Analysis of NT-proBNP Baseline Levels in APOLLO as a Predictor of Survival in Hereditary Transthyretin-Mediated (hATTR) 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 the transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract4
- Affecting approximately 50,000 worldwide10, median survival of 4.7 years following diagnosis with a reduced survival of 3.4 years for patients presenting with cardiomyopathy9
- Multisystem disease with heterogeneous clinical presentation; amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidney1,8,9
- Accumulation of amyloid fibrils in nerves can lead to manifestations of polynuropathy, including peripheral neuropathy, autonomic dysfunction, and motor weakness causing fine and gross motor impairments whereas accumulation in the heart can lead to cardiomyopathy
- Disease penetrance and rate of progression may be influenced by TTR genotype6,7
- Limited treatment options are available. Continued high unmet medical need for novel therapeutic options

N-terminal Pro B-type Natriuretic Peptide (NT-proBNP)

- NT-proBNP is a serum biomarker released into circulation from the heart because of increased myocardial wall tension and stress
- Clinical studies in patients with light chain (AL) amyloidosis have shown NT-proBNP to be predictive of clinical outcome and survival in patients with cardiac involvement; studies are suggesting its use as a potential surrogate endpoint for treatment efficacy in a hATTR amyloidosis population9
- A recent analysis demonstrated that NT-proBNP levels had prognostic utility for outcomes, not only in AL amyloidosis, but also in ATTR amyloidosis8,9

Patisiran, an Investigational RNAi Therapeutic

- Lipid nanoparticles formulation of siRNA targeting hepatic production of mutant and wild type TTR (Figure 1)
- Phase 2 and Phase 2 Open-Label Extension (OLE): positive multi-dose results in patients with hATTR amyloidosis, patisiran generally well tolerated11,12
- Phase 3, APOLLO study: met primary efficacy endpoint (mNIS+7) and all secondary endpoints with a favorable safety profile11,12
- Global OLE: ongoing13

Objective

- Evaluate the predictive value of baseline NT-proBNP in survival in patients enrolled in the APOLLO study

Methods

APOLLO Study Design

- Phase 3, randomized (2:1), double-blind study of patisiran 0.3mg/kg or placebo IV every 3 weeks in patients with hATTR amyloidosis patients with polyneuropathy (Figure 2)
- 126 (95%) patients had cardiac involvement on the basis of prespecified criteria: left ventricular (LV) wall thickness ≥13 mm and absence of aortic valve disease or hypertension1

Statistical Methods

- Post hoc analyses were conducted to assess the prognostic factors for survival using univariate and multivariate Cox regression models. The potential risk for mortality assessed included baseline NT-proBNP, genotype, FAP stage, cardiac subgroups, and age of disease onset
- NT-proBNP was treated as a continuous variable following logarithmic transformation as well as a binary variable using a cut off value of 3000 ng/mL
- The outcome variable is overall survival (months) and the model includes baseline NT-proBNP as a categorical covariate (<3000 ng/mL vs. ≥3000 ng/mL)

Results

APOLLO Baseline Demographics

- Overall, 225 patients with 39 different genotypes were enrolled in the APOLLO study (Table 1), of which the baseline NT-proBNP was ≥3000 ng/mL for 196 patients and <3000 for 29 patients (Table 2)

Table 1: APOLLO Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=196)</th>
<th>Patisiran (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>63 (34, 80)</td>
<td>62 (24, 83)</td>
</tr>
<tr>
<td>Gender, males</td>
<td>58 (73%)</td>
<td>109 (73.6%)</td>
</tr>
<tr>
<td>NT-proBNP Diagnosis</td>
<td>2.60 (0.0, 16.5)</td>
<td>2.39 (0.0, 21.0)</td>
</tr>
<tr>
<td>TTR Genotype</td>
<td>40 (51.9)</td>
<td>56 (37.8)</td>
</tr>
<tr>
<td>Non-V30M</td>
<td>37 (48.1)</td>
<td>92 (62.2)</td>
</tr>
<tr>
<td>Plasma, Mean (min, max)</td>
<td>5.4 (2.8, 7.5)</td>
<td>5.3 (3.1, 7.7)</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>143.2</td>
<td>259.0</td>
</tr>
<tr>
<td>Median</td>
<td>485.7</td>
<td>756.4</td>
</tr>
<tr>
<td>Geometric Mean (CV%)</td>
<td>711.1 (151.1)</td>
<td>726.9 (103.0)</td>
</tr>
<tr>
<td>Cardiac Subgroup</td>
<td>36 (46.8)</td>
<td>90 (60.8)</td>
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</tbody>
</table>

Impact of Baseline NT-proBNP on Survival

- NT-proBNP was the key significant factor predictive of survival based on univariate and multivariate analyses
- Risk of death increased with higher baseline NT-proBNP (hazard ratio =2.9 [95% CI: 1.8, 4.8, p-value=0.017]) per unit increment in log (NT-proBNP)
- Patients with NT-proBNP above 3000 ng/mL (n=29) had a 19.3-fold (95% CI, 5.9, 62.8, p-value=0.007) increased risk for mortality compared to those below 3000 ng/mL (n=196) (Figure 3)

Table 2: APOLLO Baseline Demographics by Baseline NT-proBNP Threshold

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NT-proBNP ≤3000 ng/mL (N=196)</th>
<th>NT-proBNP &gt;3000 ng/mL (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>65 (59.5, 70.0)</td>
<td>65 (59.5, 70.0)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>21 (72.4%)</td>
<td>21 (72.4%)</td>
</tr>
<tr>
<td>Genotype</td>
<td>108 (55.1)</td>
<td>33 (42.6)</td>
</tr>
<tr>
<td>Non-V30M</td>
<td>88 (44.9)</td>
<td>33 (42.6)</td>
</tr>
<tr>
<td>NVHA Class</td>
<td>101 (51.5)</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>NVHA Class I</td>
<td>93 (47.4)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>406.1 (166.5, 924.18)</td>
<td>4257.3 (3867.38, 5949.67)</td>
</tr>
<tr>
<td>Geometric Mean (CV%)</td>
<td>385.6 (164.8)</td>
<td>4900.0 (40.3)</td>
</tr>
</tbody>
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Safety

- Majority of adverse events were mild or moderate in severity (Table 3); causes of death were consistent with natural history; frequency of death trended lower in the patisiran group compared with placebo group
- Majority of AEs were mild or moderate in severity
- Periphera edema
- Did not result in any treatment discontinuations and decreased over time
- NT-proBNP-related reactions (RPRs)
- Majority mild in severity that decreased over time; led to treatment discontinuation in 1 patient
- No severe, life-threatening or serious RPRs
- No safety signals regarding cardiac dysfunction, hypertension, infection, or osteopenia/osteoporosis
- No safety signals regarding liver function tests, hematologic including thrombocytopenia, or renal dysfunction related to patisiran
- Safety in cardiac subpopulation comparable to overall study population

Summary

- A post-hoc exploratory analysis of data from the APOLLO study showed that baseline NT-proBNP serum levels were predictive of survival in hATTR amyloidosis patients. These findings underscore the value of early evaluation for cardiac involvement in hATTR amyloidosis patients, and potentially treating patients early in the course of the disease