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

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

20 April 2016

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Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN) Background

- 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 FAP[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)

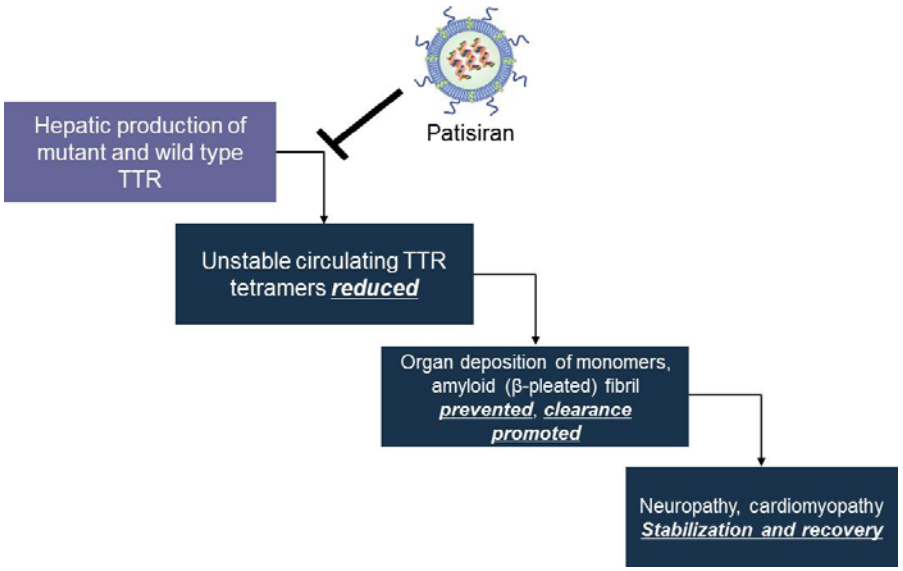
Patisiran

Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

Patisiran in clinical development

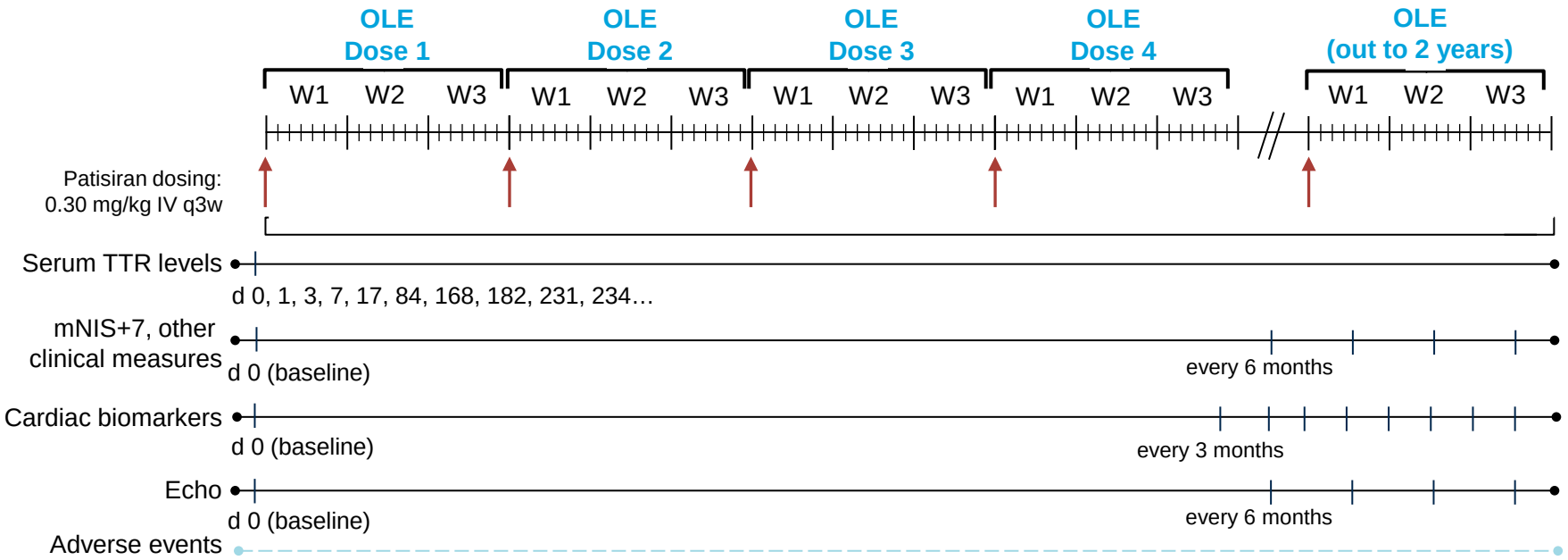
- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR
- Administered by IV infusion
- Positive Phase 1 results in human volunteers
  - Data published in New Engl J Med[1]
- 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
- APOLLO Phase 3 trial: enrollment complete, trial ongoing
- APOLLO-OLE ongoing

Patisiran Therapeutic Hypothesis



[1]Coelho et al., N Engl J Med;369:819-29 (2013)
[2]Suhr 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 complete 18 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	909
Median doses/patient to date	35 (range 27-36)
Mean treatment duration	23.5 months (range 18.8-24.7)

†6 subjects 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 February 23, 2016

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Patisiran Phase 2 OLE Preliminary Study Results*

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/L])	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	15.6	(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	(0.02-0.7)
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 subject 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 February 23, 2016*

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Patisiran Phase 2 OLE Preliminary Study Results*
Summary of Safety

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%)
Infusion related reaction	5 (18.5%)
Nausea	5 (18.5%)
Vomiting	5 (18.5%)
Wound	5 (18.5%)
Insomnia	4 (14.8%)
Neuralgia	4 (14.8%)
Urinary tract infection	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%)

- 5 patients (18.5%) with 8 reports of serious adverse events (SAEs); not related to study drug
  - One discontinuation for gastroesophageal cancer at ~20 months; patient subsequently died Aug 2015
  - 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
  - 3 patients (11.1%) had severe events 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

NOTE: Post data cut-off, a 79 year old patient who completed 24 months of treatment had a SAE of myocardial infarction (not related to study drug) resulting in death (March 2016)

Data as of February 23, 2016

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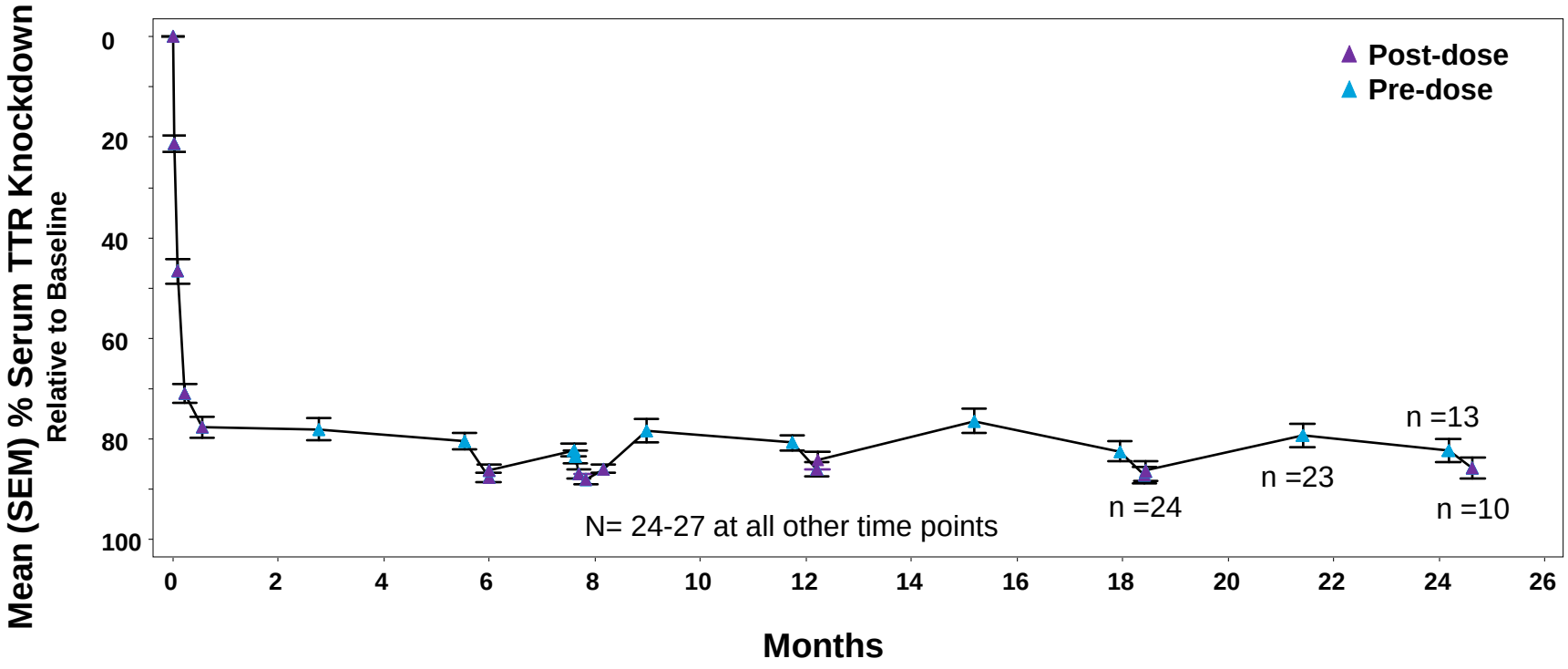
Patisiran Phase 2 OLE Preliminary Study Results*

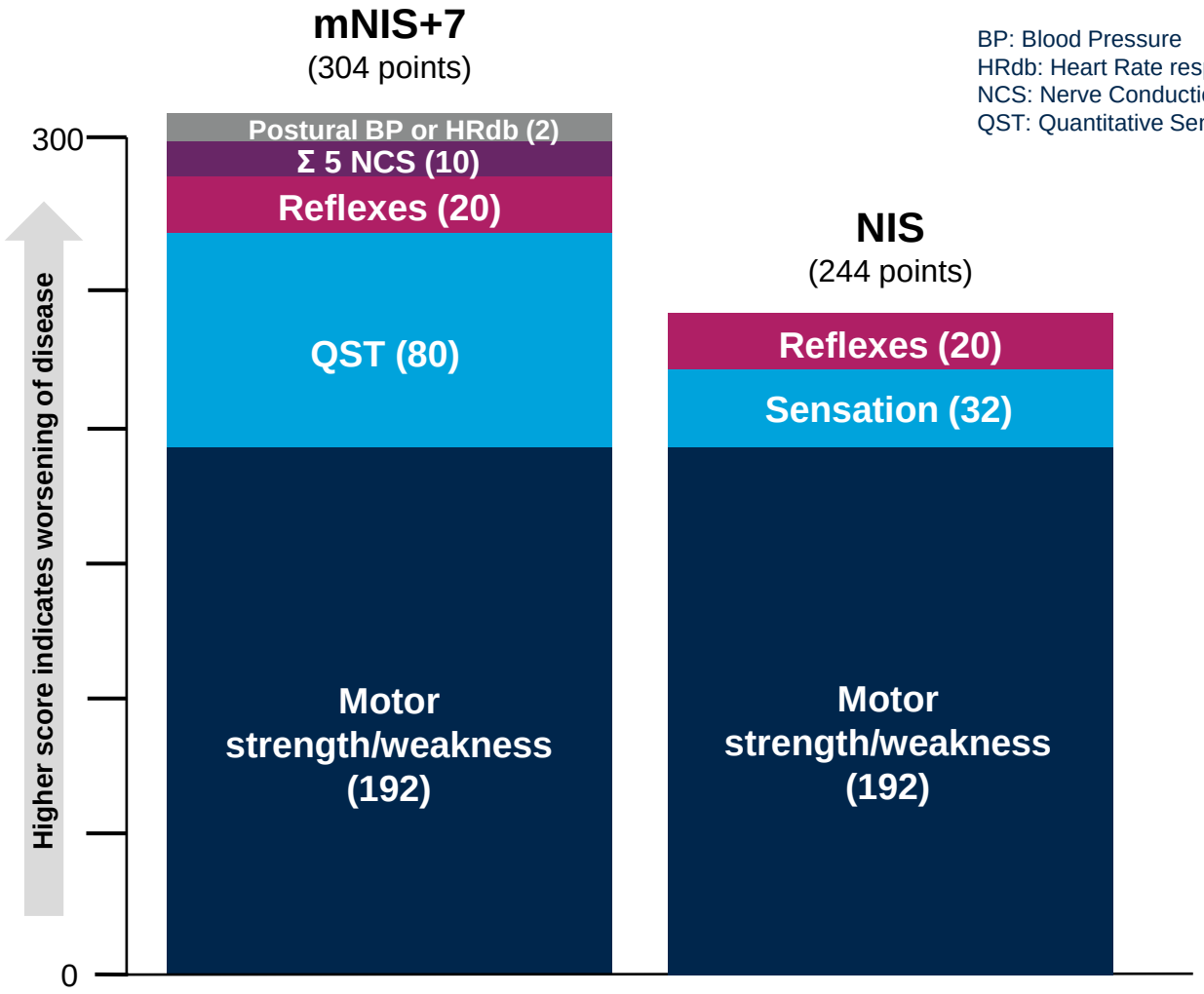
Serum TTR Knockdown



- Mean serum pre-dose TTR knockdown of approximately 80%
- Mean maximal serum post-dose TTR knockdown of 92%
- Maximal individual patient post-dose knockdown of 97%
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

*Data as of February 23, 2016

Neuropathy Impairment Scores Used in hATTR-PN Trials

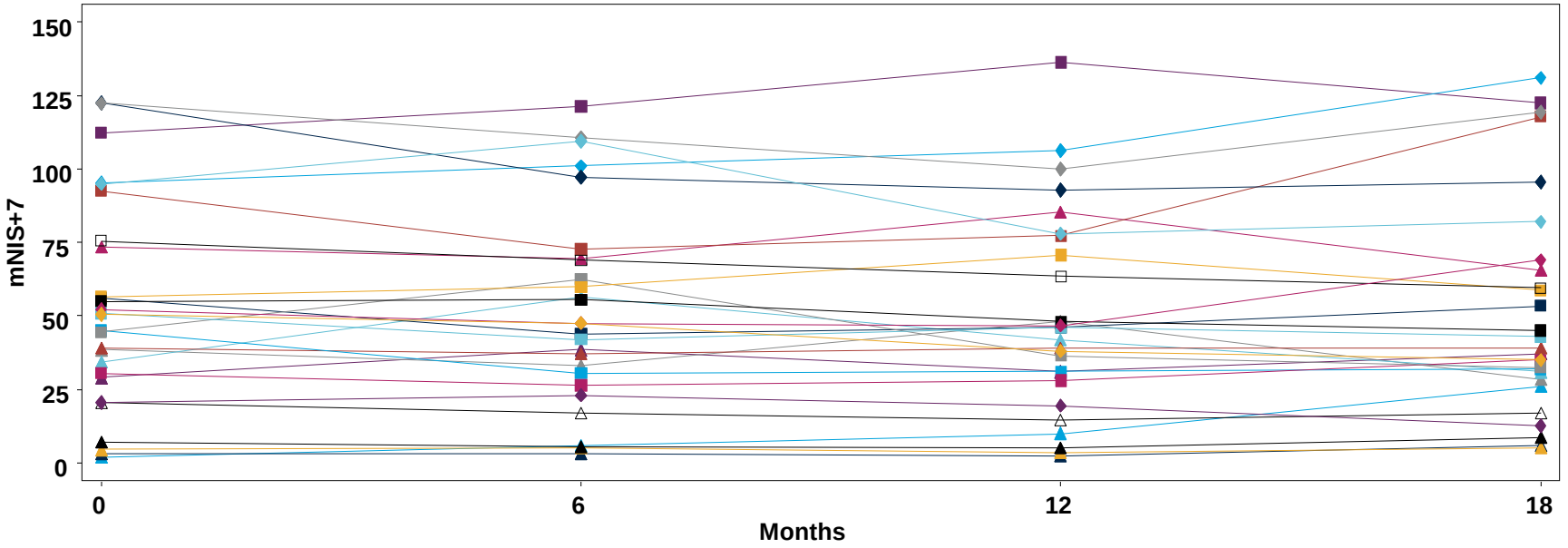


BP: Blood Pressure
HRdb: Heart Rate response to Deep Breathing
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

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

Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 Over 18 Months



	Change from Baseline to Month 18 (N=27)	
mNIS+7 component	**Mean (SEM)**	**Median (range)**
Total⁺	**-0.8 (2.7)**	**-3.1 (-26.9, 35.8)**
NIS-weakness	0.7 (1.2)	0 (-8.0, 18.3)
NIS-reflexes	0.7 (0.7)	0 (-6.0, 10.0)
QST	-2.2 (2.1)	-3 (-24.0, 21.0)
NCS Σ5	0.1 (0.2)	0 (-1.5, 2.5)
Postural BP	0 (0.1)	0 (-1.5, 1.0)

⁺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 February 23, 2016

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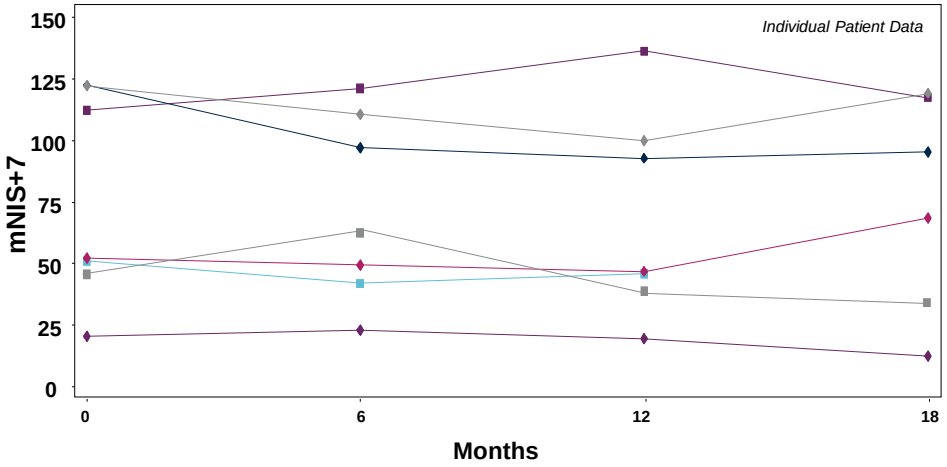
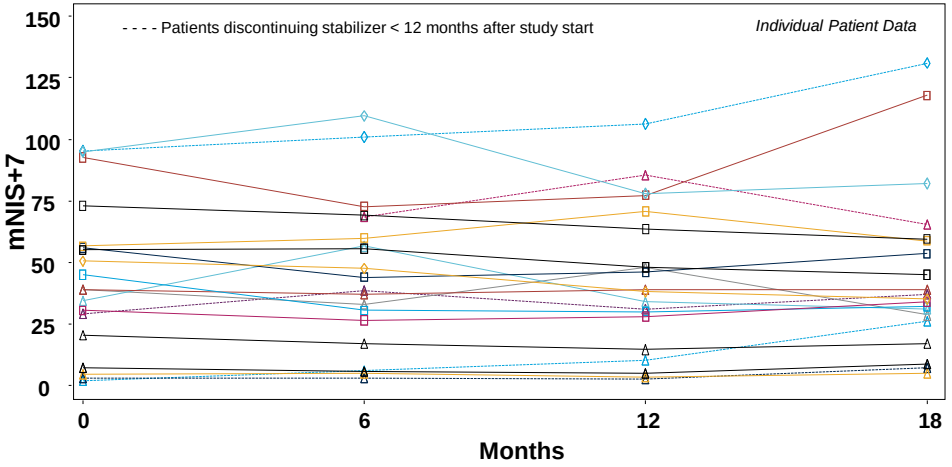
Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 Over 18 Months By Stabilizer Use

Patisiran Alone



Patisiran + Stabilizer



mNIS+7	Change from Baseline to Month 18	
	Patisiran Alone (n=7)	Patisiran + Stabilizer (n=20)
Mean Change (SEM)	-4.5 (5.5)	0.5 (3.1)
Median Change (range)	-8.0 (-26.9, 16.8)	-1.3 (-16.1, 35.8)

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

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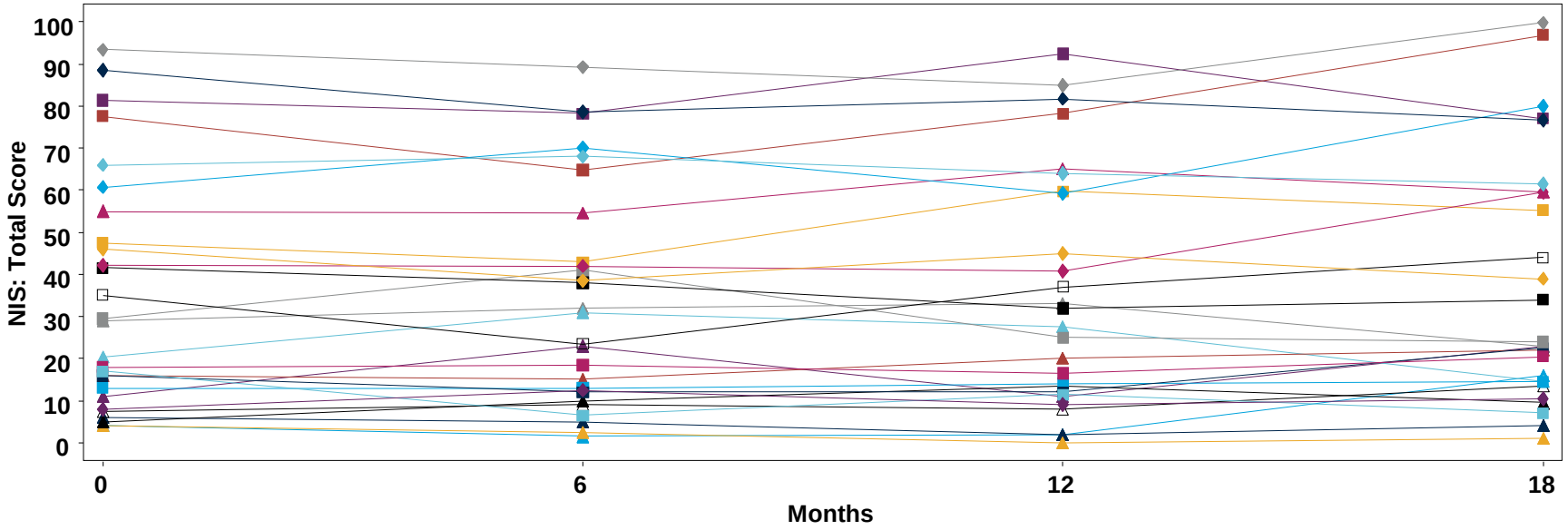
Patisiran Phase 2 OLE Preliminary Study Results*

Change in NIS Over 18 Months



	Change from Baseline to Month 18 (N=27)	
NIS component	**Mean (SEM)**	**Median (range)**
Total	**2.6 (1.7)**	**2.5 (-11.9, 19.3)**
NIS-weakness	0.7 (1.2)	0 (-8.0, 18.3)
NIS-reflexes	0.7 (0.7)	0 (-6.0, 10.0)
NIS-sensation	1.2 (0.9)	1.5 (-8.0, 10.0)

*Data as of February 23, 2016

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Patisiran Phase 2 OLE Preliminary Study Results*
ΔNIS and ΔmNIS+7 Across hATTR-PN Studies~

		Natural History (nonlinear)[#1]	Diflunisal Phase 3[+2]	Patisiran Phase 2 OLE[†*]
18 Months	ΔmNIS+7^ Mean (SEM)	22.9 (9.4)	PBO: 21.8 (2.2) Drug: 8.1 (1.9)	**-0.8 (2.7)**
	ΔNIS Mean (SEM)	18.4 (7.6)	PBO: 16.6 (3.2) Drug: 5.3 (2.9)	**2.6 (1.7)**

~ Assessments drawn from studies in patients with similar baseline neurologic impairment and not based on head-to-head studies
^ Translated algebraically from NIS (Natural History study) or NIS+7 (Diflunisal study)[1]
[#] Predicted progression of median NIS value from Gompertz curve fit[1]
[+] Linear interpolation from 2-year NIS progression measurement in longitudinal analysis set
[†] N=27 @ 18 months; 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)

SEM: Standard Error of the Mean

[1]Adams D et al., *Neurology. 85;675-682* (2015)
[2]Berk JL *et al., JAMA.* 310:2658-67 (2013)

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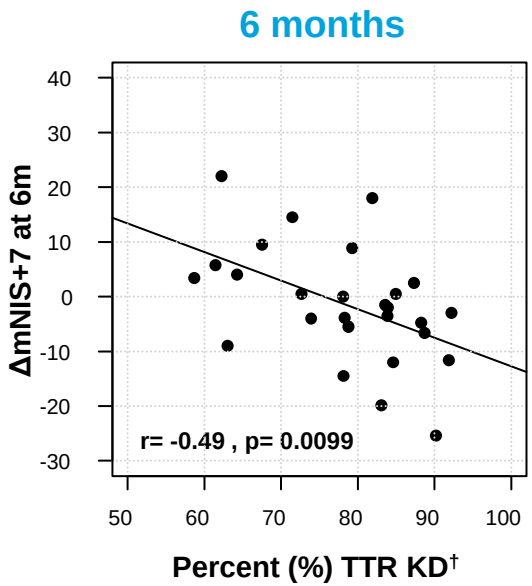
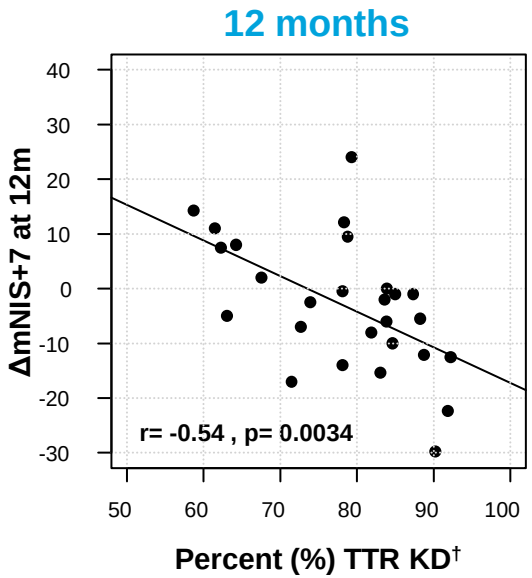
Correlation of TTR Knockdown (KD) with ΔmNIS+7
Background and Methods

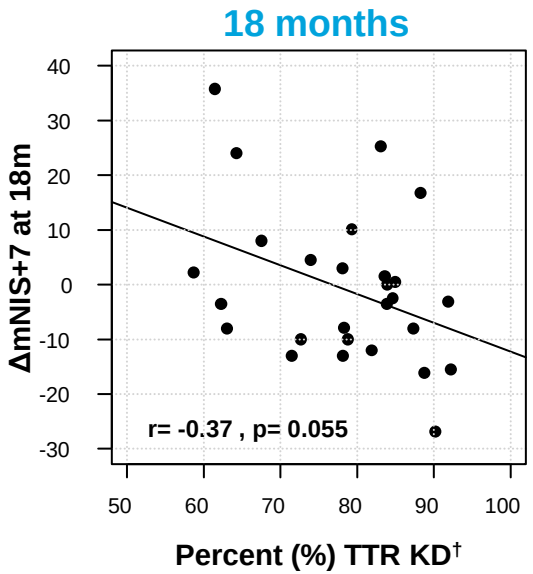
- Patisiran therapeutic hypothesis: TTR KD will result in clinical benefit in hATTR-PN
- Inter-patient variability in degree of TTR KD provides opportunity to examine relationship of TTR KD to change in neuropathy progression as measured by mNIS+7
  - Analysis of correlation between TTR knockdown and mNIS+7 change also permits assessment of patisiran treatment effect independent of concurrent TTR tetramer stabilizer use
- 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 and 18 months
  - Use of Day 17 %TTR KD level reduces impact of missed doses or missed TTR assessments over 18 months of dosing
  - Day 17 %TTR KD correlates with TTR AUC and mean %TTR knockdown in Phase 2 OLE patients ($r > 0.85$, p value < 0.0001)

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

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Patisiran Phase 2 OLE Preliminary Study Results*

Changes in Other Clinical Assessments

Assessment	Baseline		Change from Baseline to Month 18	
	N	Mean (SEM)	N	Mean (SEM)
10-Meter Walk^ (m/sec)	22	1.1 (0.1)	21	0.1 (0)
Hand Grip Strength (kg)	27	25.8 (2.3)	27	1.4 (0.6)
mBMI (kg/m2 x albumin (g/L))	27	1031.6 (32.5)	25	-32.1 (31.4)
EQ-5D (max. impairment: 0)	27	0.8 (0)	27	0 (0)
R-ODS (no limitations: 48)	26	38.1 (1.7)	26	-0.9 (0.8)
COMPASS-31 (max. impairment: 100)	27	15.6 (2.6)	27	-2.2 (1.5)
Orthostatic Intolerance	27	4.9 (1.5)	27	-1.0 (1.4)
Vasomotor	27	0.7 (0.2)	27	-0.3 (0.2)
Secretomotor	27	2.5 (0.6)	27	-0.1 (0.4)
Gastrointestinal	27	5.8 (0.8)	27	-1.0 (0.6)
Bladder	27	1.0 (0.3)	27	0.2 (0.3)
Pupillomotor	27	0.8 (0.2)	27	0.1 (0.1)
IENFD (fibers/mm)				
Location: Leg	24	3.5 (1.3)	19	-1.2 (0.4)
Location: Thigh	24	10.2 (2.0)	20	0.7 (0.9)
SGNFD (m/mm^3)				
Location: Leg	24	3.9 (0.7)	19	1.5 (0.9)
Location: Thigh	24	6.5 (0.7)	20	4.6 (1.0)
Cardiac Subgroup, N=11				
NT-proBNP (ng/L)#	9	809.8 (246.7)	8	126.4 (274.7)
Troponin I (ng/mL)#	8	0.1 (0.1)	7	-0.1 (0.1)
LV Mass (g)	11	278.1 (23.2)	11	8.0 (6.0)
LV wall thickness (cm)	11	1.6 (0.1)	11	0.1 (0)
Ejection fraction (%)	11	62.5 (2.6)	11	1.6 (1.3)
Peak longitudinal strain (%)	11	-16.6 (1.3)	11	0.3 (0.9)
10-Meter Walk (m/sec)	7	1.0 (0.1)	7	0.1 (0.1)

^ One subject 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

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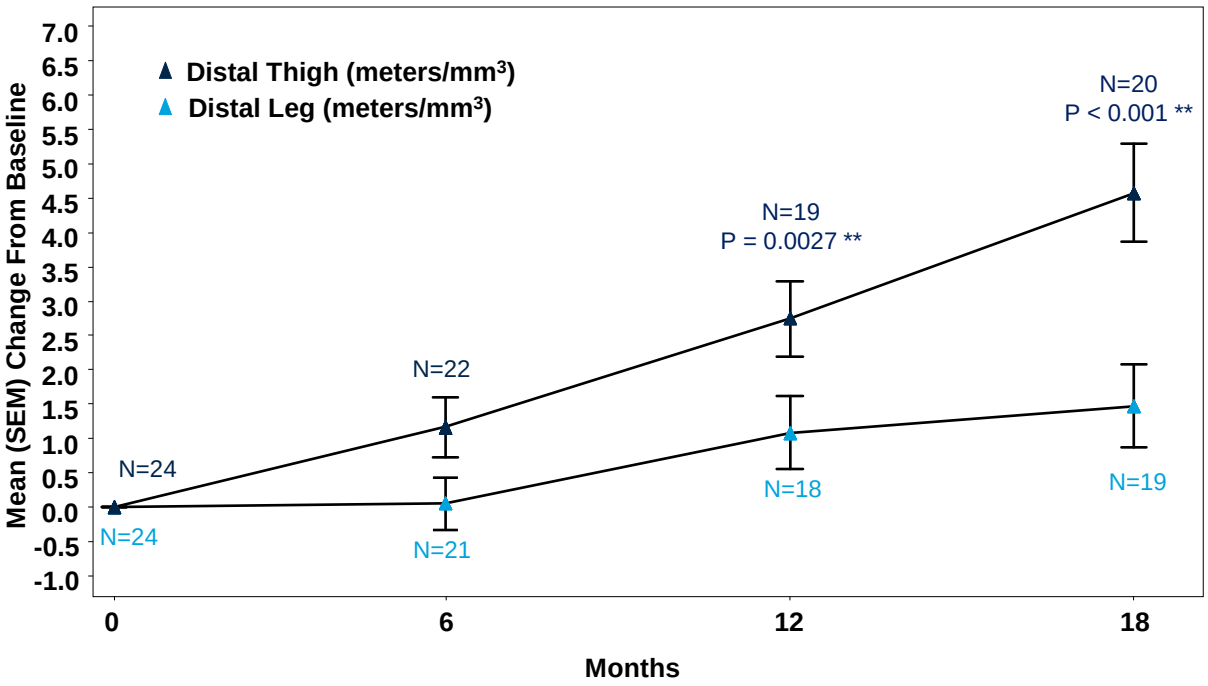
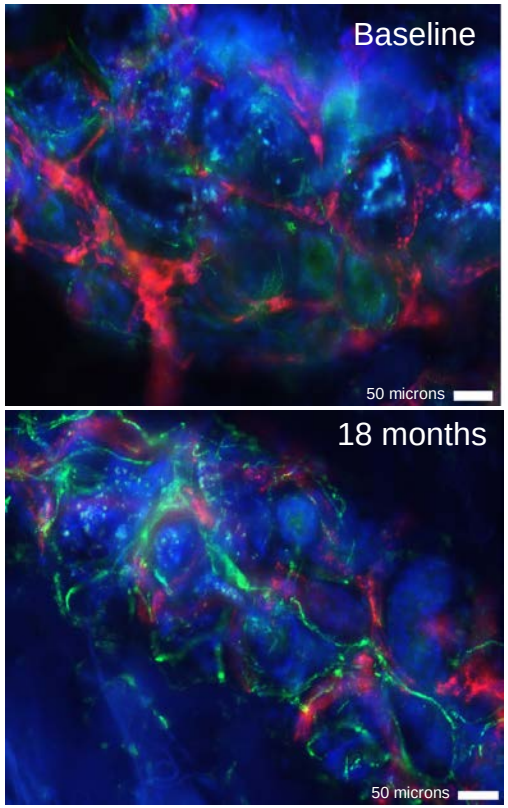
Patisiran Phase 2 OLE Preliminary Study Results*

Sweat Gland Nerve Fiber Density (SGNFD): Lower Limb



Distal thigh sweat gland innervation† in Patient 050-0005



†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 both 12 and 18 months
- Increase in distal leg SGNFD at both 12 and 18 months, although not significant
- In a separate study in hATTR-PN patients with the highly pathogenic A97S mutation,[1] SGNFD correlated to autonomic system involvement and disability burden

** 2-sided p values from paired t-test comparing post-baseline vs baseline
[1]Chao C et al., Ann Neurol. 78:272-83 (2015)
**Data as of February 23, 2016*

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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
  - 909 doses administered to date, median of 35 doses/pt, mean treatment duration of 23 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 knockdown of 92%
- Neuropathy impairment scores stable through 18 months
  - Mean change in mNIS+7 and NIS of -0.8 and 2.6 points, respectively
    - Similar results in patients with or without concurrent tetramer stabilizers
  - Compares favorably to 17-26 point mean increase in mNIS+7 or NIS estimated at 18 months from prior hATTR-PN studies in patient population with similar baseline neuropathy impairment
- Degree of TTR knockdown with patisiran correlates with subsequent change in mNIS+7
  - Greater degree of TTR knockdown correlated with greater improvement in mNIS+7
- Significant improvement of distal thigh sweat gland nerve fiber density
  - Median increase of 4.5 m/mm^3 (~77% increase) in SGNFD at the distal thigh at 18 months
- Results consistent with therapeutic hypothesis that TTR knockdown has potential to halt neuropathy progression

Data as of February 23, 2016

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Study Investigators

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- Ole Suhr
  - Umea University Hospital, Umea, Sweden
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Thank You!

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