Patisiran in Patients with hATTR Amyloidosis Post-Orthotopic Liver Transplant: 12-Month Results

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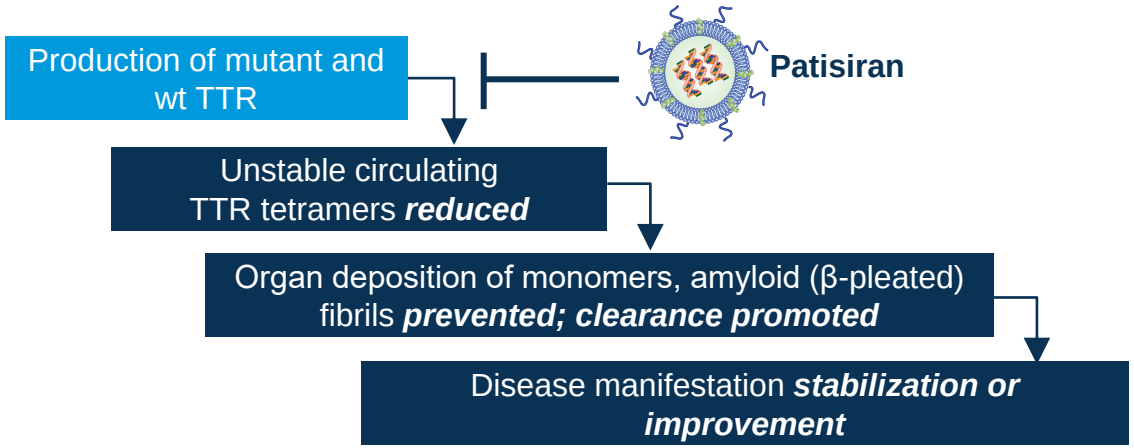
Disclosure Francisco Muñoz-Beamud

Conflict	Disclosure
Speakers bureau	Alnylam Pharmaceuticals and Pfizer
Advisory committee/ data safety monitoring board	Pfizer

Rationale for Patisiran Use in Patients with hATTR Amyloidosis and Disease Progression Post-Orthotopic Liver Transplantation (OLT)

- Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is a rare, underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by a variant in the *TTR* gene[1–5]; the majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–9]
- OLT suppresses the production of variant TTR, and has therefore been a treatment option used to slow disease progression in early-stage ATTRv amyloidosis[10,11]
- Disease progression (neurologic and cardiologic impairment) post-OLT has been reported[12–14] due to continued deposition of amyloid fibrils containing wild-type (wt) TTR[15,16]
  - Currently, no prospective study of any pharmacotherapy has been performed in patients with ATTR amyloidosis with polyneuropathy progression after OLT, which highlights the unmet need of this patient population
- Patisiran is an RNAi therapeutic, that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing variant and wt TTR[17,18]
  - Approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy; specific indications vary by country/region
  - In the Phase 3 APOLLO study (NCT01960348), patisiran was able to halt or reverse polyneuropathy and improve QOL in the majority of patients[8]

Patisiran Treatment Hypothesis



ATTRv, hereditary transthyretin (v for variant); hATTR, hereditary transthyretin-mediated; OLT, orthotopic liver transplantation; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin; wt, wild-type

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Patisiran Post-OLT Study (NCT03862807) Design

Phase 3b, Open-Label Study Conducted across Several European Countries[a]

Patient population (n=23)

- Age ≥18 years
- Received OLT for ATTRv amyloidosis ≥12 months prior to study start
- Worsening PND score after OLT[b]
- KPS ≥70%
- NYHA class ≤II
- No previous or current use of patisiran or inotersen, and will not be using a TTR stabilizer during the study
- No liver allograft rejection episodes[c] ≤6 months prior to the study

Patisiran
0.3 mg/kg IV q3w
for 12 months

Primary endpoint:

- Average of Month 6 and Month 12 TTR percent reduction

Secondary endpoints:

- Change from baseline at Month 12 in:
  - NIS
  - Norfolk QOL-DN
  - COMPASS-31
  - R-ODS
  - mBMI

Safety (frequency and severity of AEs)

Objective: To describe the 12-month efficacy and safety results of patisiran in patients with ATTRv amyloidosis who have had polyneuropathy progression post-OLT

[a]Countries: UK, Sweden, France, Germany, Italy, Portugal, Spain. [b]Disease progression was defined as a documented increase in PND score, e.g., from I to II, II to IIIA, etc., compared with the pre-OLT assessment, or a documented increase in PND score between any two assessments post-OLT. [c]Including abnormal LFTs suggestive of possible allograft rejection

AE, adverse event; ATTRv, hereditary transthyretin (v for variant); COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; IV, intravenous; KPS, Karnofsky Performance Status; LFT, liver function test; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NYHA, New York Heart Association; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; q3w, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin

Baseline Demographics and Characteristics

Baseline demographics and characteristics	Safety analysis set (n=23)
Age, years, mean (SD)	58.1 (9.9)
Male, n (%)	13 (56.5)
Race, n (%)	
White	22 (95.7)
Asian	1 (4.3)
Age at ATTRv amyloidosis diagnosis, years, mean (SD)	46.7 (11.7)
V30M genotype[a], n (%)	15 (65.2)
Previous TTR stabilizer use[b], n (%)	13 (56.5)
Age at liver transplant, years, mean (SD)	50.1 (10.8)
Time from ATTRv amyloidosis diagnosis to OLT, years, mean (SD)	3.7 (3.0)
Time from OLT to first patisiran dose, years, mean (SD)	9.4 (5.1)
Immunosuppression regimens at baseline, n (%)	
Tacrolimus	10 (43.5)
Tacrolimus + mycophenolate	7 (30.4)
Other[c]	6 (26.1)
BMI, kg/m^2, mean (SD)	23.5 (3.6)
Serum TTR level, mg/L, mean (range)	202.1 (123.7–315.1)
NIS total score, mean (range)	60.3 (7.0–136.5)
Norfolk QOL-DN score, mean (range)	66.7 (16.0–98.0)
PND score, n (%)	
I: preserved walking, sensory disturbances	1 (4.3)
II: impaired walking but can walk without stick/crutch	9 (39.1)
IIIA: walk with 1 stick/crutch	7 (30.4)
IIIB: walk with 2 sticks/crutches	6 (26.1)
NYHA class, n (%)	
0: no heart failure	13 (56.5)
I	5 (21.7)
II	5 (21.7)

- Patients received an OLT an average of 3.7 years after diagnosis
- On average, patients received their first dose of patisiran 9.4 years after the OLT
- 13 (56.5%) patients had previously received a TTR stabilizer
- At baseline, the majority (56.5%) of patients had a PND score of IIIA/B
  - 16 patients (69.6%) had experienced a 1-unit increase from first documented PND score[d] to study baseline, prior to patisiran treatment
  - 4 patients (17.4%) experienced a 2-unit increase and 3 patients (13.0%) experienced a 3-unit increase
- 10 (43.5%) patients had NYHA class I/II

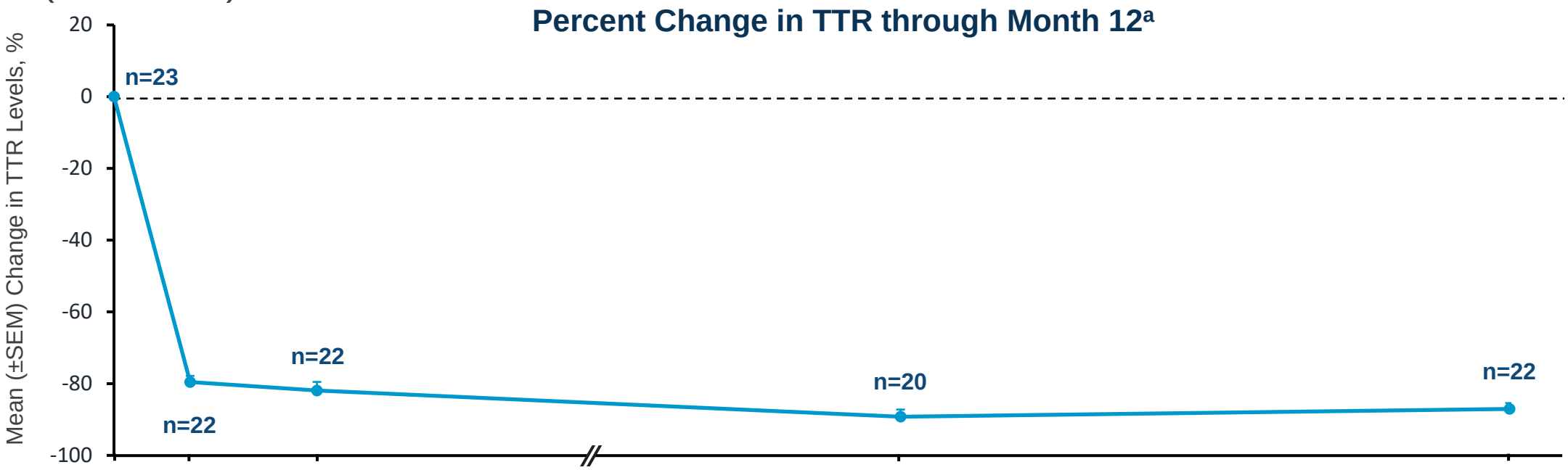
[a]Other genotypes include: S77T (3), G47A (1), G47V (1), L12V (1), F64L (1), and T116S (1). [b]Tafamidis in 11 (47.8%) patients; diflunisal in 2 (8.7%) patients. [c]Other immunosuppression regimens at baseline include: everolimus (1), ciclosporin (1), tacrolimus + everolimus (1), tacrolimus + azathioprine (1), ciclosporin + everolimus (1), ciclosporin + mycophenolate (1). [d]First documented PND score was either the most recent PND score prior to OLT, or first post-OLT PND score if no PND score prior to OLT

ATTRv, hereditary transthyretin (v for variant); BMI, body mass index; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NYHA, New York Heart Association; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin; V30M, valine to methionine at position 30 variant

Rapid and Sustained Reduction in Serum TTR Levels with Patisiran

Primary Endpoint

- Median (95% CI) TTR percent reduction from baseline (average of Month 6 and Month 12) was 91.0 (86.1, 92.3)



	BL	Wk 1–2	Wk 3	Month 6	Month 12
Mean (±SEM) TTR level, mg/L	202.1 (11.3)	41.1 (4.1)	35.5 (4.5)	21.2 (3.7)	24.9 (2.7)
Mean (±SEM) reduction from baseline, %	–	79.6 (1.7)	81.9 (2.4)	89.2 (2.0)	87.1 (1.7)

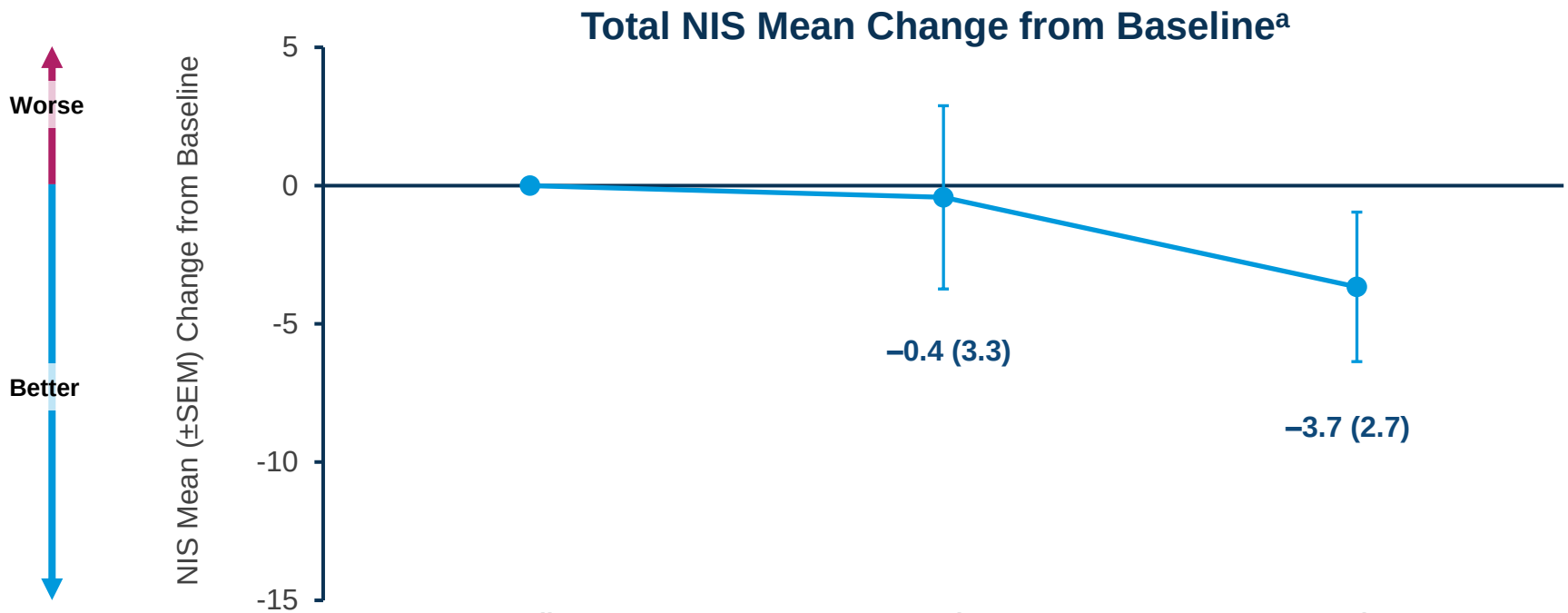
[a]Data for safety analysis set shown

BL, baseline; CI, confidence interval; SEM, standard error of the mean; TTR, transthyretin; Wk, week

Improvement in Neuropathy with Patisiran

Secondary Endpoint

- At Month 12, there was an **improvement** in neuropathy, as demonstrated by a decrease in the mean total NIS score from baseline



	Baseline	Month 6	Month 12
n	21	20	20
Mean (±SEM)	60.0 (8.9)	58.6 (9.1)	55.3 (10.1)
Mean change from baseline (±SEM)	–	–0.4 (3.3)	–3.7 (2.7)

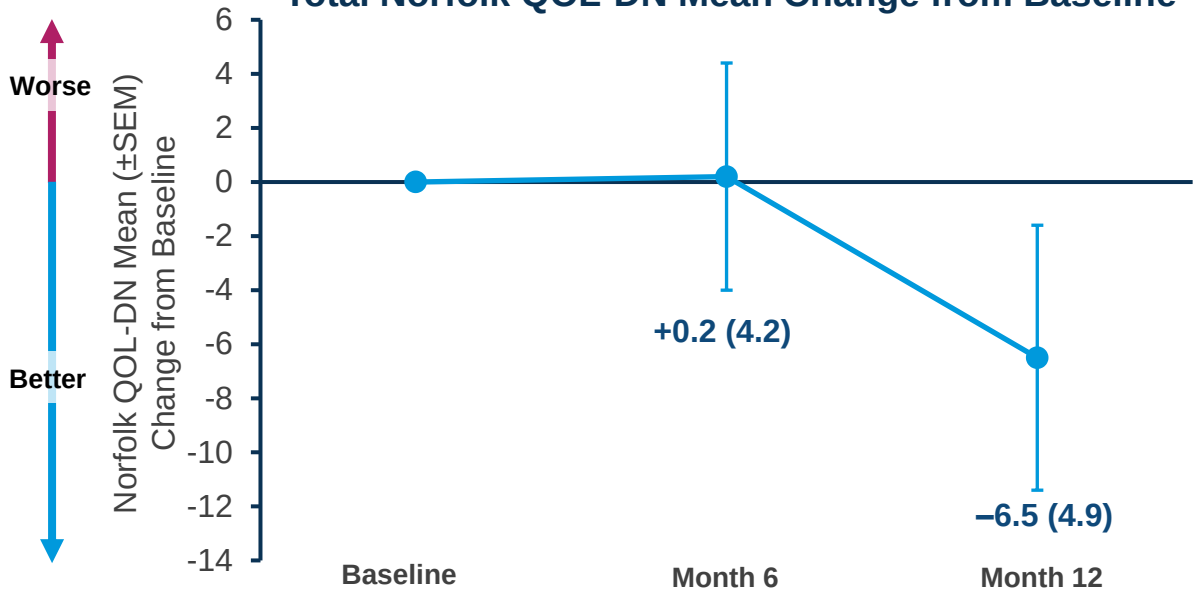
[a]Data for the per protocol analysis set shown. Twenty-one patients were included in the per protocol analysis set (meeting the criteria of ≤2 missing doses due to COVID-19)
NIS, Neuropathy Impairment Score; SEM, standard error of the mean

Improvement in QOL and Autonomic Symptoms with Patisiran

Secondary Endpoints

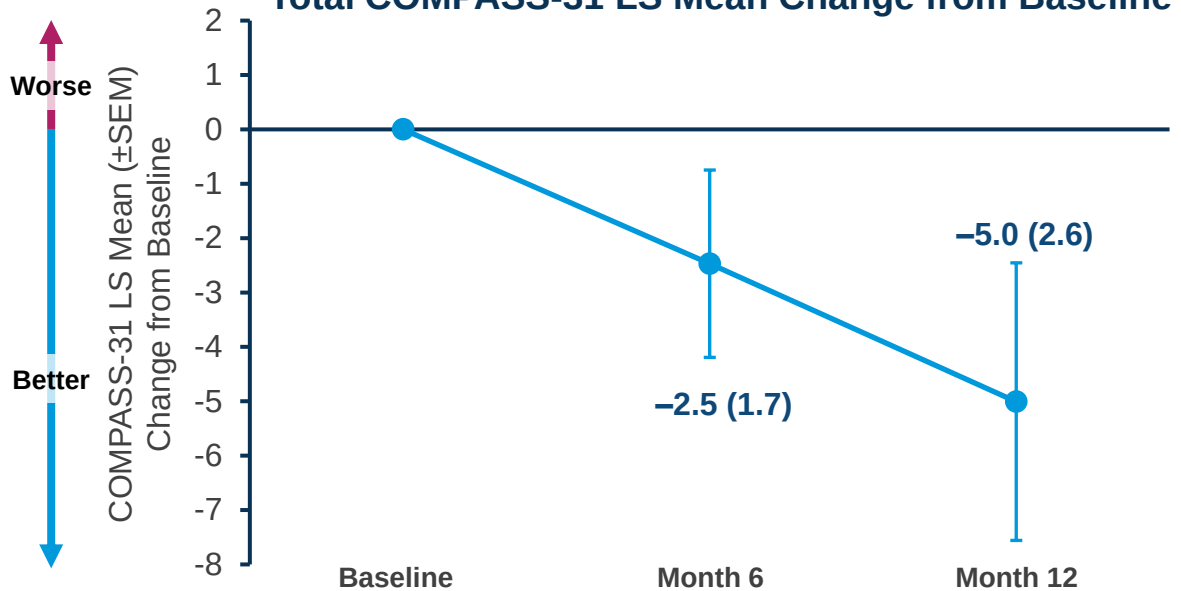
- At Month 12, there was an **improvement** in QOL (decrease in mean total Norfolk QOL-DN score) and autonomic symptoms (decrease in LS mean total COMPASS-31 score) from baseline

Total Norfolk QOL-DN Mean Change from Baseline[a]



	Baseline	Month 6	Month 12
n	21	20	21
Mean (±SEM)	65.4 (5.5)	65.3 (6.3)	59.0 (6.3)
Mean (±SEM) change from baseline	–	+0.2 (4.2)	–6.5 (4.9)

Total COMPASS-31 LS Mean Change from Baseline[a]



	Baseline	Month 6	Month 12
n	20	20	21
Mean (±SEM)	37.4 (3.7)	37.1 (3.9)	34.2 (3.9)
n	20	19	20
LS mean (±SEM) change from baseline	–	–2.5 (1.7)	–5.0 (2.6)

[a]Data for the per protocol analysis set shown. Twenty-one patients were included in the per protocol analysis set (meeting the criteria of ≤2 missing doses due to COVID-19)

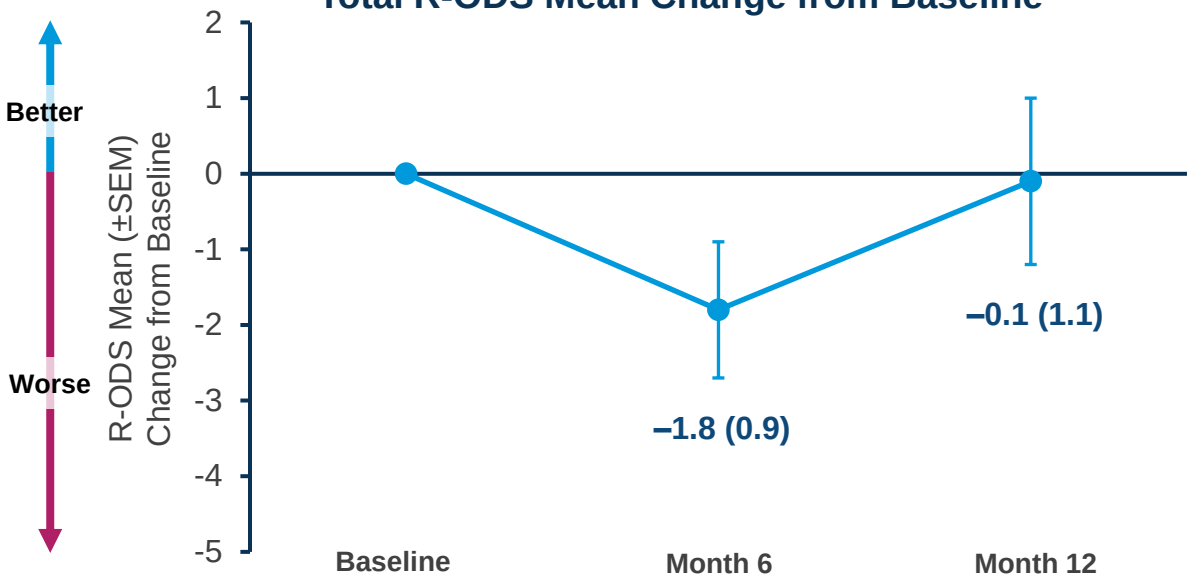
COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; LS, least squares; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; QOL, quality of life; SEM, standard error of the mean

Stabilization in Disability and Nutritional Status with Patisiran

Secondary Endpoints

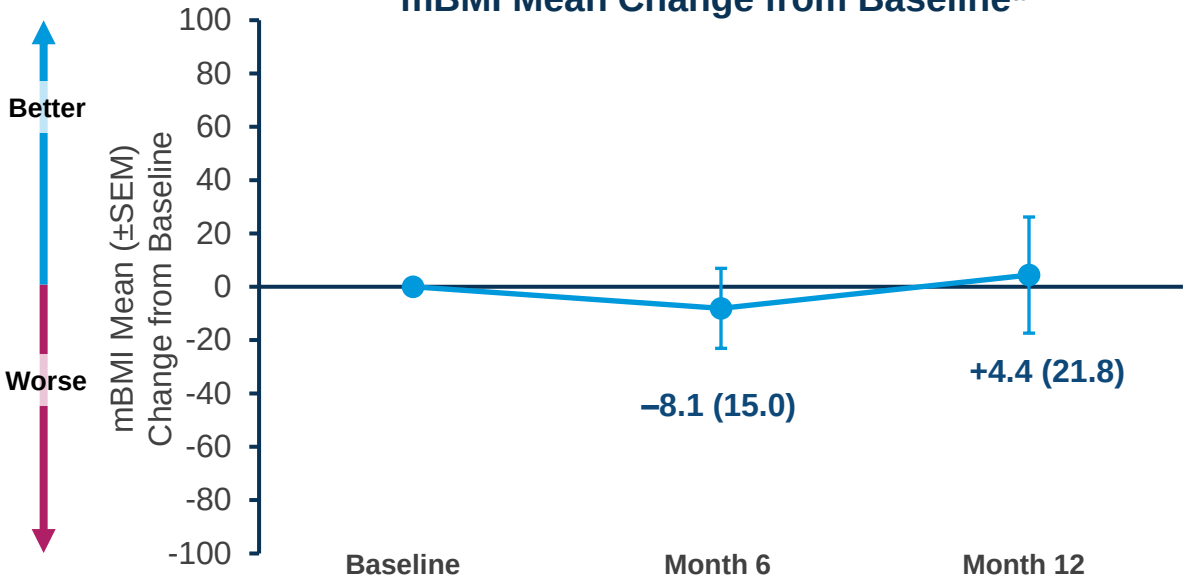
- Through 12 months, the measures of disability (total R-ODS) and nutritional status (mBMI) were **stable** relative to baseline

Total R-ODS Mean Change from Baseline[a]



	Baseline	Month 6	Month 12
n	21	20	21
Mean (±SEM)	29.1 (1.8)	27.2 (2.5)	29.0 (2.4)
Mean (±SEM) change from baseline	–	–1.8 (0.9)	–0.1 (1.1)

mBMI Mean Change from Baseline[a]



	Baseline	Month 6	Month 12
n	21	20	21
Mean (±SEM)	929.9 (29.7)	931.5 (32.4)	934.3 (28.1)
Mean (±SEM) change from baseline	–	–8.1 (15.0)	+4.4 (21.8)

[a]Data for the per protocol analysis set shown. Twenty-one patients were included in the per protocol analysis set (meeting the criteria of ≤2 missing doses due to COVID-19)
mBMI, modified body mass index; R-ODS, Rasch-built Overall Disability Scale; SEM, standard error of the mean

Patisiran Post-OLT: Summary of Safety

Majority of AEs Were Mild or Moderate

- Common adverse events (AEs) were consistent with those seen in the Phase 3 APOLLO study[1]
  - The most common AE was diarrhea (34.8%)
  - 6 (26.1%) patients experienced infusion-related reactions (IRRs)
- 13 serious adverse events (SAEs) reported in 5 (21.7%) patients; 1 SAE (IRR) considered related to patisiran
- No discontinuations due to AEs and no deaths occurred on study
- All 23 patients completed the study; 1 patient discontinued treatment but completed the study
- Liver transplant rejection in 1 patient deemed unrelated to patisiran by investigator; biopsy was consistent with mild acute cellular rejection likely due to inadequate immunosuppression (IS)
  - Patient remained on study drug and completed study
  - IS regimen modified; LFTs remained stable, mostly ranging 1–2×ULN
- Other safety:
  - LFTs were normal in the majority of patients
  - Transient ALT elevation >3×ULN associated with cholangitis in 1 patient deemed unrelated to patisiran by investigator
  - No cases of platelet count <50,000/mm^3

Patients with ≥1 event, n (%)	Safety analysis set (n=23)
Any AE	23 (100)
AEs reported in ≥10% of patients	
Diarrhea	8 (34.8)
IRR	6 (26.1)
Peripheral edema	5 (21.7)
Back pain	5 (21.7)
Cardiac failure	3 (13.0)
Fall	3 (13.0)
Fatigue	3 (13.0)
Headache	3 (13.0)
Pyrexia	3 (13.0)
UTI	3 (13.0)
AE related to study drug	8 (34.8)
Any SAE[a]	5 (21.7)
SAE related to study drug[b]	1 (4.3)
AE leading to discontinuations	0
AE leading to study drug interruption	5 (21.7)
AE leading to death	0

[a]Only term reported in >1 patient was cardiac failure, occurring in 3 patients with history of cardiomyopathy. [b]Occurred after patient's first infusion, with symptoms of dizziness and gait instability requiring overnight hospitalization. The event resolved the following day without intervention and without a change in patisiran treatment

AE, adverse event; ALT, alanine transaminase; IRR, infusion-related reaction; IS, immunosuppression; LFT, liver function test; OLT, orthotopic liver transplantation; SAE, serious adverse event; ULN, upper limit of normal; UTI, urinary tract infection

1. Adams et al. *N Engl J Med* 2018;379:11–21.

Conclusions

- This is the first prospective clinical trial of a therapeutic agent in patients with ATTRv amyloidosis with polyneuropathy progression post-OLT
- Patisiran treatment showed a rapid and sustained reduction of serum TTR from baseline through Month 12
- Patisiran demonstrated improvement in measures of neuropathy, QOL, and autonomic symptoms, and stabilization of disability and nutritional status from baseline at Month 12 in patients who had previously experienced disease worsening, consistent with previous studies of patisiran treatment
- Overall, patisiran was well tolerated in this study, with no discontinuations due to AEs or deaths; no new safety concerns were identified in this patient population
- These results support the benefit of patisiran treatment in improving or stabilizing measures of disease impairment in patients with ATTRv amyloidosis with polyneuropathy progression post-OLT
- The potential of patisiran treatment in the management of ATTRv amyloidosis is of interest in other transplanted populations, such as in patients with combination organ transplants and domino liver transplantation

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AE, adverse event; ATTRv, hereditary transthyretin (v for variant), OLT, orthotopic liver transplantation; QOL, quality of life; TTR, transthyretin

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