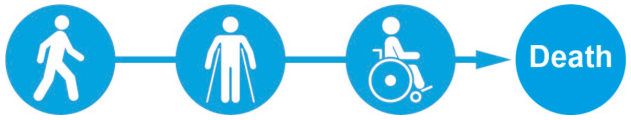
Post hoc Analysis: Impact of baseline polyneuropathy severity on patisiran treatment outcomes in the APOLLO trial

Quan D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Background and Study Design

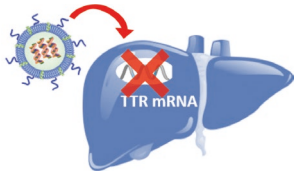
ATTRv Amyloidosis

Multisystem disease caused by abnormal amyloid accumulation across organs and tissues



Rapidly progressive, debilitating, fatal disease

Patisiran



RNAi therapeutic that inhibits synthesis of disease-causing TTR

APOLLO study (n=225)

Patisiran 0.3 mg/kg IV q3w

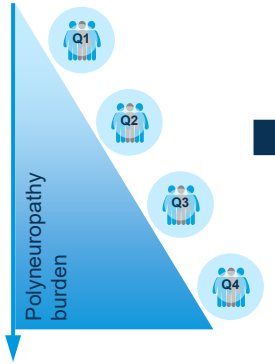
Placebo IV q3w

18 months

Side effects: infusion related reactions and upper respiratory tract infections

Post hoc analysis

Post hoc separation of patients into quartiles (Q) according to polyneuropathy severity (4 even groups based on baseline NIS score)



Assessed changes over 18 months in:

- Polyneuropathy (mNIS+7/NIS) (Primary endpoint)
- Functional measures (R-ODS, 10-MWT, grip strength)
- QOL (Norfolk QOL-DN)

Study limitations

Results

Study population

Overall population

Mostly male population

Median time 1.1–1.8 years since diagnosis

Demographics were comparable in patisiran and placebo groups within each quartile

By quartiles

Q1	Q2	Q3	Q4
NIS 6–<31	NIS 31–<57	NIS 57–<85.5	NIS 85.5–141.6

From Q1 to Q4

Increase in age

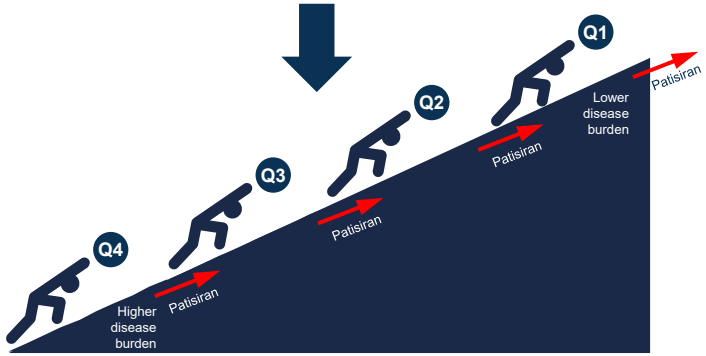
Decrease in KPS

Decrease in unassisted ambulation (PND≤II)

Overall clinical picture

A favorable effect of patisiran treatment compared with placebo was observed for all endpoints across all NIS quartiles.

Total burden remained lowest in patients who started treatment when in the lowest quartiles



Change from baseline in outcome measures

	Patisiran	Placebo
mNIS+7/NIS	Improvements across all quartiles	Continued progression across all quartiles
R-ODS	Stabilization/slight improvements in Q1 & Q2; mild worsening in Q3 & Q4	Substantial decline, worse in higher quartiles
10-MWT	Improvement in Q1; stabilization in Q2 & Q3; slight worsening in Q4	Continued progression across all quartiles
Grip strength	Slight improvements in Q1; slight worsening in Q2–4	Substantial decline across all quartiles
Norfolk QoL-DN / Norfolk QoL-DN Domain scores	Improvements in Q1 & Q2; slight worsening in Q3 & Q4	Substantial decline across all quartiles

Conclusions

- Patisiran improved neurologic function and QOL over 18 months, compared with placebo, regardless of baseline polyneuropathy severity
- Patients who initiated treatment with earlier disease had greatest benefit
- Early diagnosis and treatment has potential to maximize preservation of neurologic function and minimize QOL burden

Abbreviations

Post hoc Analysis: Impact of baseline polyneuropathy severity on patisiran treatment outcomes in the APOLLO trial

Author Information

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Background and Study Design

ATTRv Amyloidosis

Patisiran

Post hoc separation of patients into quartiles (Q) according to polyneuropathy severity (4 even groups based on baseline NIS score)

Assessed changes over 18 months in:
- Polyneuropathy (mNIS+7/NIS) (Primary endpoint)
- Functional measures (R-ODS, 10-MWT, grip strength)
- QOL (Norfolk QOL-DN)

Study limitations

Results

Study population

Overall population

By quartiles

From Q1 to Q4

Increase in age

Decrease in KPS

Decrease in unassisted ambulation (FNDHB)

eline in outcome measures

atisiran

Placebo

10-MWT

Grip strength

Norfolk QoL-DN / Norfolk QoL-DN Domain scores

Improvements in Q1 & Q2; slight worsening in Q3 & Q4

Conclusions

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Abbreviations

ATTRv Amyloidosis

- Hereditary transthyretin (ATTRv) amyloidosis, also known as hereditary transthyretin-mediated (hATTR) amyloidosis, is an underdiagnosed, rapidly progressive, debilitating, and fatal disease[1-5]
  - Variants in the transthyretin (TTR) gene cause abnormal TTR proteins to accumulate as amyloid deposits in multiple tissues, including the nerves and heart
- Polyneuropathy from ATTRv amyloidosis imparts a substantial burden, encompassing sensory and motor neuropathy and autonomic dysfunction[10-15]
  - Typically, patients are rendered wheelchair-bound or bedridden in late-stage disease, resulting in a median survival of 4.7 years following diagnosis[4,7,10,16]
- Patients with ATTRv amyloidosis also experience a decrease in quality of life (QOL), which can be worse than in other conditions associated with high morbidity/mortality, including cancer and diabetes[8,17]

1. Hanna *Curr Heart Fail Rep.* 2014;11:50-57; 2. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528-540; 3. Adams et al. *Neurology.* 2015;85:675-682; 4. Hawkins et al. *Ann Med.* 2015;47:625-638; 5. Damy et al. *J Cardiovasc Transl Res.* 2015;8:117-127; 6 . Rapezzi et al. *Eur Heart J.* 2013;34:520-528; 7. Coelho, Maurer and Suhr *Curr Med Res Opin.* 2013;29:63-76; 8. Adams et al. *N Engl J Med.* 2018;379:11-21; 9. Benson et al. *N Engl J Med.* 2018;379:22-31; 10. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 11. Gonzalez-Duarte *Clin Auton Res.* 2019;29:245-251; 12. Shin and Robinson-Papp *Mt Sinai J Med.* 2012;79:733-748; 13. Amyloidosis Research Consortium. The voice of the patient report – amyloidosis. 2016. Available from: https://www.arci.org/wp-content/uploads/2018/05/Voice-of-the-Patient.pdf; 14. Duncan D. With hope for a cure. 2018. Available from: http://amyloidosis.org/proactive-3/; 15. Mariani et al. *Ann Neurol.* 2015;78:901-916; 16. Adams et al. *Ther Adv Neurol Disord.* 2013;6:129-139; 17. Mitchell et al. *PLoS One.* 2015;10:e0143590.

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Post hoc separation of patients into quartiles (Q) according to polyneuropathy severity
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Assessed changes over 18 months in:
- Polyneuropathy (mNIS+7/NIS) (Primary endpoint)
- Functional measures (R-ODS, 10-MWT, grip strength)
- QOL (Norfolk QOL-DN)

Study limitations

Patisiran

- Patisiran, an RNA interference therapeutic targeting both the disease-causing variant and the wild-type TTR proteins, is approved in >30 countries for the treatment of hATTR amyloidosis in adults with polyneuropathy[1-6]

1. swissmedic. Abbreviated information for health care professionals for ONPATTRO 10 mg/5 ml, concentrate for solution for infusion (version September 2019). 2019. Available from: www.swissmedicinfo.ch; 2. European Medicines Agency. Summary of product characteristics: Onpattro 2 mg/mL concentrate for solution for infusion. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf; 3. Alnylam announces approval in Brazil of ONPATTRO® for the treatment of hereditary ATTR amyloidosis with polyneuropathy [Internet]. Alnylam Pharmaceuticals Inc,; 2020. Available from: https://investors.alnylam.com/press-release?id=24606;
4. Alnylam announces approval in Japan of ONPATTRO® for the treatment of hereditary ATTR amyloidosis with polyneuropathy [Internet]. Alnylam Pharmaceuticals Inc,; 2019. Available from: https://investors.alnylam.com/press-release?id=23886; 5. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use. 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210922s007lbl.pdf; 6 . CADTH. Patisiran. 2019. Available from: https://www.cadth.ca/patisiran.

Abbreviations

Results

Study population

Overall population

Mostly male population

Median time 1.1–1.2 years since diagnosis

Demographics were comparable in patisiran and placebo groups within each quartile

By quartiles

NIS 6–<31 | NIS 31–<57 | NIS 57–<85.5 | NIS 85.5–141.0

From Q1 to Q4

Increase in age

Decrease in KPS

Decrease in unassisted ambulation (FNDHB)

A favorable effect of patisiran treatment compared with placebo was observed for all endpoints across all NIS quartiles

Total burden remained lowest in patients who started treatment when in the lowest quartiles

eline in outcome measures

	Patisiran	Placebo
mNIS+7/NIS	Improvements across all quartiles	Continued progression across all quartiles
R-ODS	Stabilization/slight improvements in Q1 & Q2; mild worsening in Q3 & Q4	Substantial decline, worse in higher quartiles
10-MWT	Improvement in Q1; stabilization in Q2 & Q3; slight worsening in Q4	Continued progression across all quartiles
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- Patisiran improved neurologic function and QOL over 18 months, compared with placebo, regardless of baseline polyneuropathy severity
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Progression

QOL

Patisiran

Post hoc separation of patients into quartiles (Q) according to polyneuropathy severity (4 even groups based on baseline NIS score)

Assessed changes over 18 months in:
- Polyneuropathy (mNIS+7/NIS) (Primary endpoint)
- Functional measures (R-ODS, 10-MWT, grip strength)
- QOL (Norfolk QOL-DN)

Study limitations

APOLLO Study

- APOLLO (NCT01960348) was a multicenter, international, randomized, double-blind, placebo-controlled, Phase 3 study of patisiran in adult patients with ATTRv amyloidosis with polyneuropathy
- Eligible patients:
  - Aged 18–85 years
  - A diagnosis of ATTRv amyloidosis with a documented TTR variant
  - Polyneuropathy (Neuropathy Impairment Score [NIS] of 5–130)
  - Polyneuropathy disability [PND] score ≤IIIb (ambulatory, with or without walking aids)
  - Karnofsky Performance Status (KPS) of ≥60%
  - Adequate liver and renal function
- Patients were randomized 2:1 to receive either patisiran 0.3 mg/kg or placebo intravenously once every 3 weeks for 18 months

Abbreviations

Results

Study population

Overall population

Mostly male population

Median time 1.1–1.2 years since diagnosis

Demographics were comparable in patisiran and placebo groups within each quartile

By quartiles

NIS 6–<31 | NIS 31–<57 | NIS 57–<85.5 | NIS 85.5–141.6

From Q1 to Q4

Increase in age

Decrease in KPS

Decrease in unassisted ambulation (PND>IIIb)

Patisiran compared with placebo was observed for all endpoints across all NIS quartiles

Total burden remained lowest in patients who started treatment when in the lowest quartiles

eline in outcome measures

	Patisiran	Placebo
mNIS+7/NIS	Improvements across all quartiles	Continued progression across all quartiles
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Abbreviations

Adverse Reactions

Adverse Reactions from the Placebo-Controlled Trial that Occurred in at Least 5% of Patisiran-treated Patients and at Least 3% More Frequently than in Placebo-treated Patients

Adverse Reaction	Patisiran N=148 %	Placebo N=77 %
Upper respiratory tract infections[a]	29	21
Infusion-related reaction[b]	19	9
Dyspepsia	8	4
Dyspnea[c,d]	8	0
Muscle spasms[c]	8	1
Arthralgia[c]	7	0
Erythema[c]	7	3
Bronchitis[e]	7	3
Vertigo	5	1

[a] Includes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, pharyngitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.
[b] Infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.
[c] Not part of an infusion-related reaction.
[d] Includes dyspnea and exertional dyspnea.
[e] Includes bronchitis, bronchiolitis, bronchitis viral, lower respiratory tract infection, lung infection.

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Alnylam

Background and Study Design

ATTRv Amyloidosis

Multisystem disease caused by abnormal amyloid accumulation across organs and tissues

Rapidly progressive, debilitating, fatal

Polyneuropathy

Progression

QOL

Patisiran

Post hoc separation of patients into quartiles (Q) according to polyneuropathy severity (4 even groups based on baseline NIS score)

Assessed changes over 18 months in:
- Polyneuropathy (mNIS+7/NIS) (Primary endpoint)
- Functional measures (R-ODS, 10-MWT, grip strength)
- QOL (Norfolk QOL-DN)

Study limitations

Post hoc analysis

- This post hoc analysis evaluated the impact of baseline polyneuropathy severity, as defined by baseline NIS quartiles, on changes in various functional and QOL assessments from baseline to 18 months in patients treated with patisiran or placebo in the APOLLO study
- For this post hoc subgroup analysis, patients from the APOLLO study were divided into four quartiles based on increasing baseline NIS
  - Quartile (Q)1: 6–<31 (n=56)
  - Q2: 31–<57 (n=56)
  - Q3: 57–<85.5 (n=56)
  - Q4: 85.5–141.6 (n=57).
- Assessed changes over 18 months in:
  - Neurologic impairment (mNIS+7 [primary endpoint in APOLLO]/NIS)
  - Disability and functional status (R-ODS)
  - Gait speed (10-MWT)
  - Motor function (grip strength)
  - QOL (Norfolk QOL-DN)

Abbreviations

Results

Study population

Overall population

Mostly male population

Median time since diagnosis

Demographics were comparable in patisiran and placebo groups within each quartile

By quartiles

NIS 6–<31 | NIS 31–<57 | NIS 57–<85.5 | NIS 85.5–141.6

From Q1 to Q4

Increase in age

Decrease in KPS

Decrease in unassisted ambulation (FNDHB)

Total burden remained lowest in patients who started treatment when in the lowest quartiles

eline in outcome measures

atisiran

Placebo

R-ODS

Stabilization/slight improvements in Q1 & Q2; mild worsening in Q3 & Q4

Substantial decline, worse in higher quartiles

10-MWT

Improvement in Q1; stabilization in Q2 & Q3; slight worsening in Q4

Continued progression across all quartiles

Grip strength

Slight improvements in Q1; slight worsening in Q2–4

Substantial decline across all quartiles

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Study limitations

Study Limitations

- The sample size by treatment group within each baseline NIS quartile is relatively small and was not powered to detect significant differences between the groups defined in this post hoc analysis
- Study discontinuation occurred in 7/16 (43.8%) patients from the Q4 placebo group and 5/41 (12.2%) from the Q4 patisiran group
  - The greater proportion of missing data in the placebo group may lead to an underrepresentation of the benefit of patisiran in Q4, as patients in Q4 who discontinued due to progressive disease (0% [patisiran], 12.5% [placebo]) or death (7.3% [patisiran], 18.8% [placebo]) may otherwise have reported high levels of polyneuropathy and QOL impairment that may have further worsened the overall mean placebo scores at 18 months
- This study was not randomized by baseline NIS quartile and thus some small differences between treatment groups and quartiles are present
- NIS may be a less sensitive tool to capture the overall baseline neurologic impairment in these patients compared with the mNIS+7

Abbreviations

Results

Study population

Overall population

Mostly male population

Median time since diagnosis

Demographics were comparable in patisiran and placebo groups within each quartile

By quartiles

NIS 6–<31 | NIS 31–<57 | NIS 57–<85.5 | NIS 85.5–141.6

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	Patisiran	Placebo
	improvements across all quartiles	Continued progression across all quartiles
R-ODS	Stabilization/slight improvements in Q1 & Q2; mild worsening in Q3 & Q4	Substantial decline, worse in higher quartiles
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Abbreviations

Study Population

Baseline demographics and disease characteristics of patients across the NIS quartiles and the mITT population

Characteristic	Q1: NIS 6–<31		Q2: NIS 31–<57		Q3: NIS 57–<85.5		Q4: NIS 85.5–141.6	
	Placebo (*n*=19)	Patisiran (*n*=37)	Placebo (*n*=22)	Patisiran (*n*=34)	Placebo (*n*=20)	Patisiran (*n*=36)	Placebo (*n*=16)	Patisiran (*n*=41)
Median age, years (range)	57 (36–80)	57 (24–69)	63 (34–75)	61 (31–79)	70 (47–77)	66 (36–83)	63 (43–77)	65 (42–79)
Male sex, *n* (%)	12 (63.2)	26 (70.3)	18 (81.8)	28 (82.4)	15 (75.0)	24 (66.7)	13 (81.3)	31 (75.6)
Median time since ATTRv amyloidosis diagnosis, years (range)	1.5 (0.2–13.0)	1.8 (0.0–21.0)	1.3 (0.0–9.1)	1.1 (0.1–17.5)	1.4 (0.1–16.5)	1.3 (0.1–8.1)	1.6 (0.1–8.8)	1.7 (0.0–14.3)
TTR genotype, n (%)								
V30M	11 (57.9)	11 (29.7)	10 (45.5)	14 (41.2)	13 (65.0)	13 (36.1)	6 (37.5)	18 (43.9)
Non-V30M*	8 (42.1)	26 (70.3)	12 (54.5)	20 (58.8)	7 (35.0)	23 (63.9)	10 (62.5)	23 (56.1)
Early-onset V30M	4 (21.1)	5 (13.5)	3 (13.6)	2 (5.9)	1 (5.0)	3 (8.3)	2 (12.5)	3 (7.3)
Previous TTR stabilizer use, *n* (%)	10 (52.6)	22 (59.5)	13 (59.1)	15 (44.1)	12 (60.0)	20 (55.6)	6 (37.5)	21 (51.2)
Median NIS (range)	15.0 (7.0–30.0)	20.0 (6.0–30.0)	44.3 (31.0–56.6)	44.0 (31.5–55.6)	73.8 (57.0–80.0)	68.7 (57.0–84.5)	102.4 (85.5–125.5)	105.5 (86.0–141.6)
PND score, n (%)								
I: preserved walking, sensory disturbances	13 (68.4)	29 (78.4)	7 (31.8)	5 (14.7)	0	1 (2.8)	0	1 (2.4)
II: impaired walking without need for a stick or crutches	6 (31.6)	5 (13.5)	10 (45.5)	17 (50.0)	6 (30.0)	12 (33.3)	1 (6.3)	9 (22.0)
IIIA: walking with one stick or crutch	0	3 (8.1)	4 (18.2)	10 (29.4)	9 (45.0)	17 (47.2)	9 (56.3)	11 (26.8)
IIIB: walking with two sticks or crutches	0	0	1 (4.5)	2 (5.9)	4 (20.0)	6 (16.7)	6 (37.5)	20 (48.8)
IV: confined to wheelchair or bedridden	0	0	0	0	1 (5.0)	0	0	0
Karnofsky Performance Status, *n* (%)								
60	2 (10.5)	1 (2.7)	3 (13.6)	3 (8.8)	10 (50.0)	10 (27.8)	7 (43.8)	35 (85.4)
70–80	15 (78.9)	24 (64.9)	13 (59.1)	28 (82.4)	9 (45.0)	23 (63.9)	8 (50.0)	5 (12.2)
90–100	2 (10.5)	12 (32.4)	6 (27.3)	3 (8.8)	1 (5.0)	3 (8.3)	1 (6.3)	1 (2.4)

*Non-V30M TTR genotype represents 38 different TTR variants.

- Baseline polyneuropathy (as assessed by NIS) ranged from 6.0 to 141.6 points, reflecting the wide distribution of neurologic impairment at baseline in APOLLO
- Median age was comparable between the placebo and patisiran arms within each quartile, with patients in Q1 having a lower median age compared with patients in higher quartiles
- The majority of patients were male
- The proportion of patients with unassisted ambulation (PND≤II) was greater in Q1 (least severe disease) than Q4 (most severe disease)
- The proportion of patients with a better functional status, as indicated by higher KPS, was higher in the lower NIS quartiles and decreased in the higher NIS quartiles

Abbreviations

Overall Clinical Picture (1)

NIS, R-ODS and 10-MWT at baseline and 18 months by baseline NIS quartiles

	Q1: NIS 6–<31		Q2: NIS 31–<57		Q3: NIS 57–<85.5		Q4: NIS 85.5–141.6	
Assessment	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
NIS								
n at baseline	19	37	22	34	20	36	16	41
Mean (SEM) score at baseline	17.9 (1.8)	18.3 (1.1)	43.7 (1.7)	43.2 (1.3)	71.6 (1.6)	69.4 (1.5)	103.7 (3.2)	105.1 (2.2)
n at 18 months	13	36	14	32	15	33	9	36
Mean (SEM) score at 18 months	27.1 (3.6)	21.3 (1.9)	68.0 (5.0)	43.0 (2.9)	107.9 (7.4)	76.9 (4.0)	130.1 (4.0)	108.7 (3.6)
Mean (SEM) change from baseline to 18 months	10.8 (2.7)	2.8 (1.5)	24.9 (4.6)	–0.1 (2.9)	37.3 (7.1)	6.7 (3.4)	27.4 (4.1)	3.8 (2.7)
Mean (SEM) percent change from baseline to 18 months	75.5 (21.5)	16.7 (10.0)	59.7 (12.4)	1.3 (7.5)	53.6 (10.5)	9.3 (5.3)	27.5 (4.2)	3.7 (2.6)
R-ODS								
n at baseline	19	37	22	34	19	36	16	41
Mean (SEM) score at baseline	40.1 (1.6)	40.4 (1.4)	34.4 (1.2)	33.5 (1.5)	25.2 (1.4)	28.3 (1.3)	16.6 (1.8)	18.0 (1.1)
n at 18 months	14	36	15	32	15	34	10	36
Mean (SEM) score at 18 months	37.1 (2.3)	41.6 (1.2)	22.7 (2.1)	34.7 (1.4)	14.5 (2.0)	27.1 (1.3)	5.8 (1.1)	15.0 (1.4)
Mean (SEM) change from baseline to 18 months	–3.8 (1.2)	1.0 (1.0)	–12.9 (1.8)	0.3 (1.2)	–11.7 (1.8)	–1.4 (1.4)	–10.8 (2.5)	–2.9 (0.9)
Mean (SEM) percent change from baseline to 18 months	–9.7 (3.0)	6.1 (5.3)	–36.4 (5.2)	2.8 (4.0)	–45.7 (7.3)	–0.1 (5.7)	–57.9 (8.3)	–13.0 (6.8)
10-MWT								
n at baseline	19	37	22	34	20	36	16	40
Mean (SEM) gait speed at baseline (m/s)	1.05 (0.06)	1.14 (0.06)	0.89 (0.06)	0.90 (0.05)	0.68 (0.06)	0.71 (0.05)	0.49 (0.05)	0.46 (0.05)
n at 18 months	14	36	15	32	15	34	11	36
Mean (SEM) gait speed at 18 months (m/s)	1.00 (0.08)	1.32 (0.07)	0.59 (0.05)	0.93 (0.06)	0.33 (0.07)	0.71 (0.06)	0.25 (0.10)	0.42 (0.06)
Mean (SEM) change from baseline to 18 months (m/s)	–0.06 (0.07)	0.17 (0.05)	–0.33 (0.05)	0.01 (0.05)	–0.36 (0.08)	0.01 (0.03)	–0.28 (0.09)	–0.04 (0.04)
Mean (SEM) percent change from baseline to 18 months	–4.31 (6.07)	17.53 (7.26)	–34.67 (6.48)	5.96 (5.66)	–49.90 (10.62)	0.07 (5.76)	–61.97 (15.97)	–5.08 (8.48)

- Overall, a favorable effect of patisiran treatment compared with placebo was observed for all endpoints across all NIS quartiles
- Substantial deterioration was consistently seen across all NIS quartiles in the placebo arm, while those patients treated with patisiran demonstrated improvement or slight deterioration in the endpoints assessed
- Patients with higher baseline NIS quartiles did not perform as well on functional assessments at 18 months as those who initiated treatment at a lower NIS quartile

Overall Clinical Picture continued Abbreviations

Overall Clinical Picture (2)

Grip strength and Norfolk QOL-DN at baseline and 18 months by baseline NIS quartiles

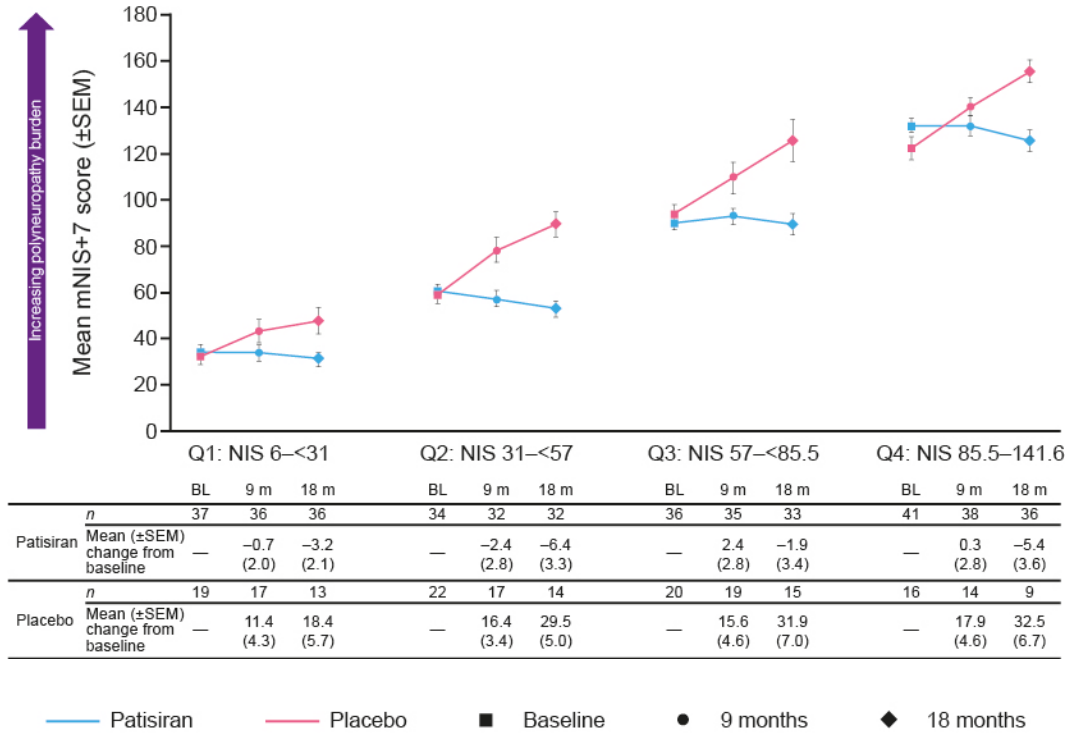
	Q1: NIS 6–<31		Q2: NIS 31–<57		Q3: NIS 57–<85.5		Q4: NIS 85.5–141.6	
Assessment	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
Grip strength								
n at baseline	19	37	22	34	20	36	16	41
Mean (SEM) grip strength at baseline (kg)	25.2 (1.8)	28.4 (2.3)	22.4 (2.5)	22.8 (2.3)	14.0 (1.3)	16.4 (1.3)	7.3 (1.4)	7.7 (1.4)
n at 18 months	14	35	15	32	16	33	11	35
Mean (SEM) grip strength at 18 months (kg)	19.1 (2.1)	29.5 (2.1)	12.9 (2.0)	21.8 (1.6)	5.6 (1.1)	14.4 (1.3)	1.3 (0.8)	6.8 (1.3)
Mean (SEM) change from baseline to 18 months (kg)	–6.6 (2.3)	0.7 (1.9)	–10.8 (2.1)	–1.6 (1.9)	–7.4 (1.1)	–2.0 (0.9)	–6.4 (1.7)	–1.3 (0.9)
Mean (SEM) percent change from baseline to 18 months	–23.1 (6.2)	8.7 (5.2)	–44.4 (5.1)	1.8 (5.3)	–58.1 (6.2)	–7.7 (5.7)	–85.8 (7.0)	12.6 (16.0)
Norfolk QOL-DN								
n at baseline	19	37	22	34	19	36	16	41
Mean (SEM) Norfolk QOL-DN score at baseline	36.4 (3.9)	39.7 (4.7)	50.9 (4.9)	54.8 (4.3)	65.4 (4.7)	59.4 (3.7)	72.9 (5.2)	81.8 (3.0)
n at 18 months	13	35	14	32	14	33	8	36
Mean (SEM) Norfolk QOL-DN score at 18 months	49.6 (9.1)	32.1 (4.9)	69.2 (7.4)	47.1 (4.6)	84.1 (5.6)	57.6 (3.6)	90.1 (4.8)	83.3 (3.2)
Mean (SEM) change from baseline to 18 months	15.6 (5.8)	–8.1 (4.0)	23.1 (4.1)	–6.1 (3.8)	22.9 (6.2)	0.5 (3.4)	18.0 (10.4)	2.8 (3.2)
Mean percent change from baseline to 18 months	49.4 (22.9)	–17.9 (9.3)	56.6 (11.8)	–4.6 (9.1)	46.7 (14.4)	12.3 (11.0)	42.4 (28.6)	6.1 (4.5)

- Overall, a favorable effect of patisiran treatment compared with placebo was observed for all endpoints across all NIS quartiles
- Substantial deterioration was consistently seen across all NIS quartiles in the placebo arm, while those patients treated with patisiran demonstrated improvement or slight deterioration in the endpoints assessed
- Patients with higher baseline NIS quartiles did not perform as well on functional assessments at 18 months as those who initiated treatment at a lower NIS quartile

Abbreviations

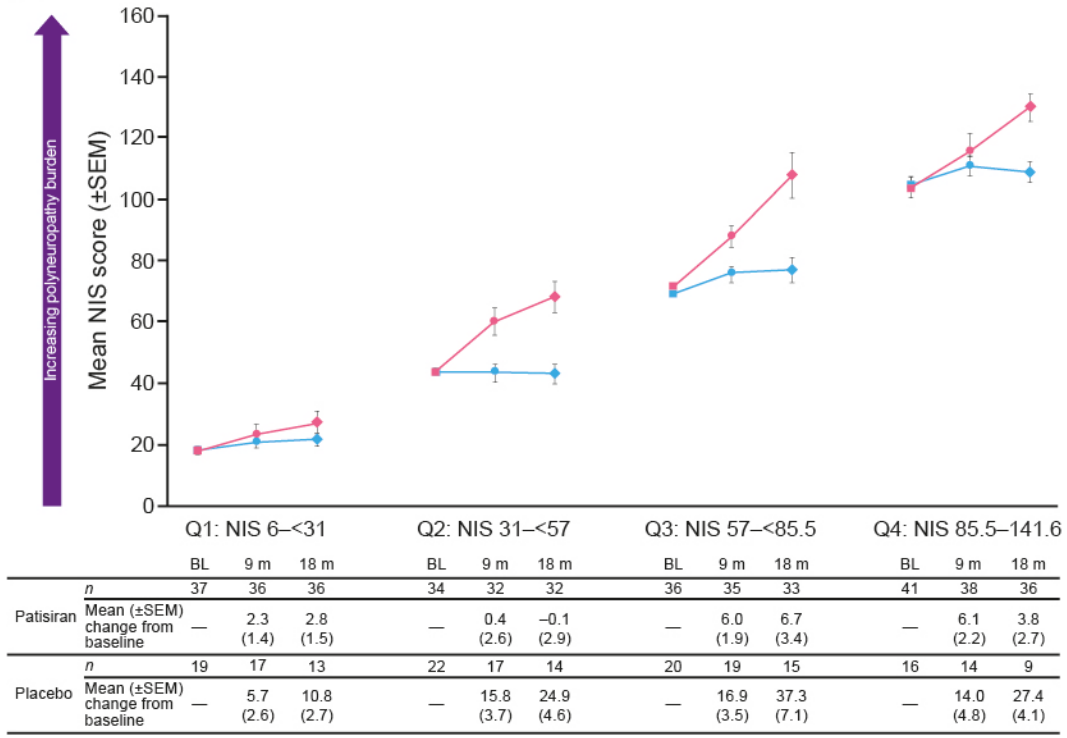
Mean mNIS+7 (A) and NIS (B) scores at baseline, 9 months, and 18 months according to baseline polyneuropathy group

(A)



		Q1: NIS 6–<31			Q2: NIS 31–<57			Q3: NIS 57–<85.5			Q4: NIS 85.5–141.6		
		BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m
Patisiran	*n*	37	36	36	34	32	32	36	35	33	41	38	36
	Mean (±SEM) change from baseline	—	−0.7 (2.0)	−3.2 (2.1)	—	−2.4 (2.8)	−6.4 (3.3)	—	2.4 (2.8)	−1.9 (3.4)	—	0.3 (2.8)	−5.4 (3.6)
Placebo	*n*	19	17	13	22	17	14	20	19	15	16	14	9
	Mean (±SEM) change from baseline	—	11.4 (4.3)	18.4 (5.7)	—	16.4 (3.4)	29.5 (5.0)	—	15.6 (4.6)	31.9 (7.0)	—	17.9 (4.6)	32.5 (6.7)

(B)



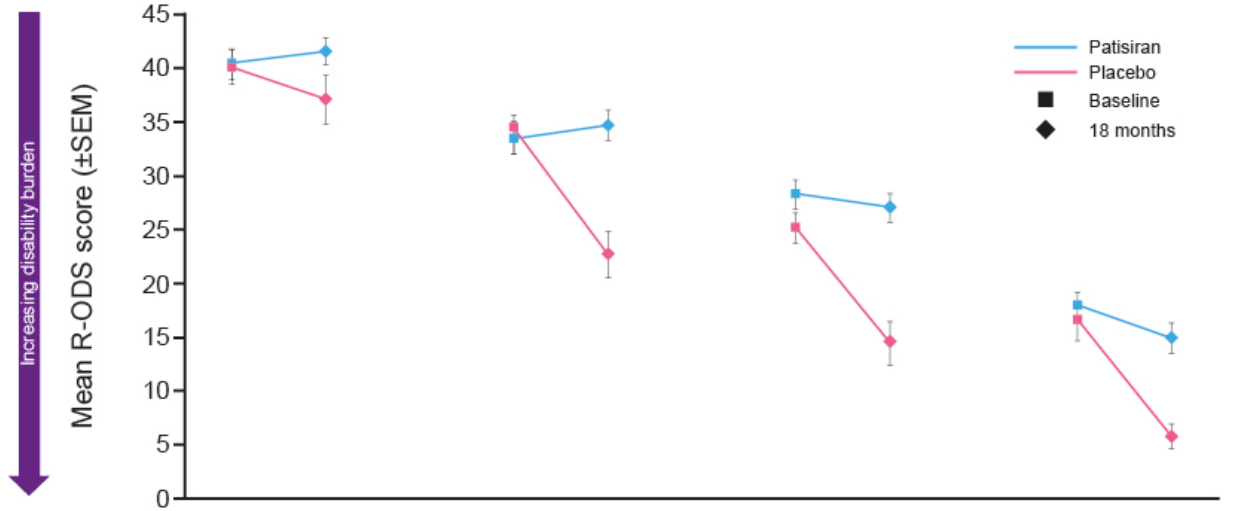
		Q1: NIS 6–<31			Q2: NIS 31–<57			Q3: NIS 57–<85.5			Q4: NIS 85.5–141.6		
		BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m
Patisiran	*n*	37	36	36	34	32	32	36	35	33	41	38	36
	Mean (±SEM) change from baseline	—	2.3 (1.4)	2.8 (1.5)	—	0.4 (2.6)	−0.1 (2.9)	—	6.0 (1.9)	6.7 (3.4)	—	6.1 (2.2)	3.8 (2.7)
Placebo	*n*	19	17	13	22	17	14	20	19	15	16	14	9
	Mean (±SEM) change from baseline	—	5.7 (2.6)	10.8 (2.7)	—	15.8 (3.7)	24.9 (4.6)	—	16.9 (3.5)	37.3 (7.1)	—	14.0 (4.8)	27.4 (4.1)

- Within each quartile, baseline mNIS+7 scores were comparable between placebo and patisiran arms
- In both treatment arms, mean±SEM baseline mNIS+7 scores were lower in Q1 (34.3±2.1 [patisiran], 32.1±5.7 [placebo]) and increased through the higher NIS quartiles (Q4: 132.1±4.9 [patisiran], 122.3±2.9 [placebo])
- By 18 months, patients across all quartiles in the patisiran arm showed an improvement in polyneuropathy, as demonstrated by a negative mean change in mNIS+7 score from baseline, ranging between −6.4 and −1.9
- In contrast, patients in the placebo arm had continued progression of polyneuropathy, as demonstrated by a positive mean change in mNIS+7, across all quartiles (ranging between 18.4 and 32.5)
- Despite the improvement in polyneuropathy among patisiran-treated patients, those in higher NIS quartiles (most severe disease at baseline) continued to exhibit more severe polyneuropathy, as demonstrated by higher mean±SEM mNIS+7 scores, at 18 months than those in the lower NIS quartiles (least severe disease at baseline) (mNIS+7 at 18 months: Q1: 31.3±2.9, Q2: 53.1±3.5, Q3: 89.2±4.2, Q4: 125.7±4.7)
- Similar findings were observed when evaluating NIS total scores by baseline NIS quartile

Abbreviations

R-ODS

Mean R-ODS score at baseline and 18 months according to baseline polyneuropathy group



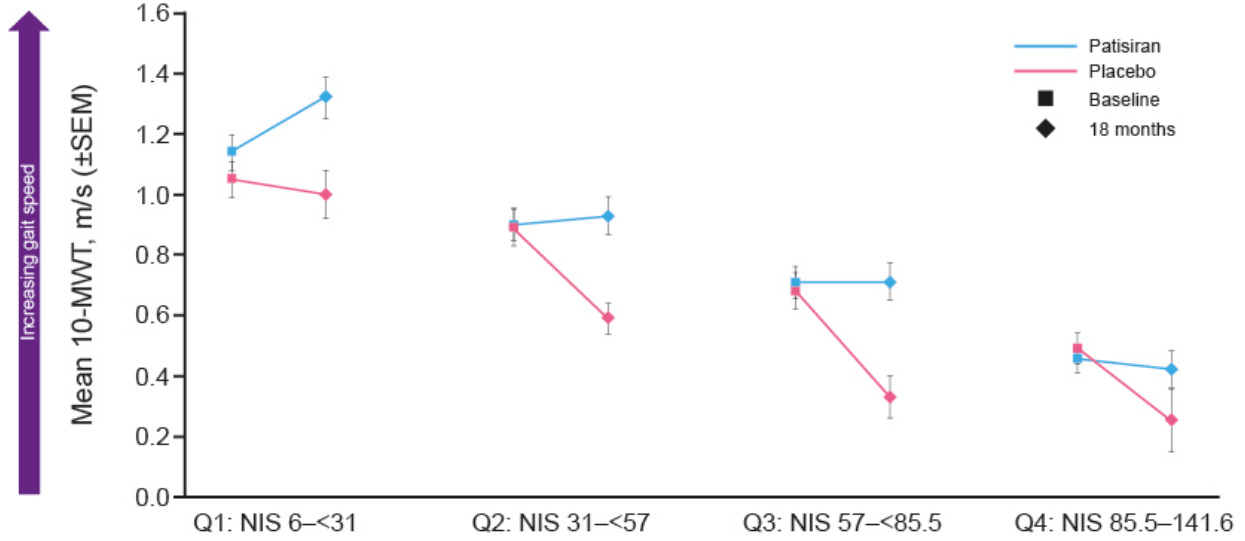
		Q1: NIS 6–<31		Q2: NIS 31–<57		Q3: NIS 57–<85.5		Q4: NIS 85.5–141.6	
		BL	18 m	BL	18 m	BL	18 m	BL	18 m
Patisiran	*n*	37	36	34	32	36	34	41	36
	Mean (±SEM) change from baseline	—	1.0 (1.0)	—	0.3 (1.2)	—	−1.4 (1.4)	—	−2.9 (0.9)
Placebo	*n*	19	14	22	15	19	15	16	10
	Mean (±SEM) change from baseline	—	−3.8 (1.2)	—	−12.9 (1.8)	—	−11.7 (1.8)	—	−10.8 (2.5)

- R-ODS showed similar baseline scores between patisiran and placebo arms within each quartile, with the highest values observed in Q1 and the lowest values in Q4
- Across all quartiles, the mean change from baseline at 18 months in R-ODS scores was consistently worse in the placebo arm than in the patisiran arm, ranging between −2.9 and 1.0 (patisiran) versus −12.9 and −3.8 (placebo)
- The R-ODS scores showed stabilization or slight improvement compared with baseline in Q1 and Q2 of the patisiran arm and mild worsening in Q3 and Q4, while the placebo arm showed substantial deterioration from baseline in functional status, with greater decline in the higher NIS quartiles

Abbreviations

10-MWT

Mean 10-MWT, in m/s, at baseline and 18 months according to baseline polyneuropathy group



		Q1: NIS 6–<31		Q2: NIS 31–<57		Q3: NIS 57–<85.5		Q4: NIS 85.5–141.6	
		BL	18 m	BL	18 m	BL	18 m	BL	18 m
Patisiran	*n*	37	36	34	32	36	34	40	36
	Mean (±SEM) change from baseline, m/s	—	0.17 (0.05)	—	0.01 (0.05)	—	0.01 (0.03)	—	−0.04 (0.04)
	Mean (±SEM) percent change from baseline	—	17.5 (7.3)	—	6.0 (5.7)	—	0.1 (5.8)	—	−5.1 (8.5)
Placebo	*n*	19	14	22	15	20	15	16	11
	Mean (±SEM) change from baseline, m/s	—	−0.06 (0.07)	—	−0.33 (0.05)	—	−0.36 (0.08)	—	−0.28 (0.09)
	Mean (±SEM) percent change from baseline	—	−4.3 (6.1)	—	−34.7* (6.5)	—	−49.9 (10.6)	—	−62.0 (16.0)

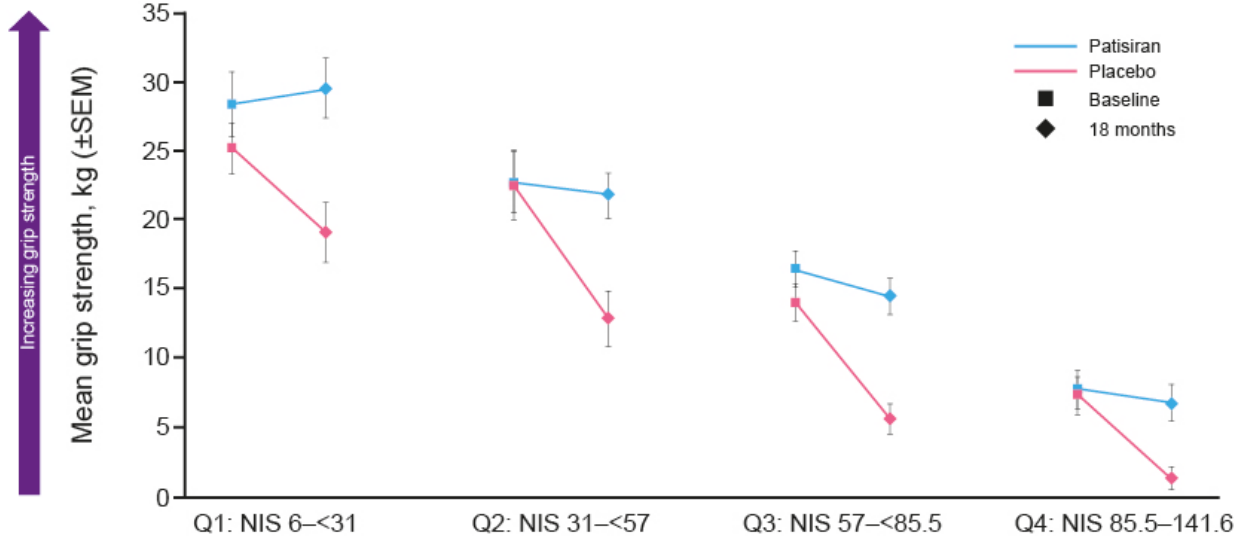
*n=14

- 10-MWT showed similar baseline scores between patisiran and placebo arms within each quartile, with the highest values observed in Q1 and the lowest values in Q4
- The mean change from baseline to 18 months was also consistently better in the patisiran arm than in the placebo arm in the 10-MWT, ranging between −0.04 and 0.17 m/s (patisiran) versus −0.36 and −0.06 m/s (placebo)

Abbreviations

Grip strength

Mean grip strength, in kg, at baseline and 18 months according to baseline polyneuropathy group



		Q1: NIS 6–<31		Q2: NIS 31–<57		Q3: NIS 57–<85.5		Q4: NIS 85.5–141.6	
		BL	18 m	BL	18 m	BL	18 m	BL	18 m
Patisiran	*n*	37	35	34	32	36	33	41	35
	Mean (±SEM) change from baseline, kg	—	0.7 (1.9)	—	−1.6 (1.9)	—	−2.0 (0.9)	—	−1.3 (0.9)
	Mean (±SEM) percent change from baseline	—	8.7 (5.2)	—	1.8 (5.3)	—	−7.7 (5.7)	—	12.6* (16.0)
Placebo	*n*	19	14	22	15	20	16	16	11
	Mean (±SEM) change from baseline, kg	—	−6.6 (2.3)	—	−10.8 (2.1)	—	−7.4 (1.1)	—	−6.4 (1.7)
	Mean (±SEM) percent change from baseline	—	−23.1 (6.2)	—	−44.4 (5.1)	—	−58.1 (6.2)	—	−85.8† (7.0)

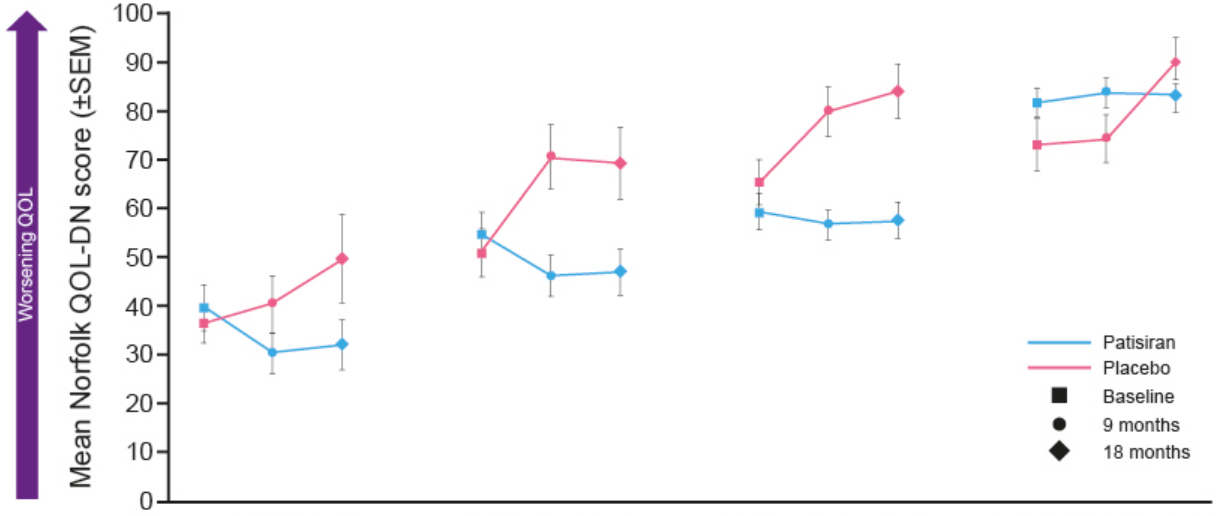
*n=32; †n=10

- Grip strength showed similar baseline scores between patisiran and placebo arms within each quartile, with the highest values observed in Q1 and the lowest values in Q4
- The mean change from baseline to 18 months was also consistently better in the patisiran arm than in the placebo arm in grip strength, ranging between −2.0 and 0.7 kg (patisiran) versus −10.8 and −6.4 kg (placebo)

Abbreviations

Norfolk QoL-DN

Mean Norfolk QOL-DN scores at baseline, 9 months, and 18 months according to baseline polyneuropathy group



		Q1: NIS 6–<31			Q2: NIS 31–<57			Q3: NIS 57–<85.5			Q4: NIS 85.5–141.6		
		BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m
Patisiran	*n*	37	36	35	34	32	32	36	35	33	41	38	36
	Mean (±SEM) change from baseline	—	−9.0 (3.3)	−8.1 (4.0)	—	−7.0 (3.2)	−6.1 (3.8)	—	−2.4 (2.8)	0.5 (3.4)	—	2.3 (2.7)	2.8 (3.2)
Placebo	*n*	19	17	13	22	17	14	19	18	13	16	13	8
	Mean (±SEM) change from baseline	—	5.0 (4.2)	15.6 (5.8)	—	18.3 (3.3)	23.1 (4.1)	—	15.9 (4.9)	22.9 (6.2)	—	4.9 (6.3)	18.0 (10.4)

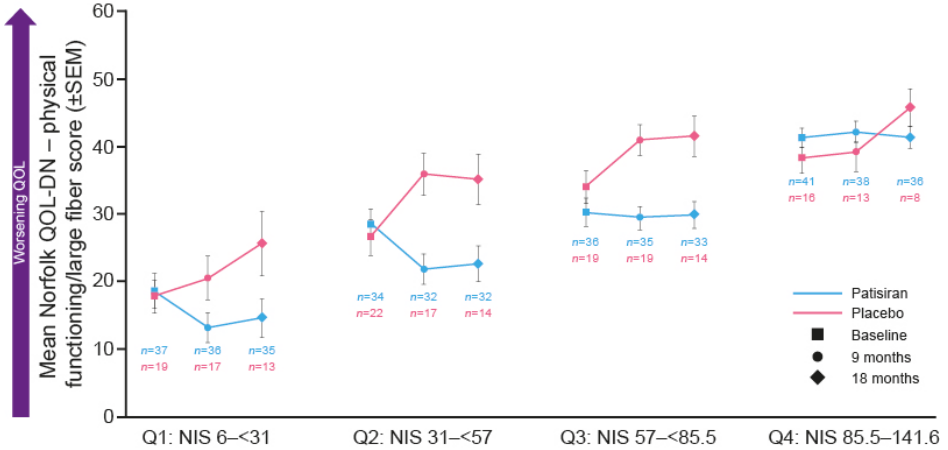
- Baseline Norfolk QOL-DN scores were generally comparable between patients in the placebo and patisiran arms within each quartile, with mean±SEM Norfolk QOL-DN scores being lowest among patients in Q1 (39.7±4.7 [patisiran], 36.4±3.9 [placebo]) and increasing through the higher NIS quartiles (Q4: 81.8±3.0 [patisiran], 72.9±5.2 [placebo])
- In Q1 and Q2, patients in the patisiran arm showed improved QOL, as demonstrated by a negative mean change in Norfolk QOL-DN from baseline to 18 months (−8.1±4.0 and −6.1±3.8, respectively)
- Patisiran-treated patients in Q3 and Q4 had a mean±SEM change from baseline to 18 months of 0.5±3.4 and 2.8±3.2, respectively
- In contrast, patients in the placebo arm experienced rapid deterioration of their QOL across all NIS quartiles from baseline to 18 months, with the mean change in Norfolk QOL-DN scores ranging between 15.6 and 23.1
- Despite experiencing an improvement in QOL when compared with placebo, patisiran-treated patients in higher NIS quartiles were unable to achieve the same level of QOL at the end of the 18 months compared with patients in the lower NIS quartiles

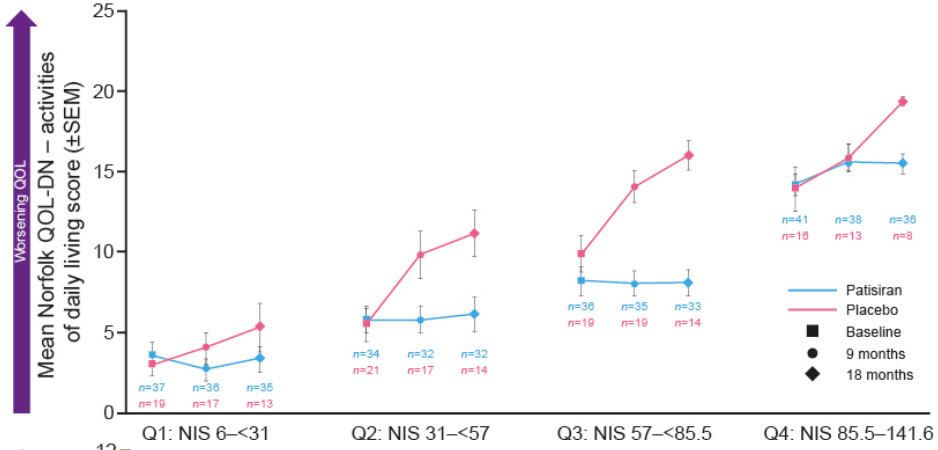
Abbreviations

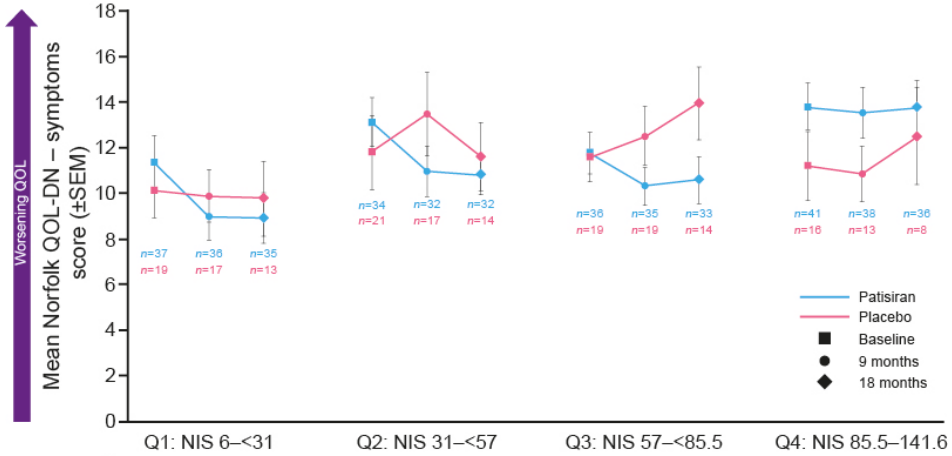
Norfolk QoL-DN Domain scores

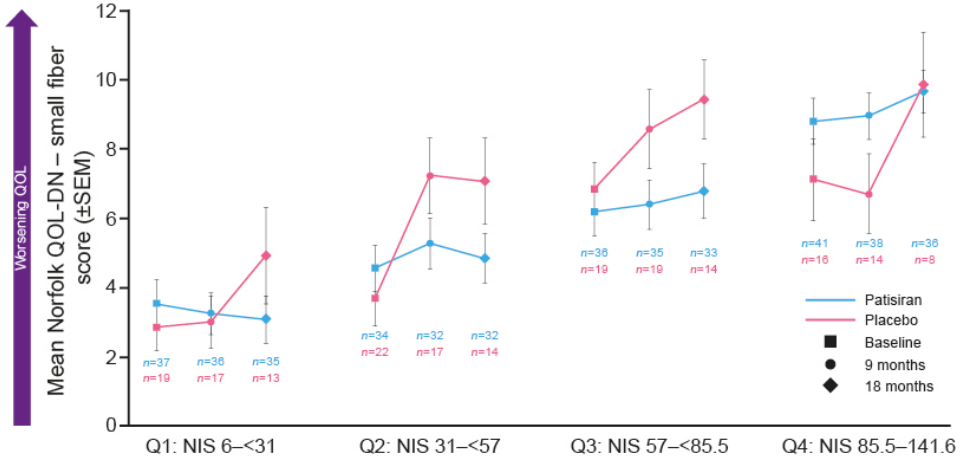
Norfolk QOL-DN subdomain scores at baseline, 9 months, and 18 months according to baseline polyneuropathy group

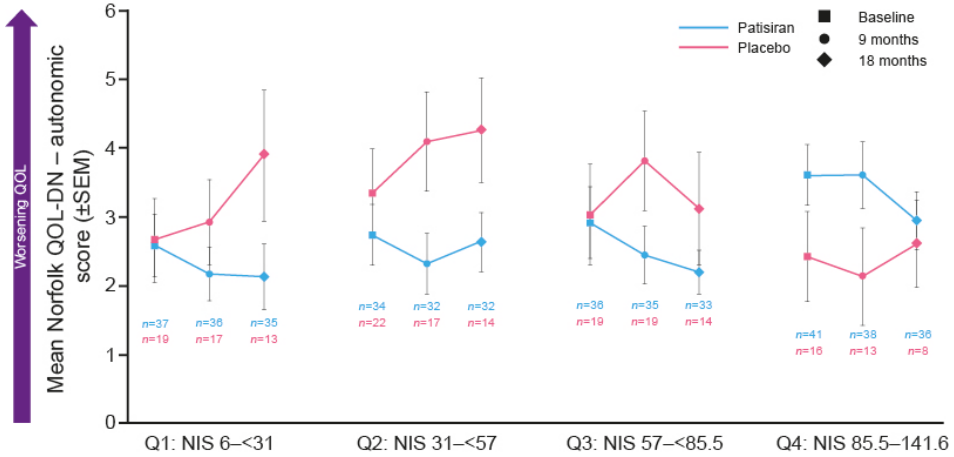
- Overall, as opposed to the substantial deterioration of Norfolk QOL-DN score observed in the placebo arm, patients who received patisiran showed improvement of QOL in Q1 and Q2, and only slight deterioration of QOL in Q3 and Q4
- Similar patterns were also observed across individual Norfolk QOL-DN domain scores











Abbreviations

Post hoc Analysis: Impact of baseline polyneuropathy severity on patisiran treatment outcomes in the APOLLO trial

Conclusions

- Treatment with the RNA interference therapeutic patisiran resulted in improvement of neurologic function and QOL over 18 months when compared with placebo regardless of baseline polyneuropathy severity
  - These results are mirrored by those from additional functional assessments including R-ODS, the 10-MWT, and grip strength
  - Patients in the placebo arm experienced rapid polyneuropathy progression across the full range of baseline disease severity
- Patients who initiated treatment with earlier disease experienced the greatest benefit in their level of neurologic function and QOL compared with those who initiated treatment with more advanced disease
  - As the overall disease burden was lowest in patients who started patisiran treatment earlier in their disease course, these data highlight that early diagnosis and treatment initiation has the potential to maximize the preservation of neurologic function and minimize burden on QOL
- The data from this study may also be helpful to physicians in clinical practice for monitoring the progression of ATTRv amyloidosis and anticipating disease trajectory across a range of disease severities
- Improved awareness of this disease and its multisystem symptomatology are key to ensuring early diagnosis and initiation of treatment, and thus allowing patients to retain a better QOL while living with ATTRv amyloidosis

Abbreviations

Post hoc Analysis: Impact of baseline polyneuropathy severity on patisiran treatment outcomes in the APOLLO trial

Quan D et al. Amyloid 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Background and Study Design

ATTRv Amyloidosis

Multisystem disease caused by abnormal amyloid accumulation across organs and tissues

Death

Rapidly progressive, debilitating, fata

Polyneuro

Progression

QOL

Patisiran

Global recruitment

Post hoc separation of patients into quartiles (Q) according to polyneuropathy severity (4 even groups based on baseline NIS score)

Assessed changes over 18 months in:
- Polyneuropathy (mNIS+7/NIS) (Primary endpoint)
- Functional measures (R-ODS, 10-MWT, grip strength)
- QOL (Norfolk QOL-DN)

Study limitations

Abbreviations

10-MWT: 10-meter walk test; ATTRv: hereditary transthyretin (v for variant); BL: baseline; hATTR: hereditary transthyretin-mediated; kg: kilograms; KPS: Karnofsky Performance Status; m: months; mITT: modified intent-to-treat; mNIS+7: modified Neuropathy Impairment Score+7; mRNA: messenger RNA; m/s: meters per second; NIS: Neuropathy Impairment Score; Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy; PND: polyneuropathy disability; Q: quartile; QOL: quality of life; R-ODS: Rasch-built Overall Disability Scale; RNA: ribonucleic acid; RNAi: RNA interference; SEM: standard error of the mean; TTR: transthyretin.

Results

Study population

Overall population

Mostly male population

Median time 1.1–1.2 years since diagnosis

Demographics were comparable in patisiran and placebo groups within each quartile

By quartiles

NIS 6–<31

NIS 31–<57

NIS 57–<85.5

NIS 85.5–141

From Q1 to Q4

Increase in age

Decrease in KPS

Decrease in unassisted ambulation (PND=B)

compared with placebo was observed for all endpoints across all NIS quartiles

Total burden remained lowest in patients who started treatment when in the lowest quartiles

eline in outcome measures

	Patisiran	Placebo
mNIS+7/NIS	Improvements across all quartiles	Continued progression across all quartiles
R-ODS	Stabilization/slight improvements in Q1 & Q2; mild worsening in Q3 & Q4	Substantial decline, worse in higher quartiles
10-MWT	Improvement in Q1; stabilization in Q2 & Q3; slight worsening in Q4	Continued progression across all quartiles
Grip strength	Slight improvements in Q1; slight worsening in Q2–4	Substantial decline across all quartiles
Norfolk QoL-DN / Norfolk QoL-DN Domain scores	Improvements in Q1 & Q2; slight worsening in Q3 & Q4	Substantial decline across all quartiles

Conclusions

- Patisiran improved neurologic function and QOL over 18 months, compared with placebo, regardless of baseline polyneuropathy severity
- Patients who initiated treatment with earlier disease had greatest benefit
- Early diagnosis and treatment has potential for preservation of neurologic function and minimize QOL burden