Reason for Stopping Transthyretin Stabilizers Prior to HELIOS-A and the Impact of Prior Stabilizer Use on the Efficacy of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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Conclusions

- **In HELIOS-A , nearly two-thirds of patients with hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, with polyneuropathy had previously received a transthyretin (TTR) stabilizer**
- **Most patients previously treated with a TTR stabilizer, either tafamidis or diflunisal, discontinued the stabilizer to participate in a clinical trial. Over a third of those who previously received tafamidis discontinued due to disease progression, most often because of worsening polyneuropathy, demonstrating an unmet need for alternative treatments that can halt or reverse polyneuropathy progression**
- **These data demonstrate that the efficacy and safety of vutrisiran appear to be unaffected by prior TTR stabilizer use; vutrisiran once every 3 months (Q3M) may be a convenient treatment option for patients with ATTRv with polyneuropathy, regardless of prior TTR stabilizer treatment history**

Background and Rationale

- ATTRv amyloidosis is a rare, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR protein that accumulates as amyloid fibrils in multiple organs and tissues[1–4]
- Current treatment strategies for ATTRv amyloidosis with polyneuropathy include TTR stabilizers which inhibit tetrameric TTR protein complex dissociation and subsequent amyloid formation[5]
  - Tafamidis is approved in the European Union for the treatment of ATTR amyloidosis in patients with Stage 1 polyneuropathy and in certain other countries outside of the US[6]
  - Diflunisal is a generic non-steroidal anti-inflammatory drug used off-label for the treatment of ATTRv amyloidosis-related polyneuropathy[7]
- Studies have shown that although these TTR stabilizing therapies slow polyneuropathy and quality of life (QOL) worsening, many patients continue to progress[7–12]
- In the HELIOS-A study, vutrisiran, an investigational, subcutaneously administered RNAi therapeutic (**Figure 1**), led to improvements in neuropathy (modified Neuropathy Impairment Score+7 [mNIS+7]) and QOL (Norfolk QOL-Diabetic Neuropathy [QOL-DN] total score) at Month 9 compared with baseline in patients with ATTRv amyloidosis with polyneuropathy and was generally well tolerated[13]

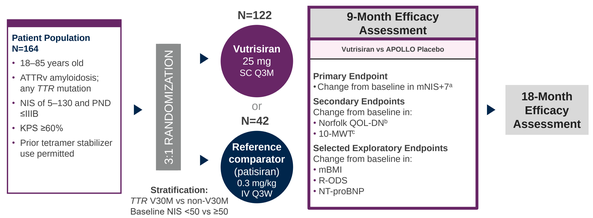
Objectives

- Summarize the reasons for TTR stabilizer treatment discontinuation prior to HELIOS-A in those patients with prior TTR stabilizer use
- Evaluate the impact of prior stabilizer use on the efficacy and safety of vutrisiran

Methods

- HELIOS-A is an open-label, global, Phase 3 study of vutrisiran in patients with ATTRv amyloidosis with polyneuropathy (NCT03759379) (**Figure 1**)
- Data from the 9-month primary efficacy analysis are presented, compared with the external placebo group (placebo arm of APOLLO study [NCT01960348]), selected on the basis of similar patient populations
- For patients receiving a TTR stabilizer prior to study drug dosing in HELIOS-A, a washout period was required (minimum washout period: diflunisal, 3 days; tafamidis, 14 days)
- The reason for stopping the TTR stabilizer as reported by the investigator was summarized
- Change from baseline to Month 9 in mNIS+7[14] and Norfolk QOL-DN[15], safety, and tolerability in patients with and without prior TTR stabilizer use was compared

Figure 1. Study Design



[a]Higher scores of mNIS+7 indicate more neuropathy impairment (range 0–304). [b]Higher scores of Norfolk QOL-DN indicate worse QOL (range −4 to 136). [c]10-MWT speed (m/s) = 10 meter/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.

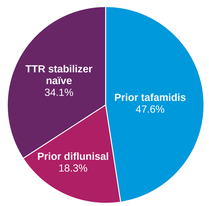
Results

Table 1. Baseline Demographics and Disease Characteristics

	APOLLO		HELIOS-A			
Characteristic	Placebo Prior TTR stabilizer use (N=41)	Placebo No prior TTR stabilizer use (N=36)	Vutrisiran Prior TTR stabilizer use (N=75)	Vutrisiran No prior TTR stabilizer use (N=47)	Patisiran Prior TTR stabilizer use (N=33)	Patisiran No prior TTR stabilizer use (N=9)
Age (years), median (range)	64.0 (34–77)	62.5 (36–80)	59.0 (31–85)	63.0 (26–81)	60.0 (31–69)	62.0 (34–81)
Males, n (%)	33 (80.5)	25 (69.4)	50 (66.7)	29 (61.7)	21 (63.6)	6 (66.7)
TTR genotype, n (%)						
V30M	23 (56.1)	17 (47.2)	41 (54.7)	13 (27.7)	18 (54.5)	2 (22.2)
Non-V30M	18 (43.9)	19 (52.8)	34 (45.3)	34 (72.3)	15 (45.5)	7 (77.8)
NIS, mean (range)	55.8 (10.5–125.5)	58.4 (7.0–122.6)	45.6 (9.0–127.0)	38.9 (5.0–88.9)	45.0 (5.5–115.6)	36.1 (8.0–82.0)
mNIS+7, mean (range)	73.2 (17.0–136.5)	76.3 (11.0–153.5)	64.7 (2.5–158.0)	54.0 (3.0–119.0)	61.5 (7.0–137.6)	47.4 (8.0–114.0)
Norfolk QOL-DN, mean (range)	52.9 (8–91)	58.4 (14–111)	45.4 (2–104)	46.9 (-1–105)	51.0 (1–125)	32.0 (5–88)
PND score, n (%)						
I: preserved walking, sensory disturbances	8 (19.5)	12 (33.3)	32 (42.7)	21 (44.7)	11 (33.3)	4 (44.4)
II: impaired walking but can walk without stick or crutch	17 (41.5)	6 (16.7)	35 (46.7)	15 (31.9)	14 (42.4)	3 (33.3)
≥IIIA: walk with 1 stick or crutch	12 (29.3)	10 (27.8)	9 (12.0)	7 (14.9)	6 (18.2)	1 (11.1)
≥IIIB: walk with 2 sticks or crutches	4 (9.8)	7 (19.4)	8 (10.7)	4 (8.5)	2 (6.1)	1 (11.1)
IV: wheelchair-bound or bedridden	0	1 (2.8)	0	0	0	0
Time since discontinuation of previous TTR stabilizer use (days), mean (range)	31.4 (6.0–148.0)	NA	58.1 (4.0–1210.0)	NA	28.5 (4.0–122.0)	NA

Figure 2. TTR Stabilizer Use Prior to HELIOS-A

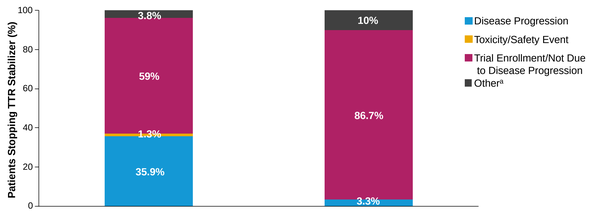
- Prior to study entry, 65.9% of patients had received a TTR stabilizer (**Figure 2**)
  - Prior tafamidis use was most commonly reported, by nearly half of patients (47.6%); prior diflunisal use was reported in 18.3%



Reasons for TTR Stabilizer Discontinuation

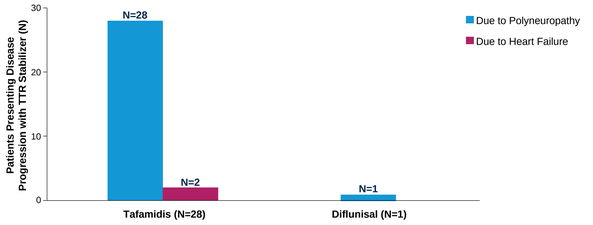
- The most common reasons for TTR stabilizer discontinuation prior to HELIOS-A were clinical trial participation/not due to disease progression and disease progression (**Figure 3**)
- In those who stopped TTR stabilizer treatment due to disease progression (tafamidis n=28, diflunisal n=1), the following reasons for disease progression with the specific signs/symptoms were provided by the investigator (**Figure 4**)
  - Tafamidis:
    - Due to worsening neuropathy (n=28/28):
      - Sensory symptoms: 89.3% (n=25/28)
      - Motor symptoms: 96.4% (n=27/28)
      - Gastrointestinal symptoms: 32.1% (n=9/28)
      - Orthostasis and/or syncope: 17.9% (n=5/28)
    - Due to worsening heart failure: 7.1% (n=2/28)
  - Diflunisal:
    - Due to worsening neuropathy:
      - Motor symptoms: 100% (n=1/1)

Figure 3. Reasons for Stopping TTR Stabilizer Prior to HELIOS-A



[a]Other reasons for stopping: discretion of investigator (tafamidis, n=1); no improvement (tafamidis, n=1); side effects/ineffective (tafamidis, n=1); nausea and leg swelling (diflunisal n=1); pre-emptive concern from patient's nephrologist of worsening renal function as drug was an NSAID (diflunisal, n=1); non-compliance (diflunisal, n=1).

Figure 4. Reason for Disease Progression while Receiving TTR Stabilizer Prior to HELIOS-A[a]

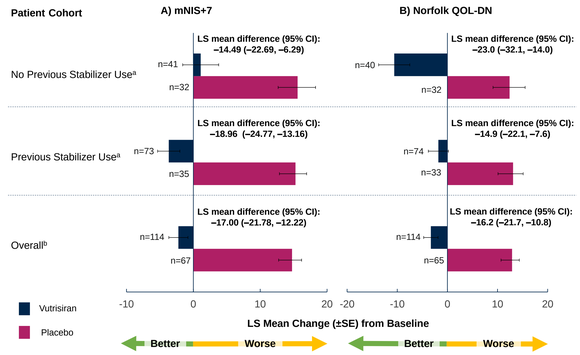


[a]Investigators could select multiple categories.

Efficacy of Vutrisiran vs Placebo in Patients with and without Prior TTR Stabilizer Use

- Compared with placebo, similar improvements in mNIS+7 and Norfolk QOL-DN were seen for vutrisiran-treated patients at Month 9, regardless of prior stabilizer use group (**Figure 5**)

Figure 5. Change from Baseline to Month 9 in A) mNIS+7 and B) Norfolk QOL-DN



[a]ANCOVA (mITT population). [b]ANCOVA/multiple imputation (mITT population).

Safety

- A preliminary review of the safety and tolerability of vutrisiran with and without prior TTR stabilizer use show generally consistent incidence of adverse events (AEs) between groups (**Table 2**)
- The majority of AEs were mild to moderate in severity in all groups

Table 2. Safety Summary in Patients with and without Prior TTR Stabilizer Use

	APOLLO — Placebo		HELIOS-A — Vutrisiran	
	Prior TTR stabilizer use	No prior TTR stabilizer use	Prior TTR stabilizer use	No prior TTR stabilizer use
At least 1 event, n (%)	(N=41) PY=49.1	(N=36) PY=47.0	(N=75) PY=80.1	(N=47) PY=51.1
AE	40 (97.6)	35 (97.2)	70 (93.3)	44 (93.6)
Related to study drug	17 (41.5)	13 (36.1)	13 (17.3)	12 (25.5)
Severe AE	14 (34.1)	14 (38.9)	6 (8.0)	9 (19.1)
Related to study drug	1 (2.4)	1 (2.8)	1 (1.3)	2 (4.3)
Serious AE	17 (41.5)	14 (38.9)	9 (12.0)	12 (25.5)
Related to study drug	0	0	2 (2.7)	0
AE leading to treatment discontinuation	6 (14.6)	5 (13.9)	1 (1.3)	1 (2.1)
Related to study drug	0	0	0	0
Death	2 (4.9)	4 (11.1)	1 (1.3)	1 (2.1)

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Abbreviations: 10-MWT, 10-meter walk test; AE, adverse event; ANCOVA, analysis of covariance; ATTRv, hereditary transthyretin (v for variant); CI, confidence interval; GI, gastrointestinal; hATTR, hereditary transthyretin-mediated; IV, intravenous; KPS, Karnofsky performance status; LS, least squares; mBMI, modified body mass index; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; NA, not available; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; PND, polyneuropathy disability score; Q3M, every 3 months; Q3W, every 3 weeks; QOL, quality of life; RNAi, ribonucleic acid interference; R-ODS, Rasch-built Overall Disability Scale; SE, standard error; TTR, transthyretin; wt, wild-type.

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