Impact of Prior TTR Stabilizer Use in Patients with Hereditary Transthyretin-Mediated Amyloidosis in the APOLLO Phase 3 Study of Patisiran

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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 tetramer 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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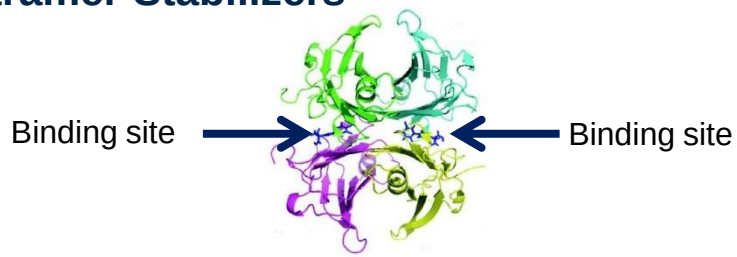
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Pathogenesis of Amyloid Formation and Mechanism of Action of TTR Tetramer Stabilizers[1–3]

Amyloid Fibril Formation

TTR Tetramer Stabilizers



TTR tetramer stabilizers bind to TTR thyroxine site to stabilize the tetramer and block the formation of amyloid fibrils

Tafamidis

- Shown to delay peripheral neurologic impairment in early-stage V30M disease[4]
- Approved in the EU and other countries outside of the US to reduce progression of polyneuropathy in patients with early-stage hATTR amyloidosis[5]

Diflunisal

- Generic NSAID that has been repurposed as a TTR stabilizer[6]
- Shown to slow the progression of neurologic impairment in hATTR amyloidosis, although it is not approved for this use[6]

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;23:109-118; 4. Coelho et al. Neurology. 2012;79:785–92;
5. Pfizer Limited. Vyndaqel. Summary of Product Characteristics 2017; 6. Berk et al. JAMA. 2013;310:2658–67

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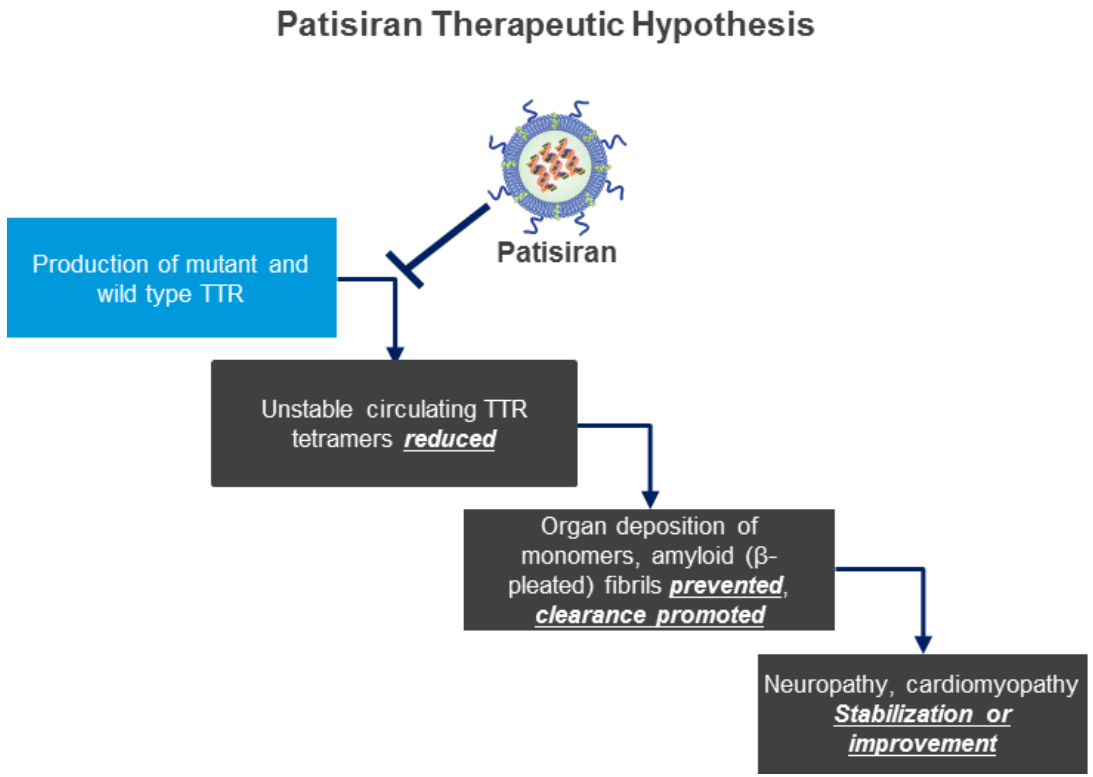
Patisiran, an Investigational RNAi Therapeutic

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]

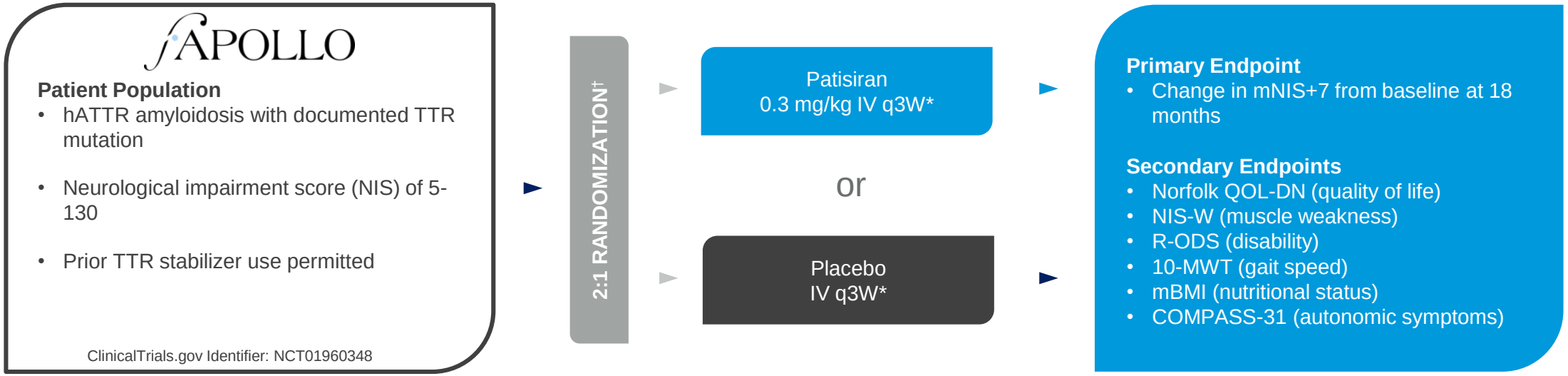
- >95% reduction of hepatic *TTR* mRNA and serum TTR protein in human V30M transgenic mice and >96% reduction in non-human primates
- Significant 70–80%* reduction in established mutant TTR protein deposits in tissues, including nerves and gastrointestinal tract, in human V30M transgenic mice (compared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

Patisiran Phase 3 APOLLO Study Design



- Prior TTR stabilizer use was a stratification factor at randomization

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

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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 TTR 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)

Adams et al. NEJM. 2018. Manuscript accepted.

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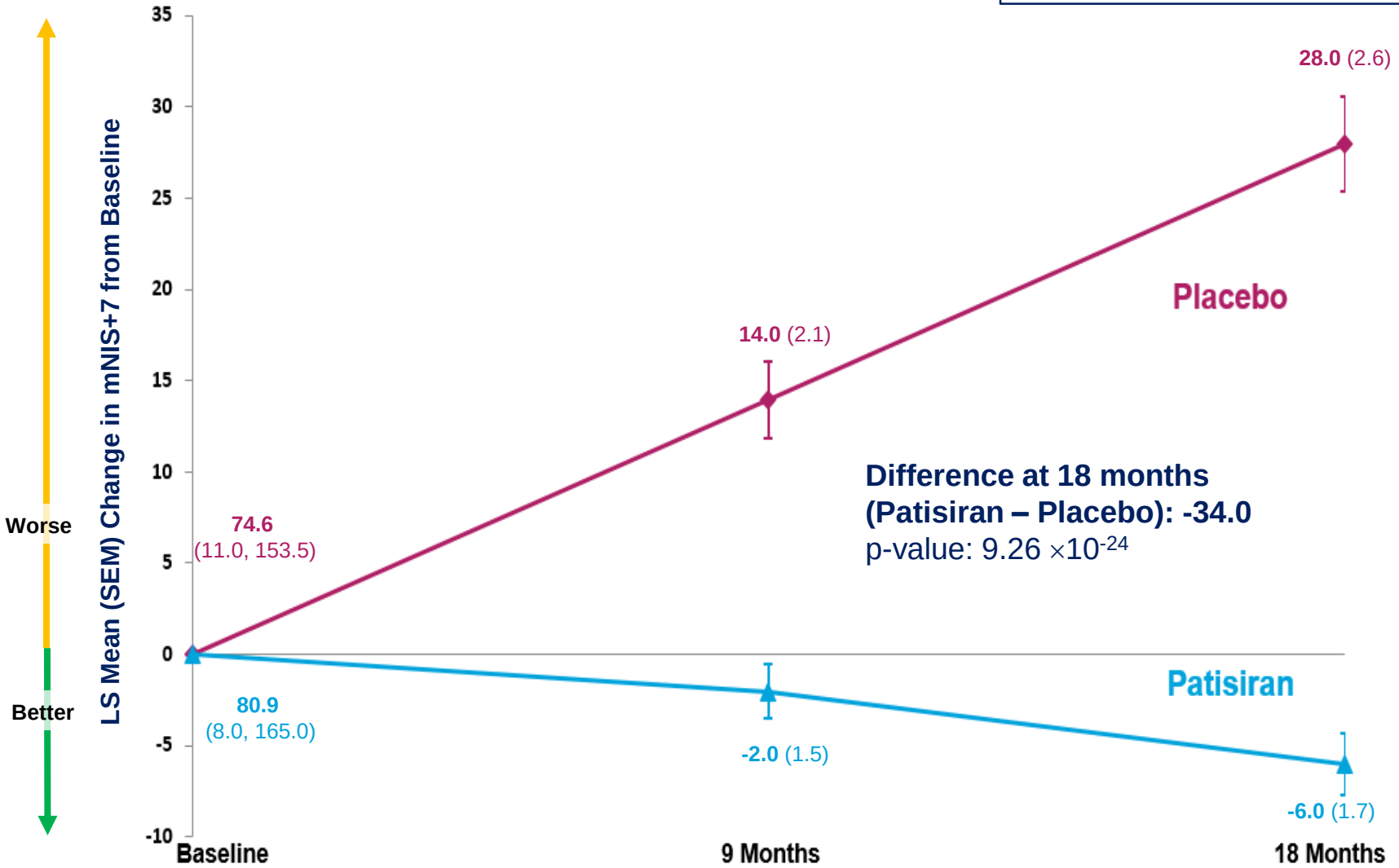
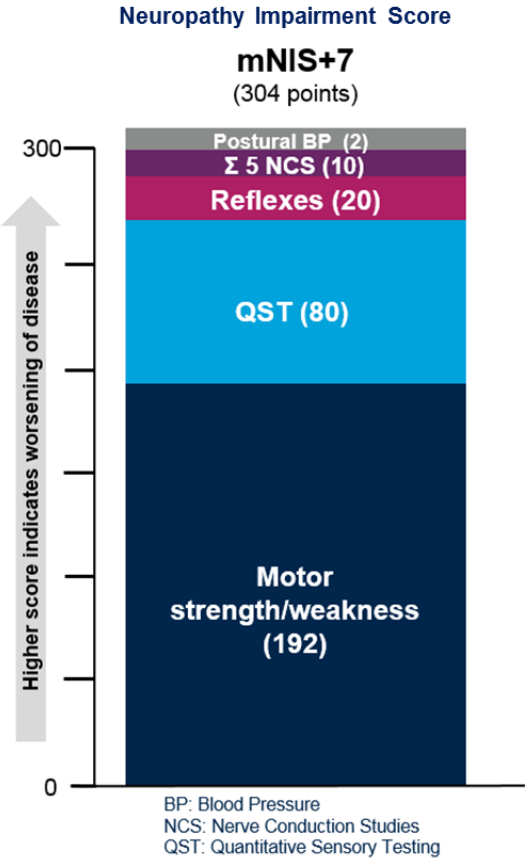
Patisiran Phase 3 APOLLO Study Results

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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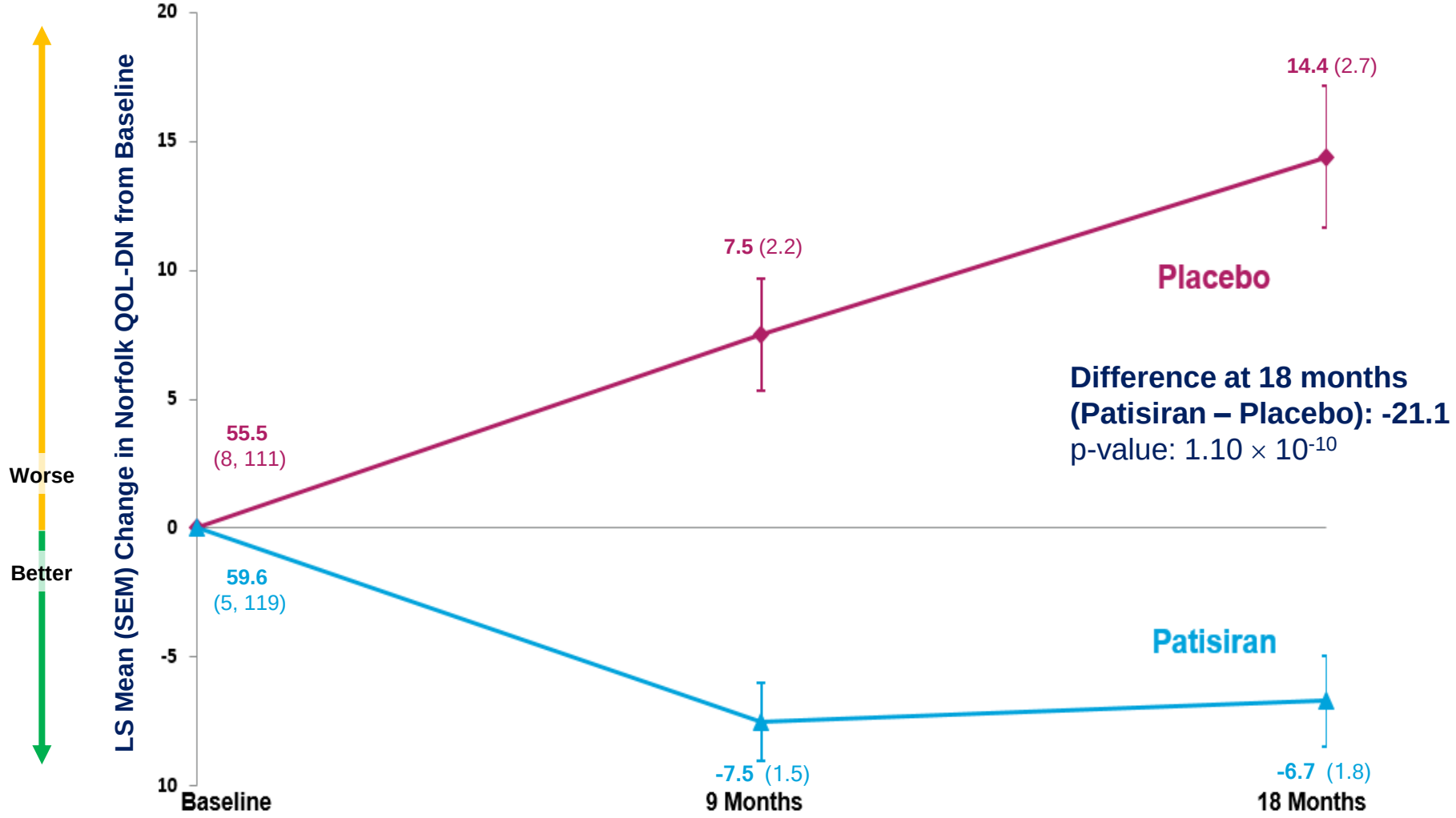
Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline

51.4% of patients in the patisiran group demonstrated improvement 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)



LS, least squares; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; SEM, standard error of the mean; Norfolk QOL-DN reference range: -4 – 136
Data previously presented at the American Academy of Neurology (AAN) 2018; April 2018, Los Angeles, CA, USA

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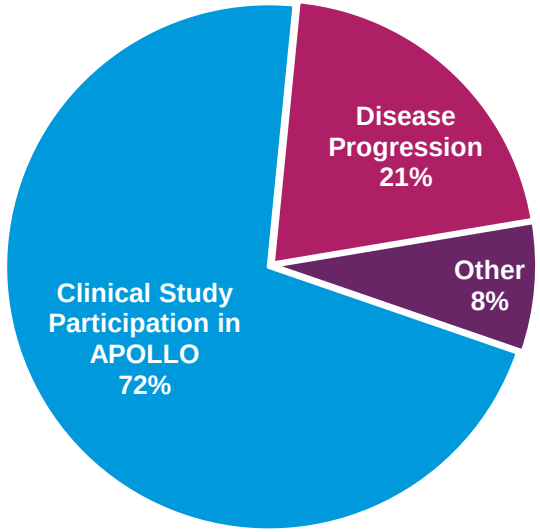
Patisiran Phase 3 APOLLO Study Results

Prior TTR Tetramer Stabilizer Use at Baseline (mITT Population)

Demographics	Placebo (N=77)	Patisiran (N=148)
Prior Tafamidis, n (%)	27 (35.1)	47 (31.8)
Time (Days) from Discontinuation of Tafamidis to Start of Study Drug, Mean (SD)	33.9 (29.9)	51.6 (65.2)
Prior Diflunisal, n (%)	14 (18.2)	31 (20.9)
Time (Days) from Discontinuation of Diflunisal to Start of Study Drug, Mean (SD)	26.5 (28.7)	58.2 (183.1)

Reasons for TTR Tetramer Stabilizer Discontinuation*

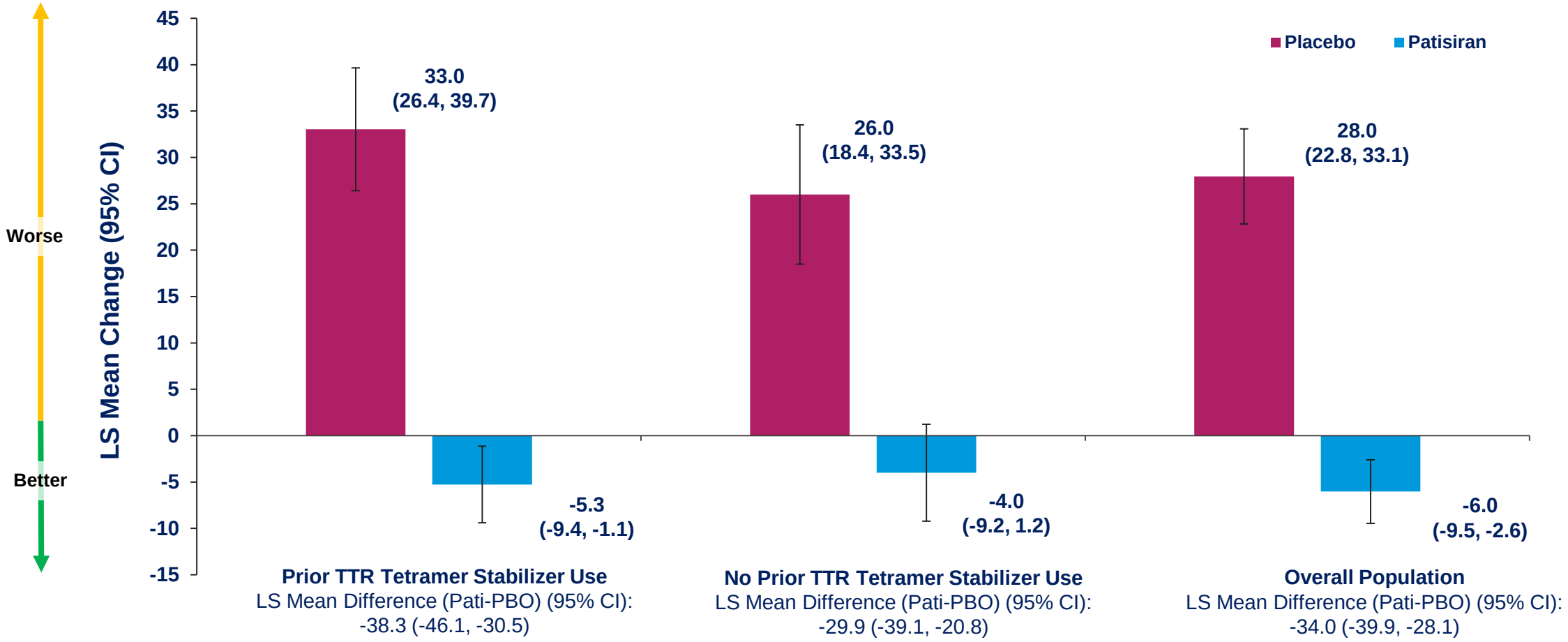
- 72% of patients with prior TTR tetramer stabilizer use discontinued therapy to join APOLLO study
- 21% of patients discontinued due to progression while on TTR tetramer stabilizer treatment
- 8% discontinued for other reasons



mITT, modified intention-to-treat
*Due to rounding, percentages may add up to >100%
Schmidt et al. Orphanet J Rare Dis. 2017;12(Suppl 1):P40

Patisiran Phase 3 APOLLO Study Results

LS Mean Change from Baseline to Month 18 in mNIS+7 by Prior TTR Tetramer Stabilizer Use



Significant improvement in neuropathy was demonstrated with patisiran relative to placebo irrespective of prior TTR tetramer stabilizer use

Interaction p-value of treatment by prior tetramer stabilizer use: 0.8419
Pre-specified subgroup analyses were performed in the subgroups of patients with/without prior TTR stabilizer use for mNIS+7 and Norfolk QOL-DN using MMRM models with baseline score as a continuous covariate and genotype (V30M vs non-V30M) as a factor
mNIS+7, modified neuropathy impairment scale + 7; MMRM, mixed effects model repeat measurement; LS, least squares; Pati, patisiran; PBO, placebo; 95% CI, 95% confidence interval

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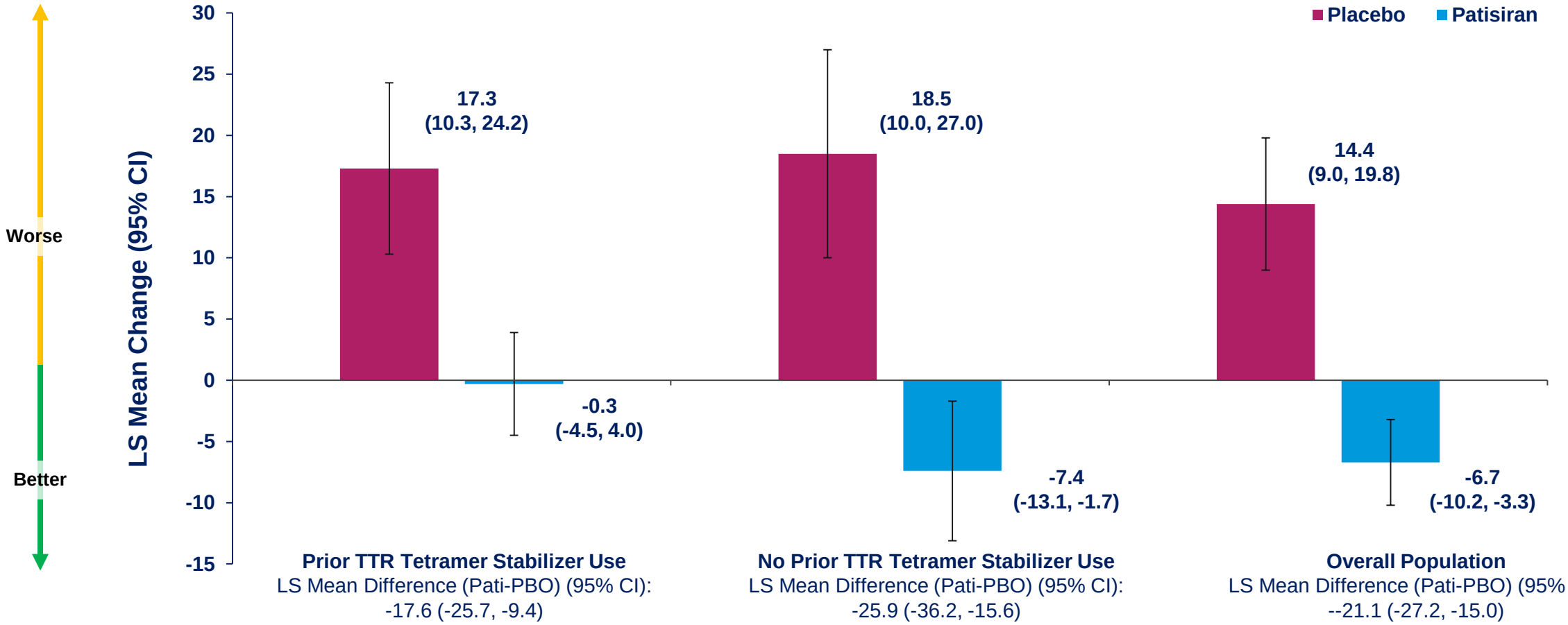
Patisiran Phase 3 APOLLO Study Results

LS Mean Change from Baseline to Month 18 in Norfolk QOL-DN by Prior TTR Tetramer Stabilizer Use



Significant improvement in QOL was demonstrated with patisiran relative to placebo irrespective of prior TTR tetramer stabilizer use

Interaction p-value of treatment by prior tetramer stabilizer use: 0.1571
Pre-specified subgroup analyses were performed in the subgroups of patients with/without prior TTR stabilizer use for mNIS+7 and Norfolk QOL-DN using MMRM models with baseline score as a continuous covariate and genotype (V30M vs non-V30M) as a factor
Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; QOL, quality of life; MMRM, mixed effects model repeat measurement; LS, least squares; Pati, patisiran; PBO, placebo; 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

Approximately 53% of patients were previously treated with TTR tetramer stabilizers; >90% of these discontinued stabilizer treatment due to disease progression or to participate in APOLLO

In a pre-specified subgroup analysis, patisiran demonstrated a significant improvement in neuropathy and QOL relative to placebo irrespective of prior TTR tetramer stabilizer use

Patisiran showed an encouraging safety and tolerability profile

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Acknowledgements

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