

## Vutrisiran: Transitioning from TTR Stabilizers (Tafamidis or Diflunisal)

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### SUMMARY

- Clinical trials designed to evaluate the transition from TTR stabilizers (tafamidis or diflunisal) to vutrisiran have not been conducted to date.
  - In the HELIOS-A study, patients were excluded from the study if they were currently taking tafamidis or diflunisal.<sup>1</sup>
  - In the HELIOS-B study, tafamidis-naïve patients for whom the Investigator planned to start tafamidis within 12 months following randomization, or patients currently taking diflunisal were excluded from the study.<sup>2</sup>

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### HELIOS-A

#### Study Design

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>1</sup>

#### Exclusion Criteria

Patients were excluded from the study if any of the following criteria apply<sup>1</sup>:

- Is currently taking tafamidis; if previously on tafamidis, the patient must have completed a 14-day wash-out prior to dosing
- Is currently taking diflunisal; if previously on diflunisal, the patient must have completed a 3-day wash-out prior to dosing

### HELIOS-B

#### Study Design

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 exposure period in the overall population and in the vutrisiran monotherapy population (patients not receiving tafamidis at baseline).<sup>3</sup>

#### Select Inclusion Criteria

Inclusion criteria for enrollment into the study included<sup>2</sup>:

- Tafamidis-naïve and not actively planning to start tafamidis treatment during the first 12 months following randomization (in addition to patients who had never taken tafamidis, those who had previously been on tafamidis and had not received any tafamidis for at least 30 days before the Screening Visit would be considered tafamidis-naïve for purposes of this study)
- On tafamidis (must be on-label use of commercial tafamidis for approved ATTR-CM indication and dose in the country of use)

#### Select Exclusion Criteria

Patients were excluded from the study if any of the following criteria applied<sup>2</sup>:

- Tafamidis-naïve patients for whom the Investigator actively planned or anticipated starting treatment with tafamidis within the first 12 months following randomization, based on clinical status, patient preference and/or commercial availability of tafamidis
- Currently taking diflunisal; if previously on this agent, must have at least a 30-day wash-out prior to dosing (Day 1)

## ABBREVIATIONS

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; wtATTR = wild-type transthyretin amyloidosis

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## REFERENCES

1. 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
2. Supplement to: Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2024. doi:10.1056/NEJMoa2409134
3. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2024. doi:10.1056/NEJMoa2409134