HELIOS-A: Study of Vutrisiran in Patients with hATTR Amyloidosis

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January 21–22, 2022 || 26th édition of the Journées de la Société Francophone du Nerf Périphérique (SFNP)
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<thead>
<tr>
<th>Conflict</th>
<th>Disclosure</th>
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<tr>
<td>Consultant</td>
<td>Alnylam Pharmaceuticals</td>
</tr>
<tr>
<td>Advisory committee/data safety monitoring board</td>
<td>Pfizer</td>
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</tbody>
</table>
Background and Rationale

**hATTR Amyloidosis, Also Known as ATTRv Amyloidosis**
- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease
- Caused by variants in the *TTR* gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues\(^1\)–\(^4\)
- The majority of individuals develop a mixed phenotype of polyneuropathy and cardiomyopathy\(^5\),\(^6\)

**Vutrisiran**
- Investigational, subcutaneously administered RNAi therapeutic targeting hepatic production of variant and wt TTR in development for the treatment of ATTR amyloidosis\(^7\),\(^8\)

**Patisiran**
- RNAi therapeutic administered via IV infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO trial\(^9\)–\(^12\)

**Therapeutic Hypothesis**
- Production of variant and wt TTR
- Unstable circulating TTR tetramers reduced
- Organ deposition of monomers, amyloid (β-pleated) fibrils prevented; clearance promoted
- Disease manifestation stabilization or improvement
- ESC-GalNAc platform utilized by vutrisiran allows for Q3M SC injection\(^9\),\(^10\)

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**ATTRv, hereditary transthyretin (v for variant); ESC, enhanced stabilization chemistry; GalNAc, N-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; IV, intravenous; Q3M, every 3 months; RNAi, ribonucleic acid interference; SC, subcutaneous; TTR, transthyretin; wt, wild-type.**

Vutrisiran Phase 3 HELIOS·A Study in Patients with Hereditary Transthyretin-Mediated Amyloidosis Polyneuropathy

Month 18 Results

• As previously reported, the primary endpoint of change from baseline in mNIS+7 at Month 9 was met

Patient Population
N=164
• 18–85 years old
• hATTR amyloidosis with polyneuropathy; any TTR mutation
• NIS 5–130 and PND ≤IIIB
• KPS ≥60%
• Prior tetramer stabilizer use permitted

3:1 RANDOMIZATION

Stratification:
TTR V30M vs non-V30M
Baseline NIS <50 vs ≥50

n=122

Vutrisiran
25 mg
SC Q3M

or

n=42

Reference comparator (patisiran)
0.3 mg/kg
IV Q3W

Efficacy Assessments
Vutrisiran vs APOLLO Placebo

Primary Endpoint (at Month 9; previously presented)
• Change from baseline in mNIS+7

Secondary Endpoints
Change from baseline in:
• mNIS+7 at Month 18
• Norfolk QOL-DN at Months 9 and 18
• 10-MWT\textsuperscript{c} at Months 9 and 18
• mBMI\textsuperscript{d} at Month 18
• R-ODS\textsuperscript{e} at Month 18

Selected Exploratory Endpoints
• Change from baseline in cardiac biomarkers, echocardiographic parameters to Month 18
• Change from baseline in Tc scintigraphy measures to Month 18

Vutrisiran vs HELIOS-A Patisiran

Secondary Endpoint
• % serum TTR reduction to Month 18

Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). \textsuperscript{1}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. \textsuperscript{2}Lower scores of mBMI (weight [in kg]/(height [in cm]\textsuperscript{2}) × serum albumin [in g/L]) indicate worse nutritional status. \textsuperscript{3}Lower scores of R-ODS indicate more disability (range, 0 to 48). Tc scintigraphy was only performed at select sites. 10-MWT, 10-meter walk test; hATTR, hereditary transthyretin-mediated amyloidosis; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life Diabetic Neuropathy; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; Tc, technetium; TTR, transthyretin.

Baseline Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>APOLLO Placebo (n=77)</th>
<th>HELIOS-A Vutrisiran (n=122)</th>
<th>HELIOS-A Patisiran (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>63 (34, 80)</td>
<td>60 (26, 85)</td>
<td>60 (31, 81)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>58 (75)</td>
<td>79 (65)</td>
<td>27 (64)</td>
</tr>
<tr>
<td>TTR genotype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V30M</td>
<td>40 (52)</td>
<td>54 (44)</td>
<td>20 (48)</td>
</tr>
<tr>
<td>Non-V30M</td>
<td>37 (48)</td>
<td>68 (56)</td>
<td>22 (52)</td>
</tr>
<tr>
<td>NIS, mean (range)</td>
<td>57 (7, 126)</td>
<td>43 (5, 127)</td>
<td>43 (6, 116)</td>
</tr>
<tr>
<td>Previous tetramer stabilizer use, n (%)</td>
<td>41 (53.2)</td>
<td>75 (61.5)</td>
<td>33 (78.6)</td>
</tr>
<tr>
<td>PND score&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I: preserved walking, sensory disturbances</td>
<td>20 (26)</td>
<td>44 (36)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>II: impaired walking but can walk without stick or crutch</td>
<td>23 (30)</td>
<td>50 (41)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>IIIA: walk with 1 stick or crutch</td>
<td>22 (29)</td>
<td>16 (13)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>IIIB: walk with 2 sticks or crutches</td>
<td>11 (14)</td>
<td>12 (10)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Cardiac subpopulation, n (%)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>36 (47)</td>
<td>40 (33)</td>
<td>14 (33)</td>
</tr>
</tbody>
</table>

<sup>a</sup>One patient (1.3%) in the external placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown on the slide).<sup>b</sup>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).<sup>c</sup>Select echocardiogram parameters were reread for the Month 18 analysis and the cardiac subpopulation was rederived 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.

LV, left ventricular; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.
Statistically Significant Improvement in Neuropathy Impairment and Quality of Life with Vutrisiran vs External Placebo at Month 18

- Improvement was observed across all prespecified patient subgroups, components, and subdomains of mNIS+7 and Norfolk QOL-DN (data not shown)
- Improvement relative to baseline\(^a\) in mNIS+7 (48.3% [vutrisiran] vs 3.9% [placebo]) and Norfolk QOL-DN (56.8% vs 10.4%)
- Consistent treatment effects in vutrisiran and patisiran groups in HELIOS-A (data not shown)

### mNIS+7 LS Mean Change from Baseline\(^b\)

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean (SEM) Change from Baseline</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (APOLLO)</td>
<td>14.76 (2.00)</td>
<td>67</td>
</tr>
<tr>
<td>Vutrisiran</td>
<td>-2.24 (1.43)</td>
<td>114</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>127</td>
</tr>
</tbody>
</table>

\(^b\)LSMD (95% CI) = -28.55 (–34.00, –23.10) \(p=6.51 \times 10^{-20}\)

### Norfolk QOL-DN LS Mean Change from Baseline\(^b\)

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean (SEM) Change from Baseline</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (APOLLO)</td>
<td>12.9 (2.2)</td>
<td>65</td>
</tr>
<tr>
<td>Vutrisiran</td>
<td>-3.3 (1.7)</td>
<td>114</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>115</td>
</tr>
</tbody>
</table>

\(^b\)LSMD (95% CI) = -21.0 (–27.1, –14.9) \(p=1.84 \times 10^{-10}\)

\(^a\)Improvement defined as patients with <0-point increase from baseline to 18 months.
\(^b\)mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted for mNIS+7 and Norfolk QOL-DN at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. \(^a\)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. \(^b\)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. ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SEM, standard error of the mean.
Statistically Significant Improvement in Secondary Endpoints with Vutrisiran vs External Placebo at Month 18

10-MWT (Gait Speed) LS Mean Change from Baseline\(^a\)

**Baseline**
- Placebo (APOLLO): -0.133 (0.025)
- Vutrisiran: -0.264 (0.036)

**Month 9**
- Placebo (APOLLO): -0.001 (0.019)
- Vutrisiran: -0.024 (0.025)

**Month 18**
- Placebo (APOLLO): 7.6 (7.9)
- Vutrisiran: 25.0 (9.5)

**LSMD (95% CI):**
- Placebo (APOLLO): 0.239 (0.154, 0.325) \(p=1.2 \times 10^{-7}\)
- Vutrisiran: -0.024 (0.025)

**mBMI (Nutritional Status) LS Mean Change from Baseline\(^a\)**

**Baseline**
- Placebo (APOLLO): -140.2 (10.1)
- Vutrisiran: 115.7 (13.4)

**Month 9**
- Placebo (APOLLO): -60.2 (10.1)
- Vutrisiran: -115.7 (13.4)

**Month 18**
- Placebo (APOLLO): 7.6 (7.9)
- Vutrisiran: 25.0 (9.5)

**LSMD (95% CI):**
- Placebo (APOLLO): 140.7 (108.4, 172.9) \(p=4.16 \times 10^{-15}\)
- Vutrisiran: -0.6 (0.5)

**R-ODS (Disability) LS Mean Change from Baseline\(^a\)**

**Baseline**
- Placebo (APOLLO): -115.7 (13.4)
- Vutrisiran: -9.9 (0.8)

**Month 9**
- Placebo (APOLLO): -115.7 (13.4)
- Vutrisiran: -9.9 (0.8)

**Month 18**
- Placebo (APOLLO): 7.6 (7.9)
- Vutrisiran: 25.0 (9.5)

**LSMD (95% CI):**
- Placebo (APOLLO): 25.0 (9.5)
- Vutrisiran: 140.7 (108.4, 172.9) \(p=4.16 \times 10^{-15}\)

\(^a\)mITT population (all randomized patients who received any amount of study drug) for all endpoints. Value of n is the number of evaluable patients at each timepoint. Data plotted for 10-MWT, mBMI and R-ODS at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. \(^b\)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. \(^c\)At baseline, the mean (±SD) mBMI was 1057.4 (233.8) in the vutrisiran group and 989.9 (214.2) in the external placebo group. \(^d\)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.

10-MWT, 10-meter walk test; ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mBMI, modified body mass index; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; SE, standard error.
Improvement in Exploratory Assessment of NT-proBNP with Vutrisiran vs External Placebo at Month 18

Change from Baseline in NT-proBNP (mITT Population)\textsuperscript{a}

\textbf{Adjustment Geometric Fold Change from Baseline}

- **Worse**
- **Better**

\textbf{Placebo (APOLLO)}
- n=75\textsuperscript{b}
- n=122\textsuperscript{b}

\textbf{Vutrisiran}
- n=52
- n=114

\textbf{Baseline}  
\textbf{Month 9}  
\textbf{Month 18}

Adjusted Geometric Fold Change Ratio at 18 Months:  
0.480 (0.383, 0.600)  
\(p=9.60 \times 10^{-10}\)

\textsuperscript{a}NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. \textsuperscript{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). Number of evaluable patients at each timepoint are shown. Data plotted for NT-proBNP at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. ANCOVA, analysis of covariance; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; NT-proBNP, N-terminal pro-brain natriuretic peptide; SE, standard error.
Assessments of Cardiac Amyloid Involvement with Vutrisiran

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

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

<table>
<thead>
<tr>
<th>Cardiac Output (L/min)</th>
<th>LS mean (SE) Change from Baseline</th>
<th>$p=1.144 \times 10^{-5}$</th>
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</thead>
<tbody>
<tr>
<td>Vutrisiran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (APOLLO)</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean LV Wall Thickness (cm)</th>
<th>$p=0.5228$</th>
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<tbody>
<tr>
<td>Vutrisiran</td>
<td>n=51</td>
</tr>
<tr>
<td>Placebo (APOLLO)</td>
<td>n=105</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Global Longitudinal Strain (%)</th>
<th>$p=0.3182$</th>
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<tbody>
<tr>
<td>Vutrisiran</td>
<td>n=48</td>
</tr>
<tr>
<td>Placebo (APOLLO)</td>
<td>n=107</td>
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<table>
<thead>
<tr>
<th>LV End-Diastolic Volume (mL)</th>
<th>$p=4.021 \times 10^{-5}$</th>
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<tbody>
<tr>
<td>Vutrisiran</td>
<td>n=49</td>
</tr>
<tr>
<td>Placebo (APOLLO)</td>
<td>n=105</td>
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<table>
<thead>
<tr>
<th>Tc Normalized LV Total Uptake (n=47)</th>
<th>68.1</th>
<th>31.9</th>
<th>64.6</th>
<th>35.4</th>
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<tbody>
<tr>
<td>Improved</td>
<td>68.1</td>
<td>31.9</td>
<td>Improved</td>
<td>64.6</td>
</tr>
<tr>
<td>Not Improved</td>
<td>31.9</td>
<td>64.6</td>
<td>Not Improved</td>
<td>35.4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tc Heart-to-Contralateral Lung Ratio (n=48)</th>
<th>28.1</th>
<th>68.4</th>
<th>3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>28.1</td>
<td>68.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Not Improved</td>
<td>68.4</td>
<td>3.5</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from Baseline in Tc Perugini Grade (n=57)</th>
<th>28.1</th>
<th>68.4</th>
<th>3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>28.1</td>
<td>68.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Stable</td>
<td>68.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td></td>
<td>3.5</td>
<td></td>
</tr>
</tbody>
</table>

$mITT$ population. $a$Patients from a planned cohort of the $mITT$ population for whom the relevant 18-month data were available. $c$Improved: $<0$ increase from baseline. $d$Not improved: $\geq 0$ increase from baseline.

LS, least squares; LV, left ventricular; $mITT$, modified intent-to-treat; SE, standard error; Tc, technetium.
Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran

- Vutrisiran achieved a mean steady-state serum TTR reduction from baseline of 88% (SD: 16%)
- TTR reduction with vutrisiran was non-inferior to that observed with the within-study patisiran reference comparator (secondary endpoint) over 18 months\(^a\)

\(^a\)As assessed by mean trough serum TTR levels.
SD, standard deviation; SE, standard error; TTR, transthyretin.
Month 18 HELIOS-A Vutrisiran Efficacy Results Consistent with APOLLO Patisiran

Findings Consistent with Similar Serum TTR Reduction Seen with Vutrisiran and Patisiran

Vutrisiran Efficacy\textsuperscript{a} vs Placebo
Standardized Effect Sizes from HELIOS-A

- Clinical Endpoints:
  - mNIS+7
  - Norfolk QOL-DN
  - 10-MWT
  - R-ODS
  - mBMI

- Cardiac Endpoints:
  - LV Wall Thickness
  - Longitudinal Strain (%)
  - LV End-Diastolic Volume
  - Cardiac Output
  - NT-proBNP

Patisiran Efficacy\textsuperscript{b} vs Placebo
Standardized Effect Sizes from APOLLO

- Clinical Endpoints:
  - mNIS+7
  - Norfolk QOL-DN
  - 10-MWT
  - R-ODS
  - mBMI

- Cardiac Endpoints:
  - LV Wall Thickness
  - Longitudinal Strain (%)
  - LV End-Diastolic Volume
  - Cardiac Output
  - NT-proBNP

\textsuperscript{a}HELIOS-A mITT population. \textsuperscript{b}APOLLO mITT population.

10-MWT, 10-meter walk test; LV, left ventricular; mBMI, modified body mass index; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; R-ODS, Rasch-built Overall Disability Scale.
HELIOS-A Safety Summary

The majority of AEs were mild or moderate in severity

- 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 heart failure), 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
- Injection-site reactions were reported in 5 patients (4.1%) receiving vutrisiran; all were mild and transient
- No safety signals regarding liver function tests, hematology, or renal function related to vutrisiran

### Table: HELIOS-A Safety Summary

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

*Data reported during 18-month treatment period.

AE, adverse event; SAE, serious AE.
Summary

- As previously reported, vutrisiran met the HELIOS-A primary endpoint (mNIS+7) at 9 months¹
- Vutrisiran met all 18-month secondary endpoints
  - Maintained statistically significant improvement in mNIS+7 compared with external placebo
  - Improvement in QOL (Norfolk QOL-DN), gait speed (10-MWT), nutritional status (mBMI), and disability (R-ODS), compared with external placebo
  - Robust and sustained TTR reduction, non-inferior to within-study patisiran
- Improvements in certain exploratory cardiac measures, including NT-proBNP, compared with external placebo
- Vutrisiran had an acceptable safety profile
  - The majority of AEs were mild or moderate in severity with the most common treatment-related AEs being injection site reactions
- HELIOS-A continues to investigate the efficacy and safety of vutrisiran through an ongoing extension period

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the HELIOS-A study.