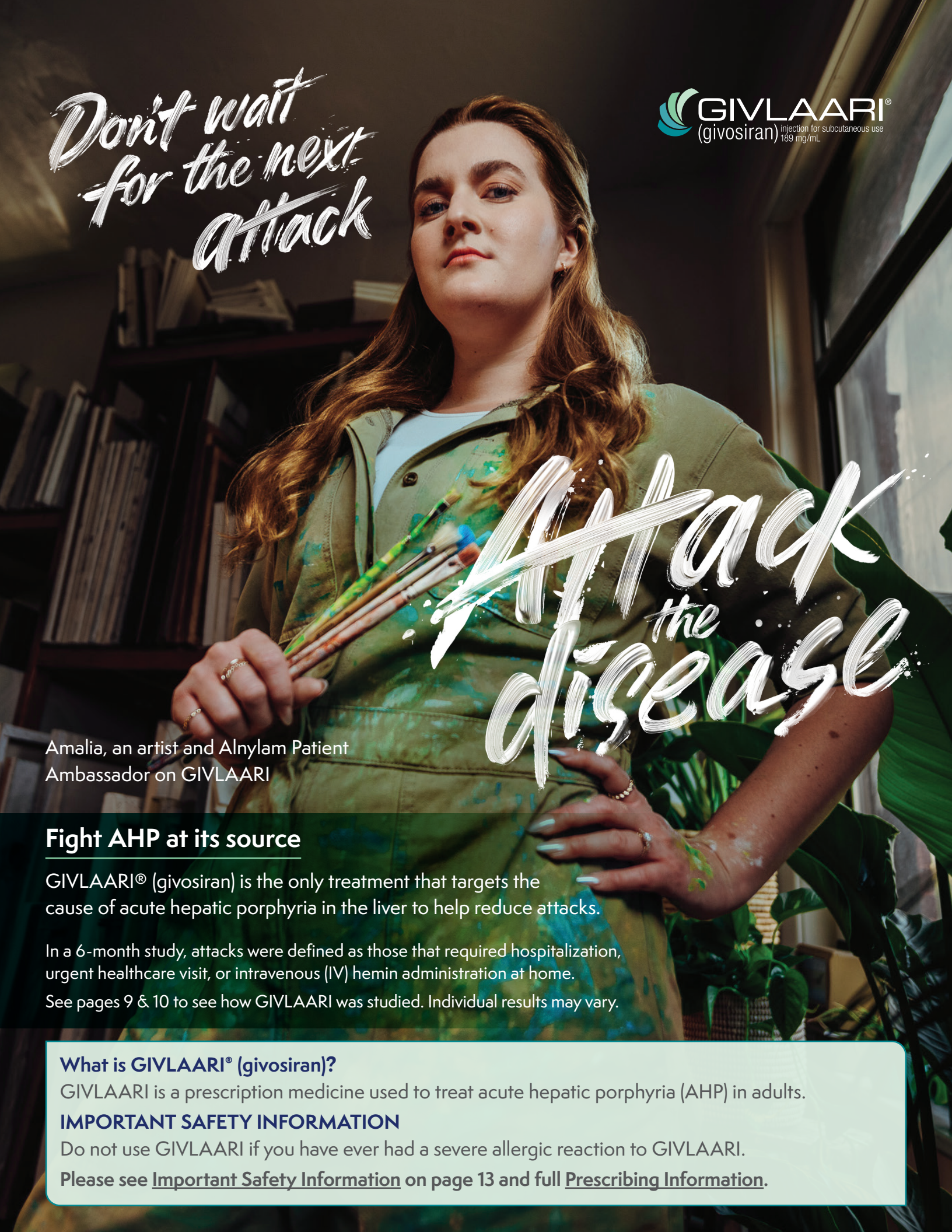


Fight AHP at its source

GIVLAARI® (givosiran) is the only treatment that targets the cause of acute hepatic porphyria in the liver to help reduce attacks.

In a 6-month study, attacks were defined as those that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.

See pages 9 & 10 to see how GIVLAARI was studied. Individual results may vary.

What is GIVLAARI® (givosiran)?

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 13 and full Prescribing Information.

CHANGE YOUR AHP STORY

Ask your doctor about GIVLAARI® (givosiran), a monthly treatment for AHP.

Acute hepatic porphyria (AHP) attacks may show up differently from one person to another, but even just one attack can be devastating.

While attacks are unpredictable and can come and go, it's important to remember that AHP is a lifelong condition that can be treated, and fewer attacks may be possible.

See inside how monthly treatment with GIVLAARI may help reduce the frequency of attacks.

IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information on page 13 and full Prescribing Information.

Amalia, an artist and Alnylam Patient Ambassador on GIVLAARI

Please see Important Safety Information on page 13 and full Prescribing Information.

WHAT IS AHP?

Acute hepatic porphyria (AHP) is a family of rare, genetic diseases that can cause severe and potentially life-threatening attacks. Some people with AHP also have chronic, debilitating symptoms when they are not having an attack.

WHAT ARE THE SYMPTOMS OF AN AHP ATTACK?

While most people with AHP experience severe abdominal pain during attacks, symptoms vary from person to person and change over time. Not every person with AHP will experience all the symptoms listed here, and some will experience symptoms more frequently or more severely than others.

- Limb, back, or chest pain
- Nausea
- Vomiting
- Confusion
- Anxiety
- Insomnia
- Seizures
- Weak limbs
- Dark or reddish urine
- Constipation
- Diarrhea
- Hallucinations

IN THE US, ABOUT
1 PERSON IN 100,000
IS DIAGNOSED WITH AHP
AND HAS SYMPTOMS.

THERE ARE 4 TYPES OF AHP:

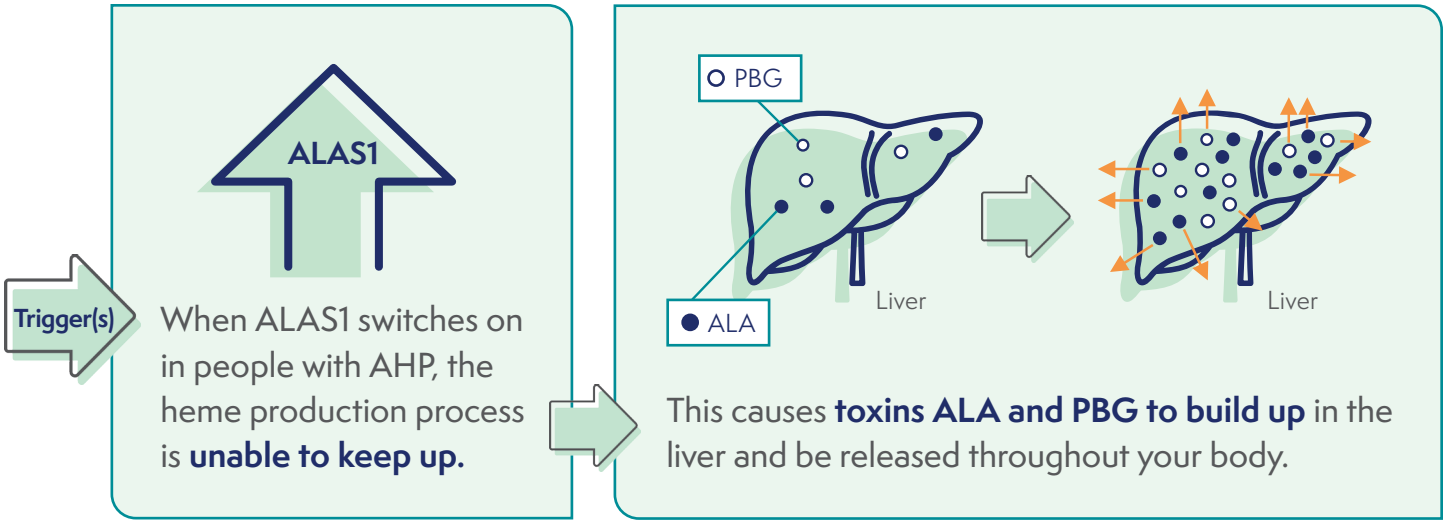
Acute intermittent porphyria (AIP)	Variegate porphyria (VP)	Hereditary coproporphyria (HCP)	ALAD-deficiency porphyria (ADP)

Most common — **Extremely rare**

ALAD=delta-aminolevulinic acid dehydratase.

HOW AHP AFFECTS YOUR BODY

Heme is an essential molecule that is made in the liver. An enzyme called ALAS1 is the "start switch" that controls the process of making heme. When ALAS1 switches on in people with AHP, the heme production process is unable to keep up. This causes **toxins ALA and PBG** to build up in the liver and be released throughout your body.



ALA and PBG are associated with attacks and other AHP symptoms. Be sure to tell your healthcare providers about all the symptoms you're experiencing

DID YOU KNOW SOME FACTORS CAN TRIGGER AHP ATTACKS?

SOME POTENTIAL ATTACK TRIGGERS INCLUDE:

- ✔ Hormonal fluctuations
- ✔ Infection
- ✔ Stress
- ✔ Use of certain medications
- ✔ Alcohol consumption
- ✔ Fasting/extreme dieting

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

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

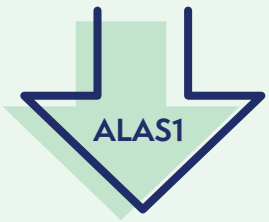
"Your pain is real; it is valid, and you don't have to go through it alone."

Amalia, an Alnylam Patient Ambassador on GIVLAARI

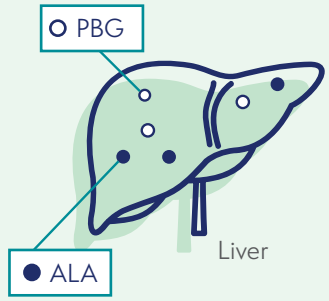
Please see Important Safety Information on page 13 and full Prescribing Information.

HOW GIVLAARI® (givosiran) WORKS

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



In the liver, **GIVLAARI reduces the level of ALAS1**.



This leads to a **reduction of toxins ALA and PBG**.

ALA and PBG are associated with attacks and other AHP symptoms.

GIVLAARI reduces the amount of ALAS1 in the liver, which leads to a reduction in levels of the toxins ALA and PBG

GIVLAARI is given as an injection under the skin (subcutaneous) by a healthcare professional. Depending on your doctor's recommendations and your insurance plan, home administration by a nurse or other healthcare professional may be an option.

GIVLAARI IS GIVEN ONCE A MONTH BY A HEALTHCARE PROFESSIONAL.

ALA=delta-aminolevulinic acid; ALAS1=delta-aminolevulinic acid synthase 1; PBG=porphobilinogen.

IMPORTANT SAFETY INFORMATION

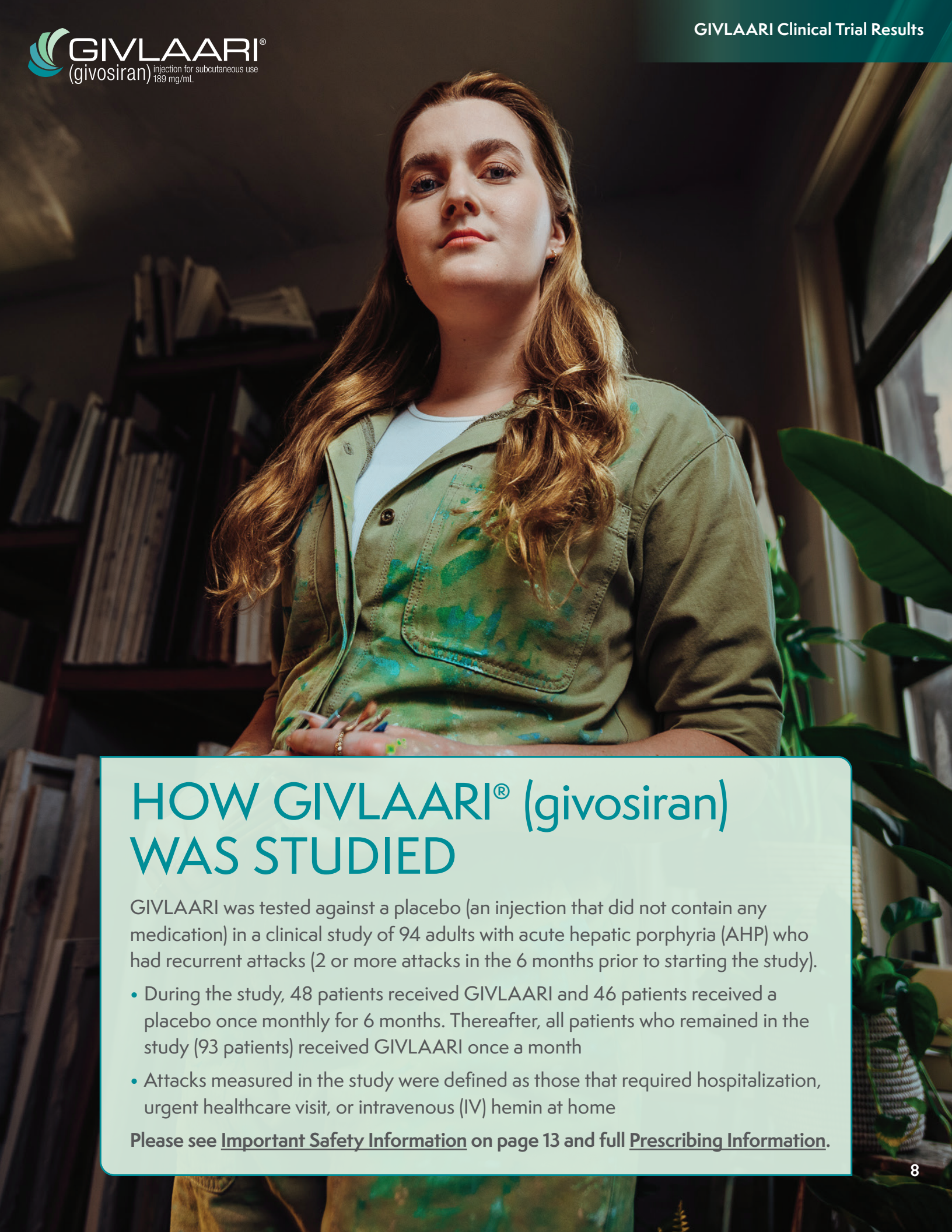
GIVLAARI can cause injection site reactions:

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.

Please see Important Safety Information on page 13 and full Prescribing Information.

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



HOW GIVLAARI® (givosiran) WAS STUDIED

GIVLAARI was tested against a placebo (an injection that did not contain any medication) in a clinical study of 94 adults with acute hepatic porphyria (AHP) who had recurrent attacks (2 or more attacks in the 6 months prior to starting the study).

- During the study, 48 patients received GIVLAARI and 46 patients received a placebo once monthly for 6 months. Thereafter, all patients who remained in the study (93 patients) received GIVLAARI once a month
- Attacks measured in the study were defined as those that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin at home

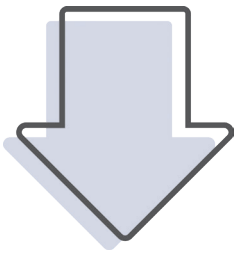
Please see Important Safety Information on page 13 and full Prescribing Information.

In a 6-month study,

PATIENTS TAKING GIVLAARI® (givosiran) EXPERIENCED

70%

fewer attacks,
on average,
compared to those
who received placebo



70%

fewer days of hemin use
to treat AHP attacks,
on average, compared
to those on placebo

- GIVLAARI was studied in adults with AHP who were experiencing recurrent AHP attacks
- After the first 6 months of treatment, patients on GIVLAARI had an average of 1.9 AHP attacks compared to 6.5 for those on placebo
- In the study, patients who experienced an attack were treated according to local standards of care, which could include hemin
- Using hemin to prevent an attack was not allowed during the study
- After the first 6 months of treatment, patients on GIVLAARI had an average of 4.7 days of hemin use compared to 12.8 days for patients on placebo

AHP=acute hepatic porphyria.

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause 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.

GIVLAARI can cause kidney problems:

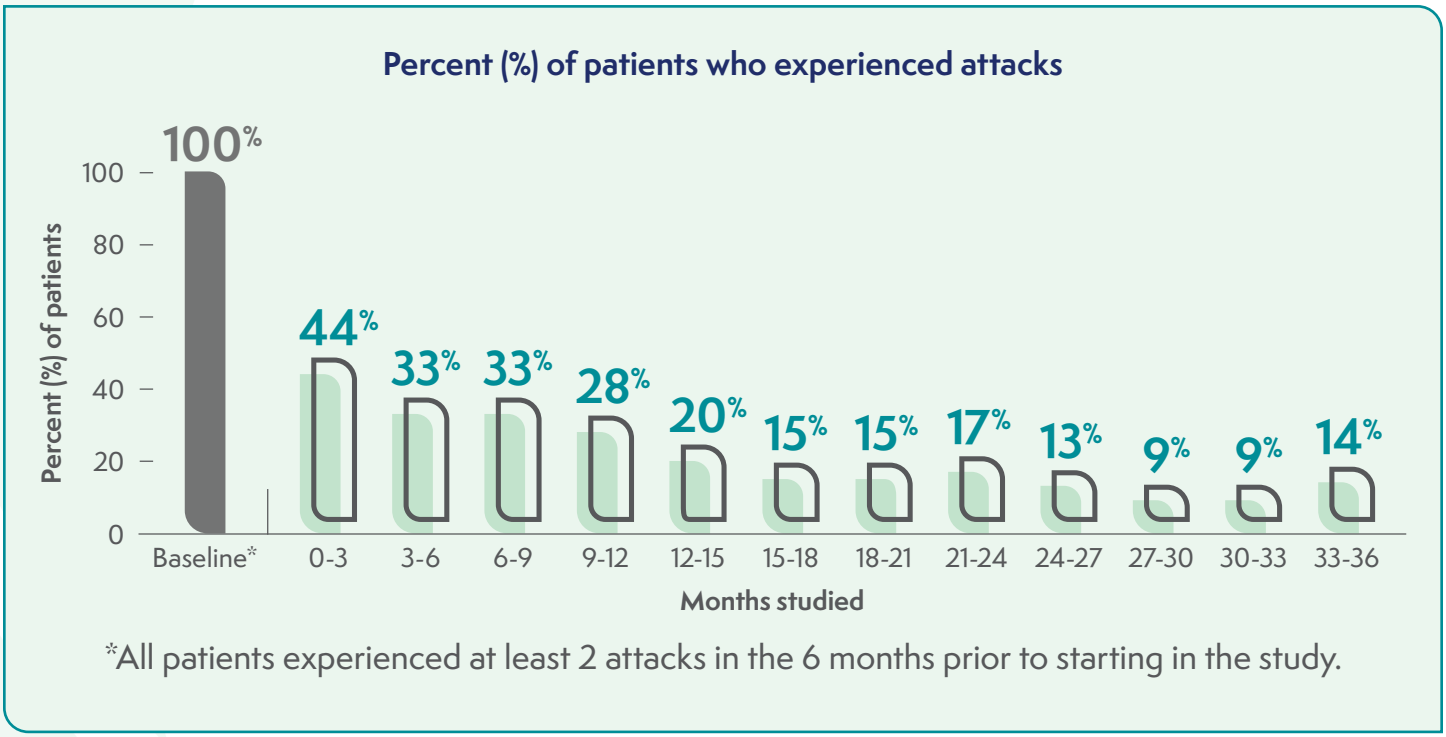
Your doctor will check how your kidneys are working while you are using GIVLAARI.

Please see Important Safety Information on page 13 and full Prescribing Information.

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

THE NUMBER OF ATTACK-FREE PATIENTS INCREASED WITH GIVLAARI® (givosiran) TREATMENT

After the 6-month study, all eligible patients who remained in the study received GIVLAARI once a month. The graph below shows the percent of patients who started on and continued taking GIVLAARI who experienced acute hepatic porphyria (AHP) attacks throughout the study, with more attack-free patients over 36 months.



*All patients experienced at least 2 attacks in the 6 months prior to starting in the study.

An attack during the study meant the patient needed hospitalization, an urgent healthcare visit, or intravenous (IV) hemin at home.

These results were observed in the clinical trial. Keep in mind that everyone responds to GIVLAARI differently.

IMPORTANT SAFETY INFORMATION

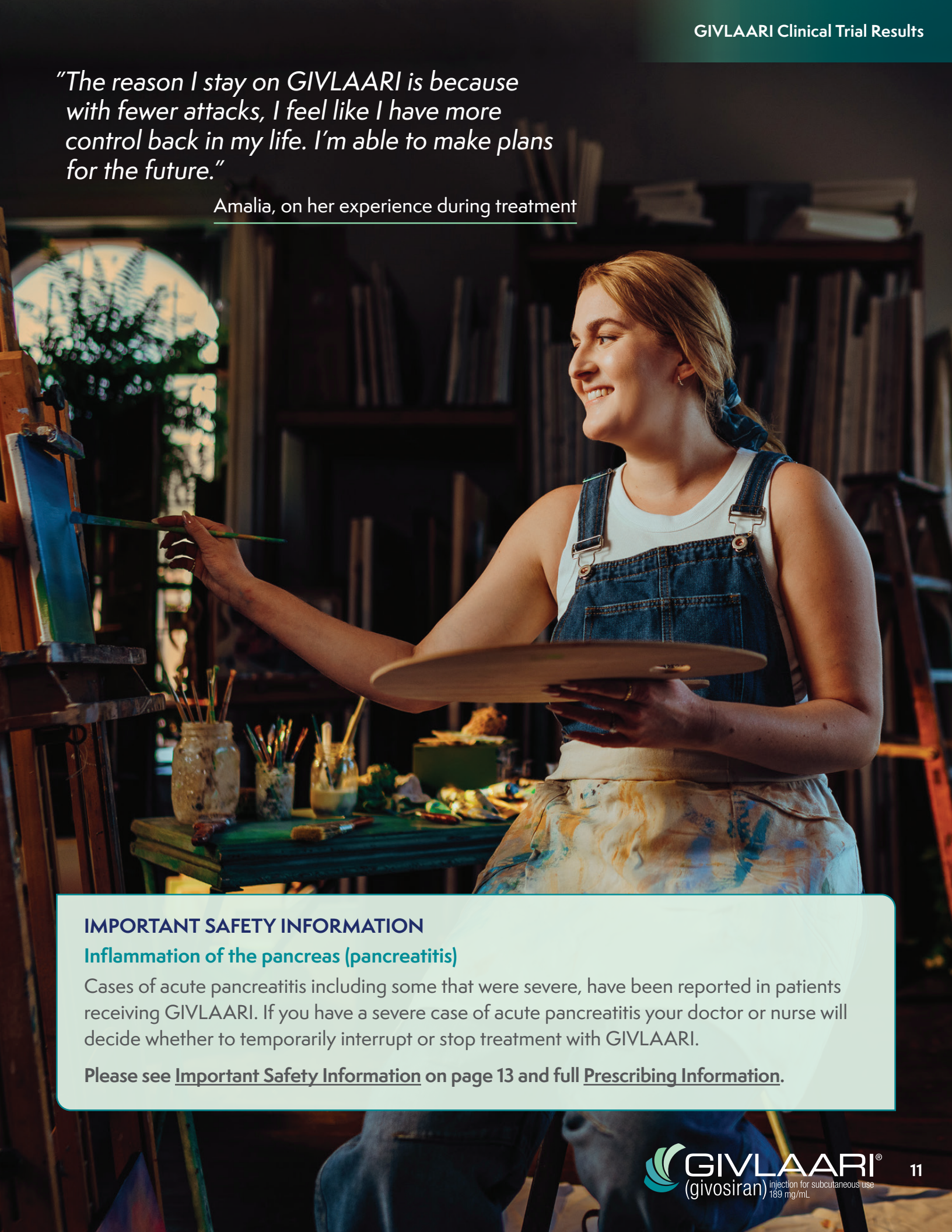
Increased blood homocysteine levels

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.

Please see Important Safety Information on page 13 and full Prescribing Information.

"The reason I stay on GIVLAARI is because with fewer attacks, I feel like I have more control back in my life. I'm able to make plans for the future."

Amalia, on her experience during treatment



IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information on page 13 and full Prescribing Information.

GIVLAARI® (givosiran) SAFETY PROFILE

Safety during the first 6 months of the study

- In the first 6 months of the study, 1 patient taking GIVLAARI stopped treatment due to changes in liver function. No patients taking placebo stopped treatment

The most common side effects in patients treated with GIVLAARI compared to those taking placebo in the first 6 months of the study were:

	GIVLAARI (48 patients)	Placebo (46 patients)
Nausea	27%	11%
Injection site reactions	25%	0%
Rash	17%	4%
Changes in kidney function	15%	4%
Changes in liver function	13%	2%
Fatigue	10%	4%

Safety through the 36-month study

- The most frequently reported adverse events occurring in ≥20% of patients 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

IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information on page 13 and full Prescribing Information.

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

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 the full Prescribing Information.

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

HOW ALNYLAM ASSIST® CAN HELP

Alnylam ASSIST®

Once you and your doctor decide GIVLAARI® (givosiran) is right for you, Alnylam Assist® offers you support services throughout your treatment with GIVLAARI in 3 key areas: understanding benefits, eligibility for financial assistance, and disease and product education.

LEARN FROM AN ALNYLAM PEL

Our Alnylam Patient Education Liaisons (PELs) have backgrounds in nursing and are experienced in educating people and their families about matters related to acute hepatic porphyria (AHP).

Your Alnylam PEL will:

- Support you with disease education
- Connect you to additional resources
- Answer questions about GIVLAARI treatment

The purpose of the 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.

Connect with an Alnylam PEL today.
Visit www.GIVLAARIpel.com to learn how.

Please see Important Safety Information on page 13 and full Prescribing Information.

"Alnylam Assist®, and our Case Manager, really helped us navigate the approval process."

Amalia, on her experience getting started with GIVLAARI

Please see Important Safety Information on page 13 and full Prescribing Information.

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

SUPPORT IS AVAILABLE TO YOU

We are committed to making GIVLAARI® (givosiran) available to those who need it. When you and your healthcare provider decide to start treatment, Alnylam Assist® will provide you with an **Alnylam Case Manager** who can provide product support throughout the GIVLAARI treatment process.

SPEAK TO AN ALNYLAM CASE MANAGER

Alnylam Case Managers are experienced in helping individuals get started on treatment and providing GIVLAARI product support. They will tailor their method of contact based on your preference.

An Alnylam Case Manager can:

Help you understand your insurance benefits

Determine your eligibility for financial assistance

Provide you with product support throughout your treatment

Please see Important Safety Information on page 13 and full Prescribing Information.

Alnylam ASSIST®

Most commercial insurance companies **offer coverage for GIVLAARI® (givosiran)**; however, if you have concerns about the cost or if you don't have coverage for GIVLAARI, Alnylam may be able to help if you're eligible.

ASK ABOUT ALNYLAM'S FINANCIAL ASSISTANCE PROGRAMS*

- **If you have commercial insurance**, our **Alnylam Assist® Commercial Copay Program** covers certain out-of-pocket costs for eligible patients
  - Patients with Medicare, Medicaid, or other government-sponsored insurance are not eligible for the Alnylam Assist® Commercial Copay Program
- If you do not have insurance, or do not have coverage for GIVLAARI, our **Patient Assistance Program** may be able to provide you with GIVLAARI at no cost,† if you are eligible
- **Talk to an Alnylam Case Manager** to learn more about **Alnylam Assist® financial assistance program** eligibility

*Individuals 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.

†Out-of-pocket costs for the administration of Alnylam products will not be covered for patients residing where it is prohibited by law or where otherwise restricted.

For more information about Alnylam Assist® or to access downloadable materials:

Visit: AlnylamAssist.com
Call: 1-833-256-2748
Monday-Friday, 8 AM-6 PM

Please see Important Safety Information on page 13 and full Prescribing Information.

FREQUENTLY ASKED QUESTIONS

Can GIVLAARI® (givosiran) be used for any type of acute hepatic porphyria (AHP)?

GIVLAARI is a prescription medicine used to treat AHP in adults. There are 4 types of AHP:

- Acute intermittent porphyria (AIP)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)
- ALAD-deficiency porphyria (ADP)

Most patients in the 6-month study had AIP, the most common type of AHP.

How is GIVLAARI given?

GIVLAARI is given once a month as a subcutaneous injection (under the skin) by a healthcare professional.

Will I need any tests while taking GIVLAARI?

GIVLAARI can cause 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 healthcare provider will decide whether to temporarily interrupt or stop treatment with GIVLAARI.

GIVLAARI can cause kidney problems. Your doctor will check how your kidneys are working while you are using GIVLAARI.

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.

Can I use hemin while using GIVLAARI?

In clinical studies, patients who experienced an attack were treated according to local standards of care, which could include hemin. Use of GIVLAARI with regularly scheduled (prophylactic) hemin was not studied in clinical trials of GIVLAARI. Talk to your doctor if you have questions about your treatment plan.

Is GIVLAARI safe to use during pregnancy?

GIVLAARI has not been studied in women who are pregnant. If you are pregnant or plan to become pregnant, it is important to discuss your treatment plan with your doctor.

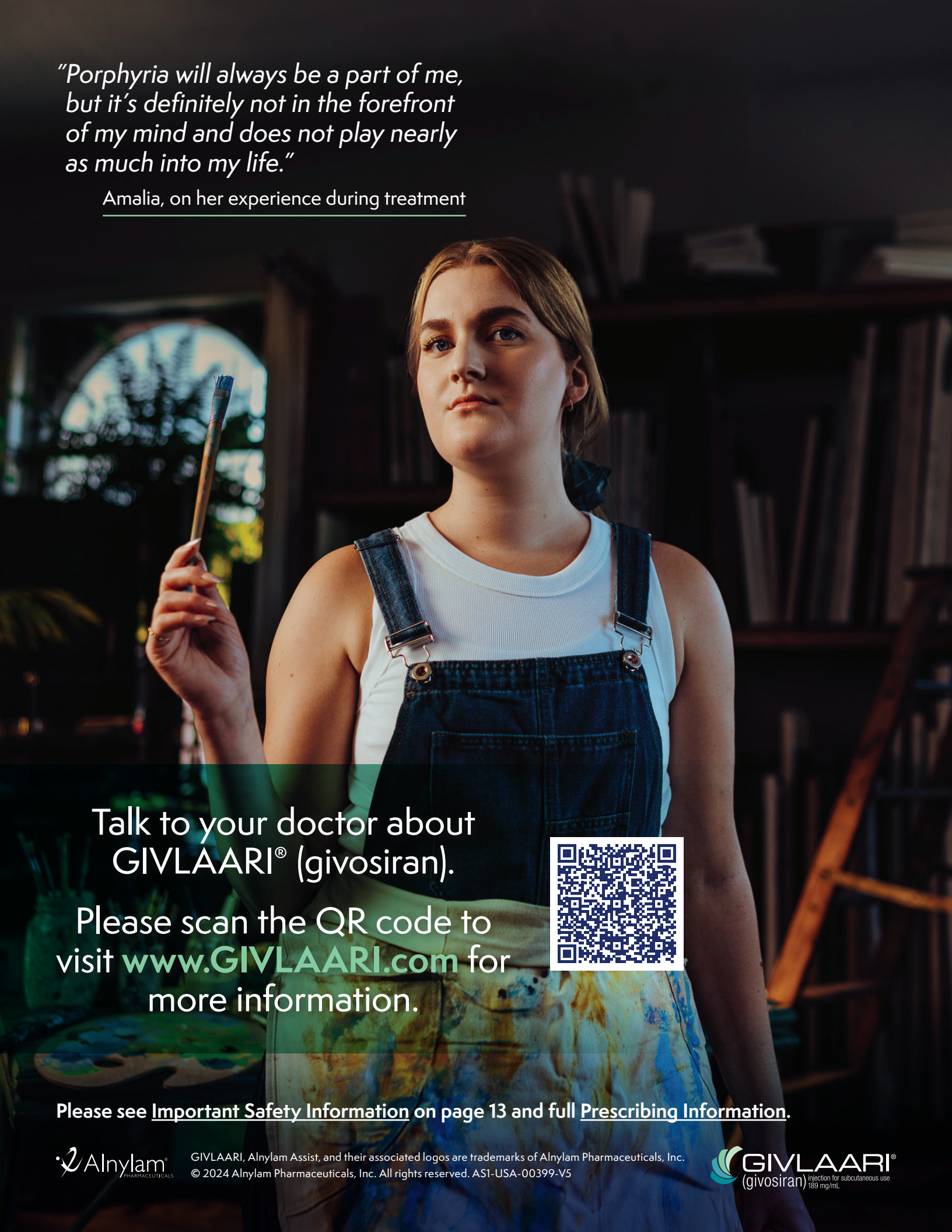
IMPORTANT SAFETY INFORMATION

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

Please see Important Safety Information on page 13 and full Prescribing Information.

Please see Important Safety Information on page 13 and full Prescribing Information.

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


"Porphyria will always be a part of me, but it's definitely not in the forefront of my mind and does not play nearly as much into my life."
Amalia, on her experience during treatment
Talk to your doctor about GIVLAARI® (givosiran).
Please scan the QR code to visit www.GIVLAARI.com for more information.
Please see Important Safety Information on page 13 and full Prescribing Information.
Alnylam PHARMACEUTICALS
GIVLAARI, Alnylam Assist, and their associated logos are trademarks of Alnylam Pharmaceuticals, Inc.
© 2024 Alnylam Pharmaceuticals, Inc. All rights reserved. AS1-USA-00399-V5
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

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

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

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 (≥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 sternebrae 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.

In a pre- and postnatal development study, givosiran administered subcutaneously to pregnant rats on gestation days 7, 13, and 19 and postnatal days 6, 12, and 18 at doses up to 30 mg/kg did not produce maternal toxicity or developmental effects in the offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of GIVLAARI in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GIVLAARI and any potential adverse effects on the breastfed child from GIVLAARI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

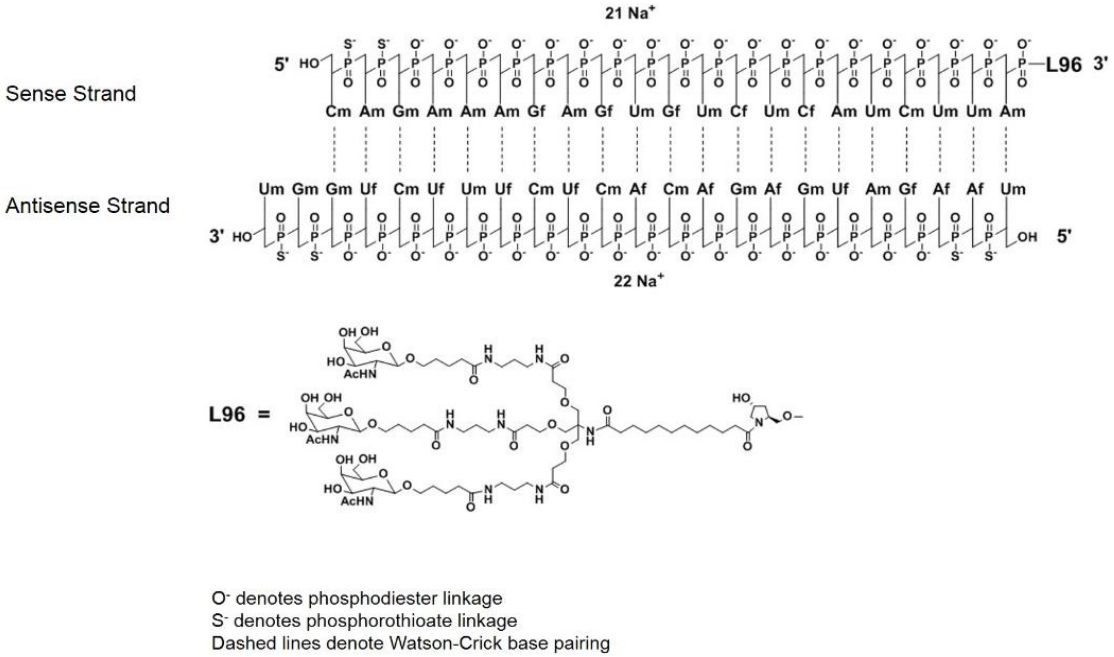
8.5 Geriatric Use

Clinical studies of GIVLAARI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

GIVLAARI is an aminolevulinate synthase 1-directed small interfering RNA (siRNA), covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes.

The structural formulas of the givosiran drug substance in its sodium form, and the ligand (L96), are presented below.



Abbreviations: Af = adenine 2'-F ribonucleoside; Cf = cytosine 2'-F ribonucleoside; Uf = uracil 2'-F ribonucleoside; Am = adenine 2'-OMe ribonucleoside; Cm = cytosine 2'-OMe ribonucleoside; Gf = guanine 2'-F ribonucleoside; Gm = guanine 2'-OMe ribonucleoside; Um = uracil 2'-OMe ribonucleoside; L96 = triantennary GalNAc (N-acetylgalactosamine)

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 C_{524} H_{651} F_{16} N_{173} Na_{43} O_{316} P_{43} S_6 with a molecular weight of 17,245.56 Da.

The molecular formula of givosiran (free acid) is C_{524} H_{694} F_{16} N_{173} O_{316} P_{43} S_6 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 excreters 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 (Vz/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/1.73m^2 estimated by the Modification of Diet in Renal Disease [MDRD] formula), and mild hepatic impairment (bilirubin ≤1×ULN and AST >1×ULN, or bilirubin >1×ULN to 1.5×ULN).The effect of end-stage renal disease (eGFR <15 mL/min/1.73m^2), 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)].*

Manufactured for: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142
Manufactured by: Ajinomoto Althea, Inc., 11049 Roselle Street, San Diego, CA 92121