First Report of MyPEAK-1: a Phase 1b/2a Study of the Safety and Efficacy of TN-201, An AAV9 Gene Therapy, In Adults With *MYBPC3*-Associated Hypertrophic Cardiomyopathy

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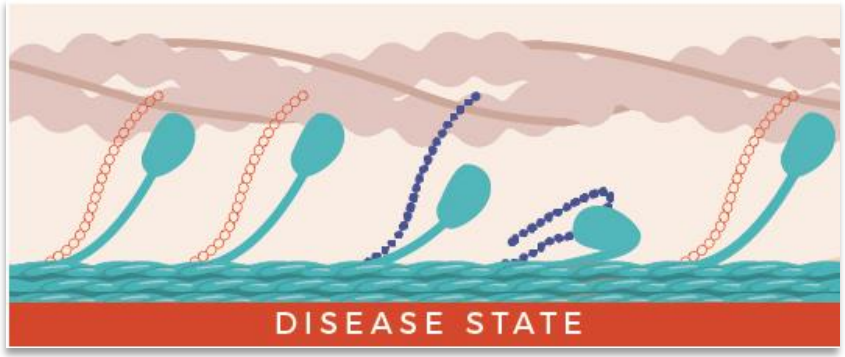
Disclosures: I am on the executive steering committee of NIH-sponsored HCMR trial

Study PI of trials sponsored by Bristol Myers Squibb, Edgewise, Viz AI, Cytokinetics, and Tenaya

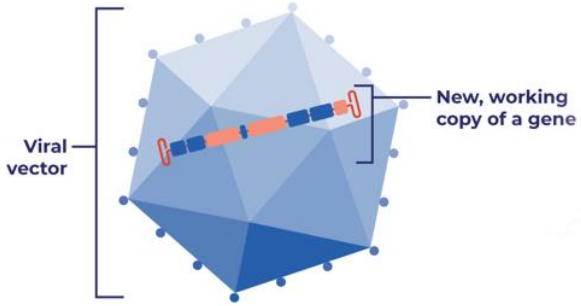
TN-201: First-in-Class Gene Therapy, Targeting Underlying Cause of Disease

MYBPC3 Pathophysiology

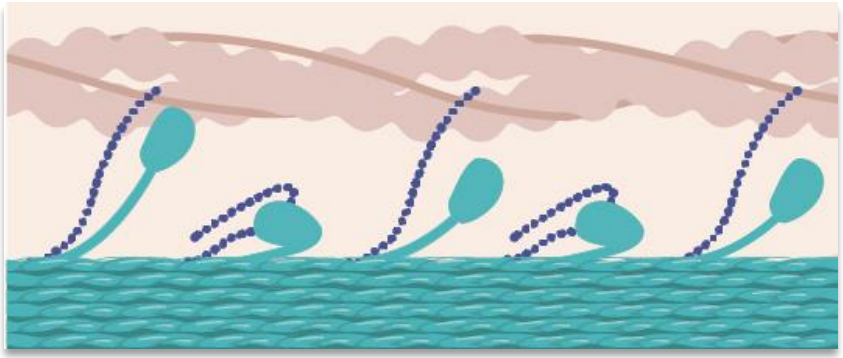


Heterozygous mutations in the *MYBPC3* gene lead to ~40% fewer MyBP-C proteins and dysregulated cardiac contractility

TN-201 Mechanism of Action



TN-201 delivers a *MYBPC3* gene to cardiomyocytes using an adeno-associated viral vector



Addition of a *MYBPC3* gene increases MyBP-C protein levels and is expected to restore cardiac function and halt progression

MyBP-C protein missing in sarcomere

MyBP-C protein present in sarcomere

MyPEAK-1: A Phase 1b/2a Trial of TN-201 in Adults with *MYBPC3*-Associated HCM

Study Objectives

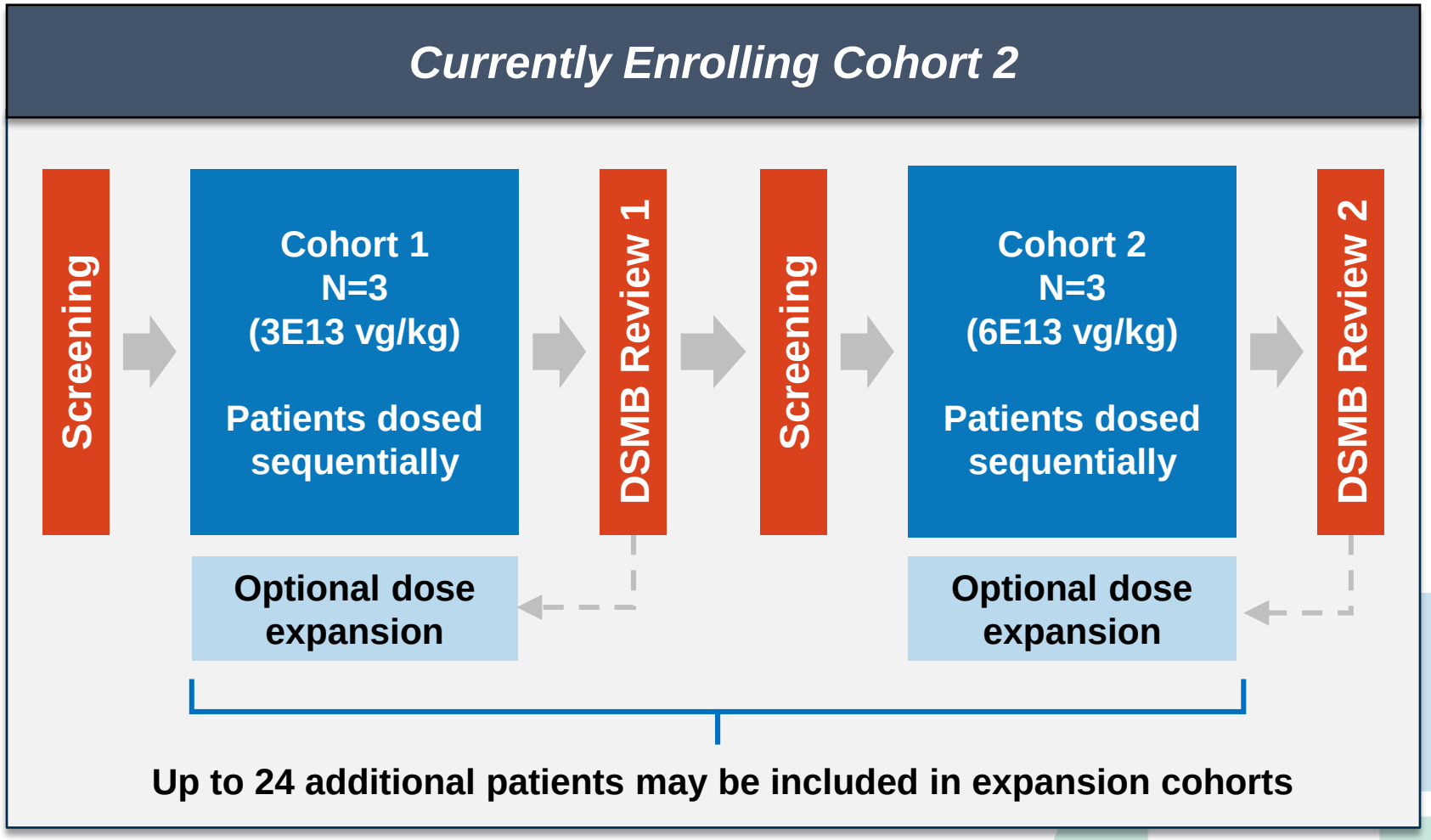
- Safety, tolerability
- Dose-finding
- Pharmacodynamics

Design

- Open-label, multi-center, dose-escalation and expansion
- 52-week trial with 4-year safety and efficacy follow-up
- Cardiac biopsy at baseline*, post-dose, and Week 52

Eligibility

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



*Baseline biopsy starting with Cohort 1, Patient 3

P/LP = pathogenic or likely pathogenic

Cohort 1 Patients Have More Severe Disease Than the Average HCM Patient

	Average HCM	Patient 1	Patient 2	Patient 3
Length of Follow-Up	-	12 months	12 months	6 months
Gender	Male (63%)[1]	Female	Female	Male
Phenotype	Nonobstructive (72%)[1]	Nonobstructive	Nonobstructive	Nonobstructive
Current Age	50y[1]	27	43	47
LVMI (g/m^2)	F: 89 | M: 104[3]	174	105	177
NYHA Class	50% ≥ Class II[4]	II	III	II
% Myectomy & Age	18%[5] | Mean = 54y[6]	24	30	39
% ICD & Age	21%[1] | Mean = 38y[2]	27	37	36
NT proBNP (pg/ml)	563[7]	1836	351	1229
Troponin I (ng/L)	27[8]	46	34	53

Typical for HCM | Abnormal for HCM | Very abnormal for HCM

Baseline Characteristics

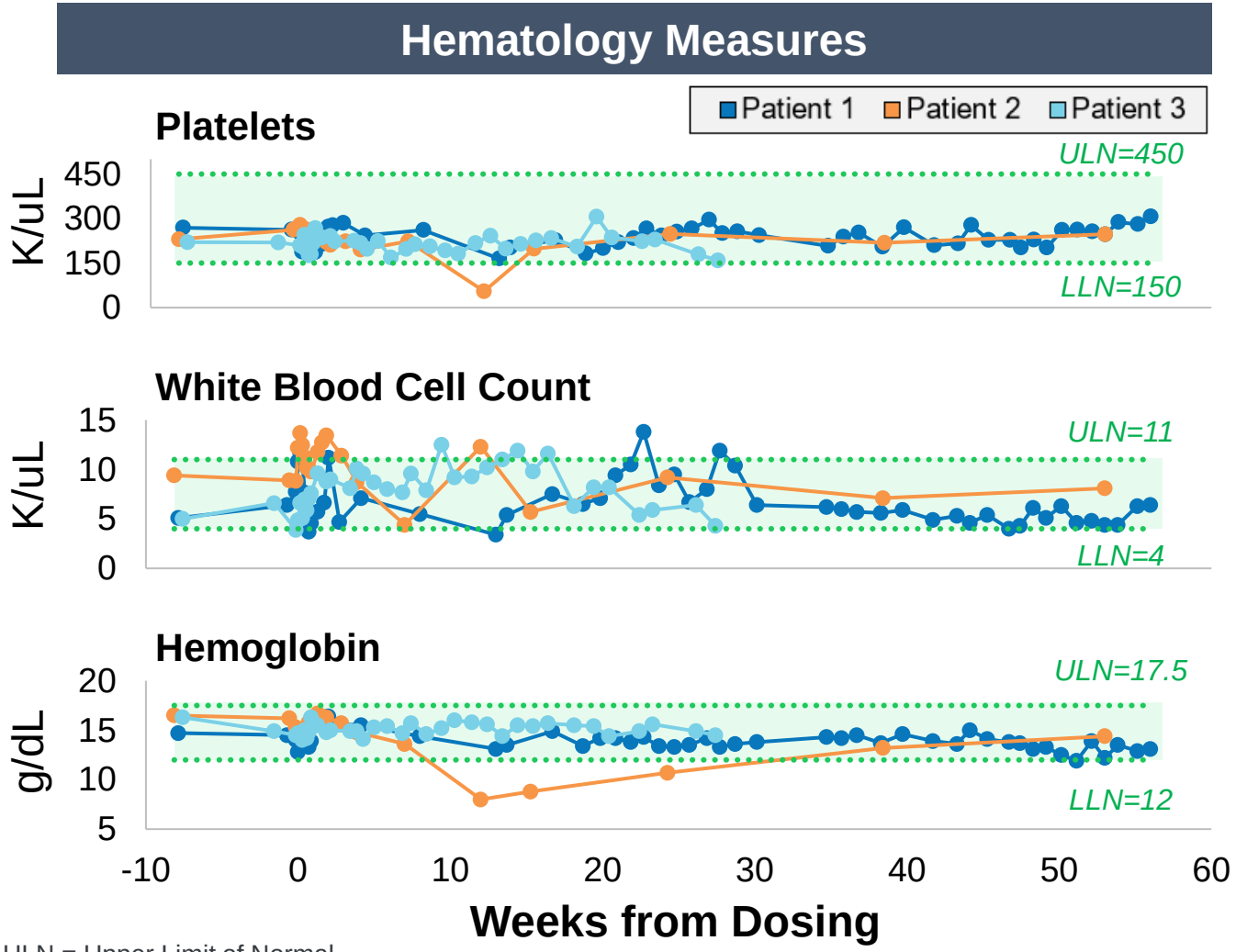
- Significant hypertrophy
- Symptomatic
- All have severe disease with ICD & myectomy
- Elevated cardiac biomarkers

[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

TN-201 Has Been Well-Tolerated

- All patients (n=3) experienced transient, reversible elevations in liver enzymes following dosing
  - All patients on prophylactic immunosuppression with prednisone and sirolimus
  - Elevations normalized after additional steroid treatment
  - One mild adverse event classified as a Serious Adverse Event (SAE) with inpatient steroids
- Majority of treatment-emergent adverse events were mild, transient or reversible
  - Two other SAEs occurred, both unrelated to TN-201
- No signs of cardiotoxicity
  - ICD requirement lifted
- No thrombotic microangiopathy. No thrombocytopenia related to TN-201
- All patients have completed every visit and remain in study

Hematology Measures Stable Up to 1 Year After Dosing



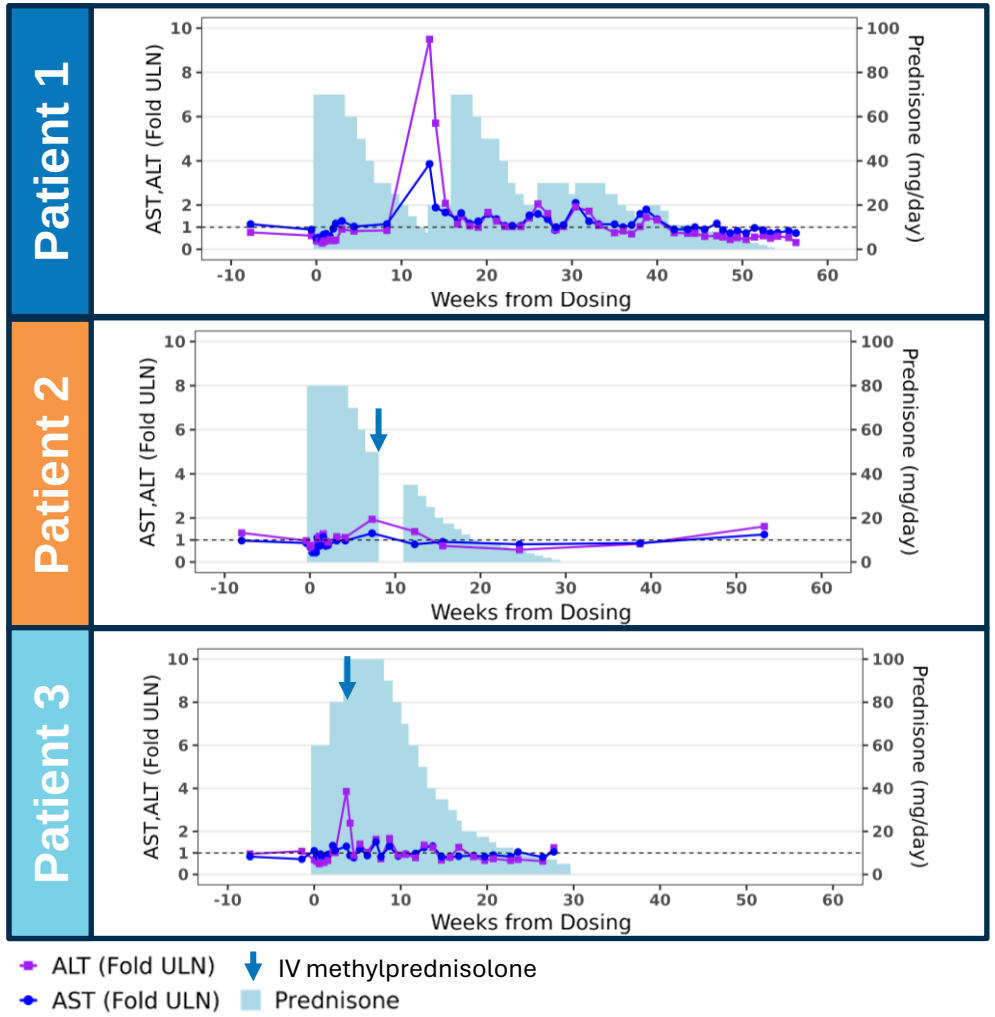
ULN = Upper Limit of Normal
LLN = Lower Limit of Normal

Interim Cohort 1 Hematology Results

- Frequent monitoring throughout
- Patients mostly in normal range with minimal changes
- Patient 2 experienced brief decline in platelets and hemoglobin due to an SAE unrelated to TN-201

Immunosuppression Is Effective in Managing Response to TN-201

Liver Enzyme Levels & Prednisone Dose

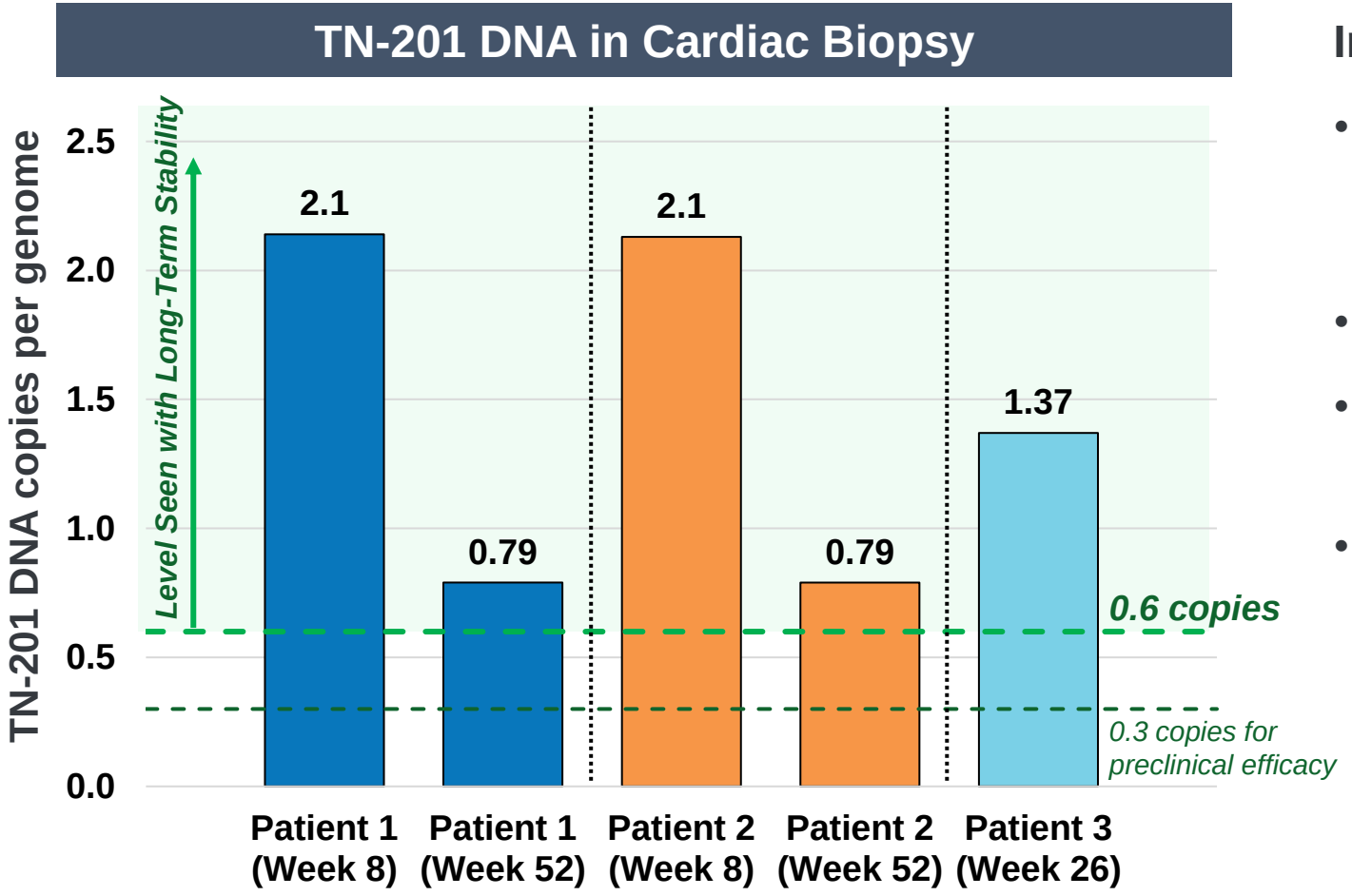


Interim Cohort 1 Immunosuppression

- Regimen: prophylactic prednisone and sirolimus
- Weekly monitoring during taper
- Changed management after Patient 1. Immunosuppression shorter and fewer events for Patients 2 & 3
- All 3 patients now off immunosuppression
- Transaminase elevations asymptomatic, no change in bilirubin
- Data consistent with approved AAV gene therapies

[1]ROCTAVIAN Package Insert, June 2023
[2]HEMGENIX Package Insert, November 2022
[3]BEQVEZ Package Insert, April 2024

TN-201 Reaches Heart as Intended and Is Stable Within Cardiomyocytes

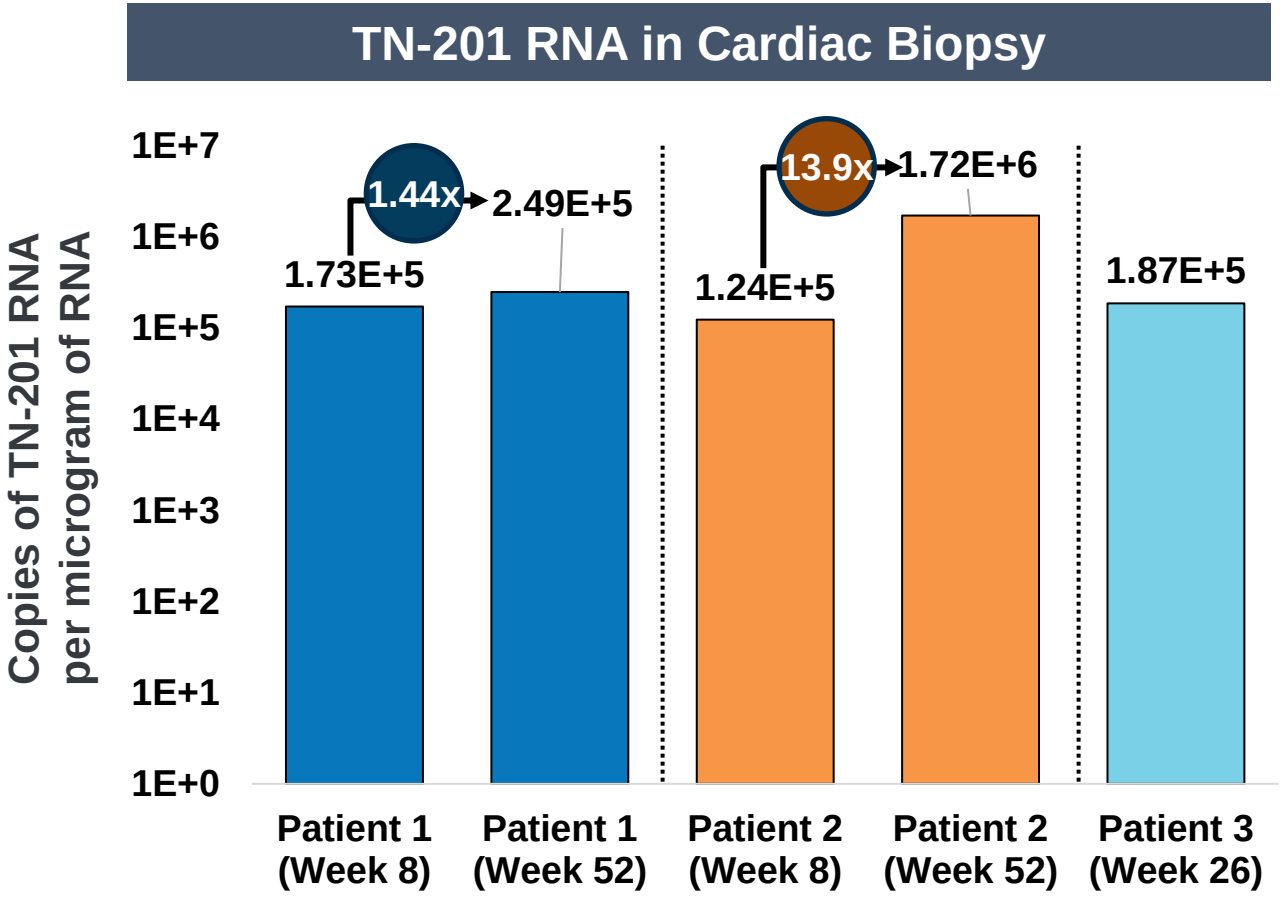


Interim Cohort 1 TN-201 DNA Results

- Patients 1 & 2 biopsies at Weeks 8 and 52 post-dose. Patient 3 at Week 26; Week 52 forthcoming
- Consistent levels across patients
- Remains in cardiomyocytes. Cleared from non-cardiomyocytes over time
- Decline in first year as expected. Similar to other gene therapies where DNA levels remain stable out ≥3 years[1]

[1]Greenberg, et al., *NEJM* 2024

TN-201 Expressed in Cardiomyocytes and Continues to Increase Over Time

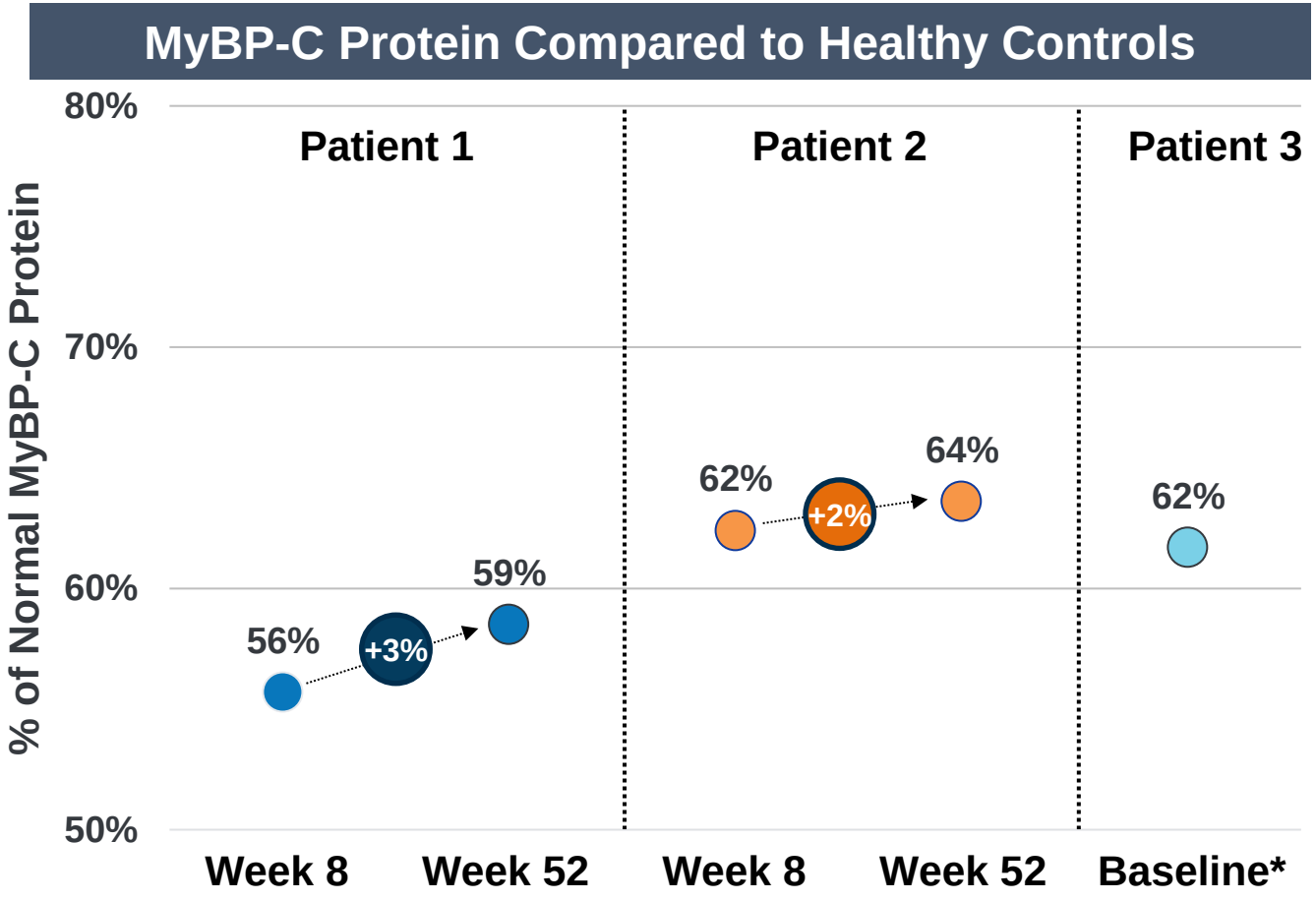


Interim Cohort 1 TN-201 RNA Results

- Assay highly specific for TN-201 RNA vs. patient's *MYBPC3* RNA
- Early expression observed in all patients
- Increases over time; may not be at steady state
- Within or above ranges observed in AAV cardiac gene therapy trials[1,2]

[1]Greenberg, et al., *NEJM* 2024
[2]Thomas, WORLD Symposium, February 2024

TN-201 Results in Modest Increase in MyBP-C Protein Levels



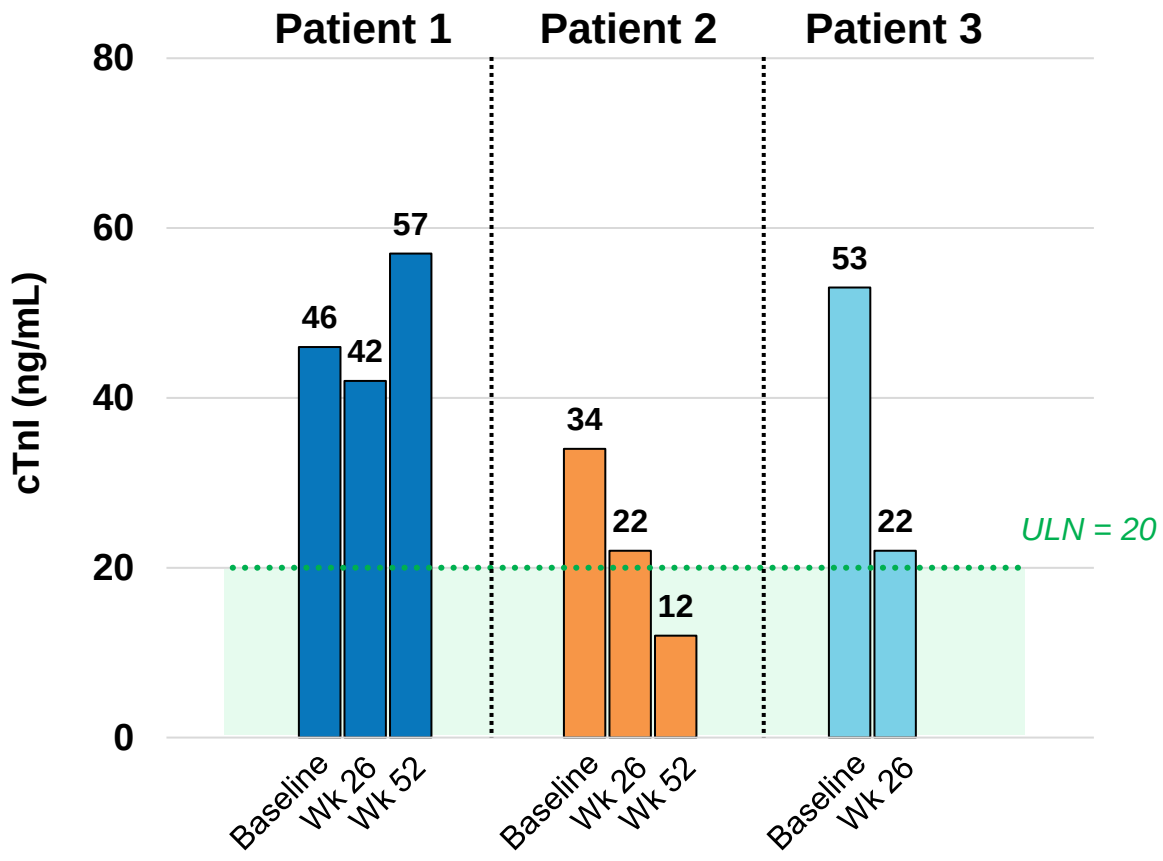
*Patient 3 Week 26 biopsy not evaluable due to low cardiomyocyte content in sample

Interim Cohort 1 MyBP-C Protein Levels

- Quantitative assay sensitive, but cannot distinguish TN-201-derived protein from endogenous MyBP-C
- Patients 1 and 2 show modest increases in protein simultaneous with increase in RNA
- No baseline biopsies for patients 1 & 2 limit ability to infer total MyBP-C increase
- Patient 3 has baseline, but Week 26 sample not evaluable. Will collect Week 52

Cardiac Biomarkers Improve or Are Stable by 52 Weeks After Dosing

Cardiac Troponin I Levels



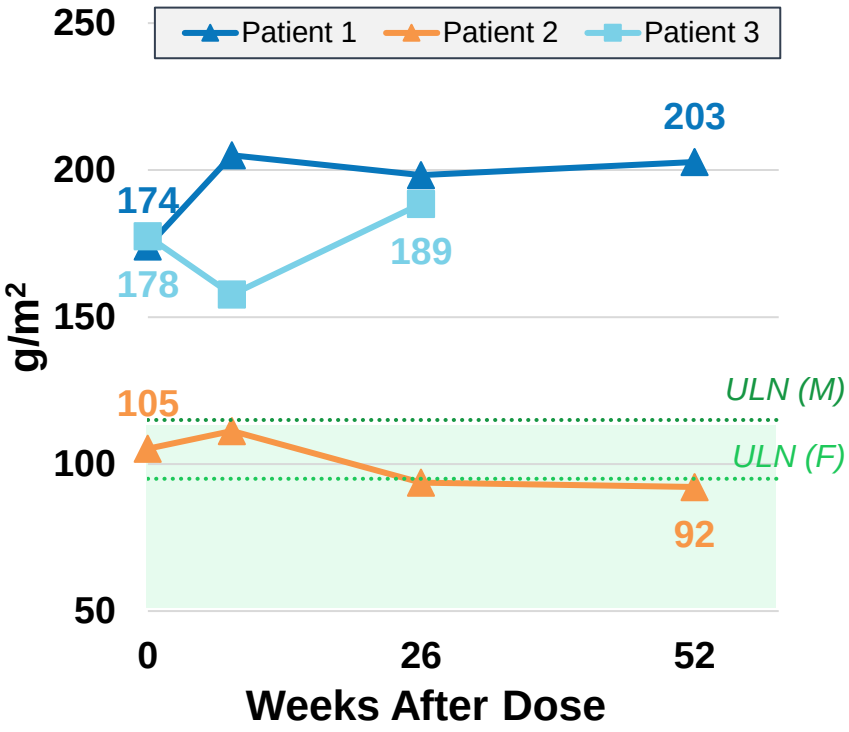
Interim Cohort 1 Cardiac Biomarker Levels

- Cardiac troponin declined ≥60% in 2 of 3 patients
- Patients 2 and 3 normal or near normal
- NT-proBNP increased with IS, but declined from or returned to baseline after IS

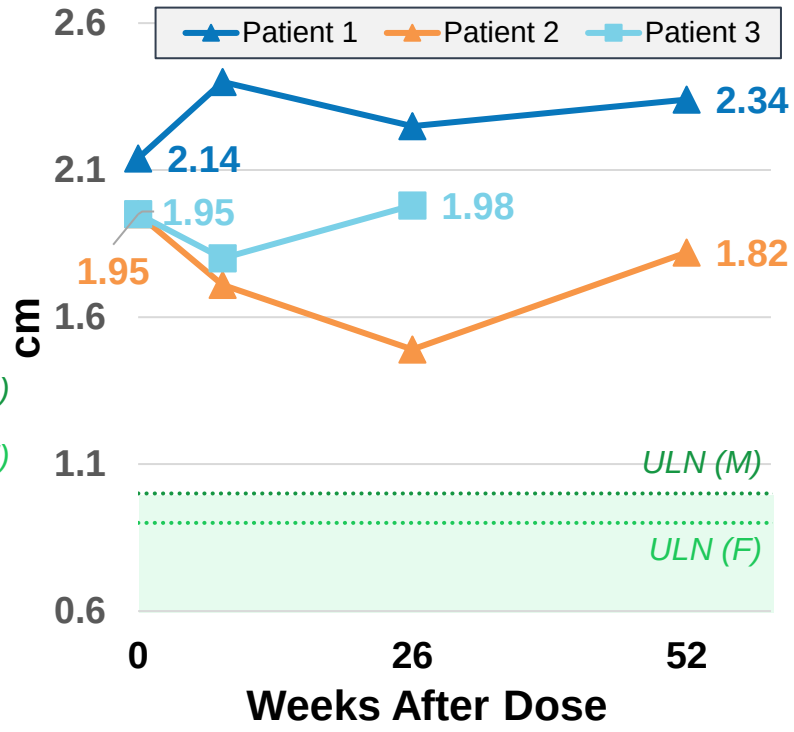
ULN = Upper Limit of Normal
IS = immunosuppression

Cardiac Structure and Function Have Improved or Are Stable

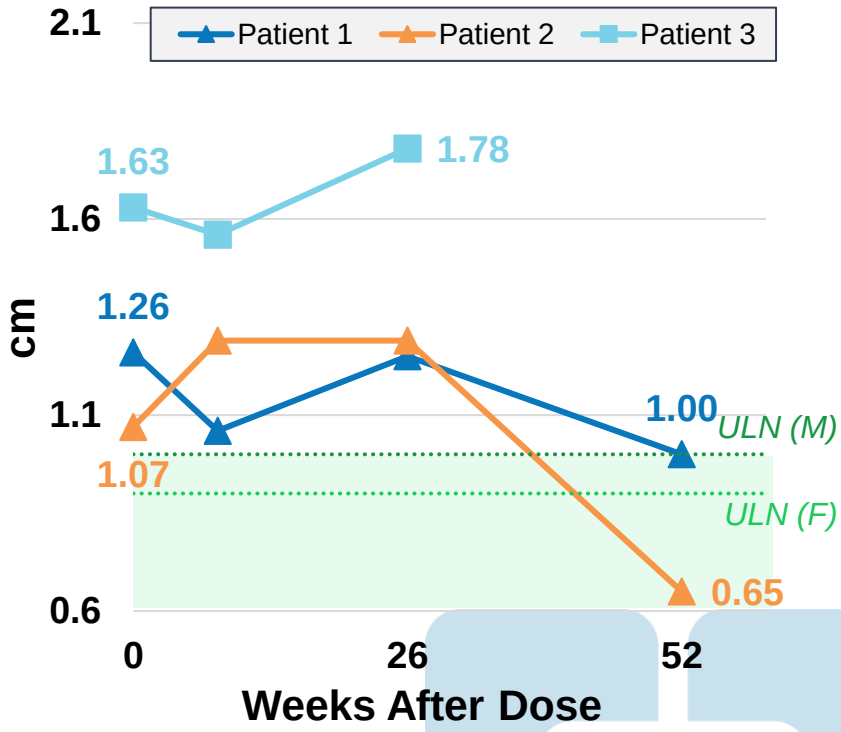
LV Mass Index



IV Septum Thickness



LV Posterior Wall Thickness



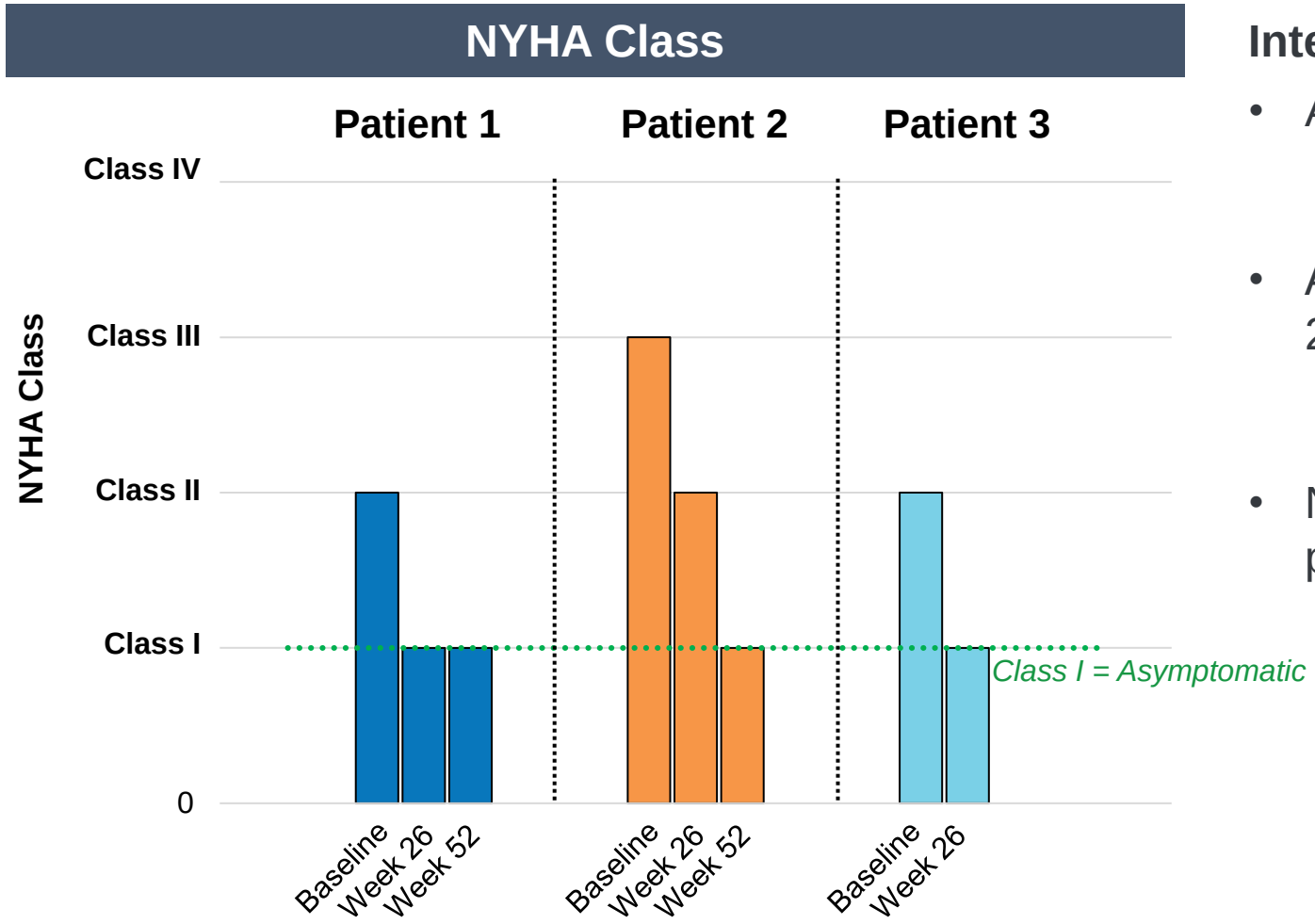
Measures of diastolic function remain stable

▲ Female ■ Male

ULN = Upper Limit of Normal
LV = Left ventricular

IV = Intraventricular

All Patients' Heart Failure Symptoms Improved and Are Now NYHA Class I



Interim Heart Failure Symptoms in Cohort 1

- All patients symptomatic at baseline
- All patients' NYHA Class improved by Week 26
- No limitation of physical activity observed in all patients

Conclusions and Future Directions

- First-ever clinical data for gene therapy for HCM
- Gene therapy can be administered and managed effectively at an HCM center
- TN-201 at 3E13 vg/kg has been well tolerated
- Robust transduction and expression at 3E13 vg/kg dose (Cohort 1)
- Biomarkers and measures of cardiac structure & function improved or were stable
- Data support continued follow-up and dose escalation to 6E13 vg/kg (ongoing)
- More data from Cohort 1 and 6E13 vg/kg dose (Cohort 2) later this year

Acknowledgments

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