HELIOS-A: Impact of Vutrisiran on Quality of Life and Functional Status in Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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## Disclosures for Senda Ajroud-Driss

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advisory board</td>
<td>Alnylam Pharmaceuticals, Amylyx Pharmaceuticals, Biogen, Orphazyme</td>
</tr>
<tr>
<td>Research support</td>
<td>Alnylam Pharmaceuticals, Amylyx Pharmaceuticals, Biogen</td>
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<td>Speakers bureau</td>
<td>Alnylam Pharmaceuticals</td>
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</tbody>
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Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease\(^1-4\)
- 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\(^5,6\)
- Progression of hATTR amyloidosis is associated with a deterioration in QOL and physical functioning\(^7-10\)

Vutrisiran

- Investigational, subcutaneously administered RNAi therapeutic targeting hepatic production of variant and wt TTR in development for the treatment of ATTR amyloidosis\(^11,12\)

Patisiran

- RNAi therapeutic administered Q3W via IV infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO trial\(^13,14\)

Therapeutic Hypothesis

Vutrisiran and patisiran act to target both 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\(^11,12\)

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ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); ESC, enhanced stabilization chemistry; GaINAc, N-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; IV, intravenous; Q3M, every 3 months; Q3W, every 3 weeks; RNAi, ribonucleic acid interference; SC, subcutaneous; TTR, transthyretin; wt, wild-type

Vutrisiran Phase 3 HELIOS-A Study

Global, Randomized, Open-Label Study in Patients with hATTR Amyloidosis with Polyneuropathy

- The 18-month QOL analysis is presented\textsuperscript{a}; for all endpoints, vutrisiran was compared with the external placebo group (placebo arm of APOLLO\textsuperscript{1}), selected on the basis of similar eligibility criteria and endpoints.

\begin{itemize}
  \item \textbf{Patient population} \\
  \textbf{N=164} \\
  \begin{itemize}
    \item 18–85 years old \\
    \item hATTR amyloidosis; any TTR variant \\
    \item NIS 5–130 and PND ≤IIIB \\
    \item KPS ≥60% \\
    \item Prior TTR stabilizer use permitted
  \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{3:1 RANDOMIZATION} \\
  \textbf{n=122} \\
  \begin{itemize}
    \item Vutrisiran 25 mg SC Q3M
  \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{n=42} \\
  \begin{itemize}
    \item Reference group (patisiran) 0.3 mg/kg IV Q3W
  \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{Primary endpoint (previously presented\textsuperscript{2})} \\
  \begin{itemize}
    \item Change from baseline in mNIS+7\textsuperscript{b} at Month 9
  \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{Selected secondary endpoints} \\
  \begin{itemize}
    \item Change from baseline in: \\
    \begin{itemize}
      \item Norfolk QOL-DN\textsuperscript{c} total score and individual domains at Months 9 and 18 \\
      \item 10-MWT\textsuperscript{d} at Months 9 and 18 \\
      \item R-ODS\textsuperscript{e} at Month 18 \\
      \item mBMI\textsuperscript{f} at Month 18
    \end{itemize}
  \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{Selected exploratory endpoints} \\
  \begin{itemize}
    \item Change from baseline in: \\
    \begin{itemize}
      \item EQ-VAS\textsuperscript{g} at Months 9 and 18 \\
      \item R-ODS and mBMI at Month 9 \\
      \item Proportion of patients with stable, improved, or worsened KPS\textsuperscript{h} from baseline at 18 months
    \end{itemize}
  \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{Secondary endpoint} \\
  \begin{itemize}
    \item % serum TTR reduction to Month 18\textsuperscript{i}
  \end{itemize}
  \end{itemize}

\textsuperscript{a}The results presented for 9- and 18-month efficacy endpoints (except for KPS) are based on a mixed-effects model for repeated measures analysis.\textsuperscript{1}Higher scores of mNIS-7 indicate more neurologic impairment (range: 0–304).\textsuperscript{2}Higher scores of Norfolk QOL ON indicate worse QOL (range: −4 to 136).\textsuperscript{3}10-MWT speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.\textsuperscript{4}Lower scores of R-ODS indicate more disability (range: 0–48). Lower scores of mBMI (weight [in kg/m\textsuperscript{2}] × serum albumin [in g/L]) indicate worse nutritional status.\textsuperscript{5}EQ-VAS (range: 0–100) 0 = best health, 100 = worst health.\textsuperscript{6}KPS measures functional status on an 11-point scale correlating to % values. 100% (normal; no evidence of disease); 0% (death). Higher scores indicate less functional impairment. Non-inferiority analysis

### Baseline Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>APOLLO Placebo (n=77)</th>
<th>Vutrisiran (n=122)</th>
<th>Patisiran (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>63 (34–80)</td>
<td>60 (26–85)</td>
<td>60 (31–81)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>58 (75.3)</td>
<td>79 (64.8)</td>
<td>27 (64.3)</td>
</tr>
<tr>
<td>Median time since hATTR amyloidosis diagnosis, years (range)</td>
<td>1.41 (0.0–16.5)</td>
<td>1.94 (0.0–15.3)</td>
<td>2.39 (0.1–12.5)</td>
</tr>
<tr>
<td>TTR genotype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V30M</td>
<td>40 (51.9)</td>
<td>54 (44.3)</td>
<td>20 (47.6)</td>
</tr>
<tr>
<td>Early-onset V30M (&lt;50 years)</td>
<td>10 (13.0)</td>
<td>25 (20.5)</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Non-V30M</td>
<td>37 (48.1)</td>
<td>68 (55.7)</td>
<td>22 (52.4)</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>NIS, mean (range)</td>
<td>57.0 (7.0–125.5)</td>
<td>43.0 (5.0–127.0)</td>
<td>43.1 (5.5–115.6)</td>
</tr>
<tr>
<td>PND scoreb, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I: Preserved walking, sensory disturbances</td>
<td>20 (26.0)</td>
<td>44 (36.1)</td>
<td>15 (35.7)</td>
</tr>
<tr>
<td>II: Impaired walking but can walk without stick or crutch</td>
<td>23 (29.9)</td>
<td>50 (41.0)</td>
<td>17 (40.5)</td>
</tr>
<tr>
<td>IIIA: Walk with 1 stick or crutch</td>
<td>22 (28.6)</td>
<td>16 (13.1)</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>IIIB: Walk with 2 sticks or crutches</td>
<td>11 (14.3)</td>
<td>12 (9.8)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Cardiac subpopulation, n (%)</td>
<td>36 (46.8)</td>
<td>40 (32.8)</td>
<td>14 (33.3)</td>
</tr>
</tbody>
</table>

a The non-V30M TTR genotype represents 24 different variants in HELIOS-A. 
bOne 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). cCardiac 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).
LV, left ventricular; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.
Vutrisiran achieved a mean steady-state serum TTR reduction from baseline of 88% (SD: 16%), which was non-inferior to that observed with the within-study patisiran reference group over 18 months (median difference [vutrisiran–patisiran] [95% CI]: 5.28% [1.17, 9.25], lower limit of CI >–10%).

**Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran**

**Percent Change from Baseline in Serum TTR Levels**
Improvement in Quality of Life with Vutrisiran vs External Placebo at Month 9\(^1\) and Month 18

- At Month 18, 56.8% of vutrisiran-treated patients had an improvement in Norfolk QOL-DN total score, relative to baseline, compared with 10.4% of patients in the external placebo group (odds ratio [95% CI]: 11.3 [5.0, 25.7])

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

\(^a\)\(mITT\) population (all randomized patients who received any amount of study drug). Value of \(n\) is the number of evaluable patients at each timepoint. Higher scores of Norfolk QOL-DN indicate worse quality of life (range: –4 to 136). 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 plotted are MMRM model data.

CI, confidence interval; LS, least squares; LSMD, LS mean difference; \(mITT\), modified intent-to-treat; MMRM, mixed-effects model for repeated measures; Norfolk QOL-DN, Norfolk Quality of Life Diabetic Neuropathy; SD, standard deviation; SE, standard error

1. Adams et al. Neurology 2021;96(15 Suppl.)1234
Higher scores of Norfolk QOL-DN indicate worse quality of life (range: −4 to 136). 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. Mean (±SD) Norfolk QOL-DN scores in individual domains were: 23.2 (13.8) in the vutrisiran group and 28.7 (13.0) in the external placebo group (physical functioning/large fiber); 5.7 (5.7) in the vutrisiran group and 7.8 (6.0) in the external placebo group (activities of daily living); 11.0 (6.1) in the vutrisiran group and 11.2 (5.8) in the external placebo group (symptoms); 4.6 (4.2) in the vutrisiran group and 5.0 (4.1) in the external placebo group (small fiber); and 2.7 (2.9) and 2.9 (2.9) in the external placebo group (autonomic).

ADL, activities of daily living; LS, least squares; Norfolk QOL-DN, Norfolk Quality of Life Diabetic Neuropathy; SD, standard deviation; SE, standard error.
Improvement in EQ-VAS with Vutrisiran vs External Placebo at Month 9 and Month 18

EQ-VAS LS Mean Change from Baseline^a

<table>
<thead>
<tr>
<th>LS mean (SE) change from baseline</th>
<th>Vutrisiran</th>
<th>Placebo (APOLLO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Month 9</td>
<td>-7.0 (2.0)</td>
<td>-11.6 (2.1)</td>
</tr>
<tr>
<td>Month 18</td>
<td>-11.6 (2.1)</td>
<td>-11.6 (2.1)</td>
</tr>
</tbody>
</table>

^a 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 are MMRM model data. At baseline, the mean (± SD) EQ-VAS was 64.5 (18.5) in the vutrisiran group and 54.6 (18.0) in the external placebo group.

CI, confidence interval; EQ-VAS, EuroQol Visual Analog Scale; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SD, standard deviation; SE, standard error.
Improvements in R-ODS and 10-MWT with Vutrisiran vs External Placebo at Month 9 and Month 18

10-MWT LS Mean Change from Baseline (m/s)\(^a\)

-10-MWT, 10-meter walk test; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; SE, standard error

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

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\(^a\)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 are MMRM model data. 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. 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.
A Higher Proportion of Patients Had Stable or Improved KPS with Vutrisiran vs External Placebo at Month 18

- The majority of patients in the vutrisiran group (71.3%) had stable or improved\(^a\) KPS at Month 18 compared with baseline (exploratory endpoint)
  - In the external placebo group, 42.8% of patients had stable or improved KPS at Month 18

\(^a\)Improvement is defined as an increase in KPS score from baseline.\(^b\)On the KPS scale of 0–100%, 17 (14%), 25 (21%), 48 (39%), 27 (22%), and 5 (4%) of vutrisiran-treated patients had a score of 60, 70, 80, 90, and 100, respectively, at baseline KPS, Karnofsky performance score
Improvement in mBMI with Vutrisiran vs External Placebo at Month 9 and Month 18

- The favorable effect of vutrisiran on mBMI compared with the external placebo group was observed at the first post-baseline assessment at Month 3

mBMI LS Mean Change from Baseline

![Graph showing mBMI LS Mean Change from Baseline](image)

- LS mean (SE) change from baseline
- Baseline
- Month 3 (Day 85)
- Month 9
- Month 18

Vutrisiran

Placebo (APOLLO)

n=68

n=122

n=77

n=113

n=114

n=115

n=71

n=77

n=122

LSMD (95% CI): 34.3 (12.6, 56.0)

LSMD (95% CI): 68.6 (45.1, 92.1)

LSMD (95% CI): 140.7 (108.4, 172.9)

p = 4.2 \times 10^{-15}

mIT1 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 are MMRM model data. 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.

CI, confidence interval; LS, least squares; LSMD, LS mean difference; mBMI, modified body mass index; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; SD, standard deviation; SE, standard error.
**HELIOS-A Vutrisiran Efficacy Results Consistent with APOLLO Patisiran at Month 18**

### Vutrisiran Efficacy\(^a\) vs External Placebo

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>HELIOS-A</th>
<th>Clinical Endpoints</th>
<th>APOLLO</th>
</tr>
</thead>
<tbody>
<tr>
<td>mNIS+7</td>
<td><img src="image1" alt="Graph" /></td>
<td>mNIS+7</td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>Norfolk QOL-DN</td>
<td><img src="image3" alt="Graph" /></td>
<td>Norfolk QOL-DN</td>
<td><img src="image4" alt="Graph" /></td>
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<tr>
<td>10-MWT</td>
<td><img src="image5" alt="Graph" /></td>
<td>10-MWT</td>
<td><img src="image6" alt="Graph" /></td>
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<tr>
<td>R-ODS</td>
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<td>R-ODS</td>
<td><img src="image8" alt="Graph" /></td>
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<tr>
<td>mBMI</td>
<td><img src="image9" alt="Graph" /></td>
<td>mBMI</td>
<td><img src="image10" alt="Graph" /></td>
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### Cardiac Endpoints

<table>
<thead>
<tr>
<th>HELIOS-A</th>
<th>APOLLO</th>
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<tbody>
<tr>
<td>LV Wall Thickness</td>
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<tr>
<td>Longitudinal Strain (%)</td>
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<tr>
<td>LV End-Diastolic Volume</td>
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<tr>
<td>Cardiac Output</td>
<td><img src="image14" alt="Graph" /></td>
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<tr>
<td>NT-proBNP</td>
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### Patisiran Efficacy\(^b\) vs Placebo

<table>
<thead>
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<th>Clinical Endpoints</th>
<th>HELIOS-A</th>
<th>Clinical Endpoints</th>
<th>APOLLO</th>
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</thead>
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<tr>
<td>mNIS+7</td>
<td><img src="image16" alt="Graph" /></td>
<td>mNIS+7</td>
<td><img src="image17" alt="Graph" /></td>
</tr>
<tr>
<td>Norfolk QOL-DN</td>
<td><img src="image18" alt="Graph" /></td>
<td>Norfolk QOL-DN</td>
<td><img src="image19" alt="Graph" /></td>
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<tr>
<td>10-MWT</td>
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<td>10-MWT</td>
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<td>R-ODS</td>
<td><img src="image22" alt="Graph" /></td>
<td>R-ODS</td>
<td><img src="image23" alt="Graph" /></td>
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<tr>
<td>mBMI</td>
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<td>mBMI</td>
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### Cardiac Endpoints

<table>
<thead>
<tr>
<th>HELIOS-A</th>
<th>APOLLO</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Wall Thickness</td>
<td><img src="image26" alt="Graph" /></td>
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<tr>
<td>Longitudinal Strain (%)</td>
<td><img src="image27" alt="Graph" /></td>
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<tr>
<td>LV End-Diastolic Volume</td>
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<tr>
<td>Cardiac Output</td>
<td><img src="image29" alt="Graph" /></td>
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<tr>
<td>NT-proBNP</td>
<td><img src="image30" alt="Graph" /></td>
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\(^a\)HELIOS-A mITT population. \(^b\)APOLLO mITT population. The HELIOS-A patisiran arm was not intended for statistical testing vs vutrisiran for the endpoints listed.

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.
Summary

- At Month 18, patients in the vutrisiran group demonstrated significant improvements in measures of
  - **Quality of life** (Norfolk QOL-DN, EQ-VAS) compared with external placebo
    - The treatment effect favoring vutrisiran over external placebo was consistent across all Norfolk QOL-DN domains at Month 18
  - **Functional status** (gait speed [10-MWT], disability [R-ODS], KPS) compared with external placebo
    - The majority (71%) of patients in the vutrisiran group improved or stabilized in the exploratory assessment of KPS score compared with baseline, whereas 43% of patients in the external placebo group improved or stabilized in KPS score compared with baseline
  - **Nutritional status** (mBMI) compared with external placebo

- The efficacy and safety of vutrisiran will continue to be characterized in the ongoing HELIOS-A randomized extension period in patients with hATTR amyloidosis with polyneuropathy
Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the **HELIOS-A study**