Phase 2 Open-Label Extension Studies with Patisiran and Revusiran

Investigational RNAi Therapeutics for the Treatment of Transthyretin-Mediated Amyloidosis

July 1, 2016

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Agenda

Welcome

- Christine Lindenboom
  Vice President, Investor Relations and Corporate Communications

Introduction

- John Maraganore, Ph.D.
  Chief Executive Officer

Review of Patisiran and Revusiran Phase 2 OLE Results

- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President of R&D, Chief Medical Officer

Q&A Session

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of our drug candidates, obtain, maintain and protect intellectual property, enforce our patents and defend our patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; our dependence on third parties for access to intellectual property; and the outcome of litigation, as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

John Maraganore, Ph.D.
Chief Executive Officer

Introduction

Akshay Vaishnaw, M.D., Ph.D.
Executive Vice President of R&D, Chief Medical Officer

Review of Patisiran and Revusiran Phase 2 Open-Label Extension Study Data

Hereditary ATTR Amyloidosis

DESCRIPTION

Orphan disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart and other tissues

Significant morbidity and fatal within

2-15

years from symptom onset

PATIENT POPULATION*

~50,000

worldwide

hATTR Amyloidosis with **polyneuropathy (hATTR-PN)**

10,000

hATTR Amyloidosis with **cardiomyopathy (hATTR-CM)**

40,000

* Ando *et al., Orphanet J Rare Dis,* 2013; Ruberg *et al., Circulation,* 2012

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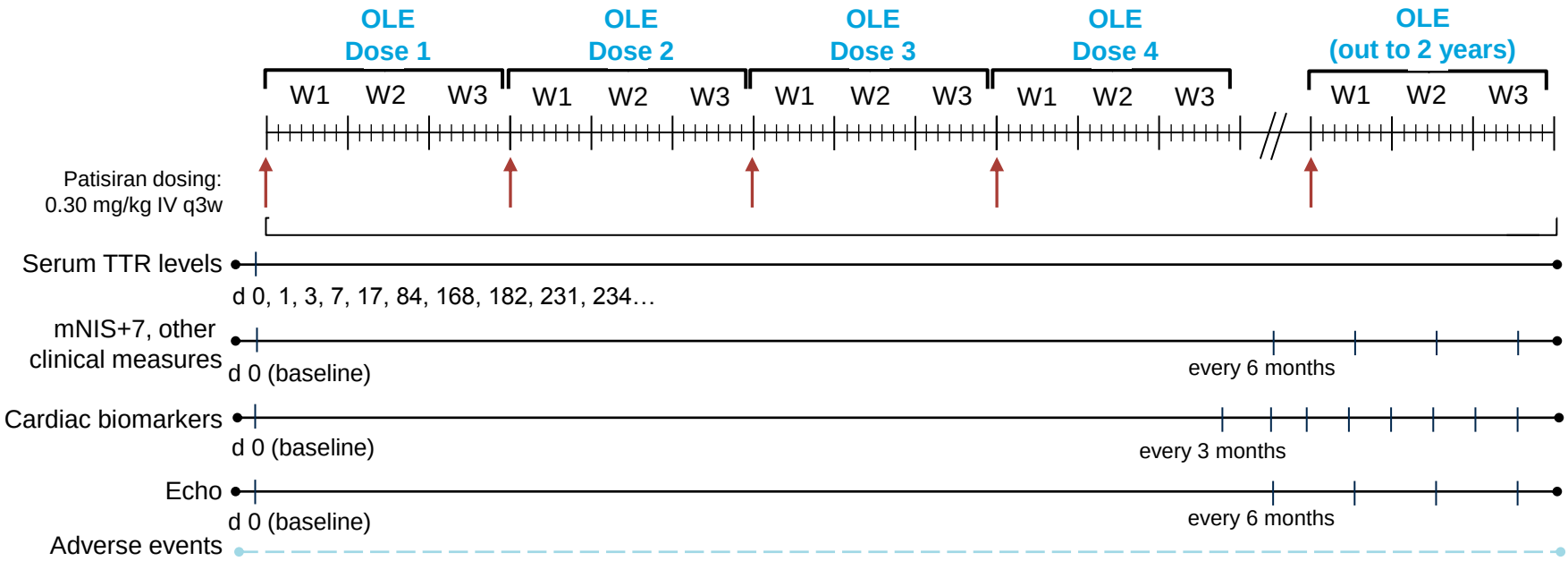
Patisiran Phase 2 OLE Study Design



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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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/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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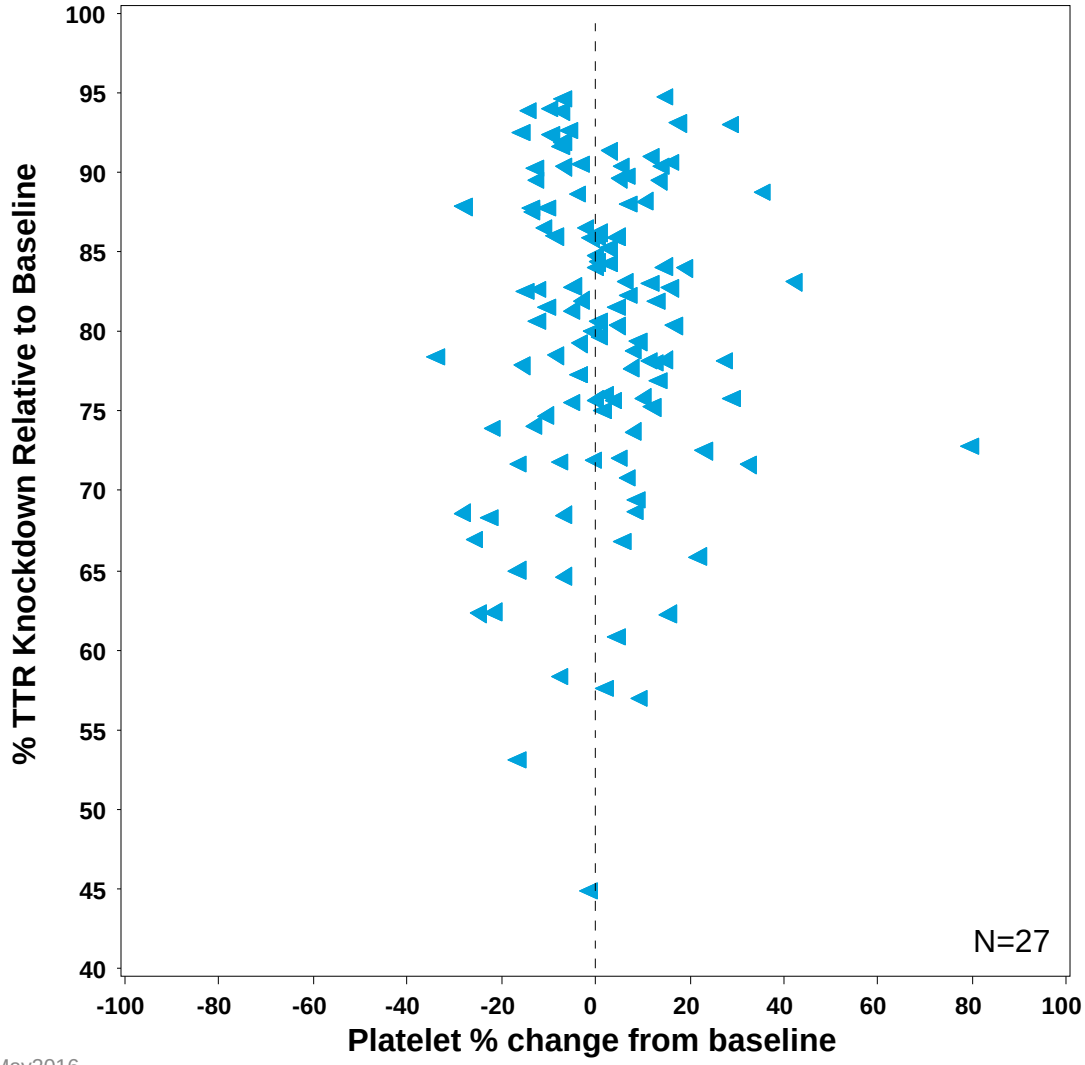
Patisiran Phase 2 OLE Preliminary Study Results*

TTR KD Effect versus Platelets for All Visits Through 24 months

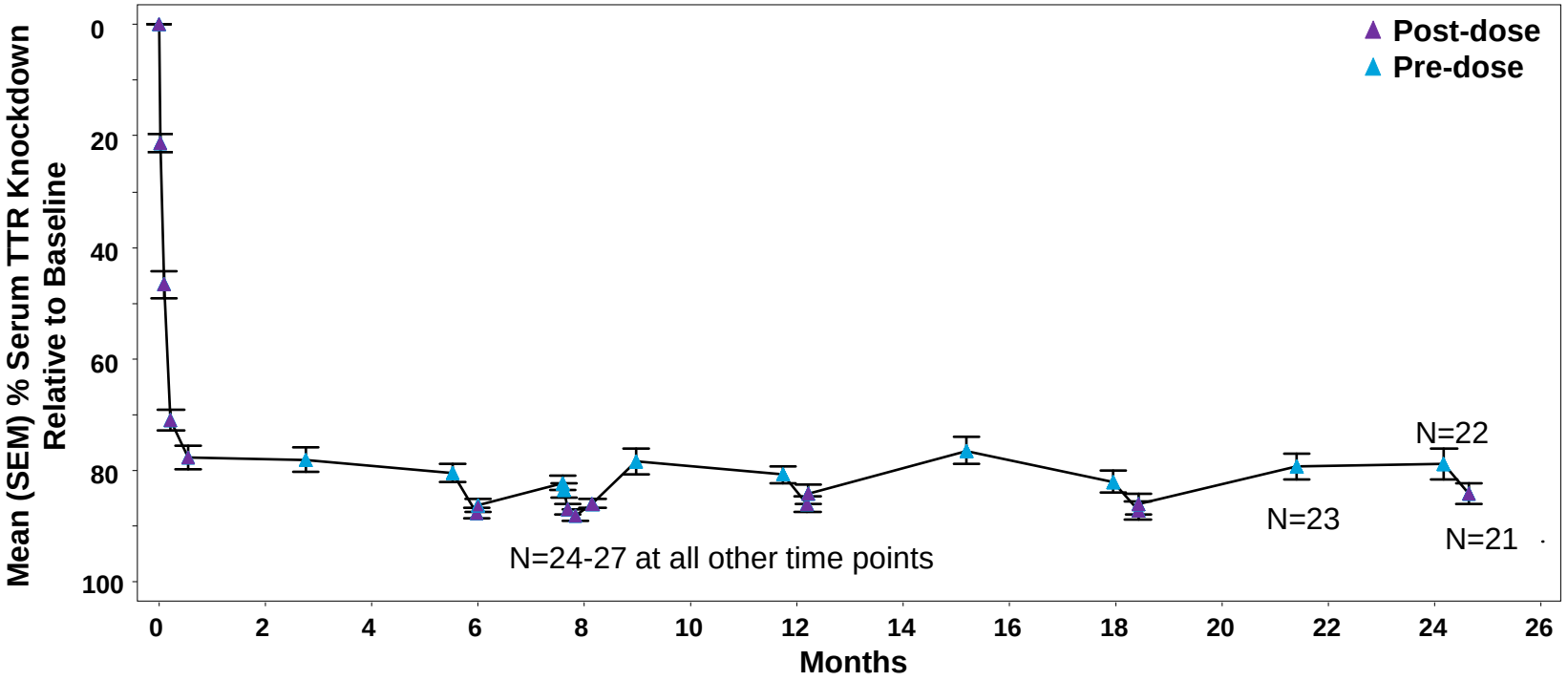
No correlation between TTR KD and change in platelets



*Data as of 12May2016

Patisiran Phase 2 OLE Preliminary Study Results*

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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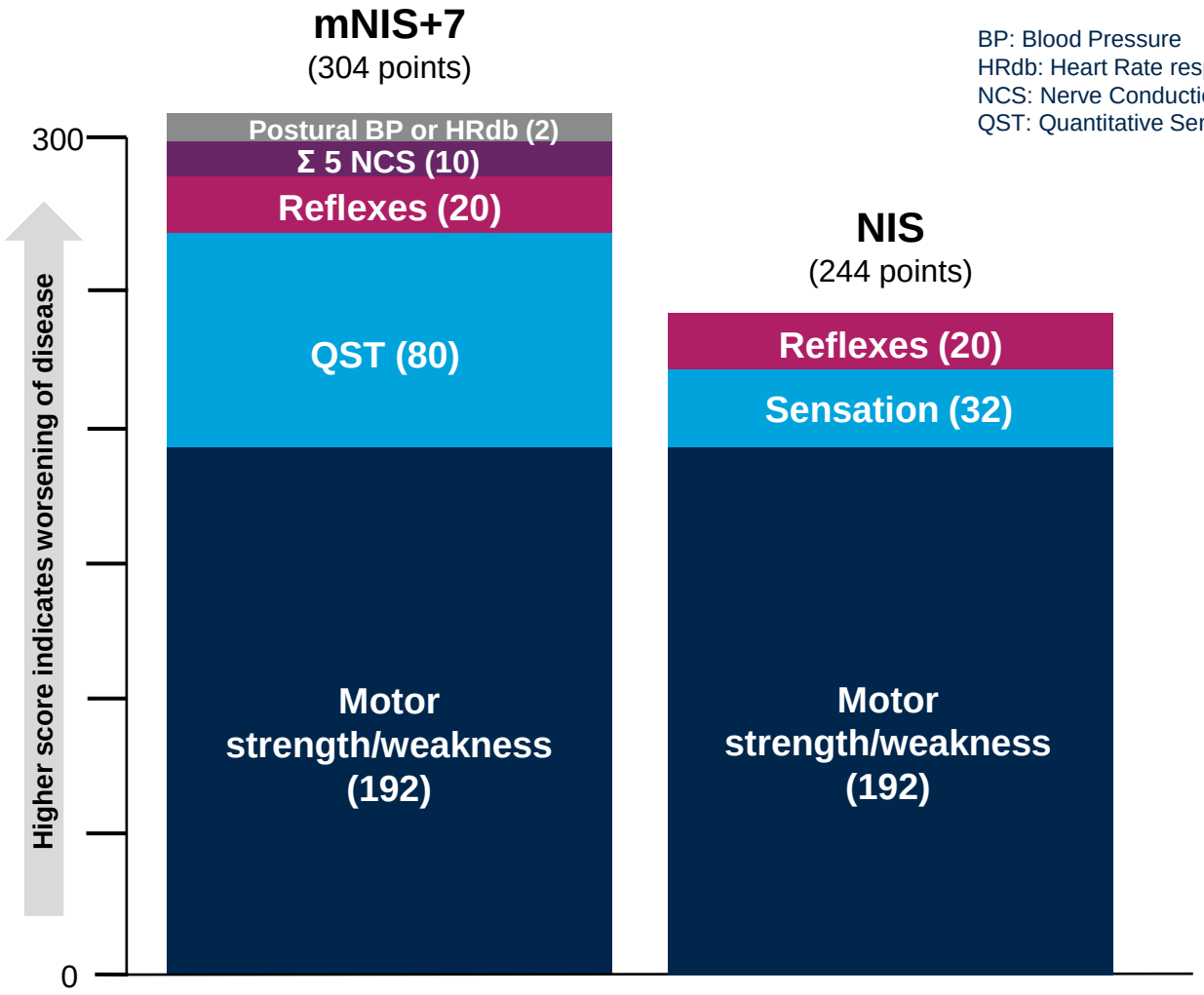
Neuropathy Impairment Scores Used in hATTR-PN Trials

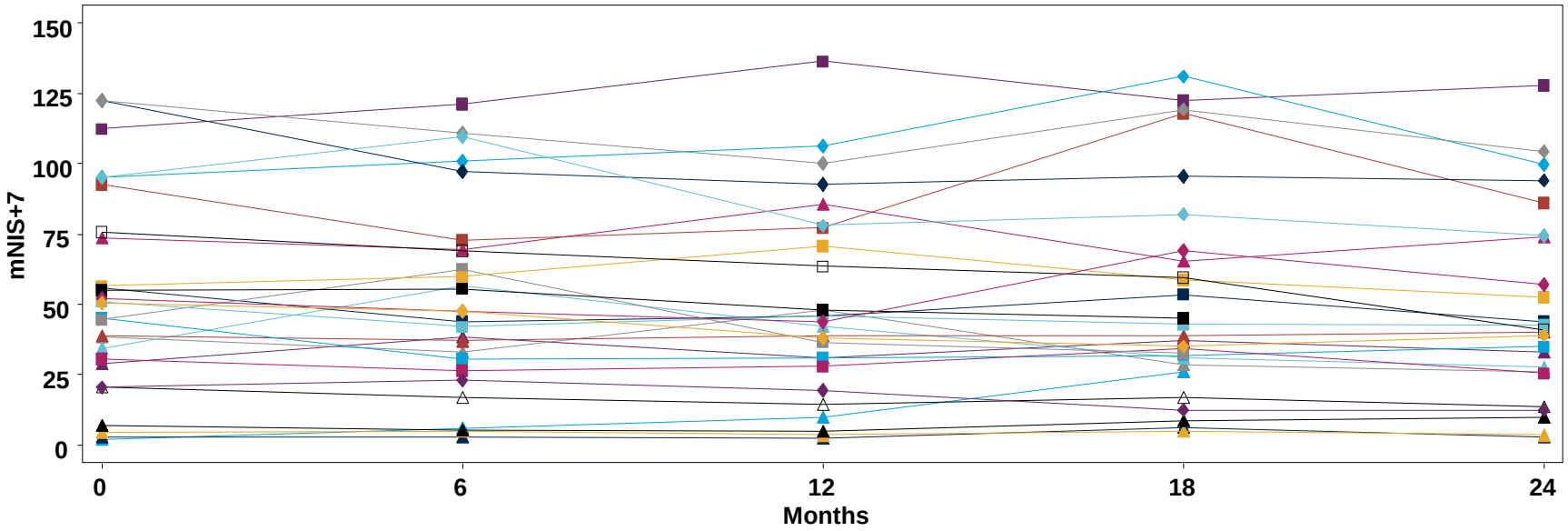


BP: Blood Pressure
HRdb: Heart Rate response to Deep Breathing
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

[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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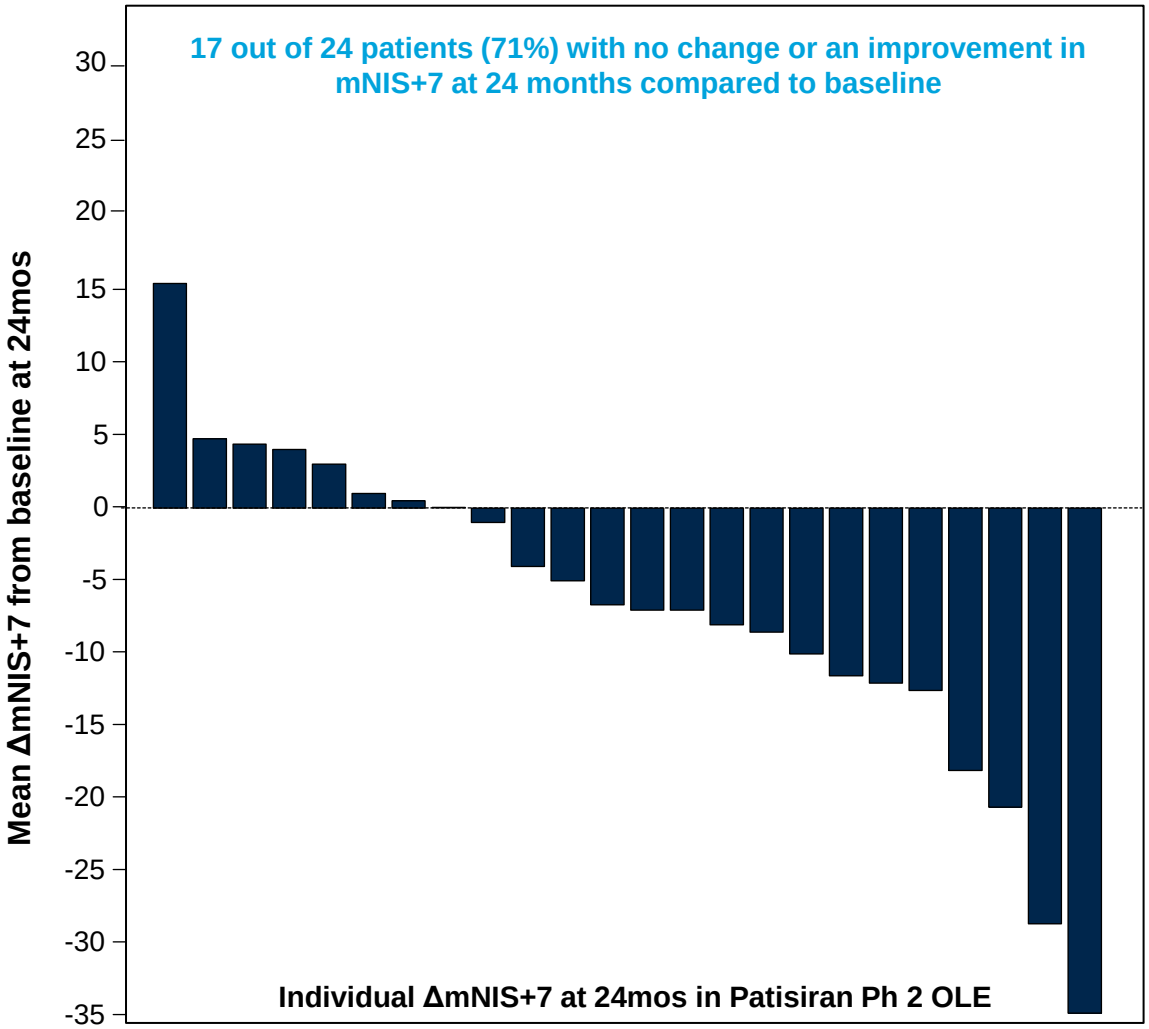
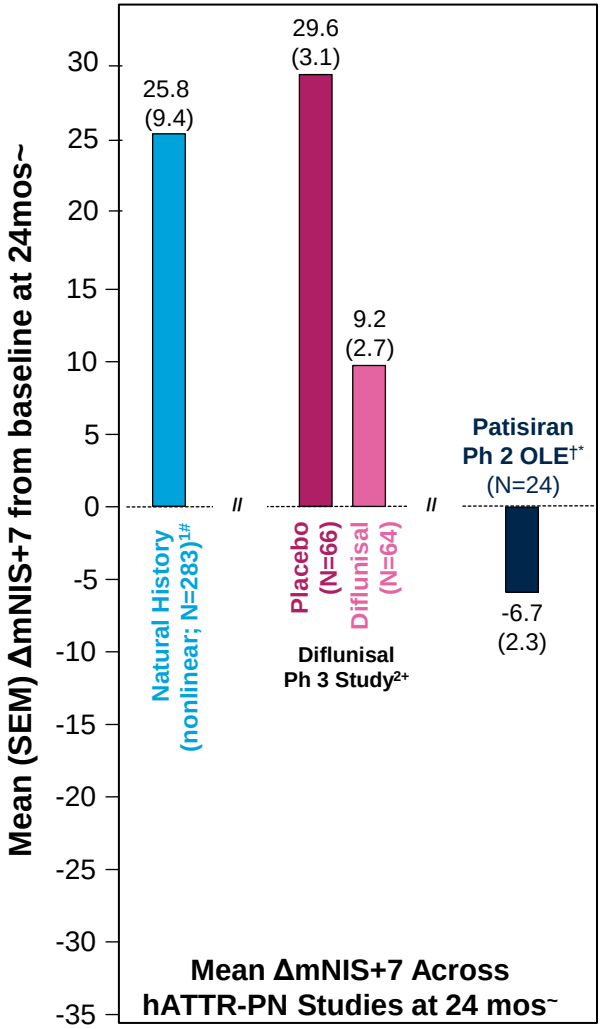
Patisiran Phase 2 OLE Preliminary Study Results*

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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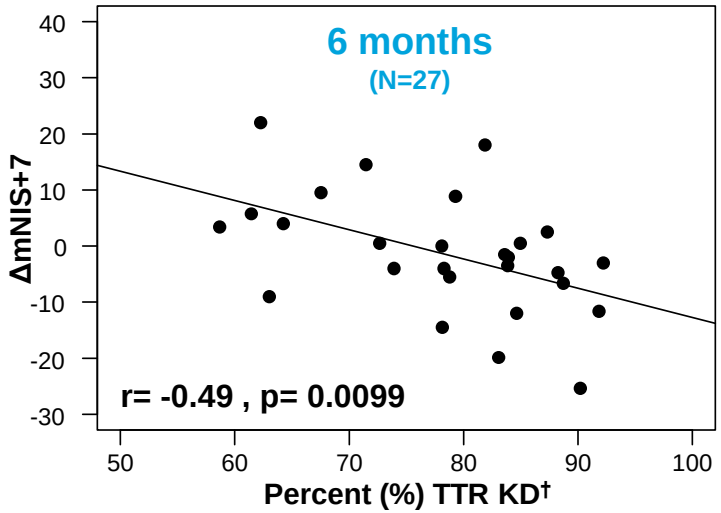
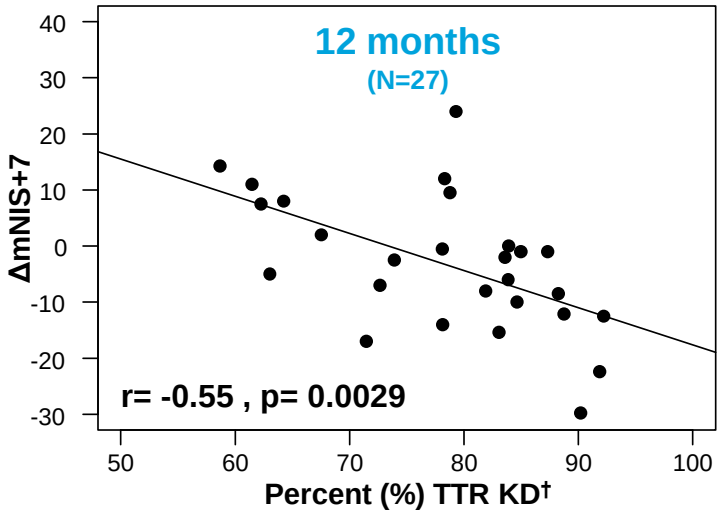
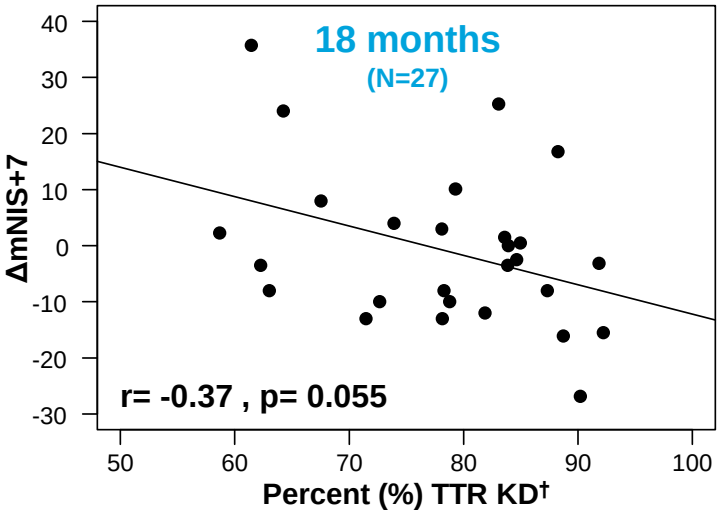
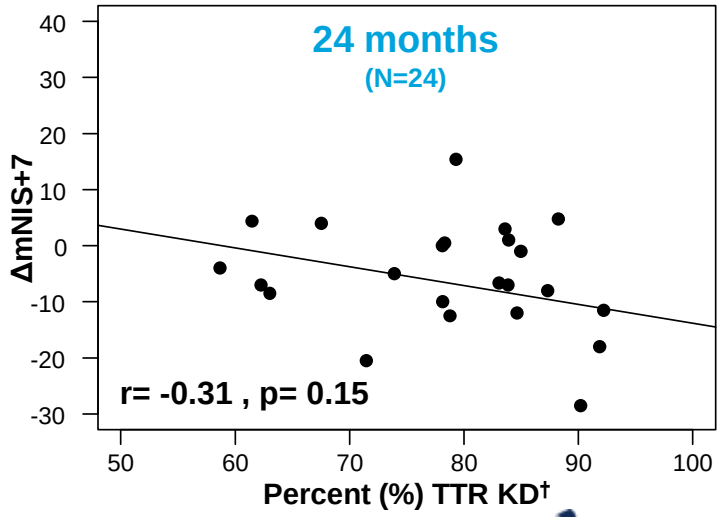
Patisiran Phase 2 OLE Preliminary Study Results*

Correlation of TTR Knockdown with ΔmNIS+7









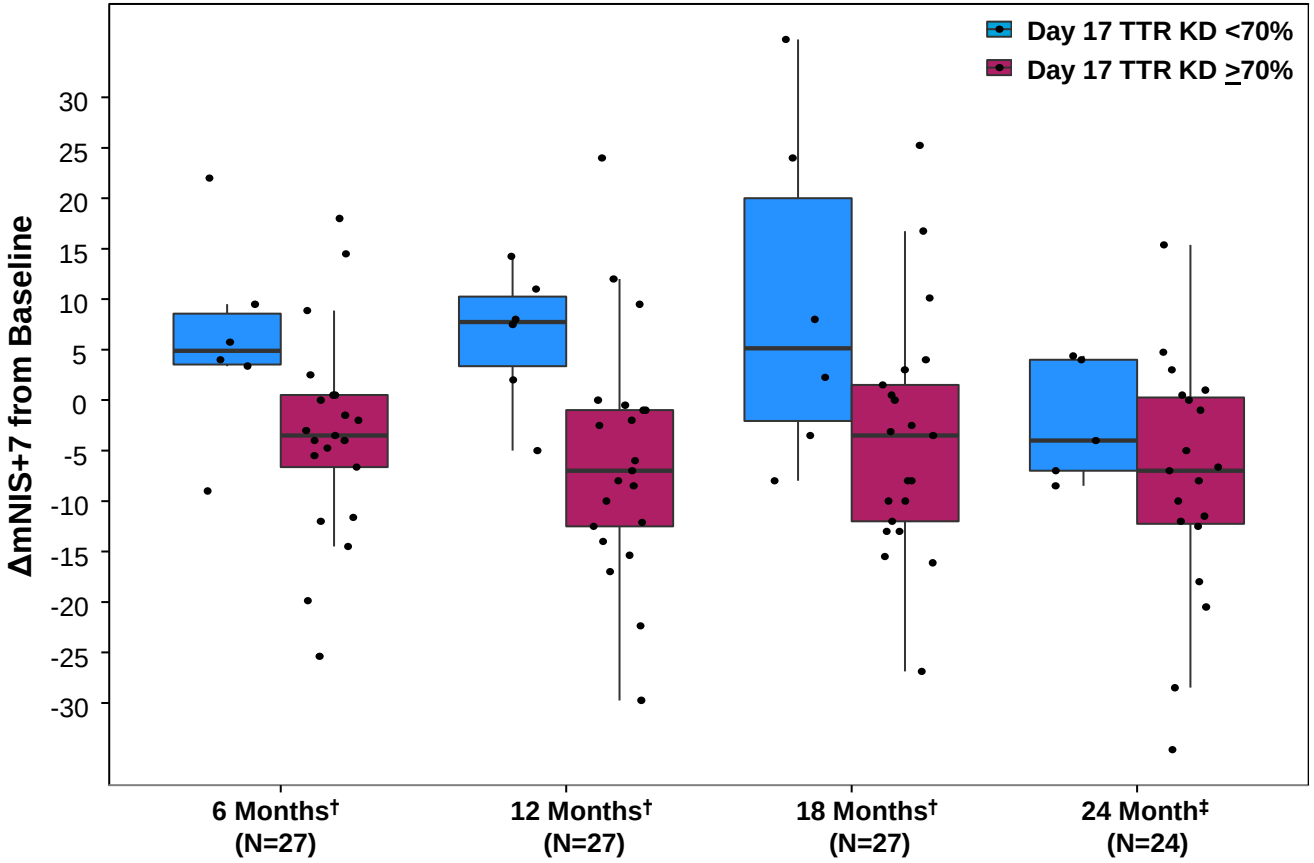
Note: three patients had missing D17 TTR: one was replaced by D7 and two replaced by D84.
† Percent (%) TTR knockdown from baseline at Day 17 post-first dose of patisiran
*Data as of 12May2016

Patisiran Phase 2 OLE Preliminary Study Results*

Change Over Time in Correlation Between %TTR KD and ΔmNIS+7

Degree of TTR knockdown with patisiran correlates with subsequent change in mNIS+7

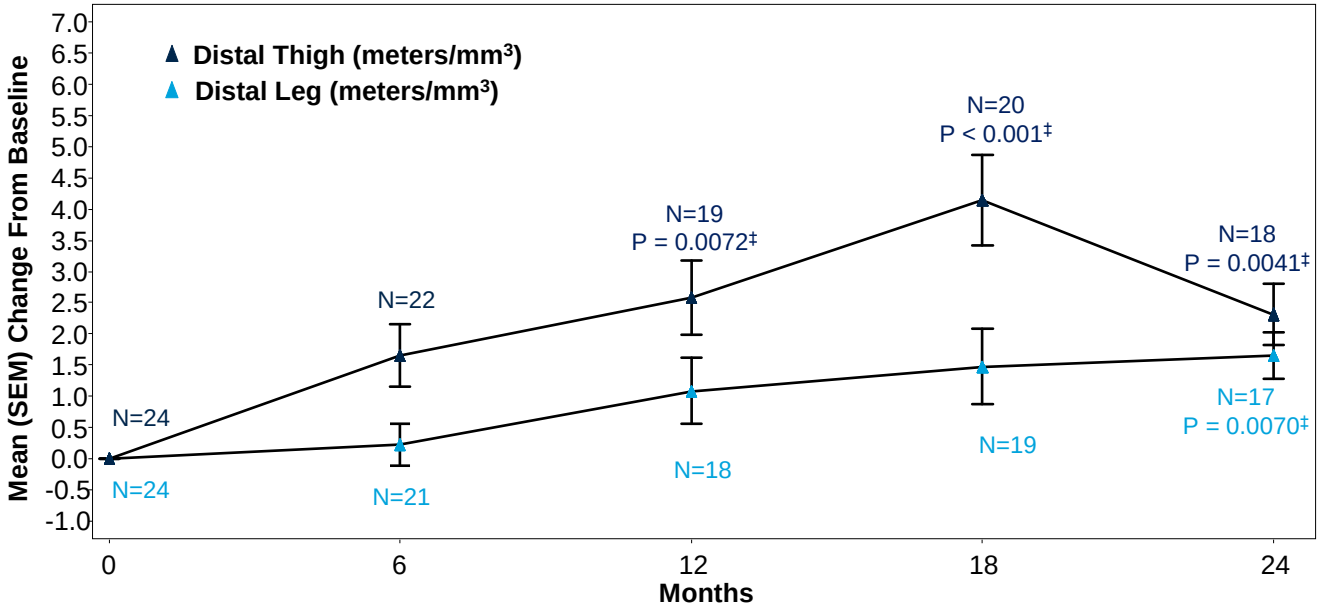
- Strongest correlation observed at 6 and 12 months
- Loss of significant correlation between 18 and 24 months suggests that lesser degrees of TTR KD (<70%) may impact neuropathy progression if maintained over longer period of time



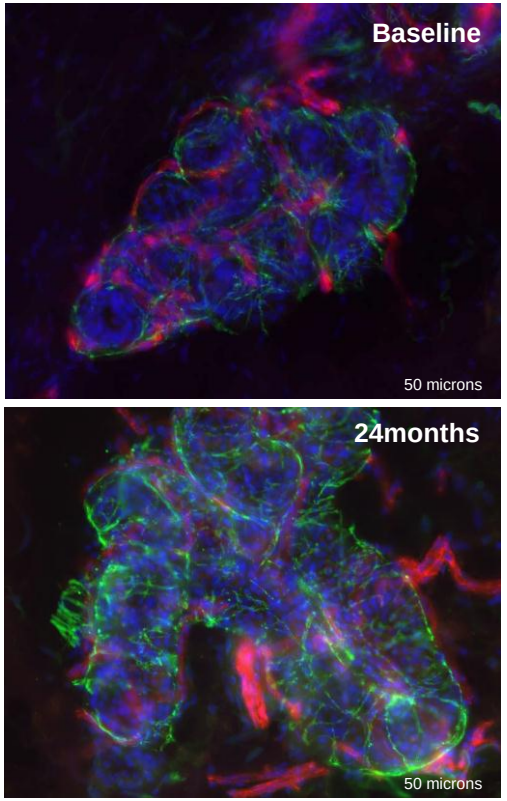
† Day 17 TTR KD <70% (n=6); Day 17 TTR KD >70% (n=21)
‡ Day 17 TTR KD <70% (n=5); Day 17 TTR KD >70% (n=19)
*Data as of 12May2016

Patisiran Phase 2 OLE Preliminary Study Results*

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*

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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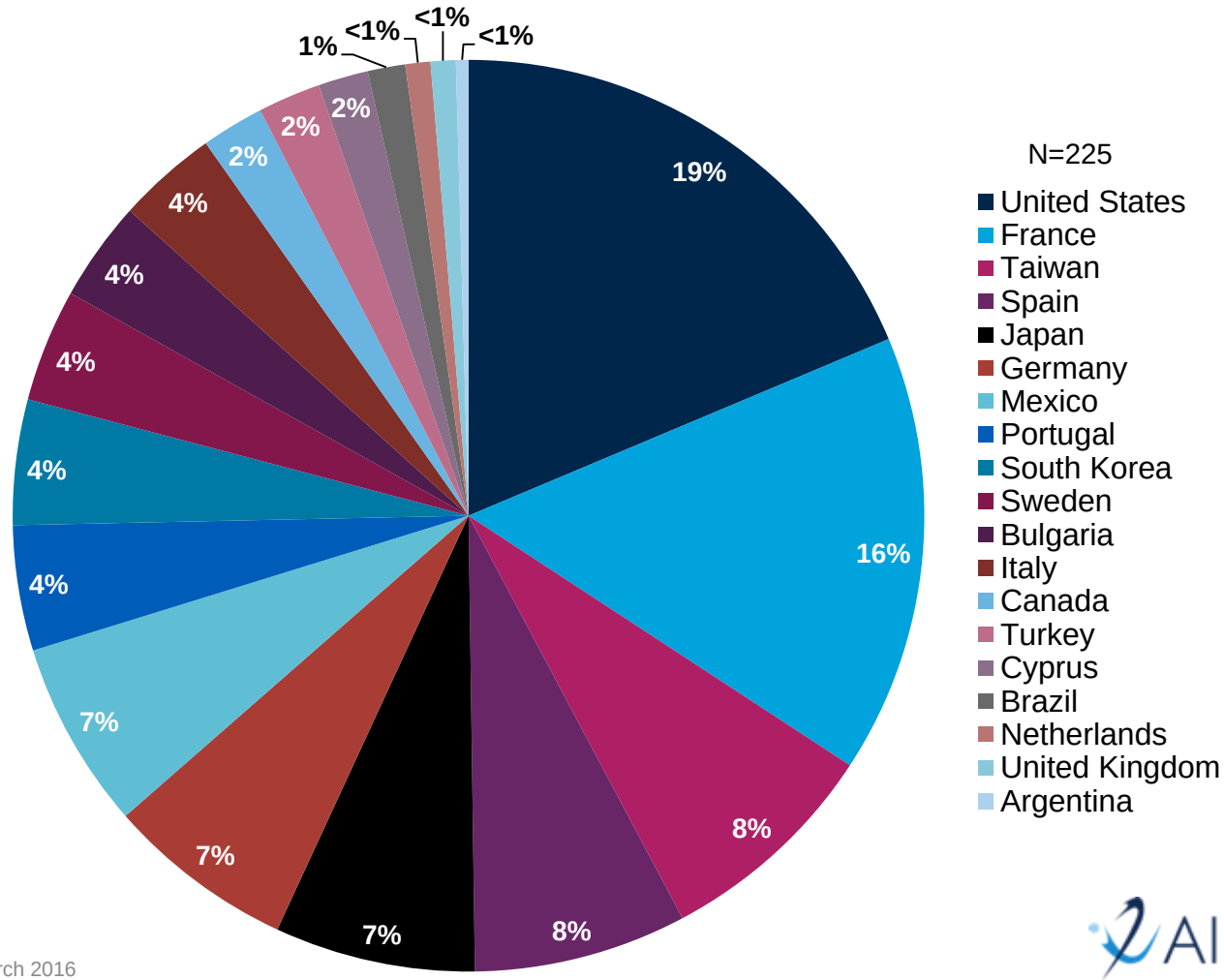
APOLLO Patisiran Phase 3 Study

Enrollment by Country

A total of 225 patients with hATTR-PN enrolled from Dec 2013 – January 2016

Patients enrolled at 44 sites in 19 countries



*Data as of 01 March 2016

APOLLO Patisiran Phase 3 Study

Baseline Demographics

Characteristic	Result
Number of patients	N=225
Median age, years (range)	62 years (24-82)
Gender, n (%) males	167 (74)
Race, n (%)	
Asian	51 (23)
Black/African or African American	6 (3)
White / Caucasian	162 (72)
Other/Missing	6 (3)
Previous tetramer stabilizer use, n (%)	119 (53)
mBMI, kg/m^2 x albumin [g/dL]	978.7 (522.1-1530.0)
Patients with cardiac involvement, n (%)	122 (54)
Mean NT-proBNP, ng/L (range)	1461 (40-7895)
Mean troponin, ng/mL (range)	0.1 (0.1-1.0)
LV wall thickness, cm (range)	1.67 (1.3, 2.6)
Ejection fraction (range)	60.6 (31.8, 82.4)

Characteristic	Result
TTR genotype, n (%)	
V30M	95 (42)
nonV30M*	130 (58)
FAP Stage, n (%)	
1	104 (46)
2	119 (53)
3	2 (1)
PND Score, n (%)	
I	57 (25)
II	65 (29)
IIIA	63 (28)
IIIB	38 (17)
IV	2 (1)
Neuropathy Impairment Scores, mean (range)	
mNIS+7	78.8 (8.0-165.0)
NIS	59.3 (6.0-141.6)

†Represents 57 different mutations, including GLU-89-GLN (n=13); THR-60-ALA (n=13); ALA-97-SER (n=15); SER-50-ARG (n=8); as well as numerous other mutations with ≤5 patients per group
Data as of 01 March 2016

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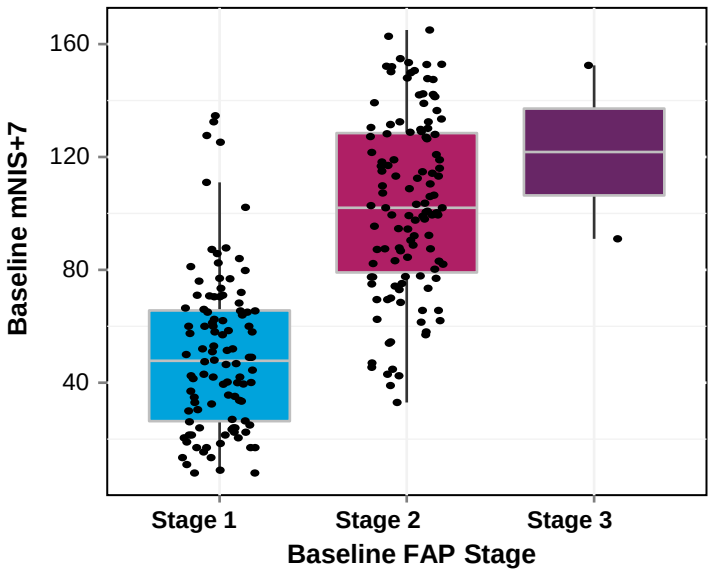
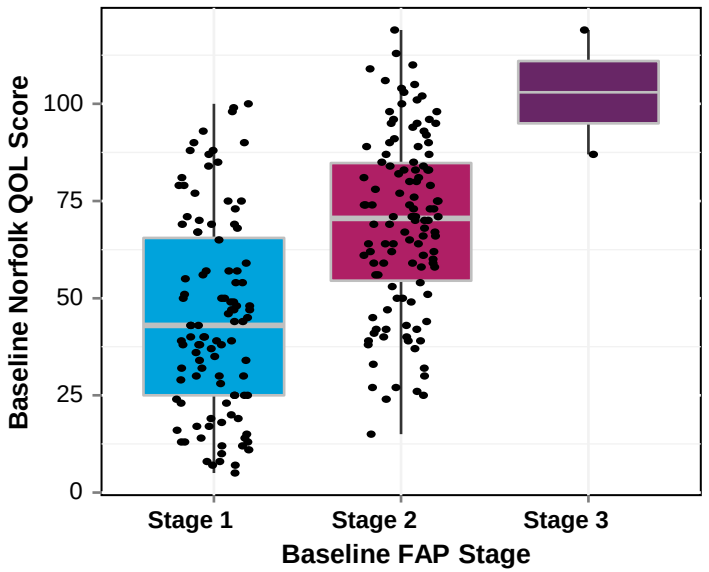
APOLLO Patisiran Phase 3 Study

Correlation Data

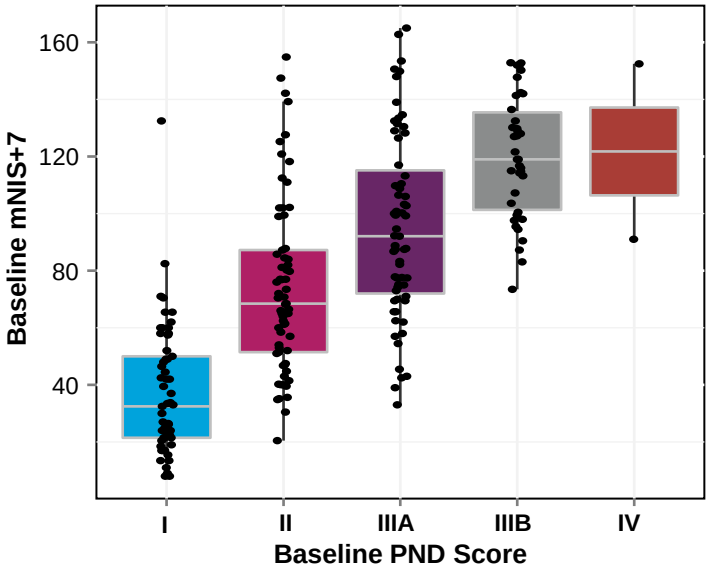
Baseline mNIS+7 vs FAP Stage



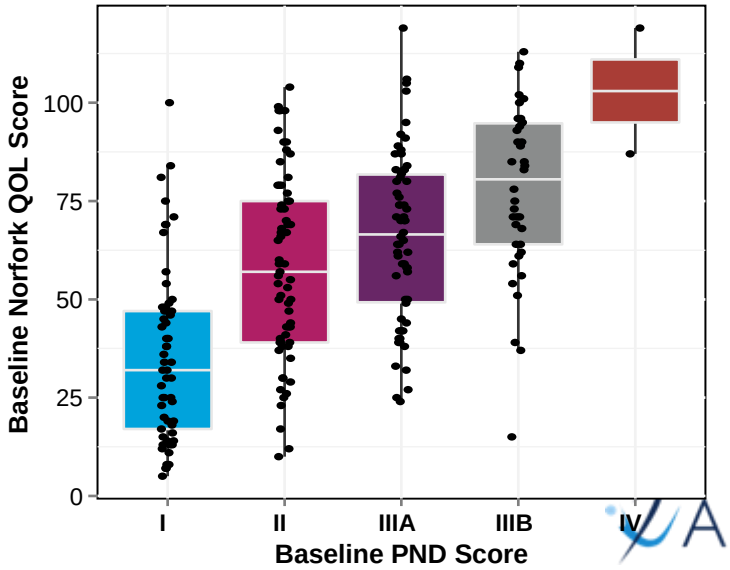
Baseline Norfolk QOL vs FAP Stage



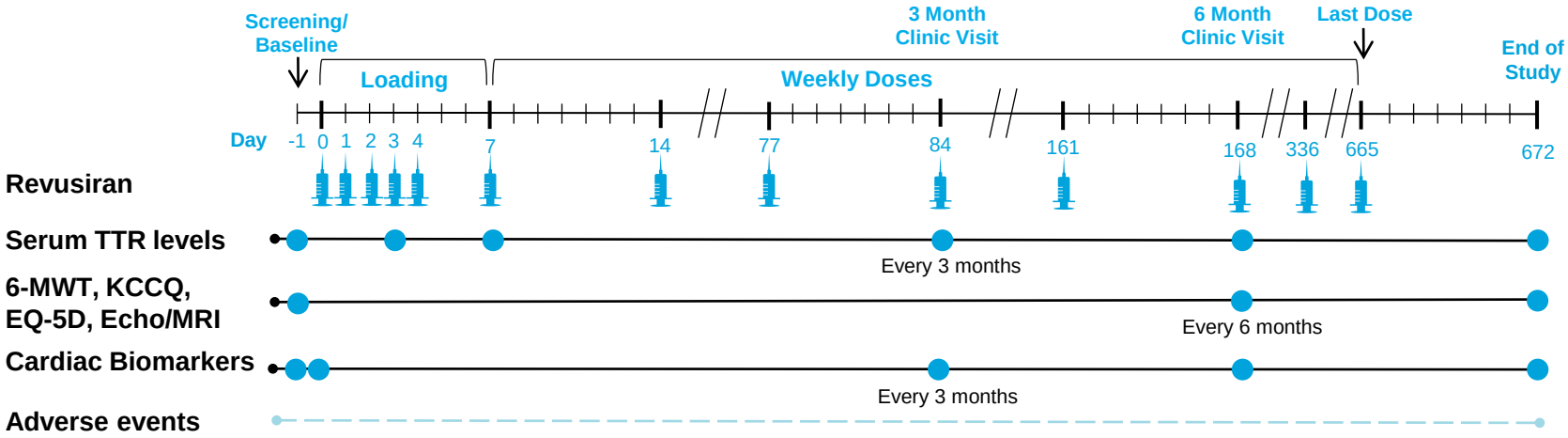
Baseline mNIS+7 vs PND Score



Baseline Norfolk QOL vs PND Score



Revusiran Phase 2 OLE Study Design



hATTR-CM and wtATTR patients previously enrolled in Phase 2 study eligible to enter Phase 2 OLE study

- Chronic dosing with clinical endpoints evaluated every 6 months
  - Clinical endpoints include those evaluated in the ENDEAVOUR Phase 3 Study
  - Dose/regimen: 500 mg, daily x 5, followed by weekly
- Study Objectives
  - Primary: Safety and tolerability of long term dosing with revusiran
  - Secondary: Effect on serum TTR and on mortality, hospitalization and 6-minute walk distance (6-MWD)
  - Tertiary: Pharmacokinetics and effects on cardiac biomarkers, cardiac imaging, NYHA class, KCCQ, and Quality of Life (EQ-5D)

Timelines are not to scale

Revusiran Phase 2 OLE Preliminary Results*

Demographics and Exposure

This presentation highlights 12 month data from the study

Characteristics		hATTR-CM (N=14)	wtATTR (N=11)	Total (N=25)
Median Age (range)		66 years (53–79)	73 years (65–79)	70 years (53–79)
Male Gender		11 (79%)	11 (100%)	22 (88%)
Race		10 White, 4 AA	11 White	21 White, 4 AA
TTR Type	**WT**		11 (100%)	11 (44%)
	T60A	7 (50%)		7 (28%)
	V122I	5 (36%)		5 (20%)
	S77Y	1 (7%)		1 (4%)
	I84S	1 (7%)		1 (4%)
NYHA Class	**I**	1 (7%)	1 (9%)	2 (8%)
	II	11 (79%)	6 (55%)	17 (68%)
	III	2 (14%)	4 (36%)	6 (24%)
Mean time from diagnosis to first dose (range)		34 months (5,94)	35 months (15,57)	35 months (5,94)
Mean eGFR (mL/min/1.73m^2)		79.8 (42–131)	60.4 (27–101)	71.2 (27–131)
Karnofsky (60/70/80/90/100)		2/2/5/4/1	1/4/4/2/0	3/6/9/6/1
Concurrent Diflunisal use		3	1	4
Exposure				
Total doses administered		788	524	1312
Mean number of doses (range)		56 (14-80)	48 (9-67)	53 (9-80)
Mean treatment duration (range)		12 months (2-18)	10 months (1-15)	11 months (1-18)

AA: African American
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Alnylam PHARMACEUTICALS

Revusiran Phase 2 OLE Preliminary Results*

Baseline Characteristics

Characteristics	Mean (range)					
	N	hATTR-CM	N	wtATTR	N	Total
mBMI (kg/m^2 x albumin [g/dL])	14	1093 (859–1812)	11	1133 (963–1287)	25	1111 (859–1812)
6-MWD (meters)	14	400 (73–617)	11	403 (305–513)	25	401 (73–617)
KCCQ Overall Summary Score	14	71.1 (22.8–98.4)	11	68.4 (43.5–88.0)	25	69.9 (22.8–98.4)
EQ-5D (max impairment=0)	14	0.83 (0.48–1.00)	11	0.78 (0.68–0.85)	25	0.81 (0.48–1.00)
Cardiac Biomarkers						
NT-proBNP (ng/L)	14	3949 (349–21310)	11	3054 (419–5652)	25	3555 (349–21310)
Troponin I (ng/mL)	14	0.15 (0.1–0.4)	11	0.13 (0.1–0.4)	25	0.14 (0.1–0.4)
Echocardiogram						
IVS Thickness (cm)	14	2.1 (1.7–2.5)	11	2.0 (1.5–2.9)	25	2.0 (1.5–2.9)
LVEF (%)	14	51 (28–69)	11	48 (27–64)	25	49 (27–69)
Longitudinal Strain (%)	14	-12.0 (-20.8 to -6.3)	11	-10.4 (-17.3 to -6.4)	25	-11.3 (-20.8 to -6.3)
Cardiac MRI						
LV Mass (g)	12	200 (135–338)	9	229 (156–387)	21	212.7 (135-387)
Stroke Volume (mL)	12	67.6 (44.6–97.2)	9	90.6 (61.9–123.4)	21	77.5 (44.6–123.4)
Global ECV	12	0.55 (0.4–0.7)	9	0.55 (0.4–0.8)	21	0.55 (0.4–0.8)

mBMI: Modified Body Mass Index; 6-MWD: 6-Minute Walk Distance; KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references; IVS: Interventricular Septum; LVEF: Left Ventricular Ejection Fraction; LV: Left Ventricular; ECV: Extracellular Volume Fraction; H/CL: heart to collateral lung; Reference Ranges: IVS 0.6-1.0 cm (M), 0.6-0.9 cm (F), LVEF >50%, Longitudinal strain: -15.9% to -21.1%, Normal Average Values: LV Mass 155 g (M), 103 g (F), Stroke Volume 78.6 mL (M), 59.3 mL (F), ECV <0.3

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Alnylam PHARMACEUTICALS

Revusiran Phase 2 OLE Preliminary Results*

Patients who discontinued due to death or disease progression had longer time from diagnosis to first dose

Characteristics		Ongoing n=11	Off Study† n=8	P-value
Median Age (range)		68 years (53-73)	73 years (62-75)	p=0.07
Male Gender		9 (82%)	7 (88%)	p=1.00
TTR Type	**V122I**	3 (27%)	-	p=0.35
	T60A	3 (27%)	4 (50%)	
	I84S	1 (9%)	-	
	S77Y	1(9%)	-	
	Wild-Type	3 (27%)	4 (50%)	
NYHA Class	**I**	2 (18%)	0	p=0.14
	II	8 (74%)	4 (50%)	
	III	1 (9%)	4 (50%)	
Time from ATTR Diagnosis to First Dose on Ph2 OLE	**Mean (range)**	25 months (6-48)	48 months (26-94)	p < 0.05
Baseline 6MWD	**Mean (range)**	468 meters (316-617)	359 meters (73-444)	p=0.08

† Patients who discontinued for reasons of death or disease progression
P-value based upon non-parametric test to determine if there were differences between Ongoing versus Off study (t-test for continuous parameters and fisher's exact test for categorical)
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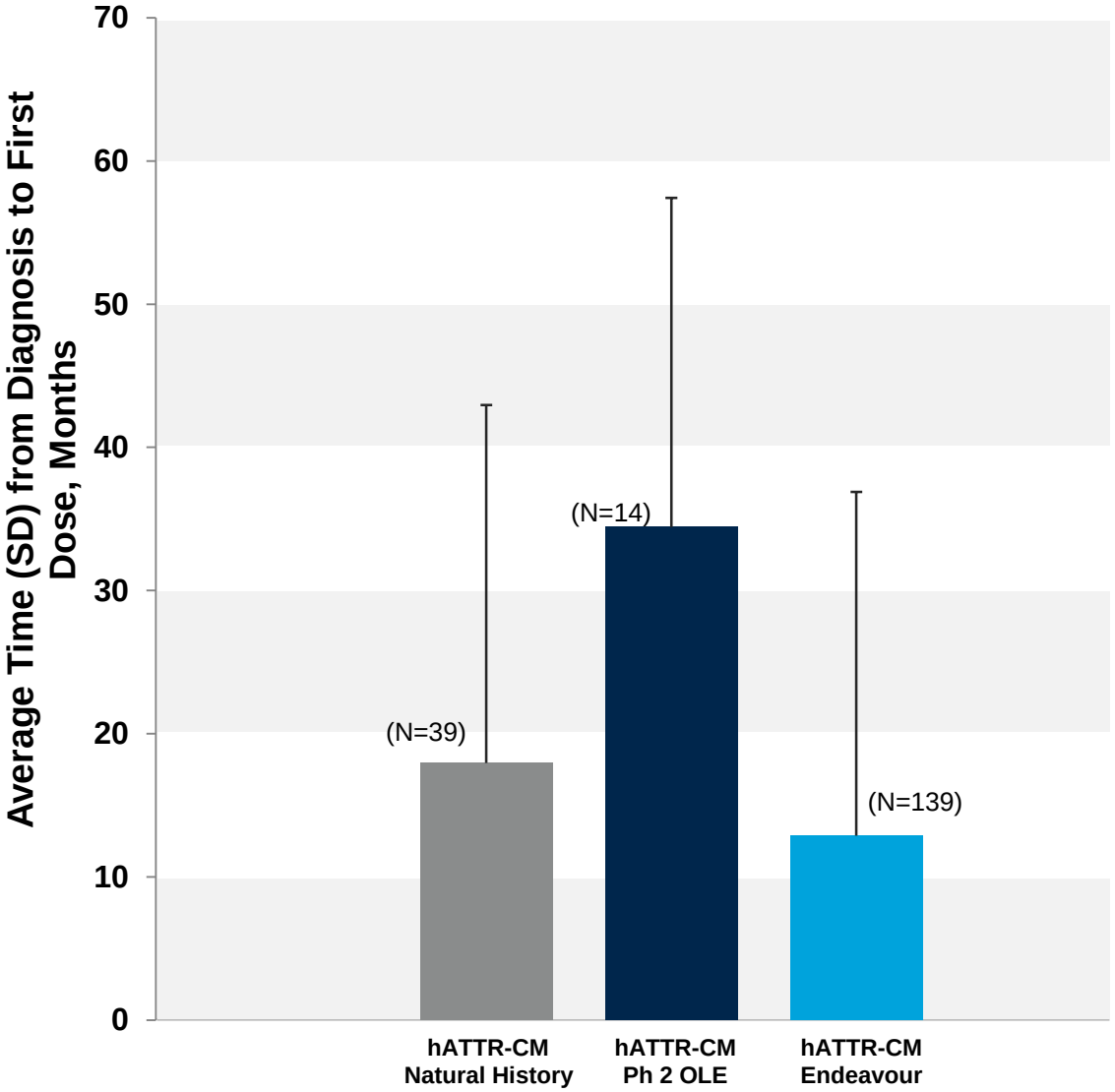
Alnylam PHARMACEUTICALS

Time from Diagnosis Across hATTR-CM Studies



SD: standard deviation bars
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Revusiran Phase 2 OLE Preliminary Results*

Summary of Safety

Common Adverse Events (AEs) reported in ≥ 20% of patients

AE by Preferred Term	Revusiran (N=25)
Patients with an AE, n (%)	25 (100%)
Cough	10 (40%)
Dizziness	10 (40%)
Injection site erythema	8 (32%)
Dyspnea	7 (28%)
Fatigue	7 (28%)
Edema peripheral	7 (28%)
Hypotension	6 (24%)
Injection site pruritus	6 (24%)
Neuropathy peripheral	6 (24%)
Atrial fibrillation	5 (20%)
Cardiac failure	5 (20%)
Constipation	5 (20%)
Fall	5 (20%)
Muscle spasms	5 (20%)
Weight decreased	5 (20%)

- 14 patients (56%) with serious adverse events (SAEs)
  - Only 1 deemed possibly related to study drug: patient with lactic acidosis, discontinued treatment; patient also had myopathy, neuropathy, hypotension, and vasoplegic shock resulting in death (all considered not related)
- 7 deaths (28%); all considered not related to study drug†
- 4 patients (16%) discontinued treatment due to drug-related AE
  - 3 patients due to recurrent localized reactions at the injection site or diffuse rash (previously reported at EC ATTR, 2015)
  - 1 patient due to lactic acidosis and other events as noted above
- Injection site reactions (ISR) reported in 12 patients (48%)
  - Majority of symptoms were mild in severity
    - Most common symptoms were erythema, pruritus, pain or swelling at the injection site
- 2 dose reductions to 250 mg weekly
  - 1 patient for recurrent injection site reactions and 1 patient for LFT elevation which resolved with continued dosing
- No other notable changes in liver function tests, renal function or hematologic parameters, including platelets

† Deaths reported as: anoxic encephalopathy due to cardiac arrest; cardiac failure aggravated (disease progression); congestive heart failure; amyloid disease progression; heart failure, hypotension, lower respiratory tract infection; vasoplegic shock (lactic acidosis, myopathy, neuropathy, hypotension); Suicide

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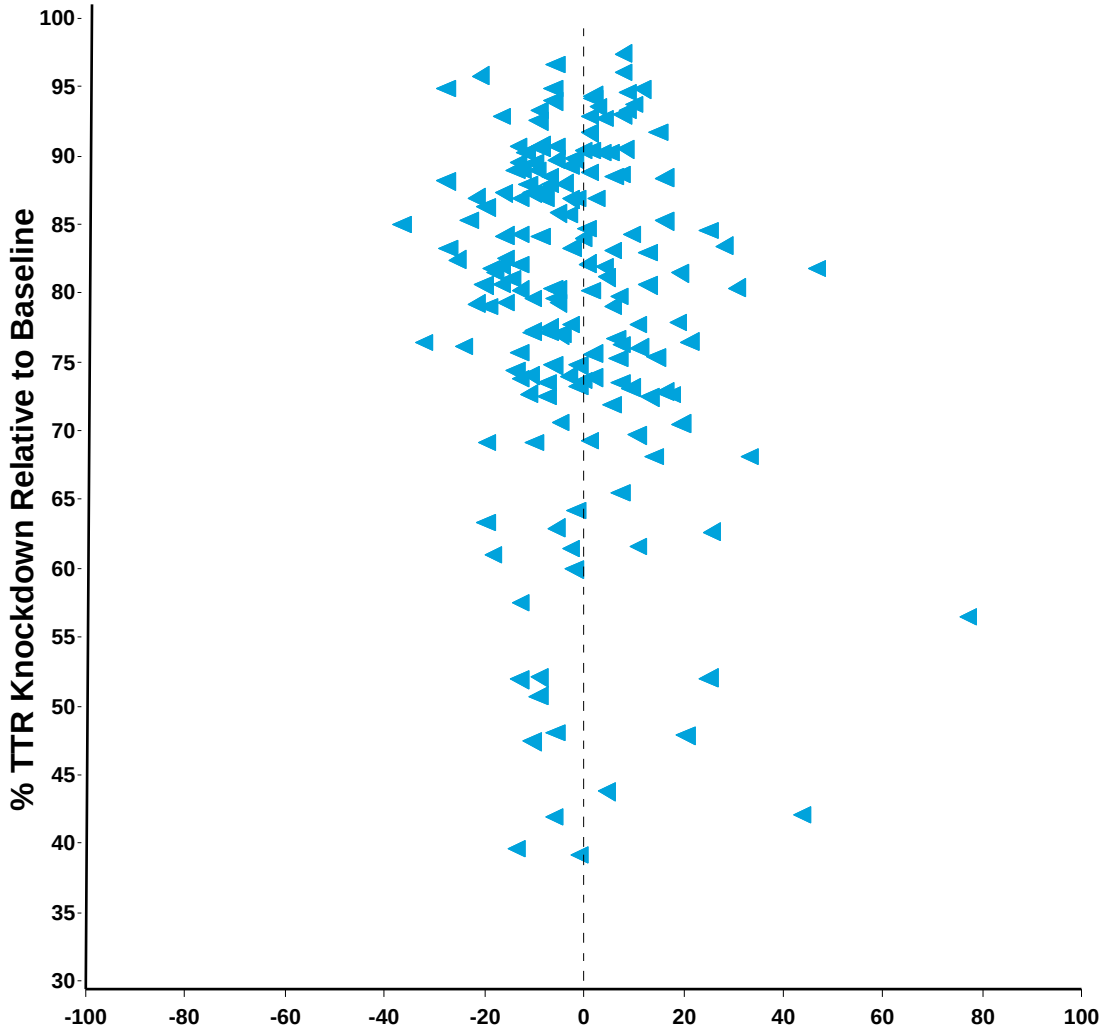
Revusiran Phase 2 OLE Preliminary Results*

TTR KD Effect versus Platelets for All Visits

No correlation between TTR KD and change in platelets



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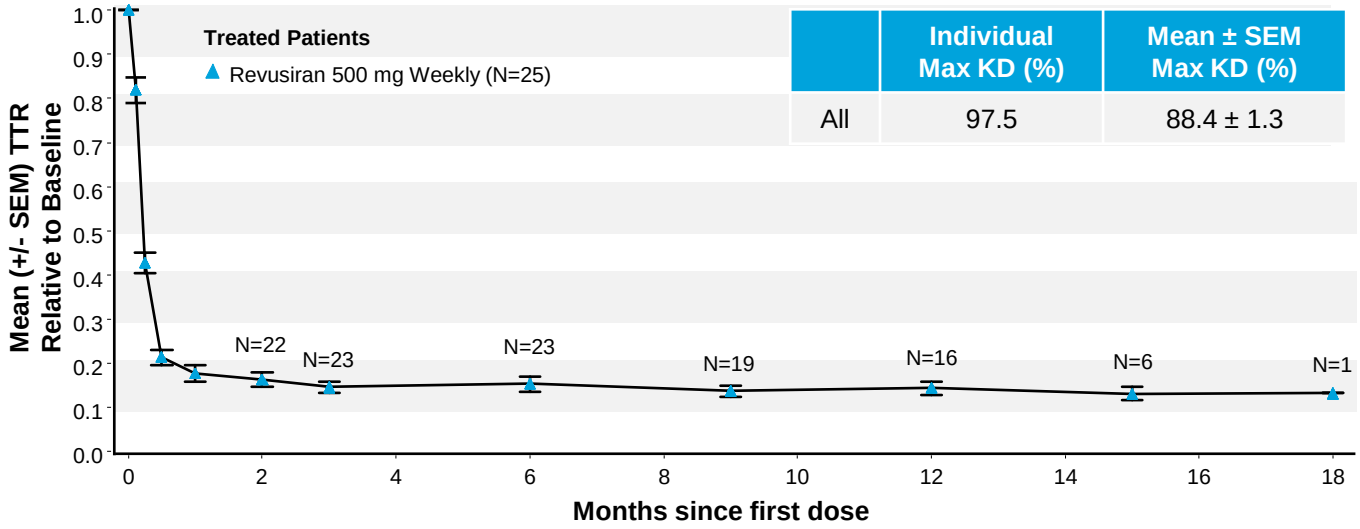
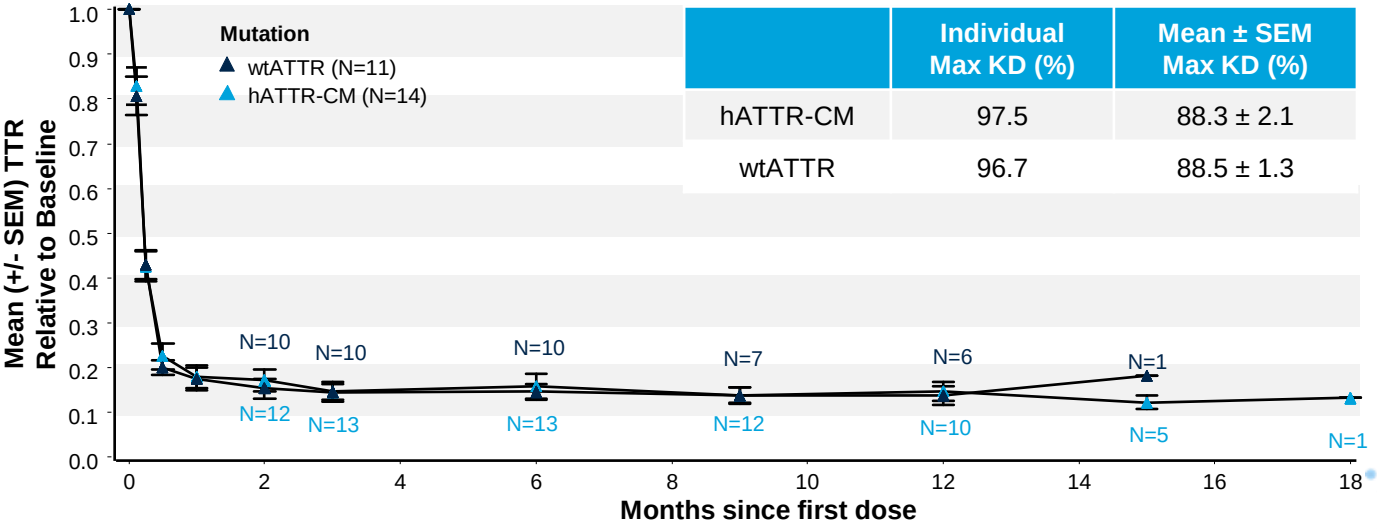
Revusiran Phase 2 OLE Preliminary Results*

Durable TTR Knockdown through 18 Months

- Longest first generation GalNAc-siRNA conjugate experience in humans to-date, low inter-patient variability and no diminished PD effect over time



	Individual Max KD (%)	Mean ± SEM Max KD (%)
All	97.5	88.4 ± 1.3

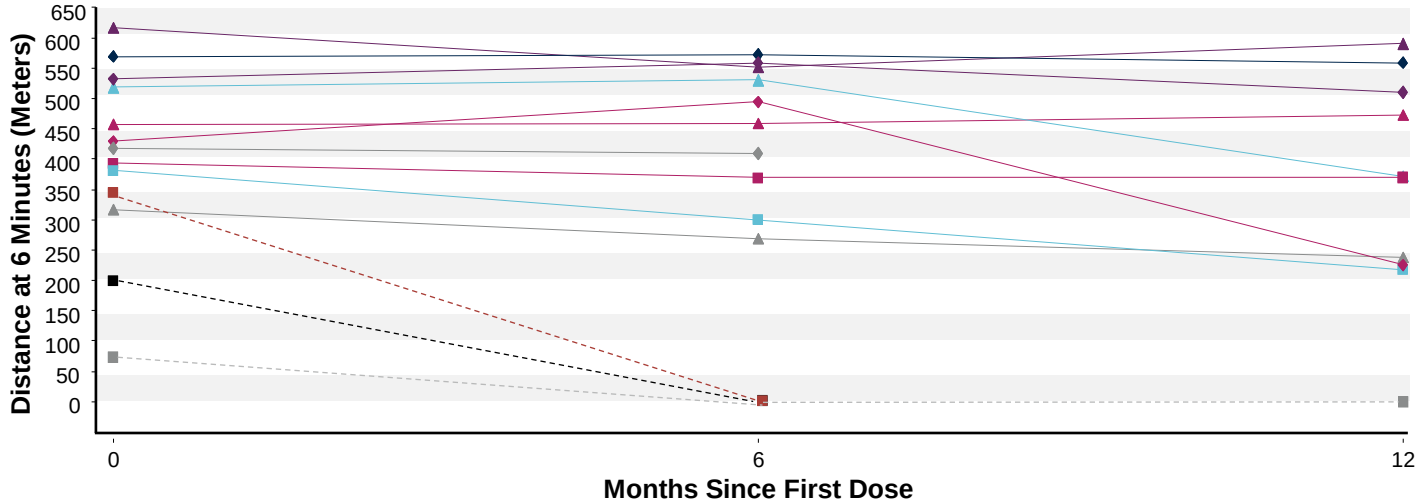


	Individual Max KD (%)	Mean ± SEM Max KD (%)
hATTR-CM	97.5	88.3 ± 2.1
wtATTR	96.7	88.5 ± 1.3

Revusiran Phase 2 OLE Preliminary Results*

Change in 6-MWD in hATTR-CM Patients

- 5 of 9 evaluable hATTR-CM patients have generally stable 6-MWD at 12 month compared to baseline with a mean change of -14 ± 8 meters



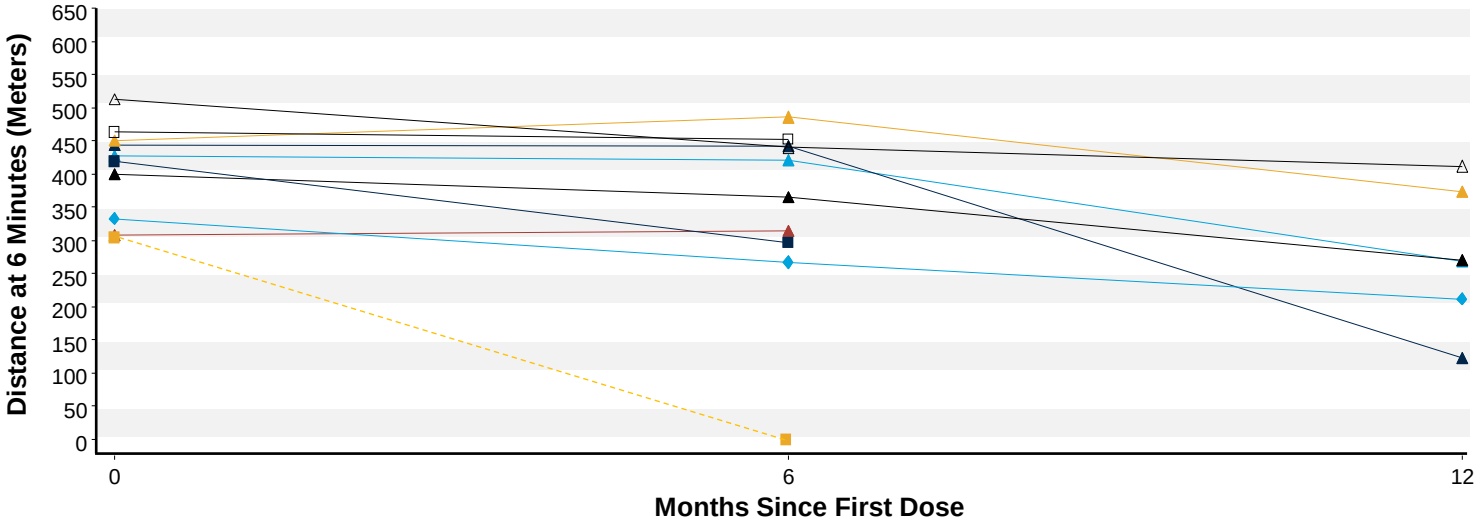
No Imputation			
	Baseline [meters]	**Δ Month 6 [meters]**	**Δ Month 12 [meters]**
Ph2 OLE	N=14	N=10	N=9
Mean ±SEM	400 ±39	-12 ±14	-73 ±26
Median (Min, Max)	406 (73, 617)	-4 (-81, 65)	-27 (-204, 15)
Natural History	N=37	N=30	N=24
Mean ±SEM	283 ±19	-23 ±21	-69 ±14
Median (Min, Max)	276 (46, 485)	-14 (-311, 209)	-57 (-188, 32)

With Imputation†			
	Baseline [meters]	**Δ Month 6 [meters]**	**Δ Month 12 [meters]**
Ph2 OLE	N=14	N=13	N=10
Mean ±SEM	400 ±39	-57 ±30	-73 ±23
Median (Min, Max)	406 (73, 617)	-24 (-345, 65)	-50 (-204, 15)
Natural History	N=39	N=32	N=27
Mean ±SEM	281 ±20	-36 ±23	-106 ±24
Median (Min, Max)	276 (46, 485)	-19 (-426, 209)	-79 (-499, 32)

† Patients too unwell to perform test at planned visit were imputed as 0 meters
*Data transfer 26May2016

Revusiran Phase 2 OLE Preliminary Results*

Change in 6-MWD in wtATTR Patients



No Imputation			
	Baseline [meters]	**Δ Month 6 [meters]**	**Δ Month 12 [meters]**
Ph2 OLE	N=11	N=9	N=6
Mean ±SEM	403 ±20	-30 ±16	-152 ±36
Median (Min, Max)	419 (305, 513)	-11 (-122, 35)	-126 (-322, -78)
Natural History	N=145	N=119	N=79
Mean ±SEM	320 ± 9	-25 ± 7	-29 ± 10
Median (Min, Max)	334 (16, 570)	-17 (-240, 136)	-11 (-259, 152)

With Imputation†			
	Baseline [meters]	**Δ Month 6 [meters]**	**Δ Month 12 [meters]**
Ph2 OLE	11	N=10	N=6
Mean ±SEM	403 ±20	-58 ±31	-152 ±36
Median (Min, Max)	419 (305, 513)	-23 (-305, 35)	-126 (-322, -78)
Natural History	N=153	N=125	N=88
Mean ±SEM	313 ±10	-30 ±7	-59 ±13
Median (Min, Max)	333 (16, 570)	-22 (-345, 136)	-30(-506, 152)

† Patients too unwell to perform test at planned visit were imputed as 0 meters

*Data transfer 26May2016

Revusiran Phase 2 OLE Preliminary Results*

Clinical Measurements

Characteristics	Actual Results at Each Visit Mean (SEM)				Changes From Baseline Mean (SEM)	
	N†	Baseline	6 Month	12 Month	Δ Month 6	Δ Month 12
mBMI (kg/m^2 x albumin [g/L])	16	1139 (58.6)	1061 (60.3)	977 (45.0)	-78 (16.8)	-162 (26.5)
KCCQ Overall Summary Score	15	79.3 (4.1)	74.5 (5.5)	63.4 (5.9)	-4.8 (2.2)	-15.9 (3.7)
EQ-5D (max impairment=0)	15	0.83 (0.04)	0.84 (0.04)	0.78 (0.04)	0.010 (0.03)	-0.055 (0.03)
Cardiac Biomarkers						
NT-proBNP (ng/L)	15	2188 (358)	2412 (401)	3136 (721)	224 (181)	949 (511)
Troponin I (ng/mL)	15	0.11 (0.02)	0.11 (0.02)	0.13 (0.02)	0.00 (0.01)	0.02 (0.02)
Echocardiogram						
IVS Thickness (cm)	16	2.1 (0.1)	2.1 (0.1)	2.1 (0.1)	0.01 (0.03)	-0.02 (0.05)
LVEF (%)	16	51.8 (2.8)	54.1 (3.5)	55.3 (3.5)	2.4 (1.9)	3.5 (2.3)
Longitudinal Strain (%)	16	-11.9 (0.9)	-12.4 (0.8)	-12.6 (0.8)	-0.5 (0.6)	-0.7 (0.7)
Cardiac MRI						
LV Mass (g)	10	240.1 (29.1)	249.2 (26.9)	251.7 (25.7)	8.5 (13.3)	10.9 (17.1)
Stroke Volume (mL)	9	86.1 (6.7)	88.0 (4.8)	92.9 (5.7)	1.9 (5.0)	6.9 (7.5)
Global ECV	9	0.51 (0.02)	0.48 (0.03)	0.54 (0.03)	-0.03 (0.02)	0.02 (0.03)

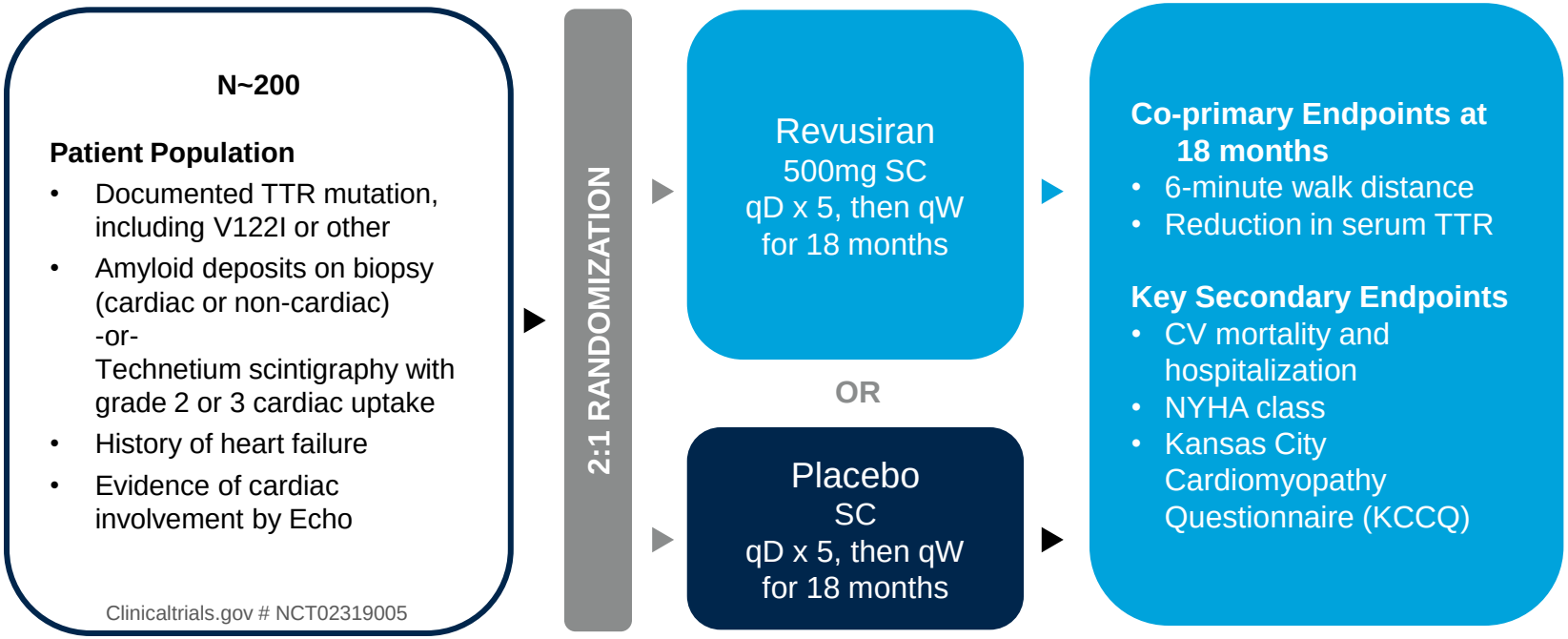
KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references; mBMI: Modified Body Mass Index; IVS: Interventricular Septum; ECV: Extracellular Volume Fraction; H/CL: heart to collateral lung

† Includes results for pooled hATTR-CM and wtATTR patients with available data at baseline and 12 months

*Data transfer 26May2016

ENDEAVOUR Phase 3 Study Design

Expect to complete enrollment by end summer and report data in early 2018



All completers eligible for revusiran treatment on Phase 3 OLE study

Statistical Considerations

- Placebo-estimated decline in 6-MWD of ~140 meters over 18 months in natural history study of 137 FAC patients (N=39 for 6-MWD data)
- 90% Power to detect as little as 39% difference in 18 mo change from baseline 6-MWD between treatment groups with significance level of $p < 0.05$
- Unblinded interim analysis for futility when ~50% of patients reach 18 months

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Q&A Session

Thank You!

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