Scientific Sessions

CARDIAC OUTCOMES FOLLOWING A SINGLE DOSE OF NEXIGURAN ZICLUMERAN IN PATIENTS WITH TRANSTHYRETIN AMYLOIDOSIS WITH CARDIOMYOPATHY OR HEREDITARY TRANSTHYRETIN AMYLOIDOSIS WITH POLYNEUROPATHY: A PHASE 1 ANALYSIS

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American Heart Association.

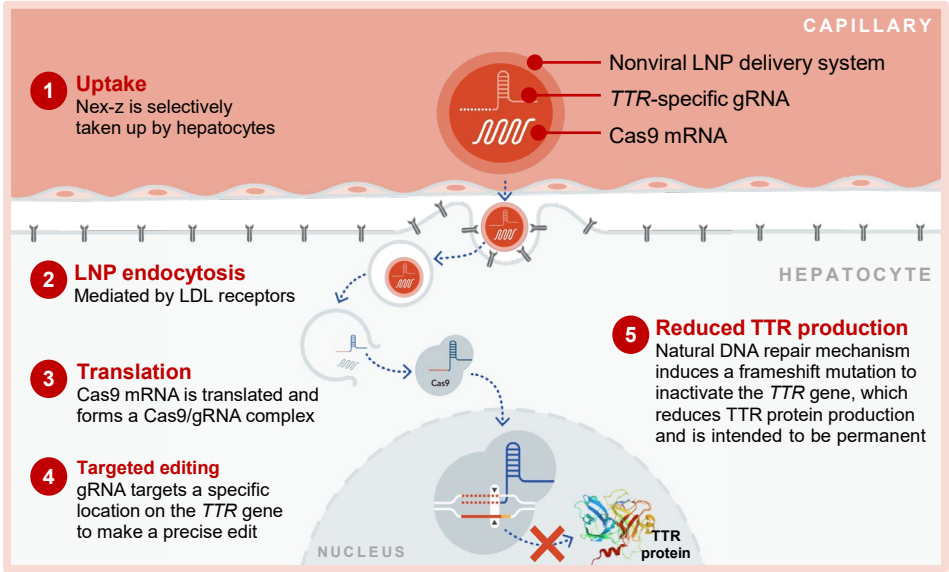
DISCLOSURES AND ACKNOWLEDGMENTS

- Dr. Razvi reports grant income from AstraZeneca, speaker fees from Alnylam Pharmaceuticals, and consulting income from BridgeBio and Bayer
- This study is funded by Intellia Therapeutics. We wish to extend our gratitude to the participants, their caregivers, and their families and the study site coordinators and staff. Medical writing and editorial support were provided by Charlotte Pettigrew, PhD, and Shannon Davis of Helios Global Group, and funded by Intellia Therapeutics

ATTR IS A PROGRESSIVE MULTISYSTEM DISEASE CAUSED BY MISFOLDING OF TTR

- ATTR arises from inherited pathogenic *TTR* variants (ATTRv) or age-related TTR misfolding[1]
- ATTR may present as polyneuropathy (ATTR-PN) or cardiomyopathy (ATTR-CM), and patients with ATTRv often have a polyneuropathy and cardiomyopathy phenotype (ATTRv-mixed)[2]
- Cardiac involvement is the leading predictor of mortality in ATTR, and preventing cardiac progression is therefore critical[2]
- In a Phase 1 trial (NCT04601051) of participants with ATTRv-PN or ATTR-CM, a single dose of nex-z produced deep and durable reductions in serum TTR, improved or stabilized measures of disease progression, and was well tolerated[3-5]

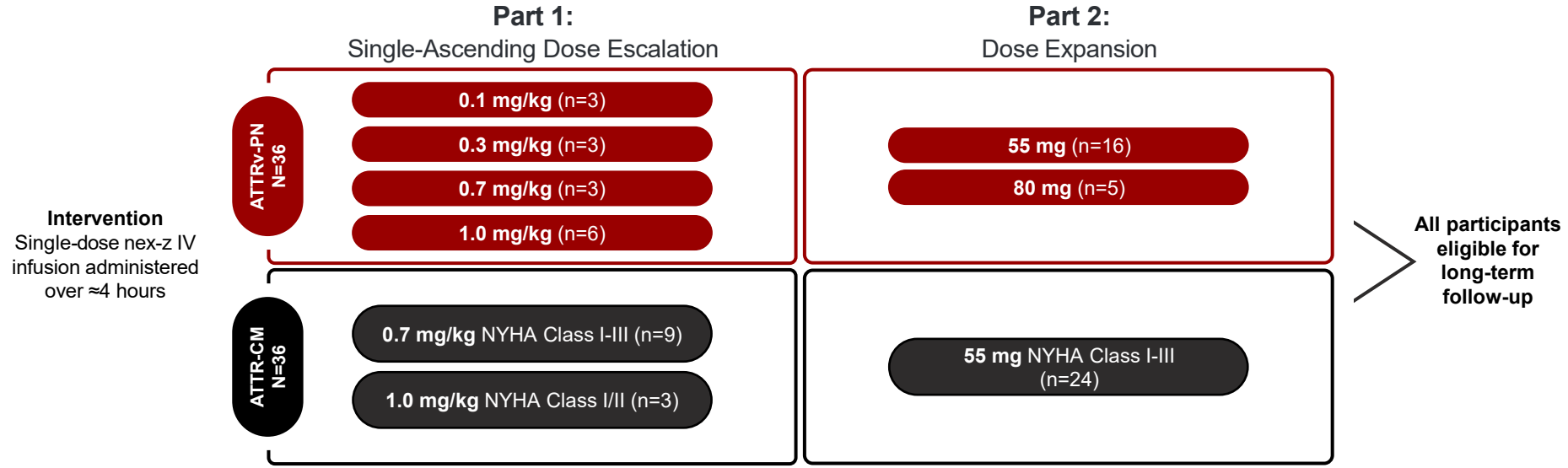
Nex-z is an *in vivo,* investigational, one-time CRISPR-based therapy designed to inactivate the *TTR* gene, whether wild-type or variant[3,4]



Objective: Assess the effects of nex-z on participants with ATTR-CM and ATTRv-mixed from the Phase 1 trial

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTR-PN, transthyretin amyloidosis with polyneuropathy; ATTRv, hereditary transthyretin amyloidosis; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; Cas9, CRISPR-associated protein 9; gRNA, guide RNA; LDL, low-density lipoprotein; LNP, lipid nanoparticle; mRNA, messenger RNA; nex-z, nexiguran ziclumeran; TTR, transthyretin. 1. Ando Y, et al. *Orphanet J Rare Dis.* 2013;8:31. 2. Porcari A, et al. *Cardiovasc Res.* 2023;118(18):3517-3535. 3. Gillmore JD, et al. *N Engl J Med.* 2021;385(6):493-502. 4. Fontana M, et al. *N Engl J Med.* 2024;391(23):2231-2241. 5. Gilmore JD, et al. Presented at: International ATTR Amyloidosis Meeting for Patients and Doctors; Sep 25-26, 2025; Baveno, Italy.

NEX-Z WAS EVALUATED IN A 2-PART, OPEN-LABEL, PHASE 1 STUDY



PRIMARY OBJECTIVES

Evaluate safety, tolerability, and PD

- Serum TTR levels

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of cardiac disease

- NT-proBNP, 6MWT, NYHA Class, KCCQ, CMR

POST HOC ASSESSMENT

The ATTRv-mixed cohort was defined as participants with ATTRv-PN with a baseline ECV ≥40% assessed by CMR.[1] Safety, PD, and efficacy in clinical measures of cardiac disease were assessed in participants with ATTRv-mixed vs ATTR-CM

Data are reported in participants who received a single dose of nex-z ≥0.3 mg/kg[a]

[a]Results exclude the 0.1 mg/kg group; participants who received nex-z 0.1 mg/kg were redosed with nex-z 55 mg. 6MWT, 6-Minute Walk Test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; CMR, cardiac magnetic resonance imaging; ECV, extracellular volume; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; nex-z, nexiguran ziclumeran; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamics; TTR, transthyretin.

1. Sheikh A, et al. *J Am Coll Cardiol.* 2026;87(5):505-518.

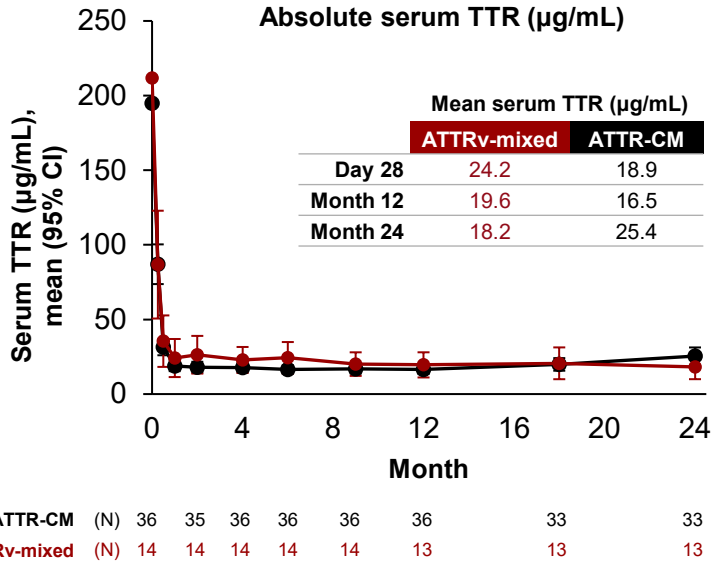
DEMOGRAPHICS AND BASELINE CHARACTERISTICS

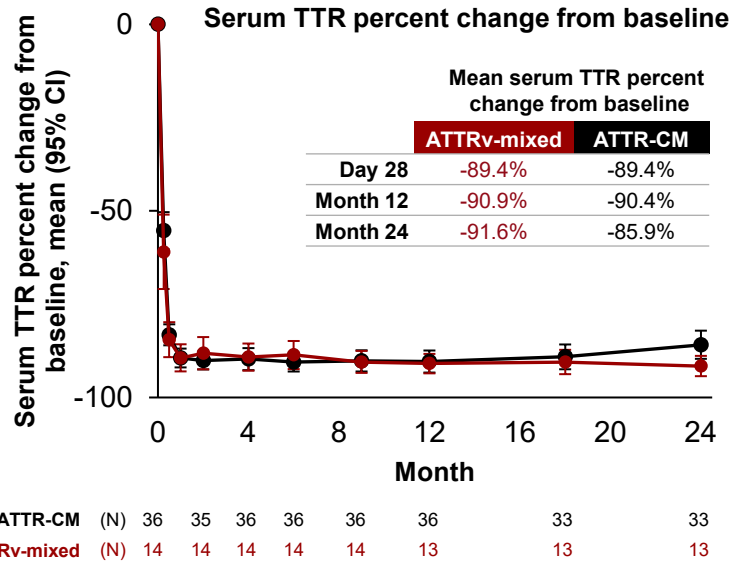
Parameter	ATTRv-mixed (N=14)	ATTR-CM (N=36)
Median age (range), y	61.0 (49-75)	78.0 (46-90)
Male, n (%)	12 (86)	35 (97)
Race, n (%)		
Asian	1 (7)	0
Black or African American	0	8 (22)
White or Caucasian	13 (93)	28 (78)
NT-proBNP, median (Q1, Q3), ng/L	359.0 (133.0, 544.0)	2051.5 (1403.5, 4222.0)
6MWT distance, median (Q1, Q3), m	412.6 (296.7, 490.7)	330.6 (275.6, 419.9)
NYHA class, n (%)		
I	9 (64)	3 (8)
II	5 (36)	15 (42)
III	0	18 (50)
KCCQ-OS score, median (Q1, Q3)	83.3 (50.0, 95.3)	70.4 (46.9, 81.5)
CMR ECV, median (Q1, Q3), %	49 (45, 61)	58 (56, 62)

- The ATTR-CM cohort had advanced cardiac disease at baseline (median NT-proBNP of 2051.5 ng/L and 50% with NYHA class III disease)
- The ATTRv-mixed cohort had less advanced disease (median NT-proBNP of 359.0 ng/L and no participants with NYHA class III disease)
- Median duration of exposure to nex-z was 24.0 months in the ATTRv-mixed cohort and 25.5 months in the ATTR-CM cohort

Data cutoff: Sep 12, 2025. In general, baseline is defined as the last measurement prior to pretreatment medications; baseline for 6MWT, KCCQ-OS, and CMR ECV is defined as the last available measurement taken prior to the start of infusion of study treatment.
6MWT, 6-minute Walk Test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; CMR, cardiac magnetic resonance imaging; ECV, extracellular volume; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; nex-z, nexiguran ziclumeran; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

NEX-Z LED TO RAPID, DEEP, AND DURABLE REDUCTIONS IN SERUM TTR IN PARTICIPANTS WITH ATTR-CM AND ATTRv-MIXED OVER 24 MONTHS

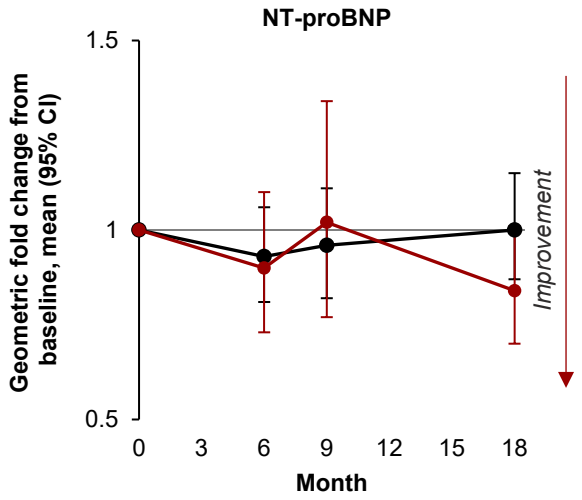


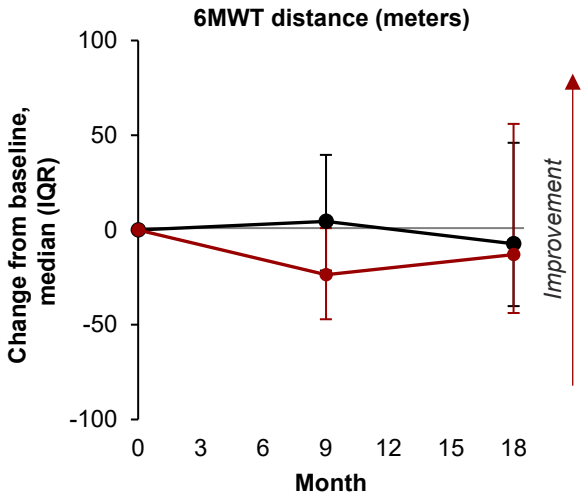


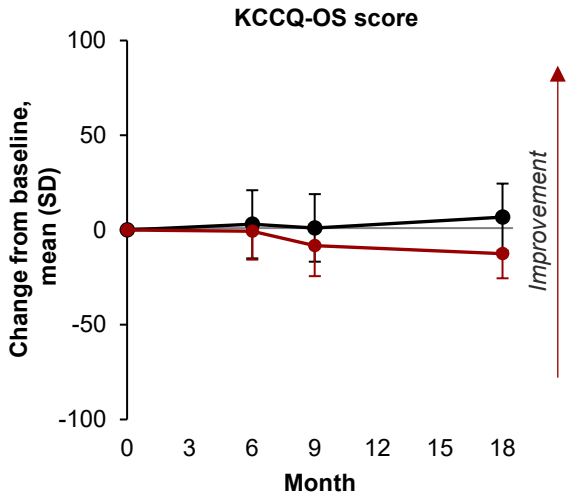
- At Day 28, mean (95% CI) serum TTR was 24.2 (11.4-36.9) in the ATTRv-mixed cohort and 18.9 (15.4-22.5) in the ATTR-CM cohort
- At Month 24, 85% in the ATTRv-mixed cohort and 79% in the ATTR-CM cohort achieved TTR levels <30 µg/mL
- 32 of 36 participants in the ATTR-CM cohort initiated tafamidis once it became available in the UK (mean [SD] starting time, 23.0 [6.6] months)
- Of 3 participants in the ATTRv-mixed cohort receiving tafamidis at the start of the trial, 2 remained on tafamidis at Month 24

Data cutoff: Sep 12, 2025. Baseline was defined as the average of the visits within 42 days prior to the start of study intervention.
ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; nex-z, nexiguran ziclumeran; TTR, transthyretin; UK, United Kingdom.

STABILITY OR IMPROVEMENT IN NT-proBNP, 6MWT, KCCQ-OS SCORE, AND NYHA CLASS THROUGH MONTH 18





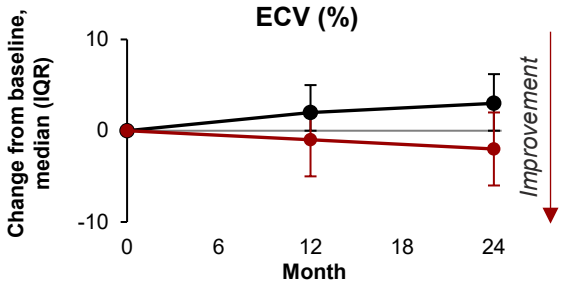


ATTR-CM	(N)	36		36	36		32	(N)	36		32		29	(N) 36 36 36 34
ATTRv-mixed	(N)	14		13	13		12	(N)	14		14		13	(N) 9 9 8 8

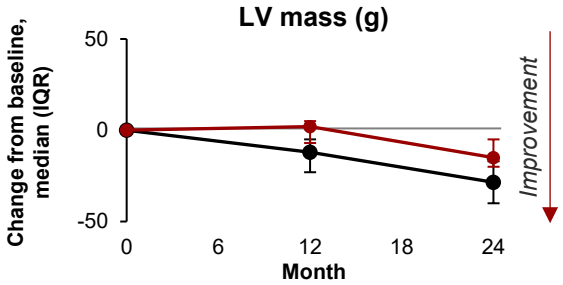
In both the ATTRv-mixed and ATTR-CM cohorts, 86% of participants experienced improvement or no change in NYHA Class at Month 18

Data cutoff: Sep 12, 2025. Baseline for NT-proBNP is defined as the last measurement prior to the start date of any pretreatment medication. Baseline for 6MWT, KCCQ-OS, and NYHA Class is defined as the last available measurement taken prior to the start of infusion of study treatment.
6MWT, 6-Minute Walk Test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

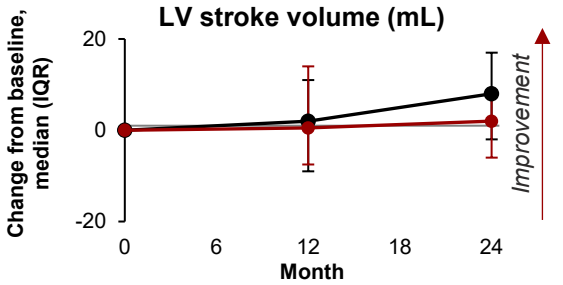
STABILITY OR IMPROVEMENT IN CARDIAC STRUCTURE, FUNCTION, AND AMYLOID BURDEN, AS ASSESSED BY CMR AT MONTHS 12 AND 24



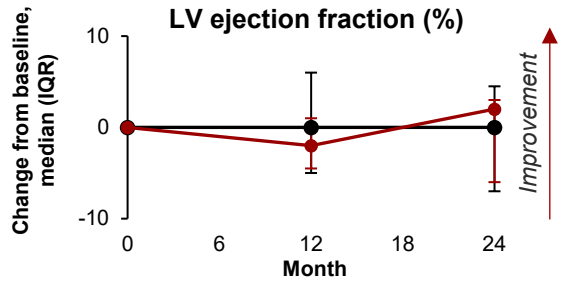
ATTR-CM	(N) 29	27	24
ATTRv-mixed	(N) 14	13	13



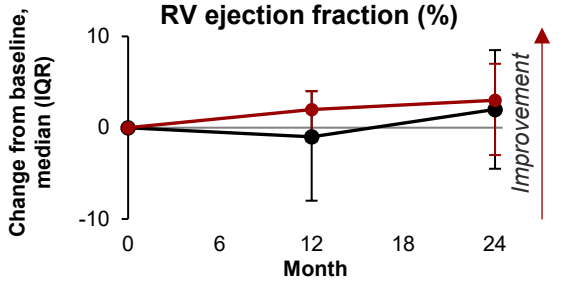
ATTR-CM	(N) 29	27	24
ATTRv-mixed	(N) 14	12	13



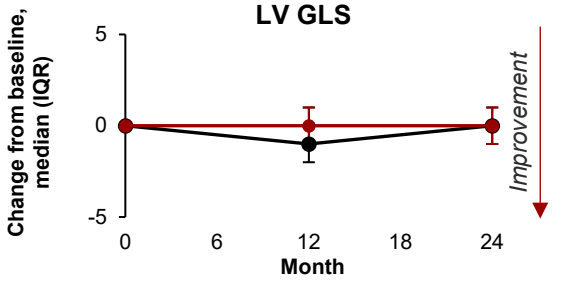
ATTR-CM	(N) 29	27	24
ATTRv-mixed	(N) 14	12	13



ATTR-CM	(N) 29	27	24
ATTRv-mixed	(N) 14	12	13



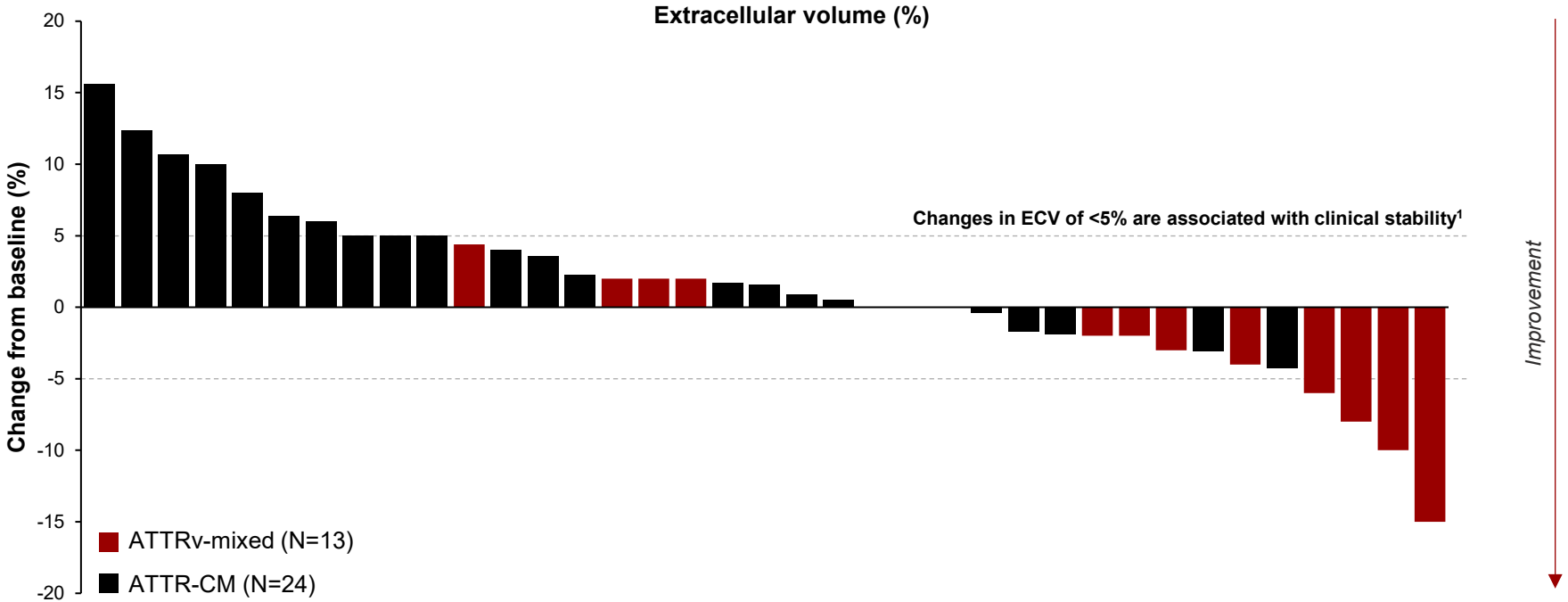
ATTR-CM	(N) 29	27	24
ATTRv-mixed	(N) 14	12	13



ATTR-CM	(N) 28	26	23
ATTRv-mixed	(N) 14	13	13

Data cutoff: Sep 12, 2025. Baseline is defined as the last available measurement taken prior to the start of infusion of study treatment.
ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; CMR, cardiac magnetic resonance imaging; ECV, extracellular volume; GLS, global longitudinal strain; IQR, interquartile range; LV, left ventricular; RV, right ventricular.

STABILITY OR IMPROVEMENT IN ECV AS ASSESSED BY CMR IN THE ATTRv-MIXED COHORT AT MONTH 24



Data cutoff: Sep 12, 2025. Baseline is defined as the last available measurement taken prior to the start of infusion of study treatment.
ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; CMR, cardiac magnetic resonance imaging; ECV, extracellular volume.
1. Patel RK, et al. *Eur Heart J.* 2025;46(46):5049-5058.

SAFETY SUMMARY AND CONCLUSIONS

Safety event, n (%)	ATTRv-mixed (N=14)	ATTR-CM (N=36)
Any TEAE	14 (100)	36 (100)
Grade ≥3	4 (29)	16 (44)
Treatment-related TEAE	10 (71)	6 (17)
Grade ≥3	1 (7)	1 (3)
Serious TEAE	4 (29)	15 (42)
TEAE leading to death	1 (7)	4 (11)
Treatment-related TEAEs occurring in >1 participant		
Infusion-related reaction	8 (57)	5 (14)
Thyroxine decrease[a]	4 (29)	0
Fatigue	2 (14)	0
AST increased	1 (7)	2 (6)

SAFETY

- Overall, nex-z was well tolerated with a favorable safety profile; most adverse events were mild or moderate in both the ATTRv-mixed and ATTR-CM cohorts

CONCLUSIONS

- A single dose of nex-z was well tolerated and produced consistent, rapid, and durable reductions in serum TTR across participants with ATTRv-mixed and ATTR-CM
- Despite advanced disease in the ATTR-CM cohort, stabilization or improvement was generally observed across cardiac outcomes
- Participants with ATTRv-mixed also demonstrated stabilization across outcomes, with trends toward improvement in NT-proBNP and cardiac structure, function, and amyloid burden observed in a proportion of participants, suggestive of partial disease reversal
- These findings suggest that early intervention in patients with ATTR may stabilize or reverse cardiac disease progression

Data cutoff: Sep 12, 2025. Treatment-related TEAEs occurring in >1 participant in either cohort are ordered by incidence in the ATTRv-mixed group.
[a]No evidence of hypothyroidism was observed.
AST, aspartate aminotransferase; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-mixed, hereditary transthyretin amyloidosis with polyneuropathy and cardiac involvement; ECV, extracellular volume; nex-z, nexiguran ziclumeran; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TEAE, treatment-emergent adverse event; TTR, transthyretin.