Impact of Patisiran, an Investigational RNAi Therapeutic, on Nutritional Status in Patients with Hereditary Transthyretin-Mediated Amyloidosis

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Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Disease Overview

- **hATTR Amyloidosis**
  - Rare, inherited, rapidly progressive, debilitating, life-threatening 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 or cardiomyopathy symptoms, yet many patients experience a variety of symptoms
    - Clinical manifestations (e.g., disease penetrance and rate of progression) are influenced by TTR genotype and geographical region

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

- Continued high unmet medical need for novel therapeutics

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

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Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Evaluation of Nutritional Status: mBMI

- Patients with hATTR amyloidosis often have poor nutritional status and unintentional weight loss due in part to severe gastrointestinal and autonomic manifestations[1–3]
  - Cachexia is a common cause of death in untreated patients[4]
- Conventional BMI measurements may not accurately reflect nutritional status due to fluid retention[5]
  - In patients with hATTR amyloidosis, low serum albumin levels can lead to fluid retention and edema[6]
  - This fluid accumulation can increase weight and BMI measurements despite worsening nutritional status[6]
- To overcome this limitation, a modified BMI (mBMI) is routinely used in patients with hATTR amyloidosis as a measure of nutritional status[6]
  - mBMI = BMI (kg/m^2) x serum albumin (g/L)
- In patients with hATTR amyloidosis, mBMI has been linked with disease progression and survival
  - mBMI has been found to correlate with neurologic function and duration of gastrointestinal symptoms[6]
  - mBMI has been shown to be associated with FAP disease stages[7]
  - mBMI <600 kg/m^2 x g/L at time of OLT has been shown to be an independent predictor of survival post OLT[8]

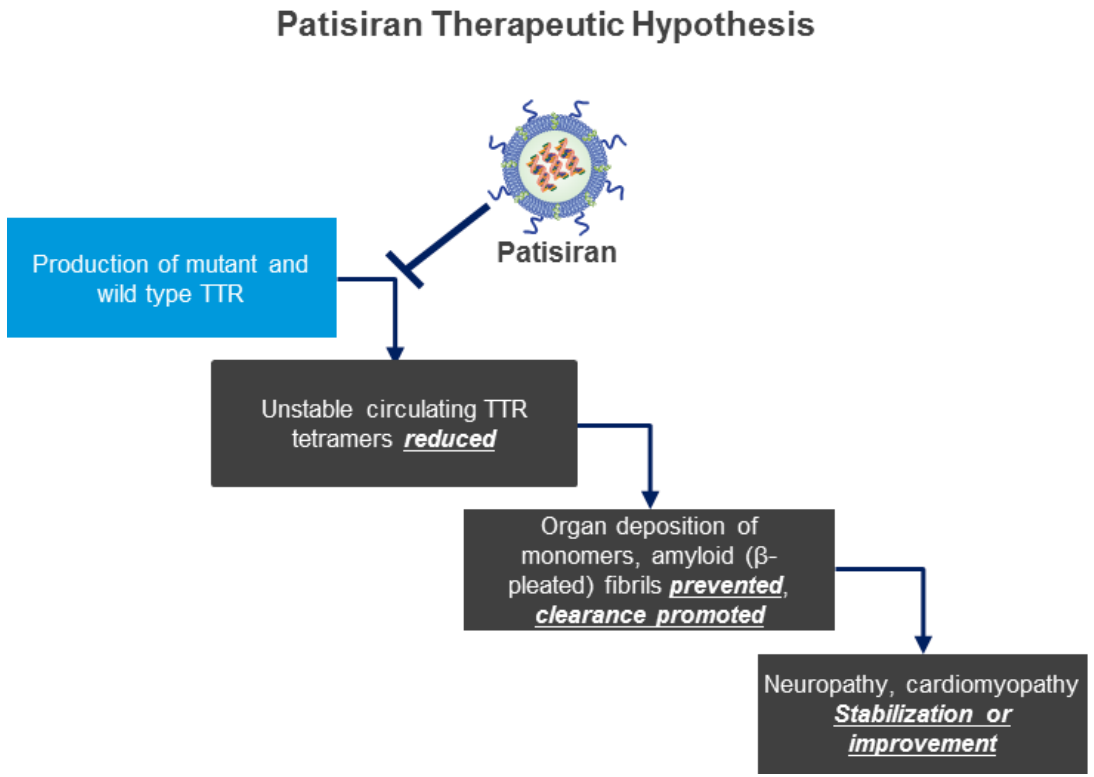
BMI, body mass index; FAP, familial amyloidotic polyneuropathy; mBMI, modified body mass index; OLT, orthotopic liver transplant

1. Planté-Bordeneuve V and Said G. Lancet Neurol. 2011;10(12):1086-1097; 2. Wixner J et al. Orphanet J Rare Dis. 2014;9:61; 3. Eshaghian S et al. Rev Cardiovasc Med. 2007;8(4):189-199; 4. Parman Y et al. Curr Opin Neurol. 2016;29 Suppl 1:S3–S13; 5. Oh TK et al. Sci Rep. 2018;8(1):4614; 6. Suhr O et al. J Intern Med. 1994;235(5):479-85; 7. Coelho T el al. Muscle Nerve. 2017;55(3):323-332; 8. Yamamoto S et al. Am J Transplant. 2007;7(11):2597-2604

Patisiran, an Investigational RNAi Therapeutic

MOA and Preclinical Data Provided Rationale for Clinical Development

Patisiran MOA: Reduces *TTR* mRNA in the Liver, Preventing Synthesis of WT and Mutant TTR Proteins[1,2]



Serum TTR Reduction Prevented TTR Protein Deposition in Preclinical Investigations[3]

- >95% reduction of hepatic *TTR* mRNA and serum TTR protein in human V30M transgenic mice and >96% reduction in non-human primates
- Significant 70–80%* reduction in established mutant TTR protein deposits in tissues, including nerves and gastrointestinal tract, in human V30M transgenic mice (compared with control)

MOA, mechanism of action; mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNAi, ribonucleic acid interference; siRNA, small interfering RNA; WT, wild type

*Some mice had complete inhibition of mutant TTR protein deposition in tissues with multiple-dose patisiran

1. Deleavey G & Damha MJ. Chem Biol. 2012;19:937-954; 2. Niemietz C et al. Molecules. 2015;20:17944-17975; 3. Butler JS et al. Amyloid. 2016;23(2):109-118

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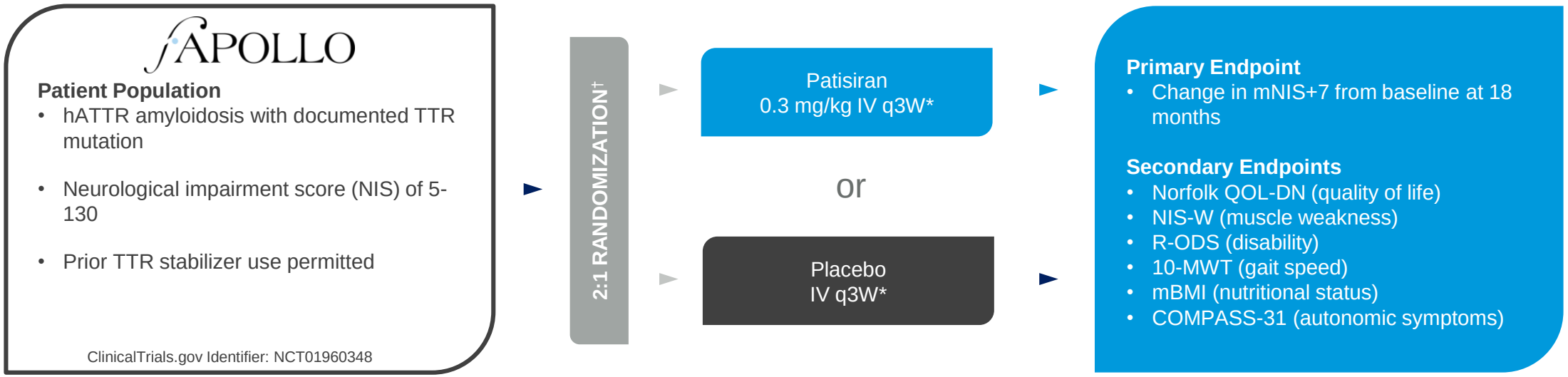
Patisiran Phase 3 APOLLO Study Design



Primary Endpoint: mNIS+7

- Composite score of polyneuropathy
- Measures: muscle strength/weakness, quantitative sensory testing, muscle stretch reflexes, nerve conduction studies, and postural blood pressure

Key Secondary Endpoint: Norfolk QOL-DN

- 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function

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

†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 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).

COMPASS-31, composite autonomic symptom score-31; 10-MWT, 10-meter walk test; 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

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)
Nutritional status		
Mean mBMI, kg/m^2 x g/L (SEM)	989.9 (24.4)	969.7 (17.3)
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)
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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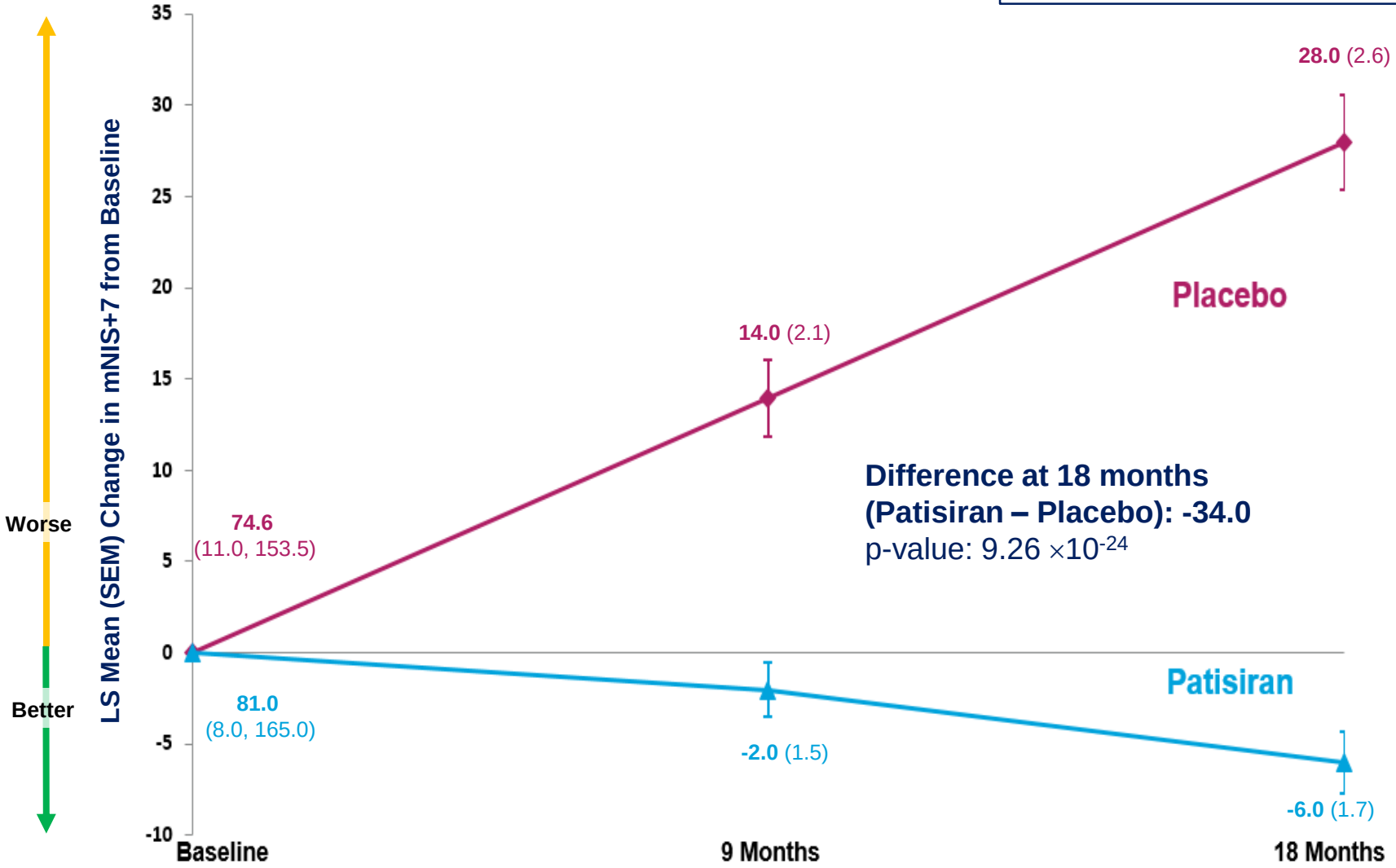
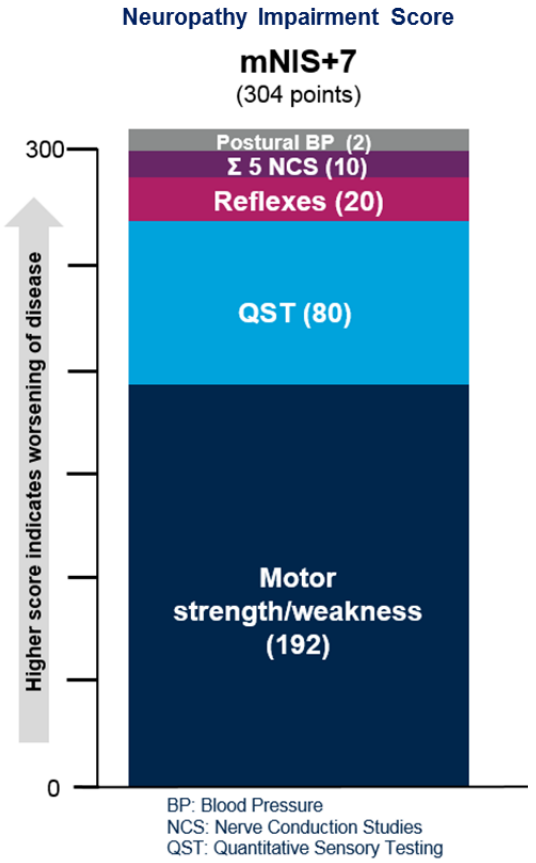
Patisiran Phase 3 APOLLO Study Results

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)





mNIS+7, modified neuropathy impairment score + 7; LS, least squares; SEM, standard error of the mean; mNIS+7 reference range: 0-304 points

Data previously presented at the American Academy of Neurology (AAN) 2018; April 2018, Los Angeles, CA, USA

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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)

Secondary endpoint; LS Mean		Placebo (N=77)	Patisiran (N=148)	Treatment Difference (Pati - PBO)	P-Value
Norfolk QOL-DN	Baseline score, mean	55.5	59.6		
	CFB to 18 mos	**14.4**	**-6.7**	**-21.1**	**1.10×10^{-10}**
NIS-W	Baseline score, mean	29.03	32.69		
	CFB to 18 mos	**17.93**	**0.05**	**-17.87**	**1.40×10^{-13}**
R-ODS	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	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/L]	Baseline score, mean	990	970		
	CFB to 18 mos	**-119.4**	**-3.7**	**115.7**	**8.83×10^{-11}**
COMPASS-31	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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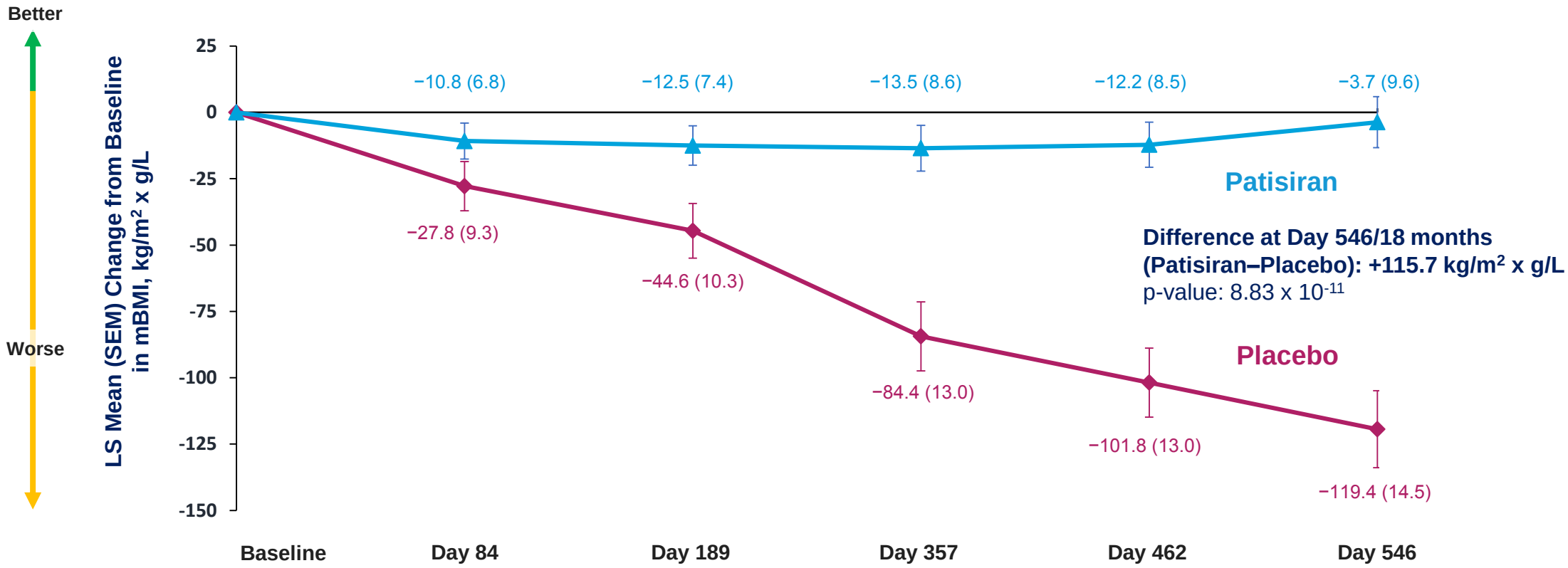
Patisiran Phase 3 APOLLO Study Results

Change in Nutritional Status (mBMI) from Baseline to Month 18



41.2% of patients in the patisiran group demonstrated improvement in mBMI compared with 6.5% of patients on placebo
(Improvement defined as >0 kg/m² x g/L increase from baseline to 18 months; patients with data at 18 months: patisiran, n=133; placebo, n=52)

Patients with data for mBMI analysis: n=218; patients with mBMI data at 18 months: n=185 (patisiran, n=133; placebo, n=52)

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Patisiran Phase 3 APOLLO Study Results

Change in Nutritional Status: Components of mBMI

Impact of patisiran on mBMI was observed in serum albumin, BMI, and weight

Serum albumin (g/L)	Placebo (N=77)	Patisiran (N=148)
Mean (SD) at baseline	41.8 (3.4)	42.1 (3.5)
Mean (SD) at 18 months	38.8 (4.3)	41.3 (4.2)
Mean (SD) change from baseline at 18 months, %	−8.3 (7.6)	−2.6 (8.7)
BMI (kg/m^2)		
Mean (SD) at baseline	23.6 (4.3)	23.0 (4.5)
Mean (SD) at 18 months†	23.0 (4.4)	23.4 (4.6)
LS mean (SEM) change from baseline at 18 months*	−1.0 (0.2) 95% CI: −1.4, −0.6	0.4 (0.1) 95% CI: 0.1, 0.7
Weight (kg)		
Mean (SD) at baseline	67.5 (15.7)	67.3 (16.6)
Mean (SD) at 18 months	66.3 (15.1)	68.8 (17.1)
Mean (SD) change from baseline at 18 months	−3.1 (4.9)	+1.2 (4.8)

†Note: Day 546 is treated as Month 18 as for mBMI
*Difference patisiran–placebo: 1.4 kg/m^2 (95% CI: 0.9, 1.9)

BMI, body mass index; 95% CI: 95% confidence interval

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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)

No deaths considered related to study drug

- Causes of death consistent with natural history

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Decreased over time
  - Did not result in any treatment discontinuations
- Infusion-related reactions (IRRs)
  - Majority mild in severity
  - Decreased over time
  - 1 patient discontinued treatment

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

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)**
IRRs	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

Summary

hATTR amyloidosis is a multisystem, progressive, life-threatening disease with high morbidity, mortality, and limited treatment options

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

Patients receiving patisiran in APOLLO maintained their mBMI over 18 months, whereas mBMI declined substantially in those receiving placebo

- This improvement in mBMI compared with placebo was seen as early as 3 months post-baseline and was associated with improvements in weight and serum albumin
- 41.2% of patients on patisiran showed improvement in mBMI at 18 months relative to baseline, compared to only 6.5% of placebo patients
  - Improvement was defined as >0 kg/m^2 x g/L increase from baseline to 18 months

Patisiran showed an encouraging safety and tolerability profile

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