

Vutrisiran: Renal-Related Adverse Events

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SUMMARY

- In the HELIOS-A study and HELIOS-B study, there were no identified safety concerns nor clinically relevant changes in laboratory measures related to renal function.^{1,2}
- In a pooled safety analysis of the phase 3 HELIOS-A and HELIOS-B studies, renal AEs defined by the “acute renal failure” SMQ were evaluated in patients who received vutrisiran for up to 58 months.³
 - In the combined vutrisiran group, renal AEs were reported in 77 out of 707 patients (10.9%; 1518.9 PY; AER: 6.3 per 100 PY).³
- A cumulative post-marketing review of Alnylam Pharmaceuticals’ global safety database did not identify any safety concerns involving renal-related AEs related to vutrisiran.⁴

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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.¹

After the 18-month treatment period, all remaining eligible patients entered the RTE and were randomized 1:1 to receive either vutrisiran 25 mg every 3 months or vutrisiran 50 mg every 6 months by subcutaneous injection.⁵

During the HELIOS-A study and RTE period, there were no safety concerns identified regarding renal function related to vutrisiran.^{1,5}

HELIOS-B Study

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.²

There were no clinically relevant changes in laboratory measures, including renal function tests, in both treatment groups.²

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.³

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).³

Renal AEs defined by the “acute renal failure” SMQ were evaluated in this analysis (**Table 1**). In the combined vutrisiran group, renal AEs were reported in 77 out of 707 patients (10.9%; 1518.9 PY; AER: 6.3 per 100 PY).³

Renal 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 renal safety concerns with vutrisiran treatment.³

Table 1. Renal Adverse Events.^{3,6}

	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
Renal events ^b	11 (6.9)	2.8	9 (11.7)	13.5	66 (12.1)	8.2	57 (17.4)	9.7

Abbreviations: AER = adverse event rate; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-years; SMQ = standardized MedDRA query; SOC = system organ class.

^aExposure-adjusted AER per 100 PY calculated as events/patient-year x 100.

^bMapped to the MedDRA “acute renal failure” comprehensive search SMQ (broad and narrow terms).

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

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns involving renal-related AEs related to vutrisiran.⁴

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; MedDRA = Medical Dictionary for Regulatory Activities; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PY = patient-years; RTE = randomized treatment extension; SMQ = standardized MedDRA query; SOC = system organ class; wtATTR = wild-type transthyretin amyloidosis.

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