Phase 2 Open-Label Extension Study of Patisiran

An Investigational RNAi Therapeutic for the Treatment of Familial Amyloidotic Polyneuropathy

Sept 28, 2015

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

- Continued high unmet medical need for novel therapeutics

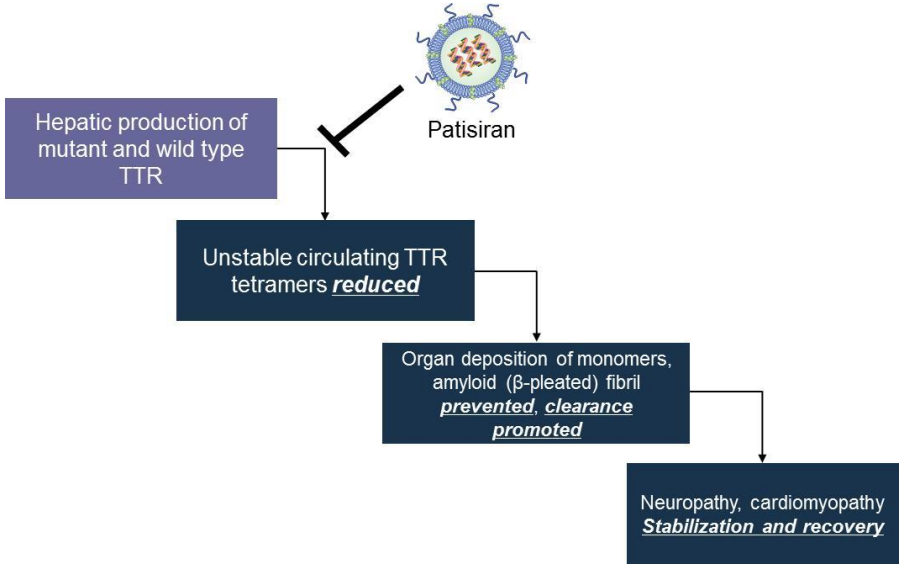
[1]Adams D et al., *Neurology. 85;675-682* (2015)
[2]Coelho T *et al., Neurology*. 79:785-92 (2012)
[3]Berk JL *et al., JAMA*. 310:2658-67 (2013)

Patisiran
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 interim data reported at ISA, April 2014; ANA, Oct. 2014; AAN, March 2015
- APOLLO Phase 3 trial ongoing

ALN-TTR 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)

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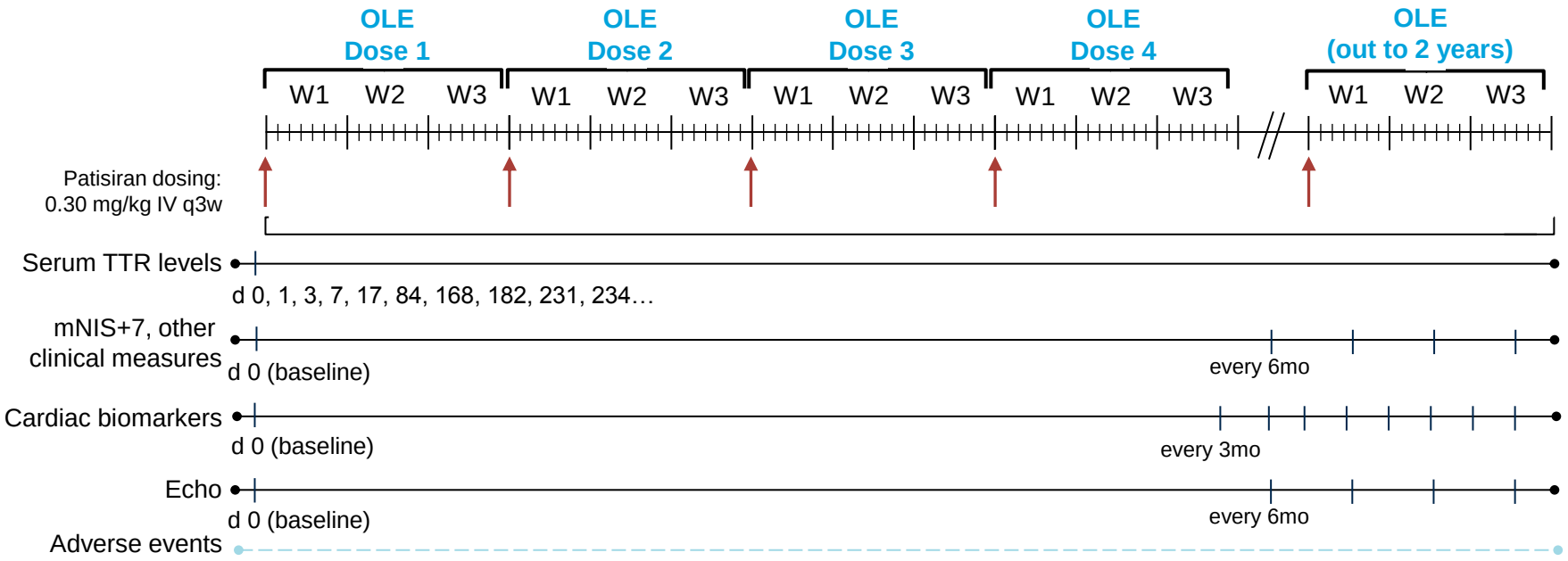
Patisiran Phase 2 OLE Study Design



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

Patisiran Phase 2 OLE Preliminary Study Results*

Demographics and Exposure

This presentation highlights 12 month data from all patients (n=27) who are participating in the OLE 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[1]	12 tafamidis, 2 diflunisal, 13 none
Exposure	**Result**
Total doses administered	669
Median doses/patient to date	25 (range 18-31)
Mean treatment duration	16.9 months (range 11.8 – 20.9)

[1] 6 subjects reported stabilizer use (5 on diflunisal, 1 on tafamidis) at the time of first dose but subsequently stopped approximately 1 to 18 months into the study.
**Data as of July 15, 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 (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[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	245.6	(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[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 (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] 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 July 15, 2015

Patisiran Phase 2 OLE Preliminary Study Results* Summary of Safety

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

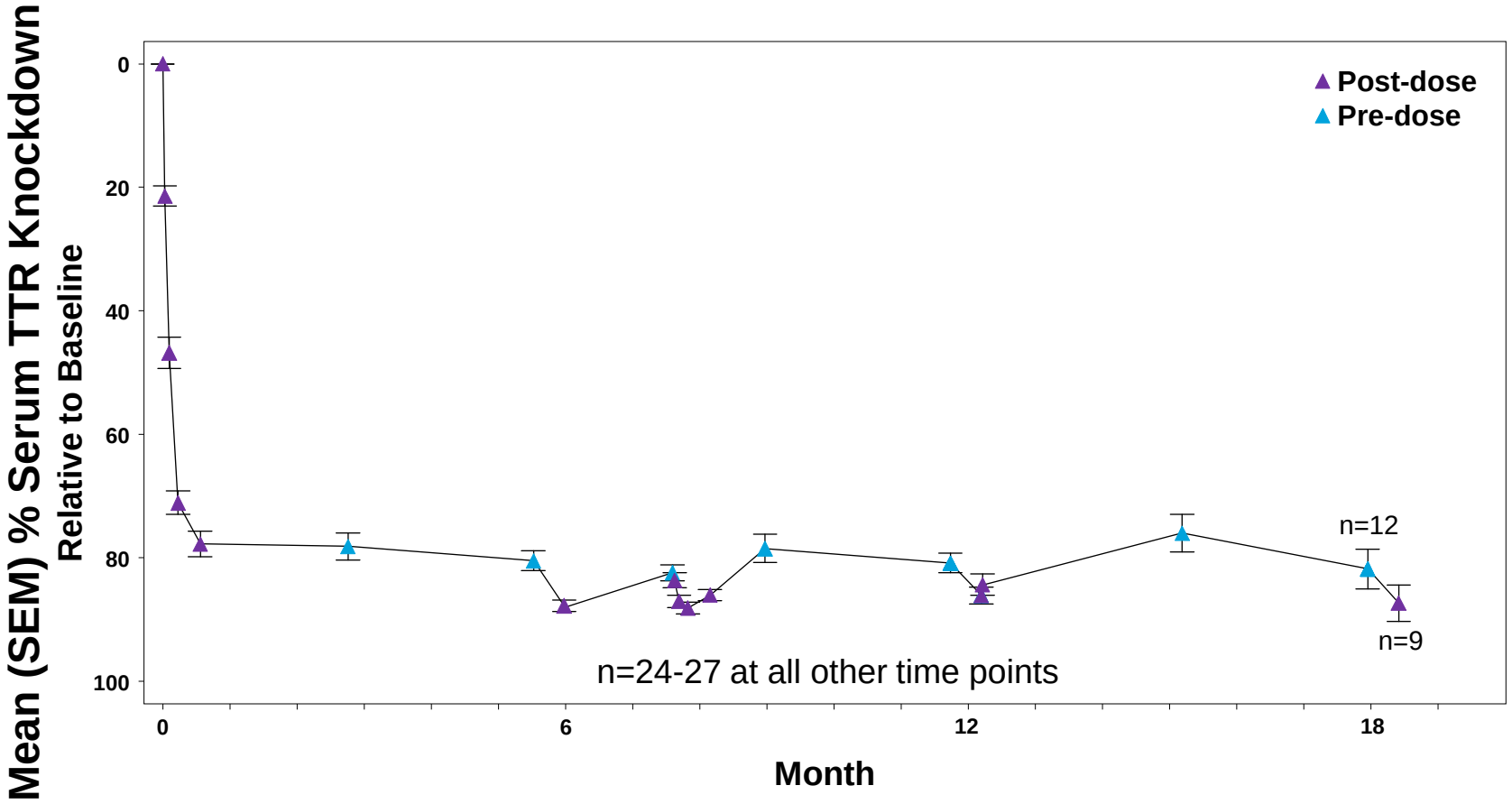
AE by Preferred Term	Patisiran (n=27)
Flushing	6 (22.2%)
Diarrhea	5 (18.5%)
Infusion related reaction	5 (18.5%)
Nasopharyngitis	5 (18.5%)
Wound	5 (18.5%)
Neuralgia	4 (14.8%)
Urinary tract infection	4 (14.8%)
Vomiting	4 (14.8%)
Anemia	3 (11.1%)
Bronchitis	3 (11.1%)
Edema peripheral	3 (11.1%)
Insomnia	3 (11.1%)

- 5 patients with 7 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 2 reports (distal femur fracture/proximal tibia fracture/osteonecrosis/ligament rupture and dehydration/acute prerenal failure/urinary tract infection); one patient with 2 reports (ankle fracture/foot fracture/osteonecrosis and arthrodesis); one patient with venous thrombosis of the lower limb; one patient with foot abscess and osteomyelitis
- Majority of AEs were mild or moderate
  - 2 patients (7.4%) had severe events (not related)
- Most common related AEs in ≥ 2 patients were flushing (6 patients [22.2%]) and infusion related reaction (5 patients [18.5%])
  - All related AEs were mild or moderate
- No clinically significant changes in liver function tests, renal function, or hematologic parameters

*Data as of July 15, 2015

Patisiran Phase 2 OLE Preliminary Study Results*

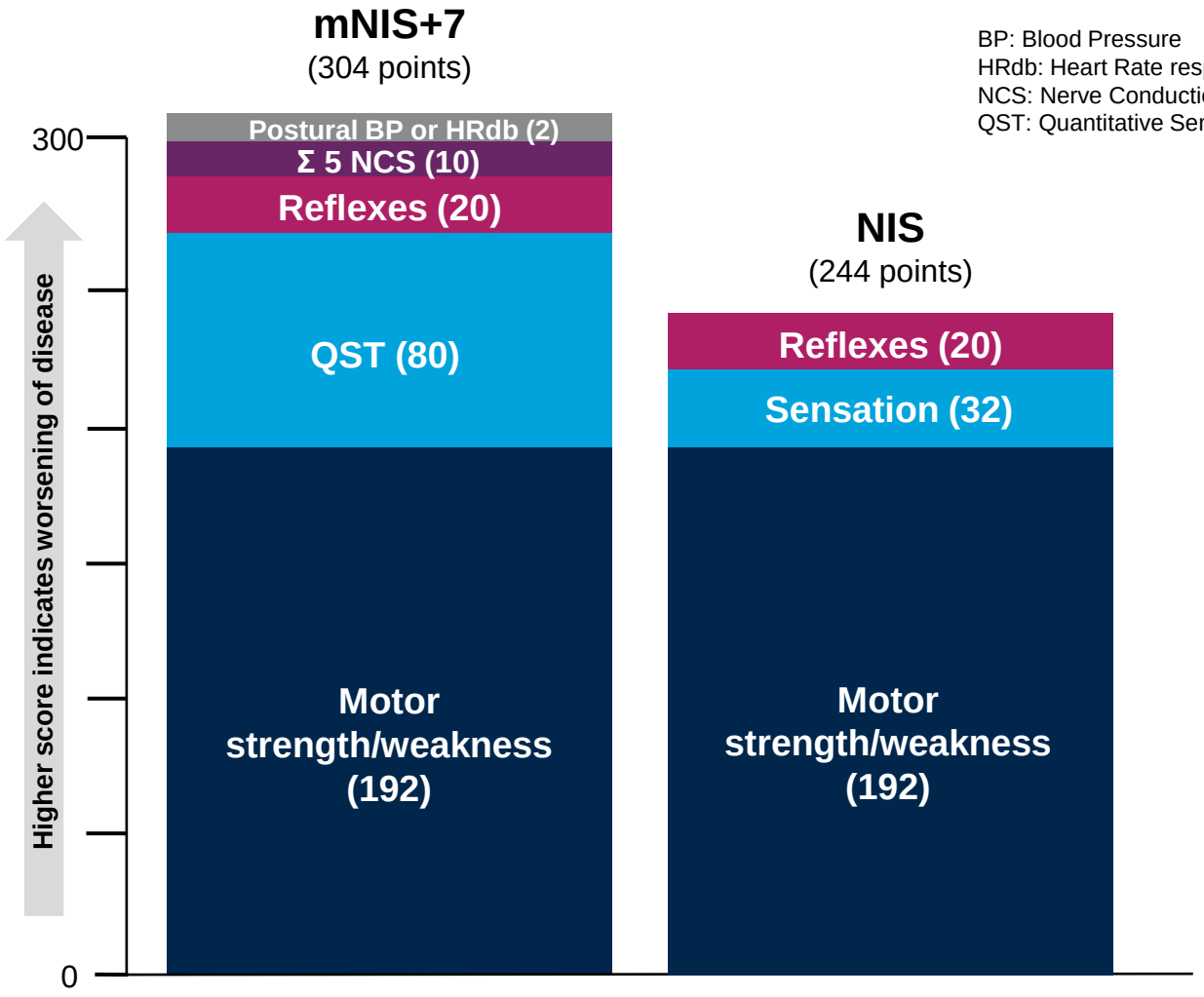
Serum TTR Knockdown



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

Data as of July 15, 2015

Neuropathy Impairment Scores
Used in FAP Trials

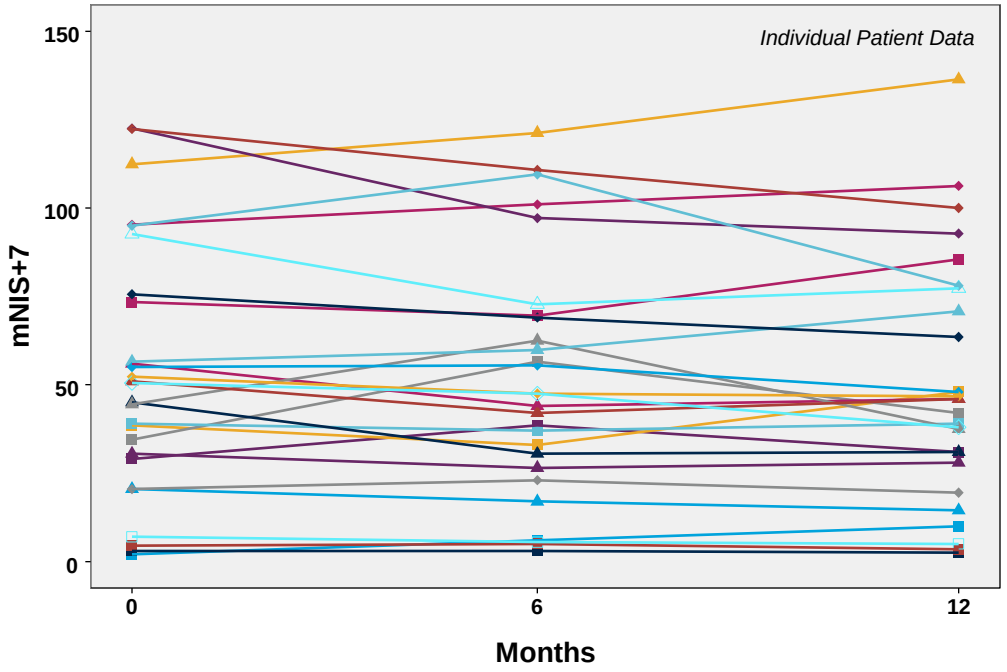


BP: Blood Pressure
HRdb: Heart Rate response to Deep Breathing
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

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

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=27)	
mNIS+7 component	Mean (SEM)	Median (range)	Mean (SEM)	Median (range)
Total⁺	**-1.4 (2.1)**	**-2.0 (-25.4, 22)**	**-3.1 (2.3)**	**-2.5 (-29.8, 24.0)**
NIS-weakness	0.2 (1.2)	0 (-9.9, 16)	0 (0.7)	0 (-10.4, 8.3)
NIS-reflexes	-0.7 (0.5)	0 (-8, 3)	0.1 (0.5)	0 (-9.0, 4.0)
QST#	-1.1 (1.5)	-1.5 (-15, 16)	-3.4 (1.9)	-2.5 (-23.0, 19.0)
NCS Σ5	0.2 (0.1)	0 (-1.5, 1.5)	-0.1 (0.2)	0 (-2.0, 3.5)
Postural BP	0 (0.1)	0 (-1, 1)	0 (0.1)	0 (-1.5, 2.0)

⁺Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
QST: N=26 for 6 and 12-mo. comparisons.

Data as of July 15, 2015

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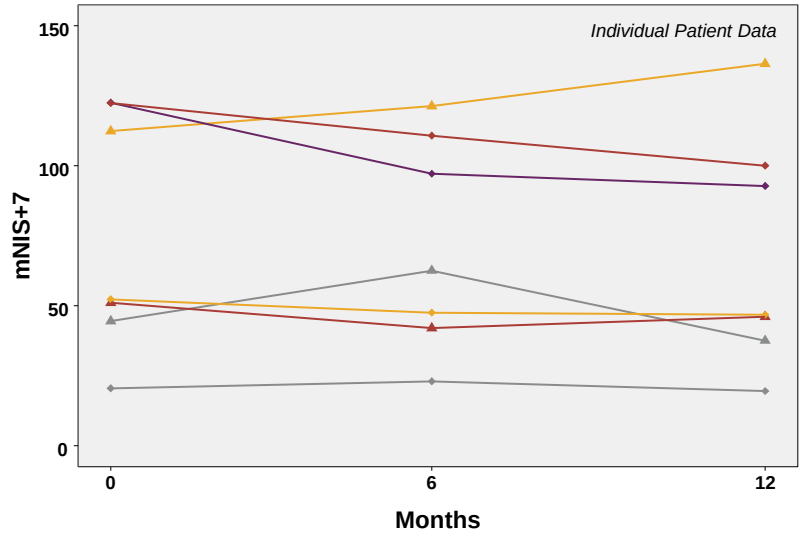
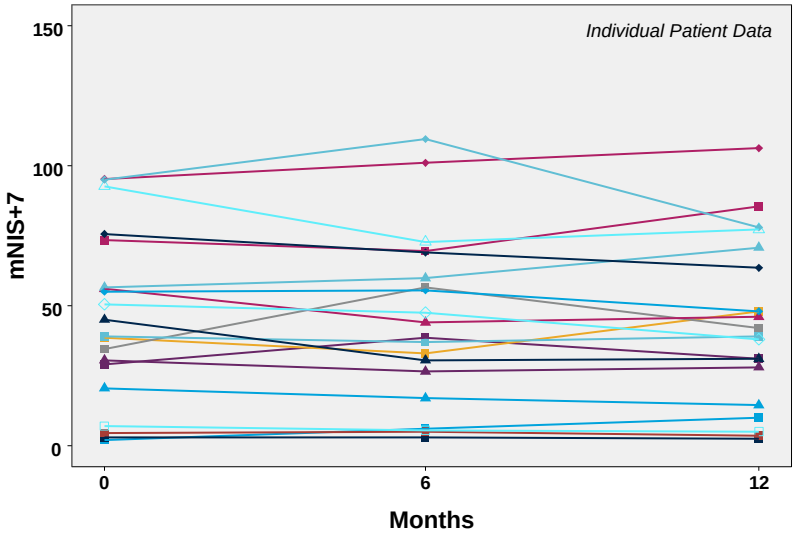
Patisiran Phase 2 OLE Preliminary Study Results*

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

Patisiran Alone



Patisiran + Stabilizer



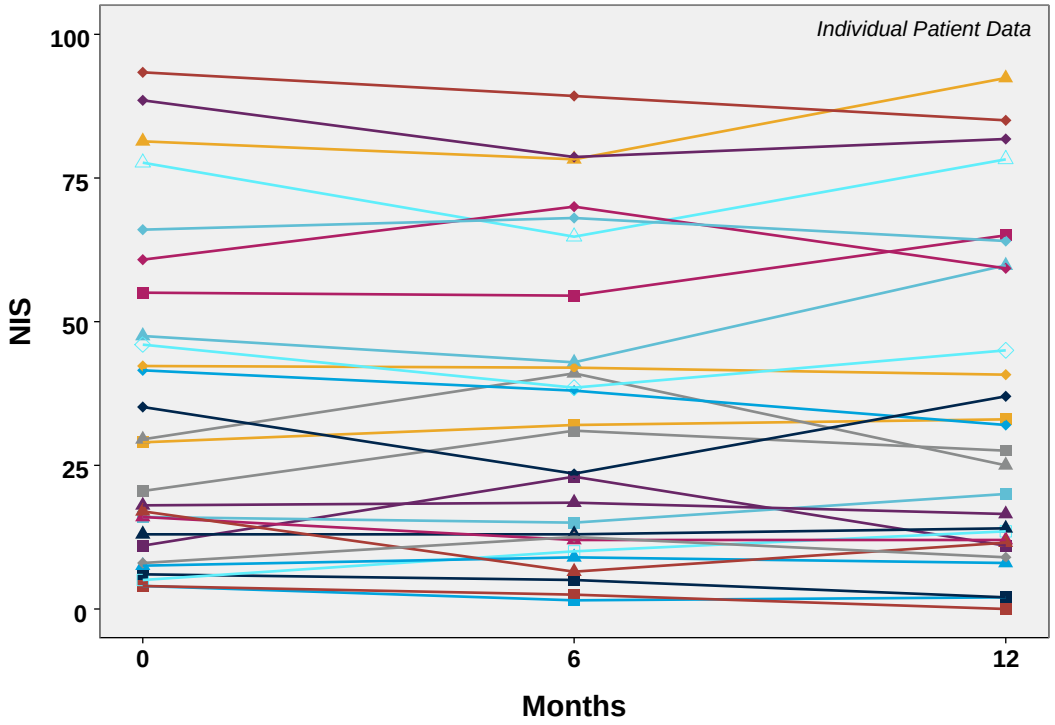
	6 months		12 months	
	Patisiran Alone	Patisiran + Stabilizer	Patisiran Alone	Patisiran + Stabilizer
N	7	20	7	20
Mean Change (SEM)	-3.1 (5.4)	-0.8 (2.1)	-6.7 (6.5)	-1.8 (2.2)
Median Change	-4.8	-1.8	-5.5	-1.5

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 July 15, 2015

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=27)	
NIS component	Mean (SEM)	Median (range)	Mean (SEM)	Median (range)
Total	**-0.7 (1.3)**	**-1.0 (-12.9, 12)**	**0.2 (1.1)**	**-1.0 (-9.5, 12.3)**
NIS-weakness	0.2 (1.2)	0 (-9.9, 16)	0 (0.7)	0 (-10.4, 8.3)
NIS-reflexes	-0.7 (0.5)	0 (-8, 3)	0.1 (0.5)	0 (-9.0, 4.0)
NIS-sensation	-0.3 (0.7)	0 (-9.5, 5)	0 (0.7)	0.5 (-7.0, 8.0)

Data as of July 15, 2015

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

		Natural History (nonlinear)[#1]	Tafamidis Fx1A-201[§2]	Diflunisal Phase 3[+3]	Patisiran Phase 2 OLE[†*]
12 Months	Mean (SEM) ΔmNIS+7^	17.8 (8.5)	Prestudy: 17.3 (3.5) Drug: 6.6 (3.7)	PBO: 14.0 (2.2) Drug: 7.0 (1.9)	**-3.1 (2.3)**
	Mean (SEM) ΔNIS	14.3 (6.8)	Prestudy: 13.9 (2.8) Drug: 5.3 (3.0)	PBO: 10.1 (3.2) Drug: 4.1 (2.9)	**0.2 (1.1)**

~ Assessments drawn from studies in patients with similar baseline characteristics and not based on head-to-head studies
^ Translated algebraically from NIS (Natural History study, Tafamidis study) or NIS+7 (Diflunisal study)[1]
[#] Predicted progression of median NIS value from Gompertz curve fit[1]
[§] Estimated from prestudy rate of change; drug rate as reported
[+] Linear interpolation from 2-year NIS progression measurement in longitudinal analysis set
[†] N=27; patisiran results similar in patients with/without concurrent TTR stabilizer therapy; mNIS+7 using full mNIS+7 set (with partial imputation for 2 patients)

SEM: Standard Error of the Mean

[1]Adams D et al., *Neurology. 85;675-682* (2015)
[2]Tafamidis EMA assessment report (2011)
[3]Berk JL *et al., JAMA.* 310:2658-67 (2013)
*Data as of July 15, 2015

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Patisiran Phase 2 OLE Preliminary Study Results*

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)	21	-0.7 (0.5)
Hand Grip Strength (kg)	27	25.8 (2.3)	27	-0.4 (0.9)	27	0.7 (0.6)
mBMI (kg/m2 x albumin (g/L))	27	1031.6 (32.5)	26	-1.9 (14.2)	27	0.8 (21.0)
EQ-5D (max. impairment: 0)	27	0.8 (0)	27	0 (0)	27	0 (0)
R-ODS (no limitations: 48)	26	38.1 (1.7)	26	-0.5 (0.8)	26	-1.4 (0.8)
COMPASS-31 (max. impairment: 100)	27	15.6 (2.6)	27	1.7 (2.0)	27	0.1 (2.0)
Orthostatic Intolerance	27	4.9 (1.5)	27	1.5 (1.6)	27	0.7 (1.8)
Vasomotor	27	0.7 (0.2)	27	-0.2 (0.2)	27	-0.3 (0.2)
Secretomotor	27	2.5 (0.6)	27	0.5 (0.6)	27	0.1 (0.4)
Gastrointestinal	27	5.8 (0.8)	27	-0.3 (0.4)	27	-0.6 (0.4)
Bladder	27	1.0 (0.3)	27	0.1 (0.3)	27	0 (0.2)
Pupillomotor	27	0.8 (0.2)	27	0.1 (0.2)	27	0.2 (0.1)
IENFD (fibers/mm)						
Location: Leg	24	3.4 (1.2)	22	-0.5 (0.5)	18	-0.5 (0.6)
Location: Thigh	24	10.2 (2)	22	-1.2 (0.7)	20	-1.2 (0.8)
SGNFD (m/mm^3)						
Location: Leg	24	3.9 (0.7)	21	0.1 (0.5)	18	1.0 (0.7)
Location: Thigh	24	6.8 (0.7)	22	1.7 (0.7)	19	2.6 (0.8)
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/mL)#	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)	10	-10.0 (18.3)
LV wall thickness (cm)	11	1.6 (0.1)	11	0 (0)	10	0 (0.1)
Ejection fraction (%)	11	62.5 (2.6)	11	-1.7 (2)	9	-2.2 (1.6)
Peak longitudinal strain (%)	11	-16.6 (1.3)	11	-0.5 (1.1)	10	-0.5 (0.7)
10-Meter Walk (sec)	7	12.1 (2)	7	-1.2 (0.7)	7	-1.1 (1.3)

^ 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 July 15, 2015

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Patisiran Phase 2 OLE Preliminary Study Results*
Summary

- Patisiran generally well tolerated in FAP patients out to 21 months
  - 669 doses administered to date, median of 25 doses/pt, mean treatment duration of 17 mo
  - No drug-related SAEs
  - Most common related AEs were flushing (22.2%) and IRRs (18.5%), both mild in severity
  - No treatment discontinuations due to drug-related AEs
  - No clinically significant LFT or renal function changes
  - Includes patients on concurrent tetramer stabilizers
- Sustained mean serum TTR knockdown of approximately 80% for over 18 months with mean maximal knockdown of 91%
- Neuropathy impairment scores stable *with all patients* having completed 12 months of study drug dosing
  - Mean change in mNIS+7 and NIS of -3.1 and +0.2 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 July 15, 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

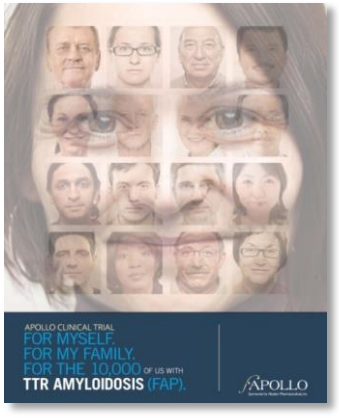
Placebo IV infusion q3W

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 (APOLLO-OLE)



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 (IA) of variance for sample size adjustment
- Potential IA for efficacy under consideration; regulatory discussions pending

Clinicaltrials.gov # NCT01960348

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Patisiran Phase 2 OLE Study Investigators

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Thank You!

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