Effect of RNAi Therapeutics Patisiran and Vutrisiran on Orthostatic Hypotension Due to Dysautonomia in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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Conclusions

- **Patients with hereditary-transthyretin mediated (hATTR) amyloidosis who received patisiran treatment in the Phase 3 APOLLO study showed improvement or stabilization of their postural blood pressure (PBP) over time and were able to maintain their PBP over 36 months of additional patisiran treatment in the Global Open-Label Extension (OLE) study**
- **PBP deteriorated in patients in the APOLLO-placebo group, but improved upon patisiran initiation in the Global OLE**
  - **Deterioration of PBP to a symptomatic range without active treatment indicates the importance of early intervention**
- **In the Phase 3 HELIOS-A study, PBP stabilization was observed in the vutrisiran and patisiran arms**
- **As previously reported, patisiran and vutrisiran have acceptable safety profiles**
- **These data quantify the benefits of the RNAi therapeutics patisiran and vutrisiran on the autonomic function of patients with hATTR amyloidosis with polyneuropathy**

Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- A rare, underdiagnosed, inherited, rapidly progressive, fatal disease,[1–4] caused by variants in the transthyretin (*TTR*) gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs[1–4]
  - The majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[5,6]
- Orthostatic hypotension, due to autonomic neuropathy, is a common yet hard-to-treat disease manifestation in patients with hATTR amyloidosis[7]
  - Fatigue, muscle weakness, and deterioration in cardiac function that are associated with this disease can further exacerbate orthostatic symptoms[8]

Patisiran

- RNAi therapeutic administered once every 3 weeks (Q3W) via intravenous (IV) infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO study[9,10]
- In APOLLO, improvement of autonomic symptoms (measured using the Composite Autonomic Score-31 [COMPASS-31] questionnaire) was previously demonstrated with patisiran treatment compared with placebo at 18 months[11]
  - Improvement from baseline was also noted in individual domains, including orthostatic intolerance

Vutrisiran

- A subcutaneously administered RNAi therapeutic targeting hepatic production of variant and wild-type (wt) TTR, that was recently approved for the treatment of the polyneuropathy of hATTR amyloidosis, based on the Phase 3, HELIOS-A study[12,13]
- ESC-GalNAc platform utilized by vutrisiran allows for a once every 3 months (Q3M) subcutaneous (SC) injection[12,13]

Objective

- In this analysis we evaluated the quantitative effect of patisiran and vutrisiran on orthostatic hypotension in patients with hATTR amyloidosis with polyneuropathy across the APOLLO (NCT01960348), Global OLE (NCT02510261), and HELIOS-A (NCT03759379) studies

Methods

- APOLLO: Phase 3, global, double-blind, placebo-controlled study of patisiran in patients with hATTR amyloidosis with polyneuropathy (**Figure 1**)
  - Patients who completed APOLLO (APOLLO-placebo, APOLLO-patisiran) were eligible to enroll into the ongoing Global OLE (patisiran 0.3 mg/kg IV Q3W for all patients)
- HELIOS-A: Phase 3, global, open-label study of vutrisiran 25 mg SC Q3M in patients with hATTR amyloidosis with polyneuropathy (**Figure 1**)
  - For the majority of endpoints, vutrisiran was compared with the external placebo group (placebo arm of APOLLO[10]), selected on the basis of similar eligibility criteria and endpoints
  - Patients receiving patisiran formed the reference group, which was included to test for non-inferiority in TTR reduction
- Primary endpoint for APOLLO and HELIOS-A was change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7) vs APOLLO placebo at Month 18 (APOLLO) and Month 9 (HELIOS-A)
- Orthostatic hypotension was calculated as the mean of 2 supine readings of systolic blood pressure (SBP; [mmHg]) taken 15 minutes apart minus the lowest SBP upon standing at 1, 3, and 5 minutes
  - A smaller reduction in SBP between supine and upright positions indicates better PBP
  - The severity of orthostatic hypotension was categorized as follows:
    - Normal: <20 mmHg reduction. Moderate: 20 ≤ reduction <30 mmHg. Severe: ≥30 mmHg reduction

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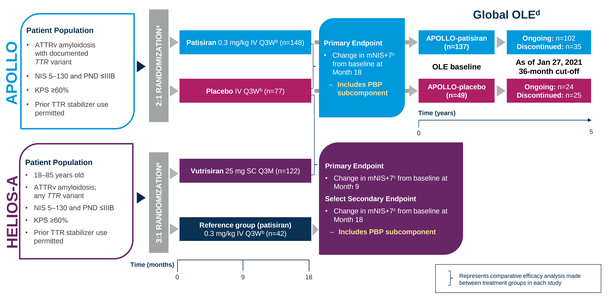
Methods (cont')

Figure 1. Study Design of APOLLO, Global OLE, and HELIOS-A



[a]Stratification factors for randomization include: NIS (<50 vs ≥50), early-onset V30M (<50 years of age at onset) vs all other variants (including late-onset V30M), and previous TTR stabilizer use (tafamidis or diflunisal) vs no previous TTR stabilizer use. [b]To reduce likelihood of IRRs, patients receive the following premedication or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine). [c]Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0 to 304). [d]The Global OLE also recruited patients from the Phase 2 OLE patisiran study; these patients were not included in this analysis. [a]Factors for randomization include NIS (<50 vs ≥50) and *TTR variant* (V30M vs non-V30M).

Results

Primary Efficacy of Patisiran and Vutrisiran

- In APOLLO, at Month 18, the primary endpoint of change in mNIS+7 from baseline was met in favor of patisiran, and improvements in all secondary endpoints were observed vs placebo
- In HELIOS-A, at Month 9, the primary endpoint of change in mNIS+7 from baseline was met in favor of vutrisiran, and all secondary endpoints were improved vs external placebo at Month 18

Baseline Demographic and Disease Characteristics

- Patients in APOLLO and HELIOS-A had characteristics that were widely overlapping at the respective study baselines, and the two populations were clinically comparable (**Table 1**)
- In HELIOS-A, a lower proportion of patients met the pre-specified criteria for inclusion in the cardiac subpopulation than in APOLLO (**Table 1**)

Table 1. Baseline Characteristics

	APOLLO		Global OLE		HELIOS-A	
	Placebo (n=77)	Patisiran (n=148)	APOLLO-placebo (n=49)	APOLLO-patisiran (n=137)	Vutrisiran (n=122)	Patisiran (n=42)
Age, median (range), years	63 (34–80)	62 (24–83)	66 (36–78)	63 (26–84)	60 (26–85)	60 (31–81)
Sex – male, n (%)	58 (75)	109 (74)	37 (76)	102 (74)	79 (65)	27 (64)
Time since hATTR amyloidosis diagnosis, median (range), years	1.4 (0.0–16.5)	1.3 (0.0–21.0)	2.83 (1.7–18.1)	2.98 (1.6–22.7)	1.9 (0.0–15.3)	2.4 (0.1–12.5)
Time since hATTR amyloidosis diagnosis to first patisiran dose,[a] median (range), years	—	—	2.77 (1.77–18.15)	1.40 (0.07–21.11)	—	—
TTR genotype, n (%)						
V30M	40 (52)	56 (38)	24 (49)	56 (41)	54 (44)	20 (48)
Non-V30M	37 (48)	92 (62)	25 (51)	81 (59)	68 (56)	22 (52)
mNIS+7 score,[b] mean (range)	75 (11.0–153.5)	81 (8.0–165.0)	101 (22.0–190.0)	75 (8.0–199.0)	61 (2.5–158.0)	58 (7.0–137.6)
Cardiac subpopulation,[c] n (%)	36 (47)	90 (61)	25 (51)	72 (53)	40 (33)	14 (33)

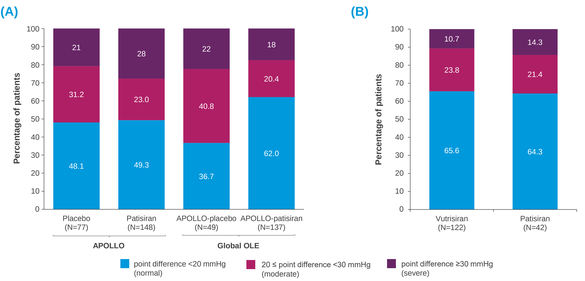
[a]First patisiran dose could have occurred in APOLLO or Global OLE (APOLLO-placebo group). [b]Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0 to 304). [c]Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline LV wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).

PBP Categories at Study Baselines

- The severity of orthostatic hypotension was comparable in both treatment arms of the APOLLO study, and in both treatment arms of the HELIOS-A study, at baseline (**Figure 2A and 2B**)
- In the APOLLO placebo arm, the proportion of patients with normal PBP decreased from APOLLO baseline to Global OLE baseline (**Figure 2A**)
- In contrast, in the APOLLO patisiran arm, there was a marked increase in the proportion of patients with normal PBP from APOLLO baseline to Global OLE baseline (**Figure 2A**)

Results (cont')

Figure 2. Percentage of Patients with Each PBP Category at APOLLO and Global OLE Baselines (A) and at HELIOS-A Baseline (B)

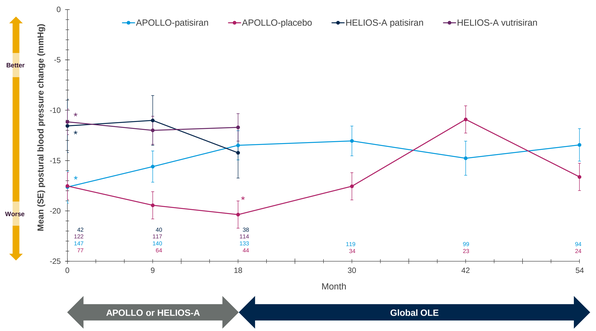


PBP is the categorized difference between (the average of 2 supine measurements taken 15 minutes apart) and (the lowest of upright measurements taken at 1, 3, and 5 minutes).

Change in Observed PBP over Time (Figure 3)

- Patients who received treatment with patisiran in the APOLLO study showed improvement or stabilization of their PBP to 18 months and were able to maintain their PBP over an additional 36 months of patisiran treatment in the Global OLE
- PBP worsened in the APOLLO-placebo group, but improved upon patisiran initiation in the Global OLE
- In HELIOS-A, stabilization in PBP was seen in the vutrisiran and patisiran arms

Figure 3. Change in Observed PBP across All Studies

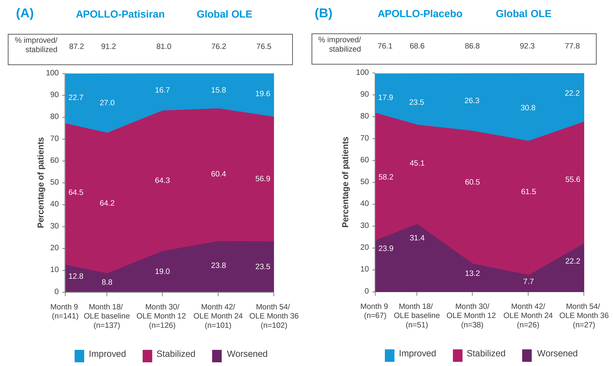


*Denotes the start of active treatment for specified studies.
Change in PBP indicates the change in SBP between a supine and a standing position. Improvement indicated by a smaller decline in the SBP between supine and upright readings.

Change in PBP Status Over Time from Study Baselines

- Among patients with an assessment at 18 months in APOLLO, **91.2%** of patients in the patisiran arm had improvement or stabilization in PBP compared with APOLLO baseline (**Figure 4A**)
- The majority of patients in the APOLLO-patisiran group (≥**76.5%** at each timepoint assessed) showed improvement or stabilization in PBP from APOLLO baseline with an additional 36 months of patisiran treatment in the Global OLE (**Figure 4A**)
- Among patients who received placebo in APOLLO with an assessment at 18 months, **68.6%** had improvement or stabilization in PBP at Month 18 with a subsequent increase to 77.8% after 36 months of patisiran treatment in the Global OLE (**Figure 4B**)
- At 36 months in the Global OLE, study discontinuation was greater in the APOLLO-placebo group than in the APOLLO-patisiran group
  - The greater proportion of missing data in the APOLLO-placebo group may lead to an underrepresentation of the benefit of patisiran

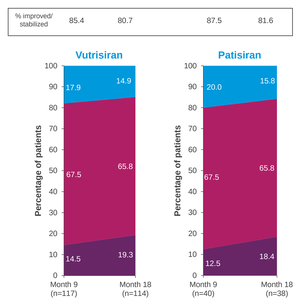
Figure 4. Change in PBP Status from APOLLO Baseline in Patisiran-treated (A) and Placebo-treated (B) Patients



Improved: post-baseline PBP is lower than baseline PBP; worsened: post-baseline PBP is higher than baseline PBP. Patients with data at Month 9 and Month 18 are shown. These results are conditional probabilities.

- The vutrisiran and patisiran treatment groups both maintained stable PBP during HELIOS-A (among patients with assessment at 18 months) (**Figure 5**)

Figure 5. Change in PBP Status from HELIOS-A Baseline in Vutrisiran- and Patisiran-treated Patients



Improved: post-baseline PBP is lower than baseline PBP; worsened: post-baseline PBP is higher than baseline PBP. Patients with data at Month 9 and Month 18 are shown. These results are conditional probabilities.

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