Relationship Between Transthyretin Knockdown and Change in mNIS+7: Findings from the Patisiran Phase 2 Open-label Extension and Phase 3 APOLLO Studies for Patients with 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 mutation a in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in multiple organs including nerves, heart, and GI tract[1-3]

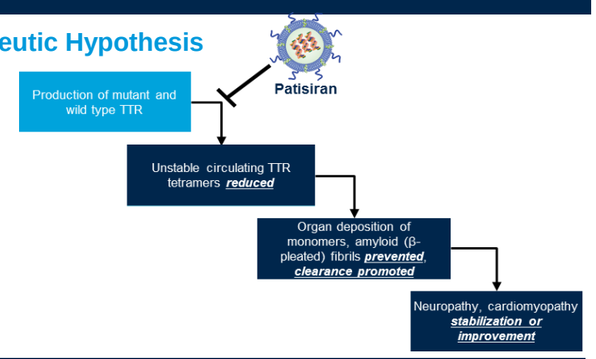
Patisiran

- Lipid nanoparticle formulation of siRNA targeting hepatic production of wild type (WT) and mutant TTR (Figure 1)

Objective

- Evaluate the relationship between the degree of TTR knockdown (KD) and change in neurologic impairment over time in patients with hATTR amyloidosis enrolled in Phase 2 and Phase 3 studies of patisiran

Figure 1: Patisiran Therapeutic Hypothesis



Methods

Datasets

- Longitudinal measurement of TTR knockdown and mNIS+7 was conducted for up to 24 months among patients in the Phase 2 and Phase 3 studies of patisiran
- Data was pooled across patients treated with placebo and patisiran (0.3 mg/kg IV, q3W) to evaluate the relationship between TTR knockdown and mNIS+7

Phase 2 study; ALN-TTR02-003

- 2-year open-label extension study evaluating long-term safety and clinical activity of patisiran in patients with hATTR amyloidosis with polyneuropathy[4]
  - mNIS+7 assessments were conducted every 6 months for up to 24 months
  - TTR knockdown was measured throughout the treatment period

Phase 3 study (APOLLO); ALN-TTR02-004

- 18-month, randomized (2:1), double-blind, placebo-controlled study evaluating clinical efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy[5]
  - mNIS+7 assessments conducted at 9 and 18 months
  - TTR knockdown was measured throughout the treatment period

Analysis methods

- Longitudinal model of mNIS+7 progression was selected
- Population mixed-effects modeling evaluated impact of TTR knockdown on mNIS+7 progression while controlling for the following covariates:
  - Genotype (V30M versus nonV30M)
  - Prior or concomitant use of tetramer stabilizers
  - Age of disease onset (<50 years of age, ≥ 50 years of age)
  - Baseline Demographics (age, body weight, gender)
  - Baseline TTR
- Simulations were conducted to understand:
  - Natural progression of TTR KD and mNIS+7 progression among patients in the placebo arms
  - Impact of TTR knockdown from patisiran-treatment on the course of the disease
  - Effect of these covariates on this relationship

Results

Pooled Data Summary

- Included 252 patients treated with patisiran or placebo from the APOLLO (n=225) and the Phase 2 studies (n = 27)
- Larger proportion were males; median age 62 – 64 years; baseline mNIS+7 was slightly higher in APOLLO relative to Ph2 study (Table 1)

Table 1: Covariate Summaries in the Pooled Analysis Dataset by Study and Treatment

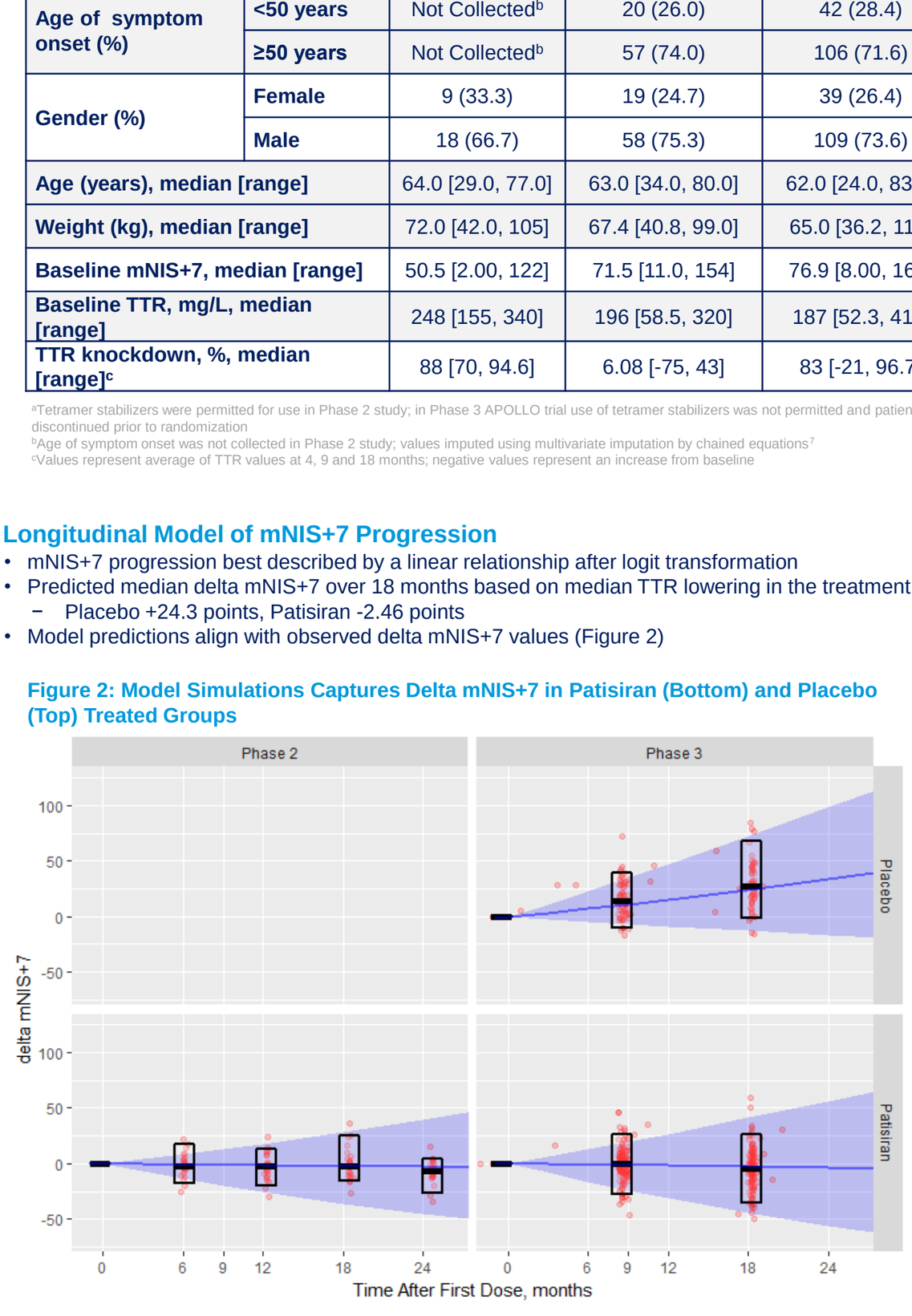
Study		Phase 2 Study	Phase 3 Study (APOLLO)	
Treatment		Patisiran (N=27)	Placebo (N=77)	Patisiran (N=148)
Genotype (%)	**OTHER**	7 (25.9)	37 (48.1)	92 (62.2)
	V30M	20 (74.1)	40 (51.9)	56 (37.8)
Prior or concomitant use of tetramer stabilizers (%)[a]	**No**	7 (25.9)	35 (45.5)	71 (48.0)
	Yes	20 (74.1)[a]	42 (54.5)	77 (52.0)
Age of symptom onset (%)	**<50 years**	Not Collected[b]	20 (26.0)	42 (28.4)
	≥50 years	Not Collected[b]	57 (74.0)	106 (71.6)
Gender (%)	**Female**	9 (33.3)	19 (24.7)	39 (26.4)
	Male	18 (66.7)	58 (75.3)	109 (73.6)
Age (years), median [range]		64.0 [29.0, 77.0]	63.0 [34.0, 80.0]	62.0 [24.0, 83.0]
Weight (kg), median [range]		72.0 [42.0, 105]	67.4 [40.8, 99.0]	65.0 [36.2, 110]
Baseline mNIS+7, median [range]		50.5 [2.00, 122]	71.5 [11.0, 154]	76.9 [8.00, 165]
Baseline TTR, mg/L, median [range]		248 [155, 340]	196 [58.5, 320]	187 [52.3, 411]
TTR knockdown, %, median [range][c]		88 [70, 94.6]	6.08 [-75, 43]	83 [-21, 96.7]

[a]Tetramer stabilizers were permitted for use in Phase 2 study; in Phase 3 APOLLO trial use of tetramer stabilizers was not permitted and patients discontinued prior to randomization
[b]Age of symptom onset was not collected in Phase 2 study; values imputed using multivariate imputation by chained equations[7]
[c]Values represent average of TTR values at 4, 9 and 18 months; negative values represent an increase from baseline

Longitudinal Model of mNIS+7 Progression

- mNIS+7 progression best described by a linear relationship after logit transformation
- Predicted median delta mNIS+7 over 18 months based on median TTR lowering in the treatment arms
  - Placebo +24.3 points, Patisiran -2.46 points
- Model predictions align with observed delta mNIS+7 values (Figure 2)

Figure 2: Model Simulations Captures Delta mNIS+7 in Patisiran (Bottom) and Placebo (Top) Treated Groups

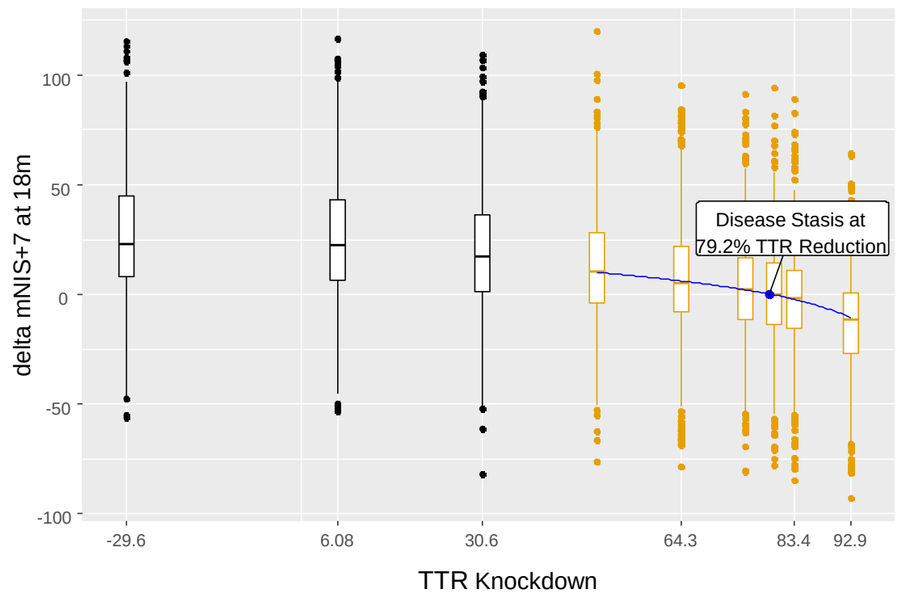


Blue line: median of the predicted; blue shaded area: 5th and 95th percentiles of the predicted; black box: 5th and 95th percentiles of the observed data; black cross bar: 50th percentile of the observed data.

TTR Knockdown to mNIS+7 Relationship

- TTR knockdown is log-linearly related to change in mNIS+7 (Figure 3)
- Higher TTR knockdown is predicted to lead to greater mNIS+7 improvement
- TTR knockdown of greater than 80% predicted to show improvement in mNIS+7 compared to baseline, i.e., delta mNIS+7 < 0

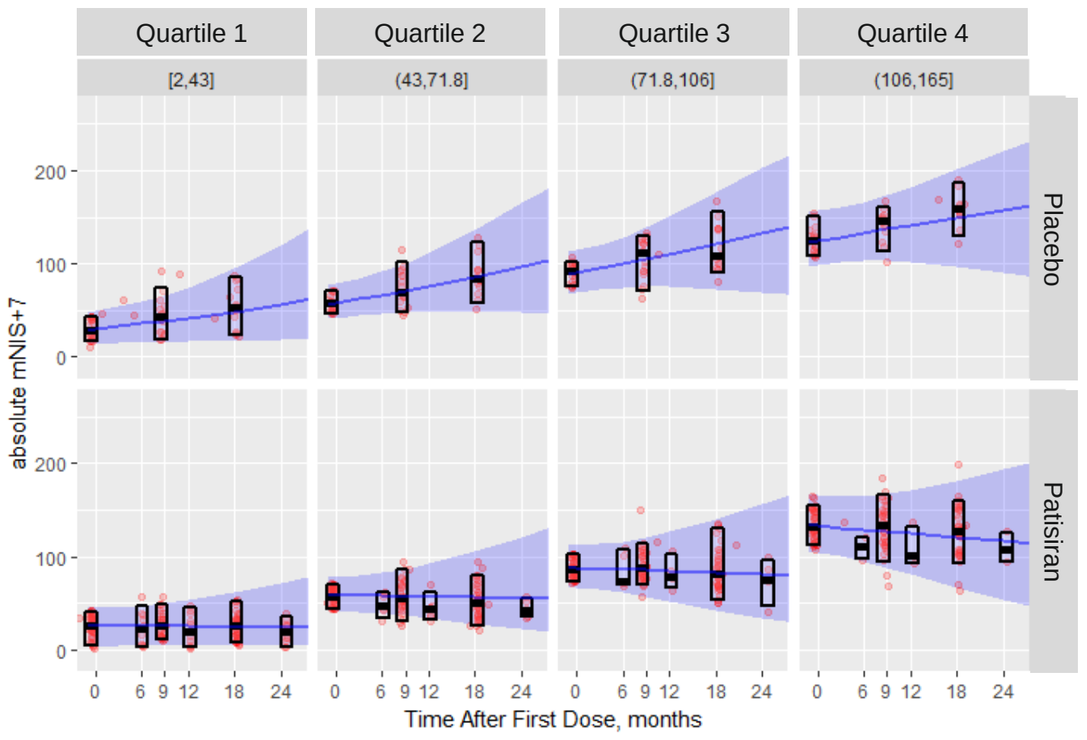
Figure 3: Relationship Between Delta mNIS+7 and TTR Knockdown



Impact of Baseline mNIS+7 on Rate of Disease Progression

- Rate of mNIS+7 progression similar across all degrees of baseline disease severity, as measured by mNIS+7 (Figure 4, upper panels)
- Patisiran halts and reverses progression across all baseline mNIS+7 values (Figure 4, bottom panels)
- Rate of neuropathy impairment is greater in placebo treated group compared to extent of improvement in the patisiran treated group over 18 months; underscoring early treatment to halt disease accumulation with time

Figure 4: Time-Course of mNIS+7 by Quartiles of Baseline mNIS+7 Values in Placebo (Top panels) and Patisiran Treated Groups (Bottom Panels)



Blue line: median of the predicted; blue shaded area: 5th and 95th percentiles of the predicted; black box: 5th and 95th percentiles of the observed data; black cross bar: 50th percentile of the observed data; (a,b]: values greater than a are included in the interval; [a,b]: values greater than or equal to a are included in the interval.

Summary

- Greater knockdown in circulating TTR levels is consistently associated with greater improvement in neurologic impairment (as measured by mNIS+7) in patients with hATTR amyloidosis
- Greater than ~80% TTR lowering is associated with disease reversal at the population level
- Patients should be treated with patisiran early in the course of the disease to prevent accumulation of progressive neuropathy impairment

mNIS+7, Modified Neuropathy Impairment Score + 7; RNA interference; WT, wild type. References: 1. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 2. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 3. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748; 4. Adams et al. Neurology. 2017;88:15 Supplement S27.004 (NCT01961921); 6. Adams, D. Orphanet J Rare Dis 2017, 12(Suppl 1):O9 – oral presentation EU ATTR ; 02 Nov; 17; 7. van Buuren et al. J of Royal Stat Software. 2011; 45(3): 1-67. Disclosures: Hollis Lin, Gabriel Robbie and Varun Goel are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.