into scar tissue or areas that are reddened, inflamed, or swollen.
 - If injecting into the abdomen, avoid a 5 cm diameter circle around the navel.
 - If more than one injection is needed for a single dose of GIVLAARI, the injection sites should be at least 2 cm apart from previous injection locations.
- Discard unused portion of the drug.

3 DOSAGE FORMS AND STRENGTHS

Injection: 189 mg/mL clear, colorless-to-yellow solution in a single-dose vial

4 CONTRAINDICATIONS

GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactic Reaction

Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials) [see *Adverse Reactions* (6.1)]. 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.

5.2 Hepatic Toxicity

Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients treated with GIVLAARI in the placebo-controlled trial [see *Adverse Reactions* (6.1)]. 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. For resumption of dosing after interruption, see *Dosage and Administration* (2.1).

5.3 Renal Toxicity

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI [see *Adverse Reactions* (6.1)]. In the placebo-controlled study, 15% of the patients in the GIVLAARI arm 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.

5.4 Injection Site Reactions

Injection site reactions have been 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. Among 12 patients with reactions, the highest severity of the reaction was mild among 11 (92%) patients and moderate in one (8%) patient. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration [see *Adverse Reactions* (6.1)].

5.5 Blood Homocysteine Increased

Increases in blood homocysteine levels have occurred in patients receiving GIVLAARI [see *Adverse Reactions* (6.1)]. 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. The clinical relevance of the elevations in blood homocysteine during treatment with GIVLAARI is unknown. 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).

5.6 Pancreatitis

Cases of acute pancreatitis, some severe, have been reported in GIVLAARI-treated patients.

Consider acute pancreatitis as a potential diagnosis in GIVLAARI-treated patients with signs/symptoms of acute pancreatitis including acute upper abdominal pain, clinically significant elevation of pancreatic enzymes, and/or imaging findings of acute pancreatitis, to ensure appropriate management. Consider interruption and/or discontinuation of GIVLAARI treatment for severe cases.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Anaphylactic Reaction [see Warnings and Precautions (5.1)]
- Transaminase Elevations [see Warnings and Precautions (5.2)]
- Serum Creatinine Increase [see Warnings and Precautions (5.3)]
- Injection Site Reactions [see Warnings and Precautions (5.4)]
- Blood Homocysteine Increased [see Warnings and Precautions (5.5)]
- Pancreatitis [see Warnings and Precautions (5.6)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the pivotal placebo-controlled, double-blind study (ENVISION), 48 patients received 2.5 mg/kg GIVLAARI and 46 patients received placebo, administered once monthly via subcutaneous injection for up to 6 months. Patients received GIVLAARI for a median of 5.5 months (range 2.7-6.4 months). Of these, 47 patients received ≥ 5 months of treatment. The most frequently occurring ($\geq 20\%$ incidence) adverse reactions reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%). Permanent discontinuation occurred in one patient due to elevated transaminases.

Table 1: Adverse Reactions that Occurred at Least 5% More Frequently in Patients Treated with GIVLAARI Compared to Patients Treated with Placebo

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)		

Adverse reactions observed at a lower frequency occurring in placebo-controlled and open-label clinical studies included anaphylactic reaction (one patient, 0.9%) and hypersensitivity (one patient, 0.9%).

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 [see Warnings and Precautions (5.5)].

6.2 Immunogenicity

As with all oligonucleotides, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In placebo-controlled and open-label clinical studies, 1 of 111 patients with AHP (0.9%) developed treatment-emergent anti-drug antibodies (ADA) during treatment with GIVLAARI. No clinically significant

differences in the clinical efficacy, safety, pharmacokinetic, or pharmacodynamic profiles of GIVLAARI were observed in the patient who tested positive for anti-givosiran antibodies.

6.3 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Acute pancreatitis

7 DRUG INTERACTIONS

7.1 Effect of GIVLAARI on Other Drugs

Sensitive CYP1A2 and CYP2D6 Substrates

Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates [see *Clinical Pharmacology* (12.3)], 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In animal reproduction studies, subcutaneous administration of givosiran to pregnant rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses that produced maternal toxicity (see *Data*).

There are no available data with GIVLAARI use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Consider the benefits and risks of GIVLAARI for the mother and potential adverse effects to the fetus when prescribing GIVLAARI to a pregnant woman.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Porphyria attacks during pregnancy, often triggered by hormonal changes, occur in 24% to 95% of AHP patients, with maternal mortality ranging from 2% to 42%. Pregnancy in AHP patients is associated with higher rates of spontaneous abortion, hypertension and low birth weight infants.

Data

Animal Data

In an embryo-fetal development study in pregnant rabbits, givosiran was administered subcutaneously at doses of 0.5, 1.5, and 5 mg/kg/day during organogenesis (gestational days 7-19) or 20 mg/kg as a single administration on gestation day 7. Administration of givosiran was maternally toxic based on decreased body weight gain at all dose levels tested and resulted in increased postimplantation loss starting at 1.5 mg/kg/day. An increased incidence of skeletal variations of the sternbrae was observed at 20 mg/kg. The 1.5 mg/kg/day dose in rabbits is 5 times the maximum recommended human dose (MRHD) of 2.5 mg/kg/month normalized to 0.089 mg/kg/day, based on body surface area. In a combined fertility and embryo-fetal development study in female rats, givosiran was administered subcutaneously at doses of 0.5 to 5 mg/kg/day during organogenesis (gestational days 6-17). The 5 mg/kg/day dose (9 times the normalized MRHD based on body surface area) was associated with a skeletal variation (incomplete ossification of pubes) and produced maternal toxicity.

GIVLAARI is supplied as a sterile, preservative-free, 1-mL colorless-to-yellow solution for subcutaneous injection containing 189 mg givosiran in a single-dose, 2-mL Type 1 glass vial with a fluoropolymer-coated rubber stopper and a flip-off aluminum seal. GIVLAARI is available in cartons containing one single-dose

vial each. GIVLAARI is formulated in Water for Injection. Sodium hydroxide and/or phosphoric acid may have been added for pH adjustment during product manufacturing.

The molecular formula of givosiran sodium is C₅₂₄ H₆₅₁ F₁₆ N₁₇₃ Na₄₃ O₃₁₆ P₄₃ S₆ with a molecular weight of 17,245.56 Da.

The molecular formula of givosiran (free acid) is C₅₂₄ H₆₉₄ F₁₆ N₁₇₃ O₃₁₆ P₄₃ S₆ with a molecular weight of 16,300.34 Da.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver *ALAS1* mRNA. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.

12.2 Pharmacodynamics

The pharmacodynamic effects of GIVLAARI were evaluated in chronic high excretors treated with 0.035 to 2.5 mg/kg single dose and AHP patients treated with 2.5 to 5 mg/kg once monthly and 2.5 to 5 mg/kg once quarterly dose via subcutaneous injection. Dose-dependent reduction in urinary *ALAS1* mRNA, ALA and PBG levels was observed over the 0.035 to 5 mg/kg dose range (0.14 to 2-fold the approved recommended dosage). Median reductions from baseline in urinary ALA and PBG of 83.7% and 75.1%, respectively, were observed 14 days after the first dose of GIVLAARI 2.5 mg/kg once monthly in AHP patients. Maximal reductions in ALA and PBG levels were achieved around Month 3, with median reductions from baseline of 93.8% for ALA and 94.5% for PBG, and were sustained thereafter with repeated once monthly dosing.

Cardiac Electrophysiology

The effect of GIVLAARI on the QTc interval was evaluated in a double-blind, placebo-controlled study and the open-label extension in 94 patients. No large mean increase in QTc (i.e. >20 ms) was detected at the 2.5 mg/kg once monthly dose level. A dedicated thorough QT study has not been conducted with GIVLAARI.

12.3 Pharmacokinetics

The pharmacokinetics of givosiran and its active metabolite [AS(N-1)3' givosiran] were evaluated following single and multiple dosing in chronic high excreter subjects and AHP patients as summarized in Table 2.

Table 2. Pharmacokinetic Parameters of Givosiran and Its Active Metabolite

		Givosiran	AS(N-1)3' Givosiran
General Information			
Steady-State Exposure	C _{max} [Mean (CV%)]	321 ng/mL (51%)	123 ng/mL (64%)
	AUC ₂₄ [Mean (CV%)]	4130 ng·h/mL (43%)	1930 ng·h/mL (63%)
Dose Proportionality		- Steady-state maximum plasma concentration (C_{max}) and area under the curve (AUC) for givosiran and AS(N-1)3' givosiran increase proportionally over the 0.35 mg/kg to 2.5 mg/kg once monthly dose range (0.14 to 1-fold the approved recommended dosage). - C_{max} and AUC for givosiran and AS(N-1)3' givosiran increase slightly greater than proportionally at doses greater than 2.5 mg/kg once monthly.	
Accumulation		No accumulation of givosiran or AS(N-1)3' givosiran was observed following multiple dosing.	
Absorption			
T _{max} [Median (range)]		3 (0.5-8) hours	7 (1.5-12) hours
Distribution			
Apparent Central Volume of Distribution (V _z /F) [Mean (RSE%)] ^a		10.4 L (2.3%)	
Protein Binding		90% ^b	Not evaluated
Organ Distribution		Givosiran and AS(N-1)3' givosiran distribute primarily to the liver after subcutaneous dosing.	
Elimination			
Half-Life [Mean (CV%)]		6 hours (46%)	6 hours (41%)
Apparent Clearance [Mean (CV%)] ^a		35.1 L/hr (18%)	64.7 L/hr (33%)
Metabolism			
Primary Pathway		Givosiran is metabolized by nucleases to oligonucleotides of shorter lengths. Givosiran is not a substrate of CYP enzymes ^c .	
Active Metabolite		The active metabolite, AS(N-1)3' givosiran, is equipotent to givosiran in plasma and the AUC ₀₋₂₄ represents 45% of givosiran AUC, at the approved recommended givosiran dosage.	
Excretion			
Primary Pathway		The dose recovered in urine was 5%-14% as givosiran and 4%-13% as AS(N-1)3' givosiran ^d .	
^a Based on population PK model estimation.			
^b Givosiran plasma protein binding was concentration-dependent and decreased with increasing givosiran concentrations (from 92% at 1 µg/mL to 21% at 50 µg/mL).			
^c Based on in vitro study result.			
^d After single and multiple subcutaneous doses of givosiran 2.5 mg/kg and 5 mg/kg.			

Specific Populations

No clinically meaningful differences in givosiran pharmacokinetics or pharmacodynamics (percent reduction in urinary ALA and PBG) were observed based on age (19 to 65 years), sex, race/ethnicity, mild, moderate or severe renal impairment (eGFR ≥ 15 to < 89 mL/min/1.73m² estimated by the Modification of Diet in Renal Disease [MDRD] formula), and mild hepatic impairment (bilirubin $\leq 1 \times$ ULN and AST $> 1 \times$ ULN, or bilirubin $> 1 \times$ ULN to $1.5 \times$ ULN). The effect of end-stage renal disease (eGFR < 15 mL/min/1.73m²), and moderate to severe hepatic impairment on givosiran pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Effect of givosiran on CYP1A2 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased caffeine (sensitive CYP1A2 substrate) AUC by 3.1-fold and C_{max} by 1.3-fold [see *Drug Interactions* (7.1)].

Effect of givosiran on CYP2D6 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased dextromethorphan (sensitive CYP2D6 substrate) AUC by 2.4-fold and C_{max} by 2.0-fold [see *Drug Interactions* (7.1)].

Effect of givosiran on other CYP450 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased losartan (CYP2C9 substrate) AUC by 1.1-fold with no change in C_{max}; increased omeprazole (sensitive CYP2C19 substrate) AUC by 1.6-fold and C_{max} by 1.1-fold; increased midazolam (sensitive CYP3A4 substrate) AUC by 1.5-fold and C_{max} by 1.2-fold. These changes in exposure were not considered clinically relevant.

In Vitro Studies

Effect of givosiran on CYP450 Enzymes: In vitro studies indicate that givosiran does not directly inhibit or induce CYP enzymes; however, because of its pharmacological effects on the hepatic heme biosynthesis pathway, givosiran has the potential to reduce the activity of CYP enzymes in the liver.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a carcinogenicity study in Sprague Dawley rats administered 25, 50, or 100 mg/kg givosiran by subcutaneous injection every 28 days for up to 89 weeks (males) or 85 weeks (females), givosiran doses in rats were 2, 3, and 6 times, respectively, the MRHD based on body surface area. A statistically significant increase in hepatocellular adenomas occurred in males at 100 mg/kg/month, the clinical significance of which is uncertain.

In a carcinogenicity study in male and female Tg.rasH2 mice administered givosiran by subcutaneous injection every 28 days for 26 weeks, up to 1500 mg/kg, givosiran was not carcinogenic.

Givosiran was not genotoxic in the in vitro bacterial reverse mutation (Ames) assays, an in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes or the in vivo micronucleus assay in rats.

In fertility and early embryonic development studies, givosiran administered subcutaneously once weekly at doses up to 30 mg/kg in male and female rats prior to and during mating, and continuing in females throughout organogenesis, resulted in no adverse effects on fertility or reproductive function in male or female animals.

14 CLINICAL STUDIES

The efficacy of GIVLAARI in patients with acute hepatic porphyria was evaluated in the ENVISION trial (NCT03338816), a randomized, double-blind, placebo-controlled, multinational study.

ENVISION enrolled 94 patients with acute hepatic porphyria (AHP) (89 patients with AIP, 2 patients with variegate porphyria [VP], 1 patient with hereditary coproporphyria [HCP], and 2 patients with no identified mutation). Eligible patients were randomized 1:1 to receive once monthly subcutaneous injections of GIVLAARI 2.5 mg/kg or placebo during the 6-month double-blind period. In this study, inclusion criteria specified a minimum of 2 porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous

hemin administration at home in the 6 months prior to study entry. After the 6-month treatment period patients were enrolled in an open label extension period for up to 30 months. Ninety-three patients were enrolled in the open label extension period. Hemin use during the study was permitted for the treatment of acute porphyria attacks.

The median age of patients studied was 37.5 years (range 19 to 65 years), 89% of patients were female, and 78% were white. GIVLAARI and placebo arms were balanced with respect to historical porphyria attack rate, hemin prophylaxis prior to study entry, use of opioid medications, and patient-reported measures of pain symptoms between attacks.

Efficacy in the 6-month double-blind period was measured by the rate of porphyria attacks that required hospitalizations, urgent healthcare visit, or intravenous hemin administration at home.

Efficacy results for GIVLAARI are provided in Table 3. On average, AHP patients on GIVLAARI experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo.

Table 3. Rate of Porphyria Attacks^a and Days of Hemin Use in Patients with AHP Over the 6-Month Double-blind Period of ENVISION

	Patients with AHP	
	GIVLAARI (N=48)	Placebo (N=46)
Mean Rate (95% CI) of Porphyria Attacks	1.9 (1.3, 2.8)	6.5 (4.5, 9.3)
Rate Ratio ^b (95% CI) (GIVLAARI/placebo)	0.3 ^c (0.2, 0.4)	
Mean Days (95% CI) of Hemin Use	4.7 (2.8, 7.9)	12.8 (7.6, 21.4)
Ratio ^b (95% CI) (GIVLAARI/placebo)	0.3 ^d (0.1, 0.5)	
^a Attacks that require hospitalization, urgent healthcare visits, or intravenous hemin administration at home.		
^b Adjusted for prior hemin prophylaxis status and historical attack rates. A ratio <1 represents a favorable outcome for GIVLAARI.		
^c p < 0.0001		
^d p = 0.0002		

GIVLAARI also resulted in a reduction in hemin use, urinary ALA, and urinary PBG.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

GIVLAARI (givosiran) is a clear, colorless-to-yellow ready-to-use solution available in single-dose vials of 189 mg/mL in cartons containing one vial (NDC 71336-1001-1).

16.2 Storage and Handling

Store at 2°C to 25°C (36°F to 77°F).

Store GIVLAARI in its original container until ready for use.

17 PATIENT COUNSELING INFORMATION

Advise patients of the potential risks of GIVLAARI treatment:

- **Anaphylactic Reaction:** Inform patients about the risk and possible symptoms of severe hypersensitivity reactions that could occur [see *Warnings and Precautions* (5.1)].

- **Hepatic Toxicity:** Inform patients that transaminase elevations may occur, and that laboratory testing will be conducted in the first 6 months of treatment and as clinically indicated thereafter *[see Warnings and Precautions (5.2)]*.
- **Renal Toxicity:** Inform patients that increases in serum creatinine and decreases in eGFR have been reported and that laboratory testing will be conducted as clinically indicated *[see Warnings and Precautions (5.3)]*.
- **Injection Site Reactions:** Inform patients of the signs and symptoms of injection site reactions (examples include redness, pain, itching, rash, discoloration, or localized swelling) *[see Warnings and Precautions (5.4)]*.
- **Blood Homocysteine Increased:** Inform patients that increases in blood homocysteine levels have been reported when using GIVLAARI, and that laboratory testing will be conducted prior to and during treatment with GIVLAARI. Vitamin supplementation may be considered for elevated blood homocysteine levels *[see Warnings and Precautions (5.5)]*.

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