HELIOS-A: Results from the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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HELIOS·A

Conclusions

- **As previously reported, vutrisiran met the primary endpoint (mNIS+7) at 9 months in HELIOS-A[1]**
- **Vutrisiran met all secondary endpoints at 18 months**
  - **Statistically significant improvement in mNIS+7 versus external placebo**
  - **Improvement in quality of life (QOL) (Norfolk QOL-DN), gait speed (10-MWT), nutritional status (mBMI), and disability (R-ODS) versus external placebo**
  - **Robust and sustained TTR reduction, non-inferior to within-study patisiran**
- **Vutrisiran treatment led to improvements in certain exploratory cardiac measures compared with external placebo**
- **A sub-analysis in patients with the V122I/T60A *TTR* variants, historically associated with cardiomyopathy, indicated both cardiac and neurologic impairment at baseline**
  - **In patients with the V122I/T60A *TTR* variants, vutrisiran had a beneficial effect on neuropathy, QOL, and cardiac stress (NT-proBNP) versus external placebo in this population**
- **Vutrisiran had an acceptable safety profile, with the majority of AEs being mild or moderate in severity during the 18-month treatment period**
- **The efficacy and safety of vutrisiran will continue to be characterized in the ongoing HELIOS-A randomized extension period**

Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- A rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease[2–5]
- Caused by variants in the *TTR* gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues, including nerves, heart, GI tract, and musculoskeletal tissues[2–5]
- V122I and T60A variants have been historically associated with cardiomyopathy, but recent evidence suggests these patients develop a multisystem disease[5–7]
  - The majority of individuals with hATTR amyloidosis develop a mixed phenotype of both polyneuropathy and cardiomyopathy[8,9]

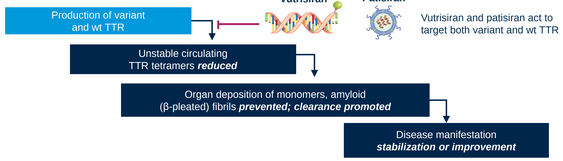
Vutrisiran

- An investigational, subcutaneously (SC) administered, RNAi therapeutic targeting hepatic production of variant and wild-type (wt) TTR, in development for the treatment of ATTR amyloidosis[10,11] (**Figure 1**)
- ESC-GalNAc platform utilized by vutrisiran allows for a Q3M SC injection[11,12]

Patisiran

- RNAi therapeutic administered via intravenous infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO trial[12–14] (**Figure 1**)

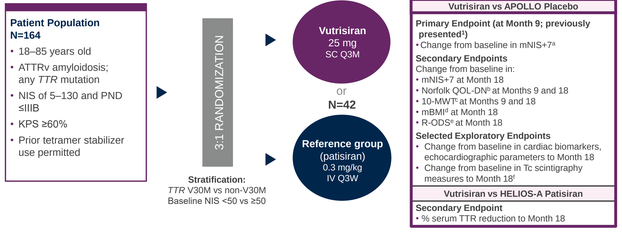
Figure 1. Therapeutic Hypothesis



Methods

- HELIOS-A is a Phase 3, global, open-label study of vutrisiran 25 mg SC Q3M in patients with ATTRv amyloidosis with polyneuropathy (**Figure 2**)
- The 18-month efficacy analysis is presented; for primary and secondary endpoints, vutrisiran was compared with the external placebo group (placebo arm of APOLLO[13]), selected on the basis of similar patient populations and endpoints
  - A sub-analysis of neurologic and cardiac endpoints for patients with V122I/T60A variants is also reported

Figure 2. Study Design



[a]Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). [b]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). [c]10-MWT speed (m/s) = 10 meters/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. [d]Lower scores of mBMI (weight [in kg/m^2] × serum albumin [in g/L]) indicate worse nutritional status. [e]Lower scores of R-ODS indicate more disability (range, 0 to 48). [f]Tc scintigraphy was only performed at select sites.

Baseline Demographic and Disease Characteristics

- Patients in HELIOS-A had characteristics that were widely overlapping with patients in the external placebo group, and the two populations were clinically comparable (**Table 1**)
- Patients in the HELIOS-A study had a wide range of disease severity and encompassed 26 different *TTR* variants

Results

Table 1. Baseline Characteristics

Characteristic	APOLLO Placebo (n=77)		HELIOS-A	
	mITT (n=77)	V122I/T60A (n=5)	Patisiran (n=42)	Vutrisiran (n=122)	
				mITT (n=122)	V122I/T60A (n=20)
Age, median (range), years	63 (34–80)	68 (57–75)	60 (31–81)	60 (26–85)	66 (37–72)
Males, n (%)	58 (75.3)	4 (80.0)	27 (64.3)	79 (64.8)	12 (60.0)
TTR genotype, n (%)					
V30M	40 (51.9)	0	20 (47.6)	54 (44.3)	0
Non-V30M	37 (48.1)	5 (100.0)	22 (52.4)	68 (55.7)	20 (100.0)
NIS, mean (range)	57.0 (7.0–125.5)	34.0 (11.5–60.0)	43.1 (5.5–115.6)	43.0 (5.0–127.0)	31.6 (8.0–73.0)
Previous tetramer stabilizer use, n (%)	41 (53.2)	5 (100.0)	33 (78.6)	75 (61.5)	4 (20.0)
PND score[a], n (%)					
I: preserved walking, sensory disturbances	20 (26.0)	1 (20.0)	15 (35.7)	44 (36.1)	9 (45.0)
II: impaired walking, but can walk without stick or crutch	23 (29.9)	3 (60.0)	17 (40.5)	50 (41.0)	8 40.0)
IIIA: walk with 1 stick or crutch	22 (28.6)	1 (20.0)	7 (16.7)	16 (13.1)	3 (15.0)
IIIB: walk with 2 sticks or crutches	11 (14.3)	0	3 (7.1)	12 (9.8)	0
Baseline LV wall thickness (cm), mean (SD)	1.6 (0.3)	1.7 (0.3)	1.4 (0.4)	1.4 (0.4)	1.5 (0.5)
Baseline global longitudinal strain (%), mean (SD)	−16.3 (3.7)	−14.5 (4.3)	−15.2 (4.0)	−15.8 (4.0)	−14.2 (4.1)
Baseline NYHA class[b], n (%)					
No heart failure	N/A	N/A	21 (50.0)	68 (55.7)	5 (25.0)
Class I	40 (51.9)	1 (20.0)	5 (11.9)	11 (9.0)	1 (5.0)
Class II	36 (46.8)	3 (60.0)	16 (38.1)	43 (35.2)	14 (70.0)
NT-proBNP[c], median (range)	562.8 (25.0–16,497.8)	1909.0 (51.9– 4240.2)	387.7 (5.0–14,324.2)	287.4 (5.0–18,755.0)	840.8 (20.0–7588.2)
Cardiac subpopulation[d], n (%)	36 (46.8)	1 (20.0)	14 (33.3)	40 (32.8)	6 (30.0)

[a]One patient (1.3%) in external mITT placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown in Table 1). [b]NYHA class of no heart failure was not included in the APOLLO assessments. No patient had an NYHA class >II. NYHA class missing for 1 (1.3%) patient in the APOLLO placebo mITT group, and 1 (20%) patient in the APOLLO placebo V122I/T60A group. [c]NT-proBNP missing for 2 patients in the APOLLO placebo mITT group. [d]Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history). Select echocardiogram parameters were re-read for the Month 18 analysis and the cardiac subpopulation was re-derived based on baseline LV wall thickness values after the re-read. As a result, in the Month 18 analysis the cardiac subpopulation status of 9 patients receiving vutrisiran was reclassified and 1 patient receiving patisiran was added to the cardiac subpopulation compared with the cardiac subpopulation defined in the Month 9 analysis.

Neuropathy Impairment (mNIS+7) and Quality of Life (Norfolk QOL-DN)

- As previously reported, the primary endpoint of change from baseline in mNIS+7 compared with the external placebo group at Month 9 was met[1]
- Vutrisiran achieved statistically significant improvement in mNIS+7 and Norfolk QOL-DN at 18 months, compared with the external placebo group (**Figure 3A and 3B**)

Figure 3A. mNIS+7 LS Mean Change from Baseline[a]

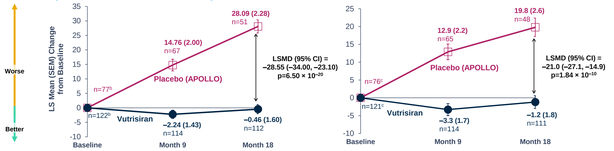


Figure 3B. Norfolk QOL-DN LS Mean Change from Baseline[a]

[a]mITT population. [a]At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in the external placebo group. [a]At baseline, the mean (±SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. Data at Month 9 are ANCOVA/multiple imputation model data and data at Month 18 are MMRM model data. Value of n is the number of evaluable patients at each timepoint.

Gait Speed (10-MWT), Nutritional Status (mBMI), and Disability (R-ODS)

- Vutrisiran achieved statistically significant improvement in 10-MWT, mBMI, and R-ODS at 18 months, compared with the external placebo group (**Figure 4A, 4B, and 4C**)

Figure 4A. 10-MWT (Gait Speed) LS Mean Change from Baseline[a]

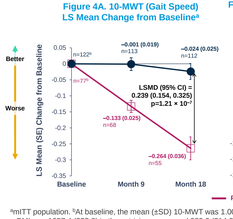


Figure 4B. mBMI (Nutritional Status) LS Mean Change from Baseline[a]

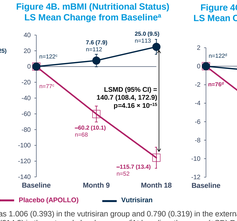
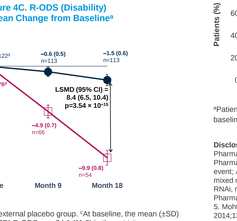


Figure 4C. R-ODS (Disability) LS Mean Change from Baseline[a]



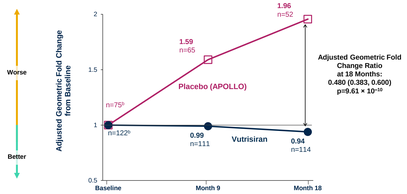
Placebo (APOLLO) Vutrisiran

[a]mITT population. [a]At baseline, the mean (±SD) 10-MWT was 1.006 (0.393) in the vutrisiran group and 0.790 (0.319) in the external placebo group. [a]At baseline, the mean (±SD) mBMI was 1057.4 (238.8) in the vutrisiran group and 989.9 (214.2) in the external placebo group. [a]At baseline, the mean (±SD) R-ODS was 34.1 (11.0) in the vutrisiran group and 29.8 (10.8) in the external placebo group. Data at Month 9 are ANCOVA/multiple imputation model data and data at Month 18 are MMRM model data. Value of n is the number of evaluable patients at each timepoint.

Assessment of Cardiac Stress and Function

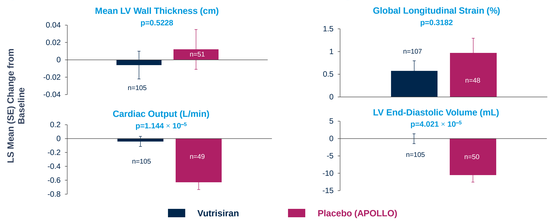
- Vutrisiran treatment achieved a reduction in NT-proBNP at Month 18 compared with external placebo (exploratory endpoint) (**Figure 5A**)

Figure 5A. Change from Baseline in NT-proBNP (mITT Population)[a]



- Echocardiographic parameters at Month 18 trended toward improvement with vutrisiran compared with the external placebo group (exploratory endpoints) (**Figure 5B**)

Figure 5B. Echocardiographic Parameters LS Mean Change from Baseline (mITT Population)[c]

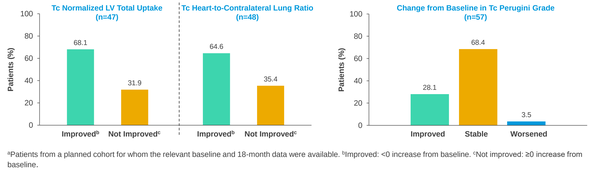


[a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. [b]At baseline, NT-proBNP geometric mean (SE) was 273.0 (42.2) ng/L in the vutrisiran group (n=122) and 531.3 (86.7) ng/L in the APOLLO placebo group (n=75). [c]Data at Month 9 are ANCOVA/multiple imputation model data and data at Month 18 are MMRM model data. Value of n is the number of evaluable patients at each timepoint.

Assessment of Cardiac Uptake of ^{99m}Technetium on Scintigraphy

- Cardiac uptake of ^{99m}Tc on scintigraphy imaging at Month 18 was reduced with vutrisiran in most patients compared with baseline in a planned cohort (exploratory endpoints) (**Figure 6**)

Figure 6. Scintigraphy Parameters LS Mean Change from Baseline[a]



[a]Patients from a planned cohort for whom the relevant baseline and 18-month data were available. [b]Improved: <0 increase from baseline. [c]Not improved: ≥0 increase from baseline.

Assessment of Various Endpoints in the V122I/T60A Population with Vutrisiran

- In patients with a V122I/T60A variant, vutrisiran led to a benefit in neuropathy (mNIS+7), QOL (Norfolk QOL-DN), and NT-proBNP levels compared with external placebo at Month 18 (**Table 2**), similar to that observed in the mITT population

Table 2. V122I/T60A Population

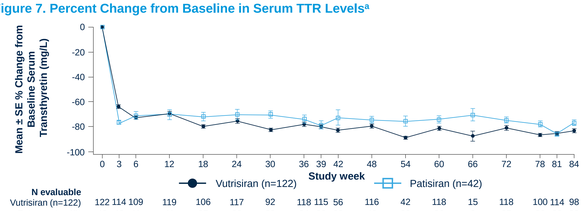
Characteristic (change from baseline at 18 months)[a]	APOLLO	HELIOS-A		
	Placebo (n=77[b])	Placebo V122I/T60A (n=5[c])	Vutrisiran mITT (n=122[d])	Vutrisiran V122I/T60A (n=20[e])
mNIS+7, mean (SD) change from baseline	27.9 (22.3)	33.5 (41.2)	0.2 (13.9)	−3.3 (13.6)
Norfolk QOL-DN, mean (SD) change from baseline	20.2 (21.1)	12.3 (18.8)	−2.4 (20.8)	−5.7 (22.3)
NT-proBNP, mean (SD) change from baseline	1310.6 (3318.3)	1419.7 (2135.5)	91.9 (1035.5)	175.0 (943.3)

[a]Data are arithmetic mean change from baseline, whereas previously reported data were LS mean changes from baseline for the mITT population. LS mean changes cannot be calculated in this analysis due to small patient numbers. [b]Number of evaluable patients: mNIS+7, n=51; Norfolk QOL-DN, n=48; NT-proBNP, n=52. [c]Number of evaluable patients: all measures, n=3. [d]Number of evaluable patients: mNIS+7, n=112; Norfolk QOL-DN, n=111; NT-proBNP, n=114. [e]Number of evaluable patients: all measures, n=18.

Serum TTR Levels

- Vutrisiran achieved a mean steady-state serum TTR reduction from baseline of 88% (SD: 16%) (**Figure 7**)
- TTR reduction with vutrisiran was non-inferior to that observed with the within-study patisiran reference group (secondary endpoint) over 18 months (median TTR difference [vutrisiran-patisiran] [95% CI], 5.28% [1.17, 9.25], lower limit of confidence interval >−10%)

Figure 7. Percent Change from Baseline in Serum TTR Levels[a]



N evaluable																				
Vutrisiran (n=122)	122	114	109	119	106	117	92	118	115	56	116	42	118	15	118	100	114	98
Patisiran (n=42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38	32

[a]As assessed by mean trough serum TTR levels.

Safety[a]

- No drug-related discontinuations or deaths
- Three study discontinuations (2.5%) due to AEs in the vutrisiran arm (two due to death, as previously reported; one due to a non-fatal heart failure event), none of which were considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- As previously reported, two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in the vutrisiran group included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness
  - All except arthralgia and pain in extremity were reported at a similar or lower frequency than external placebo
- Injection-site reactions were reported in 5 patients (4.1%) receiving vutrisiran, all mild and transient
- No safety signals regarding liver function tests, hematology, or renal function related to vutrisiran

Table 3. HELIOS-A 18-Month Safety Summary

At least one event, n (%)	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
AEs	75 (97.4)	119 (97.5)	41 (97.6)
SAEs	31 (40.3)	32 (26.2)	18 (42.9)
Severe AEs	28 (36.4)	19 (15.6)	16 (38.1)
AEs leading to treatment discontinuation	11 (14.3)	3 (2.5)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)

[a]Data reported during 18-month treatment period.

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