Phase 2 Open-Label Extension (OLE) Study of Patisiran

An Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

04 July 2016 | ISA | Uppsala, Sweden

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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)

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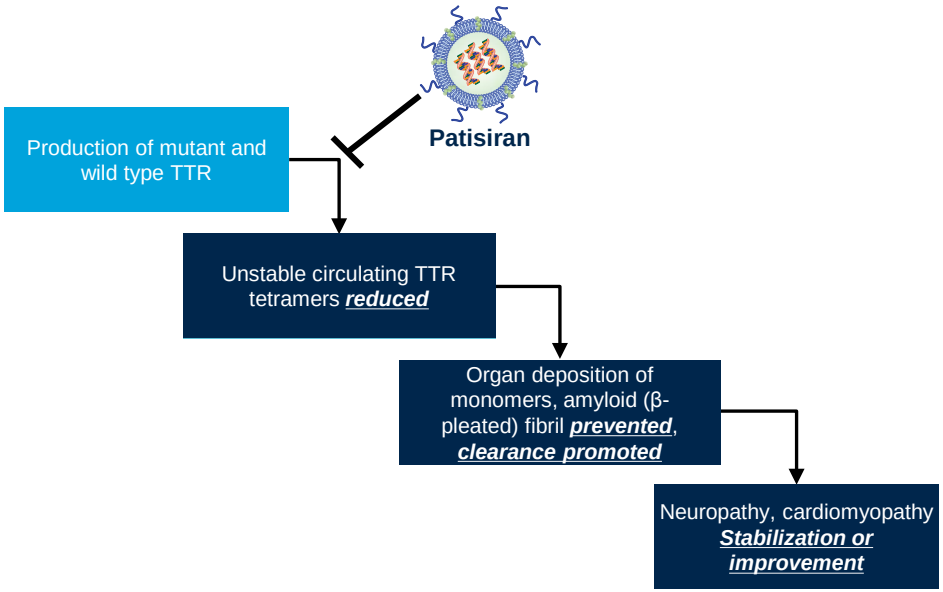
Patisiran

Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

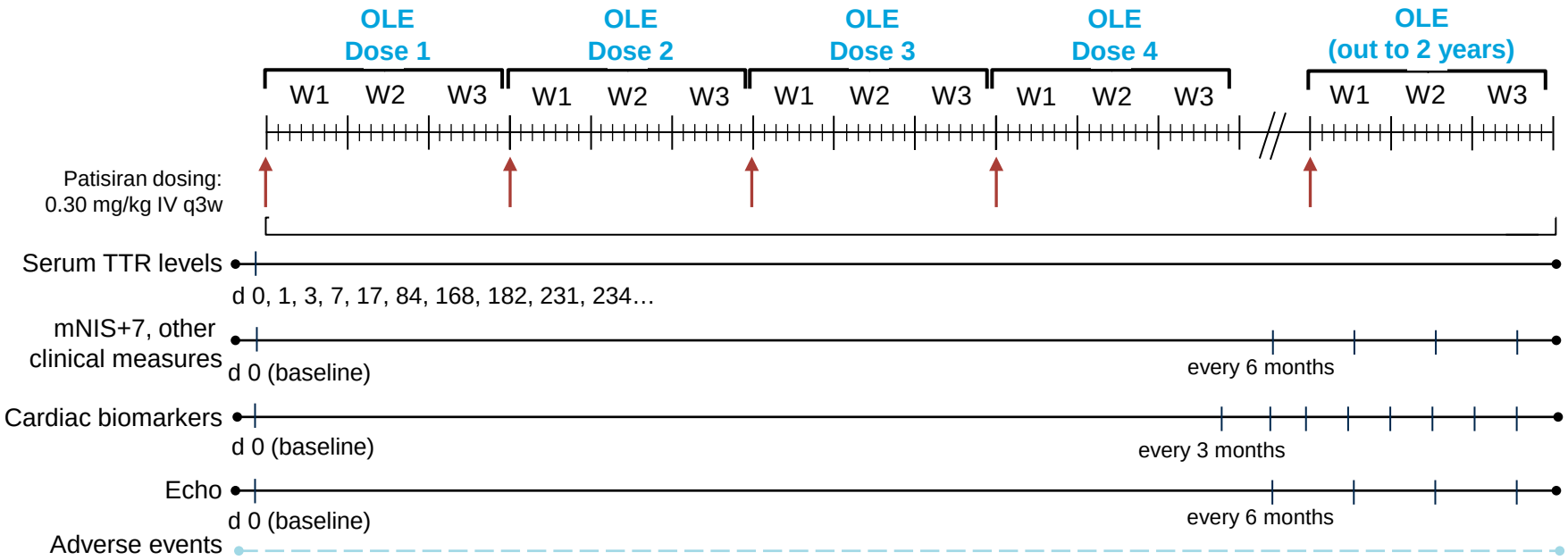
- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR
- Administered by IV infusion
- Positive Phase 1 results in human volunteers
  - Data published in New Engl J Med[1]
- 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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Baseline Characteristics

Characteristic	N	Mean	(range)
mNIS+7[a] (max impairment: 304)	27	52.9	(2.0 - 122.5)
NIS (max impairment: 244)	27	34.8	(4.0 – 93.4)
10-meter walk test (m/sec)	22	1.1	(0.4 - 2.2)
Hand grip strength (kg)	27	25.8	(3.2 - 49.3)
mBMI (kg/m^2 x albumin [g/dL])	27	1031.6	(728.6 - 1379.6)
EQ-5D-5L QOL (max impairment: 0)	27	0.8	(0.3 - 1.0)
R-ODS[b] (no limitations: 48)	26	38.1	(15.0 - 48.0)
COMPASS-31[c] (max impairment: 100)	27	15.9	(0.0 - 46.1)
Serum TTR (µg/mL)	27	245.3	(155.0 - 340.0)
Cardiac subgroup: N = 11			
V30M/non-V30M (N)	11	8/3	
NT-proBNP (ng/L)	9	809.8	(105.0 - 2070.0)
Troponin I[d] (ng/mL)	8	0.1	(0.03 - 0.7)
LV wall thickness (cm)	11	1.6	(1.3 - 1.9)
10-meter walk test (m/sec)	7	1.0	(0.4 - 1.5)

[a] Partial imputation was used to recover mNIS+7 score for one patient missing QST at Baseline
[b] R-ODS: Rasch-built Overall Disability Score, a 24-item questionnaire used to capture activity and social participation (Van Nes SI et al., *Neurology* 2011); raw scores are presented
[c] COMPASS-31: 31-item questionnaire used to evaluate 6 autonomic domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor) (Sletten *et al., Mayo Clin Proc*. 2012)
[d] Values recorded as '< LLOQ' were imputed to be LLOQ/2

*Data as of 12May2016

Patisiran Phase 2 OLE Preliminary Study Results*

Summary of Safety and Tolerability

Common Adverse Events (AEs) in ≥10% of patients

AE by Preferred Term	Patisiran (N=27)
Flushing	7 (25.9%)
Diarrhea	6 (22.2%)
Nasopharyngitis	6 (22.2%)
Urinary tract infection	6 (22.2%)
Vomiting	6 (22.2%)
Wound	6 (22.2%)
Infusion related reaction	5 (18.5%)
Nausea	5 (18.5%)
Insomnia	4 (14.8%)
Neuralgia	4 (14.8%)
Pyrexia	4 (14.8%)
Anemia	3 (11.1%)
Bronchitis	3 (11.1%)
Edema peripheral	3 (11.1%)
Macular degeneration	3 (11.1%)
Musculoskeletal pain	3 (11.1%)
Osteoporosis	3 (11.1%)

- 6 patients (22.2%) with 9 reports of serious adverse events (SAEs); not related to study drug
  - One discontinuation for gastroesophageal cancer at ~20 months; patient subsequently died
  - One death due to myocardial infarction after patient completed 24 months of treatment
  - One patient with 3 reports (distal femur fracture/proximal tibia fracture/osteonecrosis/ligament rupture, dehydration/acute prerenal failure/urinary tract infection and thermal burn); one patient with 2 reports (ankle fracture/foot fracture/ osteonecrosis and ankle arthrodesis); one patient with venous thrombosis of the lower limb; one patient with foot abscess and osteomyelitis
- Majority of AEs were mild or moderate
  - 4 patients (14.8%) had severe AEs not related to study drug
  - Most common related AEs reported in >3 patients were flushing (6 patients [22.2%]) and infusion related reaction (5 patients [18.5%]), all of which were mild
- No clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelets

*Data as of 12May2016

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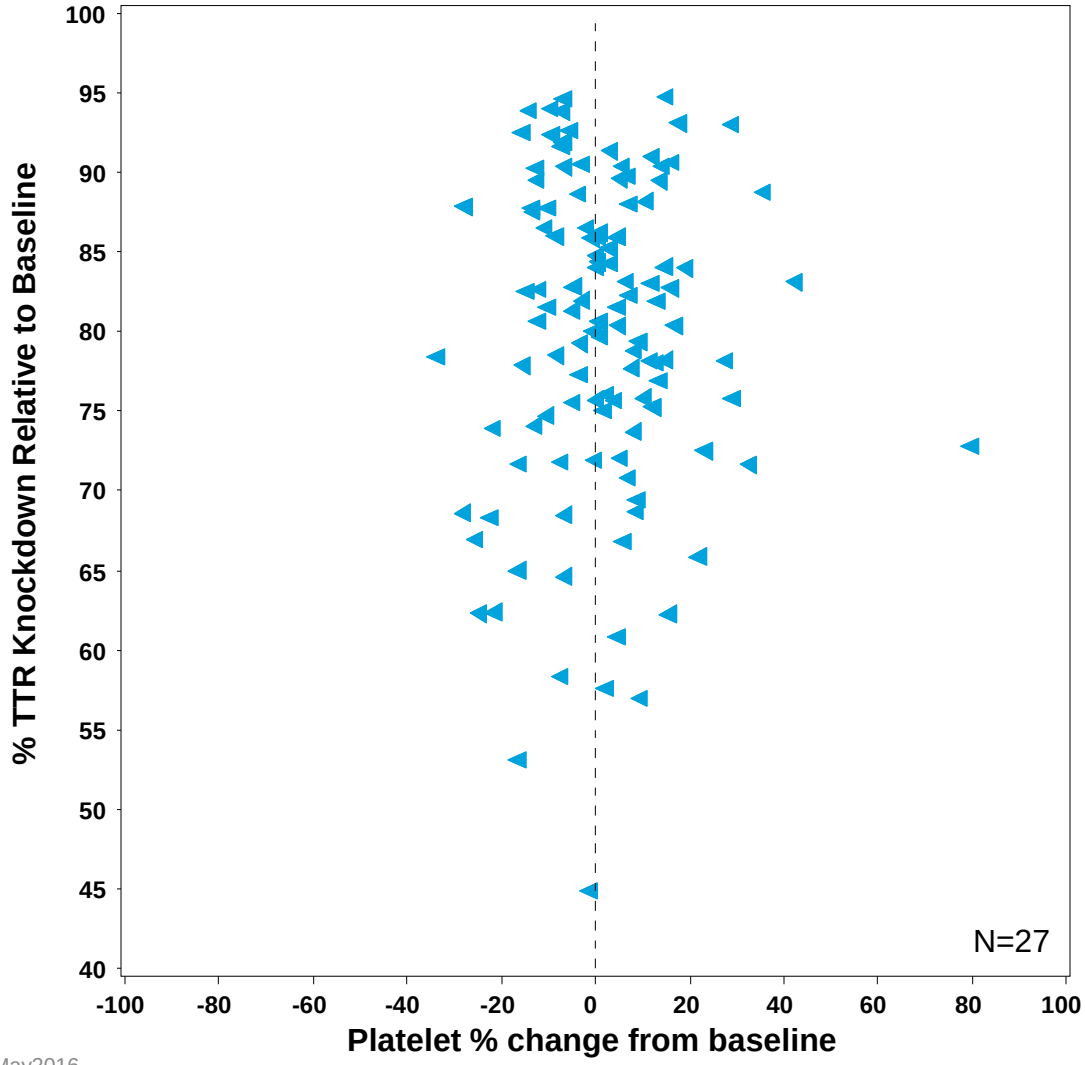
Patisiran Phase 2 OLE Preliminary Study Results*

TTR KD Effect versus Platelets for All Visits Through 24 months

No correlation between TTR KD and change in platelets



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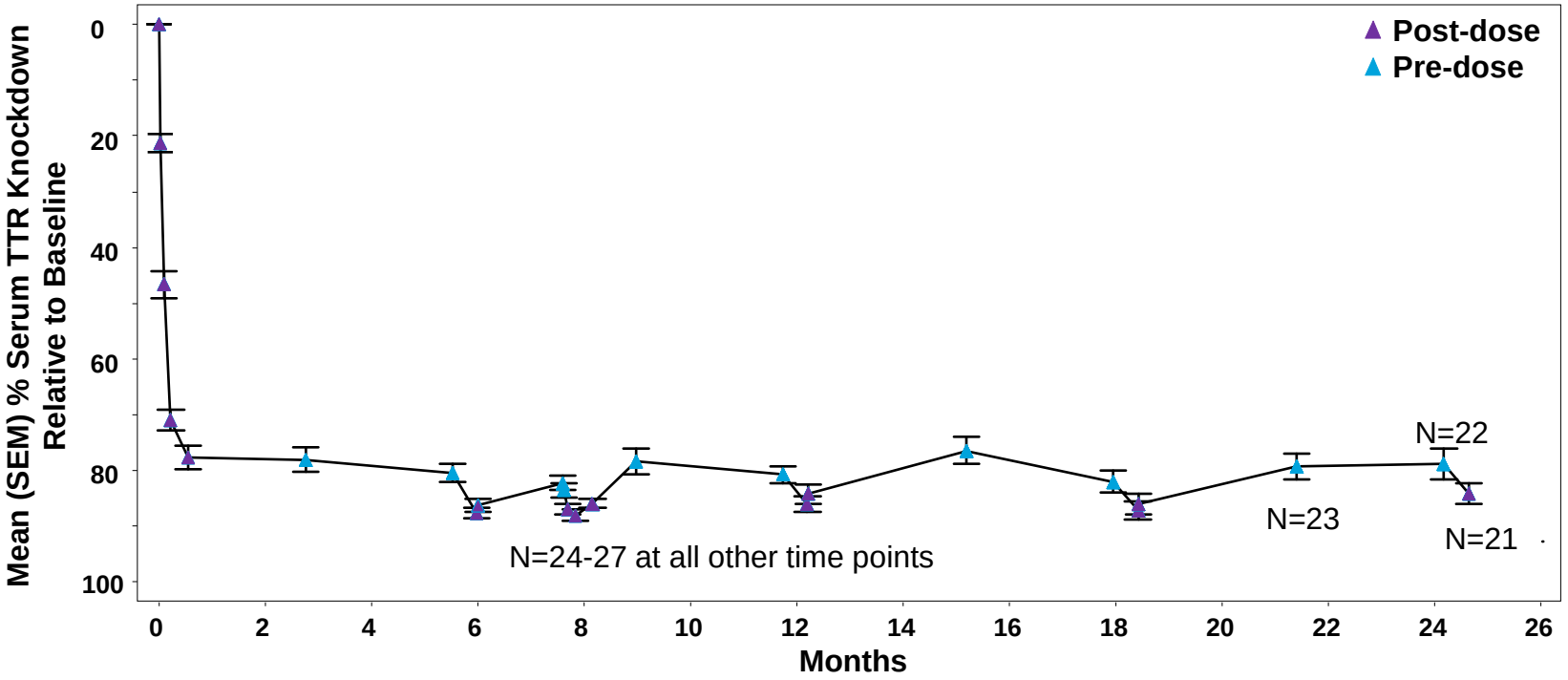
Serum TTR Knockdown



- 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

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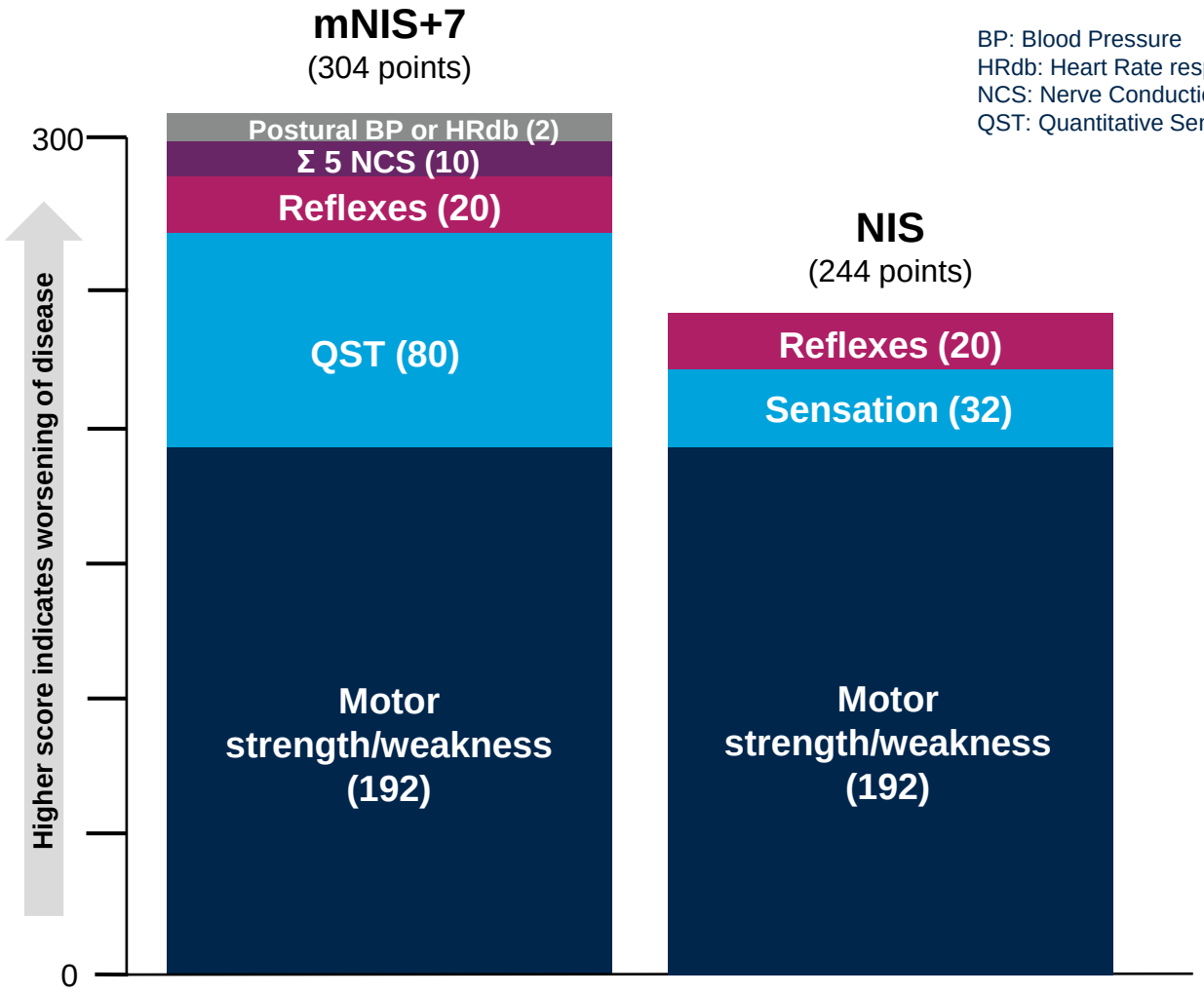
Neuropathy Impairment Scores Used in hATTR-PN Trials

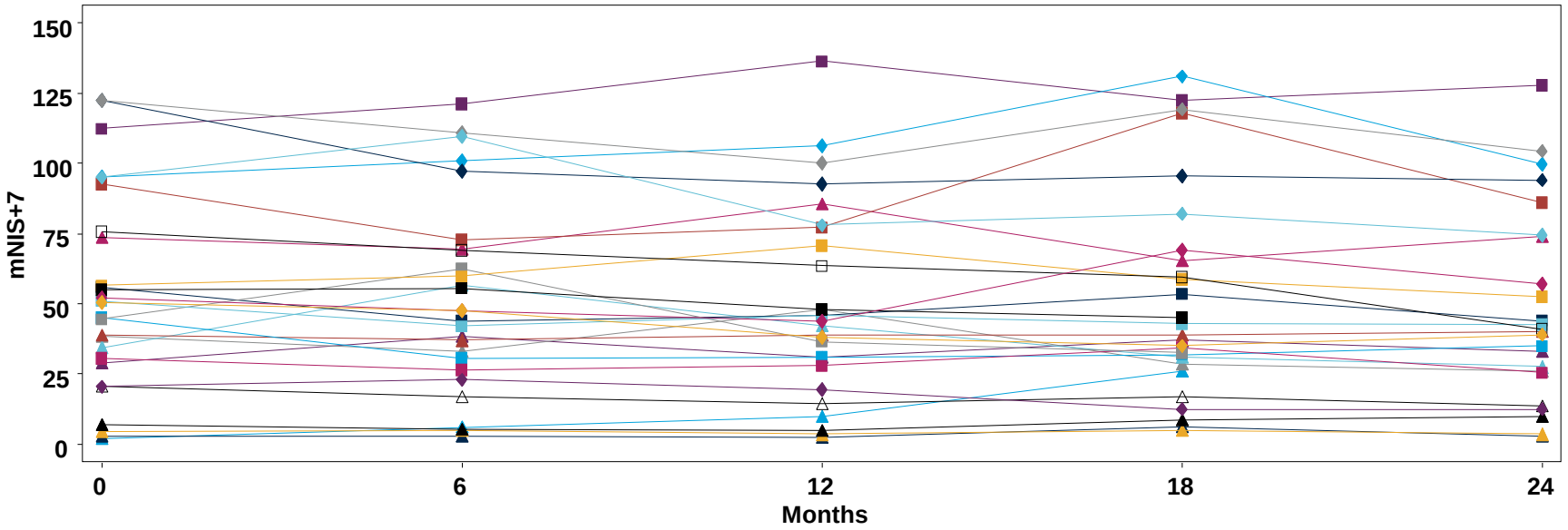


BP: Blood Pressure
HRdb: Heart Rate response to Deep Breathing
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

[1]Adams D, et al. *Neurology. 85;675-682* (2015)

Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 Over 24 Months



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 was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)

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

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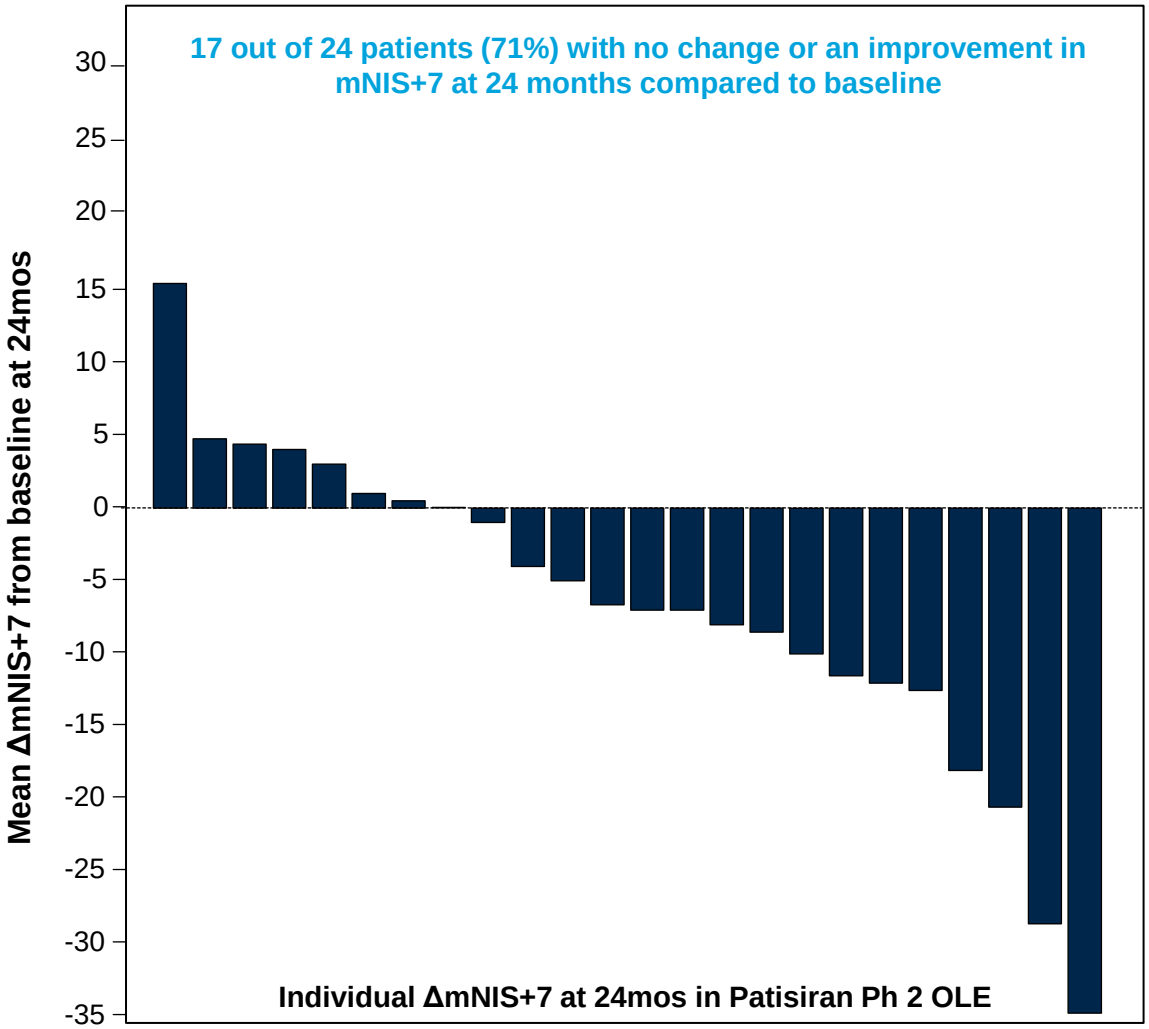
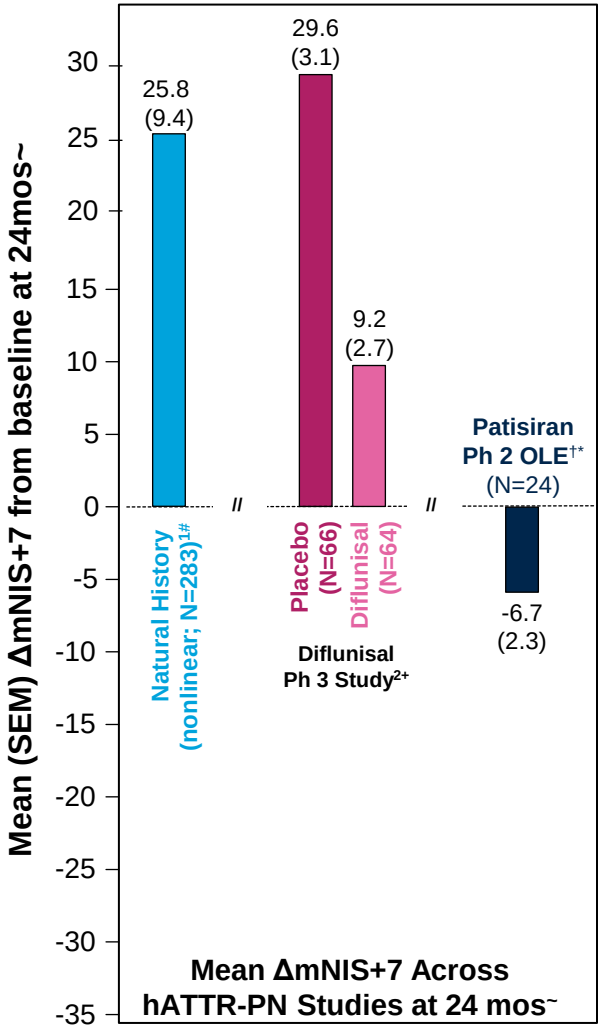
Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 at 24 Months





SEM: Standard Error of the Mean

~ Assessments drawn from studies in patients with similar baseline neurologic impairment and not based on head-to-head studies

[1]Adams D, et al. *Neurology. 85;675-682* (2015); [#]Predicted progression of median NIS value from Gompertz curve fit[1]

[2]Berk JL, *et al. JAMA.* 310:2658-67 (2013); [+]Linear interpolation from 2-year NIS progression measurement in longitudinal analysis set

[†] Patisiran results similar in patients with/without concurrent TTR stabilizer therapy; mNIS+7 using full mNIS+7 set; partial imputation was 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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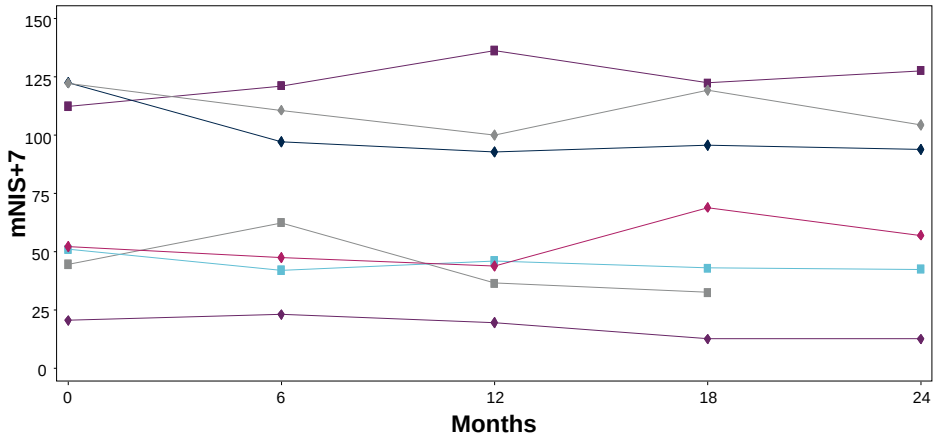
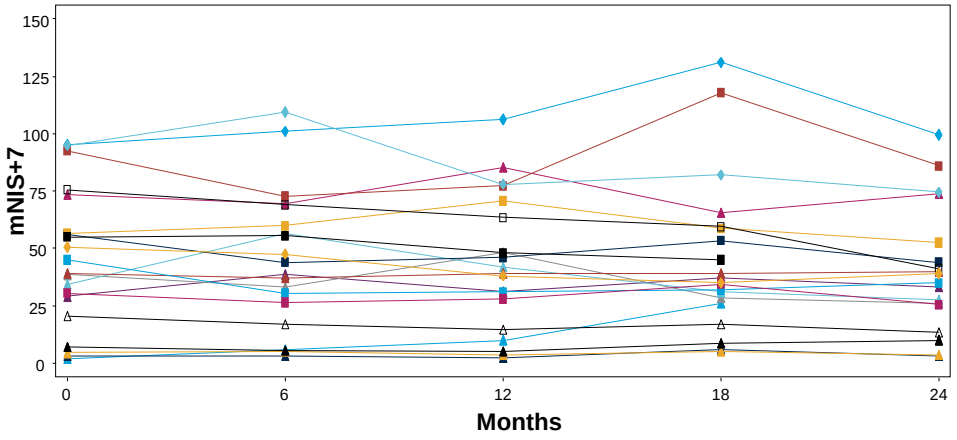
Change in mNIS+7 Over 24 Months By Stabilizer Use

Patisiran Alone



Patisiran + Stabilizer



mNIS+7	Change from Baseline to Month 24	
	Patisiran Alone (n=6)	Patisiran + Stabilizer (n=18)
Mean Change (SEM)	-7.1 (6.4)	-6.6 (2.3)
Median Change (range)	-8.3 (-28.5, 15.4)	-5.8 (-34.6, 4.4)

Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit).

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

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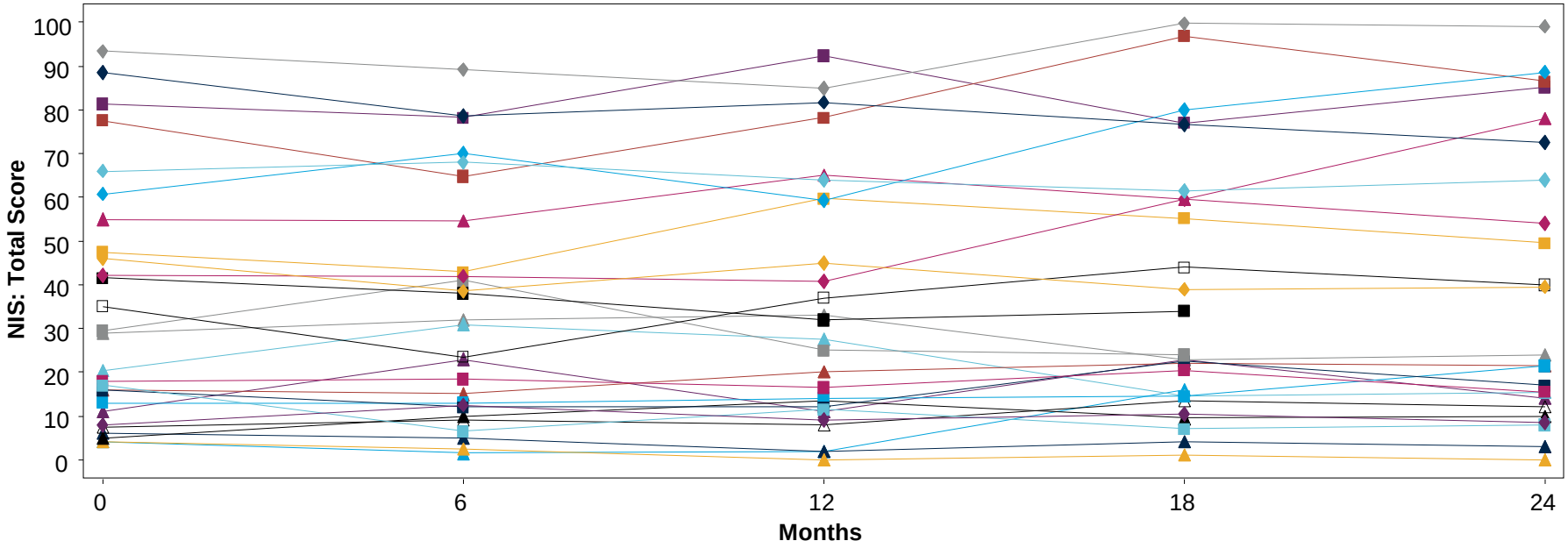
Change in NIS Over 24 Months



NIS component	Change from Baseline to Month 24 (N=24)	
	Mean (SEM)	Median (range)
Total	**2.6 (1.9)**	**2.5 (-16.0, 27.9)**
NIS-weakness	1.4 (1.5)	0 (-13.5, 24.4)
NIS-reflexes	-0.1 (0.5)	0 (-6.0, 7.0)
NIS-sensation	1.4 (0.9)	2.0 (-8.0, 7.0)

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

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Changes in Other Clinical Assessments

Assessment	Baseline		Change from Baseline to Month 24	
	N	Mean (SEM)	N	Mean (SEM)
10-Meter Walk^ (m/sec)	22	1.1 (0.1)	18	0.05 (0.04)
Hand Grip Strength (kg)	27	25.8 (2.3)	24	1.9 (1.3)
mBMI (kg/m^2 x albumin [g/dL])	27	1031.6 (32.5)	23	-60.6 (35.2)
EQ-5D (max. impairment: 0)	27	0.8 (0.03)	24	-0.02 (0.02)
R-ODS (no limitations: 48)	26	38.1 (1.7)	24	-1.7 (0.8)
COMPASS-31 (max. impairment: 100)	27	15.9 (2.6)	24	0.5 (1.9)
Orthostatic Intolerance	27	4.9 (1.5)	24	0.7 (1.8)
Vasomotor	27	0.7 (0.2)	24	-0.4 (0.3)
Secretomotor	27	2.7 (0.6)	24	0.4 (0.5)
Gastrointestinal	27	5.8 (0.8)	24	-0.6 (0.5)
Bladder	27	1.0 (0.3)	24	0.1 (0.4)
Pupillomotor	27	0.8 (0.2)	24	0.3 (0.2)
IENFD (fibers/mm)				
Location: Leg	24	3.5 (1.3)	17	-0.1 (0.5)
Location: Thigh	24	10.2 (2.0)	18	-1.7 (0.7)
SGNFD (m/mm^3)				
Location: Leg	24	3.9 (0.7)	17	1.7 (0.5)
Location: Thigh	24	6.8 (0.7)	18	2.3 (0.7)
Cardiac Subgroup, N=11				
NT-proBNP (ng/L)#	9	809.8 (246.7)	7	-50.3 (197.3)
Troponin I (ng/mL)#	8	0.1 (0.1)	7	-0.1 (0.1)
LV Mass (g)	11	278.1 (23.2)	6	-0.8 (14.5)
LV wall thickness (cm)	11	1.6 (0.1)	6	-0.04 (0.1)
Ejection fraction (%)	11	62.5 (2.6)	6	-0.3 (2.3)
Peak longitudinal strain (%)	11	-16.6 (1.3)	6	1.7 (0.7)
10-Meter Walk (m/sec)	7	1.0 (0.1)	6	0.06 (0.05)

^ One patient with an SAE due to ankle injury prior to month 6 was removed from the 10-meter walk analysis.
# Values reported as <LLOQ were imputed to be LLOQ/2 for the analysis.
IENFD: Intraepidermal nerve fiber density; SGNFD: Sweat gland nerve fiber density; SEM: Standard Error of the Mean
*Data as of 12May2016

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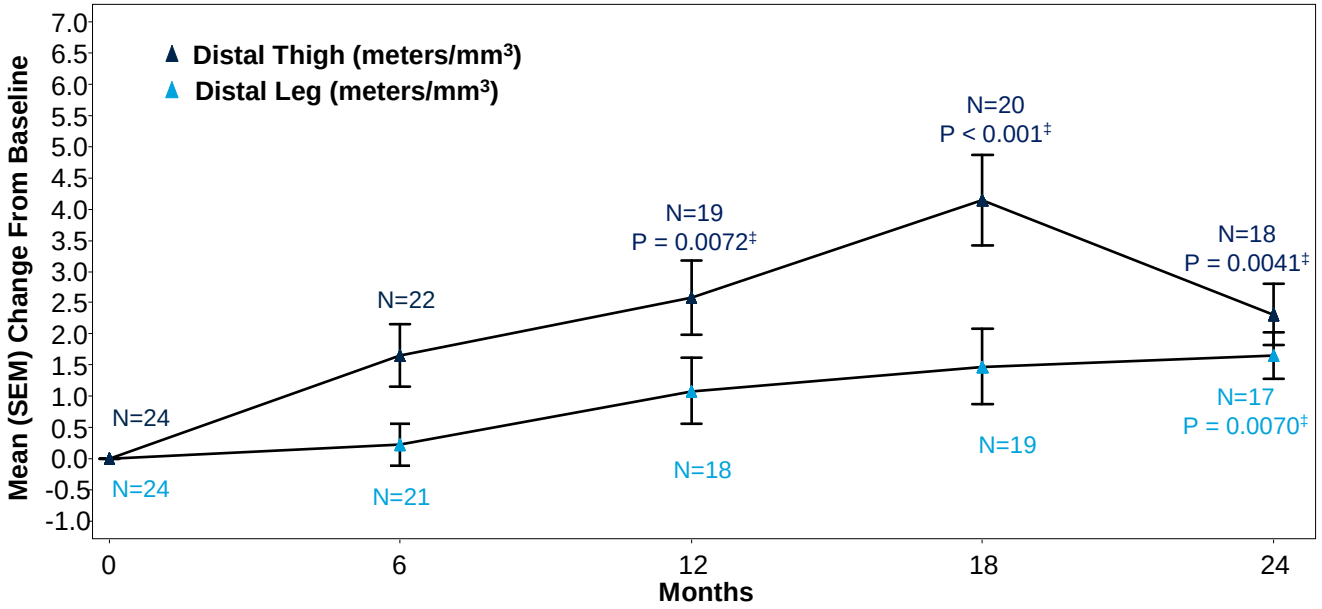
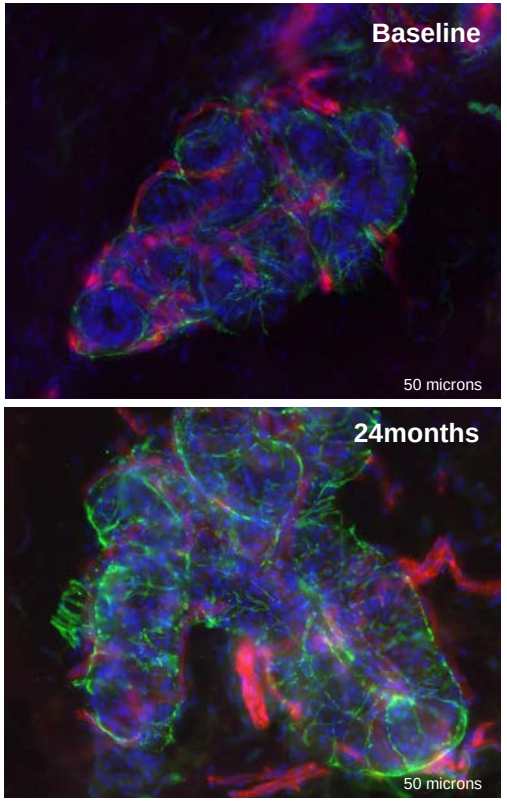
Sweat Gland Nerve Fiber Density (SGNFD): Lower Limb



Distal thigh sweat gland innervation† in Patient 010-0004



†Green: PGP 9.5 (nerve fibers)
Red: CD31 (blood vessels)
Blue: DAPI (nuclei)

- Blinded analysis of tandem skin punch biopsies performed at central lab
- Statistically significant increase in distal thigh SGNFD at 12, 18, and 24 months and distal leg SGNFD at 24 months
- In a separate study in hATTR-PN patients with the highly pathogenic A97S mutation,[1] SGNFD correlated to autonomic system involvement and disability burden

SEM: Standard Error of the Mean
[1]Chao C et al., Ann Neurol. 78:272-83 (2015)
‡2-sided p values from paired t-test comparing post-baseline vs baseline
*Data as of 12May2016

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Patisiran Phase 2 OLE Preliminary Study Results*
Summary

Patisiran generally well tolerated in patients with hATTR-PN out to 25 months

- 931 doses administered to date, median of 35 doses/pt, mean treatment duration of 24 months
- No drug-related SAEs and majority of AEs were mild or moderate
- Most common related AEs were flushing (22.2%) and IRRs (18.5%), all of which were mild in severity

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

Preliminary evidence of improvement in neuropathy impairment score 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
- Compares favorably to an estimated mean 26-30 point increase in mNIS+7 at 24 months based upon analyses of historical data sets in untreated hATTR-PN patients with similar baseline neuropathy impairment
- Similar results in patients with or without concurrent tetramer stabilizers
- Statistically significant improvement in sweat gland nerve fiber density in thigh and leg

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

*Data as of 12May2016

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Study Investigators

- **David Adams**
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Thank You!

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