Phase 2 Open-Label Extension Study of Patisiran

An Investigational RNAi Therapeutic for the Treatment of Familial Amyloidotic Polyneuropathy

April 21, 2015

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Disclosure

Financial support from Pfizer for participation in medical advisory boards, for organizing symposia, participating in scientific congress

Financial support from Alnylam Pharmaceuticals, Inc. for participation in medical advisory board, in participating in scientific congress

Familial Amyloidotic Polyneuropathy (FAP)
Background

- 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
  - 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
    - EU approval of Pfizer's Vyndaqel® (tafamidis) for Stage 1 FAP in 2011[1]
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[2]

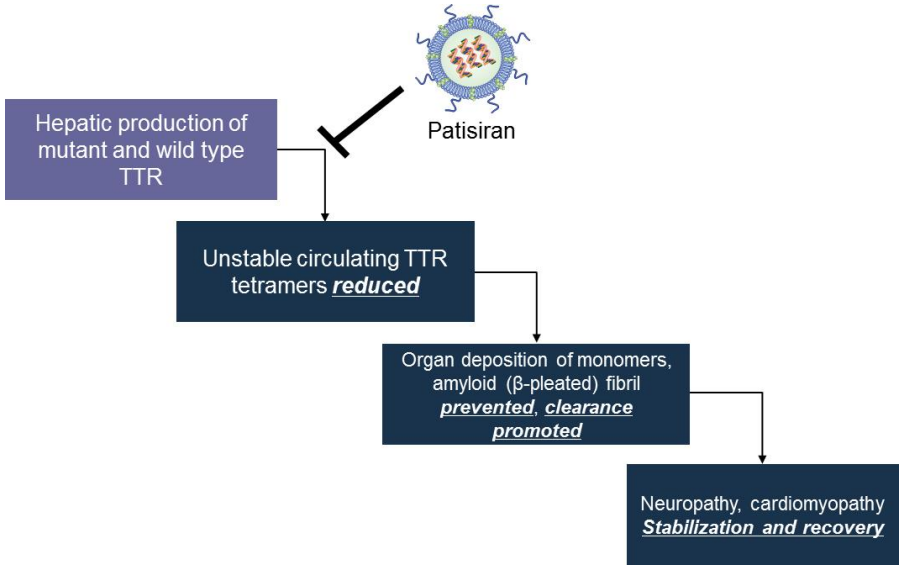
- Continued high unmet medical need for novel therapeutics

[1]Coelho T *et al., Neurology.* 79:785-92 (2012)
[2]Berk JL *et al., JAMA.* 310:2658-67 (2013)

Patisiran
Familial Amyloidotic Polyneuropathy (FAP)

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 FAP patients[2]
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Includes clinical endpoints measured every 6 months
  - Positive initial data reported at ISA, April 2014; ANA, Oct. 2014
- APOLLO Phase 3 trial ongoing



[1]Coelho et al., N Engl J Med;369:819-29 (2013); [2]Int'l Symp. FAP, Nov. 2013

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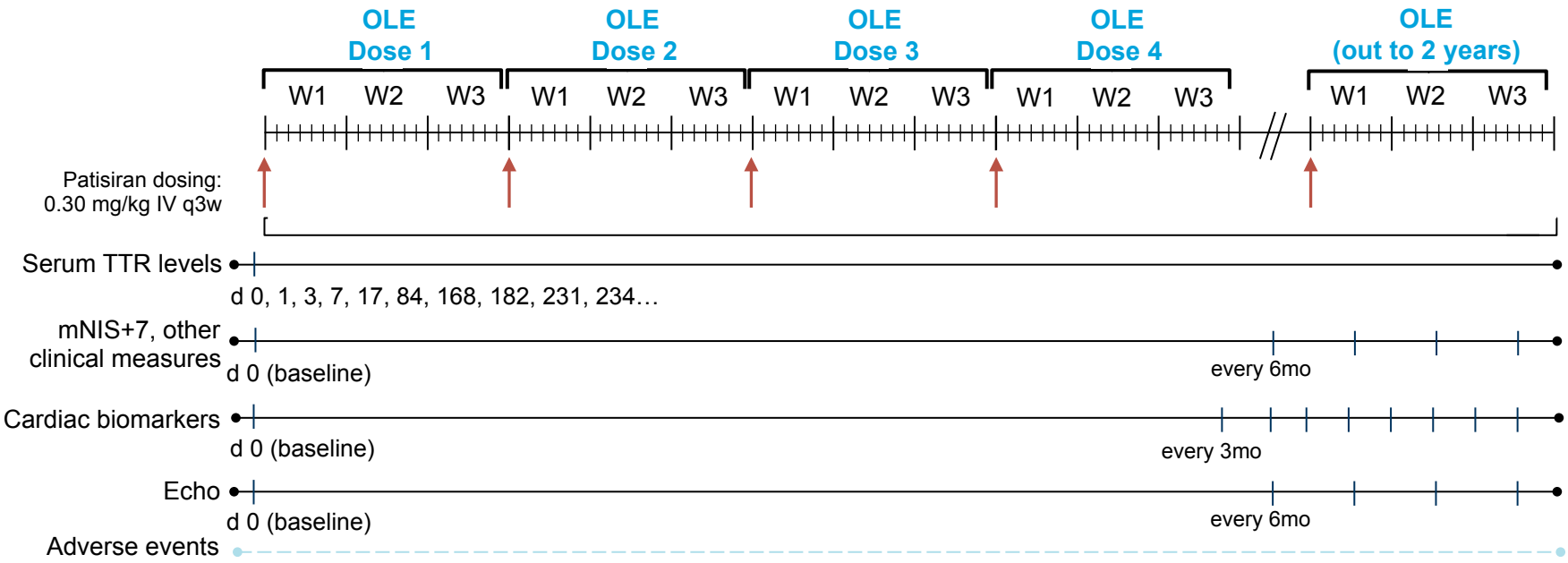
Patisiran Phase 2 OLE Study Design



FAP 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
- Study objectives
  - Primary: Safety and tolerability of long-term dosing with patisiran
  - Secondary: 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

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 • II: 10 • IIIa: 2 • IIIb: 1
Concurrent tetramer stabilizer use at baseline	13 tafamidis, 7 diflunisal, 7 none	
Current tetramer stabilizer use[1]	12 tafamidis, 6 diflunisal, 9 none	
Total doses administered	511	
Median doses/patient to date	19 (range 13-24)	
Mean treatment duration	12.8 months (range 8.4-16.7)	

1. *2 subjects: one on diflunisal , one on tafamidis, reported stabilizer use at the time of first dose but had subsequently stopped using stabilizer.*

**Data as of March 13, 2015*

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[b] (sec)	22	10.1	(4.6 – 22.0)
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[c] (no limitations: 48)	24	38.2	(15.0-48.0)
COMPASS-31[d] (max impairment: 100)	26	16.2	(0.0 - 46.1)
Serum TTR (µg/mL)	27	245.6	(154.6 – 339.9)
Cardiac subgroup: N = 11			
V30M/non-V30M (N)	11	8/3	
NT-proBNP (ng/L)	9	809.8	(105.0 - 2070.0)
Troponin I[e] (ng/mL)	8	0.1	(0.02 - 0.7)
LV wall thickness (cm)	11	1.6	(1.3 - 1.9)
10-meter walk test (sec)	7	12.1	(6.7 - 22)

[a] Partial imputation was used to recover mNIS+7 score for one subject missing QST at Baseline

[b] One subject excluded due to leg fracture

[c] 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

[d] 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)

[e] Values recorded as '< LLOQ' were imputed to be LLOQ/2

Data as of March 13, 2015

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Patisiran Phase 2 OLE Preliminary Study Results*
Safety and Tolerability - TEAEs Related or Possibly Related

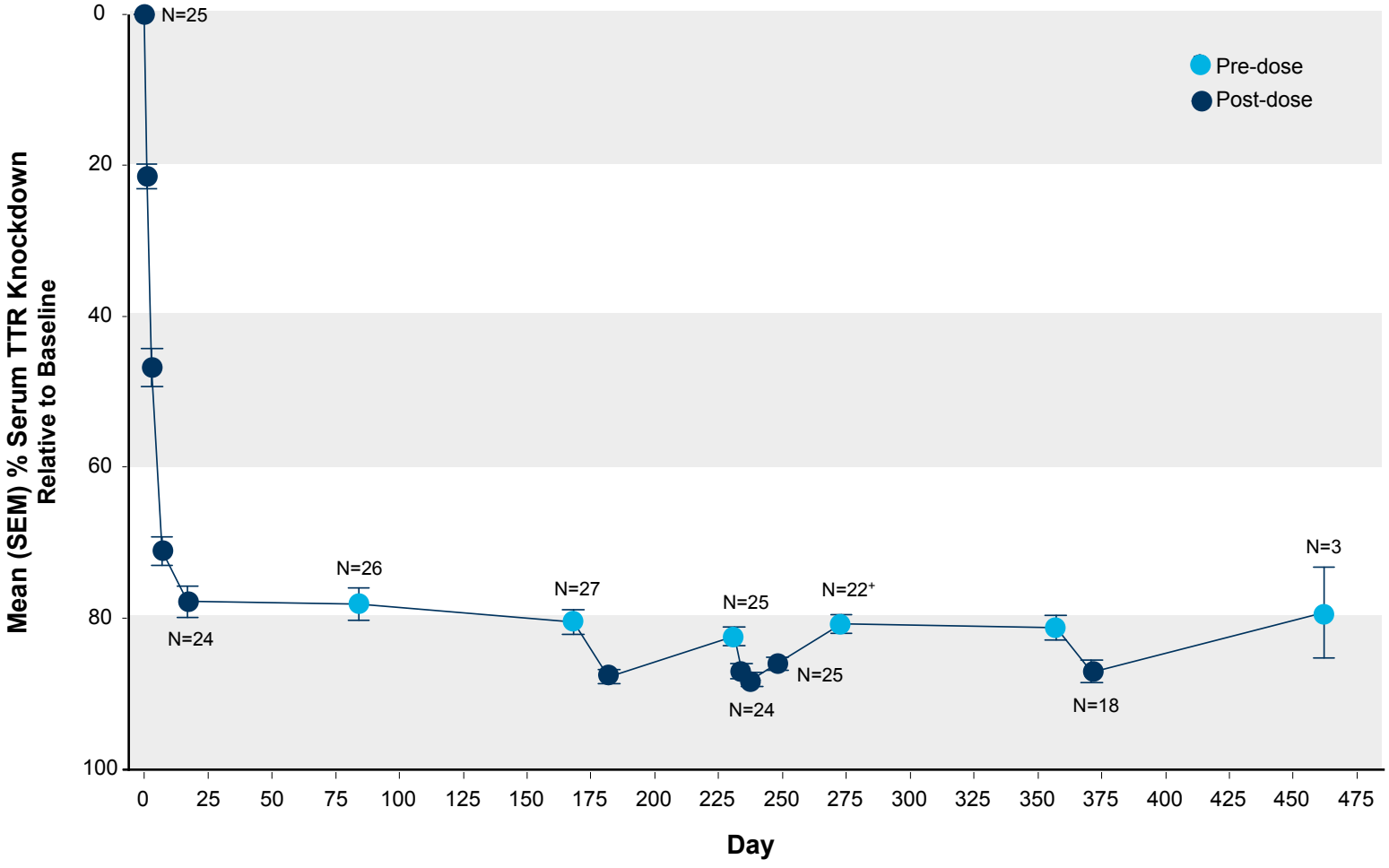
Preferred Term	n (%)	Severity
Flushing	6 (22.2%)	Mild
Infusion-related reaction	5 (18.5%)	Mild
Diarrhea	2 (7.4%)	Mild-Moderate
Peripheral Edema	2 (7.4%)	Mild
Ectropion	1 (3.7%)	Moderate
Fatigue	1 (3.7%)	Moderate
Infusion site irritation	1 (3.7%)	Moderate
Neuralgia	1 (3.7%)	Mild
Impairment of taste	1 (3.7%)	Mild
Insomnia	1(3.7%)	Mild
Alopecia	1 (3.7%)	Mild

- All TEAEs mild to moderate in severity
- No clinically significant changes in liver function tests, renal function, or hematologic parameters
- No study discontinuations
- 3 subjects with 4 SAEs (unrelated to study drug): One subject with 2 separate events (distal femur/proximal tibia fracture with osteonecrosis and dehydration/acute renal failure), one subject with ankle/foot fracture with osteonecrosis, and one subject with a lower limb venous thrombosis

*Data as of March 13, 2015

Patisiran Phase 2 OLE Preliminary Study Results*

Serum TTR Knockdown



- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

Data as of March 13, 2015

+ One Day 273 value removed for subject that missed two consecutive doses immediately prior to measurement

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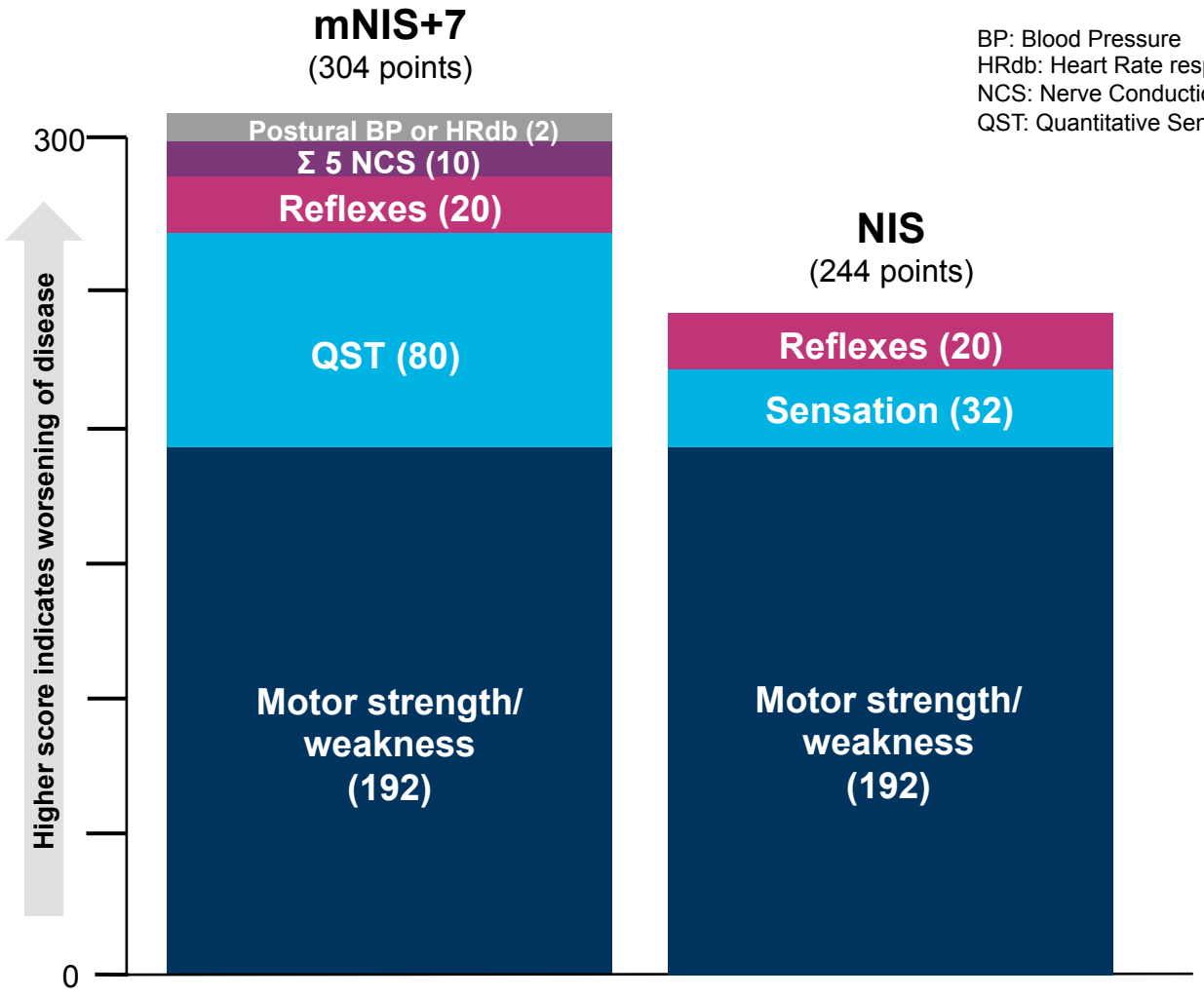
Neuropathy Impairment Scores
Used in FAP Trials



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

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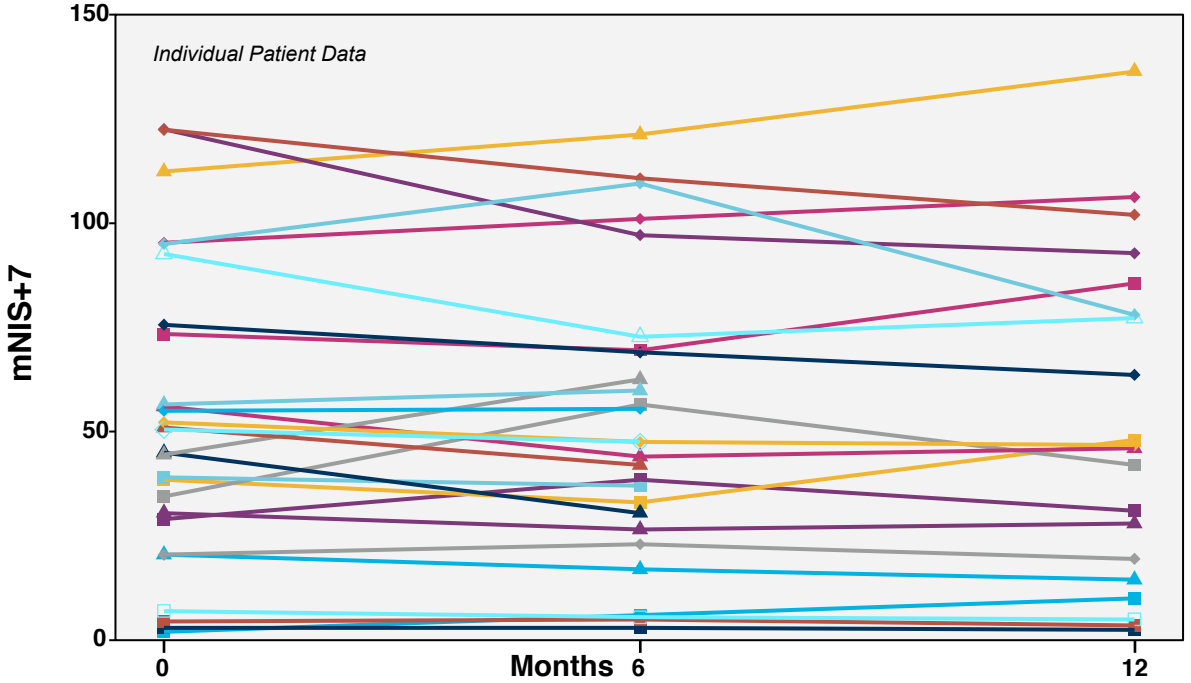
Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 at 6 and 12 Months



	Change from Baseline to Month 6 (n=27)		Change from Baseline to Month 12 (n=20)	
mNIS+7 component	Mean (SEM)	Median (range)	Mean (SEM)	Median (range)
Total	**-1.4 (2.1)**	**-2.0 (-25.4, 22)**	**-2.5 (2.9)**	**-1.5 (-29.8, 24)**
NIS-weakness	0.2 (1.2)	0 (-9.9, 16)	-0.5 (0.9)	0 (-10.4, 6)
NIS-reflexes	-0.7 (0.5)	0 (-8, 3)	0.6 (0.4)	0 (-5.5, 4)
QST#	-1.1 (1.5)	-1.5 (-15, 16)	-2.6 (2.4)	-2.0 (-23, 19)
NCS Σ5	0.2 (0.1)	0 (-1.5, 1.5)	-0.1 (0.3)	0 (-2, 3.5)
Postural BP+	0 (0.1)	0 (-1, 1)	-0.1 (0.1)	0 (-1.5, 0.5)

Partial imputation was used to recover two mNIS+7 datapoints: A subject missing QST at Baseline, and another subject missing NIS-W (one replicate) and Postural BP (other replicate) at 12 mos. # QST: N=26, 19 for 6 and 12-mo. comparisons, respectively. + Postural BP: N=19 for 12-mo. comparison

*Data as of March 13, 2015

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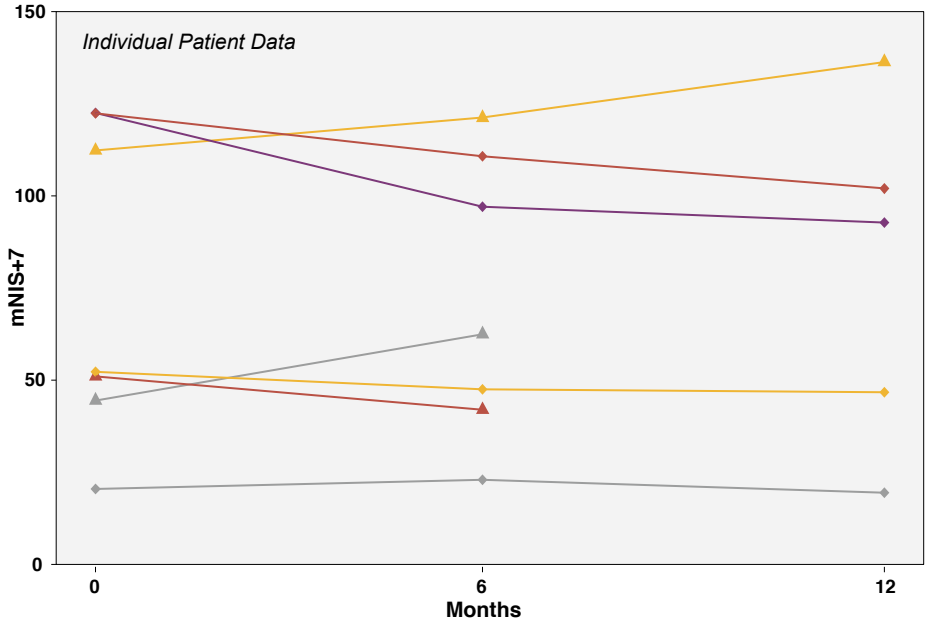
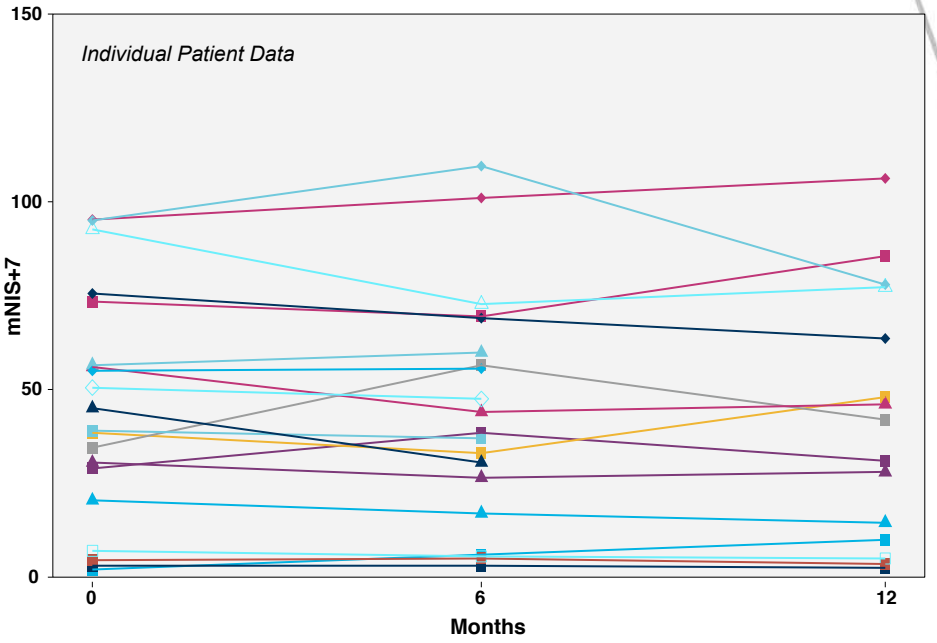
Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 at 6 and 12 Months By Stabilizer Use

Patisiran Alone



Patisiran + Stabilizer



	6 months		12 months	
	Patisiran Alone	Patisiran + Stabilizer	Patisiran Alone	Patisiran + Stabilizer
N	7	20	5	15
Mean Change (SEM)	-3.1 (5.4)	-0.8 (2.1)	-6.5 (9.2)	-1.1 (2.5)
Median Change	-4.8	-1.8	-5.5	-1.0

Partial imputation was used to recover two mNIS+7 data points: A subject missing QST at Baseline, and another subject missing NIS-W (one replicate) and Postural BP (other replicate) at 12 mos.

*Data as of March 13, 2015

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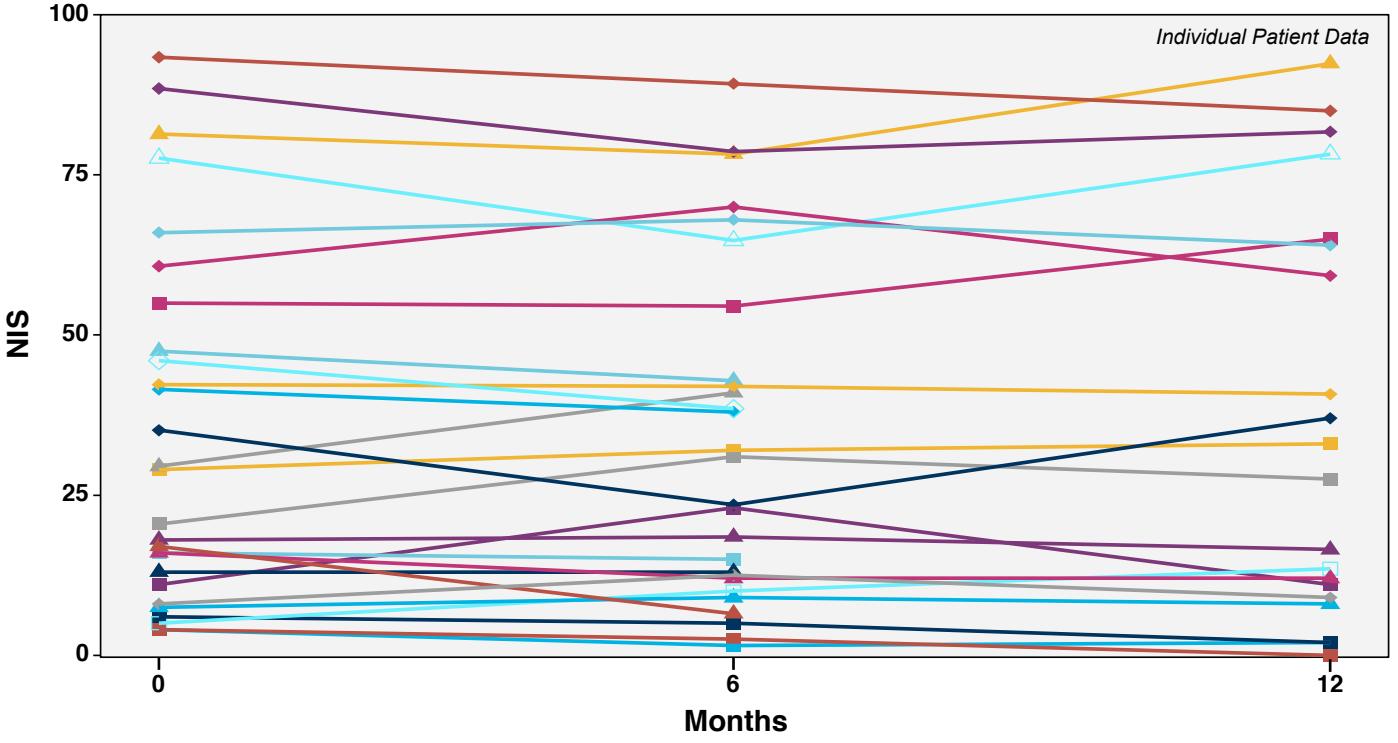
Patisiran Phase 2 OLE Preliminary Study Results*

Change in NIS at 6 and 12 Months



	Change from Baseline to Month 6 (n=27)		Change from Baseline to Month 12 (n=20)	
NIS component	Mean (SEM)	Median (range)	Mean (SEM)	Median (range)
Total	**-0.7 (1.3)**	**-1.0 (-12.9, 12)**	**0.4 (1.2)**	**-0.8 (-8.4, 11)**
NIS-weakness	0.2 (1.2)	0 (-9.9, 16)	-0.5 (0.9)	0 (-10.4, 6)
NIS-reflexes	-0.7 (0.5)	0 (-8, 3)	0.6 (0.44)	0 (-5.5, 4)
NIS-sensation	-0.3 (0.7)	0 (-9.5, 5)	0.4 (0.8)	0.5 (-5, 8)

*Data as of March 13, 2015

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Patisiran Phase 2 OLE Preliminary Study Results*
Comparison of ΔNIS and ΔmNIS+7 Across FAP Studies

		Natural History (linear)~	Natural History (nonlinear)#	Tafamidis Fx1A-201§	Diflunisal Phase 3+	Patisiran Phase 2 OLE
6 Months	Mean (SEM) ΔmNIS+7 ^	8.9 (5.7)	10.3 (5.7)	PBO: 8.7 (2.0) Drug: 2.5 (2.9)	PBO: 7.4 (6.9) Drug: 2.3 (6.0)	-1.4 (2.1)†
	Mean (SEM) ΔNIS	7.2 (4.6)	8.3 (4.6)	PBO: 7.0 (1.6) Drug: 2.0 (2.3)	PBO: 5.8 (5.4) Drug: 1.6 (4.8)	-0.7 (1.3)
12 Months	Mean (SEM) ΔmNIS+7 ^	NA	17.8 (8.5)	PBO: 17.3 (3.5) Drug: 6.6 (3.7)	PBO: 12.6 (4.0) Drug: 5.1 (3.6)	-2.5 (2.9)†
	Mean (SEM) ΔNIS	NA	14.3 (6.8)	PBO: 13.9 (2.8) Drug: 5.3 (3.0)	PBO: 10.1 (3.2) Drug: 4.1 (2.9)	0.4 (1.2)

^ Translated algebraically from NIS (Natural History study, Tafamidis study) or NIS+7 (Diflunisal study)
~ Linear interpolation between 0 and 12 month progression for median NIS value (from Gompertz curve fit)
# Predicted progression of median NIS value from Gompertz curve fit
§ PBO (Placebo) rate estimated from pre-study rate of change; drug rate as reported
+ Linear interpolation from 2-year NIS progression measurement in longitudinal analysis set
† Using full mNIS+7 set (with partial imputation; N=27 at 6 mos.; N=20 at 12 mos.)
SEM: Standard Error of the Mean

**Data as of March 13, 2015*
Adams D *et al., XIVth ISA* (2014)
Tafamidis EMA assessment report (2011)
Berk JL *et al., JAMA.* 310:2658-67 (2013)

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Changes in Other Clinical Assessments*

	Baseline		6 Month		12 Month	
Assessment	N	Mean (SEM)	N	Mean (SEM) Δ from Baseline	N	Mean (SEM) Δ from Baseline
10-Meter Walk^ (sec)	22	10.1 (0.9)	20	-0.7 (0.4)	14	-1.0 (0.7)
Hand Grip Strength (kg)	27	25.8 (2.3)	27	-0.4 (0.9)	20	0.4 (0.8)
mBMI (kg/m2 x albumin (g/L))	27	1031.6 (32.5)	26	-1.9 (14.2)	23	-0.2 (21.8)
EQ-5D (max. impairment: 0)	27	0.8 (0)	27	0 (0)	19	0 (0)
R-ODS (no limitations: 48)	24	38.2 (1.8)	24	-0.8 (0.8)	18	-1.3 (1)
COMPASS-31 (max. impairment: 100)	26	16.2 (2.6)	23	1.0 (2.2)	18	-2.9 (2.4)
Orthostatic Intolerance	26	5.1 (1.6)	23	1.2 (1.6)	18	-1.3 (2.3)
Vasomotor	26	0.7 (0.3)	23	-0.1 (0.2)	18	-0.4 (0.2)
Secretomotor	26	2.8 (0.6)	23	0.5 (0.6)	18	-0.5 (0.4)
Gastrointestinal	26	5.8 (0.9)	23	-0.5 (0.4)	18	-0.8 (0.5)
Bladder	26	1.0 (0.3)	23	-0.1 (0.3)	18	-0.1 (0.2)
Pupillomotor	26	0.8 (0.2)	23	0 (0.2)	18	0.2 (0.1)
IENFD (fibers/mm)						
Location: Leg	24	3.4 (1.2)	22	-0.5 (0.5)	12	-0.8 (0.8)
Location: Thigh	24	10.2 (2)	22	-1.2 (0.7)	14	-1.9 (1.1)
SGNFD (m/mm^3)						
Location: Leg	24	3.9 (0.7)	21	0.2 (0.5)	12	1.2 (1.1)
Location: Thigh	24	6.8 (0.7)	22	1.7 (0.7)	13	2.6 (1.1)
Cardiac Subgroup, N=11						
NT-proBNP (ng/L)#	9	809.8 (246.7)	7	165.4 (60.2)	8	279.8 (256.7)
Troponin I (ng/L)#	8	0.1 (0.1)	6	-0.1 (0.1)	7	-0.1 (0.1)
LV Mass (g)	11	271.6 (22.3)	11	-9.3 (8.2)	7	6 (21.8)
LV wall thickness (cm)	11	1.6 (0.1)	11	0 (0)	7	0.1 (0.1)
Ejection fraction (%)	11	62.5 (2.6)	11	-1.7 (2)	6	-1.8 (2.1)
Peak longitudinal strain (%)	11	-15.8 (1.2)	11	-0.1 (1.1)	7	-0.4 (0.9)
10-Meter Walk (sec)	7	12.1 (2)	7	-1.2 (0.7)	4	-2.1 (2.2)

^ 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

Data as of March 13, 2015

Patisiran Phase 2 OLE Preliminary Study Results*
Summary

- Patisiran generally well tolerated in FAP patients out to 17 months
  - 511 doses administered to date, median of 19 doses/pt, mean treatment duration of 13 mo
  - No drug-related SAEs
  - Low incidence of mild flushing (22.2%) and IRRs (18.5%)
  - No clinically significant LFT or renal function changes
  - No study discontinuations
  - Includes patients on concurrent tetramer stabilizers
- Sustained mean serum TTR knockdown of approximately 80%, with mean knockdown up to 88% between doses, for approximately 16 months
- Neuropathy impairment scores stable through 12 months
  - Mean change in mNIS+7 and NIS of -2.5 and +0.4 points, respectively
  - Compares favorably to 10-18 point increase in mNIS+7 or NIS estimated at 12 months from prior FAP studies in patient population with similar baseline NIS
  - Similar results in patients with or without concurrent tetramer stabilizers
- In aggregate, results consistent with therapeutic hypothesis that TTR knockdown has potential to halt neuropathy progression

*Data as of March 13, 2015

APOLLO Phase 3 Study Design

Patient Population
- FAP: any TTR mutation, Stages 1 and 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

2:1 RANDOMIZATION

Patisiran IV infusion q3W, 0.3 mg/kg

OR

Placebo IV infusion q3W

Primary Endpoint
- mNIS+7 at 18 months

Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- mBMI
- 10-meter walk test
- COMPASS-31

Exploratory Endpoints
- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Rausch-built Overall Disability Scale

All completers eligible for patisiran treatment on Phase 3 OLE study

Statistical Considerations

- Placebo-estimated mNIS+7 progression rate of 17.8 points/yr derived from natural history study of 283 FAP patients
- Study with 90% power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha=0.05
- Blinded interim analysis of variance for sample size adjustment

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Patisiran Phase 2 OLE Investigators

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Thank You

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