CMR outcomes following one-time *in vivo* CRISPR editing with nexiguran ziclumeran in patients with ATTR-CM: phase 1 results

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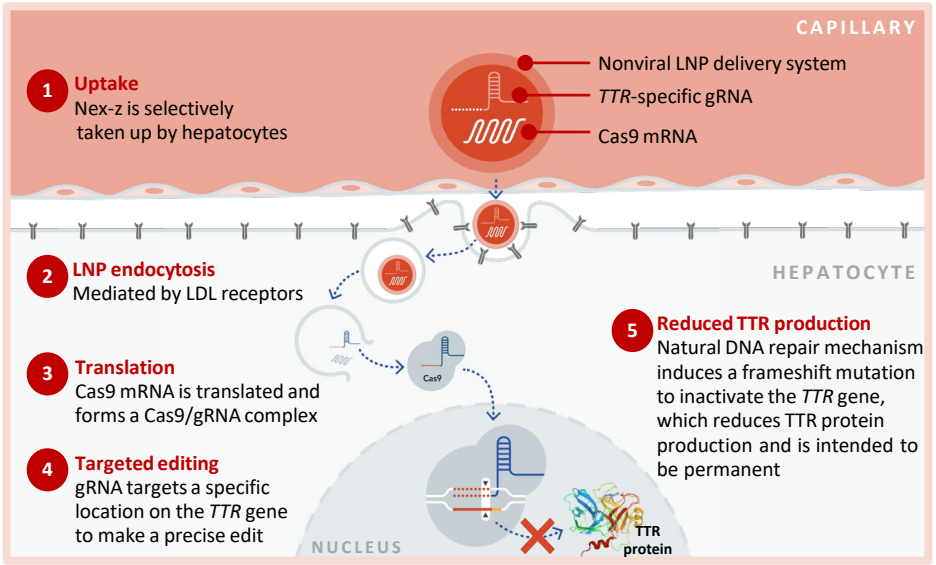
Background and purpose

- ATTR-CM is characterised by progressive cardiac remodelling and dysfunction, decline in functional capacity and QoL, frequent hospitalization, and death[1]
- Cardiovascular magnetic resonance (CMR), including extracellular volume (ECV) mapping, provides a sensitive method to quantify amyloid burden and treatment response[2,3]
  - Higher ECV is a strong and independent predictor of mortality, with risk rising 22% for every 10% absolute increase in ECV[3]
- In a Phase 1 trial (NCT04601051) of patients with ATTR-CM, a single dose of nexiguran ziclumeran (nex-z) was associated with rapid, deep, and durable TTR knockdown, favourable biomarker and functional trajectories, and was generally well tolerated[4]

Nex-z is an *in vivo* investigational one-time CRISPR/Cas9 therapy designed to inactivate the *TTR* gene, whether wild-type or variant[1,5]



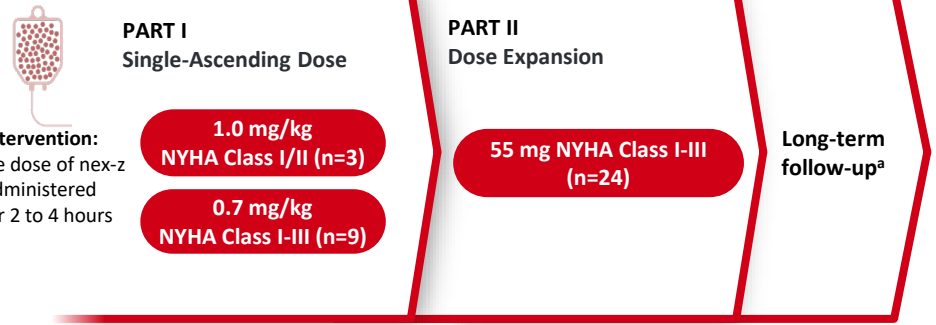
Purpose: Evaluate the impact of nex-z on cardiac structure, function, and myocardial amyloid load in patients with ATTR-CM

ATTR-CM, ATTR amyloidosis with cardiomyopathy; 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; QoL, quality of life; TTR, transthyretin.

1. Fontana M, et al. *N Engl J Med*. 2024;391(23):2231-2241. 2. Patel RK, et al. *Eur Heart J*. 2025;46(46):5049-5058. 3. Sheikh A, et al. *J Am Coll Cardiol*. 2026;87(5):505-518. 4. Gillmore JD, et al. Presented at: AHA Scientific Sessions; November 7-10, 2025; New Orleans, LA. 5. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502.

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

Two-Part, Open-Label Study in Adults With ATTR-CM



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*

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)
6MWT 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 (45, 71)
TTR genotype, n (%)	Wild type	25 (69)
	p.V142I[b]	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)

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

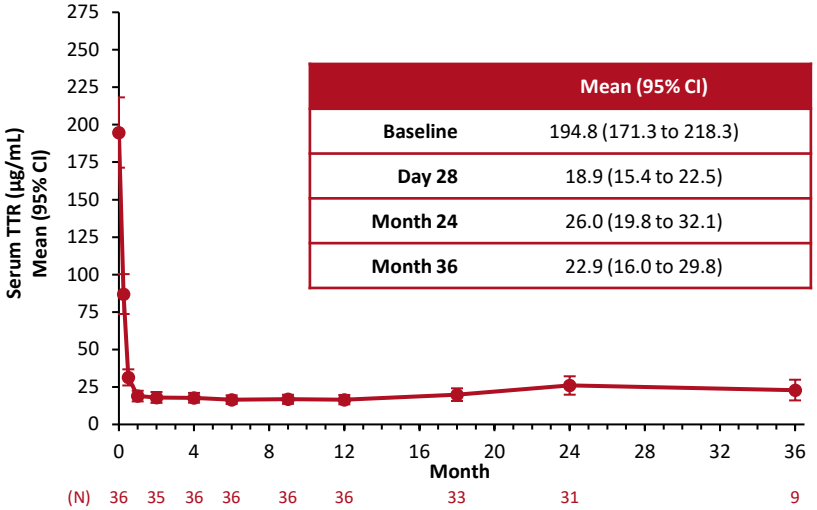
Data cutoff: 23 August 2025. Percentages may not total 100 because of rounding.

[a]Safety and TTR data are reported through Month 36 as part of long-term follow-up data (NCT05697861). As of 23 August 2025, the median (range) duration of follow-up was 25.5 (17-40) months; 30 patients have enrolled in the long-term follow-up study, with a median (range) duration of 33 (24, 44) months. [b]Includes 2 homozygous patients.

6MWT, 6-Minute Walk Test; 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; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamics; TTR, transthyretin; VO_2, oxygen consumption.

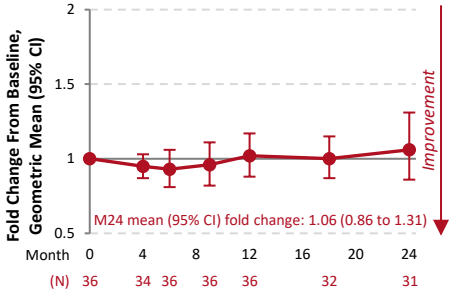
Nex-z led to durable reductions in serum TTR and stabilized or improved markers of cardiomyopathy and function in patients with ATTR-CM[1]

Absolute Serum TTR (µg/mL)

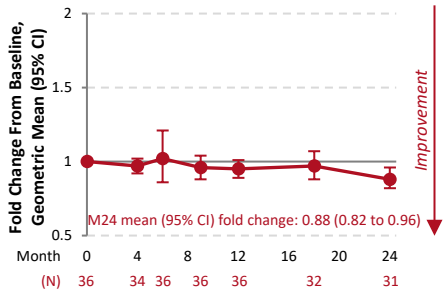


	Mean (95% CI)
Baseline	194.8 (171.3 to 218.3)
Day 28	18.9 (15.4 to 22.5)
Month 24	26.0 (19.8 to 32.1)
Month 36	22.9 (16.0 to 29.8)

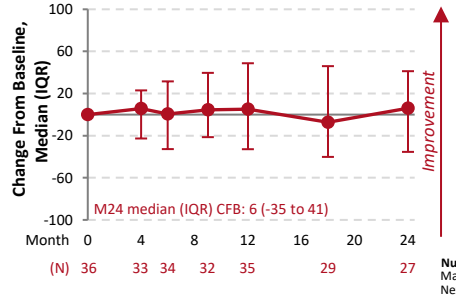
NT-proBNP



hs-Troponin T

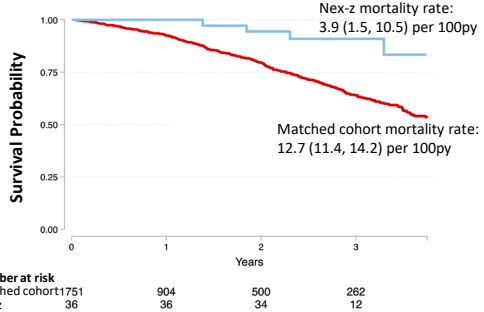


6MWT Distance (meters)



Death From Any Cause

(Post-hoc Analysis with Matched Control[a])



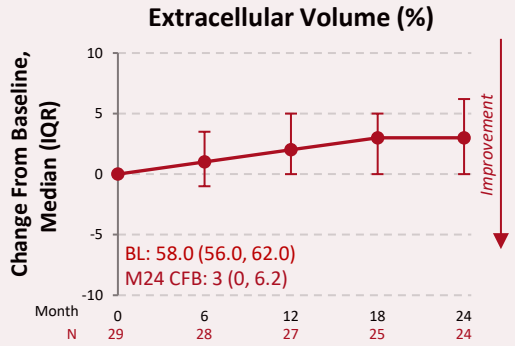
Heart Failure & World Congress on Acute Heart Failure 2026

Data cutoff: 23 August 2025. Data at Month 36 collected from patients who entered the long-term follow-up safety monitoring study (data-cutoff date, 21 August 2025). Changes in N from total population (N=36) reflect patient death (n=2), withdrawal (n=1), or missing assessment. [a]A cohort of patients with ATTR-CM from the National Amyloidosis Centre was compared with patients treated with nex-z in a post hoc analysis. Propensity scores were used to identify 1751 patients who were matched to 36 patients who received nex-z based on baseline characteristics. Mortality outcomes were compared.

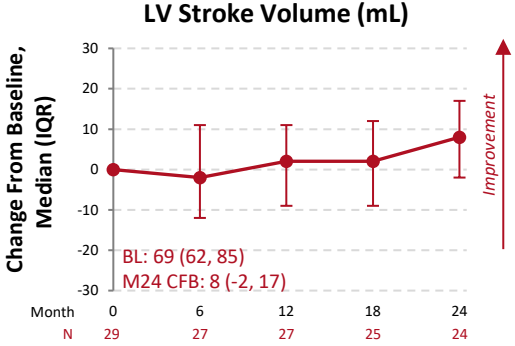
6MWT, 6-Minute Walk Test; ATTR-CM, ATTR amyloidosis with cardiomyopathy; CFB, change from baseline; HR, hazard ratio; hs, high sensitivity; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; py, patient-year; TTR, transthyretin.

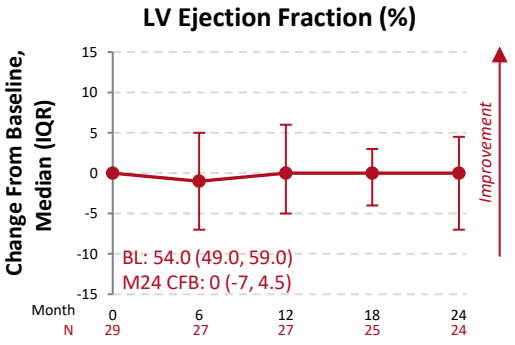
1. Gillmore JD, et al. Presented at: AHA Scientific Sessions; November 7-10, 2025; New Orleans, LA.

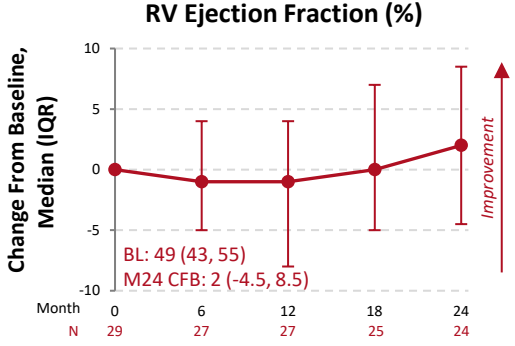
Nex-z was associated with stability of cardiac structure, function, and amyloid burden over 24 months, as assessed by CMR[a]

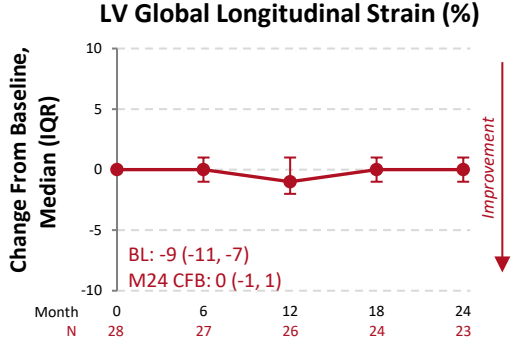


- ***Changes in ECV of <5% are associated with clinical stability[1]***
- ***Risk of mortality rises 22% for every 10% increase in ECV[2]***









Heart Failure & World Congress on Acute Heart Failure 2026

Data cutoff: 23 August 2025.

[a]29 participants underwent baseline CMR; 27 and 24 completed 1- and 2-year follow-up CMR, respectively, after a single open-label dose of nex-z. Changes in N from total population (N=36) reflect patient death (n=2), withdrawal (n=1), or missing assessment (including patients unable to have CMR imaging due to presence of cardiac device).

BL, baseline; CFB, change from baseline; CMR, cardiac magnetic resonance imaging; ECV, extracellular volume; LV, left ventricular; RV, right ventricular.

1. Patel RK, et al. *Eur Heart J.* 2025;46(46):5049-5058. 2. Sheikh A, et al. *J Am Coll Cardiol.* 2026;87(5):505-518.

Safety and conclusions

Event	All patients (N=36) 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)
Urinary tract infection	3 (8)
Acute myocardial infarction	2 (6)
Atrial flutter	2 (6)
Cardiac failure congestive	2 (6)
Pneumonia	2 (6)
Any event leading to death[b]	4 (11)

Conclusions

In this Phase 1 cohort with a high proportion of hereditary ATTR-CM, a single dose of nex-z was associated with stability of cardiac structure, function, and amyloid burden over 2 years.

These findings support the potential of gene editing to alter the natural history of amyloid deposition and disease progression in ATTR-CM.

Participants with ATTR-CM (N=36) summarised in this presentation represent one half of the cohort exposed to nex-z in this Phase 1 trial (NCT04601051); safety and efficacy in participants with ATTRv-PN is summarised in Gillmore JD, et al. *N Engl J Med*. 2025;393(14):1375-1386.

Data cutoff: 23 August 2025. At each level of summarisation (any event and preferred term), patients reporting more than one AE are counted only once.

[a]In addition, 1 patient in the long-term follow-up had unrelated serious adverse events. [b]One death was due to ischaemic 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.

AE, adverse event; ATTR-CM, ATTR amyloidosis with cardiomyopathy; ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; SAE, serious AE.