HELIOS-A: 9-month Results from the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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• David D. Adams has received personal compensation for serving as a Consultant for Alnylam Pharmaceuticals and for serving on a Scientific Advisory or Data Safety Monitoring board for Pfizer
Background and Rationale

**hATTR amyloidosis, also known as ATTRv amyloidosis**
- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease
- Caused by variants in \( TTR \) gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues\(^1\)\(^-\)\(^4\)
- Multisystem disease with a heterogeneous clinical presentation (sensory, motor, autonomic, and cardiac symptoms)\(^4\)-\(^6\)
- The majority of individuals develop a mixed phenotype of both polyneuropathy and cardiomyopathy\(^7\),\(^8\)

**Vutrisiran**
- Investigational, subcutaneously administered, RNAi therapeutic targeting hepatic production of variant and wt TTR, in development for the treatment of ATTR amyloidosis\(^9\),\(^10\)

**Patisiran**
- RNAi therapeutic administered via IV infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on phase 3 placebo-controlled APOLLO trial\(^11\)-\(^13\)

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**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**

**Vutrisiran and patisiran act to target both variant and wt TTR**

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**APOLLO: NCT01960348; ATTR, transthyretin-mediated; 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**

Randomized, Open-label Study in Hereditary Transthyretin-Mediated Amyloidosis Patients with Polyneuropathy

- Presenting 9-month primary efficacy analysis compared with the external placebo group (placebo arm of APOLLO)

**Patient Population N=164**
- 18–85 years old
- ATTR amyloidosis; any TTR mutation
- NIS of 5–130 and PND ≤IIIB
- KPS ≥60%
- Prior tetramer stabilizer use permitted

**Randomization**

9-Month Efficacy Assessment

**Primary Endpoint**
- Change from baseline in mNIS+7*

**Secondary Endpoints**
- Change from baseline in:
  - Norfolk QOL-DN†
  - 10-MWT‡

**Selected Exploratory Endpoints**
- Change from baseline in:
  - mBMI
  - R-ODS
  - NT-proBNP

**N=122**

Vutrisiran 25 mg SC Q3M

or

N=42

Reference comparator (patisiran) 0.3 mg/kg IV Q3W

**9-Month Efficacy Assessment**

Vutrisiran vs APOLLO Placebo

**N=122**

Vutrisiran 25 mg SC Q3M

or

N=42

Reference comparator (patisiran) 0.3 mg/kg IV Q3W

**18-Month Efficacy Assessment**

**Reference comparator (patisiran) 0.3 mg/kg IV Q3W**

**Presenting 9-month primary efficacy analysis compared with the external placebo group (placebo arm of APOLLO)**

*Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0 to 304). †Higher scores of Norfolk QOL-DN indicate worse quality of life (range, -4 to 136). ‡10-meter walk test 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.

10-MWT, 10-meter walk test; ATTRv, transthyretin-mediated amyloidosis (v for variant); IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro–brain natriuretic peptide; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built overall disability scale; SC, subcutaneous; TTR, transthyretin.
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 (years), median (range)</td>
<td>63 (34, 80)</td>
<td>60 (26, 85)</td>
<td>60 (31, 81)</td>
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<tr>
<td>Males, n (%)</td>
<td>58 (75)</td>
<td>79 (65)</td>
<td>27 (64)</td>
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<td>TTR genotype, n (%)</td>
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<td></td>
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<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>
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<tr>
<td>PND score*, n (%)</td>
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<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 (%)†</td>
<td>36 (47)</td>
<td>35 (29)</td>
<td>13 (31)</td>
</tr>
</tbody>
</table>

*One patient (1.3%) in external placebo group had a PND score IV defined as confined to wheelchair or bedridden (not shown on the slide). †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). NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.
Significant Improvement in Neuropathy Impairment with Vutrisiran

- Vutrisiran achieved statistically significant improvement in mNIS+7 at 9 months, compared with the external placebo group
  - Improvements across all pre-specified patient subgroups* and components of mNIS+7 (data not shown)
  - Consistent treatment effects in vutrisiran and patisiran groups in HELIOS-A (data not shown)

**mNIS+7 LS Mean Change from Baseline**

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

*Pre-specified patient subgroups included age (<65 or ≥65), sex, race, region, baseline NIS (<50 or ≥50), previous tetramer stabilizer use, genotype (V30M or non-V30M), FAP stage (I or II and III), cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history). †mITT population. At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in external placebo group. ‡Number of evaluable patients.

LS, least squares; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; SD, standard deviation; SE, standard error.
Significant Improvement in Quality of Life and Gait Speed with Vutrisiran

- Vutrisiran achieved statistically significant improvement in Norfolk QOL-DN and gait speed measured by 10-MWT at 9 months, compared with the external placebo group
  - Improvements across all pre-specified patient subgroups* and domains of Norfolk QOL-DN (data not shown)
  - Consistent treatment effects observed in vutrisiran and patisiran groups of HELIOS-A (data not shown)

Norfolk QOL-DN LS Mean Change from Baseline†

10-MWT LS Mean Change from Baseline‡

Exploratory endpoints at 9 months, including change from baseline in R-ODS, mBMI and NT-proBNP, demonstrated improvements compared with the external placebo group (data not shown)

*Pre-specified patient subgroups included age (<65 or ≥65), sex, race, region, baseline NIS (<50 or ≥50), previous tetramer stabilizer use, genotype (V30M or non-V30M), FAP stage (I or II and III), cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history). †mITT population. 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. ‡mITT population. 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. §Number of evaluable patients.

10-MWT, 10-meter walk test; LS, least squares; mBMI, modified body mass index; mITT, modified intent-to-treat; Norfolk QOL-DN, Norfolk Quality of Life- Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; R-ODS, Rasch-built overall disability scale; SD, standard deviation; SE, standard error.
Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran Similar to Patisiran in HELIOS-A

- Vutrisiran achieved a mean steady-state* serum TTR reduction from baseline of 83% (SD: 14%)

*Steady state was measured using Day 211 samples for vutrisiran.

SD, standard deviation; SE, standard error; TTR, transthyretin.
HELIOS-A Safety Summary*

Acceptable Safety Profile of Vutrisiran

The majority of AEs were mild or moderate in severity

- No drug-related discontinuations or deaths
- Two study discontinuations (1.6%) due to AEs in the vutrisiran arm by Month 9, both due to deaths, neither of which was considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- Two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in vutrisiran group included diarrhea, pain in extremity, fall, and urinary tract infections
  - Each of these events occurred at a similar or lower rate compared with the external placebo group
- Injection site reactions were reported in five 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>
<thead>
<tr>
<th>At Least One Event, n (%)</th>
<th>APOLO†</th>
<th>HELIOS-A</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (N=77) PY=96.1</td>
<td>Vutrisiran (N=122) PY=131.3</td>
</tr>
<tr>
<td>AEs</td>
<td>75 (97.4)</td>
<td>114 (93.4)</td>
</tr>
<tr>
<td>SAEs</td>
<td>31 (40.3)</td>
<td>21 (17.2)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>28 (36.4)</td>
<td>15 (12.3)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>11 (14.3)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>AEs leading to stopping study participation</td>
<td>9 (11.7)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6 (7.8)</td>
<td>2 (1.6)</td>
</tr>
</tbody>
</table>

*Cumulative safety data from first dose of study drug to data cut-off date (November 10, 2020). †External reference to reflect the type of disease-related events commonly reported in this population.

AE, adverse event; PY, patient-years; SAE, serious AE.
Summary

- HELIOS-A is a phase 3, global, open-label study of vutrisiran 25 mg SC Q3M in patients with ATTRv amyloidosis with polyneuropathy

- Vutrisiran met the primary and both secondary endpoints at 9 months, with statistically significant improvements in neuropathy impairment (mNIS+7), quality of life (Norfolk QOL-DN), and gait speed (10-MWT), compared with the external placebo group
  - The effect on neuropathy impairment (mNIS+7) and QOL (Norfolk QOL-DN) was seen across all patient subgroups (data not shown)
  - The majority of patients showed improvements in neuropathy impairment (mNIS+7) and QOL (Norfolk QOL-DN) compared with baseline (data not shown)
  - Exploratory endpoints at 9 months, including change from baseline in R-ODS, mBMI and NT-proBNP, demonstrated improvements compared with the external placebo group (data not shown)

- Treatment with vutrisiran led to rapid and sustained reduction in serum TTR levels

- Vutrisiran has an acceptable safety profile and favorable benefit: risk profile

- HELIOS-A will continue to investigate the efficacy and safety of vutrisiran through an 18-month treatment period and an extension period
Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the HELIOS-A study.