Vutrisiran: Ocular Adverse Events

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SUMMARY

- Ocular AEs by SOC were evaluated in a pooled analysis of the phase 3 HELIOS-A and HELIOS-B studies. Among a total of 707 patients who received at least one dose of vutrisiran in clinical studies, ocular AEs were reported in 106 patients (15.0%; 1518.9 PY; AER: 11.3 per 100 PY). The most common ocular AEs occurring in >2% of patients treated with vutrisiran were cataract (2.7%) and dry eye (2.1%).[1]
- No clinically notable trends or changes in ocular AEs were observed or considered attributable to the decrease in serum vitamin A levels in the HELIOS-A and HELIOS-B studies.[2]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns involving ocular AEs related to vutrisiran.[3]

INDEX

CLINICAL DATA

HELIOS-A Study

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. After the 18-month treatment period, all remaining eligible patients were eligible to receive vutrisiran in the RTE.[4]

During the 18-month treatment period, ocular AEs were reported in 35 patients (28.7%) in the vutrisiran group and 20 patients (20.6%) in the APOLLO-placebo group.[5]

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.[6]

During the double-blind treatment period, ocular AEs were reported in 47 patients (14.4%) in the vutrisiran group and 66 patients (20.1%) in the placebo group.[5]

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.[1]

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).[1]

Ocular AEs by SOC were evaluated in the analysis (**Table 1**). In the combined vutrisiran group, ocular AEs were reported in 106 out of 707 patients (15.0%; 1518.9 PY; AER: 11.3 per 100 PY). The most common ocular AEs occurring in >2% of patients treated with vutrisiran were cataract (2.7%) and dry eye (2.1%).[1]

Table 1. Ocular Adverse Events.[1,5]

	HELIOS-A				HELIOS-B			
	Vutrisiran (n=160, 539.2 PY)		APOLLO Placebo (n=77, 96.1 PY)		Vutrisiran (n=547, 979.7 PY)		Placebo (n=328, 822.4 PY)	
	n (%)	AER[a]	n (%)	AER[a]	n (%)	AER[a]	n (%)	AER[a]
Ocular events[b]	49 (30.6)	17.4	20 (20.6)	27.0	57 (10.4)	8.0	66 (20.1)	12.6

Abbreviations: AER = adverse event rate; PY = patient-years; SOC = system organ class.

[a]Exposure-adjusted AER per 100 PY calculated as events/patient-year x 100.

[b]Eye disorders SOC.

If a patient had more than one event in a given SOC, that patient was counted once for the SOC.

Ocular AEs reported in 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 ocular safety concerns with vutrisiran treatment.[1] No clinically notable trends or changes in ocular AEs were considered attributable to the decrease in serum vitamin A levels in the HELIOS-A and HELIOS-B studies.[2]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns involving ocular AEs related to vutrisiran.[3]

AMVUTTRA PRESCRIBING INFORMATION - RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the AMVUTTRA Prescribing Information[7]:

- WARNINGS AND PRECAUTIONS Section 5.1 Reduced Serum Vitamin A Levels and Recommended Supplementation
- PATIENT COUNSELING INFORMATION Section 17 Recommended Vitamin A Supplementation

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; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PY = patient-years; RTE = randomized treatment extension; SOC = system organ class; wtATTR = wild-type transthyretin amyloidosis.

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3. Alnylam Pharmaceuticals. Data on file. MED-ALL-VUTRI-2500021.
4. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26. doi:10.1080/13506129.2022.2091985
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