Background and Rationale

Hereditary ATTR (hATTR) Amyloidosis with Polyneuropathy

Inherited, rapidly progressive, life-threatening disease due to a mutation in the transthyretin (TTR) gene, causing mistfolded TTR proteins to accumulate as amyloid fibrils in multiple organs, including the nerves, heart, and gastrointestinal tract

Multisystemic disease with a heterogeneous clinical presentation, including sensory, motor and autonomic neuropathy, and cardiac dysfunction

With disease progression, symptoms increase in severity, leading to significant morbidity, disability, decreased quality of life, loss of physical function, and death

Aggressive course can lead to mortality within 2-5 years of disease onset

Limited treatment options exist, thus high unmet medical need for novel therapeutics remains

Patisiran

• An investigational RNA interference (RNAi) therapeutic in development for the treatment of hATTR amyloidosis

• Early clinical development demonstrated potent, robust, and rapid knockdown of mutant and wild-type TTR in healthy volunteers and in patients with hATTR amyloidosis

Methods

Phase 3 APOLLO Study Design

Randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy

• APOLLO trial utilized to collect patient-reported Euro Quality of Life – 5 Dimension (EQ-5D), Norfolk QOL – Diabetic Neurology (QOL-DN), Rasch-built Overall Disability Scale (R-ODS), and healthcare resource utilization

Results*

Enrollment

• 225 patients with hATTR amyloidosis with polyneuropathy enrolled from Dec 2013 – Jan 2016 at 44 sites in 19 countries

Baseline Demographics by FAP Stage

Characteristics

FAP Stage = 1
(N = 44)

FAP Stage = 2
(N = 44)

Norfolk QOL – Diabetic Neurology (QOL-DN) score, mean 45.03  69.63†

Euro Quality of Life – 5 Dimension (EQ-5D) score, mean 0.71  0.57†

Euro QOL Visual Analog Scale (EQ-VAS) score, mean 61.70†  49.66†

Rasch-built Overall Disability Scale (R-ODS) score, mean 37.41  23.02‡

Number (%) of subjects with at least:

1 hospitalization of ≥ 3 nights in duration 14 (31.8%) 32 (72.7%) 2 hospitalizations of ≥ 3 nights in duration 6 (13.6%) 12 (27.3%) 3 hospitalizations of ≥ 3 nights in duration 1 (2.3%) 5 (11.4%) 4+ hospitalizations of ≥ 3 nights in duration 0 2 (1.4%) Current level of function, n (%) Able to work 82 (95.5%) 51 (11.4%) Unable to work 4 (4.5%) 190 (44.6%) Other 7 (8.7%) 6 (5.0%) Workdays lost in the past 12 months, mean 37.43†  65.33‡

Baseline Demographics by PND Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PND Score = 1 (N = 57)</th>
<th>PND Score = 2 (N = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfolk QOL – Diabetic Neurology (QOL-DN) score, mean</td>
<td>35.51</td>
<td>65.96†</td>
</tr>
<tr>
<td>Euro Quality of Life – 5 Dimension (EQ-5D) score, mean</td>
<td>0.71†</td>
<td>0.59</td>
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<tr>
<td>Euro QOL Visual Analog Scale (EQ-VAS) score, mean</td>
<td>66.89§</td>
<td>51.34†</td>
</tr>
<tr>
<td>Rasch-built Overall Disability Scale (R-ODS) score, mean</td>
<td>34.89</td>
<td>25.88</td>
</tr>
</tbody>
</table>

Number (%) of subjects with at least:

1 hospitalization of ≥ 3 nights in duration 0 6 (3.6%) 2 hospitalizations of ≥ 3 nights in duration 1 (1.8%) 17 (10.1%) 3 hospitalizations of ≥ 3 nights in duration 0 6 (3.6%) 4+ hospitalizations of ≥ 3 nights in duration 0 2 (1.2%) Current level of function, n (%) Able to work 40 (70.2%) 27 (16.1%) Unable to work 14 (24.6%) 131 (87.0%) Other 3 (5.3%) 10 (6.0%) Workdays lost in the past 12 months, mean 51.60  45.44†

Baseline Correlation Data

Mean baseline mNIS+7 and mean baseline Norfolk QOL-DN scores increase with severity in FAP stage and PND score

Summary

• hATTR amyloidosis represents a major unmet medical need requiring early and accurate diagnosis for optimal management and delayed irrecoverable progression of disease

• Data further demonstrate that patients with hATTR amyloidosis experience considerable burden of illness early in the disease course and this burden increases with disease progression

• Dataset represents the largest controlled study of patients with hATTR amyloidosis with polyneuropathy and includes a globally representative population and a wide range of TTR mutations and disease severity

1TTR: transthyretin; FAP: familial amyloid polyneuropathy; PND: polyneuropathy disability; Rasch-Built: calculated using a Rasch model

2ClinicalTrials.gov Identifier: NCT01843868

3Data as of 18 March 2016

4Coelho T. et al. 11 Enflg J Med 189;819-29 (2013); Suhr OB et al. 11 Octav. 10:51 (2010)

Study sponsored by Alnylam Pharmaceuticals. To obtain a copy of this presentation, visit: www.alnylam.com/capella

References

1Amrylum Pharmaceuticals, Cambridge, USA; National Reference Center for FAP (NREF) / APHP INSERM U 1390 CHU Bichat, Le Kremlin-Bicêtre, France; National Institute of Medical Sciences and Nutrition - Salvador Zubiran (INN-SZUB), Mexico; Study Site – La Mele, United States; National Transplantation University Hospital, Seoul, Korea; Research Center for FAP (NNERF) / APHP/ INSERM U1195/ CHU Bicêtre, France and National Reference Center for FAP (NNERF) / APHP/ INSERM U1195/ CHU Bicêtre, France; Neurology Department, Taipei Veterans General Hospital, Taipei, Taiwan; Department of Medicine, Umea University Hospital, Umea, Sweden.

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