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

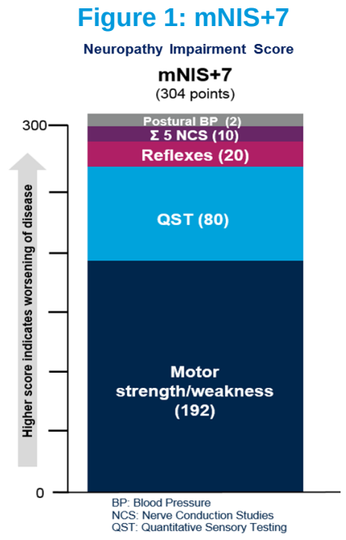
- Rare, inherited, rapidly progressive, life-threatening disease caused by a mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal (GI) tract[1-5]
- Affecting approximately 50,000 people worldwide[5,6]; median survival of 4.7 years following diagnosis with a reduced survival of 3.4 years for patients presenting with cardiomyopathy[6]
- Multisystem disease with heterogenous clinical presentation; amyloid accumulation often leads to dysfunction in multiple organs, including peripheral nervous system, heart, GI tract, and kidneys[6-8]

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 severity[8]
  - 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 polyneuropathy in hATTR amyloidosis and is a robust and clinically meaningful measure of neuropathy progression

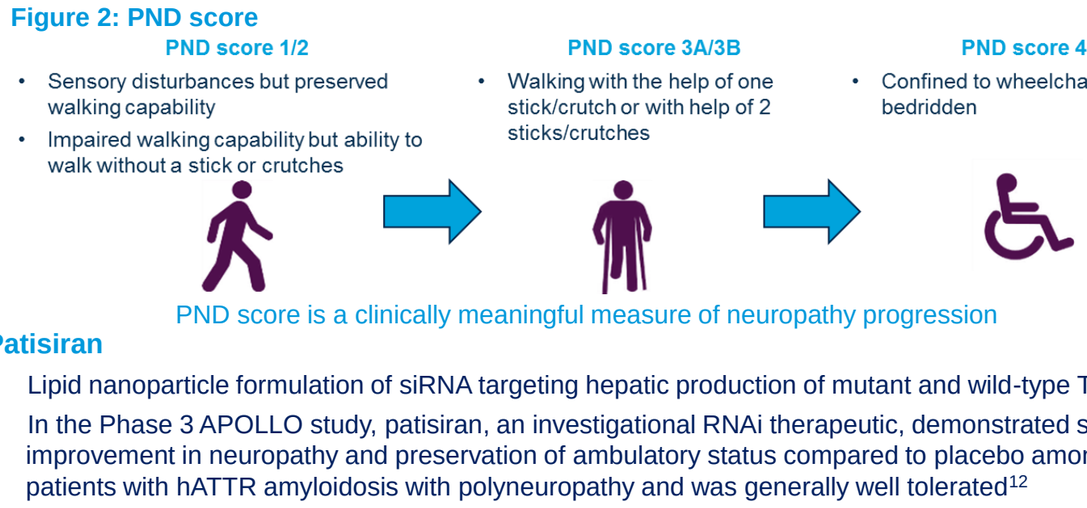
Figure 1: mNIS+7



Polyneuropathy Disability (PND) Score

- The PND score (Figure 2) is a measure of hATTR amyloidosis neuropathy stage based on ambulatory status[9-10]
- PND score has been shown to be related to neurologic impairment (as measured by Neuropathy Impairment Score (NIS) and mNIS+7) and quality of life (measured by Norfolk QOL-DN) [11]

Figure 2: PND score

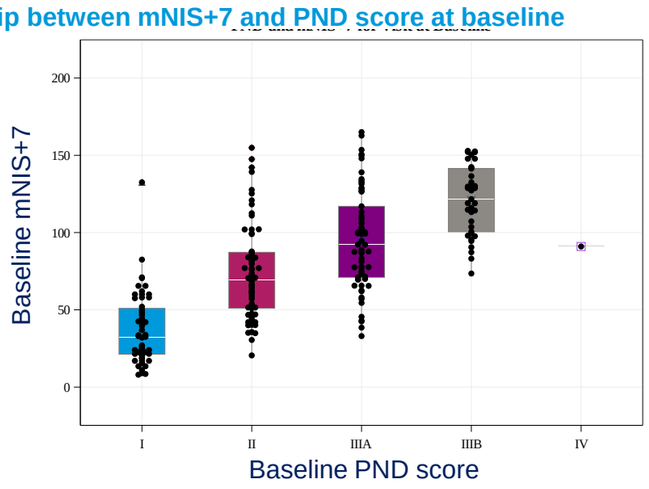


PND score is a clinically meaningful measure of neuropathy progression

Patisiran

- Lipid nanoparticle formulation of siRNA targeting hepatic production of mutant and wild-type TTR
- In the Phase 3 APOLLO study, patisiran, an investigational RNAi therapeutic, demonstrated significant improvement in neuropathy and preservation of ambulatory status compared to placebo among patients with hATTR amyloidosis with polyneuropathy and was generally well tolerated[12]
- Cross-sectional analyses support the strong relationship between mNIS+7 and PND score at baseline in the modified intent-to-treat (mITT) population (Figure 3)

Figure 3: Relationship between mNIS+7 and PND score at baseline



Objective

- Describe the relationship between longitudinal change in mNIS+7 and change in PND score in the APOLLO patient population between baseline and 18 months
- Demonstrate how changes in mNIS+7 over time impact ambulatory status for patients with hATTR amyloidosis

Methods

APOLLO Phase 3 Study Design[11]

- Multi-center, international, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy
- Primary endpoint was change in mNIS+7 between patisiran and placebo from baseline to 18 months
- PND score was an exploratory endpoint, and was included to assess change in neuropathy stage of patients with hATTR amyloidosis
- Using data from APOLLO, a predictive model using logistic regression analyses was developed to assess the relationship between change in mNIS+7 and change in PND score from baseline to 18 months

Analysis Methods

- The multinomial model used changes in mNIS+7 to predict the likelihood of a patient having improved, stabilized, or worsened PND score
  - Improved PND score is defined as improvement in ambulatory status relative to baseline (e.g., less reliance on crutches, no longer confined to wheelchair or bedridden), stabilized PND score is defined as no change in ambulatory status relative to baseline, and worsening PND score is defined as decreased ambulatory status relative to baseline (e.g., more reliance on crutches, confined to wheelchair or bedridden)
- Only patients with data at baseline and 18 months for mNIS+7 and PND score were included in this analysis (n = 185)
- The results of the model were validated with observed responses from the APOLLO study

Assumptions

- This model assumes that Δ mNIS+7 and Δ PND score are agnostic to treatment assignment (i.e., if two patients observe a 10 point NIS change, regardless of treatment assignment, their probability of worsening on PND score is the same)

Results

Model Predictions Relative to Observed Data

- To test the validity of this model in predicting the relationship between Δ mNIS+7 and Δ 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 Δ mNIS+7 and Δ PND score over the course of 18 months (Table 1)

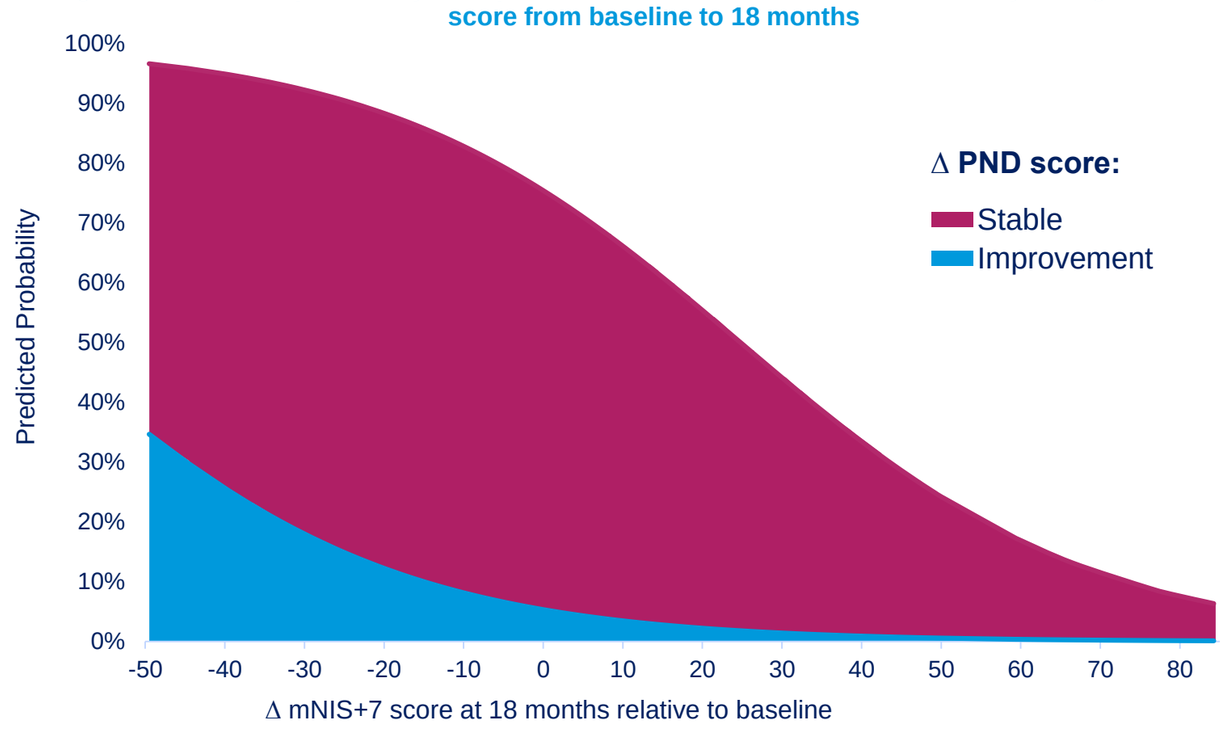
Table 1: Comparison of observed changes in PND score in APOLLO versus model predictions

	Observed changes			Model predictions
	Patisiran (n = 137)	Placebo (n = 48)	**Overall (n = 185)**	
Improved	8.8%	0.0%	**6.9%**	**6.6%**
Stabilized	69.3%	41.7%	**62.6%**	**61.9%**
Worsened	21.9%	58.3%	**31.4%**	**31.6%**

Probability of Improved/Stabilized or Improved 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 ($p < 0.0001$)
- Similarly, it is consistently observed that greater reduction in mNIS+7 is associated with a greater probability of improved PND score ($p < 0.0001$)

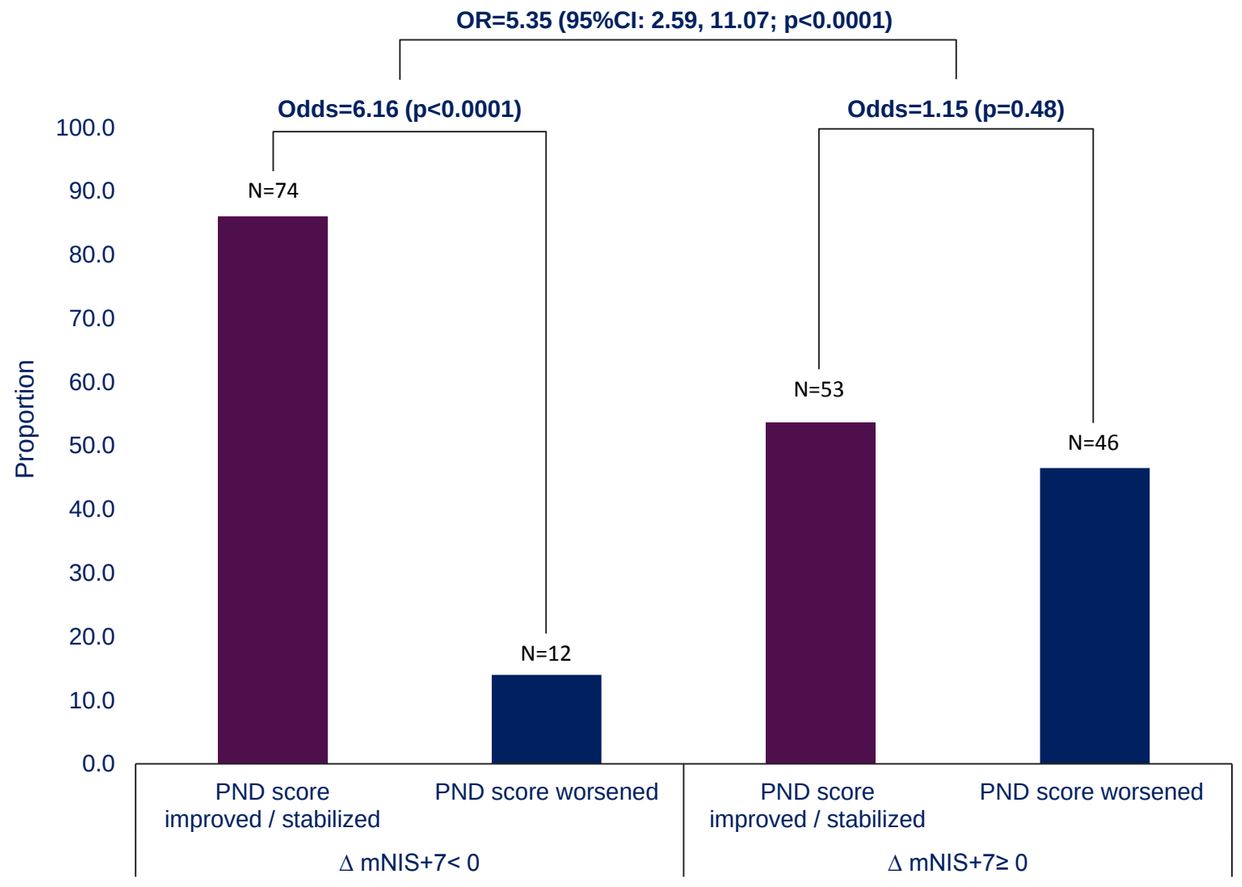
Figure 4: Predicted probability of improvement or stabilization in PND score by change in mNIS+7 score from baseline to 18 months



Odds of Improved or Stabilized PND Score from Baseline to 18 Months (Figure 5)

- Patients with Δ mNIS+7 < 0 had greater odds of improved or stabilized PND score relative to worsened
- Patients with Δ mNIS+7 ≥ 0 did not have a statistically significant difference in their likelihood of improved or stabilized PND score relative to worsened

Figure 5: Odds of improved or stabilized PND score based on mNIS+7 <0 vs ≥0 from baseline to 18 months



Limitations

- This model is unable to predict and discriminate the predicted magnitude of Δ PND score

Conclusions

- Results of this model using data from the Phase 3 APOLLO study suggest that changes in neurologic 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 polyneuropathy progression in hATTR amyloidosis

mNIS+7, Modified Neuropathy Impairment score + 7; PND, polyneuropathy disability; 95% CI, 95% Confidence Interval. References: 1. Hanna M. CurrHeart Fail Rep 2014;11(1):50–7; 2. MohtyD, et al. Arch Cardiovasc Dis 2013;106(10):528–40; 3. Adams D, et al. Neurology 2015;85(8):675–82; 4. Damy T, et al. J Cardiovasc TranslRes 2015;8(2):117–27; 5. Hawkins PN, et al. Ann Med 2015;47(8):625–38; 6. Swiecicki PL, et al. Amyloid 2015;22(2):123-31; 7. Sattianayagam AJ, et al. Eur Heart J 2012;33;1120–7; 8. Gertz MA, et al. Mayo Clin Proc 1992;67(5):428-40; 9. Suhr et al. J Intern Med 1994;235:479–85; 10. Adams. Ther Adv Neurol Disord 2013;6:129–39; 11.11-21 Adams A, et al. BMC Neuro 2017;17:181; 12. Adams D, et al. NEJM. 2018;379(1):; Disclosures: Jared Gollob, Sunita Goyal, Sonalee Agarwal, Hollis Lin are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.