Intellia THERAPEUTICS® REGENERON

Scientific Sessions

Updated Phase 1 Clinical Trial Outcomes of CRISPR Gene Editing With Nexiguran Ziclumeran in Patients With Transthyretin Amyloidosis With Cardiomyopathy

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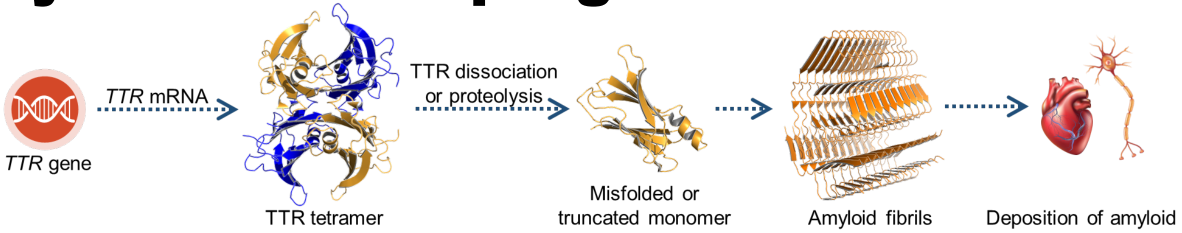
American Heart Association.

#AHA25

Disclosure

Dr. Gillmore reports consultancy agreements with Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, BridgeBio, Intellia Therapeutics, Ionis Pharmaceuticals, Lycia Therapeutics, Pfizer, and an institutional grant from Alnylam Pharmaceuticals

ATTR amyloidosis is a progressive and fatal disease



ATTR amyloidosis with cardiomyopathy (ATTR-CM) is characterized by progressive cardiac remodeling and dysfunction, decline in functional capacity and QoL, frequent hospitalization, and death[1]
This process occurs much more rapidly in patients with advanced or hereditary forms of the disease,[2] with mortality rates as high as 43% observed in untreated patients over 30 months in clinical trials[3,4]

Treatments for ATTR-CM include TTR stabilizers and *TTR* gene silencers[5]; however, patients require lifelong treatment and continue to have disease progression and mortality[3,6,7]

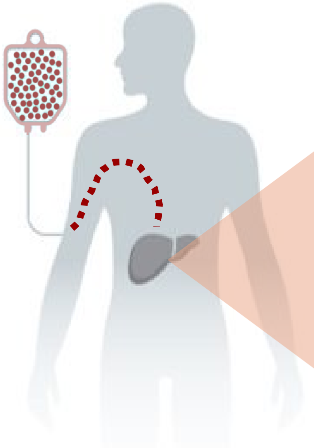
In patients with predominately mild to moderate ATTR-CM, chronic treatment with vutrisiran, a *TTR* gene silencer, led to a ~80% reduction in serum TTR and lowered the risk of death and CV events by 28%[7]

Data from trials in ATTR-PN or other forms of amyloid CM[8-11] have shown that achieving the lowest possible level of amyloid precursor protein is important to maximally impact disease progression and clinical events, including mortality
A reduction in serum TTR from 80% to 90% results in half as much TTR remaining in the serum available for new amyloid formation

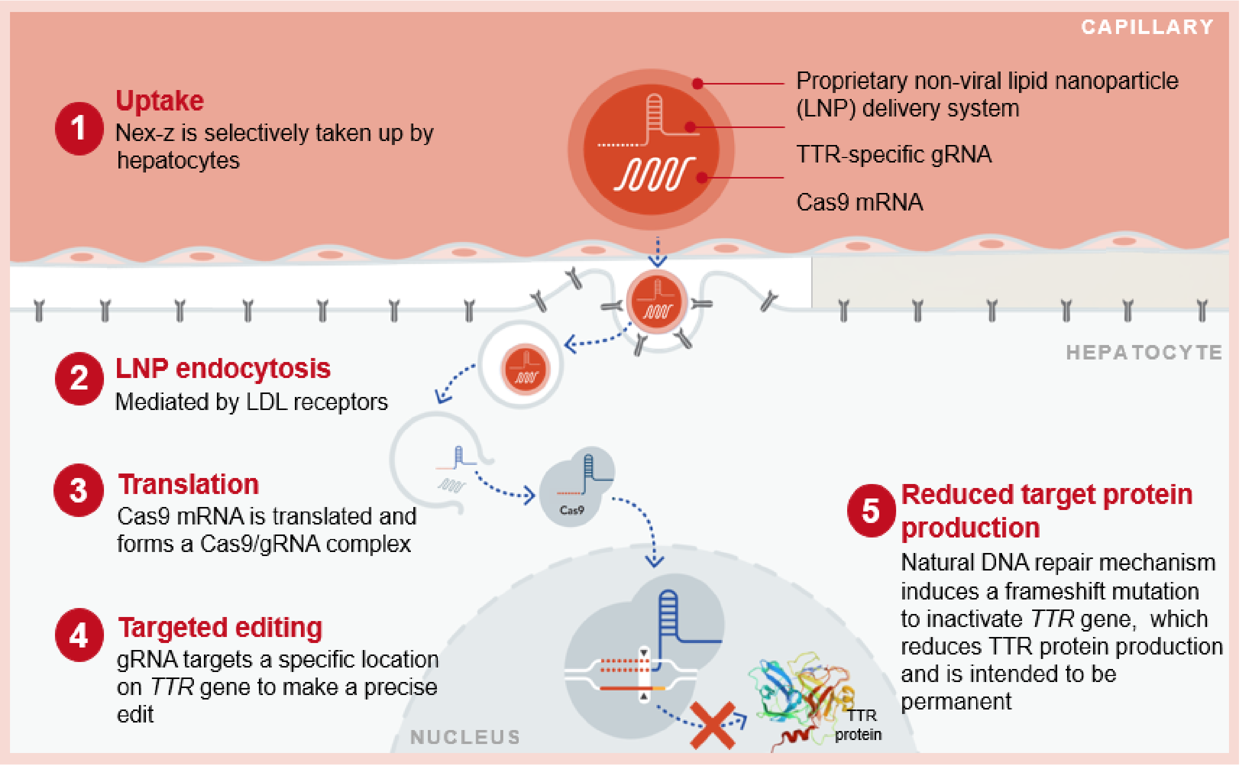
ATTR-PN, ATTR amyloidosis with polyneuropathy; ATTR-CM, ATTR amyloidosis with cardiomyopathy; CV, cardiovascular; mRNA, messenger RNA; QoL, quality of life; TTR, transthyretin.

1. Fontana M, et al. *N Engl J Med*. 2024;391(23):2231-2241. 2. Masri A, et al. *J Am Coll Cardiol CardioOnc*. 2025;7(3)282–293. 3. Nativi-Nicolau J, et al. *ESC Heart Fail*. 2021;8(5):3875-3884. 4. Maurer MS, et al. *N Engl J Med*. 2018;379(11):1007-1016. 5. Margolin E, et al. *Cardiol Ther*. 2025;14(3):385-401. 6. Kittleson MM, et al. *Circulation*. 2020;142(1):e7-e22. 7. Fontana M, et al. *N Engl J Med*. 2025;392(1):33-44. 8. Gillmore JD, et al. *Lancet*. 2001;358(9275):24-29. 9. Lachmann HJ, et al. *Br J Haematol*. 2003;122(1):78-84. 10. Palladini G, et al. *J Clin Oncol*. 2012;30(36):4541-4549. 11. Adams D, et al. *N Engl J Med*. 2018;379(1):11-21.

Nex-z is an *in vivo* investigational one-time CRISPR/Cas9 therapy designed to inactivate the *TTR* gene, whether wild-type or variant[1,2]



Nex-z is delivered as a **one-time IV infusion** over 2 to 4 hours

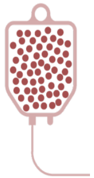


Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; IV, intravenous; LDL, low-density lipoprotein; LNP, lipid nanoparticle; mRNA, messenger RNA; TTR, transthyretin.

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.

Phase 1, two-part, open-label study of nex-z in adults with ATTR-CM

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA class I-III[1]



Single dose nex-z IV infusion administered over 2 to 4 hours

PART I – DOSING COMPLETE
Single-Ascending Dose

- 1.0 mg/kg NYHA class I/II (n=3)
- 0.7 mg/kg NYHA class I-III (n=9)

PART II
Dose Expansion

- 55 mg NYHA class I-III (n=24)

Long-term follow-up[2,a]

PRIMARY OBJECTIVES

Evaluate safety, tolerability, and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of cardiac disease

- *Biomarkers of disease progression, including NT-proBNP, hs-Troponin T, and 6MWT, cardiac imaging, and KCCQ score*

The full cohort of patients were recruited from a single center, the National Amyloidosis Centre, in the United Kingdom.

[a]Safety and TTR data are reported through Month 36 as part of long-term follow-up data.
6MWT, 6-Minute Walk Test; ATTRv-CM, hereditary ATTR amyloidosis with cardiomyopathy; ATTRwt-CM, wild-type ATTR amyloidosis with cardiomyopathy; hs, high sensitivity; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamics; TTR, transthyretin.

1. Fontana M, et al. *N Engl J Med*. 2024;391(23):2231-2241. 2. NCT05697861. Accessed Oct 20, 2025. https://clinicaltrials.gov/study/NCT05697861.

Demographics and baseline characteristics

Characteristic		All patients (N=36)
Age, median (min, max), y		78 (46, 90)
Sex, male, n (%)		35 (97)
Race, n (%)	**Black or African descent**	8 (22)
	White or Caucasian	28 (78)
NT-proBNP, median (min, max), ng/L		2052 (851, 19,624)
hs-Troponin T, median (min, max), ng/L		56 (15, 204)
eGFR, median (min, max), mL/min/1.73 m^2		64 (30, 87)
6-Minute Walk Test distance, median (min, max), m		331 (178, 580)
Peak VO_2, median (min, max), mL/kg/min		12.7 (7.8, 28.4)
CMR extracellular volume, median (min, max), %		58 (44, 71)

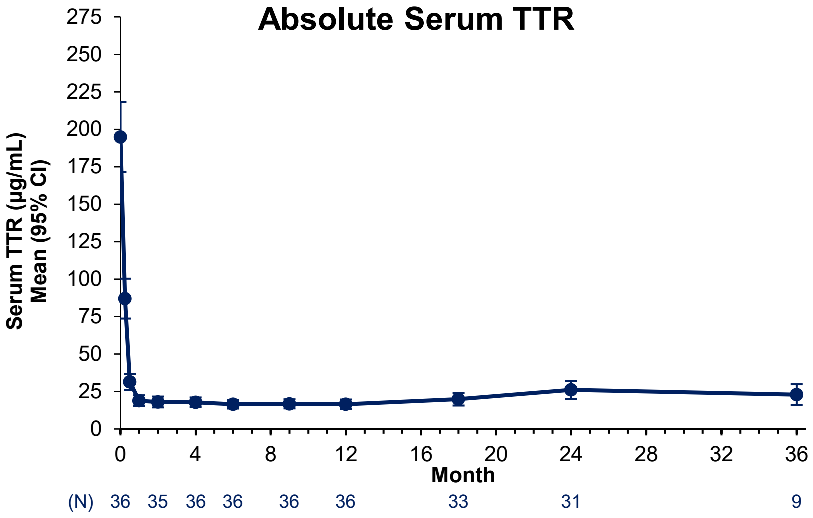
Characteristic	All patients (N=36)
***TTR* genotype, n (%)**	
Wild type	25 (69)
p.V142I[a]	7 (19)
Other mutations	4 (11)
NYHA class, n (%)	
I	3 (8)
II	15 (42)
III	18 (50)
Tafamidis use at baseline, n (%)	0 (0)

As of August 23, 2025, the median (range) duration of follow-up was 25.5 months (17 to 40)[b]

Population representative of ATTR-CM, including patients with advanced disease

Data cutoff: August 23, 2025. Percentages may not total 100 because of rounding.
[a]Includes 2 homozygous patients. [b]30 patients have enrolled in the long-term follow-up study, with a median (range) duration of 33 months (24, 44).
ATTR-CM, ATTR amyloidosis with cardiomyopathy; CKD-EPI, chronic kidney disease epidemiology; CMR, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate by CKD-EPI equation; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin; VO_2, oxygen consumption.

One-time nex-z led to consistent rapid, deep, and durable reductions in serum TTR in patients with ATTR-CM



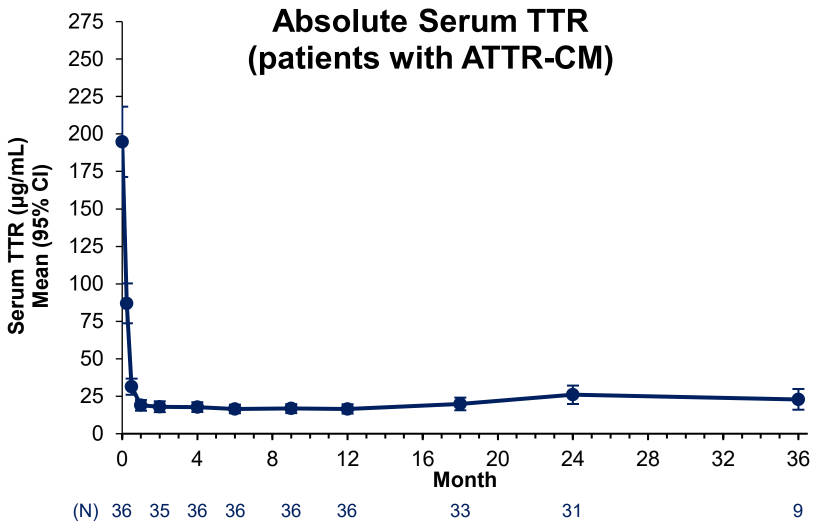
Absolute Serum TTR (µg/mL)

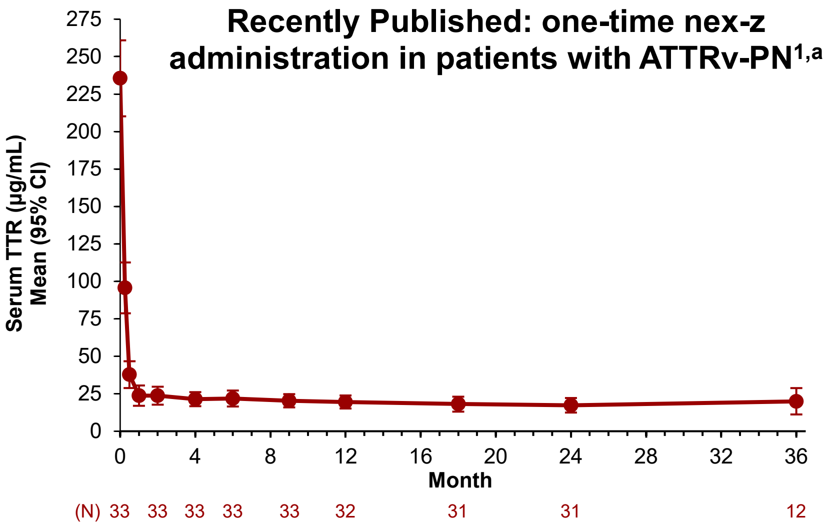
	Mean (95% CI)
Baseline	194.8 (171.3 to 218.3)
Day 28	18.9 (15.4 to 22.5)
Month 24	26.0 (19.8 to 32.1)
Month 36	22.9 (16.0 to 29.8)

- **Mean percent change in serum TTR was 89%, 86%, and 87% at Day 28, Month 24, and Month 36, respectively**
- **84% of patients achieved TTR levels <50 µg/mL and 77% <30 µg/mL as early as Day 28, which were sustained through Month 24[a]**
- **Long-term TTR levels remained low even after starting tafamidis, which was initiated in 32 patients (mean starting time, 23 months)**

Data cutoff: August 23, 2025. Data at Month 36 collected from patients who entered the long-term follow-up safety monitoring study (data-cutoff date, August 21, 2025).
Changes in N from total population (N=36) reflect patient death (n=2), withdrawal (n=1), or missing assessment.
[a]A patient must have had TTR assessments at both timepoints to be included.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; TTR, transthyretin.

One-time nex-z led to consistent rapid, deep, and durable reductions in serum TTR in patients with ATTR-CM and ATTRv-PN



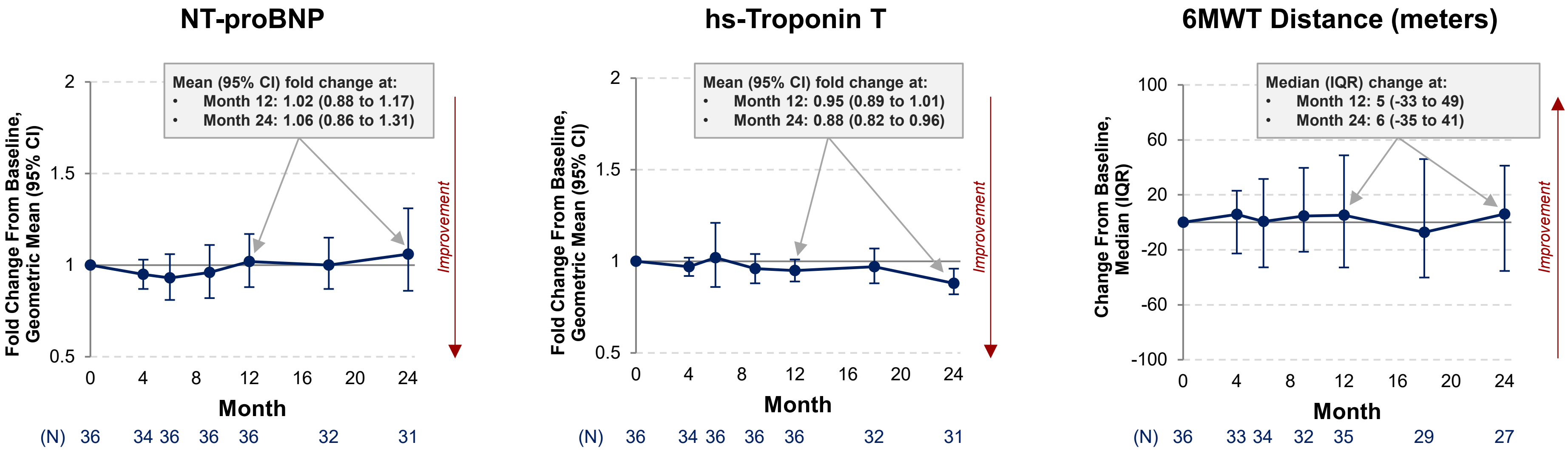


Across patients with ATTR-CM and ATTRv-PN, durable reductions in serum TTR have been observed for up to 36 months (n=21)

Data cutoff: August 23, 2025. Data at Month 36 collected from patients who entered the long-term follow-up safety monitoring study (data-cutoff date: August 21, 2025).
Changes in N from total population (N=36) reflect patient death (n=2), withdrawal (n=1), or missing assessment.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; TTR, transthyretin. [a]Results shown for patients with ATTRv-PN who received nex-z at a dose > 0.1 mg/kg.

1. Gillmore D, et al. *N Engl J Med*. 2025;393:1375-1386.

One-time nex-z treatment led to stabilization of NT-proBNP, hs-troponin T, and 6MWT over 24 months

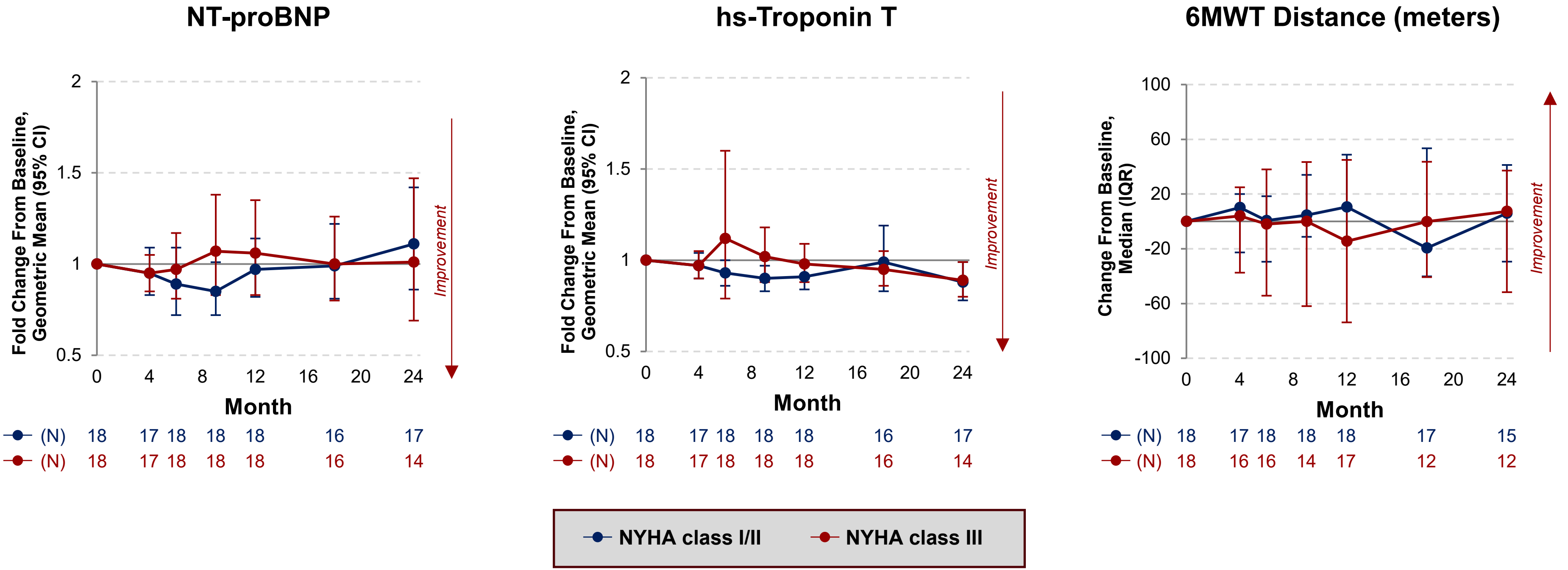


At Month 24, a total of 70%, 85%, and 69% of patients saw stabilization or improvement in NT-proBNP, hs-Troponin T, and 6MWT, respectively

Data cutoff: August 23, 2025. Changes in N from total population (N=36) reflect patient death (n=2), withdrawal (n=1), or missing assessment. Disease progression[1,2] defined as: NT-proBNP, an increase of >700 ng/L and >30%; hs-Troponin T, an increase of >10 ng/mL and >20%; 6MWT, absolute reduction of >35 m in 6MWT distance; for all markers, progression was also defined by death prior to the assessment. Improvement was defined as the equivalent counter criteria.
6MWT, 6-Minute Walk Test; hs, high sensitivity; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

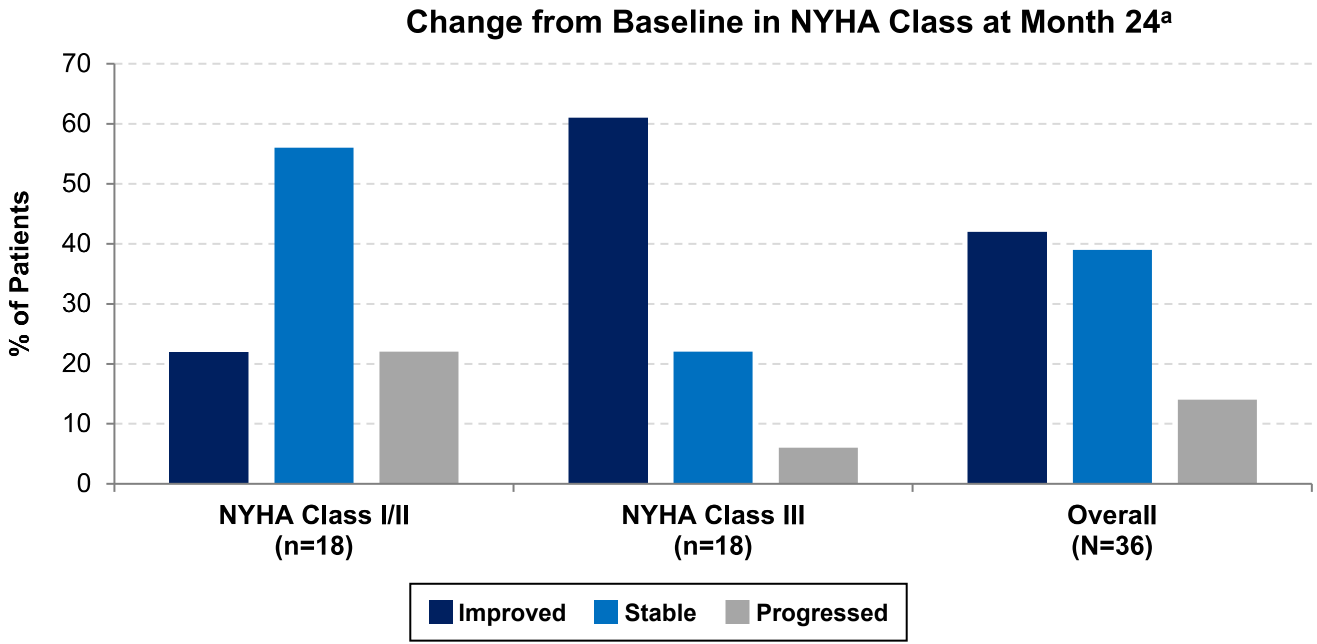
1. Ioannou A, et al. *J Am Coll Cardiol.* 2024;83(14):1276-1291. 2. Ioannou A, et al. *J Am Coll Cardiol.* 2024;84(1):43-58.

Improvement/stabilization of disease progression maintained regardless of NYHA class at baseline



Data cutoff: August 23, 2025. Changes in N from total population (N=36) reflect patient death (n=2), withdrawal (n=1), or missing assessment.
6MWT, 6-Minute Walk Test; hs, high sensitivity; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

One-time nex-z stabilized or improved functional status and symptom severity

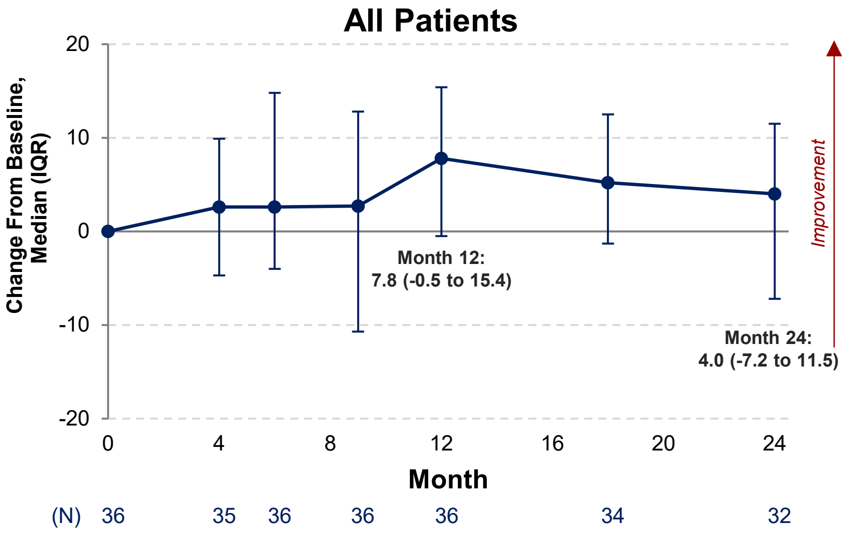


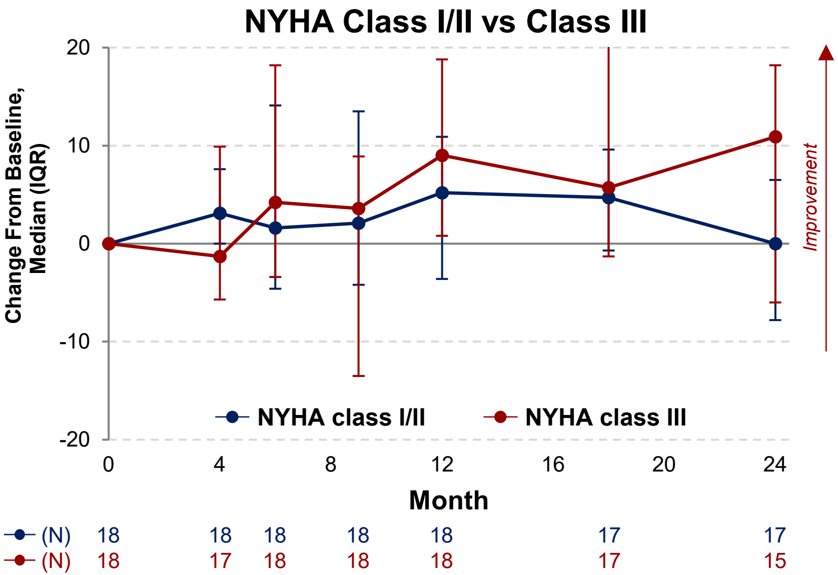
81% of patients demonstrated either no change or improvement in NYHA class at 24 months, including 83% of patients with NYHA class III

Data cutoff: August 23, 2025.
[a]Improved (progressed) is defined as an improvement (worsening) of at least one level in NYHA class from baseline. Data missing for 2 (11%) patients with NYHA class III. Death prior to assessment was considered worsening/progression (n=2).
NYHA, New York Heart Association.

One-time nex-z stabilized or improved QoL, regardless of NYHA class at baseline

Change from Baseline in KCCQ-OS Through Month 24



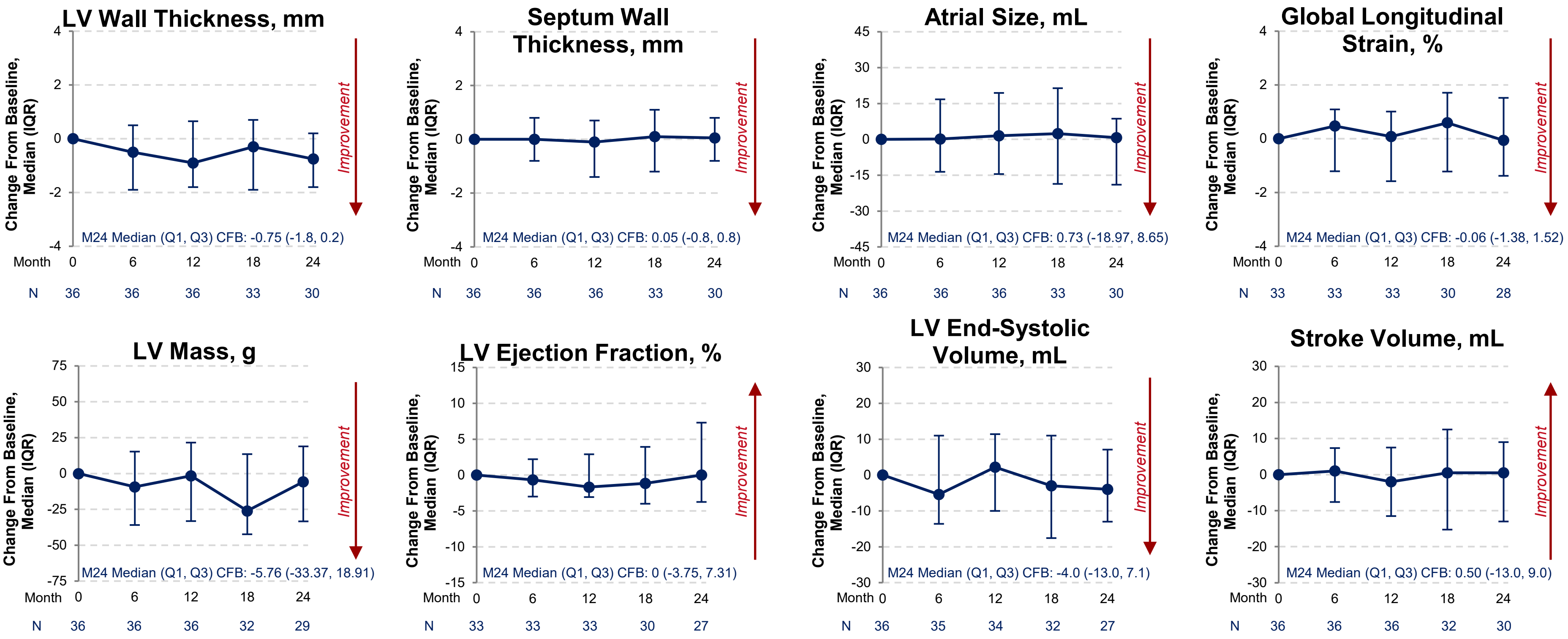


62% of patients reported stability or improvement in KCCQ-OS at 24 months

Data cutoff: August 23, 2025. Stability was defined as a change in KCCQ between ±5 points and improvement was an increase in KCCQ of ≥5 points.[1]
IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall score; NYHA, New York Heart Association; QoL, quality of life.

1. Spertus J, et al. *J Am Coll Cardiol*. 2020;76(20):2379-2390.

Echocardiographic assessments of cardiac remodeling showed a similar pattern of stability for 24 months following nex-z treatment



Data cutoff: August 23, 2025. Changes in N from total population (N=36) reflect patient death (n=2), withdrawal (n=1), or missing assessment.
CFB, change from baseline; IQR, interquartile range; LV, left ventricular.

Evaluation of mortality in patients treated with nex-z compared with a matched cohort of patients

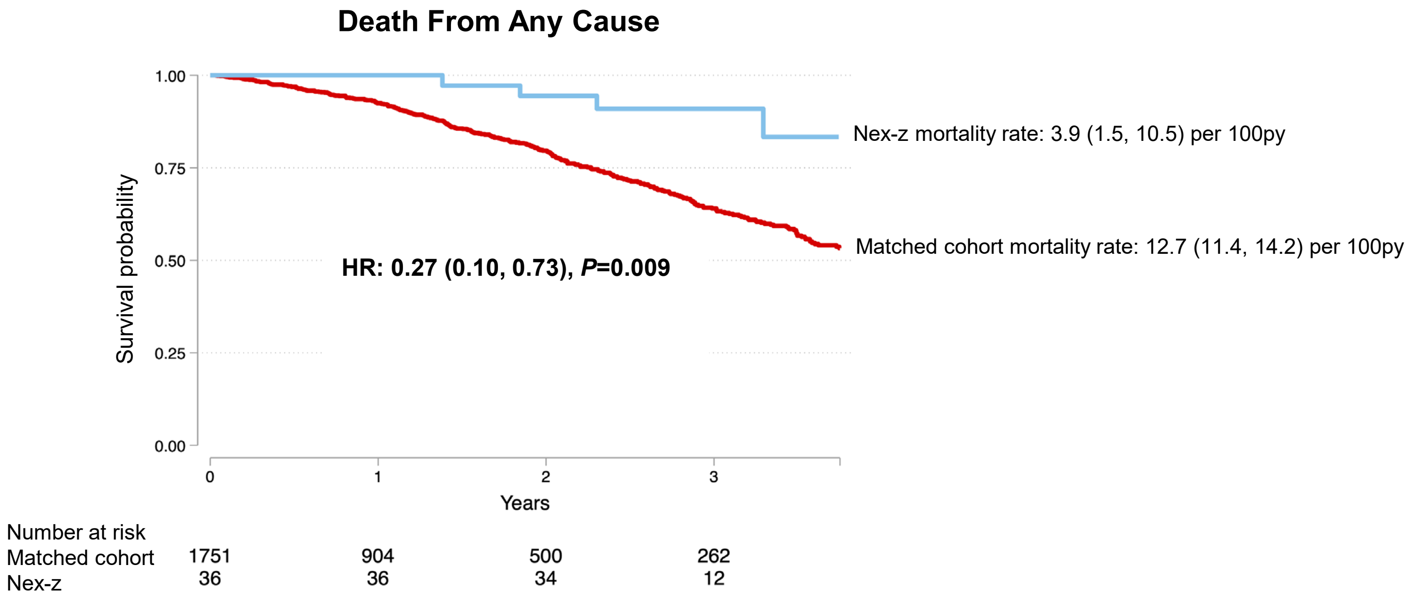
- A cohort of ATTR-CM patients from the National Amyloidosis Centre (NAC) who were not receiving stabilizers or silencers at baseline was compared to patients treated with nex-z (also from NAC) in a post-hoc analysis
- From a database of 3277 patients, propensity scores were used to identify 1751 contemporaneous NAC patients that were matched to the 36 patients who received nex-z based on their baseline characteristics
- Mortality outcomes of patients treated with nex-z were compared to the matched ATTR-CM controls from the NAC

Characteristic[a]	Patients With ATTR-CM		
	Matched cohort (N=1751)	Treated with nex-z (N=36)	*P* value
Age, mean (SD), y	77.9 (7.6)	76.5 (8.4)	0.28
Sex, Female, n (%)	43 (2.5)	1 (2.8)	0.90
Baseline year (SD)	2022 (2.7)	2022 (0.6)	0.94
NT-proBNP, geometric mean	2606	2466	0.74
***TTR* genotype, n (%)[b]**			
Wild type	1395 (79.7)	25 (69.4)	0.13
p.V142I	257 (14.7)	7 (19.4)	0.42
Echocardiogram measurements			
Septum thickness, mean (SD), mm	16.9 (2.7)	16.4 (1.6)	0.27
LVEF, mean (SD), %	49.4 (70.9)	49.2 (10.6)	0.99
eGFR, mean (SD), mL/min/1.73m^2	58.9 (17.8)	60.7 (15.3)	0.53

Patients were well matched between cohorts

[a]Numbers for patients treated with nex-z represent values at trial baseline. [b]Nex-z patient population includes 2 homozygous patients.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; CKD-EPI, chronic kidney disease epidemiology; eGFR, estimated glomerular filtration rate by CKD-EPI equation; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Center.

All-cause mortality rate in patients treated with nex-z was ~3-fold lower than that observed in a matched cohort of patients



- **A sensitivity analysis incorporating tafamidis initiation[a] as a time varying covariate yielded comparable results (HR: 0.3, 95% CI: 0.11, 0.80, *P*=0.016)**
- **Results will need to be confirmed in a prospective randomized controlled trial**

HR, hazard ratio; NAC, National Amyloidosis Center; PY, patient-year. [a]Tafamidis was initiated in patients in both cohorts shortly after it became available in the UK.
Follow up truncated to the last follow up time available for nex-z patients (44 months).

Phase 1 ATTR-CM safety summary

Event	n (%)
At least one AE	36 (100)
AEs occurring in ≥15% of patients	
Cardiac failure	13 (36)
COVID-19	8 (22)
Upper respiratory tract infection	7 (19)
Atrial fibrillation	6 (17)
Urinary tract infection	6 (17)
Treatment-related AEs in ≥5% of patients	
Infusion-related reaction	5 (14)
Aspartate aminotransferase increased	2 (6)
Any AE leading to treatment discontinuation	0
Any SAE[a]	15 (42)
SAEs occurring in ≥5% of patients	
Cardiac failure	8 (22)
Acute myocardial infarction	2 (6)
Cardiac failure congestive	2 (6)
Atrial flutter	2 (6)
Urinary tract infection	2 (6)
Pneumonia	2 (6)
Any event leading to death[b]	4 (11)

In this Phase 1 Trial

- Nex-z was generally well tolerated with IRRs being the most frequent related AE
- In the first 8 weeks post-dose, all liver enzyme elevations were transient, generally mild and no elevation was above Grade 2
- Two patients had AST elevations assessed by investigators as related to nex-z
    - One case occurred on Day 1 and the other case occurred on Day 22 post-dose
    - These elevations peaked at Grade 2 and resolved within approximately 10 days without medical intervention

Important safety update from Phase 3 MAGNITUDE Trial

- As recently disclosed, there have been cases of Grade 4 liver enzyme elevations in the Phase 3 MAGNITUDE ATTR-CM trial. These cases are under evaluation and enrollment in the trial is currently on hold

Data cutoff: August 23, 2025. [a]In addition, 1 patient in the long-term follow-up had unrelated serious adverse events. [b]One death was due to ischemic heart disease on Day 506; one due to decompensated heart failure on Day 675; one due to decompensated congestive heart failure on Day 790; and one due to heart failure, cardiac amyloidosis, and hypertension on Day 1204; all were unrelated to treatment.
At each level of summarization (any event and preferred term), subjects reporting more than one adverse event are counted only once.
AE, adverse event; AST, aspartate aminotransferase; ATTR-CM, ATTR amyloidosis with cardiomyopathy; IRR, infusion-related reaction; SAE, serious AE.

Conclusions

- In this Phase 1 study, nex-z was generally well tolerated with IRRs being the most frequent treatment-related AE
- A one-time treatment with nex-z yielded rapid, consistent, deep, and durable reductions in TTR in patients with ATTR-CM
- Compared with the natural history of disease, nex-z stabilized or improved multiple markers of cardiomyopathy, function, and cardiac remodeling, including in patients with NYHA Class III or hereditary disease
- Treatment with nex-z was associated with a low rate of mortality compared to the expected rates in patients with advanced ATTR-CM
    - As this is a single arm, open-label study, this observation needs to be confirmed in the Phase 3 MAGNITUDE trial (NCT06128629)

AE, adverse event; ATTR-CM, ATTR amyloidosis with cardiomyopathy; NYHA, New York Heart Association; IRR, infusion-related reaction; TTR, transthyretin.

Acknowledgments

We wish to extend our gratitude to:

- The patients, their caregivers, and their families
- My co-investigators and the study site staff

This study was sponsored by Intellia Therapeutics and Regeneron Pharmaceuticals. Medical writing and editorial support were provided by Gretchen Chidester, PhD, of Intellia Therapeutics and Ellen Woon, PhD, and Melissa Austin of Apollo Medical Communications, part of Helios Global Group, and funded by Intellia Therapeutics.

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