Impact of Vutrisiran on Activities of Daily Living and Functional Status in Patients with hATTR Amyloidosis

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Conclusions

- **Vutrisiran, with its unique mechanism of action that results in rapid and sustained transthyretin (TTR) knockdown, preserved the ability of patients with hereditary transthyretin amyloidosis (hATTR) to perform daily activities and engage socially, as measured by the Rasch-built Overall Disability Scale (R-ODS)**
- **Therefore, vutrisiran offers quality of life benefits in addition to the clinical benefit demonstrated in the HELIOS-A trial**

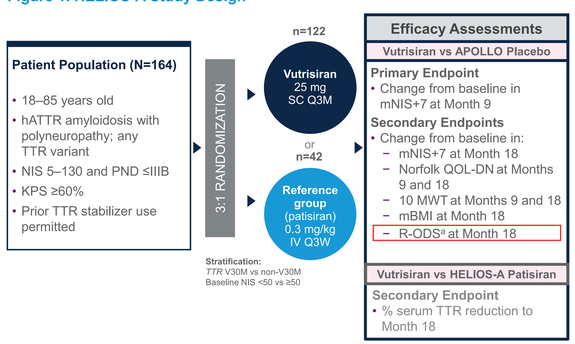
Background & Rationale

- hATTR is a rare, inherited, autosomal dominant, rapidly progressive, debilitating, and often fatal disease caused by a variant in the TTR gene that results in accumulation of toxic variant and wild-type TTR amyloid fibrils in multiple organ systems, including nerves (sensory, motor, and autonomic), heart, gastrointestinal tract, and musculoskeletal tissues[1–6]
- Polyneuropathy (PN) is one of the most frequently observed manifestations in patients with hATTR[7]
  - Peripheral nerve dysfunction can lead to pain and numbness in the extremities, while autonomic nerve dysfunction can manifest as constipation alternating with diarrhea, nausea and vomiting, orthostatic hypotension, and sexual dysfunction[7,8]
  - Disease progression eventually leads to motor weakness, decreased pain sensation, and generalized weakness and cachexia (weakness and wasting of the body due to severe chronic illness), resulting in patients experiencing deterioration in their functional status and ability to perform activities of daily living[8,9]
- Vutrisiran is an RNA interference (RNAi) therapeutic that reduces the synthesis of both variant and wild-type TTR mRNA in the liver by leveraging the naturally occurring RNAi mechanism. This results in rapid and sustained knockdown of variant and wild-type TTR protein[10,11]
  - Vutrisiran is approved for the treatment of hATTR with PN (hATTR-PN) based on the positive results from HELIOS-A (NCT03759379), a global phase 3, randomized, multicenter study (**Figure 1**)[12]
- In HELIOS-A, the R-ODS, a patient-reported, 24-item, linearly weighted scale that captures activity and social participation limitations, was measured as a secondary endpoint[13]

Objective

- To investigate the impact of vutrisiran on functional activity and social participation in patients with hATTR-PN in HELIOS-A

Figure 1. HELIOS-A Study Design



[a]Lower scores of R-ODS indicate more disability (range, 0–48).

Methods

- In this descriptive analysis, R-ODS raw scores were measured at baseline (Month [M] 0) and M18 for vutrisiran-treated patients from HELIOS-A and for placebo-treated patients from APOLLO (NCT01960348), the pivotal patisiran phase 3 trial in patients with hATTR-PN
  - The placebo arm of APOLLO was chosen since HELIOS-A was designed and powered to compare efficacy and safety of vutrisiran with this external placebo group
- In HELIOS-A, the R-ODS describes the rate of decline in activity and social participation limitations in patients with hATTR-PN
  - The raw total scores assign the same difference in ability to patients irrespective of where on the scale this difference is observed and range from 0 to 48, with lower scores indicating greater disability[13]
- In contrast, Rasch logits methodology, a scale that measures activity and social participation[13], reflects the difference in ability based on the difference in scores depending on the location on the scale where this difference is observed[13]
  - Rasch methodology models the probability that a patient will be able to complete a task as a function of both the difficulty of the task and the patient's level of ability to execute a task, allowing patient's abilities to be compared
  - R-ODS raw total scores were converted to Rasch person-location values (logits). Median logits by treatment group (vutrisiran and placebo) and visit were plotted with R-ODS item locations representing the hierarchy of difficulty in performing various activities

Results

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	APOLLO Placebo (n=77)	HELIOS-A Vutrisiran (n=122)
Age (years), median (range)	63 (34–80)	60 (26–85)
Male, n (%)	58 (75.3)	79 (64.8)
R-ODS		
Mean (SD)	29.8 (10.8)[a]	34.1 (11.0)
Median (range)	30.5 (3–48)[a]	35.0 (5–48)
Norfolk QOL-DN, mean (SD)	55.5 (24.3)[a]	47.1 (26.3)[b]
mNIS+7, mean (SD)	74.6 (37.0)	60.6 (36.0)

[a]Baseline data are only available for 76 patients in the placebo study arm. [b]Baseline data are only available for 121 patients in the vutrisiran study arm.

Participant Characteristics

- Patient demographics and disease characteristics were clinically comparable between treatment groups (**Table 1**)
- The range of R-ODS scores at baseline indicate there was a wide variety of patient-reported disability

Impact of Vutrisiran on Activity and Social Participation

- The change in R-ODS raw scores from baseline over 18 months indicated that vutrisiran was better than placebo at preserving patients' ability to perform daily activities and therefore participate socially (**Figure 2**)
- Conversion of the raw R-ODS scores to logit scores showed that relative to baseline:
  - Vutrisiran-treated patients' ability was preserved at a level that corresponded to being able to walk approximately <1 km outdoors (**Figure 3**)
  - Placebo-treated patients reported greater limitations on their ability to perform daily activities at baseline than vutrisiran-treated patients
  - Placebo-treated patients' ability worsened to a level that corresponded to losing the ability to walk one flight of stairs, take a shower, bend and pick up an object, catch an object (e.g. a ball), or do the dishes (**Figure 3**)

Figure 3. Median R-ODS Logit Scores and Associated Activity Ability

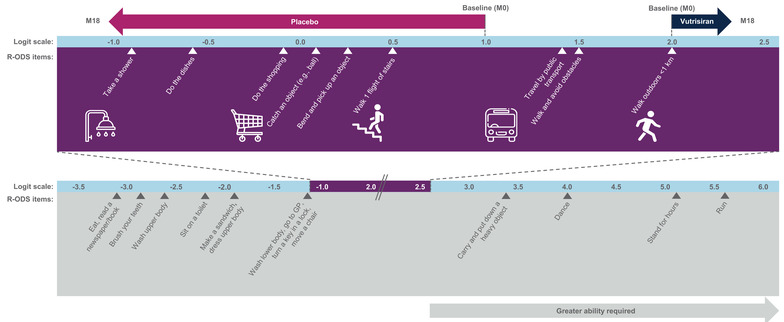
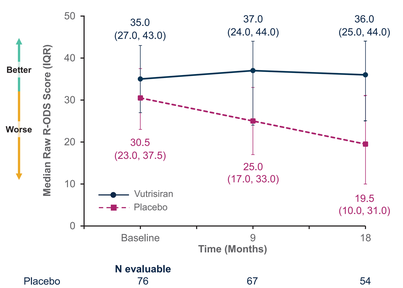


Figure 2. Median Raw R-ODS Scores Over 18 Months



N evaluable

	Baseline	9	18
Placebo	76	67	54
Vutrisiran	122	115	113

Limitations

- This was a descriptive study that examined activities of daily living in a single study, HELIOS-A, and does not include findings from other hATTR trials
- No analytical approach was used to mitigate the risk of bias arising from missing data and the associated differences in the proportion of data missingness between the vutrisiran and placebo arms, further highlighting the descriptive nature of this study

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Abbreviations: 10 MWT, 10 meter walk test; hATTR, hereditary transthyretin amyloidosis; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; IQR, interquartile range; IV, intravenous; KPS, Karnofsky Performance Status; M, Month; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PN, polyneuropathy; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; RNAi, RNA interference; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; SD, standard deviation; TTR, transthyretin.
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