Givosiran: Injection Site Reactions

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SUMMARY

- In givosiran clinical studies, ISRs were among the most frequently reported AEs occurring in patients on givosiran therapy. ISRs were described as transient and mild or moderate in severity.[1–4]
  - In the double-blind period of the ENVISION study, 12 out of 48 (25%) givosiran-treated patients experienced ISRs compared to 0 out of 26 patients who received placebo.[3]
  - In the OLE period of the ENVISION study, 37 out of 94 (39%) patients experienced ISRs.[4]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving ISRs with the use of givosiran.[5]
- No additional information is available regarding the management of ISRs.

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CLINICAL DATA

Phase 1 Study

The Phase 1 study was a multicenter, randomized, placebo-controlled, 3-part study designed to evaluate the safety, tolerability, PK, and PD of givosiran in patients with AIP.[1]

In the Phase 1 study of givosiran, ISRs (including injection site erythema and pain), were reported in 6 out of 33 (18%) patients who received givosiran and no patients who received placebo. These ISRs were all mild or moderate in severity and resolved spontaneously.[1]

Phase 1/2 Open-Label Extension Study

The Phase 1/2 OLE study was an extension of the Phase 1 clinical study to evaluate the long-term safety and tolerability of givosiran in patients with AIP for up to 48 months. All patients enrolled in the OLE were transitioned to receive subcutaneous injections of givosiran 2.5 mg/kg once a month.[2]

In the Phase 1/2 OLE study of givosiran, 7 out of 16 (44%) patients receiving givosiran experienced ISRs, most of which were erythema (38%), and all were classified as mild or moderate in severity.[2] ISRs were reported in 28 out of 1,246 (2.2%) total doses of givosiran administered. One patient receiving givosiran experienced 2 ISRs that led to treatment interruption, and which were assessed as moderate in severity and subsequently resolved. The first ISR was described as injection site erythema, pain, and pruritus. The second ISR was described as injection site erythema with associated recall phenomenon. No other ISRs led to treatment interruption or were associated with recall phenomenon.[6]

Phase 3 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.[3]

Double-Blind Phase

In ENVISION, 12 out of 48 (25%) patients receiving givosiran and no patients on placebo experienced ISRs. These ISRs were associated with 7% of givosiran doses (N=279) and were assessed to be mild or moderate in severity, and none were reported as SAEs.[3] One patient receiving givosiran experienced an ISR of erythema involving the contralateral abdomen at location of a prior injection, which suggested the possibility of a recall phenomenon. This ISR event was assessed as mild and resolved within 1 day. No ISRs led to treatment interruption, discontinuation, or withdrawal from the double-blind portion of the study. ISRs were managed by using proper technique and rotation of injection sites.[7]

Open-Label Extension Phase

Upon completion of the ENVISION 6-month double-blind period, eligible patients (N=93) continued in the optional 30-month OLE study evaluating the long-term efficacy and safety of givosiran. ISRs were observed in 37 out of 93 (39%) patients and occurred in 142 out of 2,820 (5%) total doses of givosiran administered.[4] The most common signs and symptoms of ISRs reported in ≥5% of patients were injection site erythema (25.5%), pruritus (10.6%), rash (10.6%), pain (10.6%), and swelling (9.6%). The majority of ISRs were non-serious AEs that were mild or moderate in severity.[8]

One patient (in the placebo/givosiran 1.25 mg/kg group) experienced recurrent ISRs with severity that increased from mild to severe during the OLE period, and the event was categorized as a serious AE. The serious ISR occurred within the first 5 minutes after the injection (on day 720 of the study), and was characterized as shaking chills, chest tightness, acute dyspnea, erythroderma of the face, neckline, and upper arms, swelling of the hands, and an urticarial reaction on the left and right upper arms at the injection sites. Management included dimetindene maleate and sodium chloride 0.9% and cooling elements for swelling. The event resolved in 3 hours. The event was considered related to study drug and resulted in discontinuation of the study drug and subsequent withdrawal from the study. The patient also had a concurrent elevation of blood homocysteine.[8]

Two patients experienced ISRs with potential recall reactions. One patient (described earlier in the double-blind period of the study), had an ISR of erythema which suggested the possibility of a recall phenomenon. This patient has subsequently received 20 additional doses of givosiran in the OLE without any additional ISRs or recall reactions. A second patient experienced ISRs at both the site of the most recent injection and the site of a previous injection while receiving givosiran in the OLE. The patient was treated with topical hydrocortisone gel, and the ISRs resolved. Subsequently, the patient received 10 additional doses of givosiran in the study and experienced minor ISRs without any additional cases of recall phenomenon.[9]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving ISRs with the use of givosiran.[5]

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The WARNINGS AND PRECAUTIONS section provides the following information[10]:

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.

The PATIENT COUNSELING INFORMATION section provides the following information[10]:

Advise patients of the potential risks of GIVLAARI treatment:

Injection Site Reactions

Inform patient of the signs and symptoms of injection site reactions (examples include redness, pain, itching, rash, discoloration, or localized swelling).

ABBREVIATIONS

ADR = adverse drug reaction; AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ISR = injection site reaction; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event.

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