Longitudinal Changes in mNIS+7 are Associated with Changes in Ambulatory Status in Hereditary Transthyretin-Mediated Amyloidosis

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis
• Rare, inherited, rapidly progressive, life-threatening disease caused by a mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal (GI) tract14
• Affecting approximately 50,000 people worldwide14: median survival of 4.7 years following diagnosis with a reduced survival of 3.4 years for patients presenting with cardiomyopathy2
• Multisystem disease with heterogeneous clinical presentation: amyloid accumulation often leads to dysfunction in multiple organs, including peripheral nervous system, heart, GI tract, and kidneys4,4

Measures of Disease progression

Modified Neuropathy Impairment Score +7 (mNIS+7)
• mNIS+7 (Figure 1), was developed to assess polyneuropathy disease progression in patients with hATTR amyloidosis with a broad spectrum of disease severity14
  o mNIS+7 is a multi-dimensional composite score (maximum of 304 points, which represents maximal impairment) that encompasses the totality of the sensorimotor and autonomic neuropathy in hATTR amyloidosis and is a robust and clinically meaningful measure of neuropathy progression

Polyneuropathy Disability (PND) Score
• The PND score (Figure 2) is a measure of hATTR amyloidosis neuropathy stage based on ambulatory status15
• PND score has been shown to be related to neurologic impairment (as measured by Neurologic Impairment Prognosis Score (NIS) and mNIS+7) and quality of life (measured by Norfolk QOL-DN)16

Figure 2: PND score

PND score is a clinically meaningful measure of neuropathy progression

Table 1: Comparison of observed changes in PND score in APOLLO versus model predictions

<table>
<thead>
<tr>
<th>Model predictions</th>
<th>Improved</th>
<th>Stabilized</th>
<th>Worsened</th>
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<tbody>
<tr>
<td>Observed changes</td>
<td>Improved</td>
<td>Stabilized</td>
<td>Worsened</td>
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<td>Patisran</td>
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<td>6.9%</td>
<td>6.6%</td>
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<tr>
<td>Placebo</td>
<td>0.0%</td>
<td>6.9%</td>
<td>6.6%</td>
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Results

Model Predictions Relative to Observed Data
• To test the validity of this model in predicting the relationship between ∆ mNIS+7 and ∆ PND score, mNIS+7 values observed in APOLLO were used to simulate the proportion of patients with improved, stabilized, or worsened PND score from baseline to 18 months
• The predicted proportions from this model closely matched the observed changes in PND score from the APOLLO study, suggesting that the model can reliably explain the relationship between ∆ mNIS+7 and ∆ PND score over the course of 18 months (Table 1)

Probability of Improved/Stabilized or Stabilized PND Score (Figure 4)
• It is consistently observed that greater reduction in mNIS+7 is associated with a greater probability of improved or stabilized PND score (p < 0.0001)
• Simultaneously, it is consistently observed that greater reduction in mNIS+7 is associated with a greater probability of improved PND score (p < 0.0001)

Conclusions
• Results of this model using data from the Phase 3 APOLLO study suggest that changes in neuropathy impairment (measured by mNIS+7) are highly predictive of changes in neuropathy stage, as measured by PND score, among patients with hATTR amyloidosis
• Patients with a reduction in mNIS+7 relative to baseline had substantially greater odds of improving or stabilizing in PND score over time
• These results underscore the clinical relevance of mNIS+7 in measuring neuropathy progression in hATTR amyloidosis