Leo
Living with hATTR Amyloidosis

Phase 2 Open-Label Extension (OLE) Study of Patisiran, an Investigational RNAi Therapeutic for the Treatment of Polyneuropathy due to Hereditary ATTR (hATTR) Amyloidosis: Final 24-month data

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Hereditary ATTR (hATTR) Amyloidosis

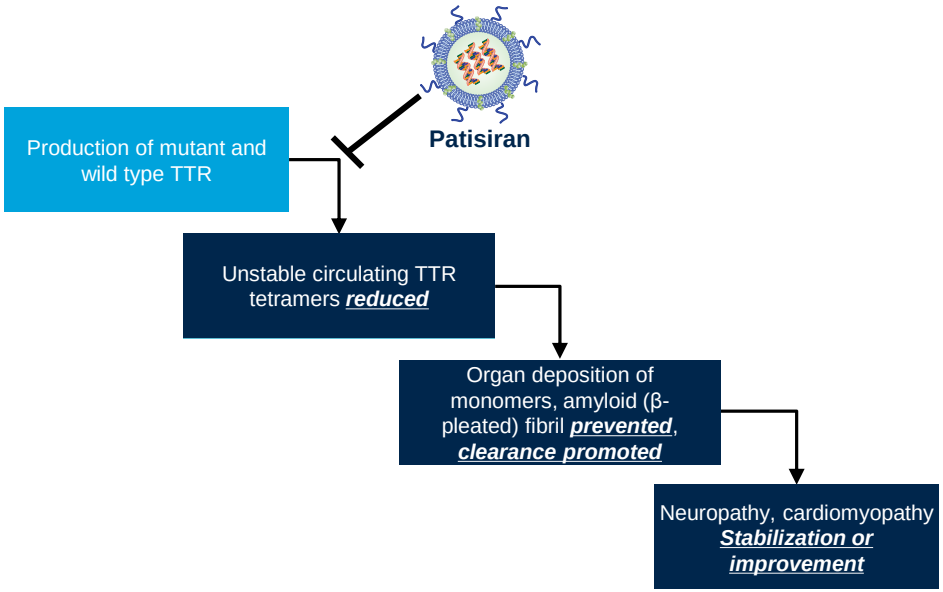
- Inherited, rapidly progressive, life-threatening disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]
  - Median survival 2-15 years[1-3]
- Multi-systemic disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms[2,6,7]
  - Disease continuum includes patients who present with predominantly polyneuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms
  - 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 EU for Stage 1 hATTR amyloidosis[8] and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[9]
- Continued high unmet medical need for novel therapeutics

1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57. 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540. 3. Adams D et al. Neurology. 2015;85(8):675-682. 4. Damy T et al. J Cardiovasc Transl Res. 2015;8(2):117-127. 5. Hawkins PN et al. Ann Med. 2015;47(8):625-638. 6. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9. 7. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748 8. Coelho T et al. Neurology. 2012;79:785-92. 9. Berk JL et al. JAMA. 2013;310:2658-67.

Patisiran: Investigational RNAi Therapeutic for Polyneuropathy due to hATTR Amyloidosis

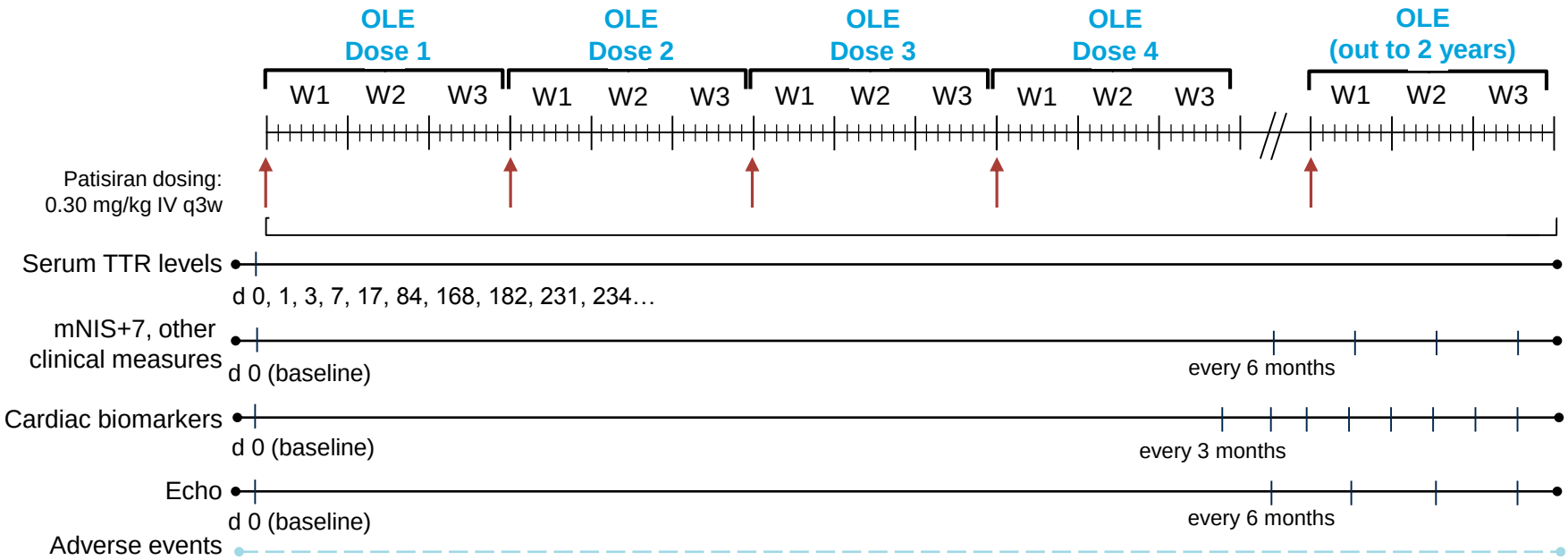
- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR
- Administered by IV infusion
- Phase 1: positive results in human volunteers[1]
- Phase 2: positive multi-dose results in patients with hATTR amyloidosis[2]
- Phase 2 Open-Label Extension (OLE): study in patients with hATTR amyloidosis completed[3]
  - Final results within this presentation
- Phase 3, APOLLO: study enrollment complete; trial ongoing[4]
- APOLLO-OLE: ongoing[5]
- Expanded Access Protocol (EAP): available in the United States[6]

Patisiran Therapeutic Hypothesis



1. Coelho T et al. N Engl J Med. 2013;369:819-29. 2. Suhr OB, et al. Orphanet J Rare Dis. 2015;10:109.
3. Clinicaltrials.gov: NCT01961921. 4. Clinicaltrials.gov: NCT01960348. 5. Clinicaltrials.gov: NCT02510261.
6. Clinicaltrials.gov: NCT02939820.

Patisiran Phase 2 OLE Study Design



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

- Up to 2 years of dosing, 0.3 mg/kg every 3 weeks; 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), QoL, 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
Clinicaltrials.gov: NCT01961921

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Patisiran Phase 2 OLE Final Study Results

Demographics and Exposure

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: 15 • II: 9 • IIIa: 2 • 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	935
Median doses/patient to date	35 (range 27 - 36)
Mean treatment duration	24.7 months (range 19- 25)

† 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

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Patisiran Phase 2 OLE Final Study Results

Baseline Characteristics

Characteristic	N	Mean	(range)
mNIS+7[a] (max impairment: 304)	27	53.0	(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	1030.5	(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 - 2070)
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

Patisiran Phase 2 OLE Final Study Results

Summary of Safety and Tolerability

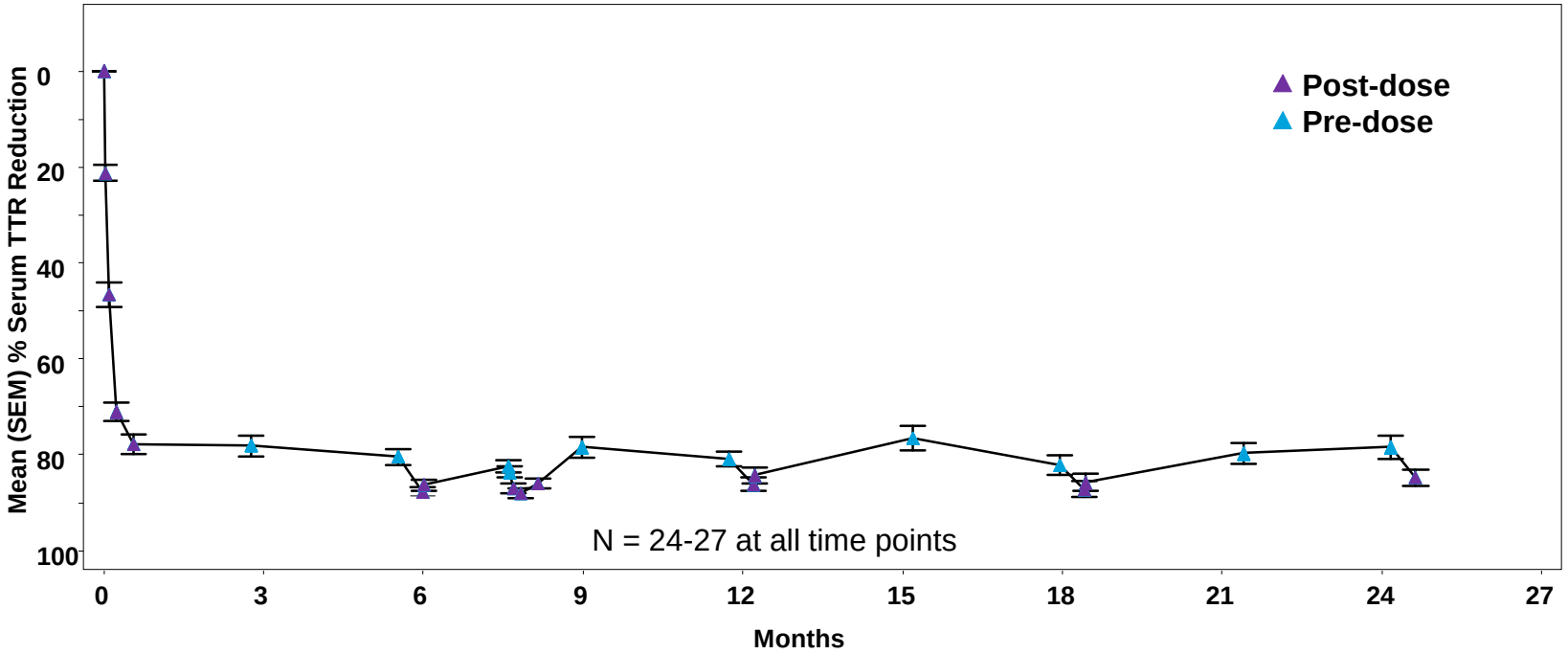
Adverse Events (AE) reported in ≥10% of patients

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

- 7 patients (25.9%) with 10 reports of serious adverse events (SAE); 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
  - One patient with pacemaker implantation due to amyloid cardiomyopathy
- Majority of AEs were mild or moderate
  - 5 patients (18.5%) had severe AEs not related to study drug
  - Related AEs reported in ≥4 patients were infusion related reaction (22.2%) and flushing (22.2%), all of which were mild
- No clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelets

Patisiran Phase 2 OLE Final Study Results

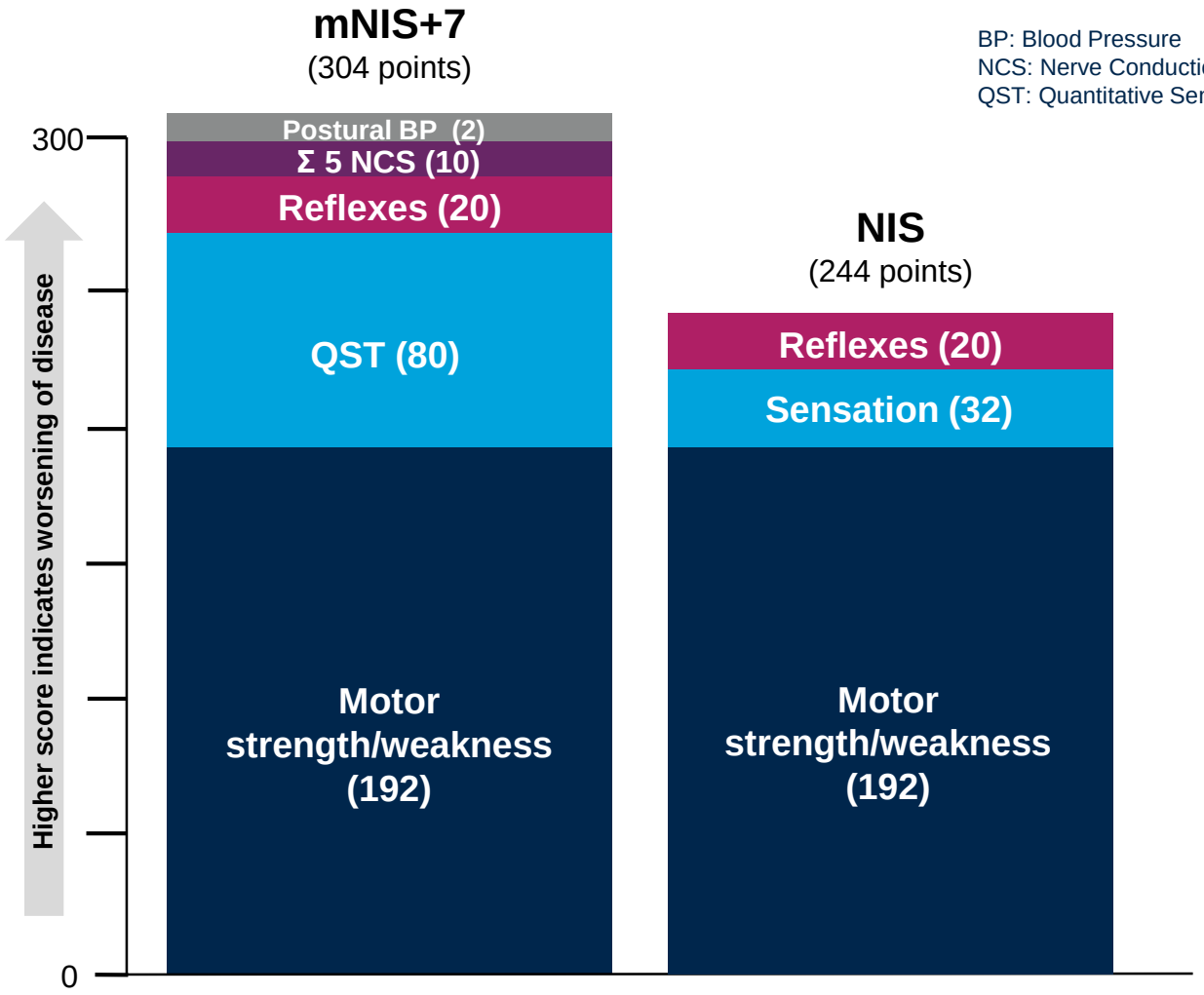
Serum TTR Knockdown



- Mean serum TTR knockdown: 82%
- Mean maximal serum TTR knockdown: 93%
- Maximal individual patient post-dose knockdown: 97%
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

SEM: Standard Error of the Mean

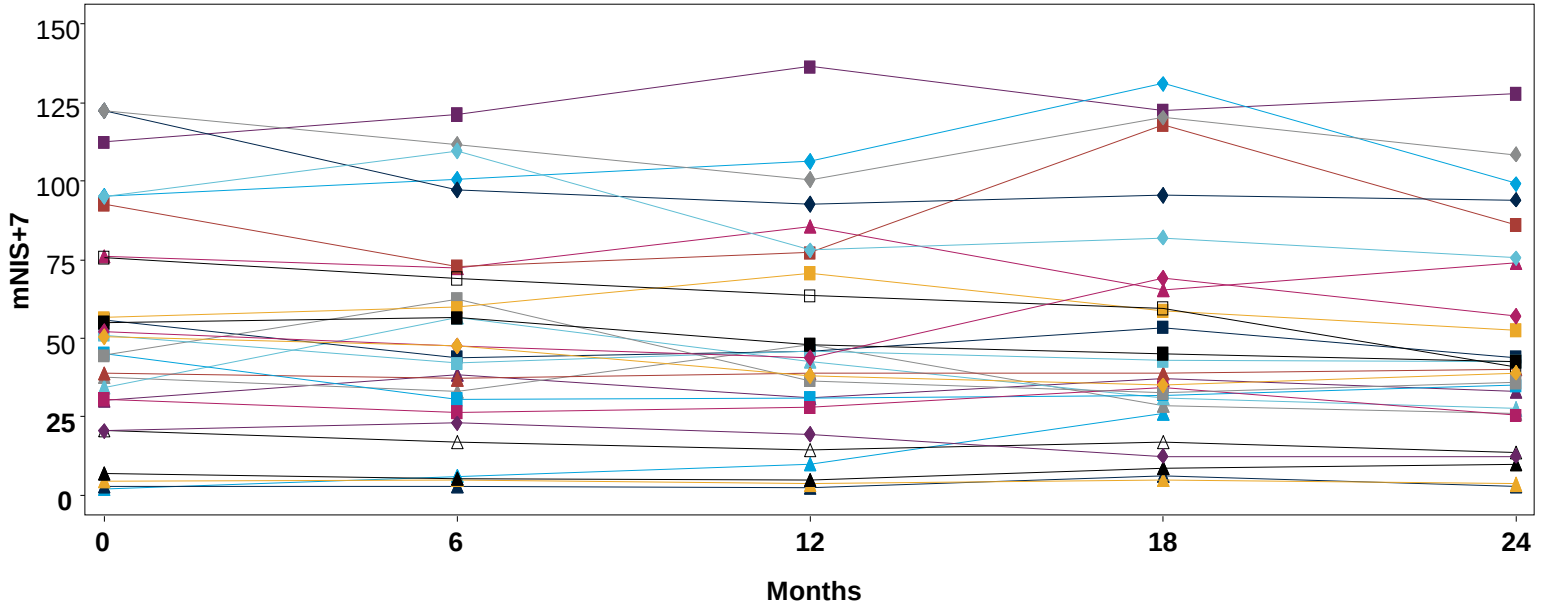
Neuropathy Impairment Scores Used in hATTR Amyloidosis Trials



Adams D et al. Neurology. 2015;85;675-682.

Patisiran Phase 2 OLE Final Study Results

Change in mNIS+7 Over 24 Months

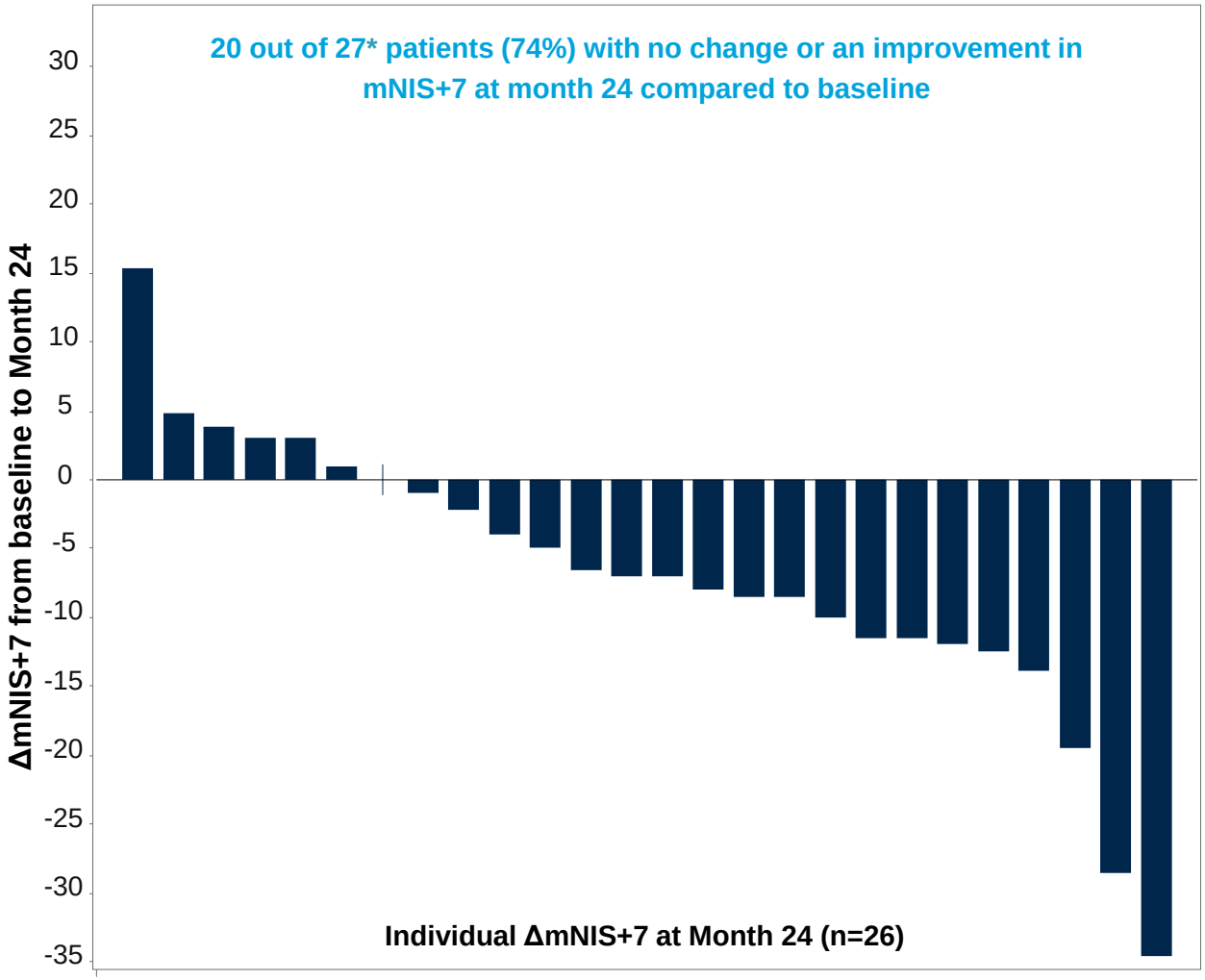


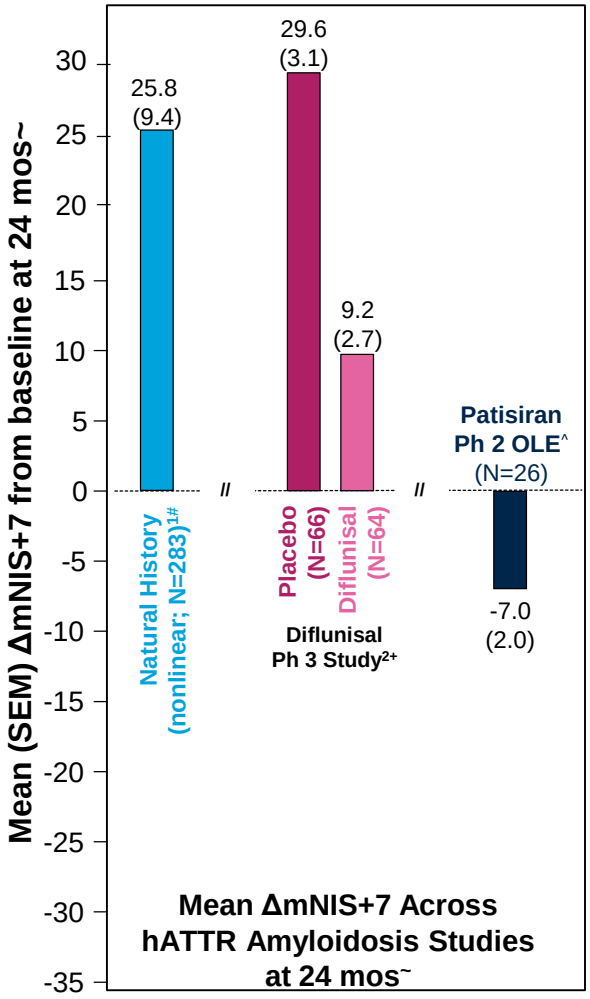
mNIS+7 component	Change from Baseline to Month 24 (N=26)	
	Mean (SEM)	Median (range)
Total+	**-7.0 (2.0)**	**-7.0 (-34.6, 15.4)**
NIS-weakness	1.2 (1.4)	0 (-13.5, 24.4)
NIS-reflexes	-0.5 (0.5)	0 (-6.0, 7.0)
QST	-7.4 (2.0)	-6.0 (-40.0, 16.0)
NCS Σ5	-0.2 (0.2)	-0.3 (-2.0, 2.5)
Postural BP	-0.1 (0.1)	0 (-1.0, 0.5)

SEM: Standard Error of the Mean
+Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)

Patisiran Phase 2 OLE Final Study Results

Change in mNIS+7 at 24 Months



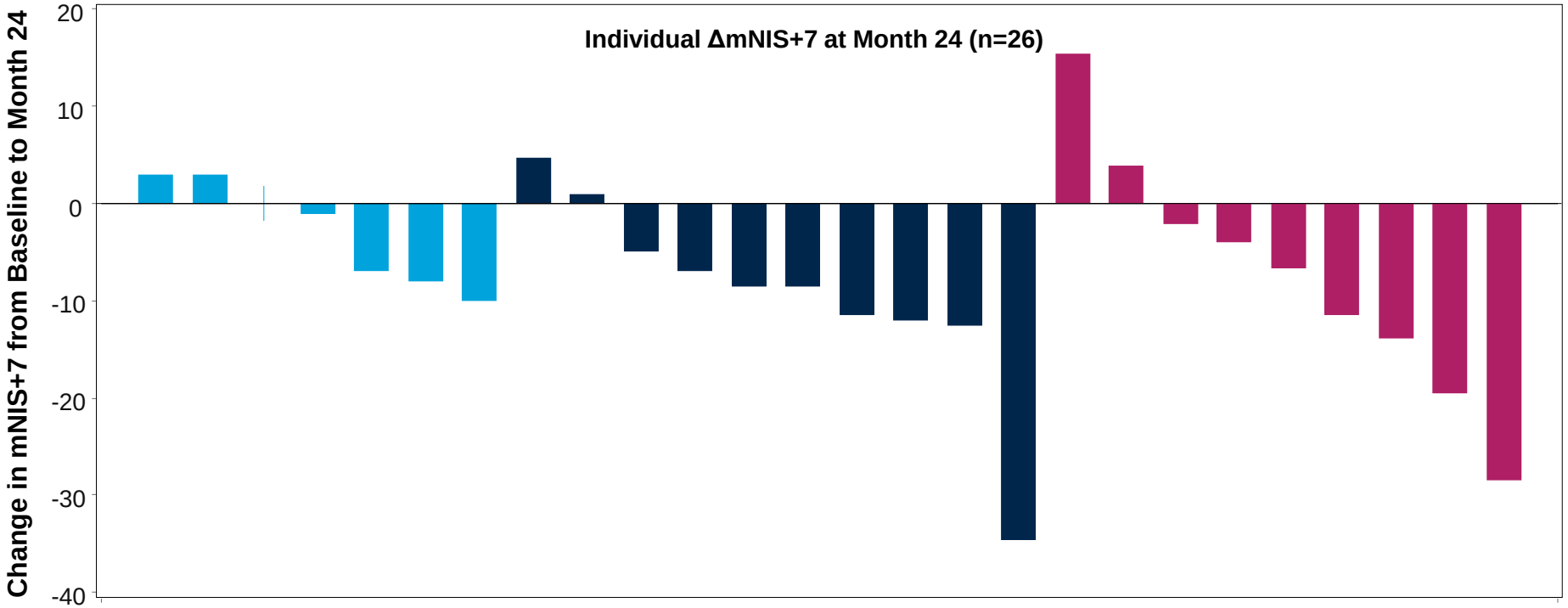


SEM: Standard Error of the Mean; *One patient discontinued prior to the Month 24 assessment and is included in the denominator
~Assessments drawn from studies in patients with similar baseline neurologic impairment and not based on head-to-head studies
#Predicted progression of median NIS value from Gompertz curve fit[1]
+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)

1. Adams D et al. Neurology. 2015;85;675-682. 2. Berk JL et al. JAMA. 2013;310:2658-67.

Patisiran Phase 2 OLE Final Study Results

Change in mNIS+7 at 24 Months by Baseline NIS Tertile



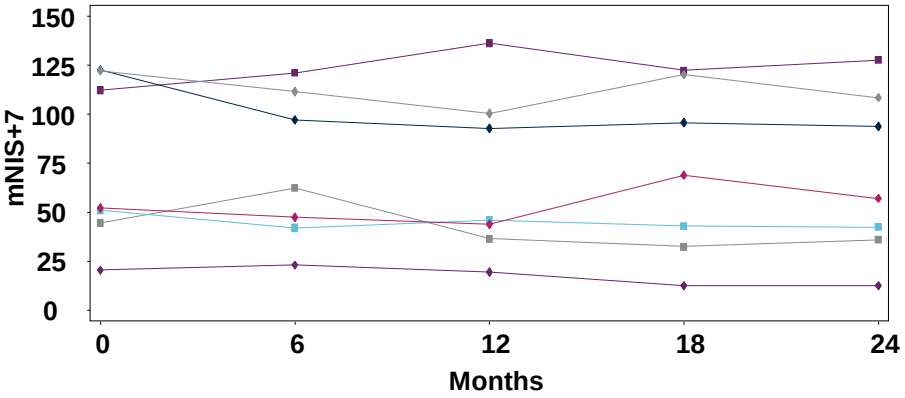
Baseline NIS Tertiles	N	Baseline NIS Range	Mean (SEM) ΔmNIS+7 from Baseline to Month 24
First Tertile	7	4-13	-2.9 (2.0)
Second Tertile	10	16-42	-9.4 (3.3)
Third Tertile	9	46-93	-7.4 (4.3)

SEM: Standard Error of the Mean

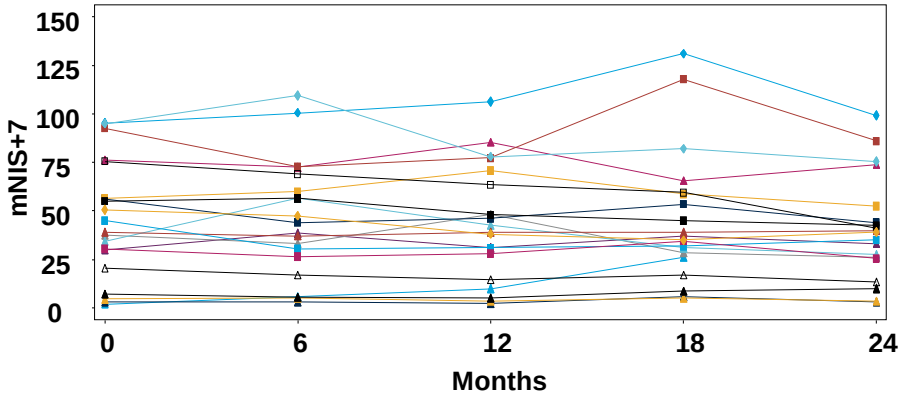
Patisiran Phase 2 OLE Final Study Results

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=7)	Patisiran + Stabilizer (n=19)*
Mean Change (SEM)	-6.8 (5.2)	-7.0 (2.1)
Median Change (range)	-8.5 (-28.5, 15.4)	-6.6 (-34.6, 3.9)

SEM: Standard Error of the Mean
Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)

*Defined as TTR stabilizer use at study entry

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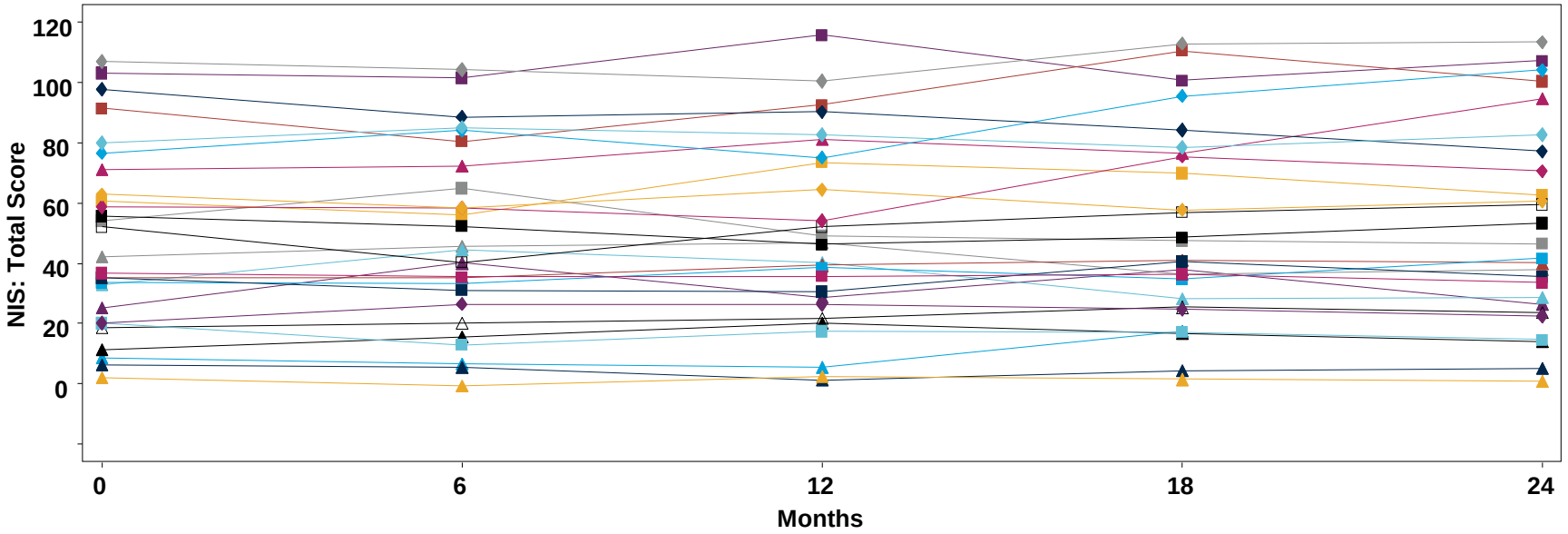
Change in NIS Over 24 Months



NIS component	Change from Baseline to Month 24 (N=26)	
	Mean (SEM)	Median (range)
Total	**1.9 (1.8)**	**1.5 (-16.0, 27.9)**
NIS-weakness	1.2 (1.4)	0 (-13.5, 24.4)
NIS-reflexes	-0.5 (0.5)	0 (-6.0, 7.0)
NIS-sensation	1.2 (0.8)	1.5 (-8.0, 7.0)

SEM: Standard Error of the Mean

Patisiran Phase 2 OLE Final Study Results

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)	21	0.03 (0.04)
Hand Grip Strength (kg)	27	25.8 (2.3)	26	1.5 (1.2)
mBMI (kg/m^2 x albumin [g/dL])	27	1030.5 (32.5)	22	-60.8 (34.9)
EQ-5D (max. impairment: 0)	27	0.8 (0.03)	26	-0.01 (0.02)
R-ODS (no limitations: 48)	26	38.1 (1.7)	25	-1.8 (0.8)
COMPASS-31 (max. impairment: 100)	27	15.9 (2.6)	26	1.3 (1.8)
Orthostatic Intolerance	27	4.9 (1.5)	26	1.1 (1.7)
Vasomotor	27	0.7 (0.2)	26	-0.4 (0.3)
Secretomotor	27	2.7 (0.6)	26	0.4 (0.5)
Gastrointestinal	27	5.8 (0.8)	26	-0.1 (0.5)
Bladder	27	1.0 (0.3)	26	0.2 (0.4)
Pupillomotor	27	0.8 (0.2)	26	0.2 (0.2)
IENFD (fibers/mm)				
Location: Leg	24	3.5 (1.3)	19	-0.1 (0.4)
Location: Thigh	24	10.2 (2.0)	20	-1.8 (0.6)
SGNFD (m/mm^3)				
Location: Leg	24	3.8 (0.7)	19	1.7 (0.5)
Location: Thigh	24	6.8 (0.7)	20	2.1 (0.6)
Cardiac Subgroup, N=11				
NT-proBNP (ng/L)[#]	9	809.8 (246.7)	8	-49.6 (170.8)
Troponin I (ng/mL)[#]	8	0.1 (0.1)	8	-0.1 (0.1)
LV Mass (g)	11	278.1 (23.2)	10	-16.7 (11.7)
LV wall thickness (cm)	11	1.6 (0.1)	10	-0.08 (0.1)
Ejection fraction (%)	11	62.5 (2.6)	10	0.6 (1.4)
Peak longitudinal strain (%)	11	-16.6 (1.3)	10	0.9 (0.9)
10-Meter Walk (m/sec)	7	1.0 (0.1)	7	0.03 (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
SEM: Standard Error of the Mean; IENFD: Intraepidermal nerve fiber density; SGNFD: Sweat gland nerve fiber density

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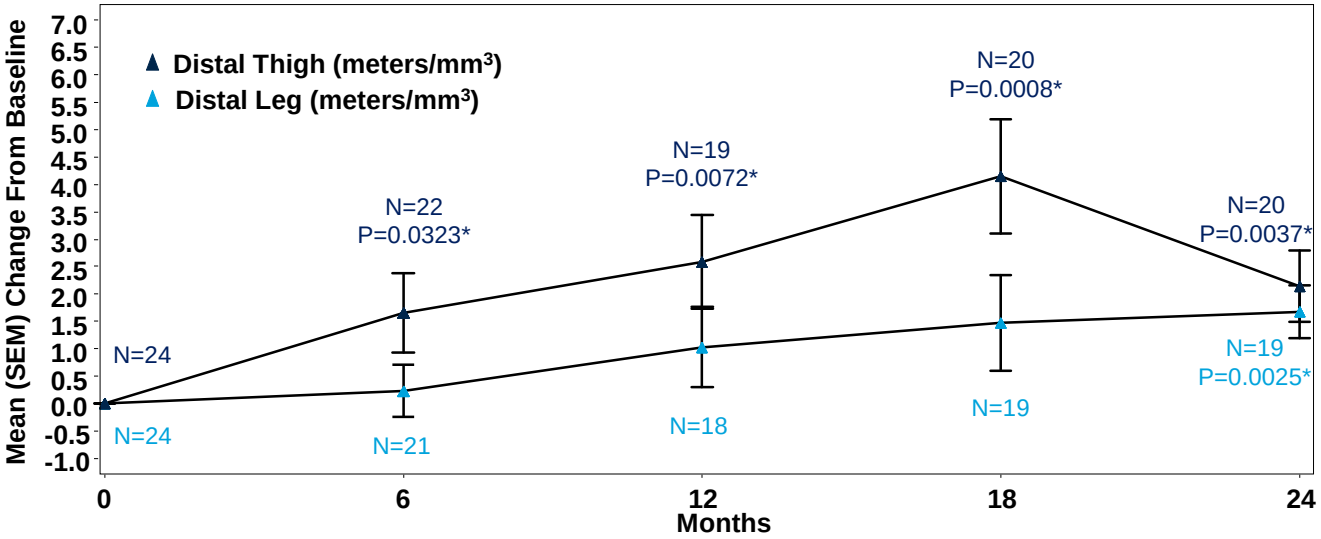
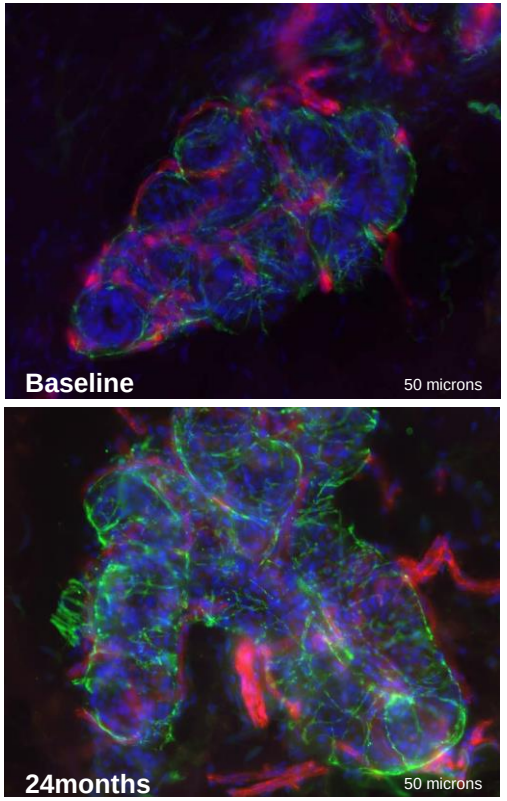
Patisiran Phase 2 OLE Final Study Results

Sweat Gland Nerve Fiber Density (SGNFD): Lower Limb



- Blinded analysis of tandem skin punch biopsies performed at central lab; statistical significance testing performed post-hoc
  - Statistically significant increase in distal thigh SGNFD at 6, 12, 18, and 24 months and in distal leg SGNFD at 24 months
- In separate study in hATTR amyloidosis patients with highly pathogenic A97S mutation,[1] SGNFD correlated to autonomic system involvement and disability burden

Distal thigh sweat gland innervation† in Patient 010-0004



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

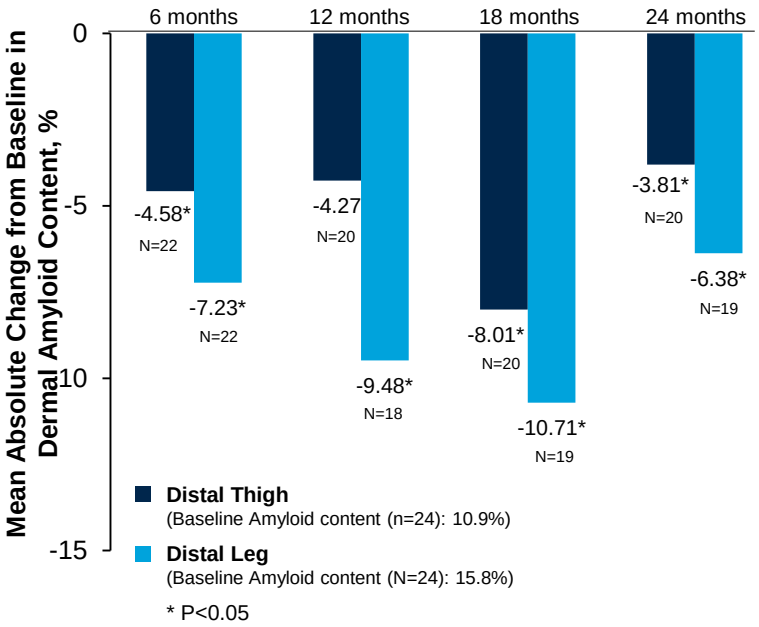
SEM: Standard Error of the Mean
[1]Chao C et al. Ann Neurol. 2015;78:272-83.
*2-sided p-values from paired t-test comparing post-baseline vs baseline

Patisiran Phase 2 OLE Final Study Results

TTR Amyloid Content in Skin: Lower Limb

- Blinded analysis of tandem skin punch biopsies performed at central lab; statistical significance testing performed post-hoc
- Dermal amyloid content in both distal thigh and distal leg decreased over time relative to baseline
  - Statistically significant decrease in absolute change for distal thigh at 6, 18 and 24 months and at all time points for distal leg

Mean Absolute Change from Baseline in Dermal Amyloid Content



* P<0.05

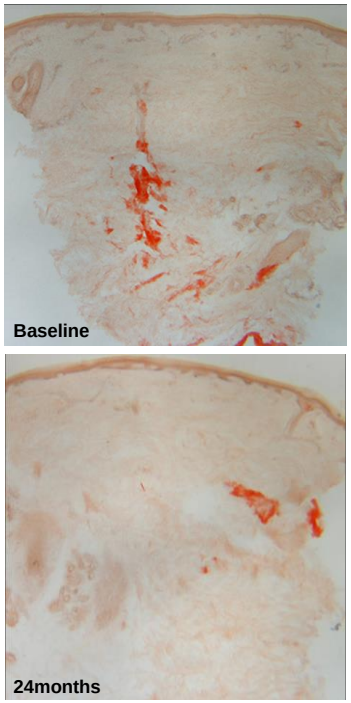
Median Relative Change from Baseline in Dermal Amyloid Content

Distal Thigh	N	Median Relative Percent Change (IQR)
6 months	22	-52.5 (-75.7, 0)
12 months†	19	-61.8 (-87.5, 0)
18 months	20	-78.2 (-89.7, -8.3)
24 months†	19	-23.8 (-78.3, 0)

Distal Leg	N	Median Relative Percent Change (IQR)
6 months	22	-48.5 (-74.3, 0)
12 months	18	-64.6 (-85.8, 0)
18 months†	18	-67.5 (-91.3, -10)
24 months†	18	-40.4 (-78.3, -21.6)

IQR, Interquartile Range; †1 patient excluded due to baseline value of 0 and a non-zero post-baseline value

Distal thigh dermal amyloid content‡ in Patient 050-0003



‡Red: Amyloid by Congo red staining

Patisiran Phase 2 OLE Final Study Results

Summary

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

- 935 doses administered, median of 35 doses/patient, mean treatment duration of 25 months
- No drug-related SAEs and majority of AEs were mild or moderate
- Drug-related AEs reported in ≥4 patients were infusion related reaction (22.2%) and flushing (22.2%), all of which were mild

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

Long-term patisiran administration resulted in improvement in neuropathy impairment score with mean 7.0-point decrease in mNIS+7 at 24 months

- Improvement or no change in mNIS+7 observed in 20 of 27 (74%) patients
- Compares favorably to expected mean 26-30 point increase in mNIS+7 at 24 months estimated from analyses of separate historical data sets in untreated hATTR patients with similar baseline neuropathy impairment
- Similar effect in patients across full range of neuropathy severity at baseline
- Similar results in patients with or without concurrent tetramer stabilizers

In exploratory analyses, observed an increase in sweat gland nerve fiber density and a decrease in dermal amyloid content in the distal thigh and leg relative to baseline

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

All eligible patients have enrolled into the APOLLO-OLE study and will continue to receive patisiran dosing

- As of April 2017, 20 patients have received ≥ 36 months of patisiran dosing; plan to present data in late 2017

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Study Investigators

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Thank You!