# Intellia Therapeutics

## Corporate Overview

August 2026

**KIM**
Living with Hereditary Angioedema

# Intellia Therapeutics' Legal Disclaimer

This presentation contains "forward-looking statements" of Intellia Therapeutics, Inc. ("Intellia", "we" or "our") within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, express or implied statements about Intellia's beliefs and expectations regarding: our ability to successfully develop and commercialize nexiguran ziclumeran ("nex-z"), previously referred to as NTLA-2001, for the treatment of transthyretin ("ATTR") amyloidosis and lonvoguran ziclumeran ("lonvo-z"), previously referred to as NTLA-2002, for the treatment of hereditary angioedema ("HAE") to address the significant unmet needs of patients and prescribers in ATTR amyloidosis and HAE, respectively; our ability to achieve upcoming objectives, including the acceptance of our biologics license application for lonvo-z for the treatment of HAE in the second half of 2026, successfully launching lonvo-z for the treatment of HAE following approval in the U.S. in the first half of 2027, scaling field sales and reimbursement teams for lonvo-z, finalize pricing for lonvo-z, finalizing price and contracting strategy for lonvo-z, and completing enrollment in MAGNITUDE-2 in the second half of 2026; our ability to optimize the impact of our collaborations on our development programs, including our collaboration with Regeneron Pharmaceuticals, Inc. ("Regeneron") and our co-development program for ATTR amyloidosis, and to advance additional development candidates; our expectations regarding our uses of capital, expenses, and ability to fund operations at least into 2028; the potential commercial opportunities for our product candidates, including the value and market potential for our product candidates, including the potential of nex-z and lonvo-z to be single-dose treatments administered in an outpatient setting, the potential of nex-z to transform the standard of care for ATTR amyloidosis, provide patients with consistently rapid, deep and durable TTR reduction, stability or improvement in the disease for most patients, improved quality of life, and reduced cardiovascular events and mortality, and represent a meaningful opportunity for significant revenues and healthcare system savings, and the potential of lonvo-z to eliminate HAE attacks and burdensome ongoing therapy for most patients; and our ability to leverage our CRISPR gene editing and other core technologies for pipeline expansion efforts and collaborations.

Any forward-looking statements in this presentation are based on management's current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: risks related to our ability to successfully develop and commercialize lonvo-z, nex-z, or any of our other product candidates; risks related to Intellia's ability to protect and maintain its intellectual property position; risks related to Intellia's relationship with third parties, including our contract manufacturers, licensors and licensees; risks related to the ability of our licensors to protect and maintain their intellectual property position; uncertainties related to the authorization, initiation and conduct of preclinical and clinical studies and other development requirements for our product candidates, including uncertainties related to regulatory approvals to conduct clinical trials; risks related to the results of preclinical studies or clinical studies not being predictive of future results in connection with future studies; the risk that clinical trial results will not be positive; risks related to the development and advancement of CRISPR gene editing and other core technologies technologies for pipeline expansion and collaborations; risks related to Intellia's future financial condition and our ability to fund our operations; risks related to Intellia's collaborations with Regeneron or our other collaborations not continuing or not being successful; and risks related to Intellia's ability to execute its strategic plans, including completing pivotal clinical trials and commercial launch of its product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause Intellia's actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in Intellia's most recent Annual Report of Form 10-K and Quarterly Report on Form 10-Q as well as discussions of potential risks, uncertainties, and other important factors in Intellia's other filings with the Securities and Exchange Commission. All information in this presentation is as of the date on its cover page, and Intellia undertakes no duty to update this information unless required by law.

# Our Vision: Leveraging CRISPR Gene Editing and Other Core Technologies to Transform the Lives of Patients

Treat patients at the **root cause of their disease**

**Single dose** treatment with potential **lifelong benefit**

**Reduce burden** for the patient **and** the healthcare system

**Best outcomes** for patients



CRISPR: clustered regularly interspaced short palindromic repeats

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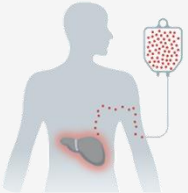
# Intellia is Leading a New Era of Medicine

Working diligently to bring the **first-ever *in vivo* CRISPR-based therapies** to patients living with severe diseases

**1st** **Positive Phase 3 Readout**
in hereditary angioedema (HAE)

**2** **Additional Phase 3 Trials**
ongoing in transthyretin amyloidosis (ATTR-CM and -PN)

**600+** **Patients Dosed**
with Intellia's investigational *in vivo* CRISPR-based therapies



**5+** **Years of Follow-Up**
in earliest dosed patients



## 6 Publications in The NEW ENGLAND JOURNAL of MEDICINE

| | |
|---|---|
| AUG 5 2021 | CRISPR-Cas9 *In Vivo* Gene Editing for Transthyretin Amyloidosis |
| JAN 31 2024 | CRISPR-Cas9 *In Vivo* Gene Editing of *KLKB1* for Hereditary Angioedema |
| OCT 24 2024 | CRISPR-Based Therapy for Hereditary Angioedema |
| NOV 16 2024 | CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy |
| SEP 25 2025 | Nexiguran Ziclumeran Gene Editing in Hereditary ATTR with Polyneuropathy |
| JUNE 13 2026 | Lonvoguran Ziclumeran - *In Vivo* CRISPR Gene Editing in Hereditary Angioedema |



CRISPR: clustered regularly interspaced short palindromic repeats; Cas9: CRISPR-associated protein 9; ATTR-CM: ATTR amyloidosis cardiomyopathy; ATTRv-PN: hereditary ATTR amyloidosis polyneuropathy; KLKB1: kallikrein B1

# Intellia's Pipeline Advancing Toward Significant Near-Term Milestones

| Program | Indication | Research/ Preclinical | Early-Stage Clinical | Late-Stage Clinical | BLA Submission | |
|---|---|---|---|---|---|---|
| Lonvo-z[1] | Hereditary Angioedema (HAE) | | | | | Intellia THERAPEUTICS |
| Nex-z[2] | Transthyretin Amyloidosis with Polyneuropathy (ATTRv-PN) | | | | | LEAD Intellia THERAPEUTICS REGENERON |
| | Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM) | | | | | LEAD Intellia THERAPEUTICS REGENERON |
| REGV131-LNP1265[3] | Hemophilia B | | | | | REGENERON |
| AVC-201<br>AVC-203 | Acute Myeloid Leukemia (AML)<br>B-cell malignancies | | | | | AVENCELL[4] |
| Other Ongoing Research Programs | Various | | | | | Intellia[5] THERAPEUTICS REGENERON AVENCELL kyverna |

Lead refers to lead development and commercial party.
1. Lonvo-z (lonvoguran ziclumeran), formerly referred to as NTLA-2002. 2. Nex-z (nexiguran ziclumeran), formerly referred to as NTLA-2001; Regeneron shares in approximately 25% of worldwide development costs and commercial profits for the ATTR program and has an option to enter into a co-promotion agreement for the U.S. commercialization. 3. Hemophilia B is being advanced solely by Regeneron; Intellia is eligible for milestones and royalties. 4. AVC-201 and AVC-203 are wholly owned by AvenCell and utilize proprietary allogeneic cell engineering technology licensed from Intellia. 5. Intellia is advancing both wholly owned and partnered programs. ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy



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# Key Upcoming Objectives

## Lonvo-z HAE

- ✓ Present topline Phase 3 HAELO data by mid-2026
- ✓ Present additional Phase 3 HAELO data at EAACI in June 2026
- ○ Announce BLA acceptance by FDA in second half of 2026
- ○ U.S. approval and commercial launch in first half of 2027

## Nex-z ATTR

- ✓ Resume patient enrollment in Phase 3 MAGNITUDE trial in ATTR-CM
- ✓ Resume patient enrollment in Phase 3 MAGNITUDE-2 trial in ATTRv-PN
- ○ Complete enrollment in MAGNITUDE-2 in second half of 2026

**Existing cash resources expected to fund operations at least into 2028, excluding any potential commercial revenues from lonvo-z**

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ATTR: transthyretin amyloidosis; ATTR-CM: ATTR amyloidosis cardiomyopathy; ATTRv-PN: hereditary ATTR amyloidosis polyneuropathy; BLA: biologics license application; HAE: hereditary angioedema

# Lonvoguran Ziclumeran (lonvo-z) for Hereditary Angioedema

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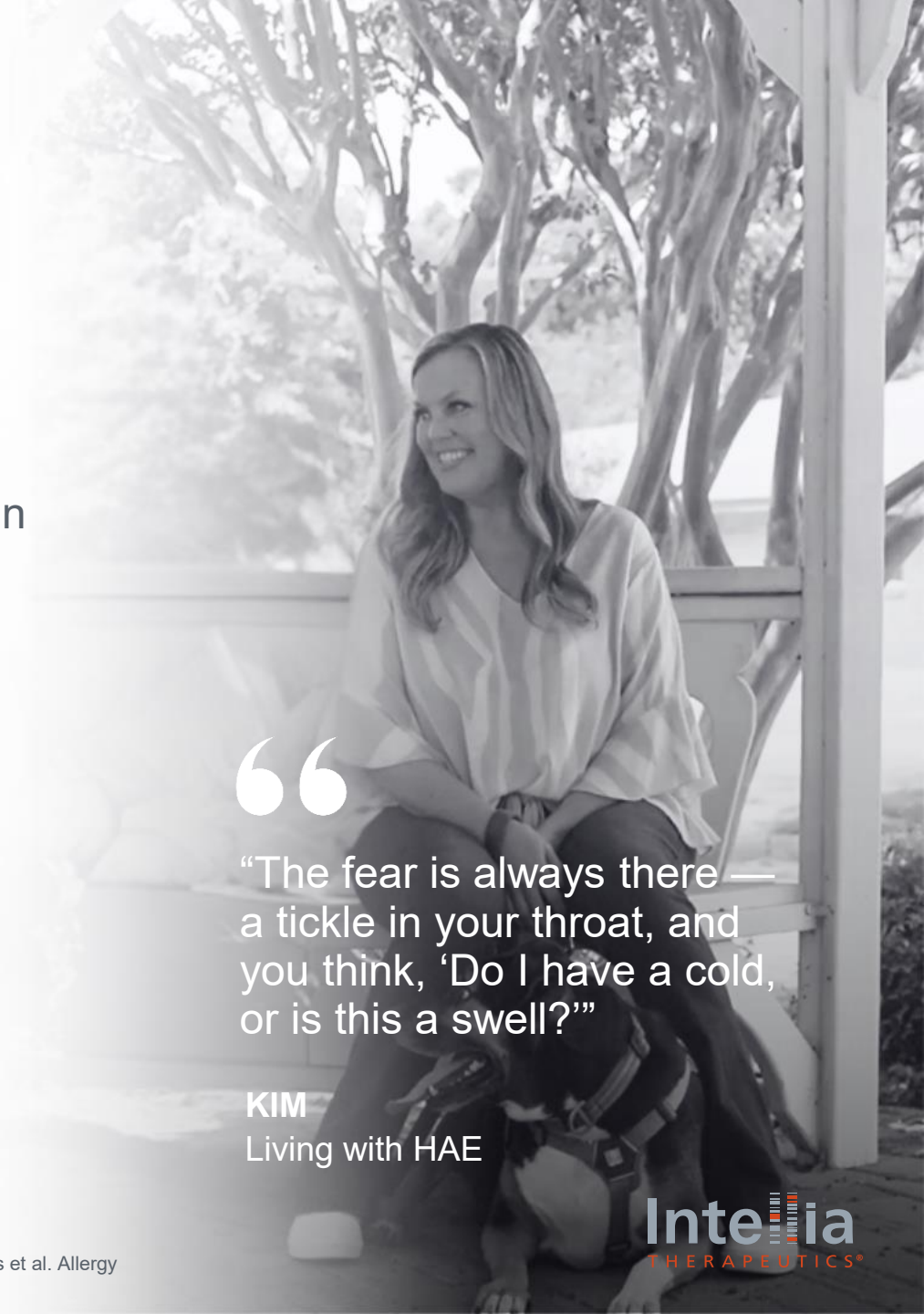
# Hereditary Angioedema (HAE): Currently a Lifelong Condition with Significant Burden

## Rare, genetic and life-threatening disease

- Caused by a hereditary deficiency or dysfunction of the C1 inhibitor protein that leads to an imbalance in the kallikrein-kinin system and an overproduction of bradykinin
- Patients experience unpredictable, recurrent, painful and potentially life-threatening swelling attacks[1,2]
- Symptoms often begin in the first decade of life and typically worsen in puberty[3,4]
- Attacks can be triggered by stress, trauma, infection, fatigue and hormones[2]

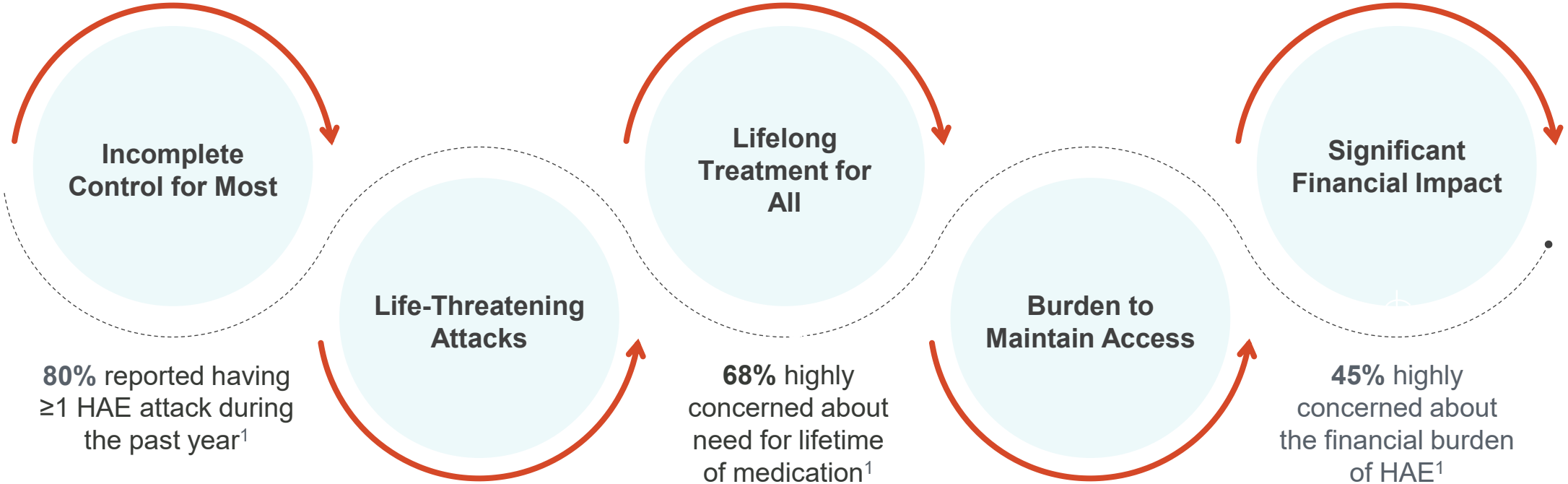





1. Zuraw et al. N Engl J Med. 2008 Sep 4;359(10):1027-36. 2. Busse and Christiansen, N Engl J Med. 2020 Mar 19;382(12):1136-1148. 3. Norris et al. Allergy Asthma Proc. 2022 Sep 1;43(5):388-396. 4. Pancholy et al. Curr Opin Pediatr. 2019 Dec;31(6):863-868.

# Despite Available Treatments, Many Patients are Unable to Break the Chronic Cycle of Managing Their HAE

## Patient-Reported Burdens






1. Busse et al. *Allergy Asthma Proc*. 2026 Mar 1;47(2):92-101. 2. Lumry WR, Settipane RA. *Allergy Asthma Proc*. 2020 Nov 1;41(Suppl 1):S08-S13. HAE: hereditary angioedema

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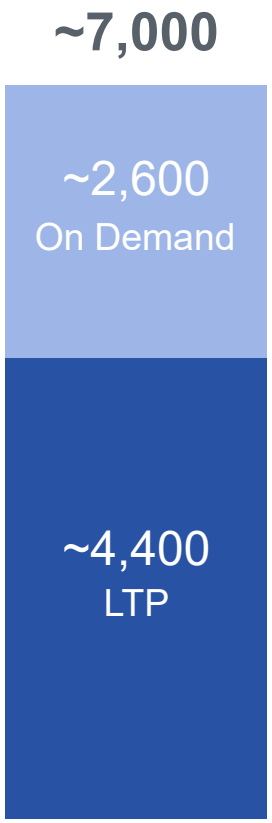
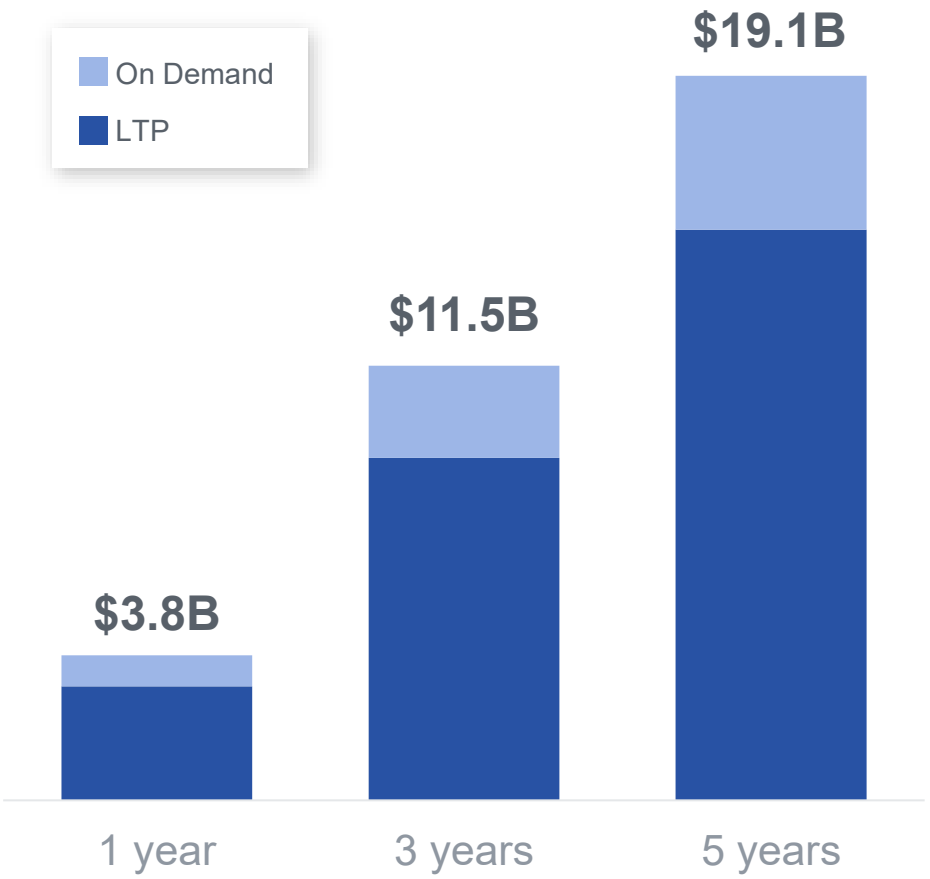
# The Cumulative Costs for Chronic HAE Treatments are Sizable

## U.S. Treated Patients with Type 1 & 2 HAE[1]




## Average Age of HAE Diagnosis in U.S.[2]

## Cumulative U.S. Healthcare System Costs for Chronic and On-Demand HAE Therapies[3]






1. Castaldo et al. Allergy Asthma Immunol, 2025. 2. Banerji et al. Annals of Allergy, Asthma & Immunology, June 2020. 3 IPD Analytics. Market & Financial Insights. Published April 2026. Assumes weighted average cost of LTP agents of $684,000 and total on demand HAE market size $812M; excludes annual price increases. B: billion; HAE: hereditary angioedema; LTP: long-term prophylaxis

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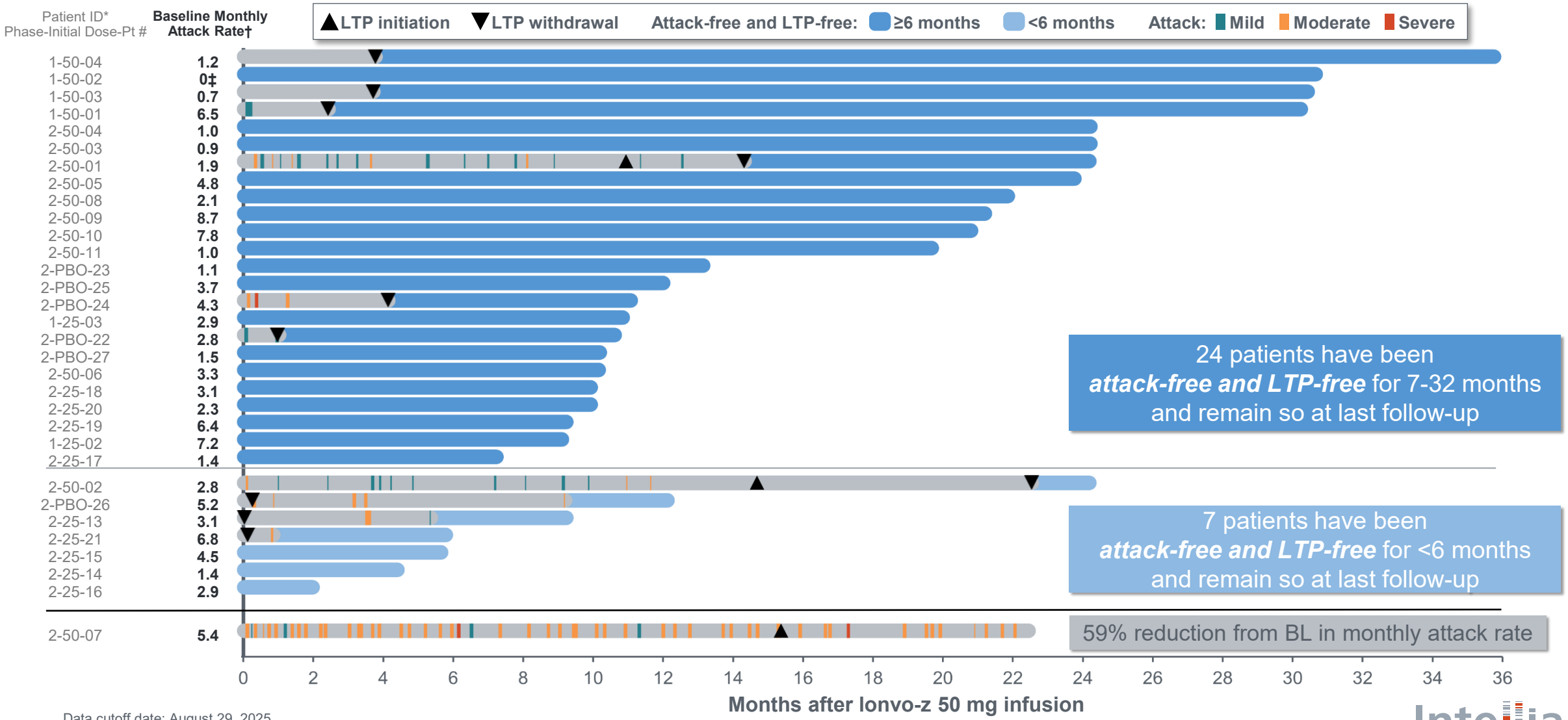
# Lonvo-z Has the Potential to be a One-Time Treatment for Hereditary Angioedema

- First and only investigational therapy that **targets the *KLKB1* gene**, to reduce production of kallikrein protein at its source
- Observations from Phase 1/2 trial:
  - Consistently **rapid, deep and durable kallikrein reductions**
  - **Freedom from HAE attacks** and **ongoing therapy** for most patients
  - **Well-tolerated** safety profile
- Lonvo-z is being developed as a **one-time IV infusion** administered in an **outpatient setting**

Based on interim lonvo-z Phase 1 data as of data cutoff February 12, 2025. Studies are ongoing to assess this investigational product.
IV: intravenous; *KLKB1*: kallikrein B1

# Pooled Analysis of Phase 1/2 Clinical Data: After Becoming Attack-Free and LTP-Free for ≥6 Months, All Patients Maintained Their Response

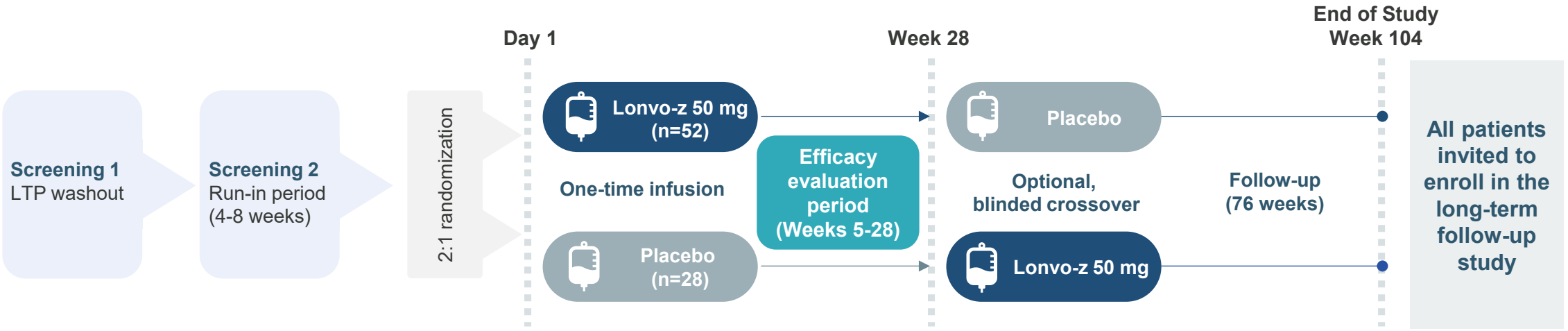



Data cutoff date: August 29, 2025

Phase 1 eligibility was determined by historical attack period. * Patient IDs align with prior Phase 1 and Phase 2 publications. † Baseline is defined as the screening period (50 mg initial dose or 25 mg to 50 mg) or for PBO to 50 mg as the time from informed consent to 50 mg infusion or start of any LTP, whichever occurred first. ‡ Patient had 0.9 attacks per month in the 3 months prior to screening. This presentation includes data for an investigational product not yet approved by regulatory authorities. BL: baseline; LTP: long-term prophylaxis; mg: milligram; PBO: placebo; Pt: patient.

HAELO Clinical Trial

# A Placebo-Controlled, Double-Blind, Randomized Phase 3 Trial of Lonvo-z as a One-Time HAE Treatment




## Stratification

Baseline number of investigator-confirmed HAE attacks per month from Screening 2 to Randomization

## Primary Endpoint

Time-normalized number of investigator-confirmed HAE attacks from Weeks 5 through 28

## Key Secondary Endpoints

- Time-normalized number of investigator-confirmed HAE attacks requiring on-demand treatment from Weeks 5 through 28
- Time-normalized number of moderate or severe investigator-confirmed HAE attacks from Weeks 5 through 28
- Investigator-confirmed HAE attack-free status from Weeks 5 through 28
- Change from baseline to Week 28 in AE-QoL Questionnaire total score

**Pre-specified primary analysis when ≥60 patients reached Week 28**

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ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT06634420.
AE-QoL: Angioedema Quality of Life; EOS: end of study; HAE: hereditary angioedema; LTP: long-term prophylaxis; mg: milligram

# HAELO Phase 3 Demographics and Baseline Characteristics

| Demographic Characteristics | Lonvo-z (n=52) | Placebo (n=28) |
|---|---|---|
| **Age, median years (range)** | **42 (23 – 71)** | **40 (19 – 76)** |
| **Female, n (%)** | **35 (67%)** | **20 (71%)** |
| **Enrolled in United States, n (%)** | **26 (50%)** | **13 (46%)** |
| **Hereditary angioedema type, n (%)** | | |
| Type 1 | **49 (94%)** | **25 (89%)** |
| Type 2 | **3 (6%)** | **3 (11%)** |
| **Long-term prophylaxis at study entry, n (%)** | **35 (67%)** | **22 (79%)** |
| Lanadelumab | 25 (48%) | 12 (43%) |
| C1 esterase inhibitor | 5 (10%) | 3 (11%) |
| Berotralstat | 4 (8%) | 1 (4%) |
| Garadacimab | 1 (2%) | 3 (11%) |
| Other | 2 (4%) | 3 (11%) |
| **On-Demand therapy only, n (%)** | **17 (33%)** | **6 (21%)** |
| **Historic typical attack severity, n (%)** | | |
| Mild | 7 (14%) | 5 (18%) |
| Moderate | 30 (58%) | 20 (71%) |
| Severe | 15 (29%) | 3 (11%) |
| **Monthly attack rate during run-in, mean (SD)*** | **3.5 (1.8)** | **3.5 (1.9)** |

**Median follow-up for enrolled patients: 7.5 months**

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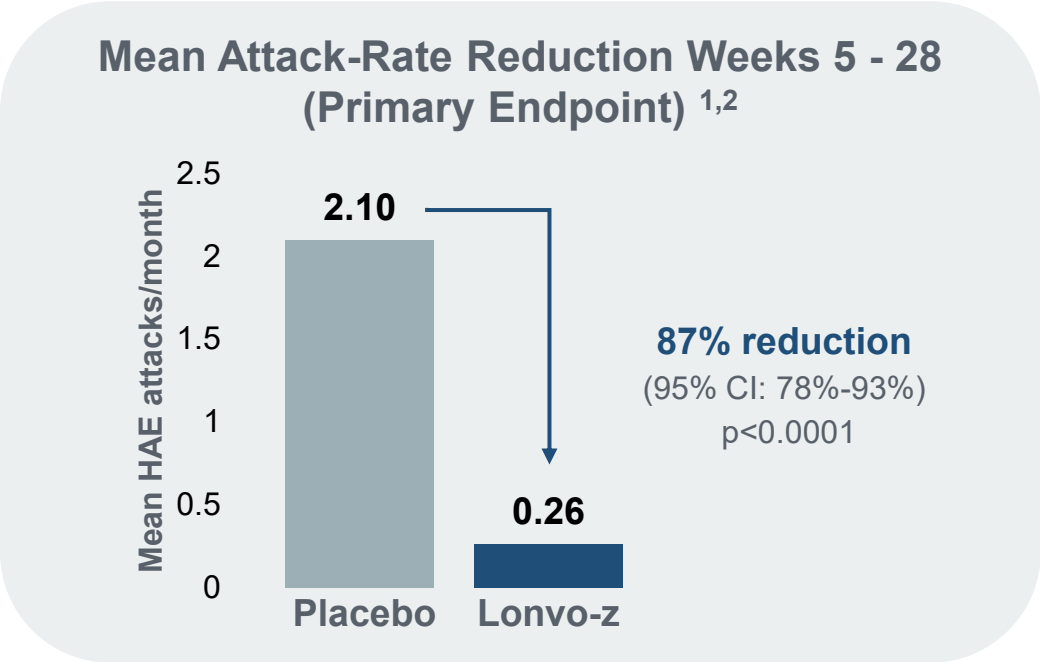
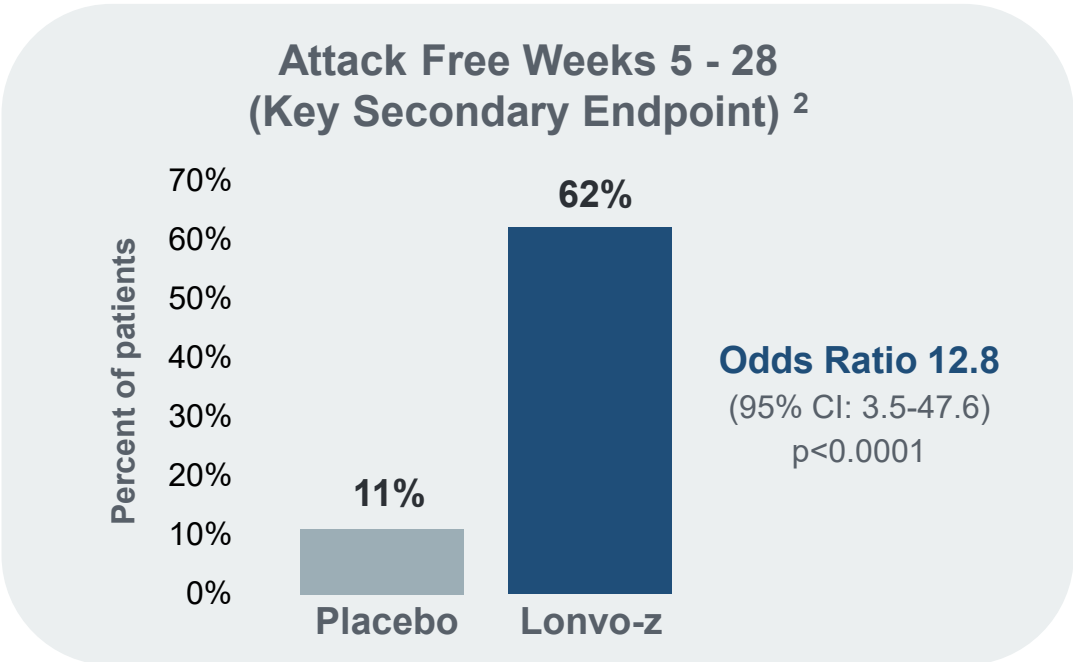
Data cutoff: February 10, 2026

* Run-in period is from Screen-2 visit to randomization. This presentation includes data for an investigational product not yet approved by regulatory authorities. SD: standard deviation

# HAELO Trial Achieved its Primary and All Key Secondary Endpoints




**All other key secondary endpoints were achieved with high statistical significance (p<0.0001)**

Data cutoff: February 10, 2026

1. Model-based HAE attack rate using a Poisson regression model with Pearson Chi-square scaling of standard error with treatment arm and baseline attack rate (> 3 vs ≤ 3 attacks/month) as covariates. 2. Includes assessments up to and including Week 28, or the latest assessment prior to the data cut-off date for patients who did not reach Week 28. CI: confidence interval; HAE: hereditary angioedema



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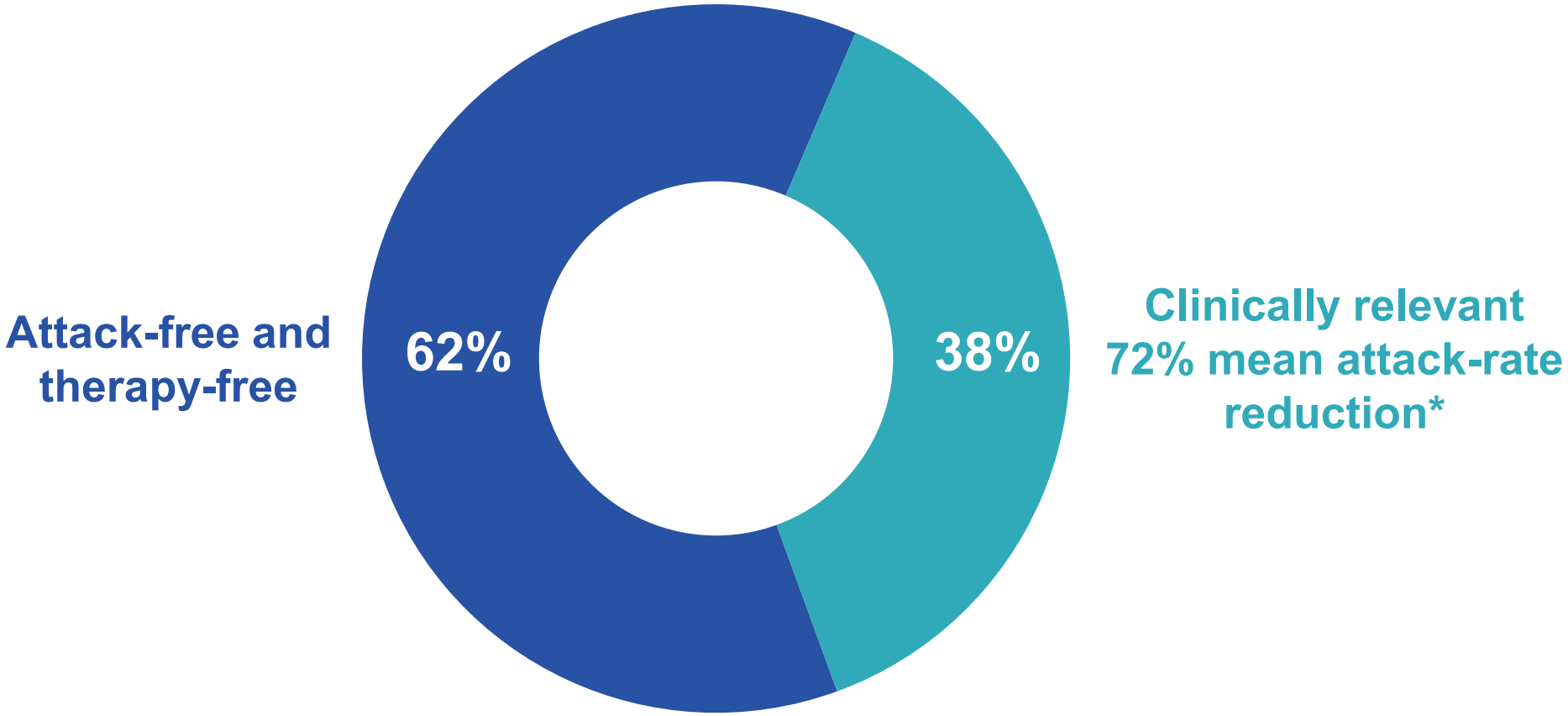
# 100% of Patients in Lonvo-z Arm Experienced Attack-Rate Reduction from Baseline During Weeks 5-28




**All patients who received lonvo-z at baseline or in crossover were LTP-free**

* Patients with ≥1 attack during weeks 5-28
Data cutoff: February 10, 2026
Post-hoc, exploratory analysis. LTP: long-term prophylaxis



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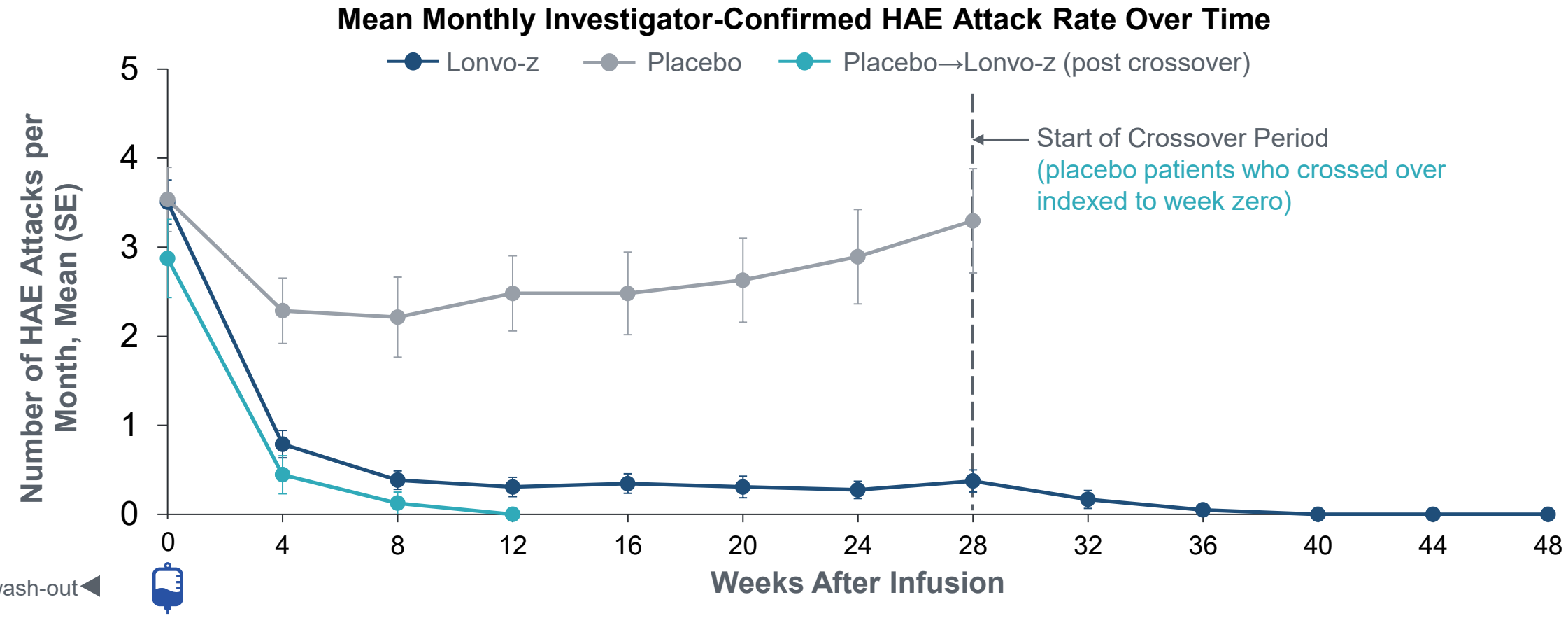
# Attack-Rate Reduction Observed Quickly Following Lonvo-z Dosing; Further Reduction Observed in Early Crossover Data Following Week 28




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lonvo-z (n) | 52 | 52 | 52 | 52 | 52 | 52 | 50 | 44 | 43 | 20 | 8 | 6 | 3 |
| Placebo (n) | 28 | 28 | 28 | 27 | 27 | 27 | 25 | 21 | 0 | 0 | 0 | 0 | 0 |
| Placebo→Lonvo-z (n) | 20 | 20 | 8 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Data cutoff: February 10, 2026.
Mean attack rates at week zero were calculated using data from the Screening-2 visit to randomization. For patients in the "placebo to lonvo-z" crossover group, week zero attack rates were calculated from the Screening-2 visit to either the date of lonvo-z crossover administration (minus 1) or the start date of LTP (minus -1), whichever occurred first. During the efficacy evaluation period, two patients in the placebo arm restarted LTP due to a high number of attacks. For these patients, data were censored at the time of LTP initiation and only attacks occurring prior to LTP initiation were included in the analysis. Both patients discontinued LTP before receiving the lonvo-z crossover infusion. HAE: hereditary angioedema; LTP: long-term prophylaxis; mg: milligram; SE: standard error



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# Favorable Safety and Tolerability Data

| Primary Observation Period (Weeks 1 – 28) | Lonvo-z (N=52) | Placebo (N=28) |
|---|---|---|
| **TEAEs in ≥10% of patients, n (%)** | | |
| Infusion-related reaction | 32 (62%) | 5 (18%) |
| Headache | 10 (19%) | 3 (11%) |
| Fatigue | 7 (14%) | 3 (11%) |
| Nasopharyngitis | 7 (14%) | 9 (32%) |
| Back pain | 6 (12%) | 3 (11%) |
| Upper respiratory tract infection | 6 (12%) | 2 (7%) |
| **Serious TEAEs** | **0** | **1 (4%)*** |
| **Grade ≥3 TEAEs** | **0** | **0** |

- No SAEs or Grade ≥3 TEAEs reported in lonvo-z arm
- All IRRs were mild or moderate and were transient
- No meaningful difference between arms in clinical chemistries; single Grade 2 ALT elevation observed in lonvo-z arm that self-resolved in one week
- Consistent safety and tolerability data observed in crossover following week 28 as of data cutoff

Data cutoff: February 10, 2026
* One patient in the placebo group experienced a serious TEAE, which was Grade 2 supraventricular tachycardia, on Day 39 and resolved in 2 days. ALY: alanine aminotransferase; IRR: infusion-related reaction; SAE: serious adverse event; TEAE: treatment-emergent adverse event



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# Additional HAELO Perspectives

## Significant Patient Enthusiasm

80 patients enrolled (original target: ≥60)

All patients dosed within nine months

~70% of patients washed out of LTP to enroll

## Diverse Mix of Patients

Multi-national trial with ~50% of enrolled patients in U.S.; broad age range

Population includes patients:

*With complete HAE control; partial control at entry*

*Who were on LTP and/or on-demand therapies at entry*

## Extensive (and Still Expanding) Phase 3 Database

Longest Phase 3 trial undertaken in HAE to date, once completed

Largest cohort of patients receiving proposed label dose (50 mg of lonvo-z)



HAE: hereditary angioedema; LTP: long-term prophylaxis; mg: milligram

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# Lonvo-z: Unique Potential to Eliminate Attacks and Ongoing Therapy with One Treatment

## PHASE 3 CROSS-TRIAL COMPARISON*

Chronic long-term prophylaxis (LTP) therapies

| Product | % of Patients Attack & Therapy Free* | % Attack Reduction vs. Placebo* | % of Patients Attack Free* | Lifetime Dosing Burden |
|---|---|---|---|---|
| **lonvo-z** (investigational) | 62% | 87% | 62% | 1x infusion |
| berotralstat[1] | 0% | 44% | n/a | Daily oral tablets |
| C1 est. inh.[2] | 0% | 87% | n/a | 104 injections / year |
| donidalorsen[3] | 0% | 55-81% | 35-53% | 7–13 injections / year |
| garadacimab[4] | 0% | 89% | 62% | 13 injections / year |
| lanadelumab[5] | 0% | 74-87% | 31-44% | 13–26 injections / year |

*For illustrative purposes only.*

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* This graphic includes data from the blinded time periods of distinct clinical trials with their own enrollment criteria and methodologies. Cross-trial comparisons have inherent limitations and should be interpreted with caution. 1. berotralstat label. 2. C1 esterase inhibitor label. 3. donidalorsen label. 4. garadacimab label. 5. lanadelumab label.

# Nearing Completion of Readiness Efforts for a Successful Planned Launch in 1H 2027

- Established core commercialization team
- Deployed field medical team
- Finalized overall launch strategy
- Commenced payer engagement
- Continued patient advocacy group/medical society engagements
- Finalized distribution model for launch
- Identified potential treatment centers
- Initiated rolling BLA submission with FDA

2025 Accomplishment  2026 Accomplishment

## Priorities ahead…

- BLA acceptance
- Scale field sales and reimbursement teams
- Finalize pricing
- Finalize contracting strategy

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BLA: Biologics License Application; FDA: U.S. Food and Drug Administration; KOL: key opinion leader

# Nexiguran Ziclumeran (nex-z) for ATTR Cardiomyopathy (CM) and ATTR Polyneuropathy (PN)

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# Transthyretin Amyloidosis (ATTR): Large and Growing Market with Significant Unmet Need

## Severe, fatal, progressive disease with shortened life expectancy

- CM patients have debilitating shortness of breath, arrythmias, reduced mobility and quality of life, as well as a high rate of hospitalization
- Wild-type disease, the most common form, occurs with aging and manifests as heart failure; inherited TTR mutations lead to rapidly progressive heart failure and/or polyneuropathy
- 250,000 to 500,000 ATTR patients worldwide[1-4]; increasing rate of diagnosis due to an aging population and improved disease awareness
- PN presents as motor and sensory dysfunction, muscle wasting, weight loss, as well as autonomic neuropathy with severe GI symptoms

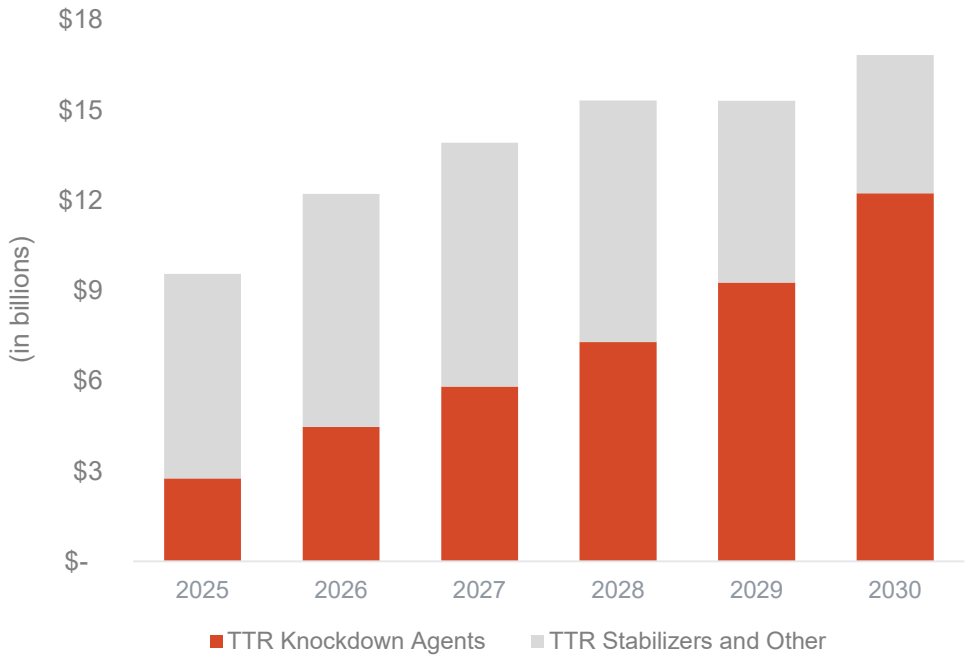
## Despite available treatments, significant unmet need persists

- Inconsistent and slow TTR lowering response observed with silencers[5]
- In Phase 3 trials of silencer or stabilizer therapies for CM, the annual rate of CV events or death is high at ~15% of enrolled patients in the first year[5,6]
- Even on existing therapies, CM patients have a marked decline in quality of life and functional capacity as measured by 6MWT[5,6]
- Treatment adherence due to frequent administration/polypharmacy remains an issue

1. Hawkins et al, Annals of Medicine, 2015. 2. Maurer et al, Circulation: Heart Failure, 2019. 3. Nativi-Nicolau et al, ESC Heart Failure, 2021. 4. Gillmore et al, American Heart Association Scientific Sessions, 2022. 5. Fontana et al, NEJM, 2024. 6. Gillmore et al, NEJM, 2024. CM: cardiomyopathy; CV: cardiovascular; GI: gastrointestinal; PN: polyneuropathy; TTR: transthyretin; 6MWT: 6-Minute Walk Test

# Seeking to Meet Patient and Provider Needs in a Large and Growing ATTR Market

Global ATTR market projected to reach **~$16.8B dollars by 2030**[1]




Patients want a **highly effective** therapy **and freedom** from chronic treatment[2]

*"It would be incredible to have a **one-time therapy**. This would get rid of the mental energy and anxiety I get from going to infusion centers."*

**U.S. ATTRv-PN Patient**

*"My number one wish would be a **cure**."*

**U.S. ATTR-CM Patient**

*"This treatment could help me get my life back. I would feel more comfortable going back to work knowing there is a **permanent treatment**."*

**UK ATTR-CM Patient**

**If approved, nex-z would enter a large and growing market with a strong potential value proposition**

1. Consensus analyst forecasts per FactSet (Dec. 2025). 2. Intellia commissioned ATTR patient and caregiver interviews (n=46). 3. Intellia commissioned physician quantitative survey (n=232) based on nex-z target product profile. ATTR-CM: ATTR amyloidosis cardiomyopathy; ATTRv-PN: hereditary ATTR amyloidosis polyneuropathy; TTR: transthyretin



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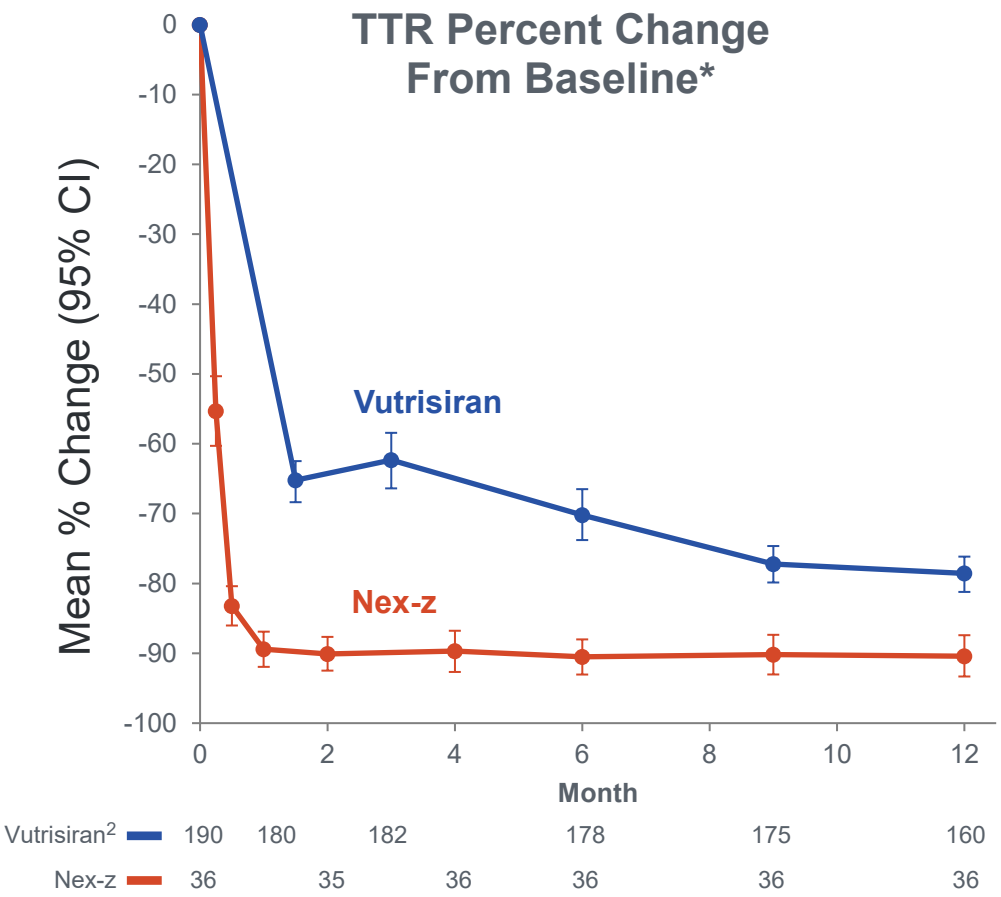
# Nex-z Has the Potential to Transform the Standard of Care for ATTR Amyloidosis

- First and only investigational therapy that **targets the *TTR* gene**, to reduce production of TTR protein at its source
- Potential to provide patients with:
  - Consistently rapid, deep and durable TTR reduction
  - Stability or improvement in disease measures
  - Improved quality of life
  - Reduced CV events and mortality
- Nex-z is being developed as a **one-time IV infusion** administered in an **outpatient setting**

Based on interim nex-z Phase 1 data as of data cutoff August 21, 2024. Studies are ongoing to assess this investigational product. ATTR amyloidosis: transthyretin amyloidosis; CV: cardiovascular; IV: intravenous

# Nex-z Led to Consistent Rapid, Deep and Durable Reductions in Serum TTR: Cross-Trial Comparison to Vutrisiran TTR Profile from HELIOS-B




**Research has shown a correlation between deeper reductions in TTR and increased clinical benefit[1-5]**

* This graphic includes data from distinct clinical trials with their own enrollment criteria and methodologies. Cross-trial comparisons have inherent limitations and should be interpreted with caution. Vutrisiran data digitized from HELIOS-B: Fontana et al, NEJM, 2024. Nex-z data from: Gillmore et al. NEJM, 2024. 1. Gillmore JD, et al. Lancet, 2001. 2. Lachmann HJ, et al. Br J Haematol, 2003. 3. Palladini G, et al. J Clin Oncol., 2012. 4. Lachmann HJ, et al. NEJM, 2007. CI: confidence interval; TTR: transthyretin



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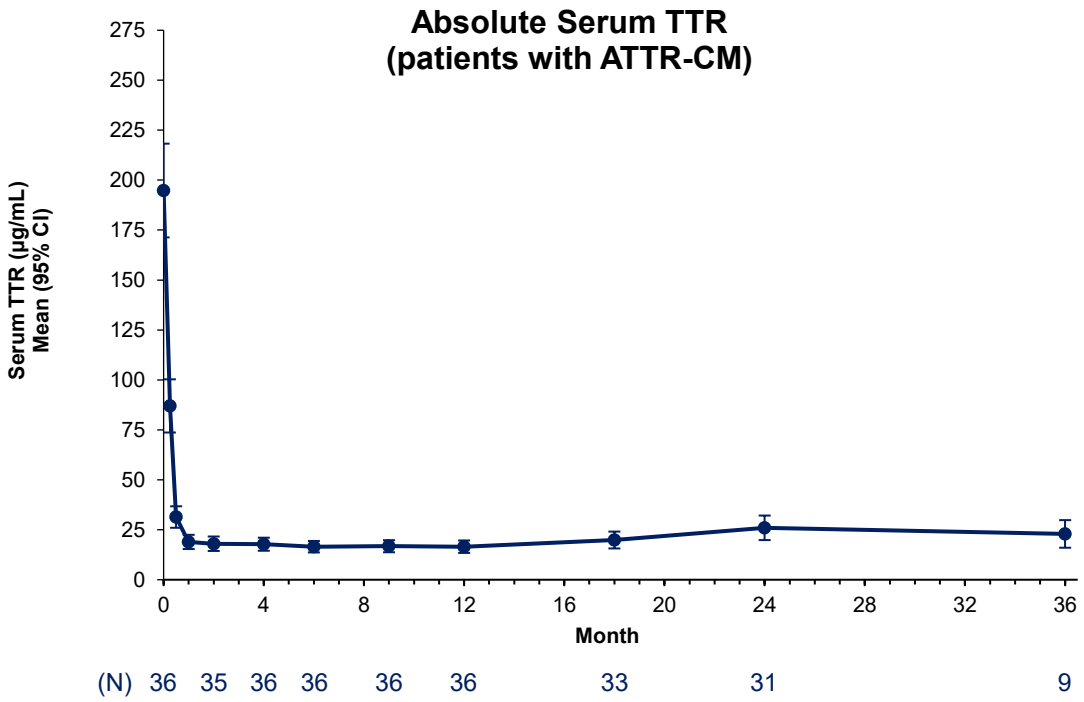
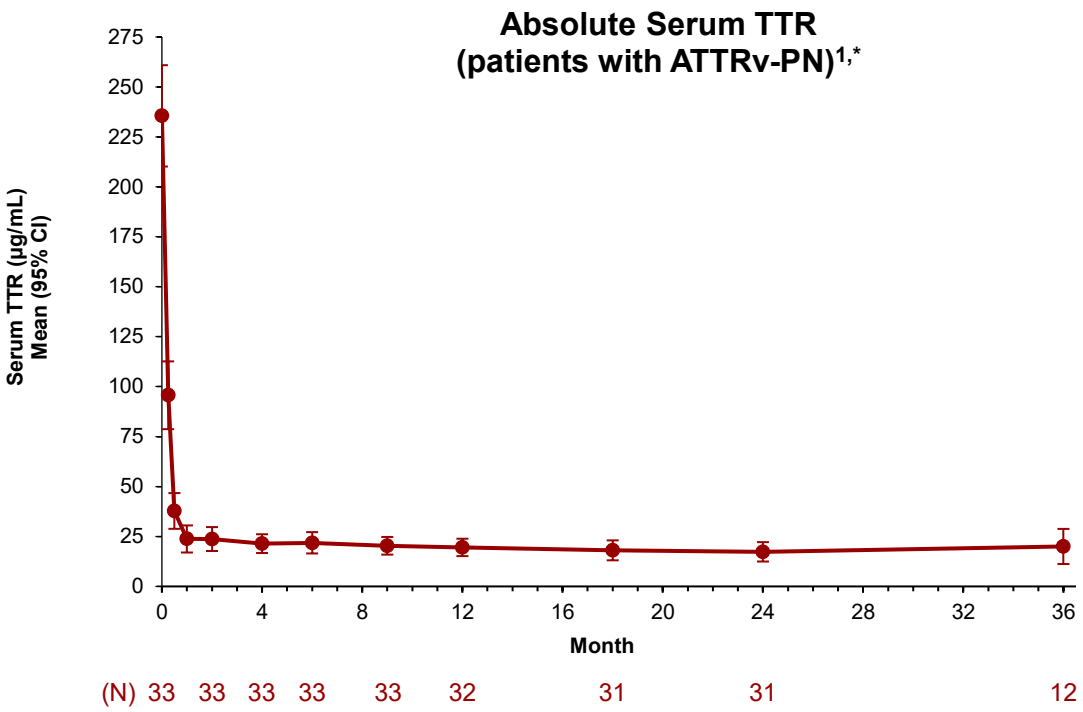
# Phase 1 Clinical Data: One-time Nex-z Dose Led to Consistent, Rapid, Deep and Durable Serum TTR Reduction

American Heart Association. Scientific Sessions
November 7-10, 2025 | Scientific Sessions
November 8-10, 2025 | Exhibits
Ernest N. Morial Convention Center | New Orleans, LA




From *The New England Journal of Medicine*, Gillmore JD, et al, Nexiguran ziclumeran gene editing in hereditary ATTR with polyneuropathy, Volume 393, Page no. 1375-1386. Copyright © 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

**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 date: 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. * Results shown for patients with ATTRv-PN who received nex-z at a dose > 0.1 mg/kg. 1. Gillmore D, et al. NEJM, 2025. ATTR-CM: ATTR amyloidosis with cardiomyopathy; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; CI: confidence interval; TTR: transthyretin



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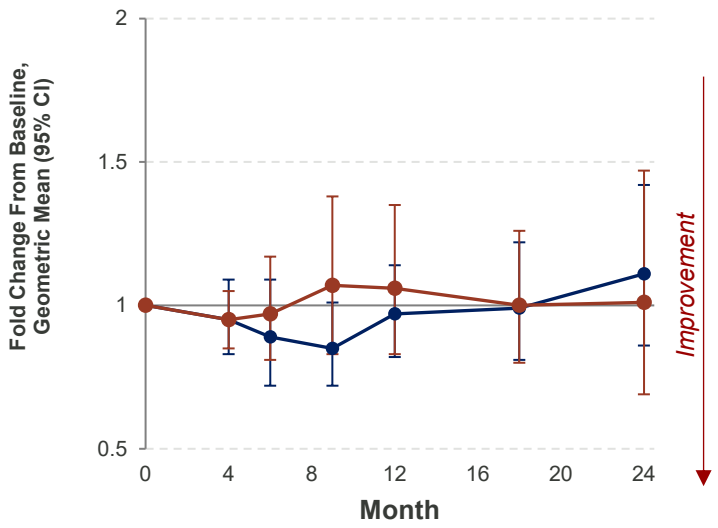
# Phase 1 ATTR-CM Clinical Data: Improvement/Stabilization of Disease Progression Maintained Regardless of NYHA Class

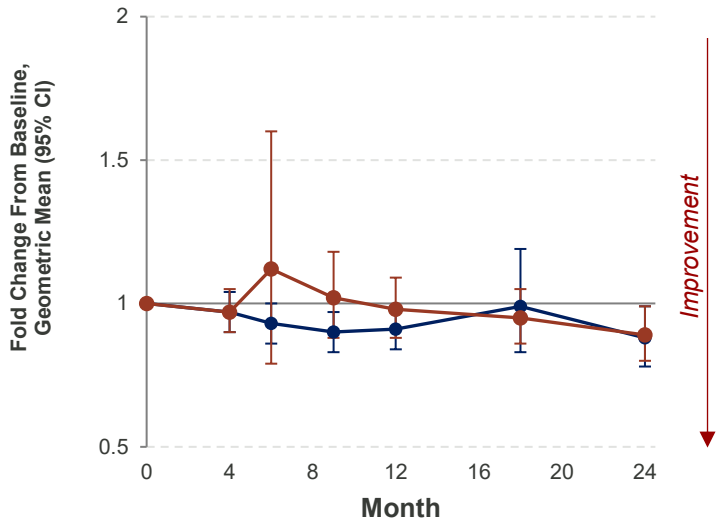
American Heart Association. Scientific Sessions
November 7-10, 2025 | Scientific Sessions
November 8-10, 2025 | Exhibits
Ernest N. Morial Convention Center | New Orleans, LA

## NT-proBNP



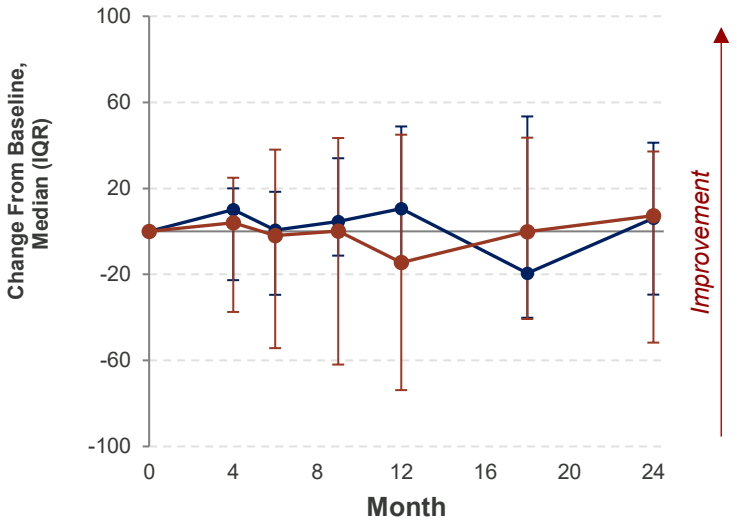

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (N) | 18 | 17 | 18 | 18 | 18 | 16 | 17 |
| (N) | 18 | 17 | 18 | 18 | 18 | 16 | 14 |

## hs-Troponin T




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (N) | 18 | 17 | 18 | 18 | 18 | 16 | 17 |
| (N) | 18 | 17 | 18 | 18 | 18 | 16 | 14 |

## 6MWT Distance (meters)




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (N) | 18 | 17 | 18 | 18 | 18 | 17 | 15 |
| (N) | 18 | 16 | 16 | 14 | 17 | 12 | 12 |

NYHA class I/II — NYHA class III

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

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# Evaluation of Mortality in Patients Treated with Nex-z Compared with a Matched Cohort of Patients

American Heart Association. Scientific Sessions
November 7-10, 2025 | Scientific Sessions
November 8-10, 2025 | Exhibits
Ernest N. Morial Convention Center | New Orleans, LA

- 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* | 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 (%)**** | | | |
| 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**

* Numbers for patients treated with nex-z represent values at trial baseline. ** Nex-z patient population includes two homozygous patients.
ATTR-CM: ATTR amyloidosis cardiomyopathy; CKD-EPI: chronic kidney disease epidemiology; eGFR: estimated glomerular filtration rate by CKD-EPI equation; LVEF: left ventricular ejection fraction; mL: milliliter; NAC: National Amyloidosis Center; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SD: standard deviation; *TTR*: transthyretin



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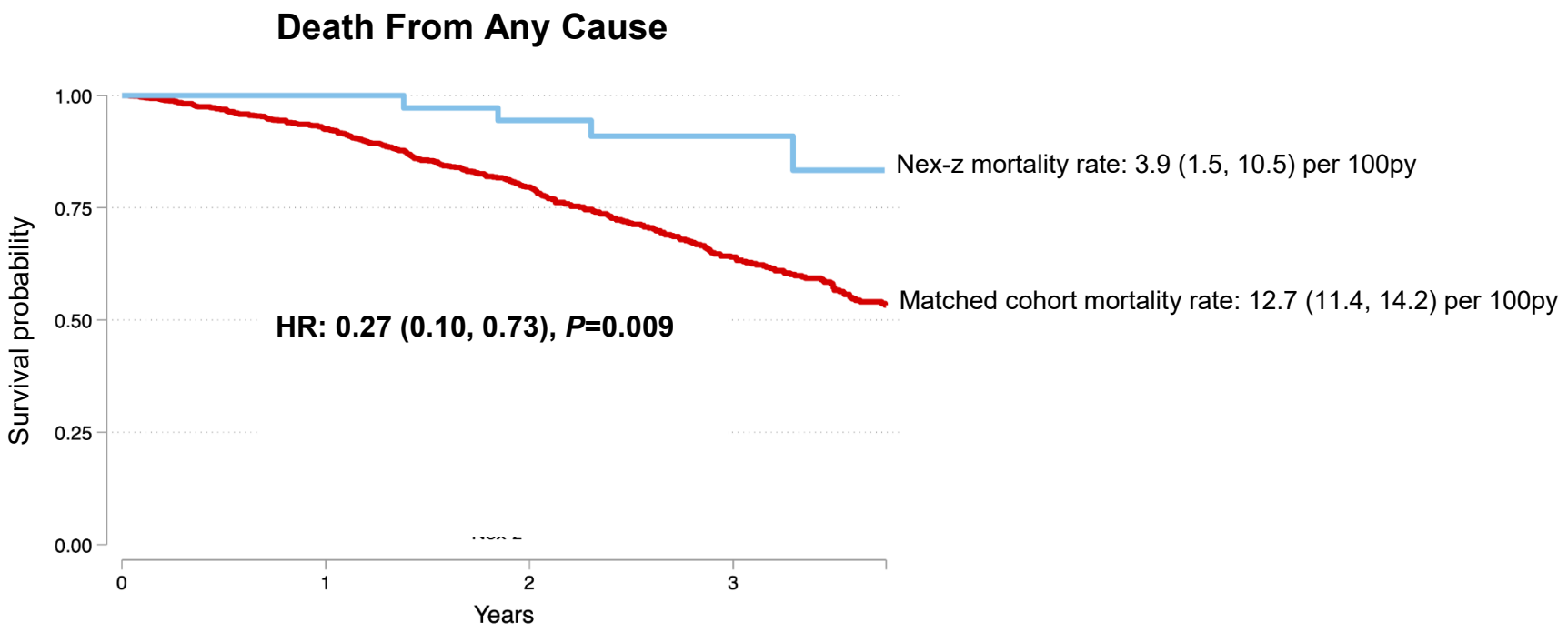
# Phase 1 ATTR-CM Clinical Data: All-Cause Mortality Rate was ~3-Fold Lower than that Observed in a Matched Cohort of Patients

American Heart Association. Scientific Sessions
November 7-10, 2025 | Scientific Sessions
November 8-10, 2025 | Exhibits
Ernest N. Morial Convention Center | New Orleans, LA




| Number at risk | | | | |
|---|---|---|---|---|
| Matched cohort | 1751 | 904 | 500 | 262 |
| Nex-z | 36 | 36 | 34 | 12 |

- **A sensitivity analysis incorporating tafamidis initiation* 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**

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* 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). ATTR-CM: ATTR amyloidosis cardiomyopathy; HR: hazard ratio; NAC: National Amyloidosis Center; PY: patient-year

# Phase 1 ATTR-CM Safety Summary

American Heart Association. Scientific Sessions
November 7-10, 2025 | Scientific Sessions
November 8-10, 2025 | Exhibits
Ernest N. Morial Convention Center | New Orleans, LA

| 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*** | 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**** | 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

Data cutoff date: August 23, 2025
* In addition, 1 patient in the long-term follow-up had unrelated serious adverse events. ** 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 cardiomyopathy; IRR: infusion-related reaction; SAE: serious AE

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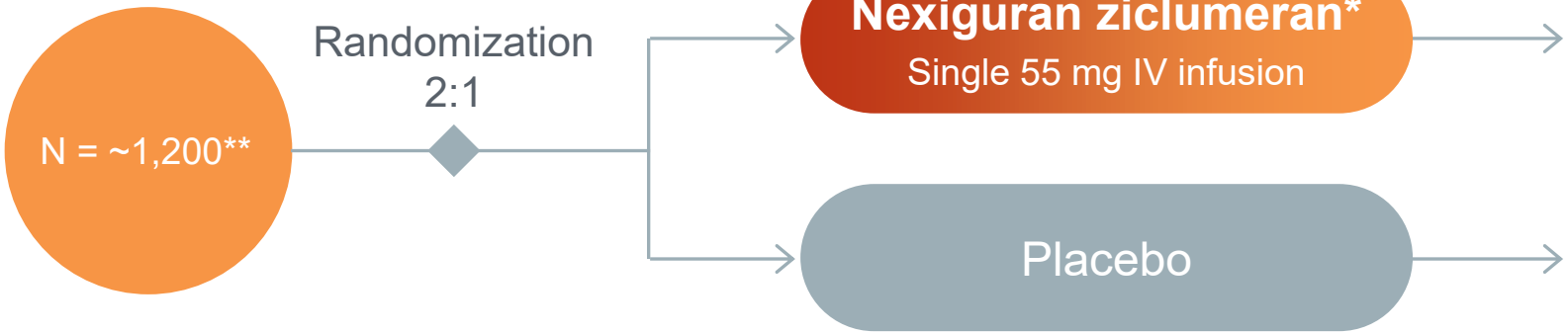
MAGNITUDE
CLINICAL TRIAL

# A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Nexiguran Ziclumeran (nex-z)* 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 ≥ 600 pg/mL

## Stratification:

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

## Trial 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
* Formerly referred to as NTLA-2001
** Subject to health authority review
CV: Cardiovascular; TTR: Transthyretin; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary; NHYA: New York Heart Association; NT-proBNP: N-terminal-pro-B-type natriuretic peptide; NAC: National Amyloidosis Centre

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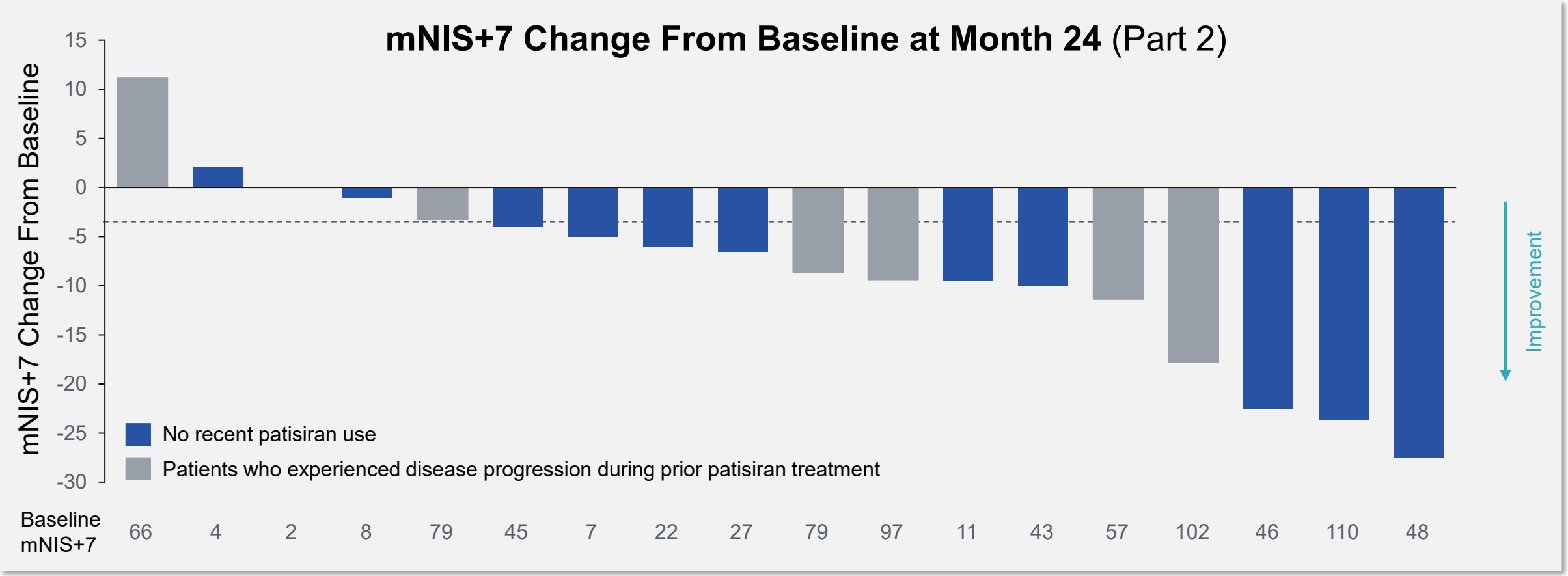
# At Month 24, Majority of Patients With ATTRv-PN Experienced Improvements in mNIS+7

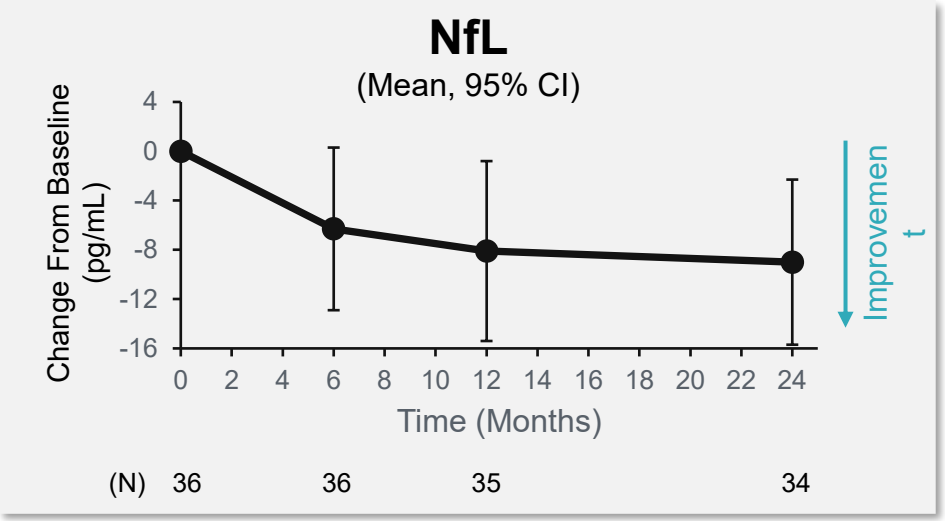


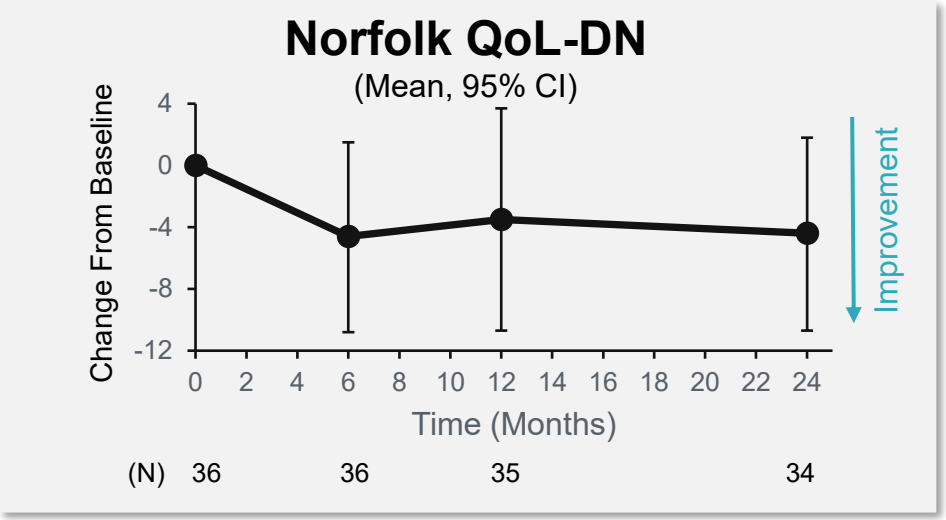

- The mean change in mNIS+7 at Month 24 was -8.5 points
- 13/18 (72%) patients had improvements in mNIS+7 which exceeded the clinically meaningful threshold of a ≥4-point reduction[1]

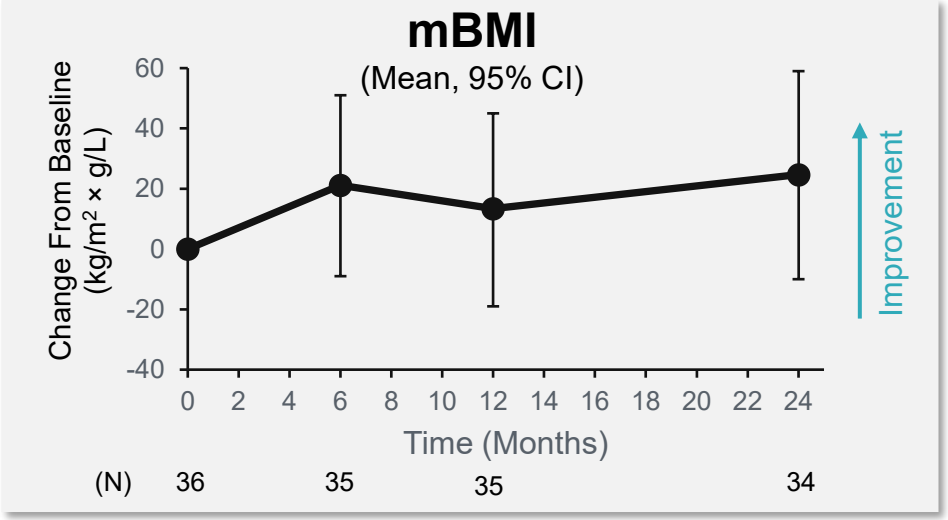
Data cutoff date: April 11, 2025

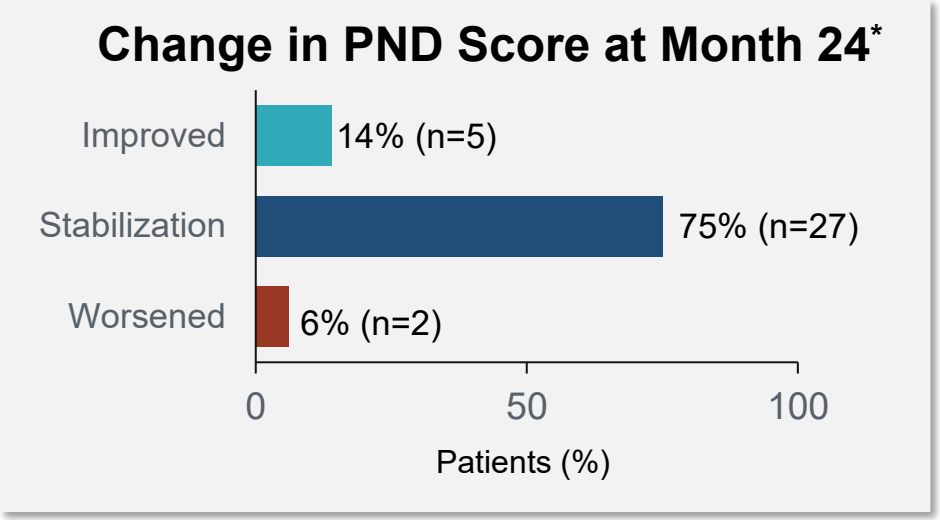
Gillmore JD, et al. NEJM, 2025. Copyright © 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Dotted line indicates cutoff for clinically meaningful improvement (Folkvaljon F, et al. Muscle Nerve, 2025). 1. mNIS+7 ranges from 0 to 304, with higher values indicating increased impairment. ATTRv-PN: hereditary ATTR amyloidosis polyneuropathy; mNIS+7: modified neuropathy impairment score +7

# Multiple ATTRv-PN Disease-Related Clinical Measures Show Stability or Improvement Through Month 24




Data cutoff date: April 11, 2025. Gillmore JD, et al. NEJM, 2025. Copyright © 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. 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. ATTRv-PN: hereditary ATTR amyloidosis polyneuropathy; 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

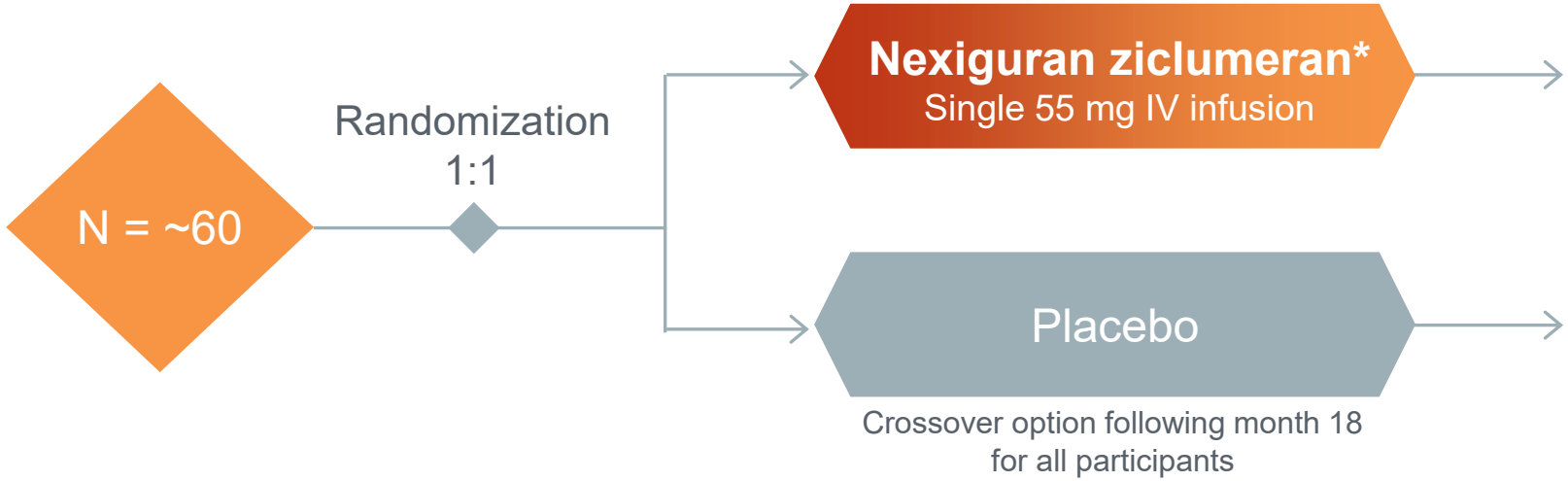
| Safety Events | All Patients (N=36) n (%) |
|---|---|
| **At least 1 AE** | 36 (100) |
| **AEs occurring in ≥15% of patients** | |
| IRR | 21 (58) |
| Headache | 10 (28) |
| Diarrhea | 8 (22) |
| Thyroxine decreased | 8 (22)* |
| AST increased | 6 (17)** |
| **Any serious AE** | 11 (31) |
| **Treatment-related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

- 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 an 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 date: April 11, 2025. Gillmore JD, et al. NEJM, 2025. Copyright © 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. * Not accompanied by thyroid-stimulating hormone elevation or symptoms of hypothyroidism. No patient had clinical hypothyroidism or TSH elevation. ** 3 patients had Grade ≥3 liver enzyme elevations. † 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. ‡ 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 polyneuropathy; IRR: infusion-related reaction; ULN: upper limit of normal

MAGNITUDE-2
CLINICAL TRIAL

# A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Nexiguran Ziclumeran (nex-z)* 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 <50 vs. ≥ 50
- *TTR* genotype: early onset V30M vs others

## Trial Duration:

- All patients must complete the month 18 visit

Clinicaltrials.gov ID: NCT06672237
* Formerly referred to as NTLA-2001
mNIS+7: Modified Neuropathy Impairment Score +7; TTR: Transthyretin; NIS: Neuropathy Impairment Score; PND: Polyneuropathy Disability; Norfolk QOL-DN: Quality of Life-Diabetic Neuropathy; mBMI: Modified Body Mass Index



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