Vutrisiran: Injection Site Reactions

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

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SUMMARY

- In the HELIOS-A study, 5 out of 122 patients (4.1%) in the vutrisiran arm reported transient and mild ISRs.[1] None of the ISRs led to treatment discontinuation.[2]
- In the HELIOS-B study, 7 out of 326 patients (2.1%) in the vutrisiran arm reported treatment-related ISRs, all non-serious, transient, and mild. None of the ISRs led to treatment discontinuation.[3]
- In a pooled analysis of the phase 3 HELIOS-A and HELIOS-B studies, treatment-related ISRs were evaluated in patients who received vutrisiran for up to 58 months.[4]
  - In the combined vutrisiran group, 2.1% of the 707 patients (1518.9 PY; AER: 1.0 per 100 PY) experienced at least one ISR. The most common ISR symptom was pain at the injection site, which occurred in 1.1% of patients in the combined vutrisiran group. All ISRs were transient and mild or moderate in severity. None of the ISRs required a change in study drug administration.[4]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns involving ISRs related to vutrisiran.[5]
- No additional information is available regarding ISRs and their duration or management. The management of ISR events is at the clinical discretion of the healthcare professional.

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CLINICAL DATA

HELIOS-A

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[1]

Patients with a history of intolerance to subcutaneous injection(s) were excluded from the study.[6]

Per the study protocol, an ISR was defined as a local reaction at or near the site of injection, including reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (e.g., as may occur with swelling or hematoma). A systemic reaction that included the injection site, such as generalized urticaria, other distinct entities, or conditions like lymphadenopathy that may be near the injection site, was not considered an ISR.[6]

Five out of 122 patients (4.1%) in the vutrisiran arm reported mild and transient ISRs, occurring in 0.6% of the 836 total doses of vutrisiran administered.[1] No patient had more than one ISR. None of the ISRs led to treatment discontinuation. Symptoms included bruising, erythema, pain, pruritus, and warmth.[2]

HELIOS-B

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind period, all remaining eligible patients were allowed to receive vutrisiran in an OLE.[7]

Patients with a history of intolerance to subcutaneous injection(s) were excluded from the study.[8]

During the double-blind period of the study, treatment-related ISRs were reported in 7 out of 326 (2.1%) patients in the vutrisiran arm and 8 out of 328 (2.4%) patients in the placebo arm. All ISRs were non-serious, transient, and mild in severity. None of the ISRs led to treatment discontinuation.[3]

Pooled Safety Analysis of HELIOS-A and HELIOS-B

A pooled safety analysis including data from 707 patients who received at least one dose of vutrisiran at any time during the HELIOS-A and HELIOS-B studies was conducted to evaluate the safety of vutrisiran in patients with ATTR who received treatment for up to 58 months.[4]

The HELIOS-A vutrisiran group consisted of 160 patients who received at least one dose of vutrisiran in the initial 18-month treatment period (n=122) or initially received patisiran in the treatment period and were re-randomized to receive vutrisiran during the RTE (n=38). The HELIOS-B vutrisiran group consisted of 547 patients who received at least one dose of vutrisiran during the double-blind treatment period (n=326) or initially received placebo during the double-blind period and transitioned to vutrisiran in the OLE (n=221).[4]

Treatment-related ISRs and associated signs and symptoms were evaluated in this analysis. In the combined vutrisiran group, 2.1% of the 707 patients (1518.9 PY; AER: 1.0 per 100 PY) experienced at least one ISR. In the HELIOS-B placebo group, 2.4% of the 328 patients (822.4 PY; AER: 1.1 per 100 PY) experienced an ISR. The most common ISR symptom was pain at the injection site, which occurred in 1.1% of patients in the combined vutrisiran group. None of the reported ISRs were serious or severe, 94.7% were mild, and 5.3% were moderate in severity, and all were transient with none requiring a change in study drug administration.[4]

ISR AEs reported for patients who received vutrisiran for up to 58 months in the pooled analysis were consistent with those reported for patients who received vutrisiran during the randomized periods of HELIOS-A and HELIOS-B. There were no ISR safety concerns with vutrisiran treatment.[4]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns involving ISRs related to vutrisiran.[5]

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The **ADVERSE REACTION** section provides the following information[9]:

> *Injection site reactions were reported in 5 (4%) patients treated with AMVUTTRA. Reported symptoms included bruising, erythema, pain, pruritus, and warmth. Injection site reactions were mild and transient.*

ABBREVIATIONS

AE = adverse event; AER = adverse event rate; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; ISR = injection site reaction; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PY = patient years; RTE = randomized treatment extension; wtATTR = wild-type transthyretin amyloidosis.

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