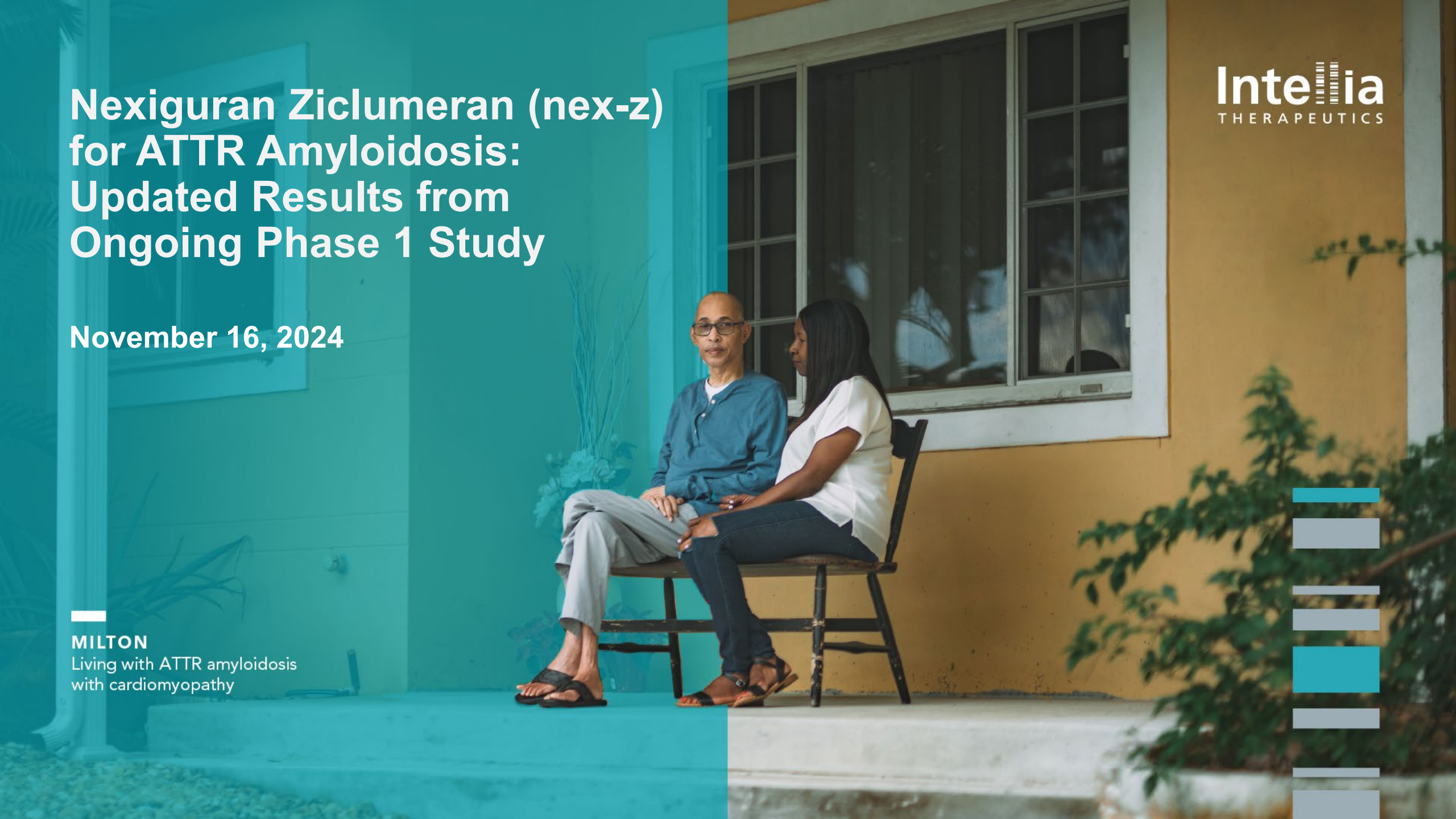
Nexiguran Ziclumeran (nex-z) for ATTR Amyloidosis: Updated Results from Ongoing Phase 1 Study

November 16, 2024



Intellia THERAPEUTICS

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Agenda

Welcome

Introduction
Dr. John Leonard *Chief Executive Officer*, Intellia Therapeutics

ATTR-CM Phase 1 Data Update
Dr. Marianna Fontana *Professor of Cardiology and Honorary Consultant Cardiologist at the National Amyloidosis Centre, Division of Medicine,* University College London

Nex-z Clinical Development Summary
Dr. David Lebwohl *Chief Medical Officer*, Intellia Therapeutics

Q&A Session

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Intellia THERAPEUTICS

Milton
Living with ATTR amyloidosis with cardiomyopathy

NANCY
Living with ATTR amyloidosis with polyneuropathy

Nex-z Has the Potential to Reset the Standard of Care for ATTR Amyloidosis

- First and only investigational therapy that **targets the *TTR* gene**, to reduce production of TTR protein at its source
- **Consistently rapid, deep and durable TTR reduction** achieved in all patients treated
- Favorable trends of **disease stabilization or improvement** observed across multiple markers of disease progression
- Nex-z is being developed as a one-time IV infusion administered in an outpatient setting

Nexiguran ziclumeran (nex-z, also known as NTLA-2001);
ATTR amyloidosis, transthyretin amyloidosis; IV, intravenous;
Based on interim nex-z Phase 1 data as of data cutoff August 21, 2024.
Studies are ongoing to assess this investigational product.

REGENERON Intellia THERAPEUTICS

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#AHA24

Nexiguran Ziclumeran (nex-z, Also Known as NTLA-2001), an Investigational *In Vivo* CRISPR-Based Therapy for Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR-CM): Interim Report of the Phase 1 Study

Marianna Fontana,[1] Jörg Täubel,[2] Ed Gane,[3] Björn Pilebro,[4] David Adams,[5] Scott Solomon,[6] Brian Claggett,[6] Jessica Kachadourian,[7] Ricardo Rocha,[7] Joy Olbertz,[7] Peijuan Zhu,[7] Carri Boiselle,[7] Derek Smith,[7] Adia Leung,[7] David E. Gutstein,[8] Alison Sonderfan,[7] Liron Walsh,[7] and Julian D. Gillmore[1]

[1]National Amyloidosis Centre, Division of Medicine, University College London, London, UK; [2]Richmond Pharmacology, London, UK; [3]University of Auckland, Auckland, New Zealand; [4]Umea University, Umea, Sweden; [5]CHU de Bicêtre, AP-HP, University Paris-Saclay, Le Kremlin-Bicêtre, France; [6]Brigham and Women's Hospital, Boston, MA; [7]Intellia Therapeutics, Cambridge, MA; [8]Regeneron Pharmaceuticals, Tarrytown, NY

American Heart Association.

American Heart Association. 100 YEARS Bold Hearts

Disclosures

- Dr. Fontana reports consultancy/advisory boards for Alexion/Caelum Biosciences, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio/Eidos, Cardior Pharmaceuticals, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Novo Nordisk, Pfizer, and Prothena
- Research grants from: Alnylam, AstraZeneca, BridgeBio, and Pfizer
- Salary from British Heart Foundation Intermediate Fellowship

The present study was funded by Intellia Therapeutics and Regeneron Pharmaceuticals, Inc.

ATTR Amyloidosis Is a Progressive and Fatal Disease

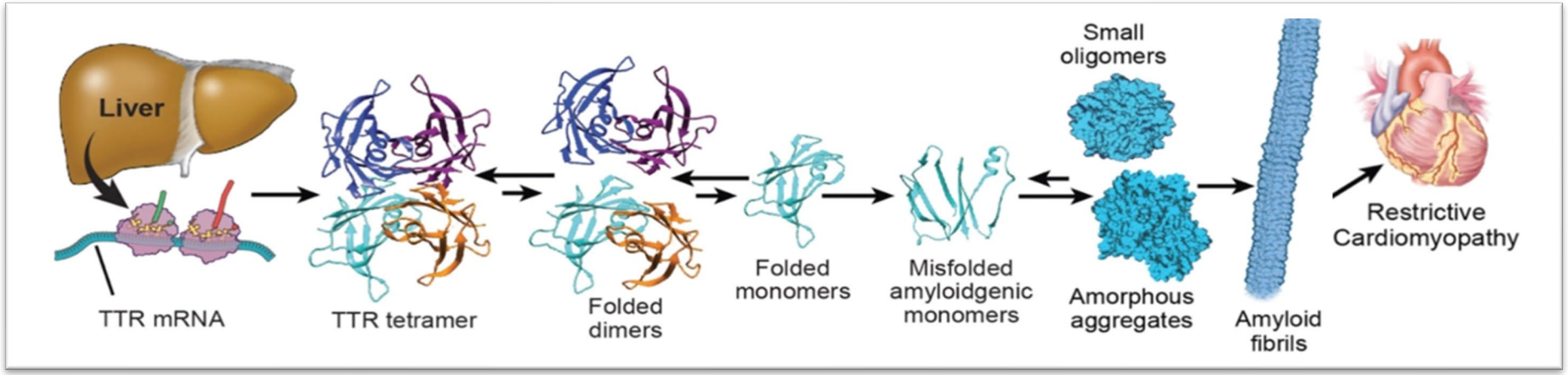


Figure modified from Ruberg FL, et al. *J Am Coll Cardiol* 2019;73:2872-2891.

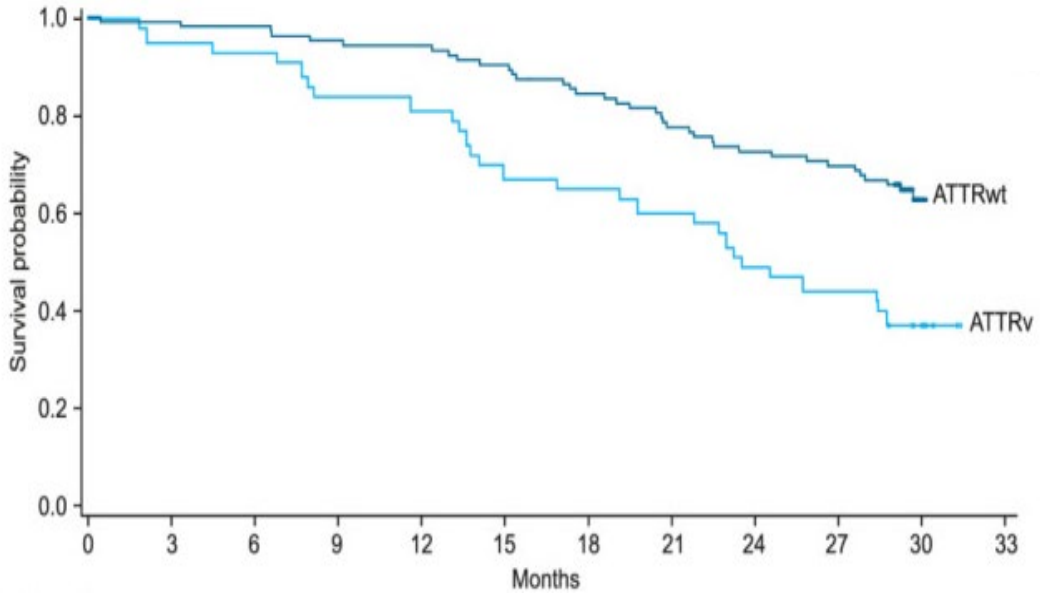
- Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) results from accumulation of wild type or variant TTR amyloid fibrils in the heart, and is a progressive and fatal disease[1]
- ATTR-CM is an often underdiagnosed cause of heart failure, and is estimated to impact 200,000-500,000 patients globally[2-4]
- Currently available treatments for ATTR-CM include TTR stabilizers and *TTR* gene silencers; however, quality of life and functional capacity continue to decline, and they require lifelong administration

mRNA, messenger RNA; TTR, transthyretin.

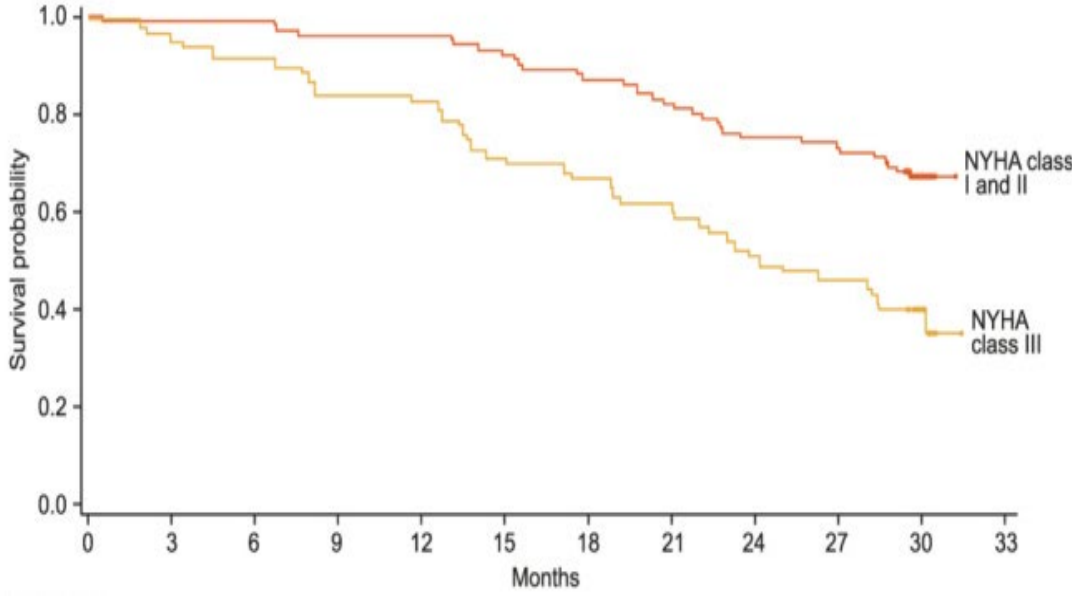
1. Ruberg FL, et al. *J Am Coll Cardiol* 2019;73(22):2872-2891. 2. Maurer M, et al. *Circ Heart Fail.* 2019;12(9):e006075. 3. Nativi-Nicolau JN, et al. *Heart Fail Rev.* 2021;27(3):785-793. 4. Gillmore JD, et al. Presented at: American Heart Association® Scientific Sessions; Chicago, IL; November 5, 2022.

Probability of Survival in Patients With Either Hereditary Disease (ATTRv) or NYHA Class III

All-Cause Mortality by Genotype[1]
ATTR-ACT patients receiving placebo



All-Cause Mortality by NYHA Class at Baseline[1]
ATTR-ACT patients receiving placebo

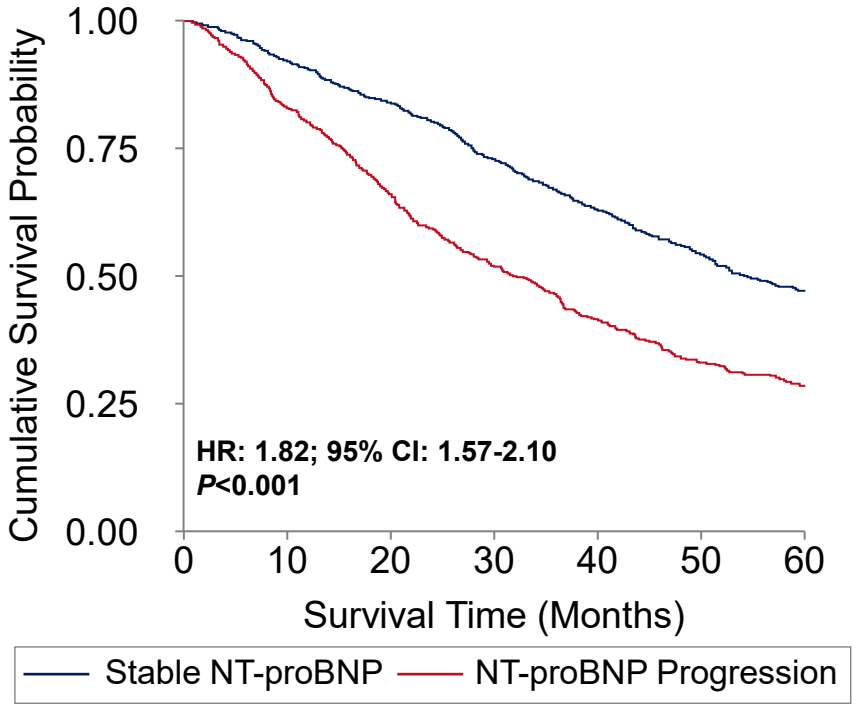


Mortality rates are higher in patients with hereditary disease or those with NYHA class III[1]

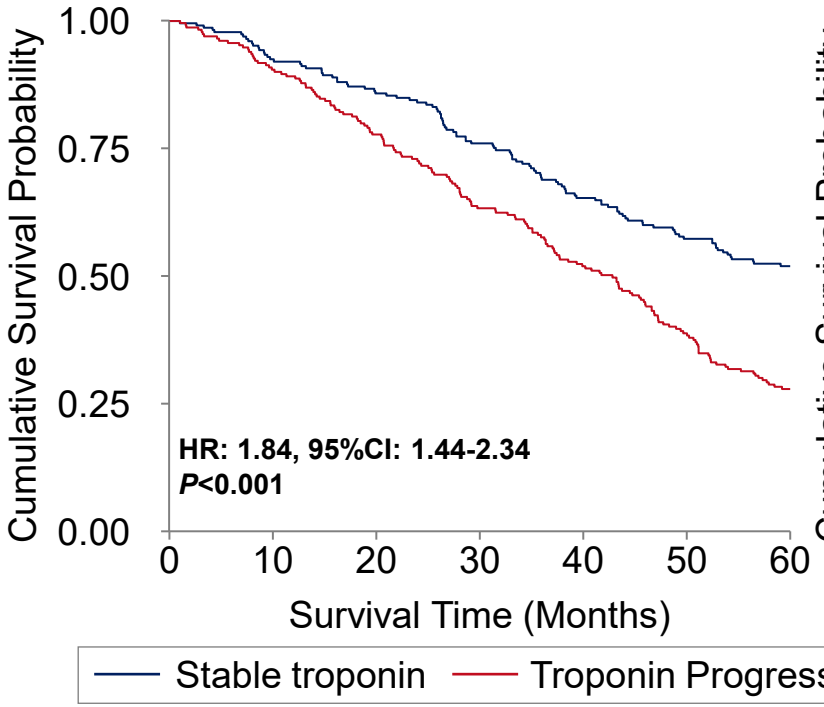
[a]All patients in this analysis were receiving treatment with placebo.
ATTRv, hereditary/variant ATTR amyloidosis; ATTRwt, wild-type ATTR amyloidosis; NYHA, New York Heart Association.
1. Nicolau JN, et al. *ESC Heart Fail*. 2021;8(5):3875-3884.

Worsening of NT-proBNP, Troponin T, and 6MWT Is Associated With an Even Greater Risk of Death in Patients With ATTR-CM

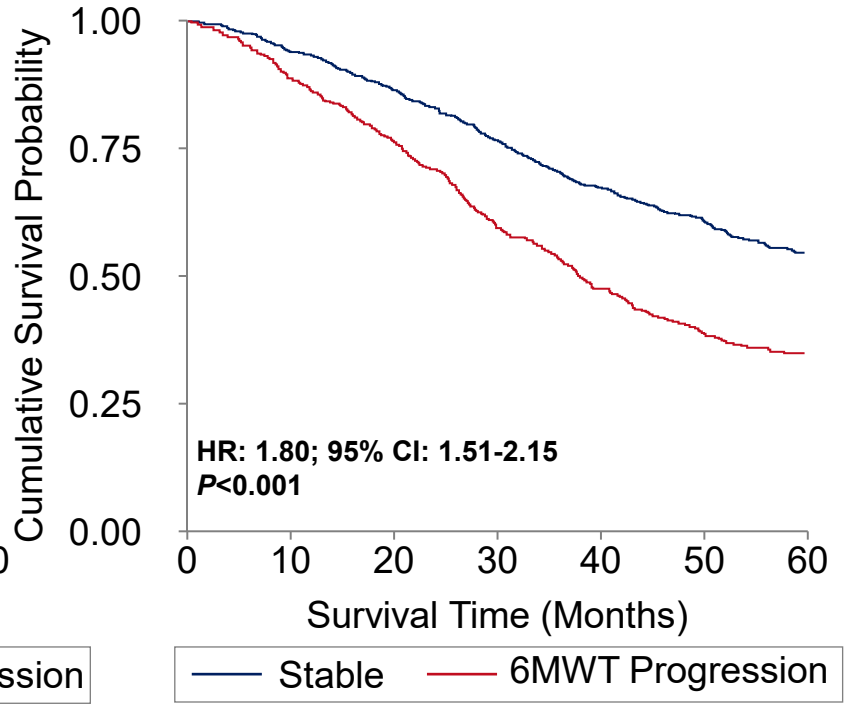
Survival according to NT-proBNP progression[1]
Increase of >700 ng/L and >30%



Survival according to troponin progression[1]
Increase of >10 ng/L and >20%



Survival according to 6MWT progression[2]
Reduction of >35 m



In patients with ATTR-CM (≈80% NYHA class I/II)[1], worsening of NT-proBNP, troponin T, and 6MWT occurred at 12 months in 35%, 50% and 40%, respectively

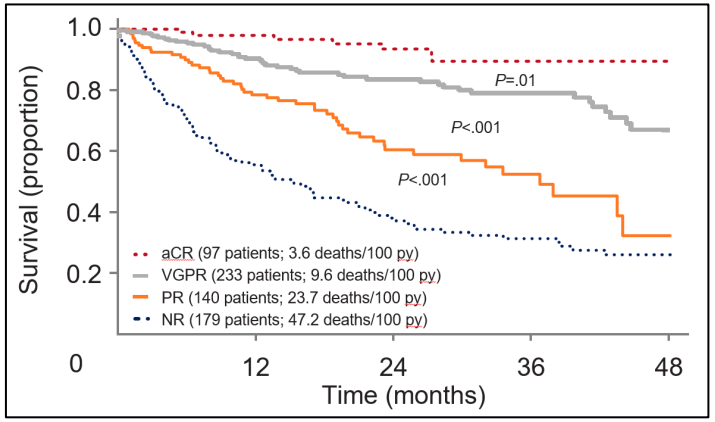
6MWT, 6-Minute Walk Test; ATTR-CM, ATTR amyloidosis with cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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.

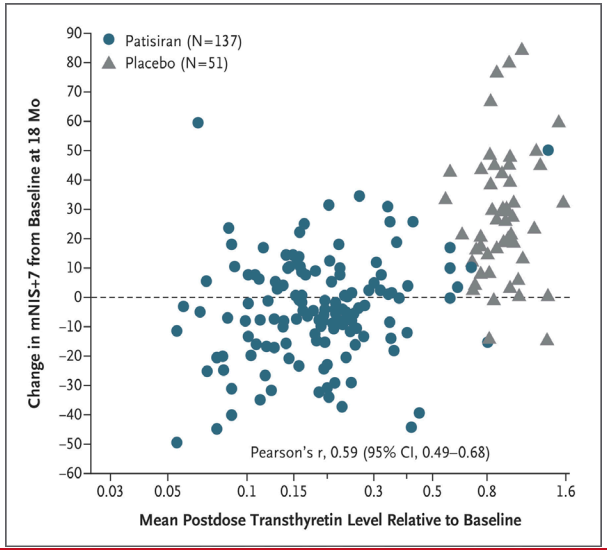
TTR Lowering Has Proven to Lead to Improved Clinical Outcomes in ATTR Amyloidosis

- In patients with ATTR-CM, vutrisiran, a *TTR* gene silencer, led to a lower risk of death and CV events[1]
  - Mean TTR reductions of ≈80% reached at 6 months
  - Mean (SD) absolute TTR levels were 50 (46) µg/mL
- Achieving the lowest possible level of amyloid precursor protein is likely to be important to maximally impact disease progression in ATTR-CM
  - Greater suppression in the amyloid precursor protein, in amyloid A protein (AA) and immunoglobulin light chain amyloidosis, is associated with better outcomes[2-4]
  - Deeper reductions in TTR levels have been correlated with increased clinical benefit in patients with ATTRv-PN[5]

Survival Based on Hematologic Response in AL Amyloidosis[4]



Correlation of Reduction in TTR Levels With Change in mNIS+7 From Baseline to 18 Months[5]

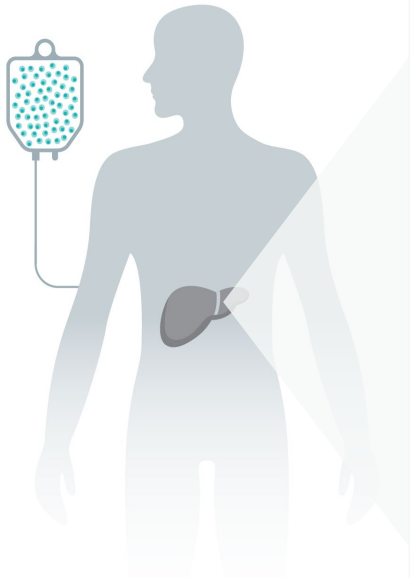


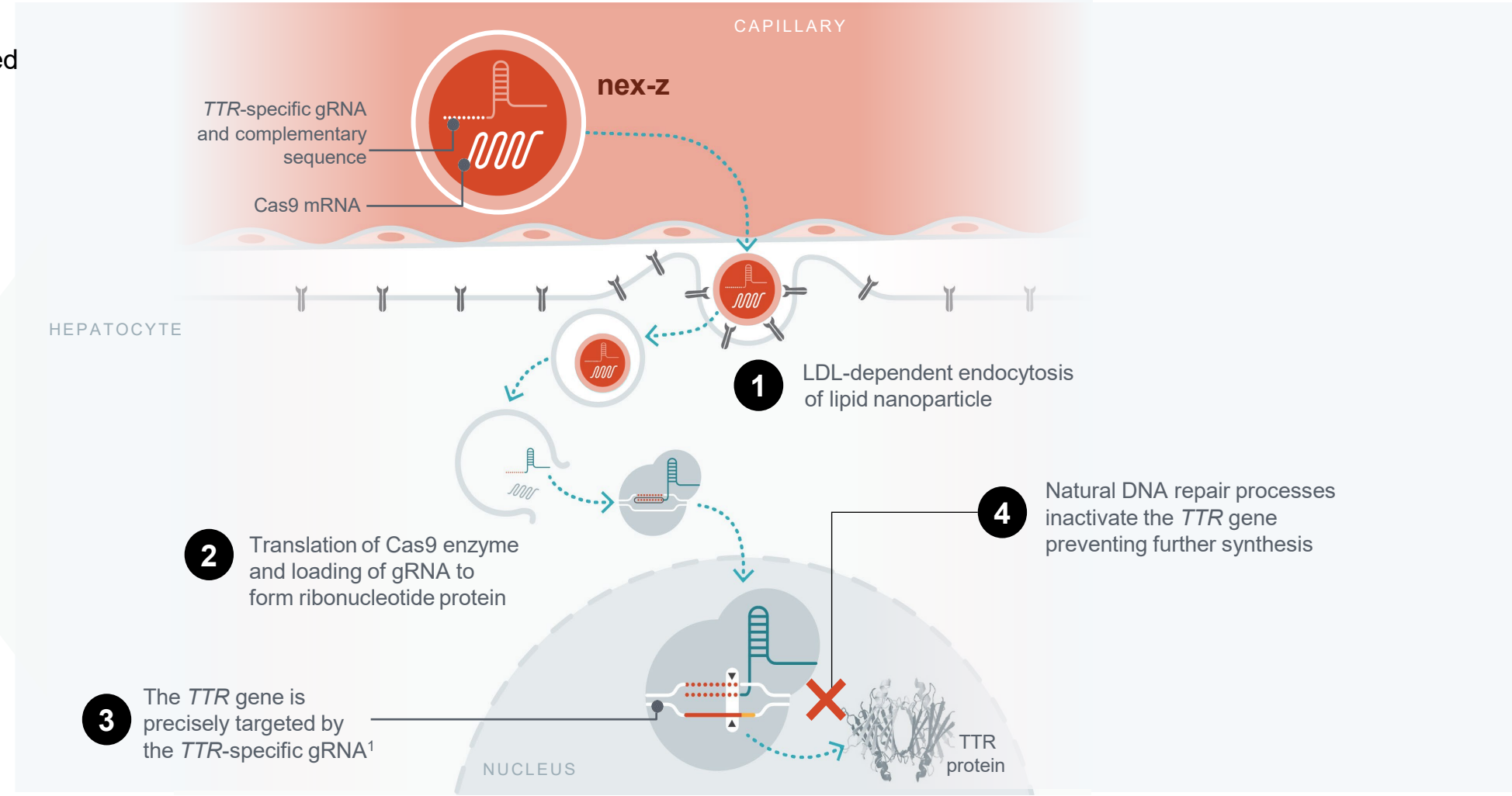
aCR, amyloid complete response; AL, immunoglobulin light chain; CM, cardiomyopathy; CV, cardiovascular; mNIS, modified Neuropathy Impairment Score; NR, no response; PR, partial response; PN, polyneuropathy; TTR, transthyretin; VGPR, very good partial response.

1. Fontana M, et al. *N Engl J Med.* 2024; DOI: 10.1056/NEJMoa2409134. 2. Gillmore JD, et al. *Lancet.* 2001;358(9275):24-29. 3. Lachmann HJ, et al. *Br J Haematol.* 2003;122(1):78-84. 4. Palladini G, et al. *J Clin Oncol.* 2012;30(36):4541-4549. 5. Adams D, et al. *N Engl J Med.* 2018;379(1):11-21.

Nex-z, an *In Vivo* Investigational CRISPR/Cas9 Therapy, Inactivates the *TTR* Gene, Whether Wild-Type or Variant, With a One-Time Treatment[1]

A one-time IV infusion delivered over 4 hours is used to administer nex-z, a CRISPR/Cas9 gene editing therapy[2]





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

1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Intellia Therapeutics. Data on file.

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

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I-III

Intervention:
Single dose administered via an IV infusion

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)**

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, cardiopulmonary exercise test, cardiac imaging, and KCCQ score*

Clinicaltrials.gov ID: NCT04601051

[a]NYHA class I-III and NT-proBNP >600 pg/mL (or, if patient has known diagnosis of atrial fibrillation, NT-proBNP >1000 pg/mL).
[b]Patients with non-ATTR amyloidosis or known leptomeningeal ATTR amyloidosis were excluded.
6MWT, 6-Minute Walk Test; 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.

Demographics and Baseline Characteristics

Characteristic	All patients (N=36)
Age, median (min, max), y	78.0 (46, 90)
Sex, male, n (%)	35 (97)
Black or African descent	8 (22)
White or Caucasian	28 (78)
NT-proBNP, median (min, max), ng/L	2052 (851, 19624)
hs-Troponin T, median (min, max), ng/L	56 (15, 204)
eGFR, median (min, max), mL/min/1.73 m^2	65.1 (32.7, 96.3)
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 (45, 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)

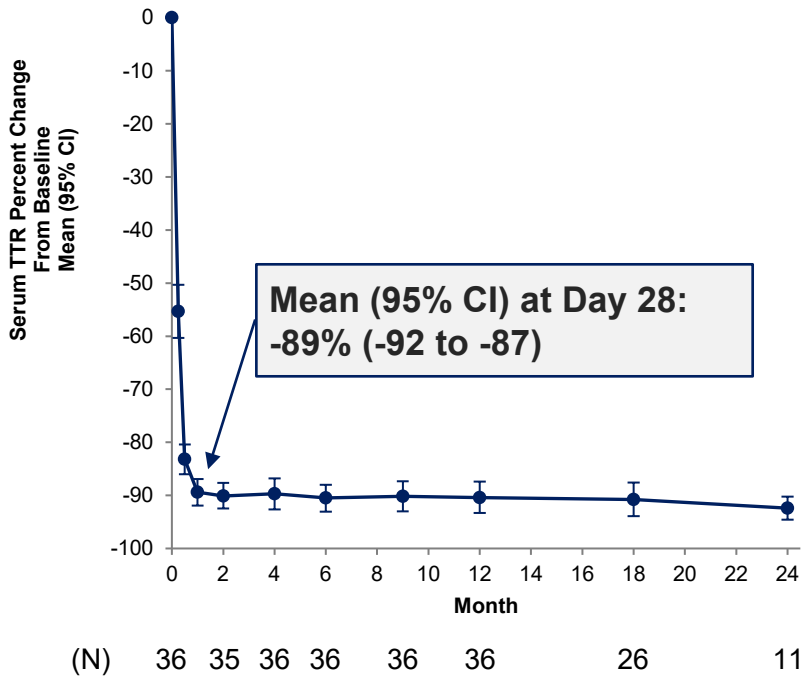
Population representative of ATTR-CM, including patients with advanced disease

Data cutoff August 21, 2024. Percentages may not total 100 because of rounding.
[a]Includes 2 homozygous patients.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; CMR, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin; VO_2, oxygen consumption.

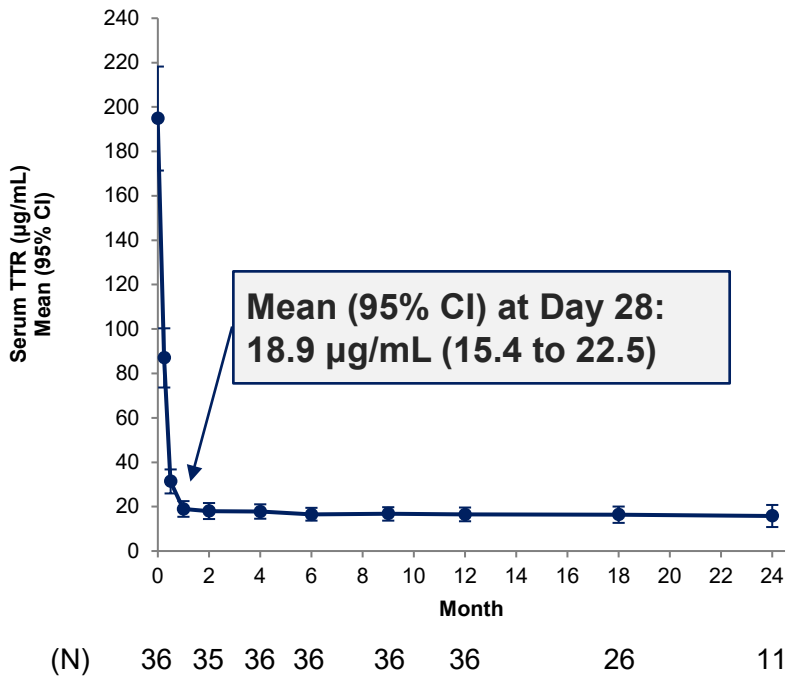
Nex-z Led to Deep, Rapid, and Durable Reductions in Absolute Serum TTR in Every Patient Following a Single Dose

Change in Serum TTR Levels Through Month 24

Percent Change From Baseline



Absolute Serum TTR



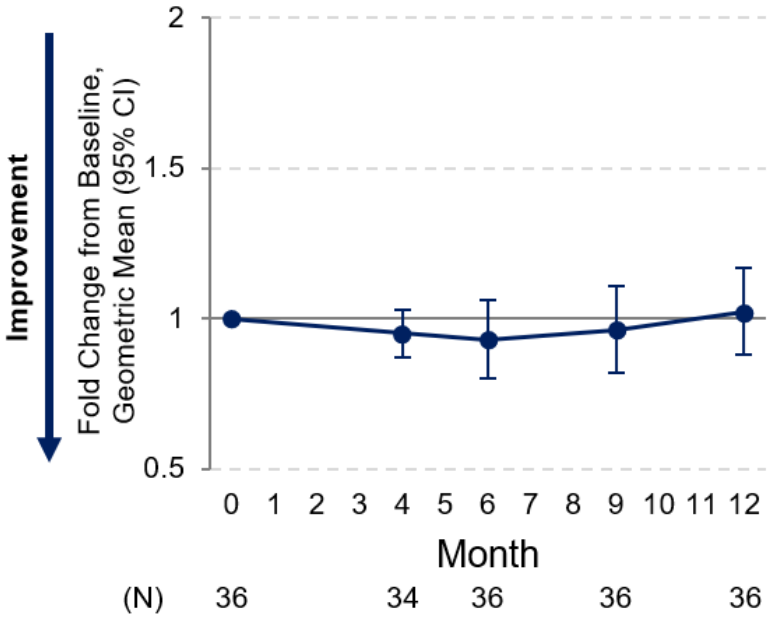
Similar serum TTR reductions were observed in every patient, regardless of baseline TTR level or genotype.
Mean absolute serum levels of 18.9 µg/mL achieved at Day 28, with levels remaining virtually unchanged through 24 months.

Data cutoff August 21, 2024.
TTR, transthyretin.

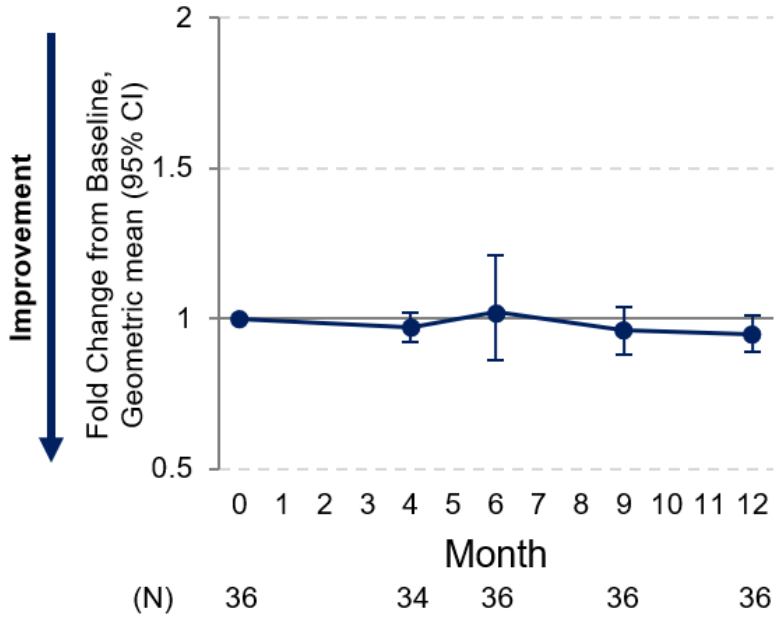
Nex-z Treatment Led to Stability of NT-proBNP, hs-Troponin T, and 6MWT Over 12 Months

Markers of Disease Progression[1]

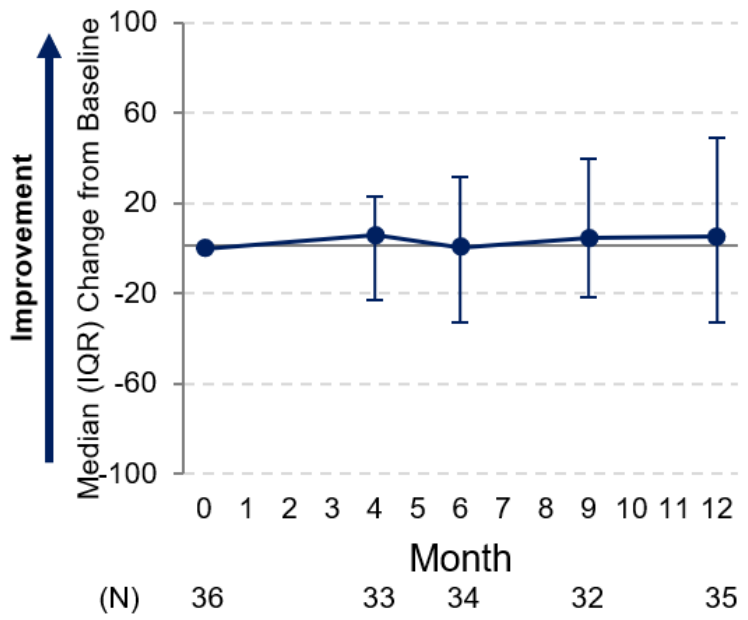
NT-proBNP



hs-Troponin T

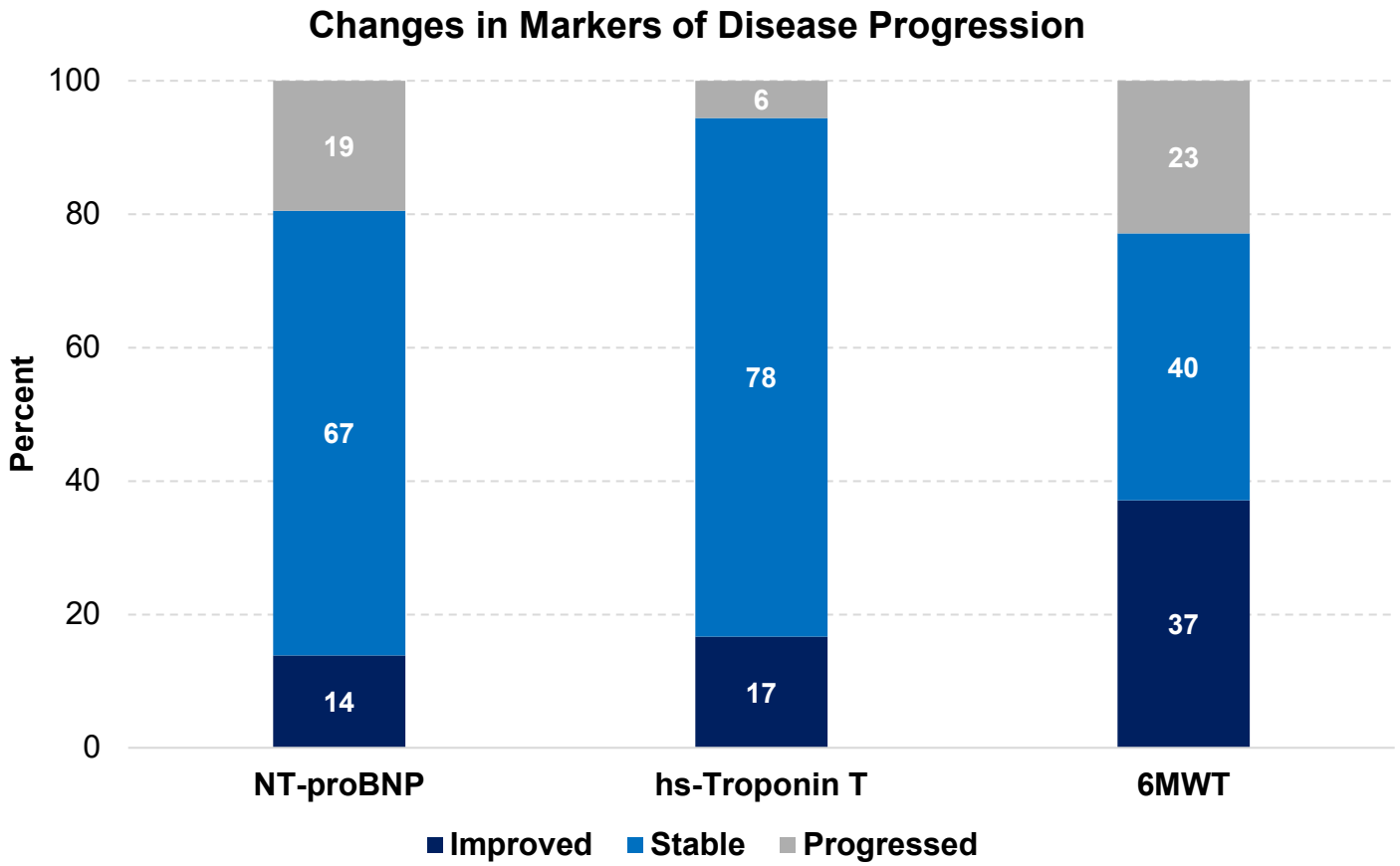


6MWT Distance (meters)



Data cutoff August 21, 2024.
6MWT, 6-Minute Walk Test; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
1. Ioannou A. et al. *J Am Coll Cardiol*. 2024;83(14):1276-1291.

Nearly 80% of Patients Demonstrated Stability or Improvement in Markers of Disease Progression



Disease Progression Criteria[1,2]:

- NT-proBNP: an increase of >700 ng/L and >30%
- hs-Troponin T: an increase of >10 ng/mL and >20%
- 6MWT: an absolute reduction of >35 m in 6MWT distance

Improvement was defined as the equivalent counter criteria

83% of NYHA class I/II patients and 47% of NYHA class III patients had no worsening in any marker at 12 months

Data cutoff August 21, 2024. Percentages may not total 100 because of rounding.
6MWT, 6-Minute Walk Test; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
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.

Evidence of Stability or Improvement in Symptoms and QOL in Most Patients Following nex-z Treatment

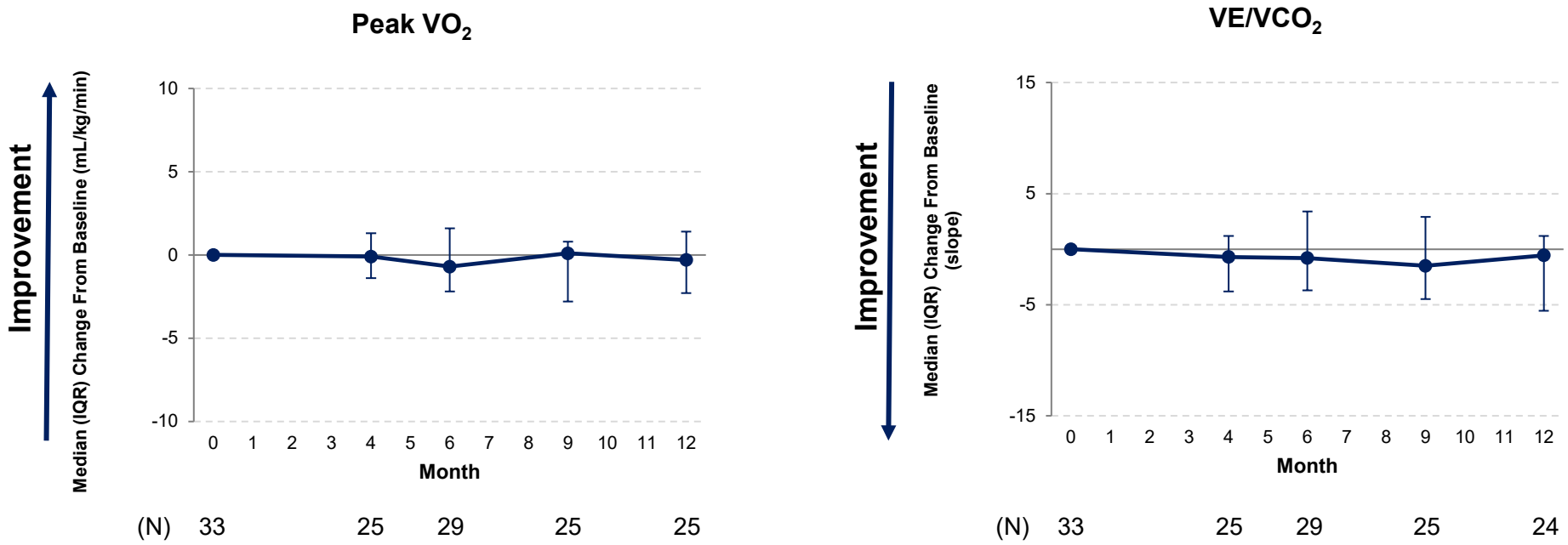
Endpoint	Overall (N=36)	NYHA Class I/II (N=18)	NYHA Class III (N=18)
KCCQ Overall Score at month 12			
Median change (IQR)	7.8 (-0.5, 15.4)	5.2 (-3.6, 10.9)	9.0 (0.8, 18.8)
Change in NYHA Class at month 12[a]			
Improved, n (%)	17 (47)	4 (22)	13 (72)
No change, n (%)	16 (44)	11 (61)	5 (28)
Worsened, n (%)	3 (8)	3 (17)	0 (0)

92% of patients demonstrated either no change or improvement in NYHA Class at 12 months including improvement in 72% of patients with NYHA Class III

[a]Values represent a change of at least one level in NYHA class.
IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; QOL, quality of life.

Functional Capacity Remained Stable Through 12 Months Following nex-z Treatment

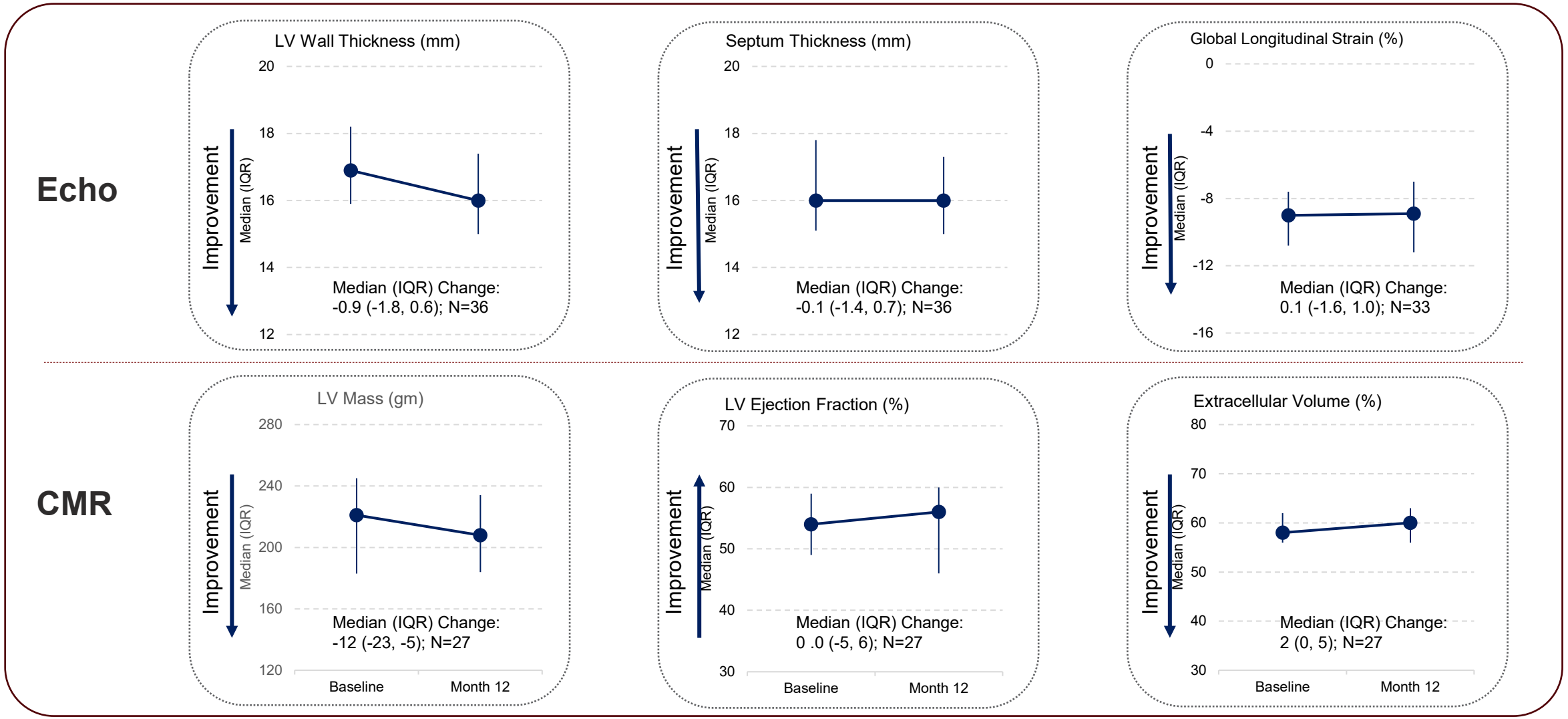
Cardiopulmonary Exercise Test



Peak VO_2 and VE/VCO_2 slope are strong prognostic markers[1] and deteriorate rapidly in ATTR-CM[2]

Data cutoff August 21, 2024.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; IQR, interquartile range; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.
1. Patel RK, et al. *JAMA Cardiol*. 2024;9(4):367-376. 2. Argirò A, et al. *Can J Cardiol*. 2024;40(3):364-369.

Imaging Assessments of Cardiac Remodeling Showed a Similar Pattern of Stability Following nex-z Treatment



Data cutoff August 21, 2024.
CMR, cardiac magnetic resonance imaging; IQR, interquartile range; LV, left ventricular.

Summary of Safety

Event	n (%)
At least one AE	34 (94)
AEs occurring in ≥15% of patients	
Cardiac failure	13 (36)
COVID-19	7 (19)
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 event leading to death[a]	1 (3)

Event	n (%)
Any SAE	14 (39)
SAEs occurring in ≥5% of patients	
Cardiac failure	5 (14)
Acute myocardial infarction	3 (8)
Urinary tract infection	3 (8)
Atrial flutter	2 (6)
Pneumonia	2 (6)
SAEs of heart failure or arrhythmia	7 (19)
Cardiac failure	5 (14)
Arrhythmia[b]	3 (8)
CV hospitalization rate[c] (n/pt/yr, 95% CI)	0.16 (0.08 to 0.36)

Data cutoff August 21, 2024. Median (min, max) follow-up for safety was 18 months (12, 27). For each preferred term, subjects reporting more than one adverse event are counted only once.
Liver enzyme elevations were transient, generally mild, and not indicative of liver injury. [a]Only one death occurred (ischemic heart disease) on Day 506 after dosing; unrelated to treatment.
[b]Arrhythmia events included SAEs of atrial flutter and atrioventricular block complete, with one patient experiencing both cardiac failure and arrhythmia on the same day. [c]Includes hospitalizations for cardiac failure, arrhythmia, or stroke. AE, adverse event; CV, cardiovascular; SAE, serious AE.

Summary

- A single dose of nex-z demonstrated favorable safety and tolerability and resulted in deep, rapid, and durable reductions in serum TTR with very low variability among all patients in the study

- Reductions in TTR were accompanied by stability or improvement of several disease markers in an ATTR-CM population with advanced disease who are expected to have rapid disease progression and high mortality rates

- The effects of nex-z observed in this ongoing phase 1, single arm, open-label study will need to be confirmed in randomized controlled trials

ATTR-CM, ATTR amyloidosis with cardiomyopathy; TTR, transthyretin.

Conclusions

- These results represent the first clinical evidence of *in vivo* CRISPR/Cas9 gene editing in cardiomyopathy showing that targeted inactivation of the *TTR* gene may favorably impact disease progression in ATTR-CM

- These results also support the hypothesis that rapid, deep, and durable reductions in serum TTR result in meaningful clinical benefits

- The effects of nex-z on clinical outcomes are being evaluated in MAGNITUDE[a], a phase 3, global, randomized, placebo-controlled trial in patients with ATTR-CM

[a]NCT06128629.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9; TTR, transthyretin.

Acknowledgments

- We wish to extend our gratitude to the patients, their caregivers, and their families, study site coordinators, and staff

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy

Marianna Fontana, M.D., Ph.D., Scott D. Solomon, M.D., Jessica Kachadourian, Pharm.D., Liron Walsh, M.D., Ricardo Rocha, M.D., David Lebwohl, M.D., Derek Smith, M.S., Jörg Täubel, M.D., Edward J. Gane, M.B., Ch.B., Björn Pilebro, M.D., David Adams, M.D., Ph.D., Yousuf Razvi, M.B., Ch.B., Joy Olbertz, Ph.D., Pharm.D., Alexandra Haagensen, M.D., Peijuan Zhu, Ph.D., Yuanxin Xu, M.D., Ph.D., Adia Leung, M.S., Alison Sonderfan, M.S., R.D., David E. Gutstein, M.D., and Julian D. Gillmore, M.D., Ph.D.

THANK YOU

Scientific Sessions

American Heart Association. 100 YEARS Bold Hearts

#AHA24

Agenda

Welcome

Introduction
Dr. John Leonard *Chief Executive Officer*, Intellia Therapeutics

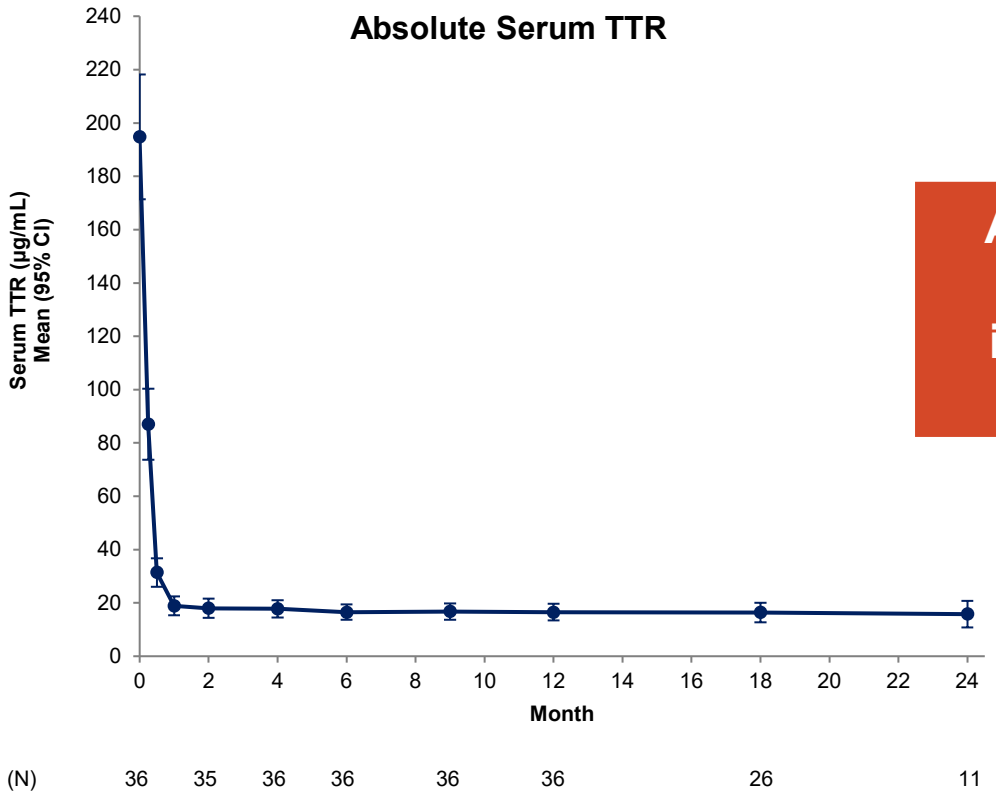
ATTR-CM Phase 1 Data Update
Dr. Marianna Fontana *Professor of Cardiology and Honorary Consultant Cardiologist at the National Amyloidosis Centre, Division of Medicine,* University College London

Nex-z Clinical Development Summary
Dr. David Lebwohl *Chief Medical Officer*, Intellia Therapeutics

Q&A Session

Intellia THERAPEUTICS

Rapid, Deep and Durable TTR Reduction in All Patients Was Associated with Stability or Improvement in Markers of Cardiac Disease Progression



Associated with stability or improvement at month 12

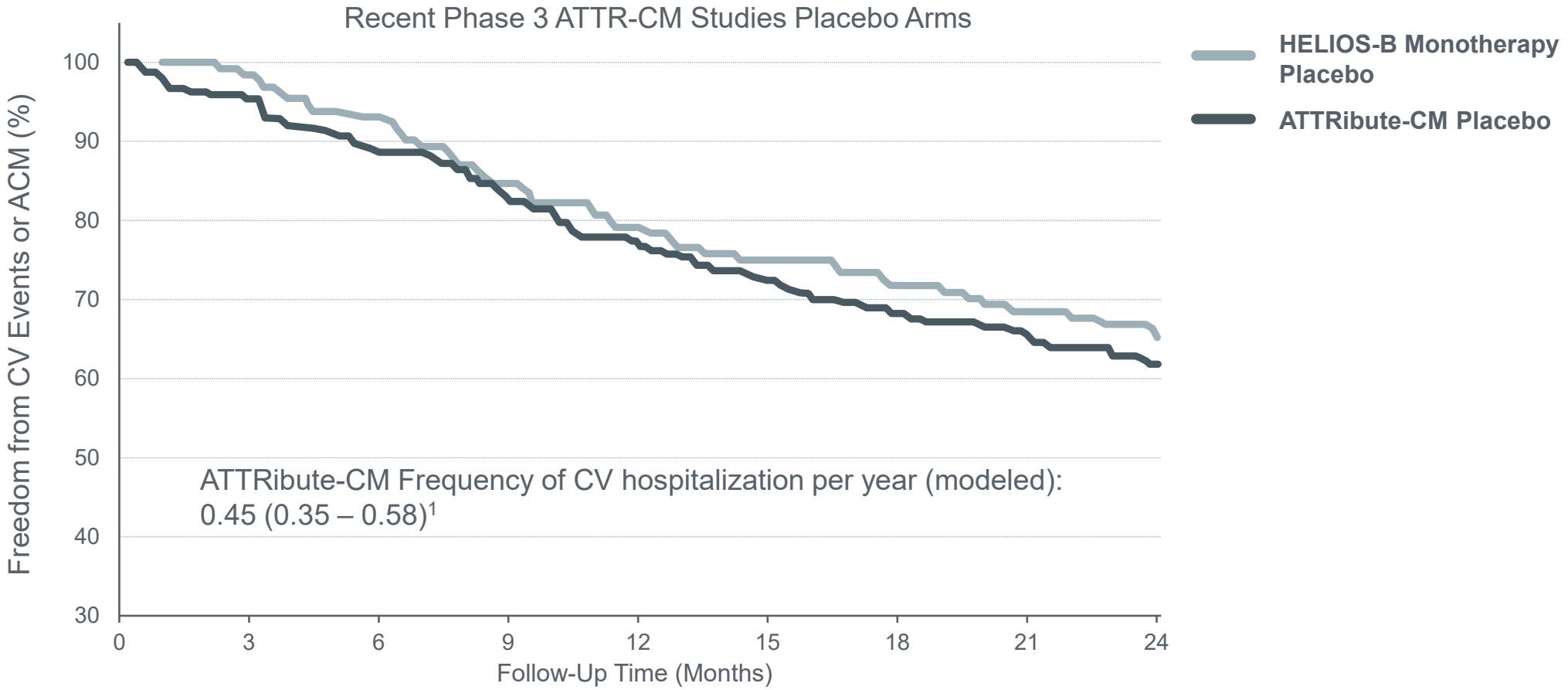
- NT-proBNP
- hs-Troponin T
- 6MWT
- KCCQ
- Cardiac Structure and Function

NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-Troponin T, high sensitivity troponin test; 6MWT, 6-Minute Walk Test; KCCQ, Kansas City Cardiomyopathy Questionnaire
Data cutoff August 21, 2024

REGENERON Intellia THERAPEUTICS

Time to First Cardiovascular (CV)-Related Hospitalization or All-Cause Mortality in Recent Phase 3 ATTR-CM Studies

Placebo patients experienced rapid disease progression and a high rate of CV events

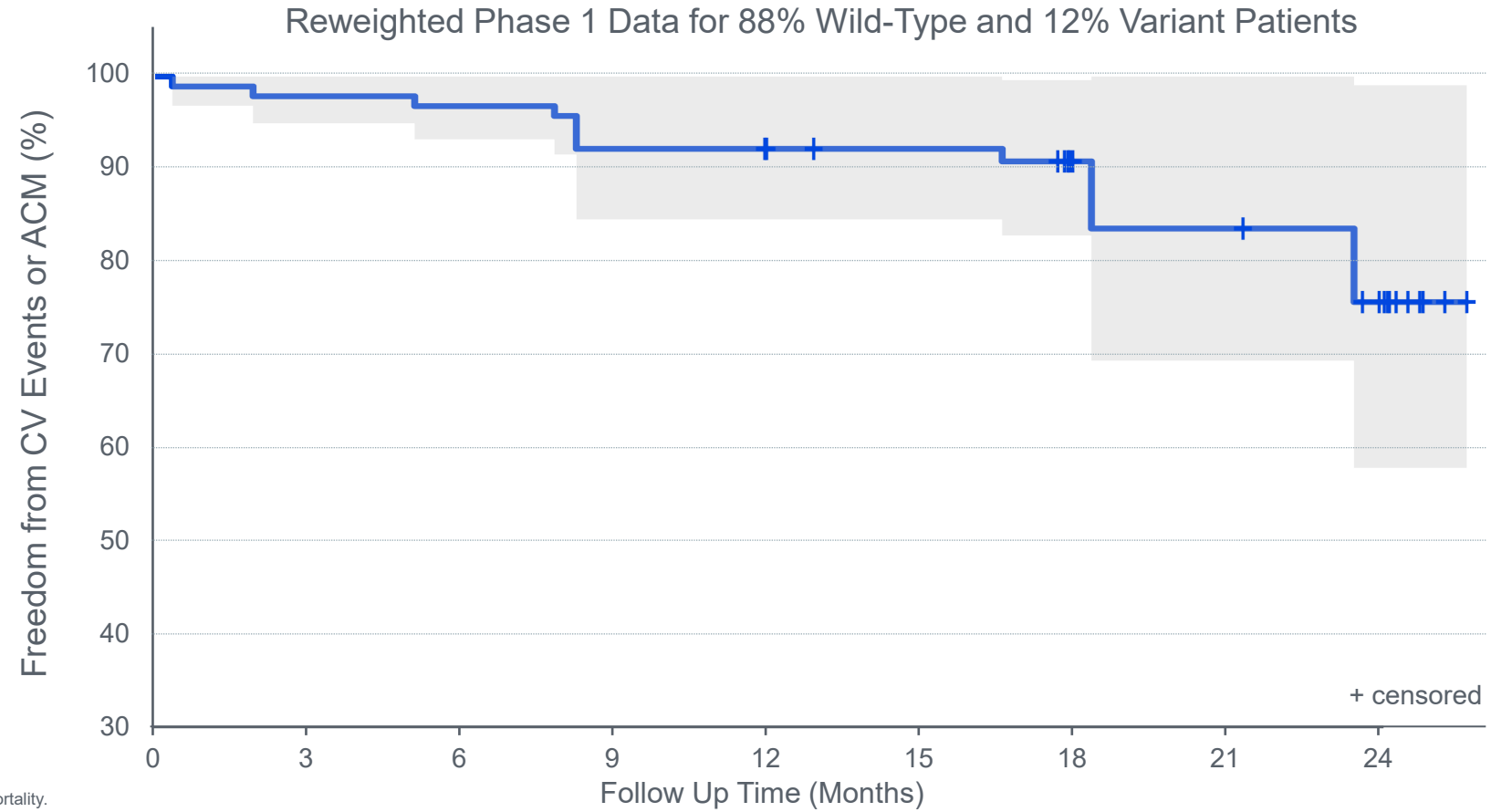


[1]Judge DP, Cappelli F, Fontana M, et al. Acoramidis Improves Clinical Outcomes In Transthyretin Amyloid Cardiomyopathy. Presented at: American Heart Association Scientific Sessions 2023; November 10 - 13; Philadelphia, PA. Accessed November 16, 2023.
Figure is generated from data digitized from Fontana M, et. al. N Engl J Med 2024; 390(10):1023-1033 and Gillmore J., et. al. NEJM 2024 DOI: 10.1056/NEJMoa2305434
This figure reflects third party information regarding distinct clinical trials with their own enrollment criteria and methodology. Cross-trial comparisons have inherent limitations and should be interpreted with caution.

REGENERON Intellia THERAPEUTICS

Favorable Time to First CV Event* and Biomarker Data in Nex-z Phase 1 Trial Supports MAGNITUDE Phase 3 Trial Design

Frequency of CV hospitalization† in nex-z Phase 1: 0.16 events/pt/yr (95% CI: 0.08 to 0.36) for a population that includes 31% Variant Patients

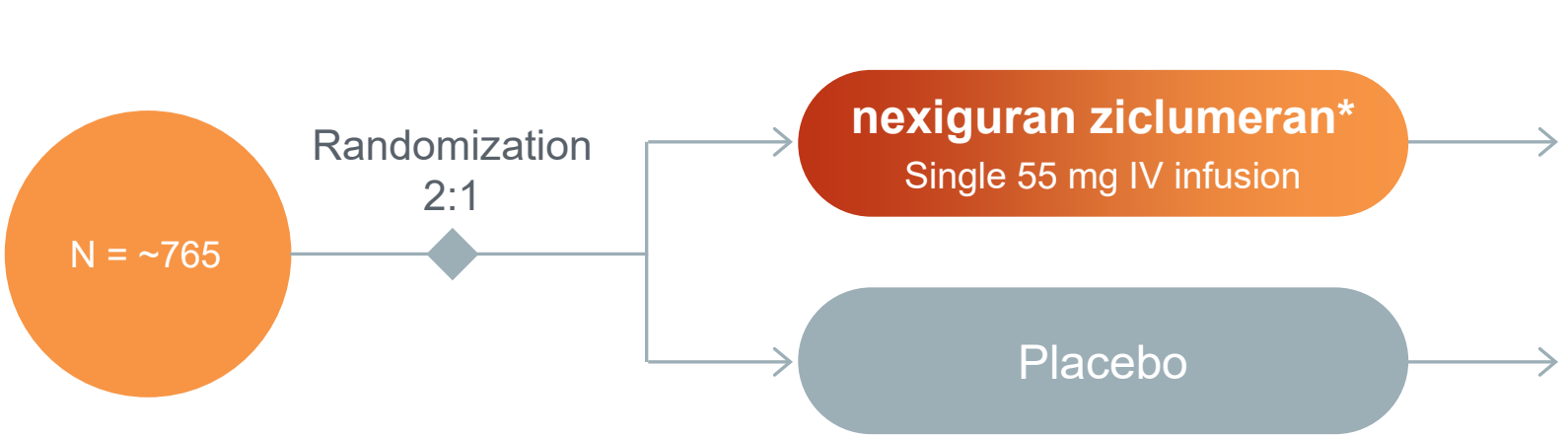


*CV event includes CV hospitalization or mortality.
Only one death occurred (ischemic heart disease) on day 506 after dosing; unrelated to treatment.
†CV hospitalization events include hospitalizations for heart failure, arrhythmia or stroke.
Figure above is a Kaplan Meier plot of the time to first CV event or death based on interim nex-z Phase 1 data for patients with ATTR-CM reweighted to match the genotype distribution from HELIOS-B
Limitations of this analysis include a small sample size, limited duration of observation period, single center for enrollment and based on serious adverse event reports
CV, cardiovascular; ACM, All-Cause Mortality; pt, patient.
Data cutoff August 21, 2024.

REGENERON Intellia THERAPEUTICS

MAGNITUDE
CLINICAL TRIAL

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate NTLA-2001 (nexiguran ziclumeran*) in Patients with ATTR Amyloidosis with Cardiomyopathy (ATTR-CM)



Primary Endpoint

- Composite endpoint of CV-related mortality and CV-related events

Key Secondary Endpoints

- Serum TTR
- KCCQ-OS score

Key Eligibility Criteria:

- Adult patients with diagnosis of either hereditary or wild-type ATTR-CM
- NYHA Class I – III
- NT-proBNP baseline ≥ 1000 pg/mL

Stratification:

- NAC stage
- TTR genotype: wild-type vs. mutant
- Concomitant tafamidis use vs. no tafamidis

Study Duration:

- Dependent on occurrence of pre-specified number of CV events and a minimum of 18 months follow-up
- Majority of patients are expected to have ≥ 30 months of follow-up for the primary analysis

Clinicaltrials.gov ID: NCT06128629
* nexiguran ziclumeran (nex-z, also known as NTLA-2001); NYHA, New York Heart Association; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary

REGENERON Intellia THERAPEUTICS

Nex-z Phase 1 Data Update in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (ATTRv-PN)

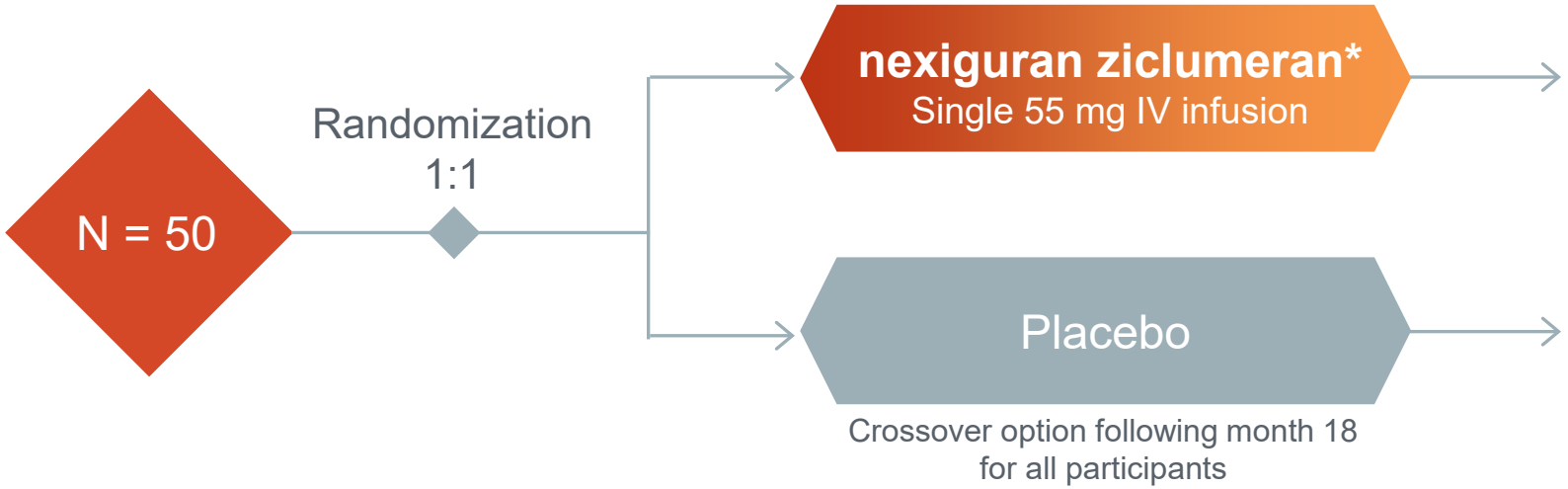
- Similar to ATTR-CM, a single dose of nex-z resulted in deep, rapid and durable reductions in serum TTR with very low variability among the ATTRv-PN patients in the study
- Reductions in TTR were accompanied by evidence of disease stabilization or improvement based on multiple clinical measures, including change in NIS, mNIS+7 and mBMI compared to baseline
  - Natural history of the disease shows progressive neurologic impairment
  - The cohort studied (n=36) included patients with early-stage disease and a subset of patients with severe neurological impairment who were previously treated with patisiran
- Favorable safety and tolerability observed to date
- Results support hypothesis that rapid, deep and durable reductions in serum TTR result in meaningful clinical benefits, which will be evaluated in MAGNITUDE-2 Phase 3 study

NIS, neurologic impairment score; mNIS+7, modified neurologic impairment; mBMI, modified body mass index
Refer to the appendix for the interim nex-z Phase 1 update for ATTRv-PN
Data cutoff August 21, 2024

REGENERON Intellia THERAPEUTICS

MAGNITUDE-2
CLINICAL TRIAL

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate NTLA-2001 (nexiguran ziclumeran*) in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (ATTRv-PN)



Primary Endpoints

- Change from baseline in mNIS+7 at month 18 and serum TTR at day 29

Key Secondary Endpoints

- Change from baseline in Norfolk QOL-DN, mBMI and serum TTR and absolute serum TTR at month 18

Key Eligibility Criteria:

- Adult patients with diagnosis of ATTRv-PN
- NIS 10 – 130
- PND score of ≤ 3B
- Naïve to silencers; washout of stabilizers

Stratification:

- NIS score <50 vs. ≥ 50
- *TTR* genotype: early onset V30M vs others

Study Duration:

- All patients have completed the month 18 visit

Clinicaltrials.gov ID: NCT06672237
* nexiguran ziclumeran (nex-z, also known as NTLA-2001); NIS, neurologic impairment score; mNIS+7, modified neurologic impairment; mBMI, modified Body Mass Index; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability

REGENERON Intellia THERAPEUTICS

Nex-z Clinical Development Plan and Next Steps

PHASE 1 → **PHASE 3** → ★

Key Findings from Ongoing Study

- ✓ Consistently rapid, deep and durable TTR reduction
- ✓ Evidence of stabilization or improvement in markers of disease progression for ATTR-CM and ATTRv-PN
  - Including ATTR-CM patients with advanced heart failure
  - Including ATTRv-PN patients with early-stage disease and a subset previously treated with patisiran
- ✓ Favorable safety and tolerability observed

MAGNITUDE CLINICAL TRIAL

MAGNITUDE-2 CLINICAL TRIAL

- Actively enrolling both ATTR-CM and ATTRv-PN pivotal trials

Potential to launch best-in-class TTR reduction agent and only single-dose treatment

REGENERON Intellia THERAPEUTICS

Q&A

Dr. John Leonard *Chief Executive Officer*, Intellia Therapeutics

Dr. Marianna Fontana *Professor of Cardiology and Honorary Consultant Cardiologist at the National Amyloidosis Centre, Division of Medicine,* University College London

Dr. David Lebwohl *Chief Medical Officer*, Intellia Therapeutics

Dr. Liron Walsh *Head of Development,* In Vivo *Programs,* Intellia Therapeutics

REGENERON Intellia THERAPEUTICS

Intellia

THERAPEUTICS

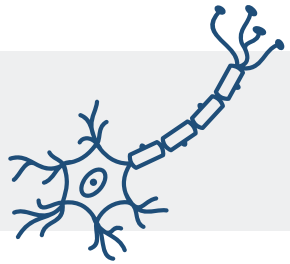
Appendix

ATTRv-PN Phase 1 Update

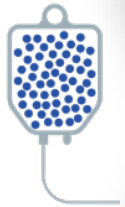
Intellia THERAPEUTICS

Nex-z Phase 1 Study in Adults with Hereditary ATTR Amyloidosis with Polyneuropathy (ATTRv-PN)

Two-part, open-label, multicenter study in adults with ATTRv-PN



INTERVENTION
Single-dose administered via an intravenous (IV) infusion



PART I: Single-Ascending Dose

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

N=15

PART II: Dose Expansion

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

N=21

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

- *Neurologic function in subjects with ATTRv-PN*

Clinicaltrials.gov ID: NCT04601051
Nex-z , nexiguran ziclumeran; PD, pharmacodynamics; PK, pharmacokinetics

REGENERON Intellia THERAPEUTICS

Demographics and Baseline Characteristics

Characteristic		PN Patients (N=36)
Age, years	Median (min, max)	61 (19, 75)
Sex, n (%)	Male	26 (72)
***TTR* genotype, n (%)**	p.V50M p.V142I p.T80A p.S97Y p.E62D Other WT	11 (31) 1 (3) 7 (19) 7 (19) 4 (11) 6 (17) 0
mBMI (kg/m2 x g/L)[1]	Mean (SD)	1174 (219.7)
NIS	Mean (SD)	Part 1 (N=15): 17 (16.7)
mNIS+7	Mean (SD)	Part 2 (N=21): 47 (33.3)
Prior exposure to patisiran mNIS+7[2]	Mean (SD)	Part 2 (N=6): 80 (17.2)

[1] mBMI, modified body mass index (BMI), is calculated as BMI (kg/m2) x albumin (g/L).
[2] Per protocol, in Part 2, up to 6 subjects with progression of ATTRv-PN symptoms despite treatment with TTR-lowering therapy were able to be dosed with NTLA-2001.
mNIS+7, modified Neurologic Impairment Score; NIS, neurologic impairment score; PN, polyneuropathy; TTR, transthyretin.
Data cutoff August 21, 2024.

REGENERON Intellia THERAPEUTICS

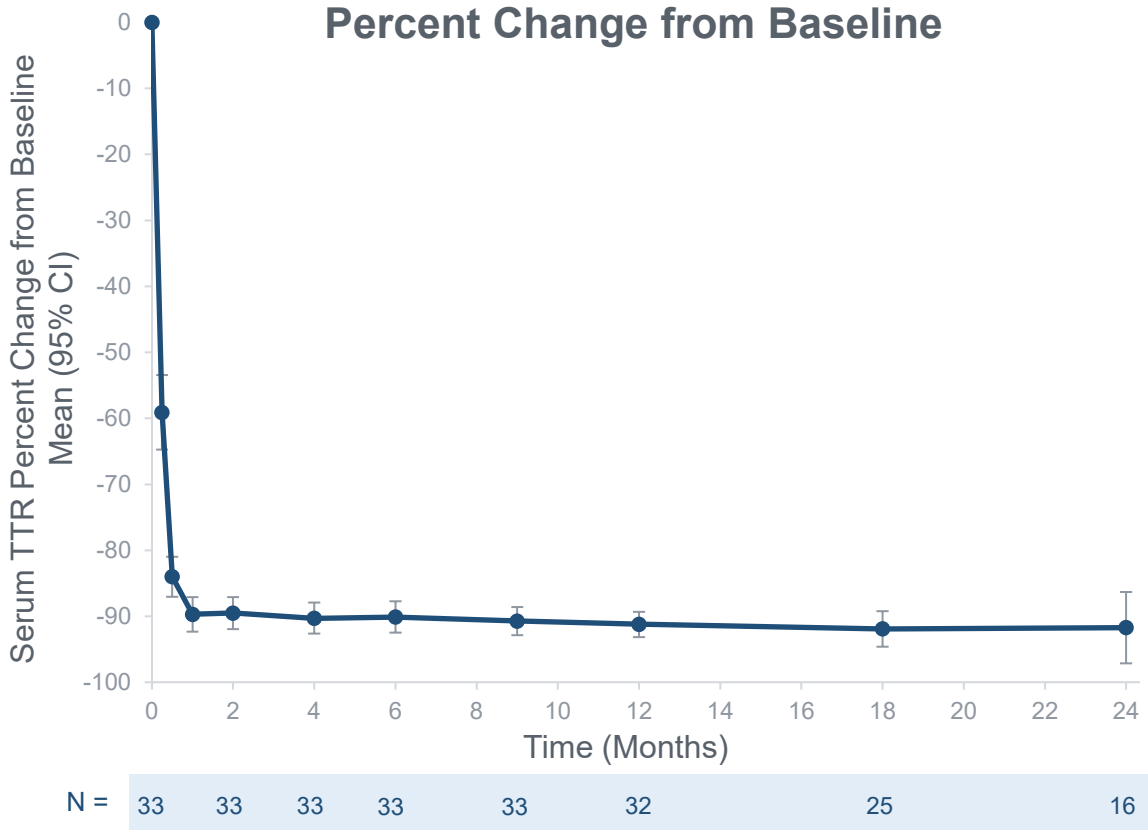
Summary of Safety

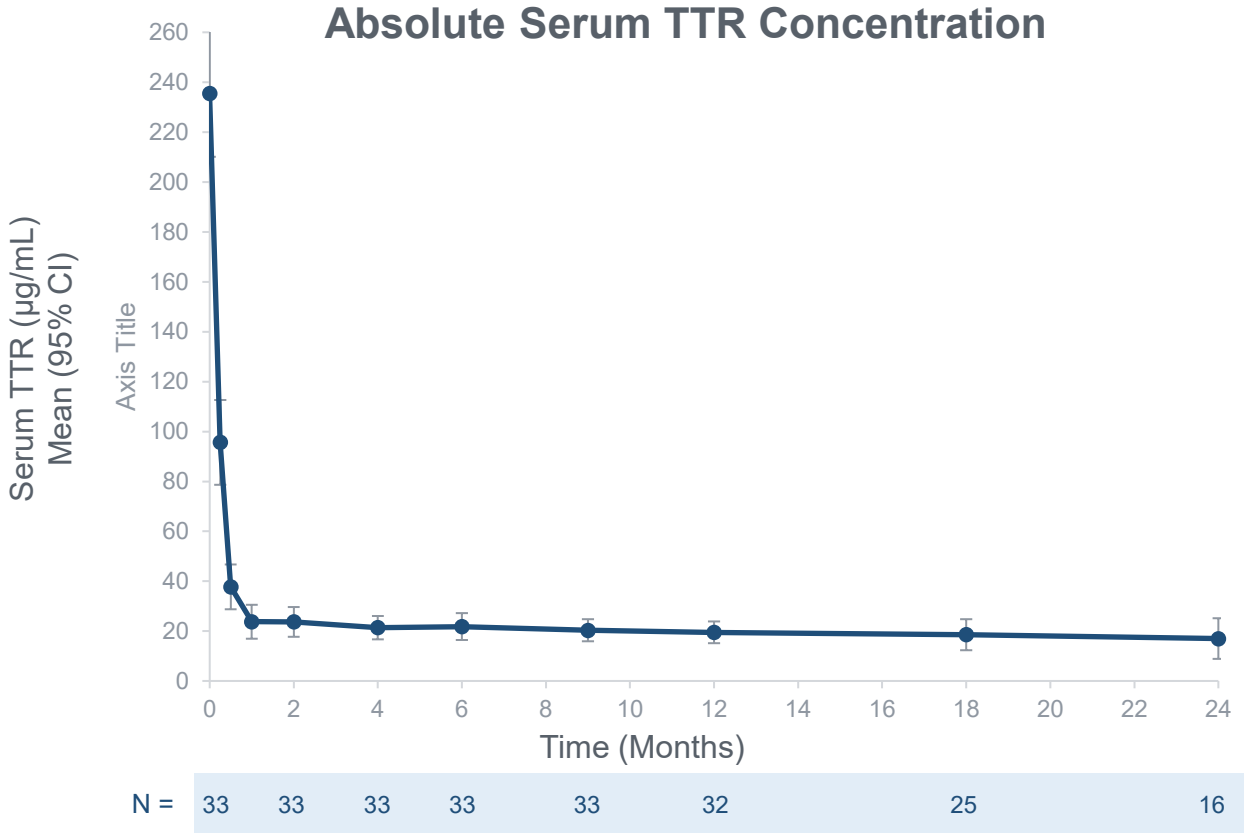
Event	n (%)
At least one AE	36 (100%)
AEs occurring in ≥ 15% of patients	
Infusion related reaction	21 (58%)
Headache	10 (28%)
Diarrhea	8 (22%)
Thyroxine decreased	8 (22%)
TRAE in ≥ 10%	
Infusion related reaction	21 (58%)
Thyroxine decreased	8 (22%)
Headache	4 (11%)
Any AE leading to treatment discontinuation	0
Any AE leading to death*	1 (3%)
Any SAE	10 (28%)
SAEs occurring in ≥ 5% of patients	0

Median (min, max) follow-up for safety was 24 months (9, 38)
* Death due to ATTR cardiomyopathy on day 273 in a patient with a medical history of ventricular tachycardia; imaging consistent with coronary atherosclerosis; unrelated to treatment
Data cutoff August 21, 2024. Adverse events are presented by preferred term and were coded using MedDRA, version 26.0.
For each preferred term, subjects reporting more than one adverse event are counted only once.
AE, Adverse Event; MedDRA, Medical Dictionary for Regulatory Activities; TRAE, treatment-related adverse event; SAE, serious adverse event

REGENERON Intellia THERAPEUTICS

Nex-z Led to Deep, Rapid and Durable Reductions in Absolute Serum TTR in Every Patient Following a Single Dose in ATTRv-PN





		Day 28	Month 12
Mean (95% CI) Serum TTR	Residual absolute TTR concentration	23.8 µg/mL (17.0 to 30.5)	19.5 µg/mL (15.2, 23.9)
	% Change from baseline in serum TTR	-90% (-92 to -87)	-91% (-93 to -89)

Figure notes: Data presented excludes the 0.1 mg/kg cohort. The three patients in the 0.1 mg/kg cohort have been re-dosed at 55 mg.
Data cutoff August 21, 2024

REGENERON Intellia THERAPEUTICS

Favorable Trends Observed Across Multiple Clinical Measures Indicating Stability or Improvement in Neuropathy

Clinical Measure	Baseline, Mean (SD)	Change from Baseline at Month 12, Mean (SD)	Change from Baseline at Month 24, Mean (SD)
Part 1: Dose-escalation portion (N=15)			
NIS	17 (16.7)	-1.9* (5.42)	-4.5 (7.40)
mBMI (kg/m2 x g/L)[1]	1217.9 (140.81)	28.2 (93.07)	54.7 (84.58)
Part 2: Dose-expansion portion (N=21)			
mNIS+7	47 (33.3)	-0.6† (11.07)	N/A
Prior exposure to patisiran mNIS+7[2] (n=6)	80 (17.2)	-6.3 (11.62)	N/A
mBMI (kg/m2 x g/L)[1]	1141.9 (260.93)	2.4‡ (94.18)	N/A

*n=14, †n=19, ‡n=20, N/A: Data for this time point is not yet available for the full cohort and will be reported in the future.
mNIS+7; modified Neurologic Impairment Score, NIS; Neurologic Impairment Score, mBMI; modified body mass index, SD; standard deviation
[1] mBMI is calculated as BMI (kg/m2) x albumin (g/L).
[2] Per protocol, in Part 2, up to 6 subjects with progression of ATTRv-PN symptoms despite treatment with TTR-lowering therapy were able to be dosed with NTLA-2001.
Data cutoff August 21, 2024

REGENERON Intellia THERAPEUTICS

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REGENERON Intellia THERAPEUTICS