Patisiran, an Investigational RNAi Therapeutic for Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: Results from the Phase 3 APOLLO Study

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Hereditary ATTR (hATTR) Amyloidosis

Disease Overview and Introduction to Patisiran, an Investigational RNA Interference (RNAi) Therapeutic

- **hATTR Amyloidosis**
  - Rare, inherited, rapidly progressive, debilitating, life-threatening, often fatal disease caused by mutations in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]
  - Median survival 4.7 years following diagnosis[6]; reduced survival (3.4 years) for patients presenting with cardiomyopathy[6-8]

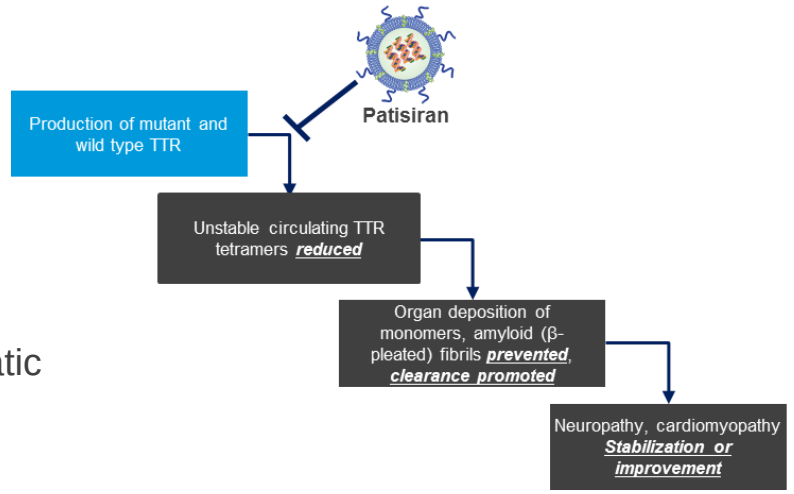
- Multisystem disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms[2,9,10]
  - Disease continuum includes patients who present with predominantly polyneuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms
    - Clinical manifestations (e.g., disease penetrance and rate of progression) is influenced by TTR genotype and geographical region

- Limited treatment options
  - Liver transplant for early-stage disease and TTR tetramer stabilizers
    - Tafamidis approved in EU for Stage 1 hATTR amyloidosis[11] and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[12]

- Continued high unmet medical need for novel therapeutics

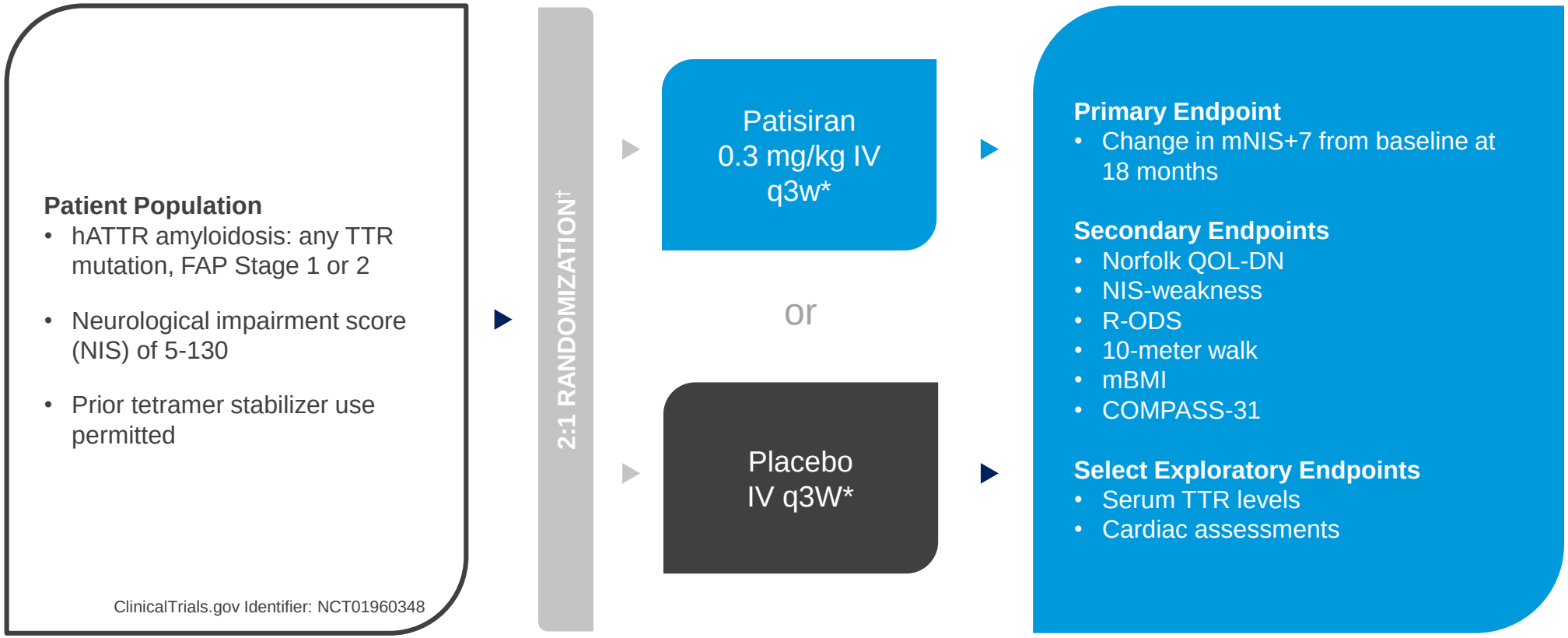
- **Patisiran, an Investigational RNAi Therapeutic**
  - Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR

Patisiran Therapeutic Hypothesis



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. Swiecicki PL et al. Amyloid 2015;22(2):123-31; 7. Sattianayagam AJ et al. Eur Heart J 2012;33;1120–7; 8. Gertz MA et al. Mayo Clin Proc 1992;67(5):428-40; 9. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 10. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748; 11. Coelho T et al. Neurology. 2012;79:785-92; 12. Berk JL et al. JAMA. 2013;310:2658-67

Patisiran Phase 3 APOLLO Study Design



†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous tetramer stabilizer use

*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).

Patients who completed study were eligible for patisiran treatment on Global OLE Study (NCT02510261)

COMPASS-31, composite autonomic symptom score-31; EQ-5D-5L, EuroQoL 5 dimensions-5L; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment scale +7; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; OLE, open-label extension; q3W, every 3 weeks; R-ODS; Rasch-built overall disability scale

Adams D, et al. BMC Neurol 2017;17(1):181

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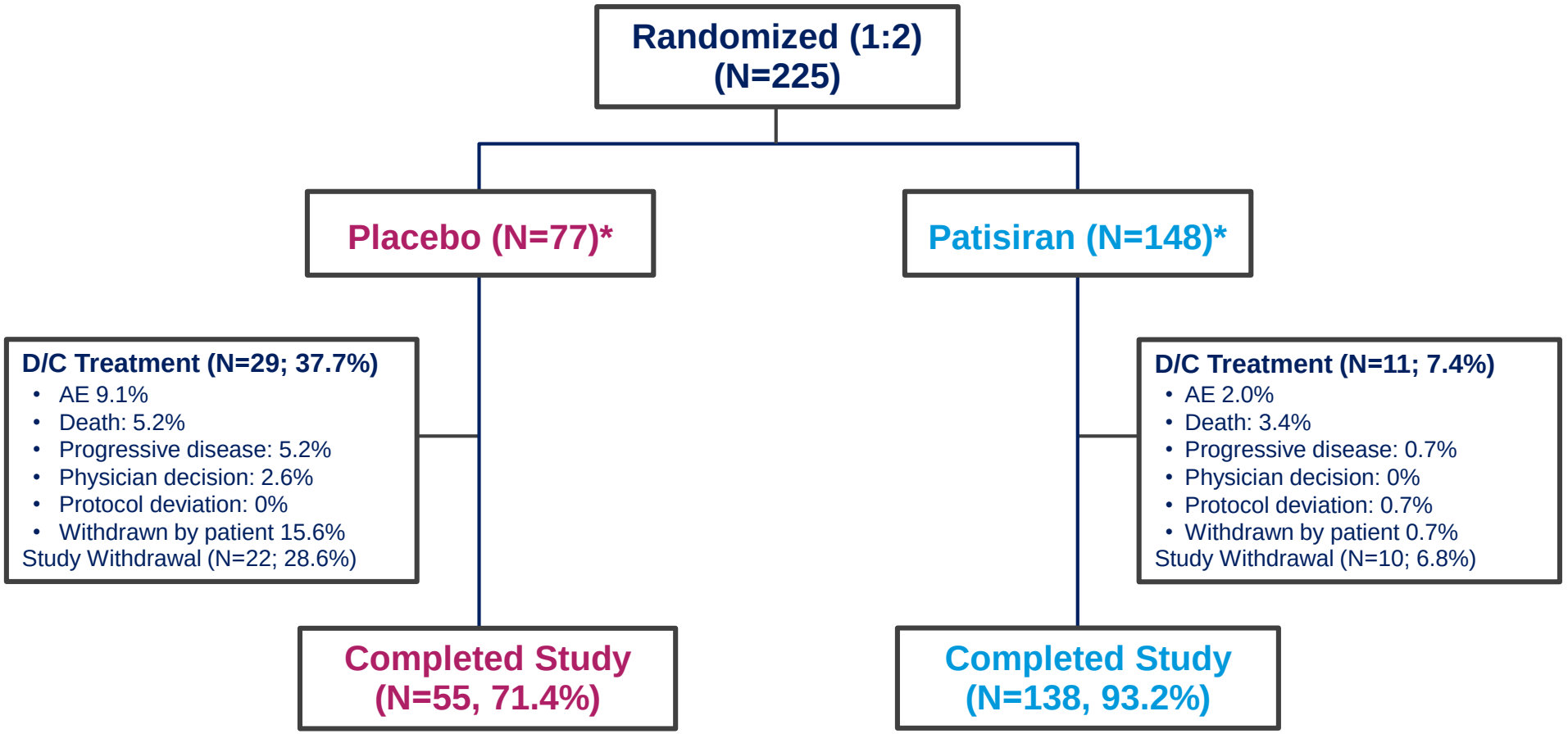
Patisiran Phase 3 APOLLO Study Results

Enrollment and Disposition

225 patients with hATTR amyloidosis with polyneuropathy from 44 sites in 19 countries enrolled between December 2013 and January 2016



*Study populations: modified intent-to-treat (mITT) population: All patients who were randomized and received at least 1 dose of patisiran or placebo (placebo, N=77; patisiran, N=148)

Discontinued (d/c) treatment: patients who permanently stopped treatment prior to the last scheduled dose (Week 78 visit); Discontinued (d/c) study: patients who stopped the study before any Month 18 (Week 79-80) assessments were performed; Progressive disease: patients who stopped treatment due to rapid disease progression; Rapid disease progression: patients who have ≥24-point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP stage progression relative to baseline at 9 months and had no major protocol deviations

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Patisiran Phase 3 APOLLO Study Results

Baseline Demographics and Disease Characteristics

Demographic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender, males	58 (75.3)	109 (73.6)
Race†		
Asian	**25 (32.5)**	27 (18.2)
Black/African or African American	1 (1.3)	4 (2.7%)
White/Caucasian	50 (64.9)	**113 (76.4)**
Region*		
North America	10 (13.0)	**37 (25.0)**
Western Europe	36 (46.8)	62 (41.9)
Rest of World	31 (40.3)	49 (33.1)
hATTR Diagnosis		
Years since hATTR diagnosis, mean (min, max)	2.60 (0.0, 16.5)	2.39 (0.0, 21.0)
TTR Genotype		
V30M	**40 (51.9)**	56 (37.8)
nonV30M‡	37 (48.1)	**92 (62.2)**
Previous tetramer stabilizer use	41 (53.2)	78 (52.7)

Disease Characteristics, n (%)	Placebo (N=77)	Patisiran (N=148)
NIS		
Mean (min, max)	57.0 (7.0, 125.5)	60.5 (6.0, 141.6)
<50	35 (45.5)	62 (41.9)
≥50 - <100	33 (42.9)	63 (42.6)
≥100	9 (11.7)	23 (15.5)
FAP Stage		
1: unimpaired ambulation	37 (48.1)	67 (45.3)
2: assistance with ambulation required	39 (50.6)	81 (54.7)
3: wheelchair bound or bedridden	1 (1.3)	0
PND Score		
I: preserved walking, sensory disturbances	20 (26.0)	36 (24.3)
II: impaired walking but can walk without stick or crutch	23 (29.9)	43 (29.1)
IIIa: walk with 1 stick or crutch	22 (28.6)	41 (27.7)
IIIb: walk with 2 sticks or crutches	11 (14.3)	28 (18.9)
IV: confined to wheelchair or bedridden	1 (1.3)	0
Cardiac Subpopulation♯	36 (46.8)	**90 (60.8)**

Blue, bolded text indicated >10% difference in either group

†Other, patisiran N=1 (0.7%); More than one race, patisiran N=2 (1.4%); missing N=1 each for placebo (1.3%) and patisiran (0.7%)

*North America: USA, CAN; Western Europe: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; Rest of world: Asia: JPN, KOR, TWN, Eastern Europe: BGR, CYP, TUR; Central & South America: MEX, ARG, BRA

‡Represents 38 different TTR mutations

♯Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)

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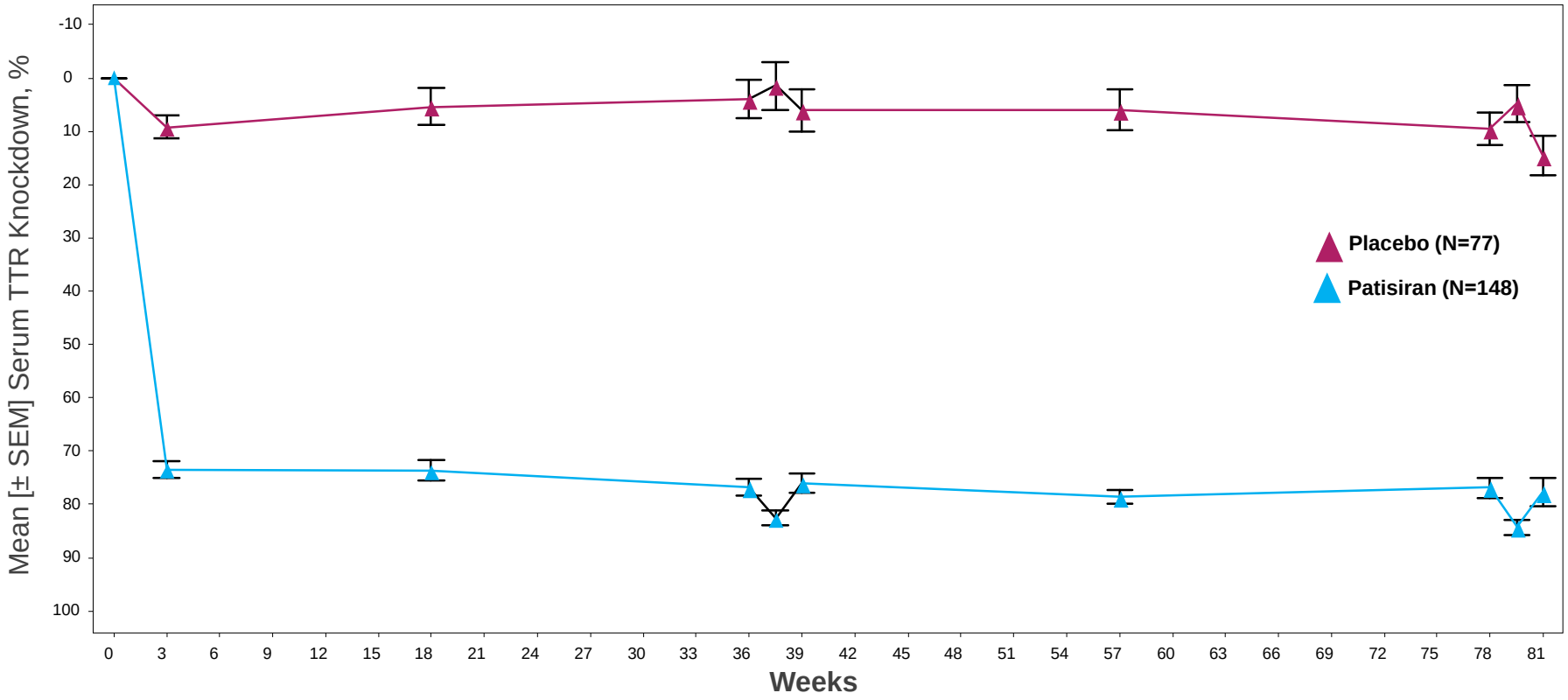
Patisiran Phase 3 APOLLO Study Results

Serum TTR Reduction

87.8% mean max serum TTR reduction from baseline for patisiran over 18 months



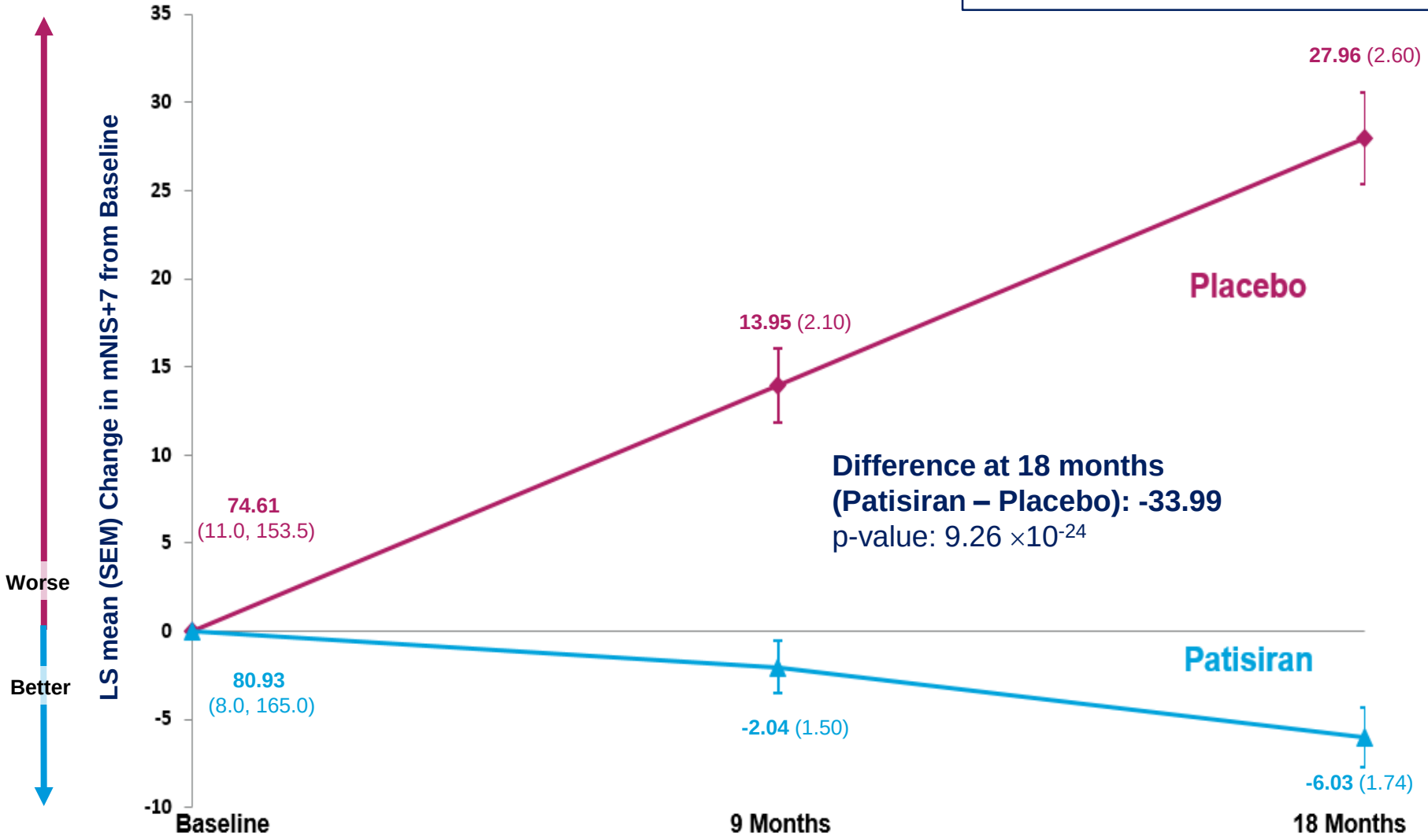
TTR Change	Change from Baseline at 9 Months		Change from Baseline at 18 Months	
	Placebo (N=77)	Patisiran (N=148)	Placebo (N=77)	Patisiran (N=148)
Mean (SEM) Serum TTR Knockdown	1.5% (4.47)	82.6% (1.36)	4.8% (3.38)	84.3% (1.48)

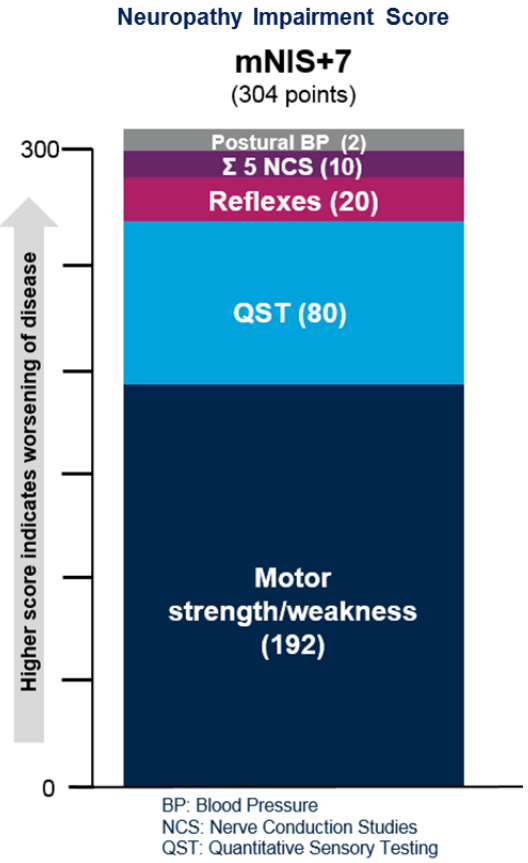
SEM, standard error of the mean

Patisiran Phase 3 APOLLO Study Results

mNIS+7: Change from Baseline

56.1% of patients in the **patisiran** group demonstrated improvement in mNIS+7 compared to **3.9%** of patients on **placebo** (odds ratio: 39.9; $p=1.82 \times 10^{-15}$; improvement defined as <0 point increase from baseline to 18 months)



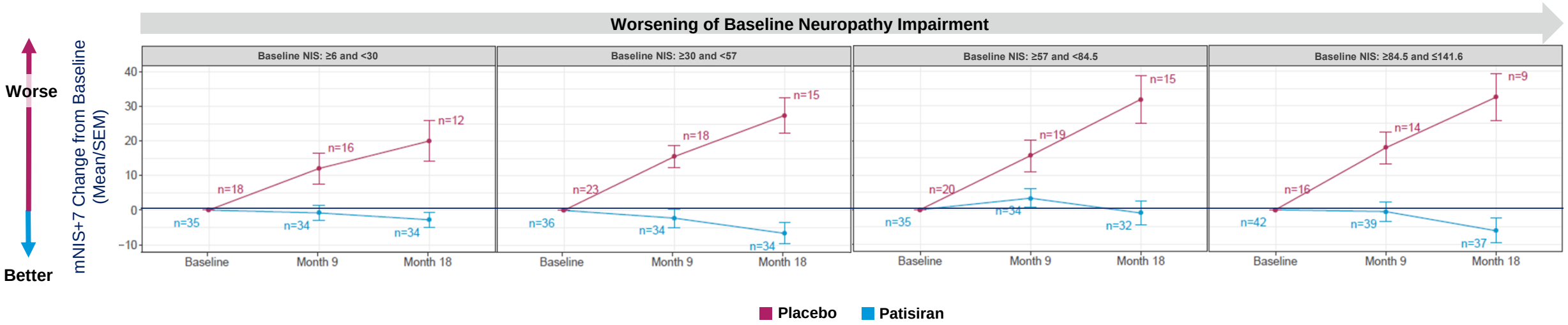


MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; mNIS+7, modified neuropathy impairment score + 7; LS, least squares; SEM, standard error of the mean
mNIS+7 reference range: 0-304 points

Patisiran Phase 3 APOLLO Study Results

mNIS+7 Change by NIS Quartiles

- mNIS+7 change at 18 months in all subgroups significantly favored patisiran
- Patisiran demonstrated benefit in patients with either early or advanced neuropathy at baseline



APOLLO data, additional analysis
mNIS+7, modified neuropathy impairment score + 7; SEM, standard error of the mean

Patisiran Phase 3 APOLLO Study Results

Secondary Endpoints: Change from Baseline (CFB) to 18 Months

All secondary endpoints achieved statistical significance at 18 months

- 51.4% of patients in the patisiran group improved in Norfolk QOL-DN compared to 10.4% of patients on placebo (odds ratio: 10.0; p=1.95 x 10^{-10}; improvement defined as <0 point increase from baseline to 18 months)
- Nominal statistical significance was achieved as early as month 9 for Norfolk QOL-DN, NIS-W, R-ODS, 10-MWT and mBMI

Secondary endpoint; LS Mean		Placebo (N=77)	Patisiran (N=148)	Treatment Difference (Pati - PBO)	P-Value
Norfolk QOL-DN (Quality of Life)	Baseline score, mean	55.5	59.6		
	CFB to 18 mos	**14.4**	**-6.7**	**-21.1**	**1.10×10^{-10}**
NIS-W (Muscle Weakness)	Baseline score, mean	29.03	32.69		
	CFB to 18 mos	**17.93**	**0.05**	**-17.87**	**1.40×10^{-13}**
R-ODS (Disability)	Baseline score, mean	29.8	29.7		
	CFB to 18 mos	**-8.9**	**0.0**	**9.0**	**4.07×10^{-16}**
10-MWT, m/sec (Gait Speed)	Baseline score, mean	0.79	0.80		
	CFB to 18 mos	**-0.24**	**0.08**	**0.311**	**1.88×10^{-12}**
mBMI, kg/m^2 x albumin [g/dL] (Nutritional Status)	Baseline score, mean	990	970		
	CFB to 18 mos	**-119.4**	**-3.7**	**115.7**	**8.83×10^{-11}**
COMPASS 31 (Autonomic Symptoms)	Baseline score, mean	30.31	30.61		
	CFB to 18 mos	**2.24**	**-5.29**	**-7.53**	**0.0008**

LS, least squares; Pati, patisiran; PBO, placebo; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; NIS-W, neuropathy impairment score-weakness; CFB, change from baseline; R-ODS, Rasch-built overall disability scale; 10-MWT, 10 meter walk test; mBMI, modified body mass index; COMPASS 31, composite autonomic symptom score questionnaire

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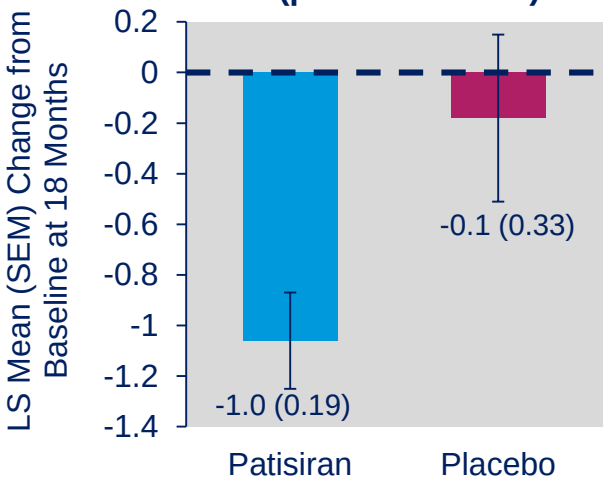
Patisiran Phase 3 APOLLO Study Results

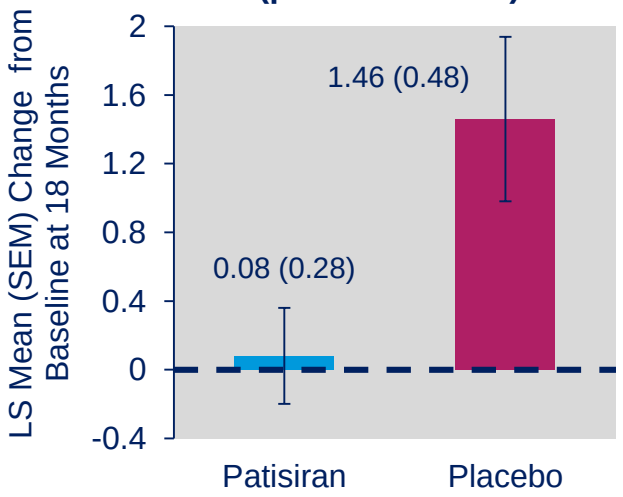
Exploratory Analysis: Cardiac Subpopulation*

- Patisiran treatment resulted in favorable improvement in mean LV wall thickness, global longitudinal strain, and NT-proBNP compared to placebo at 18 months
- Improvement was seen in additional echocardiographic parameters at 18 months: LV end-diastolic volume, interventricular septum thickness, posterior wall thickness, LV relative wall thickness, cardiac output, and LV mass

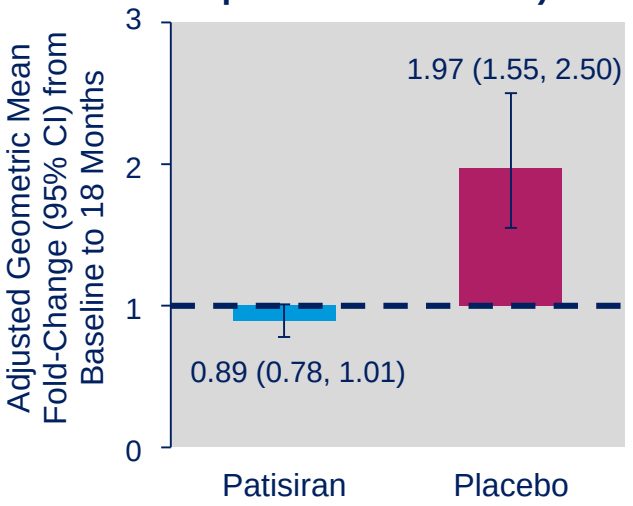
Mean LV Wall Thickness (mm)
(p-value = 0.017)



Global Longitudinal Strain (%)
(p-value = 0.015)



NT-proBNP (ng/L)
(ratio of patisiran/placebo† = 0.45;
p-value = 7.74 x 10^{-8})



*Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)

†Ratio is the adjusted geometric mean fold-change of patisiran/placebo

95% CI, 95% confidence interval; LS, least squares; LV, left ventricular, SEM, standard error of the mean

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Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability

Type of Adverse Event, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Adverse event (AE)	75 (97.4)	143 (96.6)
Severe AE	28 (36.4)	42 (28.4)
Serious adverse event (SAE)	31 (40.3)	54 (36.5)
AE leading to treatment discontinuation	11 (14.3)	7 (4.7)
AE leading to study withdrawal	9 (11.7)	7 (4.7)
Death	6 (7.8)	7 (4.7)

Overall, 13 deaths in APOLLO study; no deaths considered related to study drug

- Causes of death (e.g., cardiovascular, infection) consistent with natural history; frequency of death trended lower in the patisiran group compared with placebo group

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Did not result in any treatment discontinuations and decreased over time
- Infusion-related reactions (IRRs)
  - Majority mild in severity that decreased over time; led to treatment discontinuation in 1 patient
  - No severe, life-threatening or serious IRRs

No safety signals regarding cataracts, hyperglycemia, infection, or osteopenia/osteoporosis

No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

Safety in cardiac subpopulation comparable to overall study population

Adverse Events Occurring in ≥ 10% in Either Group

Preferred AE Term, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Diarrhea	29 (37.7)	55 (37.2)
Edema, peripheral	17 (22.1)	**44 (29.7)**
Infusion related reaction (IRR)	7 (9.1)	**28 (18.9)**
Fall	**22 (28.6)**	25 (16.9)
Constipation	13 (16.9)	22 (14.9)
Nausea	**16 (20.8)**	22 (14.9)
Dizziness	11 (14.3)	19 (12.8)
Urinary tract infection	**14 (18.2)**	19 (12.8)
Fatigue	8 (10.4)	18 (12.2)
Headache	9 (11.7)	16 (10.8)
Cough	9 (11.7)	15 (10.1)
Insomnia	7 (9.1)	15 (10.1)
Nasopharyngitis	6 (7.8)	15 (10.1)
Vomiting	8 (10.4)	15 (10.1)
Asthenia	9 (11.7)	14 (9.5)
Pain in Extremity	8 (10.4)	10 (6.8)
Muscular Weakness	**11 (14.3)**	5 (3.4)
Anemia	**8 (10.4)**	3 (2.0)
Syncope	**8 (10.4)**	3 (2.0)

Blue, bolded text: Indicates ≥5 percentage point difference in either group

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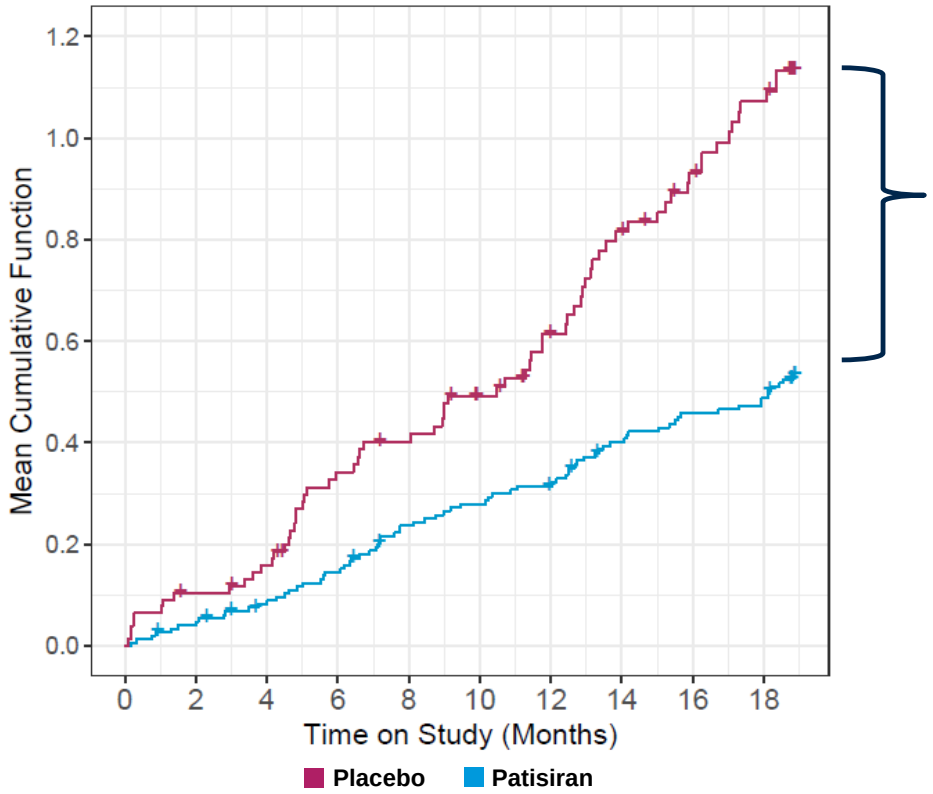
Patisiran Phase 3 APOLLO Study Results

Recurrent Hospitalization and Death Events by Treatment Arm

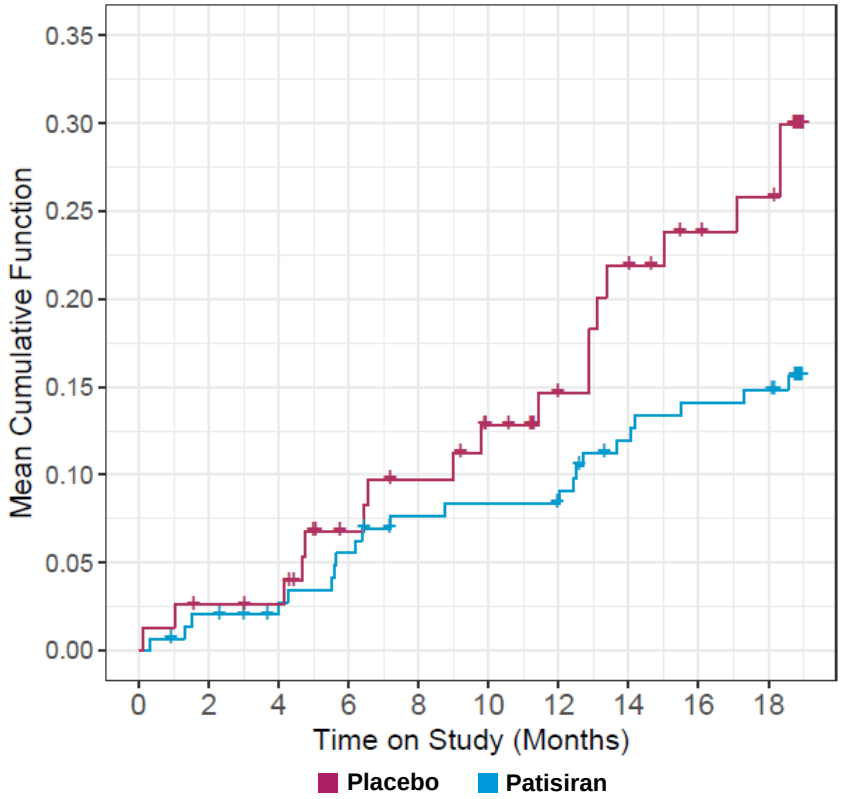
Post-hoc Analysis; Mean Cumulative Function: Average Number of Events per Patient by a Certain Time

Composite Rate of All-Cause Hospitalization and Mortality



Approximately 50% reduction in event rate*

Composite Rate of Cardiac Hospitalization and All-Cause Mortality



Approximately 45% reduction in event rate†

Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization

*For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]

†For cardiac hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.54 [0.25, 1.16]; Anderson-Gill hazard ratio (HR) 0.54 [0.28, 1.01]

AE, adverse event; CRFs, case report forms; SAEs, serious adverse events; SOC, system organ class

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Patisiran Phase 3 APOLLO Study

Summary

hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with high morbidity and mortality and limited therapeutic options

Patisiran treatment resulted in significant improvement in polyneuropathy from baseline relative to placebo

- Benefits seen in motor, sensory and autonomic neuropathy
- Positive effects observed across wide range of disease severity, benefiting patients with early and advanced disease, TTR genotypes, and in patients with cardiac involvement

Significant improvement in quality of life, reduction in disease symptoms and disability, and improvement in nutritional status, strength, and ambulation seen with patisiran relative to placebo

Favorable changes in exploratory cardiac measures in patisiran treated patients within cardiac subpopulation

- Improvement in NT-proBNP, longitudinal strain, and LV wall thickness relative to placebo

Patisiran showed an encouraging safety and tolerability profile

- Frequency of deaths trended lower in the patisiran group vs placebo group
- Key patisiran safety findings include mild to moderate peripheral edema and IRRs; only one treatment discontinuation due to these events
- No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction
- Safety in cardiac subpopulation comparable to overall study population

In post-hoc analysis, approximately 50% reduction in composite rate of all-cause hospitalization and mortality, and approximately 45% reduction in composite rate of cardiac hospitalization and all-cause mortality

99% of eligible APOLLO patients enrolled into Global OLE study

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Acknowledgments

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