CRISPR Gene Editing With Nexiguran Ziclumeran in Hereditary ATTR With Polyneuropathy: Phase 1 24-Month Report

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Disclosure

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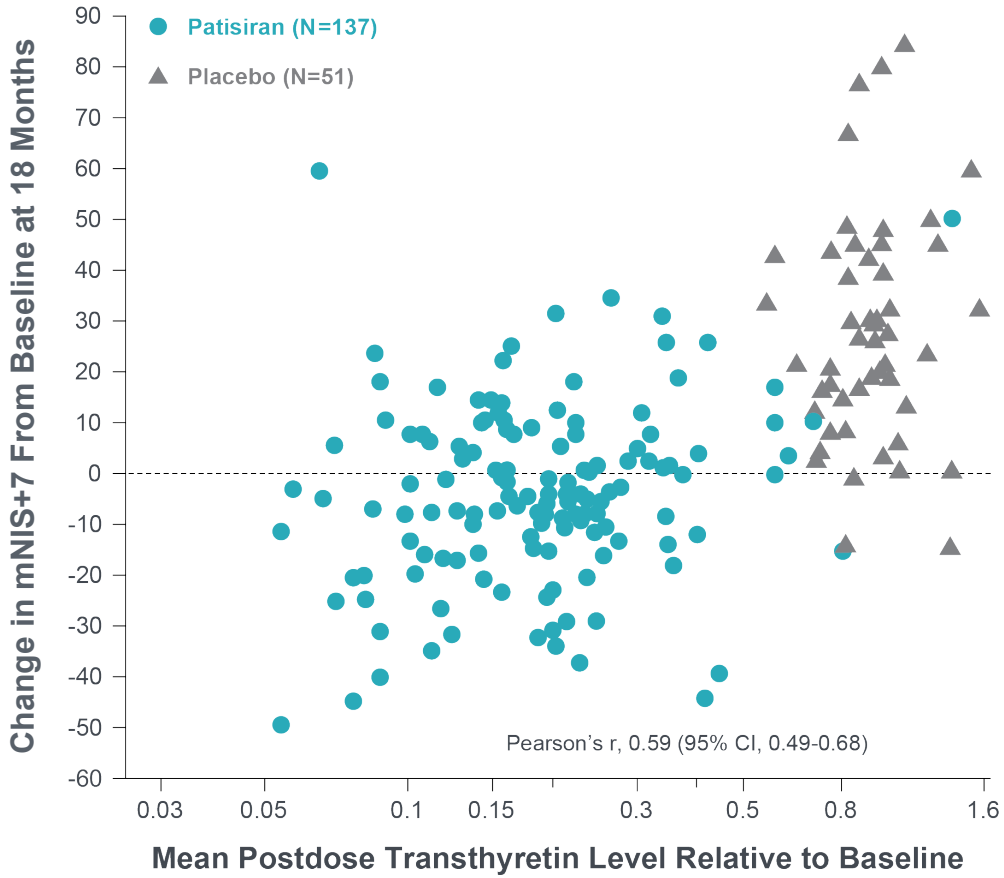
Lowering TTR has led to improved clinical outcomes in ATTR amyloidosis

- *TTR* gene silencers slow disease progression in ATTRv-PN; however, they require lifelong administration and patients continue to be at risk for early mortality[1-3]
  - Patisiran: Median TTR reduction of 81.0% at 18 months,[1] 19% mortality rate after 5 years[4]
  - Vutrisiran: Mean serum TTR reductions of 83% at steady state[5]
  - Eplontersen: Mean TTR reductions of 81.7% at Week 65[3]
- Deeper reductions in TTR levels have been correlated with increased clinical benefit in patients with ATTRv-PN[1]
  - Similarly, in systemic amyloidosis (serum amyloid A protein) and AL amyloidosis (immunoglobulin light chain), greater suppression of the amyloid precursor protein leads to better outcomes[6-9]
- A reduction in serum TTR from 80% to 90% results in half as much TTR remaining in the serum available for new amyloid formation

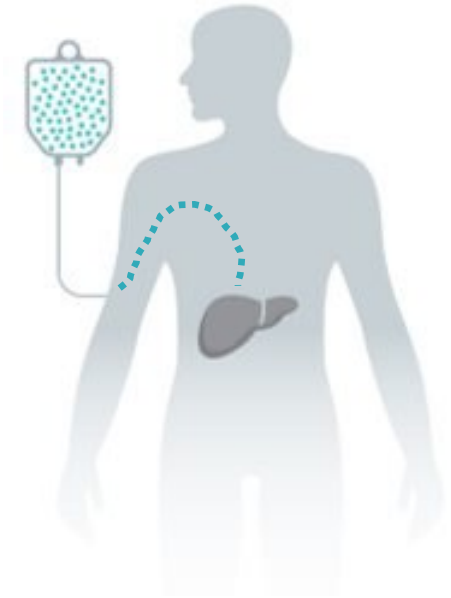
Correlation of reduction in TTR levels with change in mNIS+7 from baseline at 18 months[1]



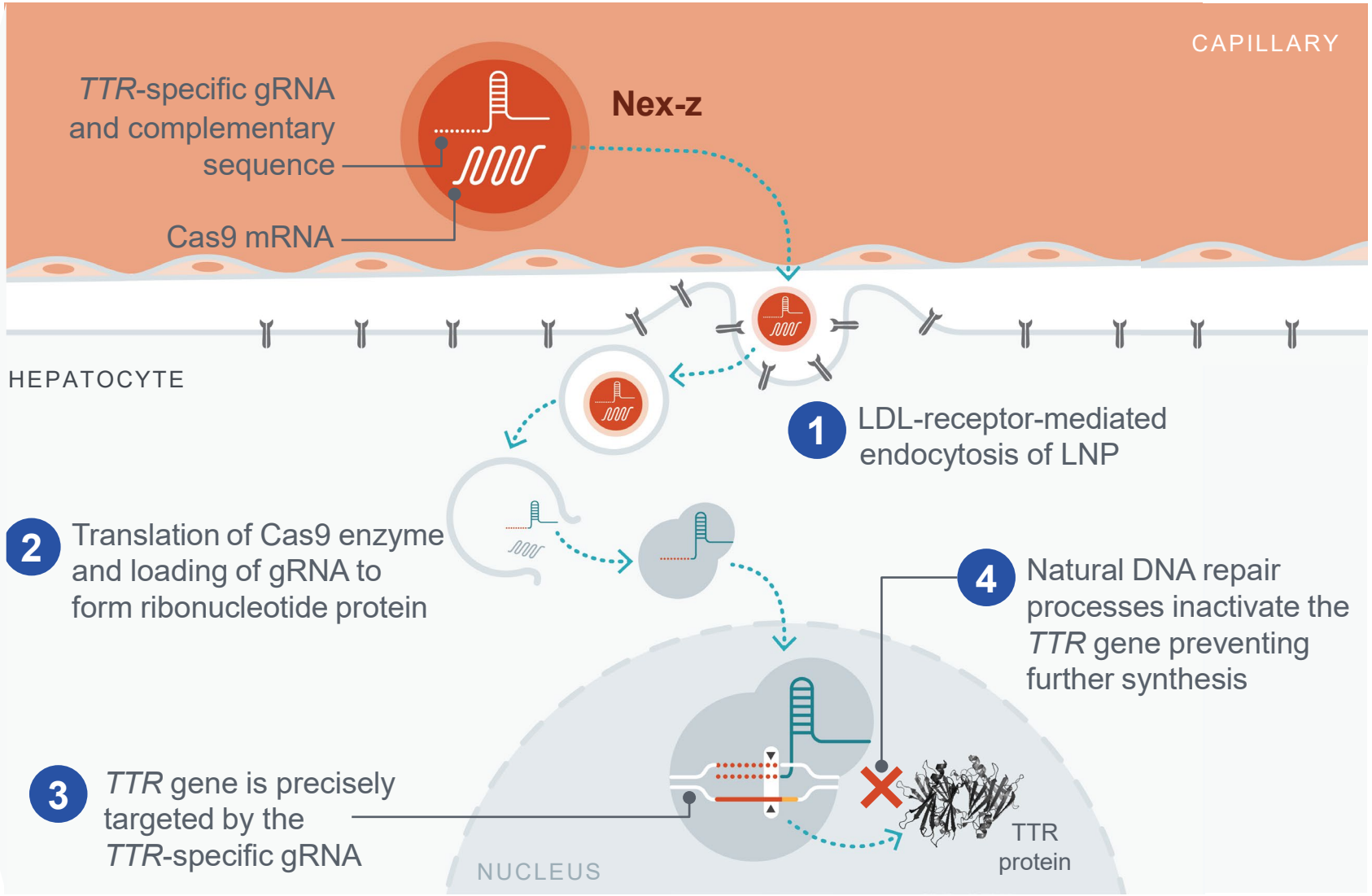
AL, amyloid light chain; ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; TTR, transthyretin.

1. Adams D, et al. *N Engl J Med.* 2018;379(1):11-21. 2. Adams D, et al. *Amyloid*. 2023;30(1):1-9. 3. Coelho T, et al. *JAMA*. 2023;330(15):1448-1458. 4. Adams D, et al. *JAMA Neurol*. 2025;82(3):228-236. 5. Amvuttra (vutrisiran). Prescribing information. Alnylam Pharmaceuticals, Inc; 2025. 6. Gillmore JD, et al. *Lancet*. 2001;358(9275):24-29. 7. Lachmann HJ, et al. *Br J Haematol.* 2003;122(1):78-84. 8. Palladini G, et al. *J Clin Oncol.* 2012;30(36):4541-4549. 9. Lachmann HJ, et al. *N Engl J Med*. 2007;356(23):2361-2371

Nex-z, an *in vivo* investigational CRISPR/Cas9 therapy, inactivates the *TTR* gene, whether wild-type or variant, with a one-time treatment[1,2]



A one-time IV infusion delivered over 4 hours is used to administer nex-z



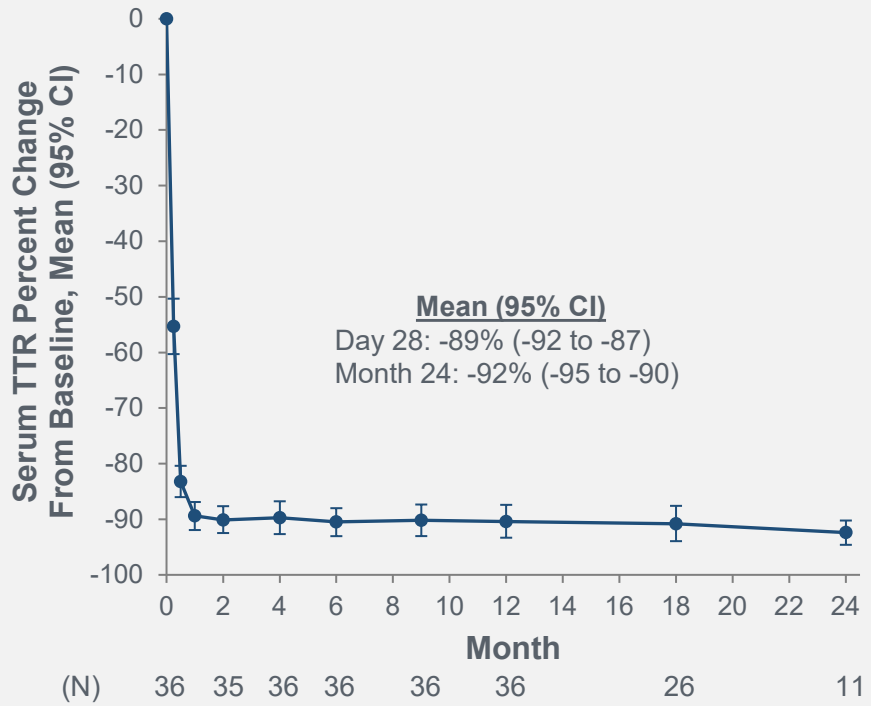
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; LDL, low-density lipoprotein; LNP, lipid nanoparticle; mRNA, messenger RNA; TTR, transthyretin.

1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Fontana M, et al. *N Engl J Med*. 2024;391(23):2231-2241.

In patients with ATTR-CM, nex-z led to deep and durable reduction in serum TTR and stability or improvement in multiple clinical outcomes

Phase 1 interim results[1,2]

Percent change in serum TTR levels through Month 24



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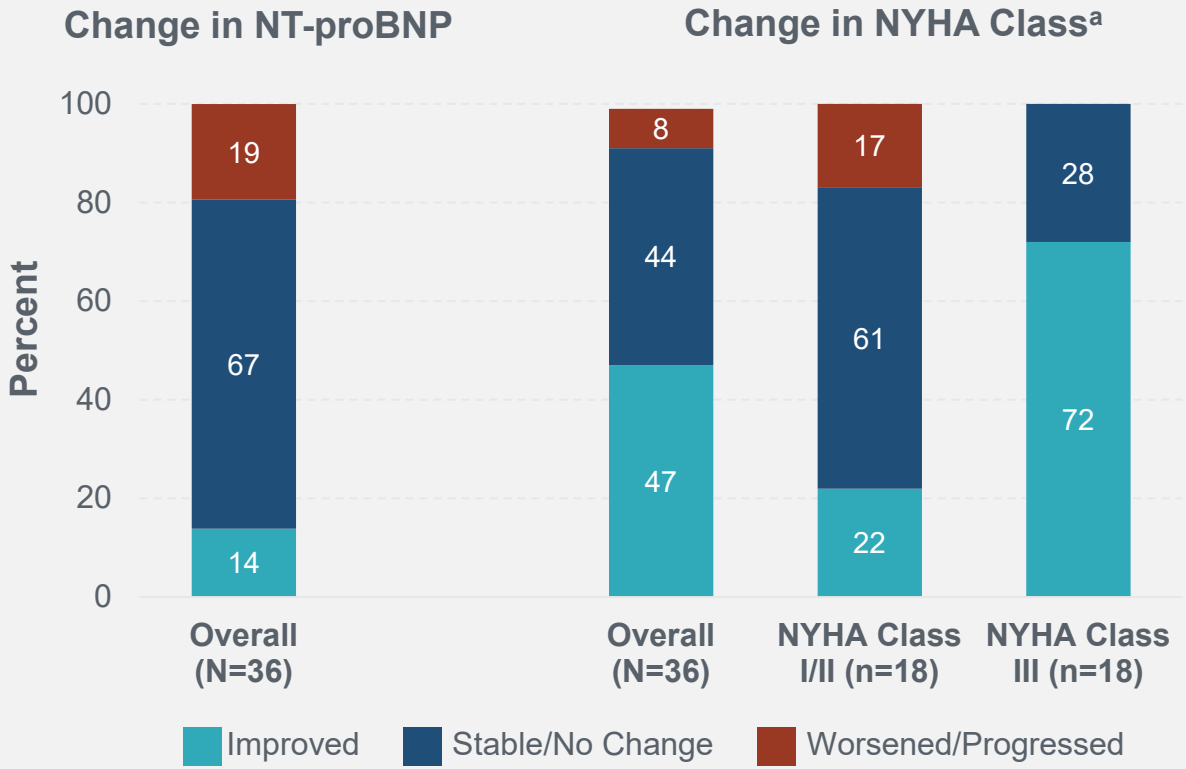
Change in markers of disease severity at Month 12



Data cutoff August 21, 2024.
Results include patients treated with a nex-z dose of 0.7 mg/kg, 1.0 mg/kg, or 55mg
NT-proNBP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin. [a]Values represent a change of at least one level in NYHA class.
1. Fontana M, et al. *N Engl J Med.* 2024;391(23):2231-2241. 2. Fontana M, et al. Presented at: AHA; Nov 16-18, 2024; Chicago, IL.

Phase 1, two-part, open-label, multicenter study of nex-z in patients with ATTRv-PN

Adults (aged 18-80 years) with ATTRv-PN, including patients who had previously progressed on patisiran

Single-dose nex-z IV infusion administered over 4 hours

PART 1: Single-Ascending Dose

N=15

- 0.1 mg/kg (n=3)[a]
- 0.3 mg/kg (n=3)
- 0.7 mg/kg (n=3)
- 1.0 mg/kg (n=6)

PART 2: Dose Expansion

N=21

- 55 mg (n=16)
- 80 mg (n=5)

PRIMARY OBJECTIVES

Evaluate safety, tolerability, and PD

- Measure serum TTR levels

SELECT SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

- Changes from baseline in NIS, mNIS+7 (Part 2 only), mBMI, Norfolk QoL-DN, NfL, and PND

Mean (range) follow-up: 27 (9 - 44) months

Phase 1 (NCT04601051); Long-term follow-up study (NCT05697861). Data cutoff April 11, 2025.

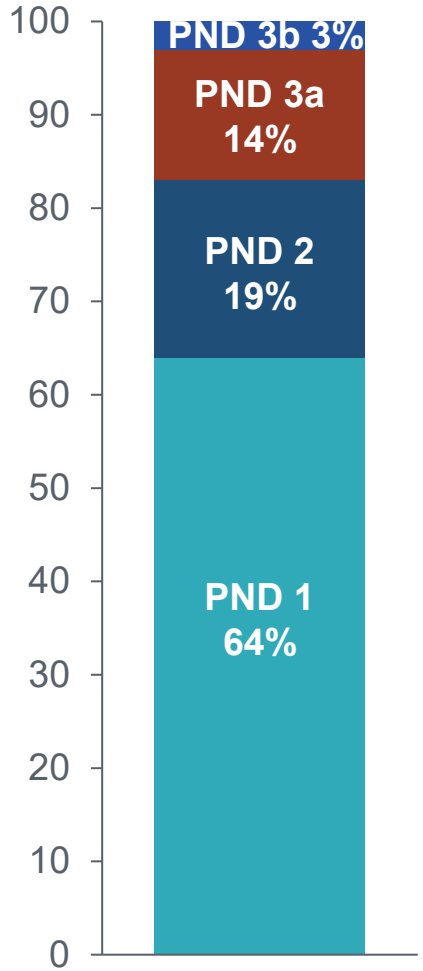
[a]Patients who received the 0.1 mg/kg dose were redosed with 55 mg after completing 24 months of follow-up.

AL, light chain; ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; FAP, Familial Amyloid Polyneuropathy, IV, intravenous; mNIS+7, modified Neuropathy Impairment Score +7; mBMI, modified body mass index; NfL, neurofilament light chain; NIS, Neuropathy Impairment Score; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PD, pharmacodynamics; PND, Polyneuropathy Disability; TTR, transthyretin.

Demographics and baseline characteristics

	All Patients (N=36)
Median age (range), years	61 (19–75)
Male, n (%)	26 (72)
Race, n (%)	
White or Caucasian	33 (92)
Other	3 (8)
NIS, mean (SD)	31 (27.4)
Prior disease progression on patisiran, mean (SD)[a]	69 (17.6)
mNIS+7, mean (SD)[b]	47 (33.3)
Prior disease progression on patisiran, mean (SD)[a]	80 (17.2)
mBMI, kg/m^2 × g/L, mean (SD)[c]	1174 (219.7)
Norfolk QoL-DN, mean (SD)	35 (31.8)
NfL, pg/mL, mean (SD)	29 (26.5)

Baseline PND Score (%)



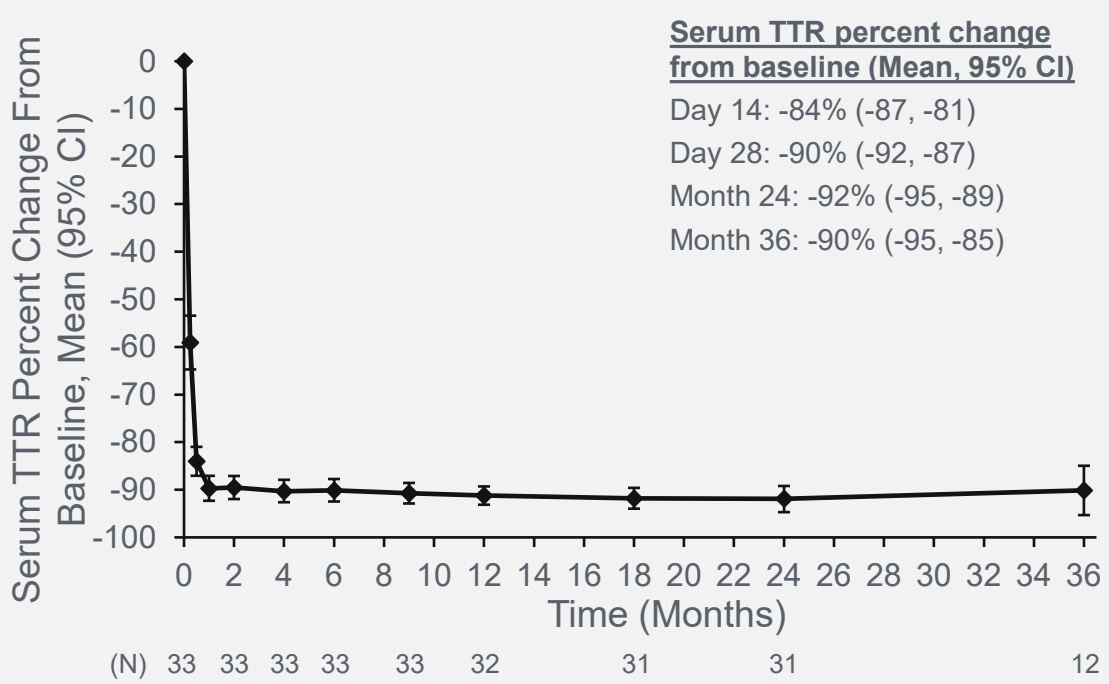
Data cutoff April 11, 2025.

[a]N=6; Patients were considered to have disease progression on ≥6 months of approved treatment for ATTRv-PN if they met any 2 of the following criteria: 1) increase in PND score ≥1 point; 2) increase in NIS ≥5 points; 3) decrease in mBMI ≥25 kg/m^2 × g/L; 4) decrease in 6-minute walk test ≥30 meters, decrease in 10-meter walk test ≥0.1 meter/second, and/or increase in Timed Get Up and Go test ≥15%. [b]Part 2 only; N=21. [c]mBMI is calculated as BMI (kg/m^2) × albumin (g/L).

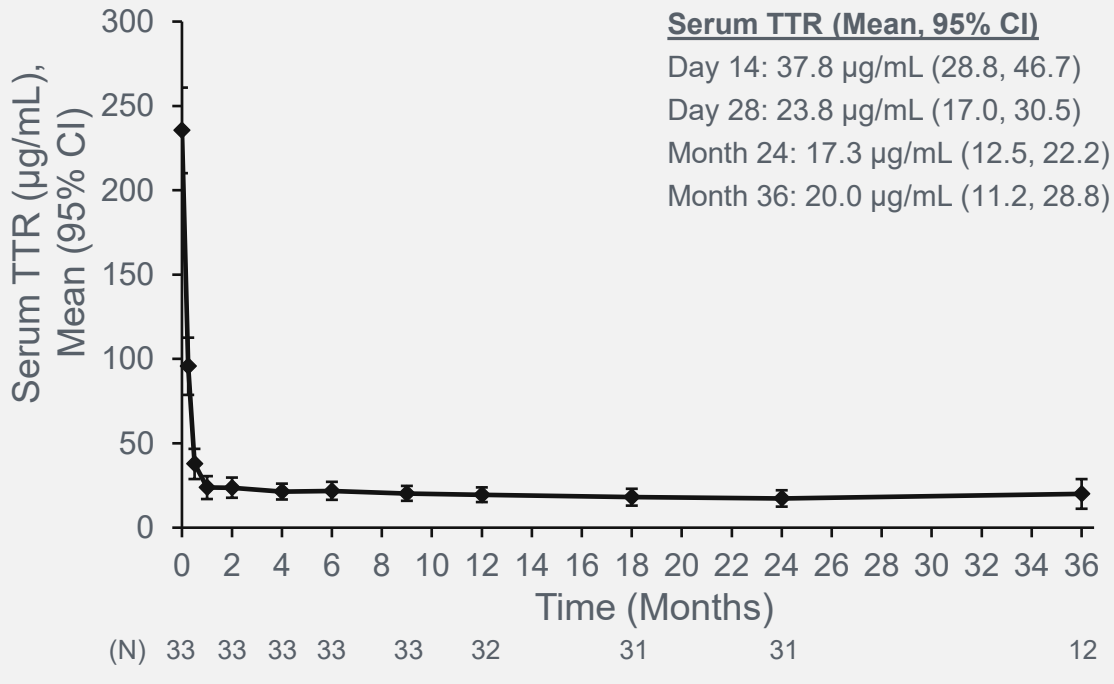
ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NfL, neurofilament light chain; NIS, Neuropathy Impairment Score; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy Questionnaire; PND, Polyneuropathy Disability.

One-time treatment with nex-z led to rapid, deep, consistent, and durable reductions in serum TTR levels with low variability

Serum TTR Percent Change from Baseline



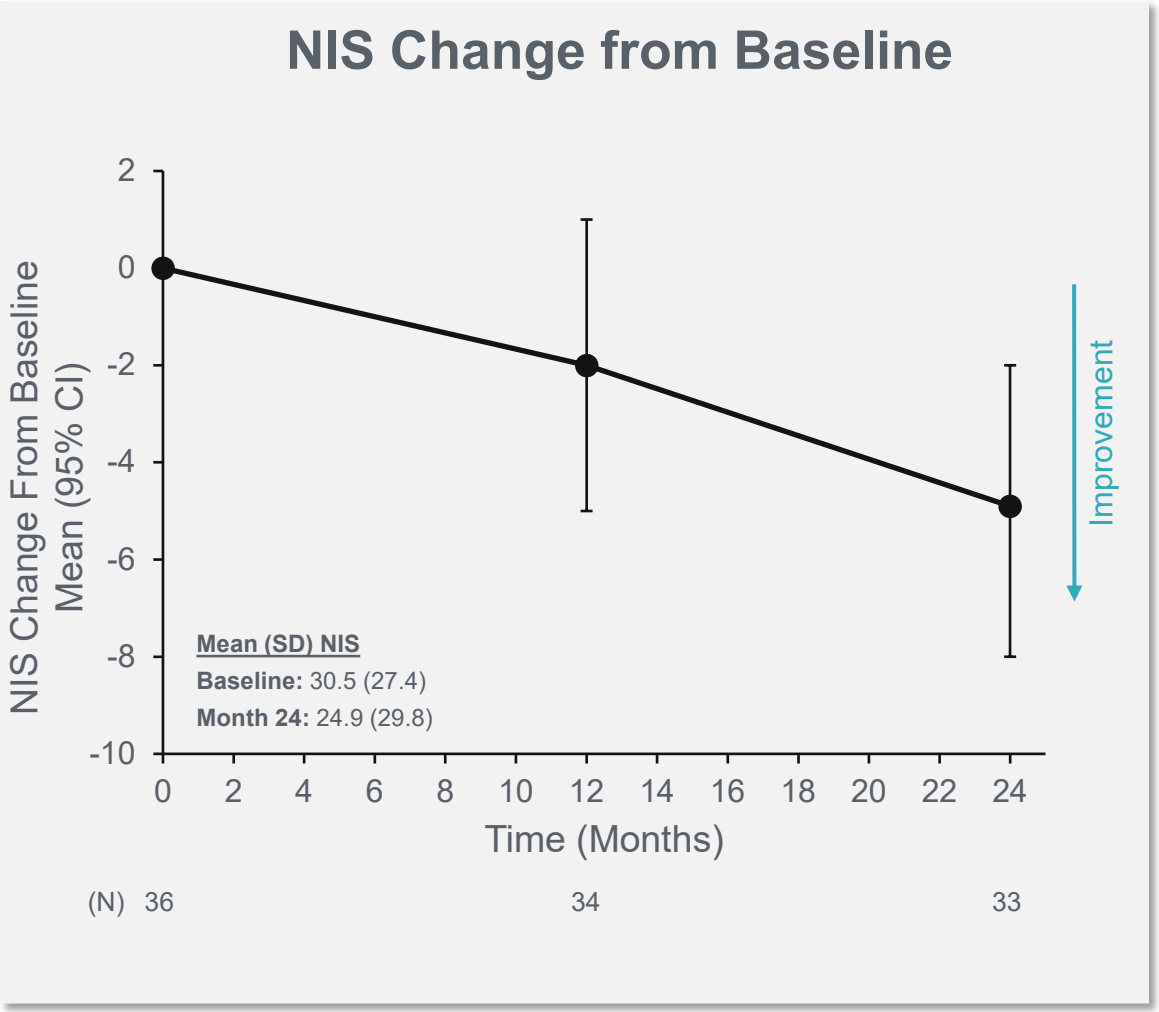
Absolute Serum TTR Concentration

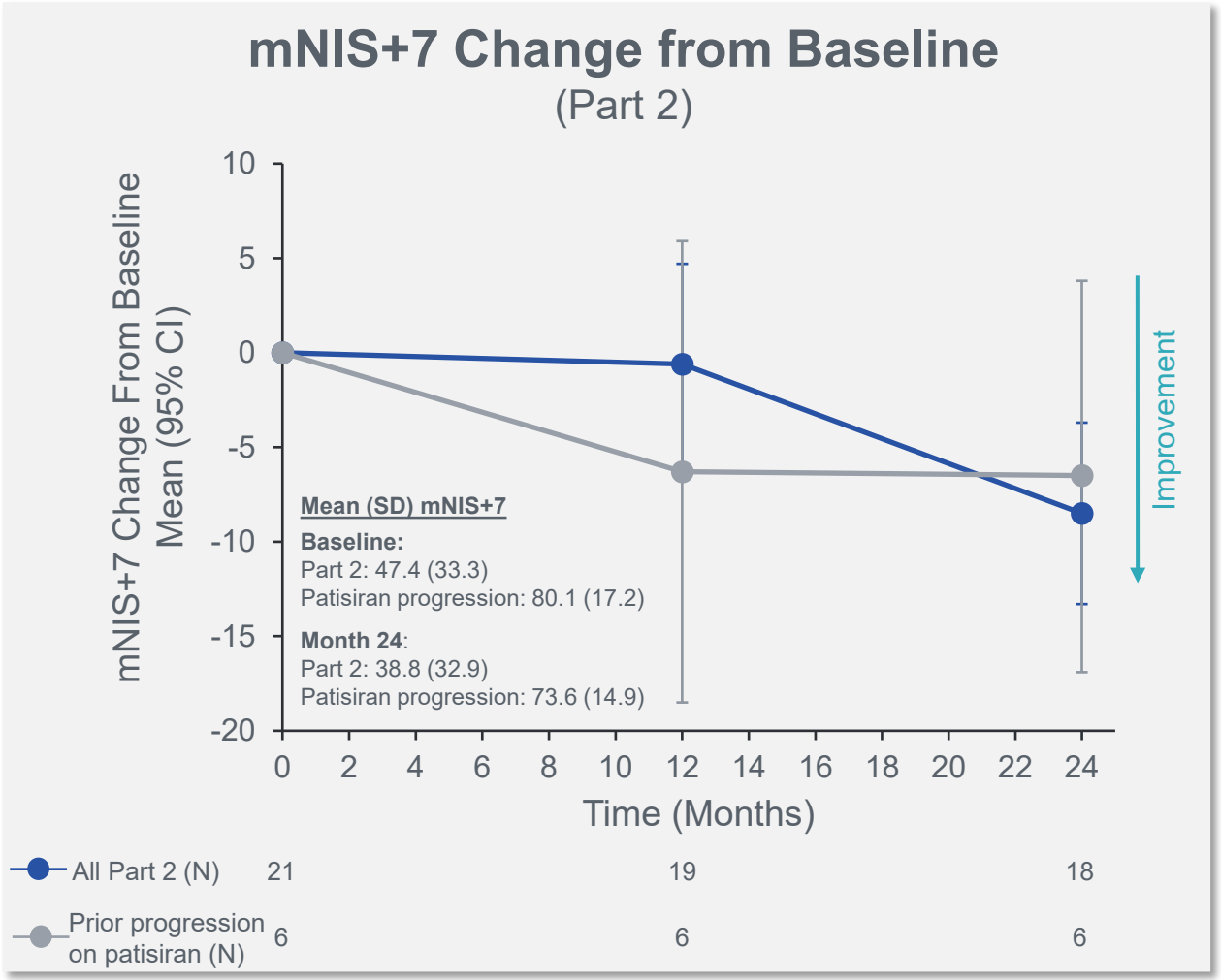


94% (29/31) of patients achieved serum TTR levels <50 µg/mL and 90% (28/31) achieved levels <30 µg/mL at Month 24

Data cutoff April 11, 2025. Data regarding the serum TTR level at month 36 were collected from patients who entered the long-term follow-up safety monitoring study (data-cutoff date, April 16, 2025).
Data presented exclude the 0.1 mg/kg cohort. The 3 patients in the 0.1 mg/kg cohort have been redosed at 55 mg.
TTR, transthyretin.

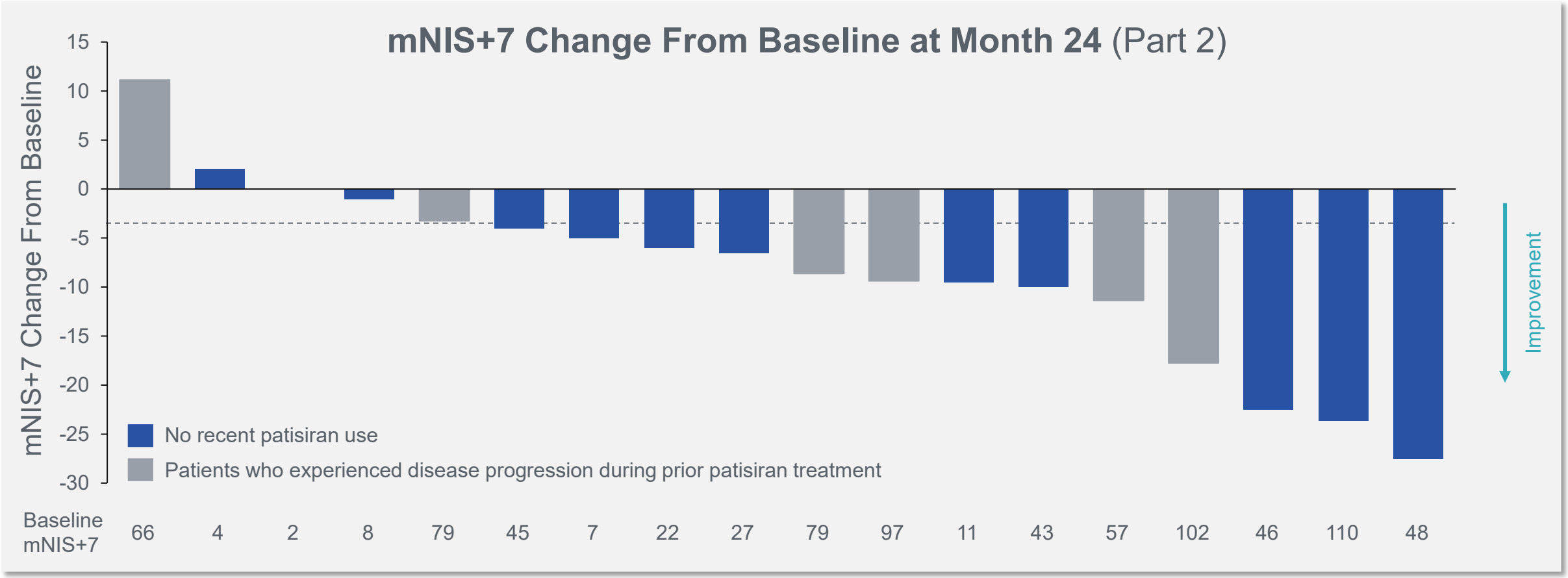
Improvements in NIS and mNIS+7 were observed following a one-time treatment with nex-z





Data cutoff April 11, 2025.
NIS ranges from 0 to 244 and mNIS+7 ranges from 0 to 304, with higher values indicating increased impairment.
mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score.

At Month 24, the majority of patients experienced improvements in mNIS+7



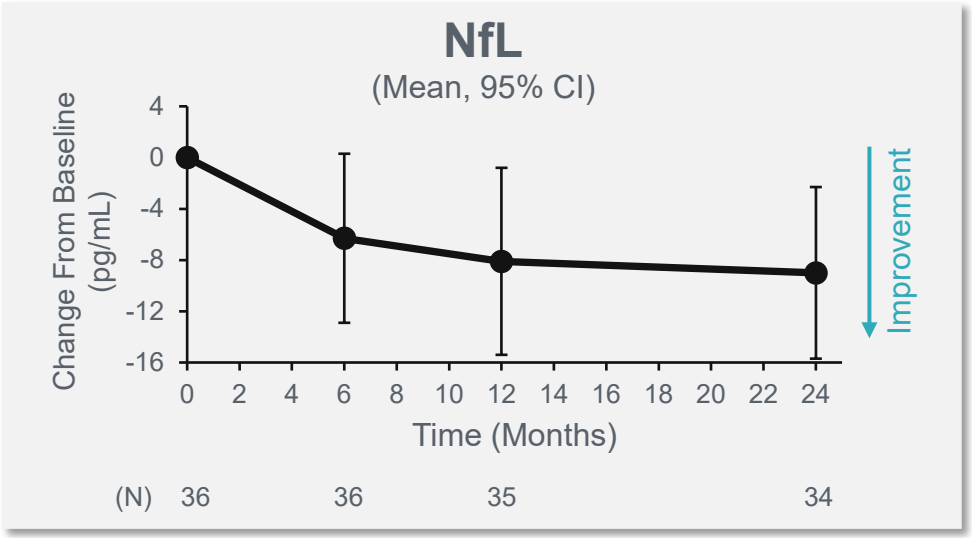
- The mean change in mNIS+7 at Month 24 was -8.5 points
- 13/18 (72%) patients had improvements in mNIS+7 which exceeded the clinically meaningful threshold of a ≥4-point reduction[1]

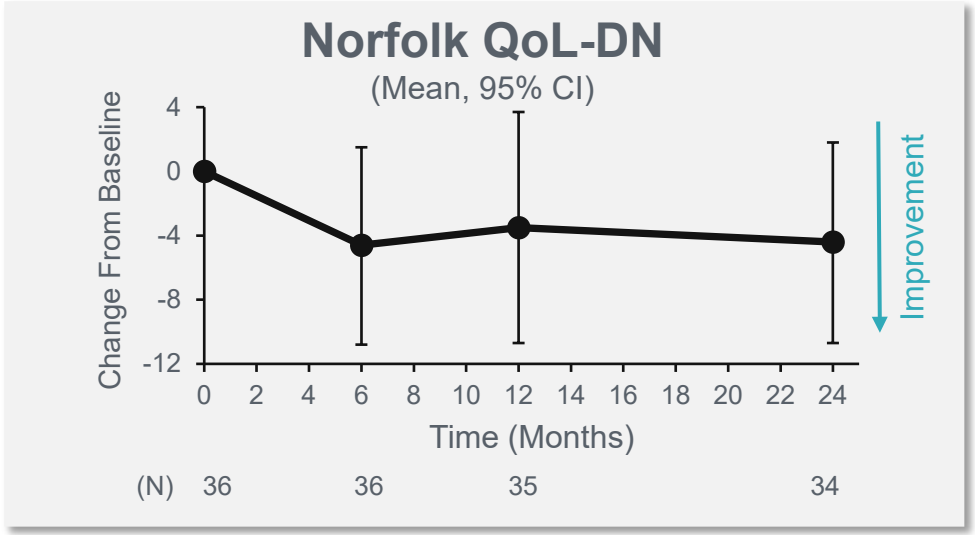
Data cutoff April 11, 2025.

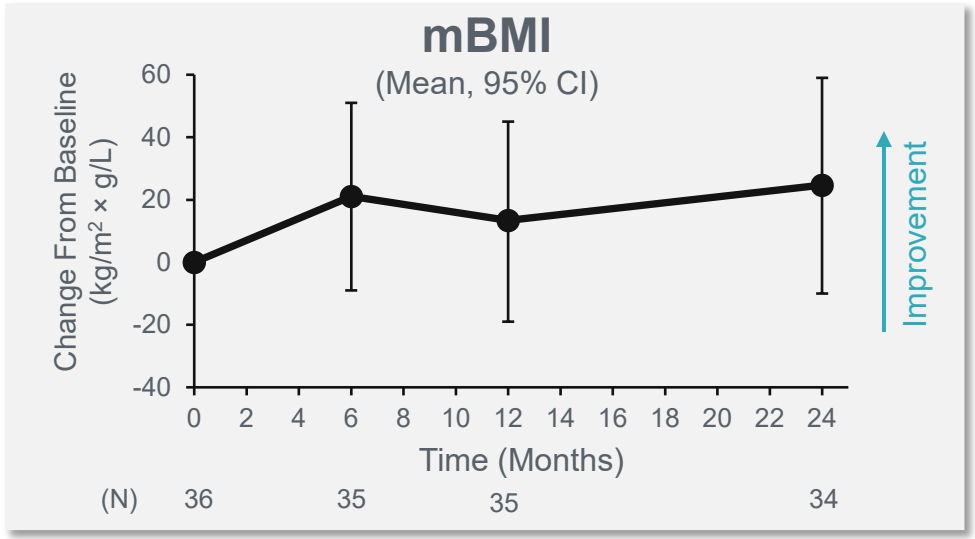
Dotted line indicates cutoff for clinically meaningful improvement (Folkvaljon F, et al. *Muscle Nerve*. 2025;71(1):96-107.)

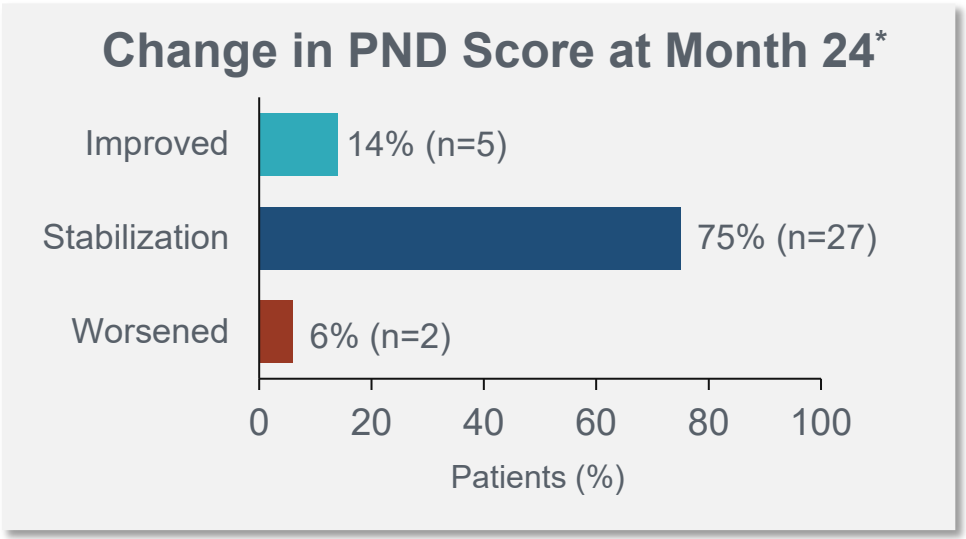
mNIS+7 ranges from 0 to 304, with higher values indicating increased impairment. mNIS+7, modified Neuropathy Impairment Score +7.

Multiple disease related clinical measures show stability or improvement though Month 24









Data cutoff April 11, 2025.

Norfolk QoL-DN total score ranges from -4 to 136, with lower scores indicating better QoL.

*Improvement, No Change, or Worsened in PND score is relative to the measurement at baseline. PND score were missing for 2 patients at Month 24. In the patient who died and the patient who discontinued, PND score remained unchanged from baseline at the last available assessment, Month 6 and Month 12, respectively.

mBMI, modified body mass index; NfL, neurofilament light chain; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PND, Polyneuropathy Disability; QoL, quality of life.

Safety summary in patients with ATTRv-PN treated with nex-z

Safety Events	All Patients (N=36) n (%)
At least 1 AE	36 (100)
AEs occurring in ≥15% of patients	
IRR	21 (58)
Headache	10 (28)
Diarrhea	8 (22)
Thyroxine decreased	8 (22)[a]
AST increased	6 (17)[b]
Any serious AE	11 (31)
Treatment-related SAEs	3 (8)[c]
Death	1 (3)[d]

- All patients received the intended dose of nex-z
- All IRRs were Grade ≤2 and resolved
- Three patients had ALT and/or AST elevations >5× ULN
  - No symptoms, changes in hepatic synthetic function, prolonged prothrombin time, or clinical sequelae; Hy's Law criteria were not met
  - Onset occurred 24 to 35 days following infusion and all returned to normal levels without intervention within 31 to 58 days
  - Two patients received a 80mg dose and one patient received a 55 mg dose (selected as the Phase 3 dose)
- The safety profile in patients with prior disease progression on patisiran was comparable to the overall study population

Data cutoff April 11, 2025.

[a]Not accompanied by thyroid-stimulating hormone elevation or symptoms of hypothyroidism. No patient had clinical hypothyroidism or TSH elevation. [b]3 patients had Grade ≥3 liver enzyme elevations. [c]One patient had grade 3 vomiting lasting 12 days, another had grade 2 ileus (Days 2-4), and the third patient had esophageal adenocarcinoma (Day 513) and prostate cancer (Day 610). This third patient had multiple risk factors for esophageal adenocarcinoma, including older age of 73 years, occupational chemical exposure including asbestos, a long history (>15 years) of smoking, heavy alcohol use, gastroesophageal reflux and recently diagnosed Barrett's esophagus [d]One patient died from sudden cardiac death associated with cardiac amyloidosis at Month 9, not considered treatment-related.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; IRR, infusion-related reaction; ULN, upper limit of normal.

Conclusions

- A one-time treatment with nex-z led to rapid, deep, consistent, and durable reductions in serum TTR levels through Year 3 in patients with ATTRv-PN
- In this Phase 1 study, nex-z favorably impacted multiple disease-relevant measures in patients with ATTRv-PN, including those who had previously progressed on patisiran
- A single dose of nex-z in patients with ATTRv-PN was well-tolerated with a favorable safety profile; adverse events were generally transient and reversible
- These efficacy and safety data are consistent with those from patients with ATTR-CM who received one-time treatment with nex-z[1]
- These results support further clinical investigation in patients with ATTRv-PN in the Phase 3 MAGNITUDE-2 study (NCT06672237)

Data cutoff April 11, 2025.

ATTR-CM, ATTR amyloidosis with cardiomyopathy; ATTR-PN, ATTR amyloidosis with polyneuropathy; ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; TTR, transthyretin.

1. Fontana M, et al. *N Engl J Med.* 2024;391(23):2231-2241.

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ORIGINAL ARTICLE

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