MyPEAK™ -1

Scientific Sessions

INTERIM DATA FROM MYPEAK-1, A PH1B/2A STUDY OF TN-201 GENE THERAPY FOR *MYBPC3*-ASSOCIATED HCM

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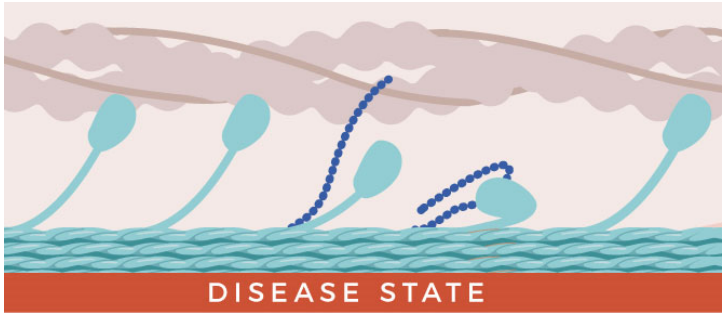
#AHA25

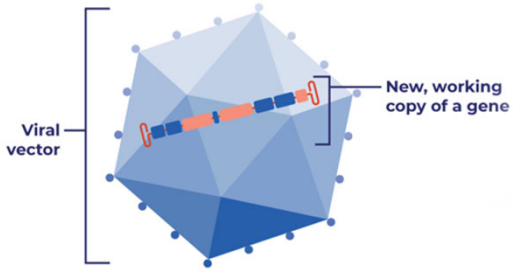
TN-201: POTENTIAL FIRST-IN-CLASS GENE THERAPY TARGETING CAUSE OF *MYBPC3*-ASSOCIATED HCM

MYBPC3 Pathophysiology

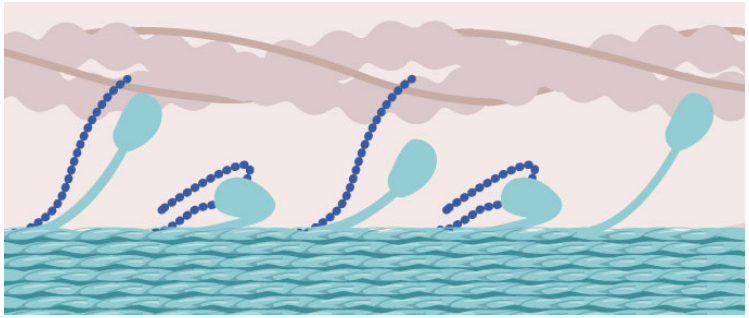


Heterozygous mutations in the *MYBPC3* gene lead to significantly **lower levels of MyBP-C protein** and dysregulated cardiac contractility[1]

TN-201 Mechanism of Action



TN-201 delivers a full-length, functional copy of the *MYBPC3* gene to cardiomyocytes using the most widely dosed capsid, AAV9[2]



Expression of the *MYBPC3* gene increases MyBP-C protein levels and is expected to restore sarcomeric function, reduce hypertrophy, and halt disease progression[3]

MyBP-C protein present in sarcomere

[1]O'Leary, et al., *J Mol Cell Cardiol* 2019
[2]Byrne, et al., *Mol Ther* 2025
[3]Greer-Short, et al., *Nat Commun* 2025

MYPEAK-1: PHASE 1B/2A TRIAL OF TN-201 IN ADULTS WITH *MYBPC3*-ASSOCIATED HCM

Study Objectives

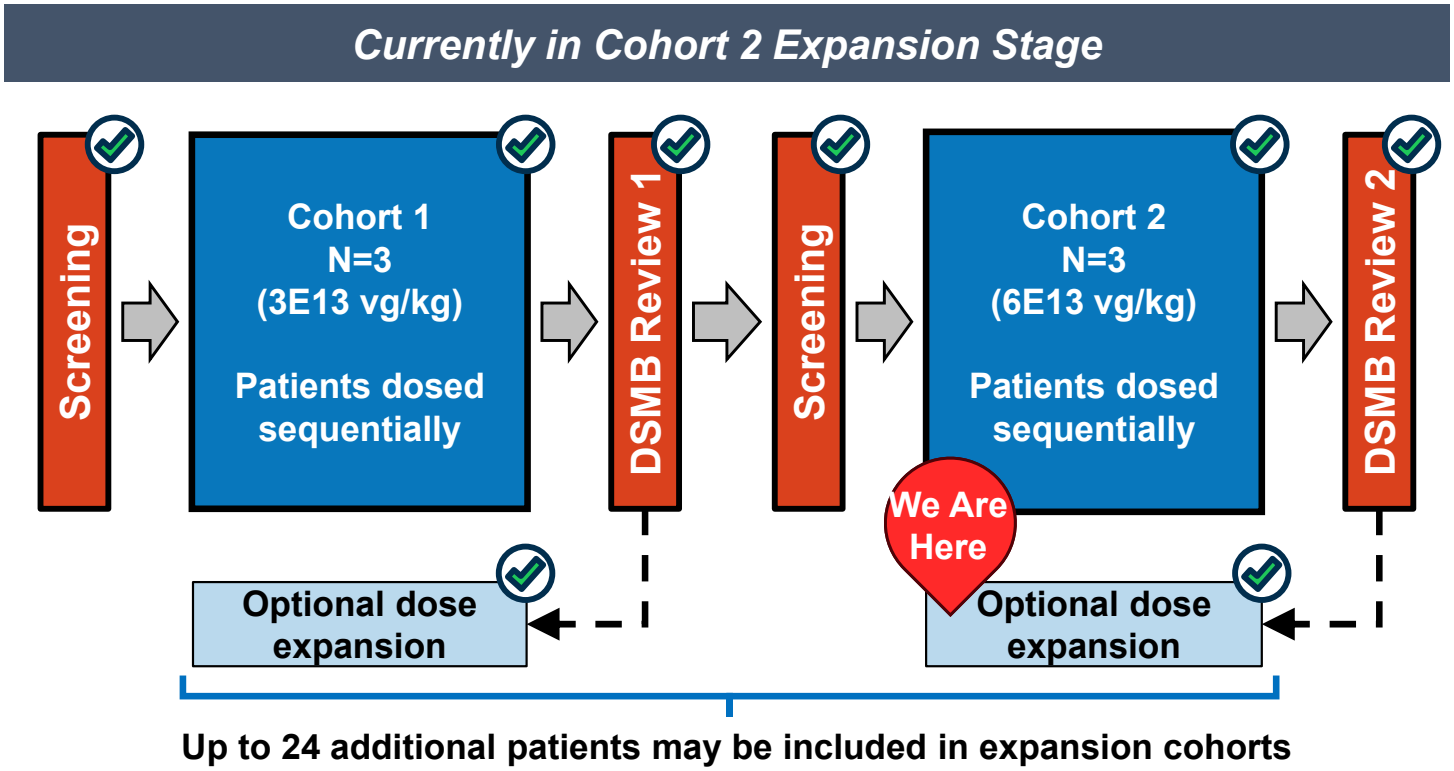
- Safety, tolerability
- Dose-finding
- Pharmacodynamics

Design

- Open-label, dose-escalation and dose expansion
- 52-week trial with 4-year safety and efficacy follow-up

Eligibility

- Age 18 to 75 with HCM
- P/LP *MYBPC3* mutation*
- NYHA Class II or III



*P/LP = pathogenic or likely pathogenic

PATIENTS IN BOTH COHORTS APPEAR MORE SEVERE THAN THE AVERAGE HCM PATIENT

	Average / % of HCM	Cohort 1			Cohort 2		
		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	Male (63%)[1]	Female	Female	Male	Female	Female	Female
Phenotype	nHCM (72%)[1]	nHCM	nHCM	nHCM	nHCM	nHCM	nHCM
Age at Dose	50y[1]	27	43	47	60	48	63
LVMI (g/m^2)	F: 89 | M: 104[3]	174	105	178	110	143	138
Myectomy	18%[5]	Yes	Yes	Yes	-	Yes	-
ICD	21%[1]	Yes	Yes	Yes	Yes	Yes	Yes
NT proBNP	563 pg/mL[7]	1884	351	913	337	1013	465
Troponin I	27 ng/L[8]	46	34	53	10	27	8
NYHA Class	50% ≥ II[4]	II	III	II	II	II	II

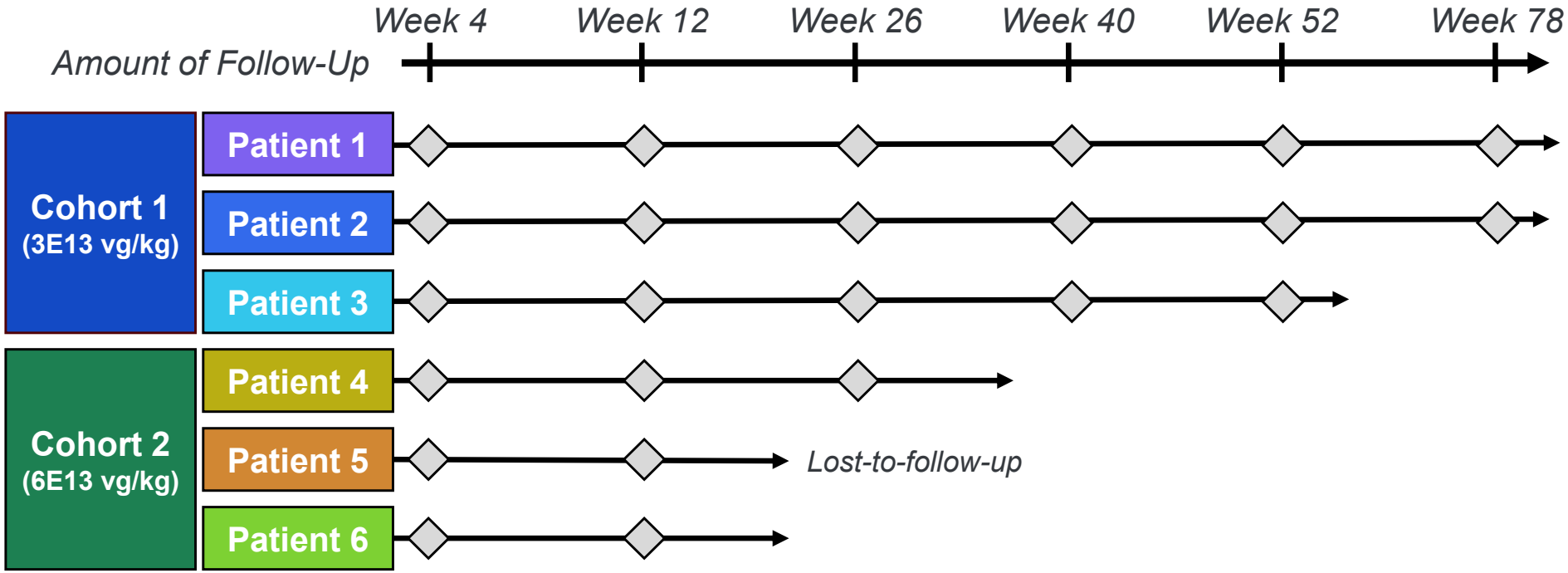
Baseline Characteristics

- Substantial hypertrophy
- All high-risk with ICD
- Majority with history of myectomy
- All symptomatic
- Anti-AAV9 neutralizing antibody titers ≤1:40

LEGEND
Typical for HCM
Abnormal for HCM
Very abnormal for HCM

[1]Ho, et al; *Circulation* 2018
[2]Rowin, et al; *Circ Arrhytm EP* 2020
[3]Olivotto, et al; *JACC* 2008
[4]Maron, et al; *JACC* Heart Fail 2018
[5]Maurizi, et al; *Circulation* 2024
[6]Cui, et al; *JACC* 2019
[7]Neubauer, et al; *JACC* 2019
[8]Okamoto, et al; *Int Heart J* 2013

COHORT 1 PATIENTS FOLLOWED FOR ≥52 WEEKS. MOST COHORT 2 PATIENTS FOLLOWED FOR ≥26 WEEKS

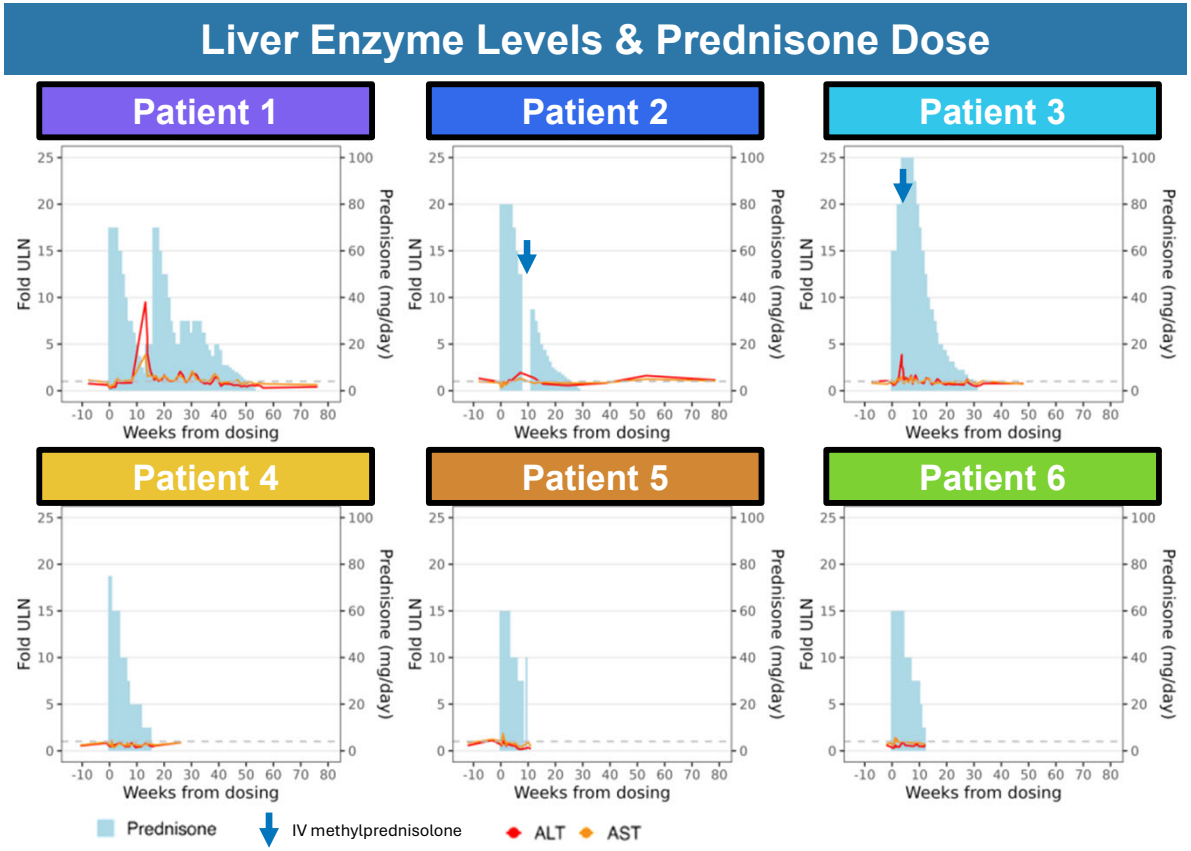


- *All patients other than Patient 5 have **completed every visit and remain in study***
- *Subsequent results come from a July 2025 data cut*

SAFETY: TN-201 HAS BEEN WELL TOLERATED AT BOTH DOSES

- Majority of treatment-emergent **adverse events** were **mild, transient and/or reversible**
  - Nausea (n=5) was the most common treatment-emergent adverse event
  - Two treatment-related serious adverse events (SAEs) occurred
    - One SAE of moderate (Grade 2) transaminase elevations, treated with IV steroid in hospital
    - One SAE of mild (Grade 1) complement elevation monitored in hospital
- Majority of patients (n=4) experienced **reversible elevations in liver enzymes**
  - Elevations normalized after additional steroid treatment
  - All transaminase elevations asymptomatic, with no change in bilirubin or liver synthetic function
- Two patients in Cohort 2 experienced **laboratory abnormalities, including complement elevation, related to innate immune response** within 1 week of dosing
  - Abnormalities **resolved in days without additional treatment or organ involvement**
- **All 6 patients have tapered off** prophylactic immunosuppression with prednisone and sirolimus
- **No signs of cardiotoxicity**, including **no declines in left ventricular ejection fraction (LVEF)**

OPTIMIZED IMMUNOSUPPRESSION SUCCESSFULLY REDUCED STEROID REQUIREMENT IN COHORT 2



IS Adjustments During Cohort 1

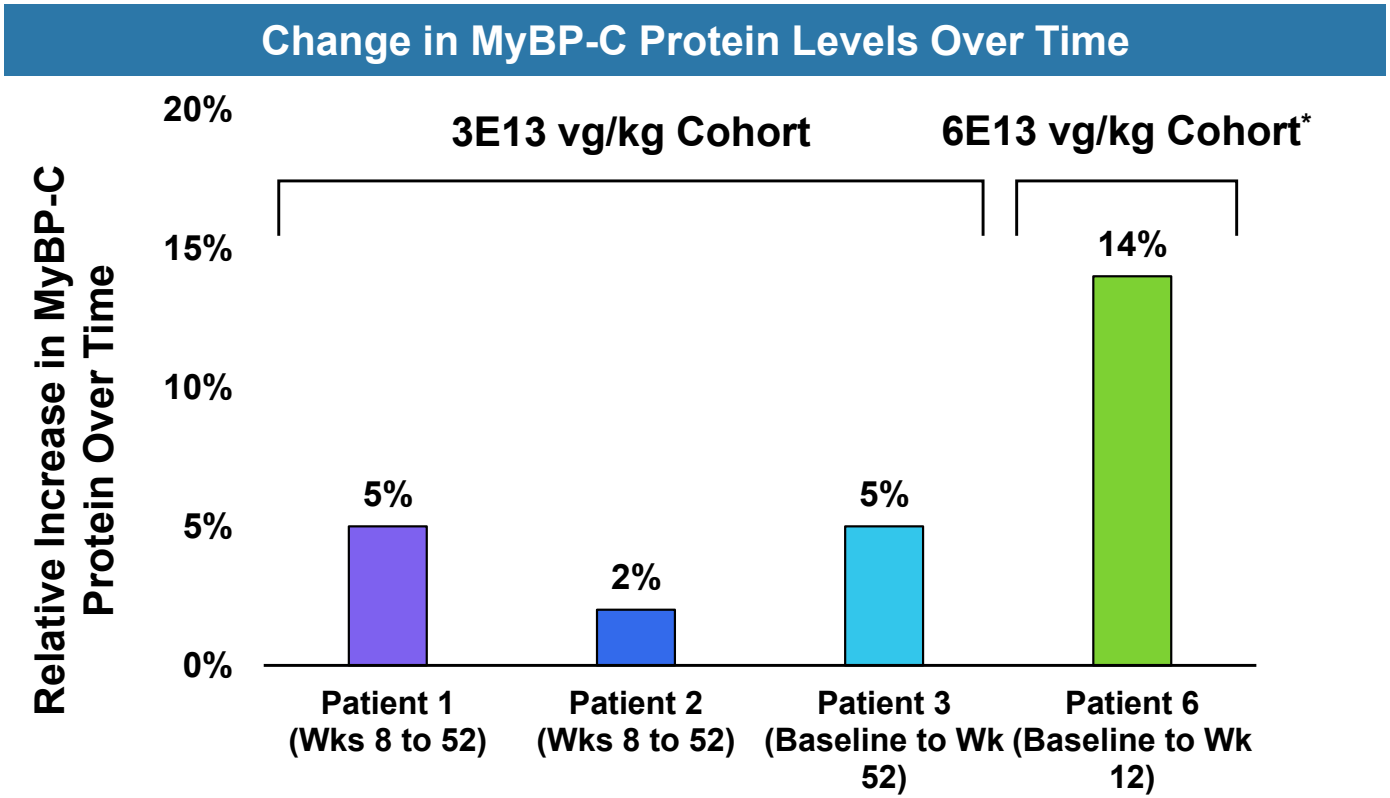
- Reduced maximum starting dose of prednisone dose from 80 mg to 60 mg
- Sirolimus initiated earlier (Day -7)
- Weekly monitoring during taper

Cohort 2 Results

- Despite higher dose of TN-201, Cohort 2 had fewer, lower elevations in AST/ALT
- Prednisone taper shorter for Cohort 2 (82±23 days) vs. Cohort 1 (262±98 days)

IS = immunosuppression

TN-201 HIGHER DOSE RESULTED IN GREATER INCREASE IN MYBP-C LEVELS



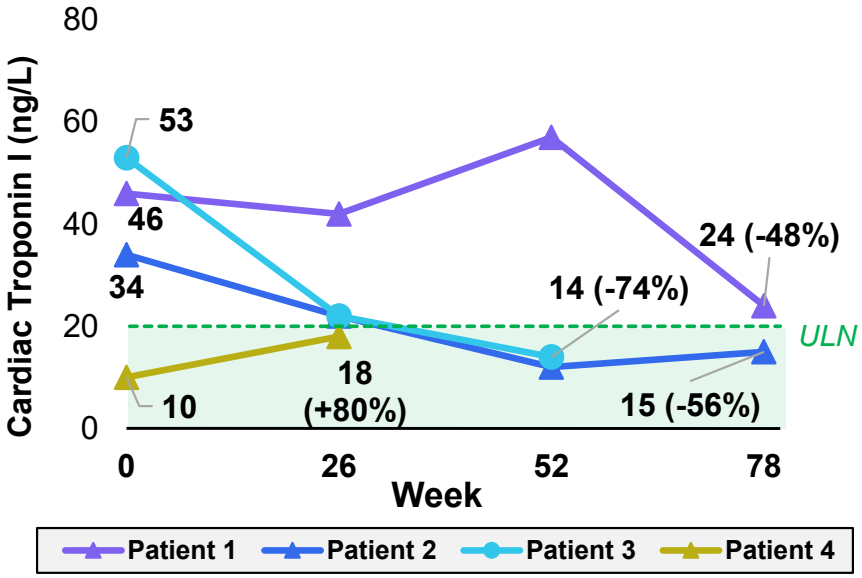
Interim MyBP-C Protein Levels

- Quantitative assay sensitive, but need baseline to quantify full amount of TN-201-derived MyBP-C protein
- Cohort 1 MyBP-C protein levels increased simultaneous with increase in RNA
- First patient from Cohort 2 shows dramatic increase only 12 weeks post-dose
- DNA and RNA similarly follow dose response in Cohort 2

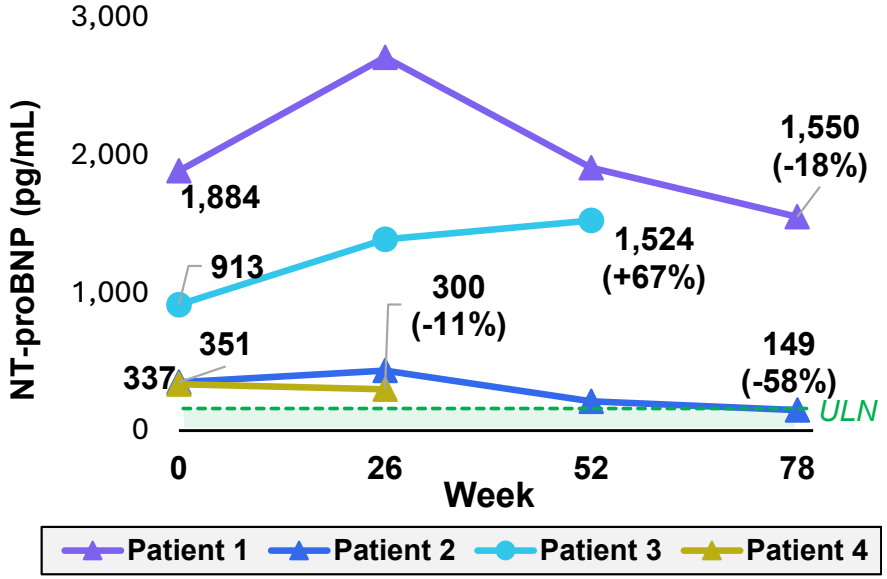
*Patients 4 and 5 had not yet provided post-dose biopsy at time of data cut

CARDIAC BIOMARKERS IMPROVED OR REMAINED STABLE 52-78 WEEKS AFTER DOSING

Cardiac Troponin I Levels Over Time (Change)



N-terminal Pro Brain Natriuretic Peptide (Change)



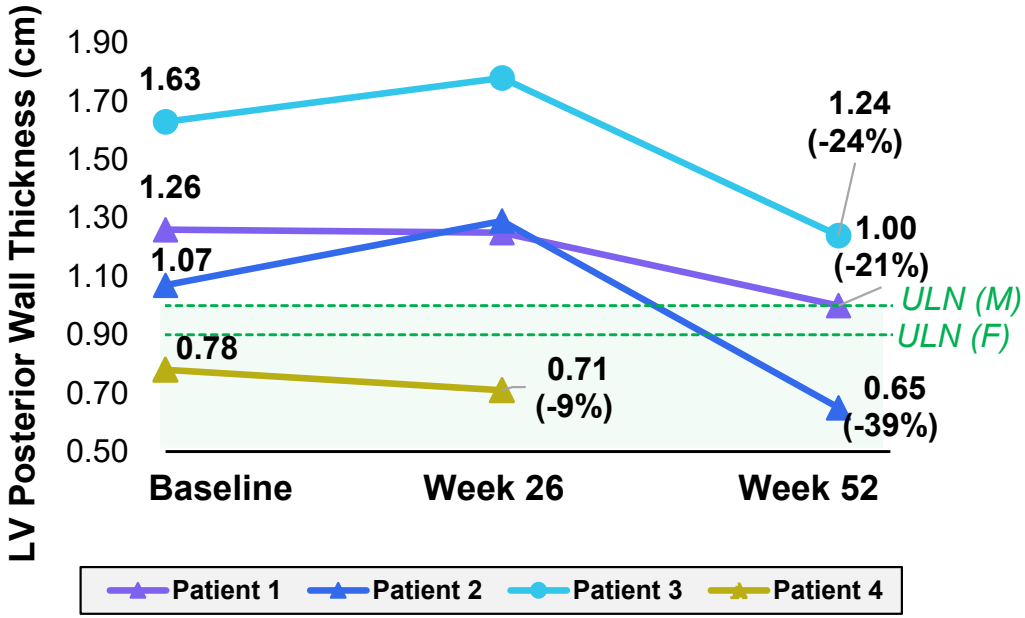
- Cardiac troponin declined 48-74% to normal or near-normal levels at most recent visit in all patients with abnormal levels at baseline and with at least 26 weeks of follow-up
- NT-proBNP increased with IS, but declined from or returned to baseline after IS in 2 of 3 patients from Cohort 1

ULN = Upper Limit of Normal
IS = immunosuppression

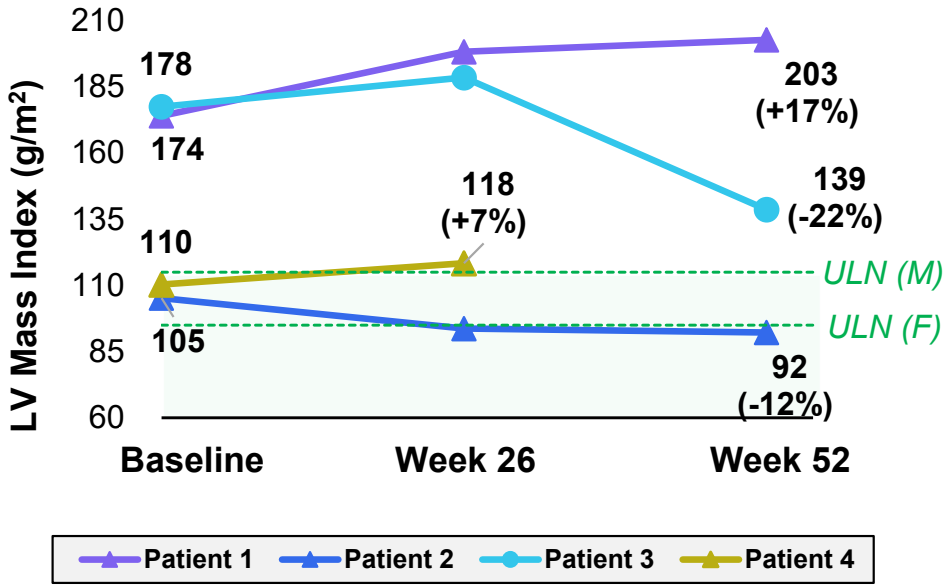
▲ Female
● Male

REDUCTIONS IN HYPERTROPHY HAVE EMERGED AFTER 6 MONTHS

Left Ventricular Posterior Wall Thickness Over Time



Left Ventricular Mass Index Over Time



- Measures of diastolic function have remained stable in patients
- **NYHA has improved to Class I in all patients with at least 26 weeks of follow-up**

ULN = Upper Limit of Normal
IS = immunosuppression

▲ Female
● Male

INTERIM DATA PROMISING, MORE FOLLOW-UP NEEDED

- Lack of biopsy samples for Patients 1 and 2 at baseline and for Patients 4 and 5 post-dose needed to quantify protein increases fully, though baseline biopsies from Patients 3 and 6 useful in interpretation
- While molecular, laboratory, and echocardiographic data come from central laboratories, potential for bias still exists due to open-label design of this first-in-human study
- Clinical meaningfulness of changes promising but more follow-up and more patients needed
- Short duration of follow up for Cohort 2 at the time of this interim analysis

CONCLUSIONS & FUTURE DIRECTIONS FOR TN-201

WELL TOLERATED

Potential first-in-class gene therapy for HCM remains well tolerated at both 3E13 vg/kg and 6E13 vg/kg doses

MECHANISM WORKS

Robust transduction and durable expression at both 3E13 vg/kg and 6E13 vg/kg doses

INDICATORS OF REMODELING

Directional improvements noted in biomarkers and markers of cardiac structure and function

MOVE DEVELOPMENT FORWARD

Data support continued dosing of patients in the future and potential expansion into other populations beyond adults, including pediatrics

MyPEAK™-1

ACKNOWLEDGMENTS

- MyPEAK-1 patients and their families
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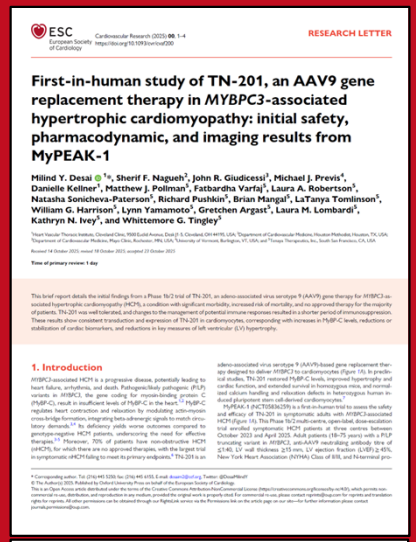
- Drs. Scott Solomon and Jon Cunningham and the team at the Cardiovascular Imaging Core Lab at Brigham
- Team at Tenaya Therapeutics, including Whit Tingley, LaTanya Tomlinson, Bardha Varfaj, Matt Pollman, Gretchen Argast, Will Harrison

Simultaneous publication of interim results available in **Cardiovascular Research:**



ESC European Society of Cardiology — Cardiovascular Research (2025) 00, 1–4 — https://doi.org/10.1093/cvr/cvaf200 — RESEARCH LETTER

First-in-human study of TN-201, an AAV9 gene replacement therapy in *MYBPC3*-associated hypertrophic cardiomyopathy: initial safety, pharmacodynamic, and imaging results from MyPEAK-1

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This brief report details the initial findings from a Phase 1b/2 trial of TN-201, an adeno-associated virus serotype 9 (AAV9) gene therapy for *MYBPC3*-associated hypertrophic cardiomyopathy (HCM), a condition with significant morbidity, increased risk of mortality, and no approved therapy for the majority of patients. TN-201 was well tolerated, and changes to the management of potential immune responses resulted in a shorter period of immunosuppression. These results show consistent transduction and expression of TN-201 in cardiomyocytes, corresponding with increases in MyBP-C levels, reductions or stabilization of cardiac biomarkers, and reductions in key measures of left ventricular (LV) hypertrophy.

1. Introduction

MYBPC3-associated HCM is a progressive disease, potentially leading to heart failure, arrhythmia, and death. Pathogenic/likely pathogenic (P/LP) variants in *MYBPC3*, the gene coding for myosin-binding protein C (MyBP-C), result in insufficient levels of MyBP-C in the heart.[1,2] MyBP-C regulates heart contraction and relaxation by modulating actin–myosin cross-bridge formation, integrating beta-adrenergic signals to match circulatory demands.[1,2] Its deficiency yields worse outcomes compared to genotype-negative HCM patients, underscoring the need for effective therapies.[3–5] Moreover, 70% of patients have non-obstructive HCM (nHCM), for which there are no approved therapies, with the largest trial in symptomatic nHCM failing to meet its primary endpoint.[6] TN-201 is an adeno-associated virus serotype 9 (AAV9)-based gene replacement therapy designed to deliver *MYBPC3* to cardiomyocytes (Figure 1A). In preclinical studies, TN-201 restored MyBP-C levels, improved hypertrophy and cardiac function, and extended survival in homozygous mice, and normalized calcium handling and relaxation defects in heterozygous human induced pluripotent stem cell-derived cardiomyocytes.[7]

MyPEAK-1 (NCT05836259) is a first-in-human trial to assess the safety and efficacy of TN-201 in symptomatic adults with *MYBPC3*-associated HCM (Figure 1A). This Phase 1b/2 multi-centre, open-label, dose-escalation trial enrolled symptomatic HCM patients at three centres between October 2022 and April 2025. Adult patients (18–75 years) with a P/LP truncating variant in *MYBPC3*, anti-AAV9 neutralizing antibody titre of ≤140, LV wall thickness ≥15 mm, LV ejection fraction (LVEF) ≥45%, New York Heart Association (NYHA) Class of II/III, and N-terminal pro-

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