Relationship Between TTR Knockdown and Change in mNIS+7

Preliminary Correlation Findings from the Phase 2 Open-Label Extension Study of Patisiran, an Investigational RNAi Therapeutic for Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

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Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

- Also known as familial amyloidotic polyneuropathy (FAP)
- Autosomal dominant hereditary amyloidosis caused by deposition of mutant and wild-type transthyretin (TTR) in nerves, gastrointestinal tract, heart, and eyes
  - Median survival 5-15 years
- Polyneuropathy is symmetrical with motor, sensory and autonomic components[1]
  - Clinical manifestations (e.g. disease penetrance and rate of progression) influenced by TTR genotype and geographical region
- Limited treatment options
  - Liver transplant for early-stage disease
  - Tetramer stabilizers
    - Tafamidis approved in the EU for Stage 1 hATTR-PN[2] and certain other countries outside the U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[3]
- Continued high unmet medical need for novel therapeutics

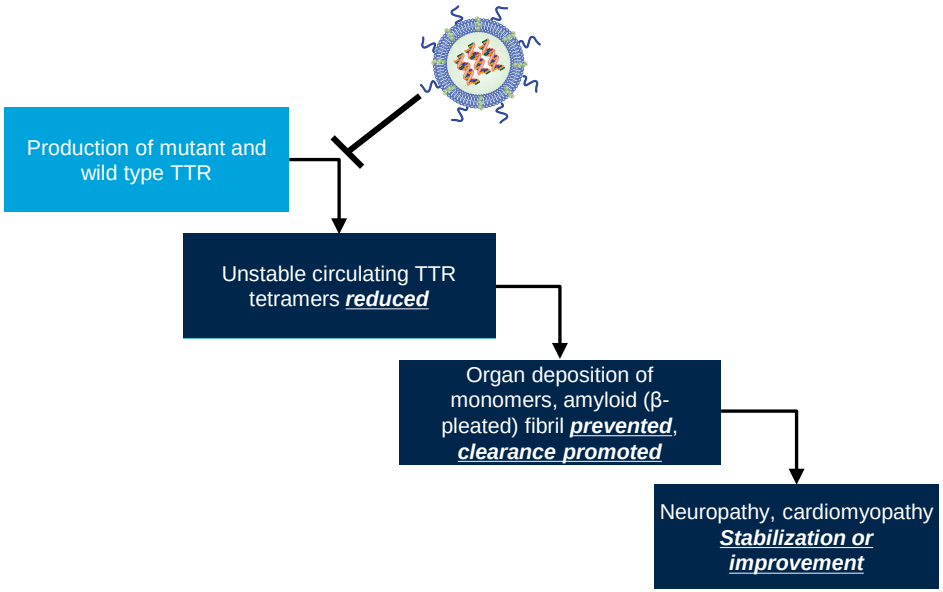
[1]Adams D et al., Neurology. 85;675-682 (2015)
[2]Coelho T et al., Neurology. 79:785-92 (2012)
[3]Berk JL et al., JAMA. 310:2658-67 (2013)

Patisiran

Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

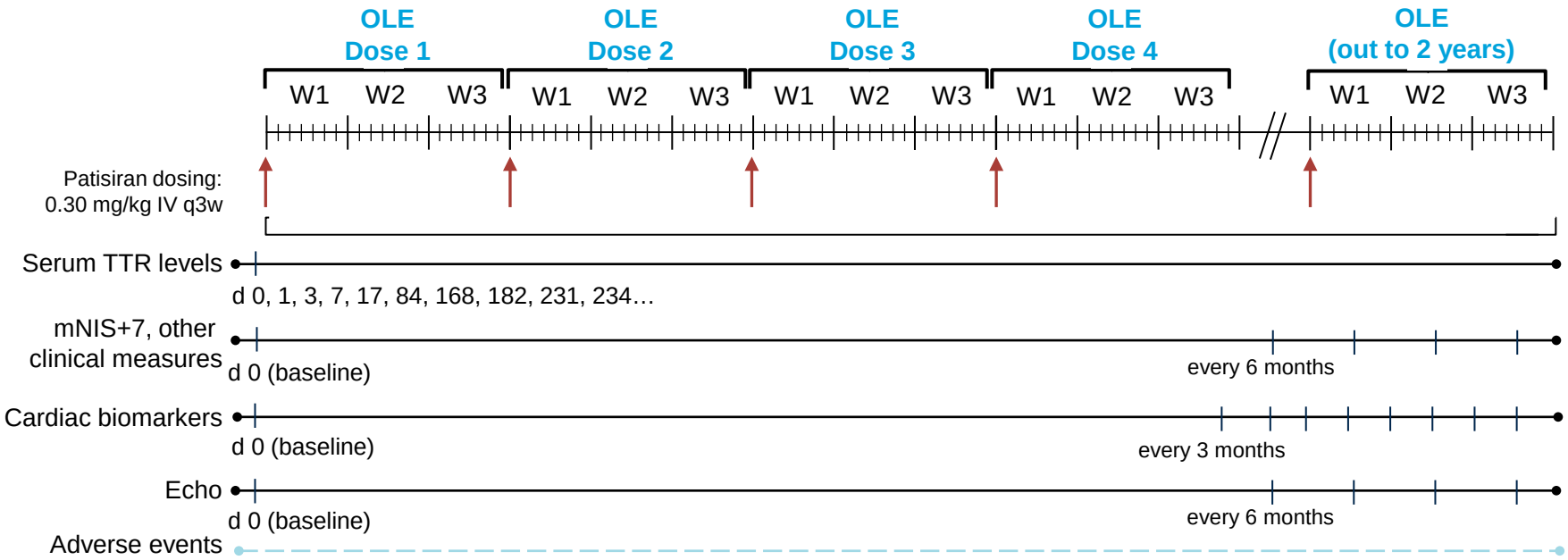
- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR
- Administered by IV infusion
- Positive Phase 1 results in human volunteers
  - Data published in New Engl J Med[1]
- Positive multi-dose Phase 2 results in patients with hATTR-PN
  - Data published in Orphanet J Rare Dis[2]
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Includes clinical endpoints measured every 6 months
  - Positive interim data reported at ISA, April 2014; ANA, Oct. 2014; AAN, March 2015; ANA, Sept. 2015; EC-ATTR, Nov 2015; AAN, April 2016
- APOLLO Phase 3 trial: enrollment complete, trial ongoing
- APOLLO-OLE ongoing

Patisiran Therapeutic Hypothesis



[1]Coelho T et al., N Engl J Med;369:819-29 (2013)
[2]Suhr OB et al., Orphanet J Rare Dis;10:109 (2015)

Patisiran Phase 2 OLE Study Design



hATTR-PN patients previously dosed on Phase 2 trial eligible to roll over onto Phase 2 OLE study

- Up to 2 years of dosing, 0.30 mg/kg every 3 weeks, with clinical endpoints evaluated every 6 months
- Primary objectives: Safety and tolerability of long-term dosing with patisiran
- Secondary objectives: Effects on neurologic impairment (mNIS+7 and NIS), quality of life, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fiber density in skin biopsies, cardiac involvement (in cardiac subgroup), serum TTR levels

Timelines are not to scale

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Patisiran Phase 2 OLE Preliminary Study Results*

Demographics and Exposure

This presentation highlights interim 24 month data for the study

Characteristic	Result
Number of patients	N=27 (includes 11 patients in cardiac subgroup)
Median age	64.0 years (range 29 - 77)
Gender	18 males, 9 females
TTR genotype	• Val30Met (V30M) = 20 • Ser77Tyr (S77Y) = 2 • Ser77Phe (S77F) = 2 • Tyr116Ser (Y116S) = 1 • Phe64Leu (F64L) = 1 • Arg54Thr (R54T) = 1
FAP stage/PND score	• Stage 1: 24 • Stage 2: 3 • I: 14 • IIIa: 2 • II: 10 • IIIb: 1
Concurrent tetramer stabilizer use at baseline	13 tafamidis, 7 diflunisal, 7 none
Current tetramer stabilizer use†	12 tafamidis, 2 diflunisal, 13 none
Exposure	**Result**
Total doses administered	931
Median doses/patient to date	35 (range 27 - 36)
Mean treatment duration	24.0 months (range 18.8 - 24.7)

† 6 patients reported stabilizer use (5 on diflunisal, 1 on tafamidis) at the time of first dose but subsequently stopped ~1 to 18 months into the study

*Data as of 12May2016

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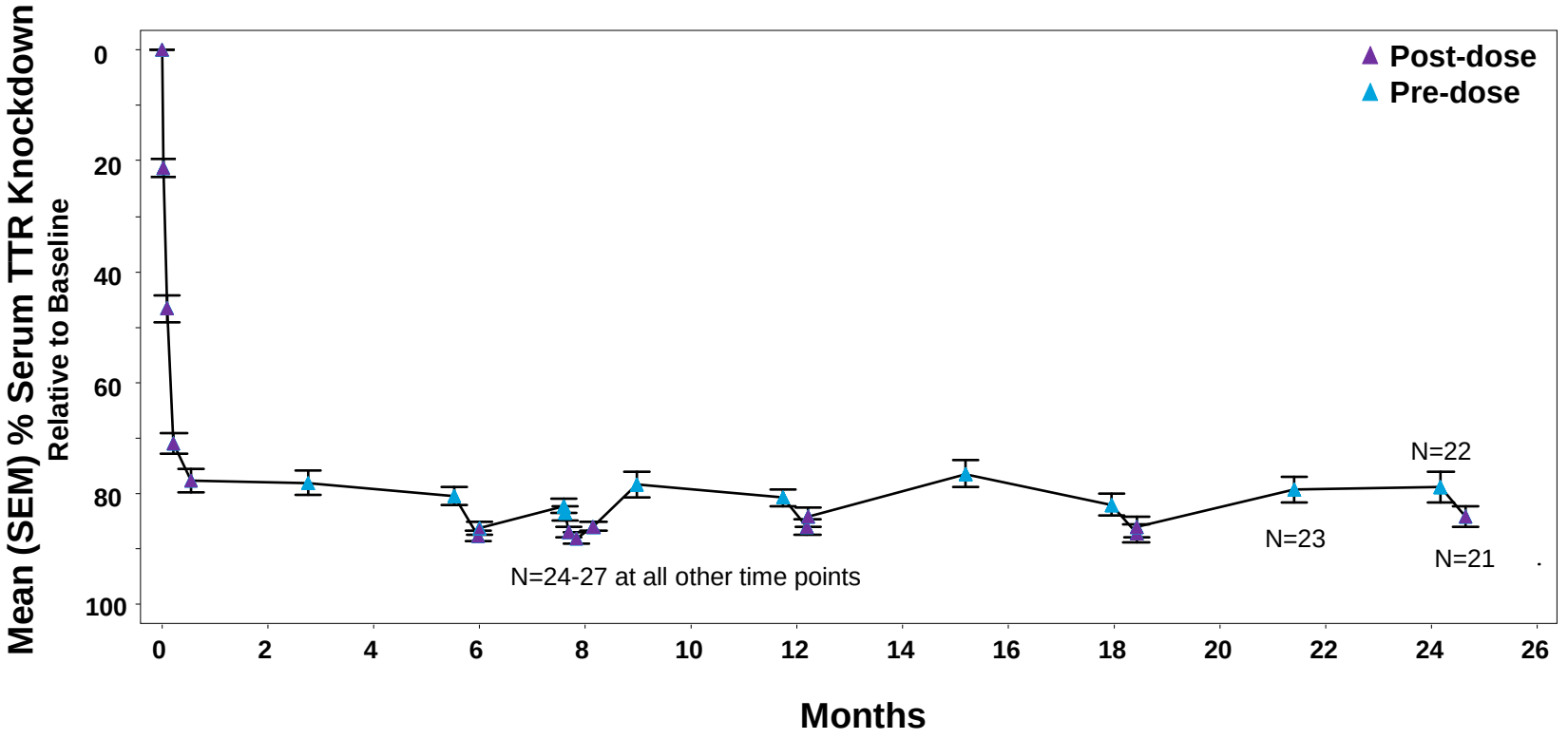
Patisiran Phase 2 OLE Preliminary Study Results*

Serum TTR Knockdown



- Mean serum pre-dose TTR knockdown of approximately 80%
- Mean serum TTR knockdown at 24 months of 84%
- Mean maximal serum post-dose TTR knockdown of 93%
- Maximal individual patient post-dose knockdown of 97%
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

SEM: Standard Error of the Mean
*Data as of 12May2016

Patisiran Phase 2 OLE Preliminary Study Results*
Summary of Safety, Tolerability and Clinical Activity

Safety and Tolerability

- Patisiran generally well tolerated in patients with hATTR-PN out to 25 months
  - 6 patients (22.2%) with 9 reports of serious adverse events (SAEs), including 2 deaths, not related to study drug
    - One discontinuation for gastroesophageal cancer at ~20 months; patient subsequently died
    - One patient died due to myocardial infarction after completing 24 months of treatment
  - Majority of AEs were mild or moderate
    - Most common related AEs were flushing (22.2%) and IRRs (18.5%), all of which were mild or moderate in severity

Clinical Activity

- Preliminary evidence of improvement in neuropathy impairment at 24 months with mean 6.7-point decrease in mNIS+7
  - Improvement or no change in mNIS+7 observed in 17 of 24 (71%) patients
  - Similar results in patients with or without concurrent tetramer stabilizers

mNIS+7 component	Change from Baseline to Month 24 (N=24)	
	Mean (SEM)	Median (range)
Total+	**-6.7 (2.3)**	**-6.8 (-34.6, 15.4)**
NIS-weakness	1.4 (1.5)	0 (-13.5, 24.4)
NIS-reflexes	-0.1 (0.5)	0 (-6.0, 7.0)
QST	-7.7 (2.2)	-6.0 (-40.0, 16.0)
NCS Σ5	-0.2 (0.2)	-0.3 (-2.0, 2.5)
Postural BP	-0.1 (0.1)	0 (-1.0, 0.5)

+Partial imputation used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
*Data as of 12May2016

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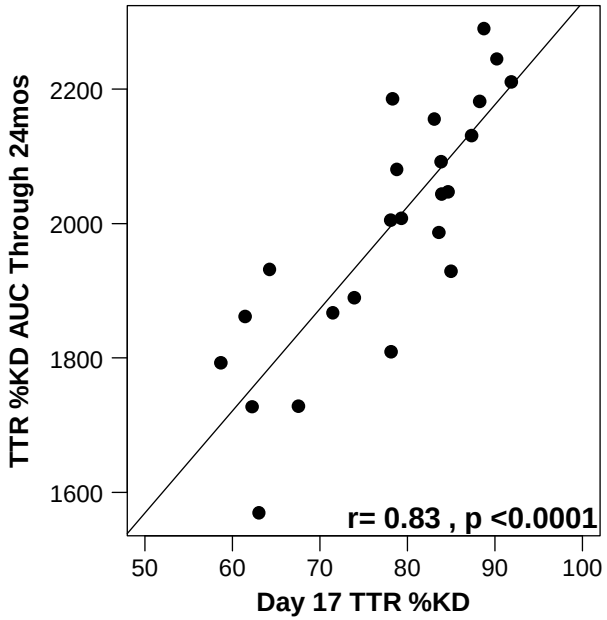
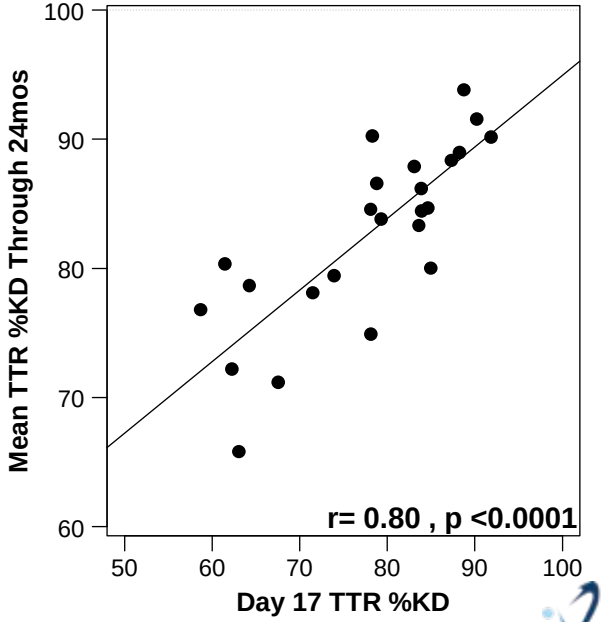
Correlation of TTR Knockdown (KD) with ΔmNIS+7
Background

- Patisiran therapeutic hypothesis: TTR knockdown can potentially halt or improve neuropathy progression
- Inter-patient variability in degree of TTR KD provides opportunity to examine relationship of TTR KD to change in neuropathy progression as measured by mNIS+7
  - Analysis of correlation between TTR knockdown and mNIS+7 change also permits assessment of patisiran treatment effect independent of concurrent TTR tetramer stabilizer use

Patisiran Phase 2 OLE Preliminary Study Results*
Methodology for Exploratory Correlations

- TTR KD 17 days post-first dose of patisiran (Day 17 %TTR KD) chosen for analysis of correlation between TTR KD and change in mNIS+7 at 6, 12, 18 and 24 months
  - Use of Day 17 %TTR KD level reduces impact of missed doses or missed TTR assessments over 24 months of dosing
  - Day 17 %TTR KD correlates with TTR area under the curve (AUC) and mean %TTR knockdown in Phase 2 OLE patients

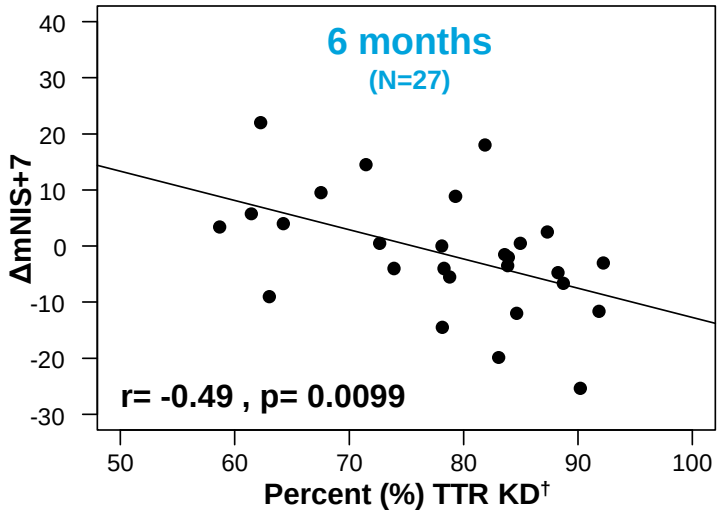


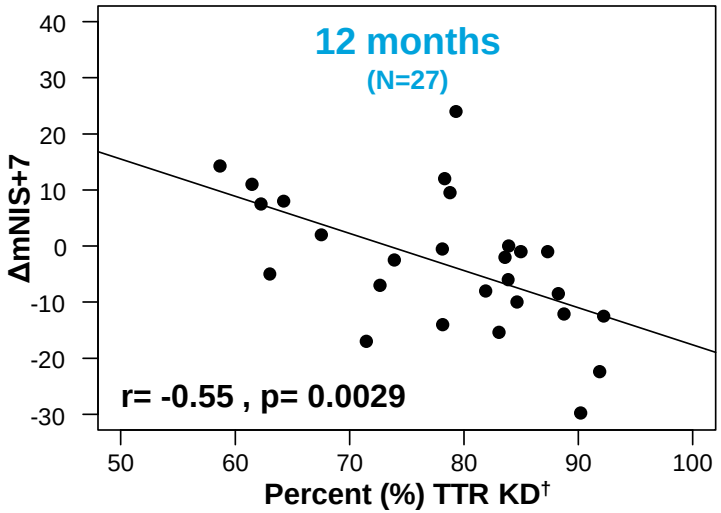


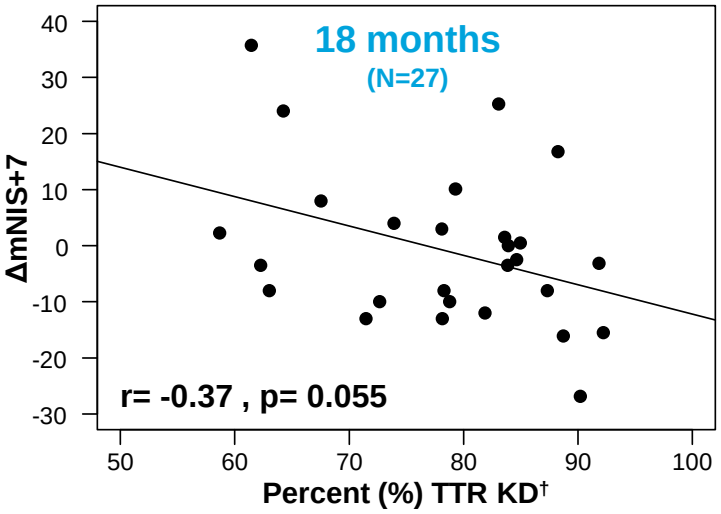
*Data as of 12May2016

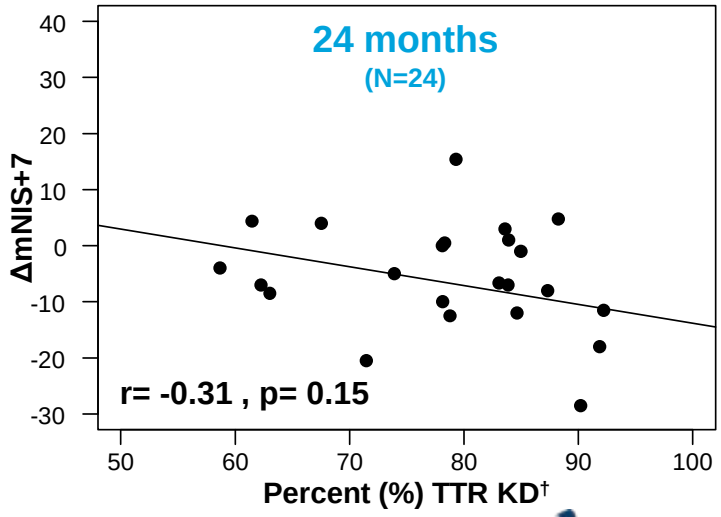
Patisiran Phase 2 OLE Preliminary Study Results*

Correlation of TTR Knockdown with ΔmNIS+7









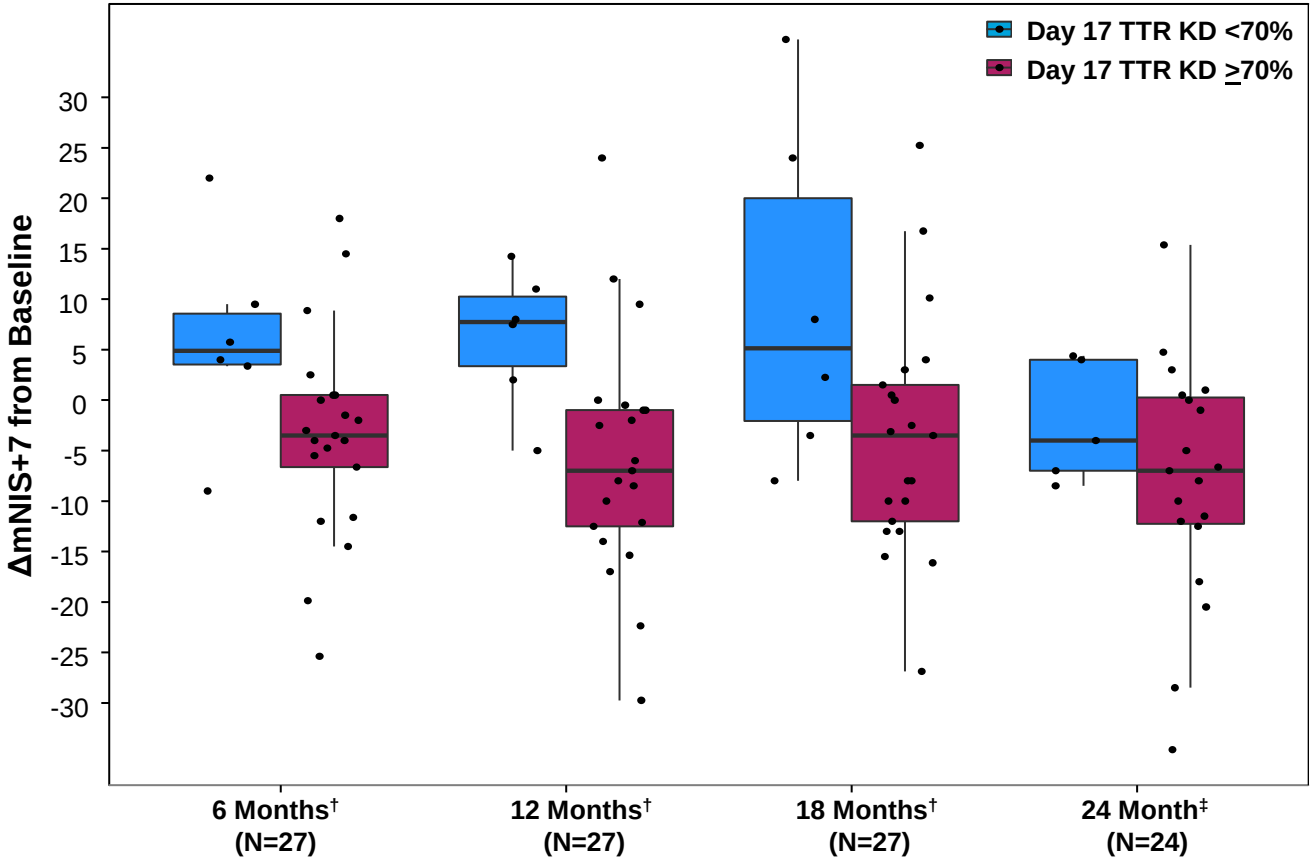
Note: three patients had missing D17 TTR: one was replaced by D7 and two replaced by D84.
† Percent (%) TTR knockdown from baseline at Day 17 post-first dose of patisiran
*Data as of 12May2016

Patisiran Phase 2 OLE Preliminary Study Results*

Change Over Time in Correlation Between %TTR KD and ΔmNIS+7

Degree of TTR knockdown with patisiran correlates with subsequent change in mNIS+7

- Strongest correlation observed at 6 and 12 months
- Loss of significant correlation between 18 and 24 months suggests that lesser degrees of TTR KD (<70%) may impact neuropathy progression if maintained over longer period of time



† Day 17 TTR KD <70% (n=6); Day 17 TTR KD >70% (n=21)
‡ Day 17 TTR KD <70% (n=5); Day 17 TTR KD >70% (n=19)
*Data as of 12May2016

Patisiran Phase 2 OLE Preliminary Study Results*
Summary

Encouraging preliminary safety and clinical activity in patients with hATTR-PN following 24 months of treatment with patisiran in the Ph 2 OLE study

- Patisiran generally well tolerated in patients with hATTR-PN with no drug-related SAEs and majority of AEs were mild or moderate
- Preliminary evidence of improvement in neuropathy impairment score with mean 6.7-point decrease in mNIS+7

Sustained mean serum pre-dose TTR knockdown of approximately 80% for over 24 months with mean maximal post-dose knockdown of 93%

Degree of TTR knockdown with patisiran correlates with subsequent change in mNIS+7

- Strongest correlation observed at 6 and 12 months
- Loss of significant correlation between 18 and 24 months suggests that lesser degrees of TTR KD (<70%) may impact neuropathy progression if maintained over longer period of time

Results consistent with therapeutic hypothesis that TTR knockdown can potentially halt or improve neuropathy progression

*Data as of 12May2016

Acknowledgments

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Study Investigators

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Thank You!

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