

## Vutrisiran: Dyspnea

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### SUMMARY

- In the HELIOS-A study, dyspnea was reported in 8 patients (6.6%) treated with vutrisiran and 0 patients in the APOLLO placebo group over the 18-month treatment period; the events were mild or moderate in severity.<sup>1</sup>
- In the HELIOS-B study, dyspnea was reported in 43 patients (13%) treated with vutrisiran and 51 patients (16%) in the placebo group during the double-blind treatment period.<sup>2</sup>
- A cumulative post-marketing review of Alnylam's global safety database did not identify any safety concerns involving dyspnea with the use of vutrisiran.<sup>3</sup>
- No additional information is available regarding dyspnea events and their management.

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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.<sup>4</sup>

#### Safety Results: Dyspnea

Dyspnea events during the HELIOS-A study were reported using the following preferred terms: Dyspnea, Dyspnea exertional, and Dyspnea paroxysmal nocturnal. At 18 months of the HELIOS-A study, dyspnea AEs were reported in 8 patients (6.6%) treated with vutrisiran and 0 patients in the APOLLO placebo group. The AEs were mild to moderate in severity and did not lead to treatment interruption, treatment

discontinuation, or withdrawal from a clinical study. The frequency of dyspnea AEs did not increase over time.<sup>1</sup> None of the dyspnea AEs were determined by the investigator to be related to treatment.<sup>5</sup>

## 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 treatment period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an OLE.<sup>6</sup>

### Safety Results: Dyspnea

During the double-blind treatment period of the HELIOS-B study, dyspnea AEs were reported in 43 patients (13%) treated with vutrisiran and 51 patients (16%) in the placebo group.<sup>2</sup>

## GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any safety concerns involving dyspnea with the use of vutrisiran.<sup>3</sup>

## ABBREVIATIONS

AE = adverse event; 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; wtATTR = wild-type transthyretin amyloidosis.

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## REFERENCES

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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
5. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2200045.
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