

## Givosiran: Anaphylactic Reactions and Hypersensitivity

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### SUMMARY

- In the Phase 1/2 OLE, 1 patient with a medical history of allergic asthma and atopy experienced a SAE of anaphylactic reaction considered to be related to givosiran treatment. The event resolved, and the patient discontinued the study.<sup>1</sup>
- In the ENVISION study, no AEs related to anaphylactic reaction were reported. One patient experienced a treatment-related AE of hypersensitivity; and 1 patient experienced treatment-related SAEs of increased blood homocysteine and hypersensitivity, which was reported as an ISR. Both patients discontinued the study.<sup>2,3</sup>
- Per the ENVISION study protocol, patients were observed for a minimum of 20 minutes after each injection. Treatments for anaphylactic reactions were readily available where patients were being dosed and followed country and/or local hospital treatment guidelines.<sup>4</sup>
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety concerns for hypersensitivity, including anaphylactic reactions, related to the use of givosiran.<sup>5</sup>

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### CLINICAL DATA

#### Phase 1/2 Open Label Extension Study

The Phase 1/2 OLE (N=16) was an extension of the Phase 1 study to evaluate the long-term safety and tolerability of givosiran in patients with AIP for up to 48 months. Upon study entry, patients received givosiran 2.5 mg/kg once monthly or 5.0 mg/kg once monthly or every 3 months. All patients enrolled in the OLE were transitioned to receive subcutaneous injections of givosiran 2.5 mg/kg once a month.<sup>1</sup>

#### Safety: Anaphylactic Reaction

One patient with a medical history of allergic asthma and atopy experienced a SAE of anaphylactic reaction considered to be related to givosiran treatment. The patient previously received 2 doses of

givosiran 5.0 mg/kg 3 months apart in the Phase 1 study, and the anaphylaxis event occurred 4 months later during the first dose of givosiran 2.5 mg/kg in the Phase 1/2 OLE. The patient developed urticaria at the injection site that extended to her limbs, facial swelling, and hypotension within 3 minutes of givosiran administration. There were no symptoms of airway compromise. The event resolved, and the patient discontinued the study.<sup>1</sup>

### **ENVISION Study**

The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrolled patients were randomized on a 1:1 basis to receive subcutaneous injections of givosiran 2.5 mg/kg (n=48) or placebo (n=46) once a month for 6 months, followed by an optional 30-month OLE. The primary endpoint was the annualized rate of composite porphyria attacks among patients with AIP at 6 months.<sup>2</sup>

Upon entering the OLE, 93 patients were assigned either givosiran 1.25 mg/kg or 2.5 mg/kg monthly, which was subsequently changed to all patients receiving 2.5 mg/kg monthly.<sup>2</sup>

### Protocol for Anaphylactic Reactions

Givosiran was administered by a qualified and authorized healthcare professional trained in the recognition and management of anaphylactic reactions. Patients were observed for a minimum of 20 minutes after each injection. Treatments for anaphylactic reactions were readily available where patients were being dosed and followed country and/or local hospital treatment guidelines.<sup>4</sup>

An anaphylactic reaction was defined as a severe, potentially fatal, systemic allergic reaction with acute onset (minutes to hours). Symptoms of an anaphylactic reaction may include skin or mucosal tissue (e.g., generalized hives, pruritus, angioedema), respiratory compromise (e.g., wheezing, bronchospasm, hypoxia), reduced blood pressure or associated symptoms (e.g., syncope, hypotonia). If an anaphylactic reaction to givosiran was suspected, the administration of givosiran was stopped immediately. Givosiran was permanently discontinued in patients for whom an anaphylactic reaction was assessed as related to givosiran.<sup>4</sup>

### Safety: Anaphylactic Reaction

In the ENVISION study, no AEs related to anaphylactic reaction were reported.<sup>3</sup>

### Safety: Hypersensitivity

One patient experienced an AE of hypersensitivity that was considered related by the Investigator and discontinued the study.<sup>2</sup>

One patient experienced concurrent SAEs of increased blood homocysteine and hypersensitivity, which was reported as an ISR.<sup>2,3</sup> The patient received givosiran 1.25 mg/kg monthly, followed by a transition to givosiran 2.5 mg/kg monthly at injection 13. The patient developed local skin reactions at the injection site, which steadily increased with each subsequent injection, and reported swelling of the hands and feet. At injection 25, the patient experienced shaking chills, chest tightness, acute dyspnea, erythroderma of the face, neckline, and both arms, swelling of the hands, and an urticarial reaction at both injection sites despite premedication with 10 mg per day of cetirizine. The patient was treated with dimethindene maleate, and the event resolved in 3 hours.<sup>6</sup> The event was considered related by the Investigator, and the patient discontinued the study.<sup>2</sup>

## GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety concerns for hypersensitivity, including anaphylactic reactions, related to the use of givosiran.<sup>5</sup>

## GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

For additional information, please refer to the following sections of the [GIVLAARI US Prescribing Information](#)<sup>7</sup>:

- CONTRAINDICATIONS Section 4
- WARNINGS AND PRECAUTIONS Section 5.1 Anaphylactic Reaction
- ADVERSE REACTIONS Section 6.1 Clinical Trial Experience
- PATIENT COUNSELING INFORMATION Section 17 Anaphylactic Reaction

## ABBREVIATIONS

AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ISR = injection site reaction; OLE = open-label extension; SAE = serious adverse event.

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## REFERENCES

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2. Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. *J Hepatol.* 2023;79(5):1150-1158. doi:10.1016/j.jhep.2023.06.013
3. Alnylam Pharmaceuticals. Data on File. MED-ALL-AS1-2200003.
4. Protocol for: Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med.* 2020;382(24):2289-2301. doi:10.1056/NEJMoa1913147.
5. Alnylam Pharmaceuticals. Data on file. MED-ALL-GIVO-2500004.
6. Petrides PE, Klein M, Schuhmann E, et al. Severe homocysteinemia in two givosiran-treated porphyria patients: is free heme deficiency the culprit? *Ann Hematol.* 2021;100(7):1685-1693. doi:10.1007/s00277-021-04547-3
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