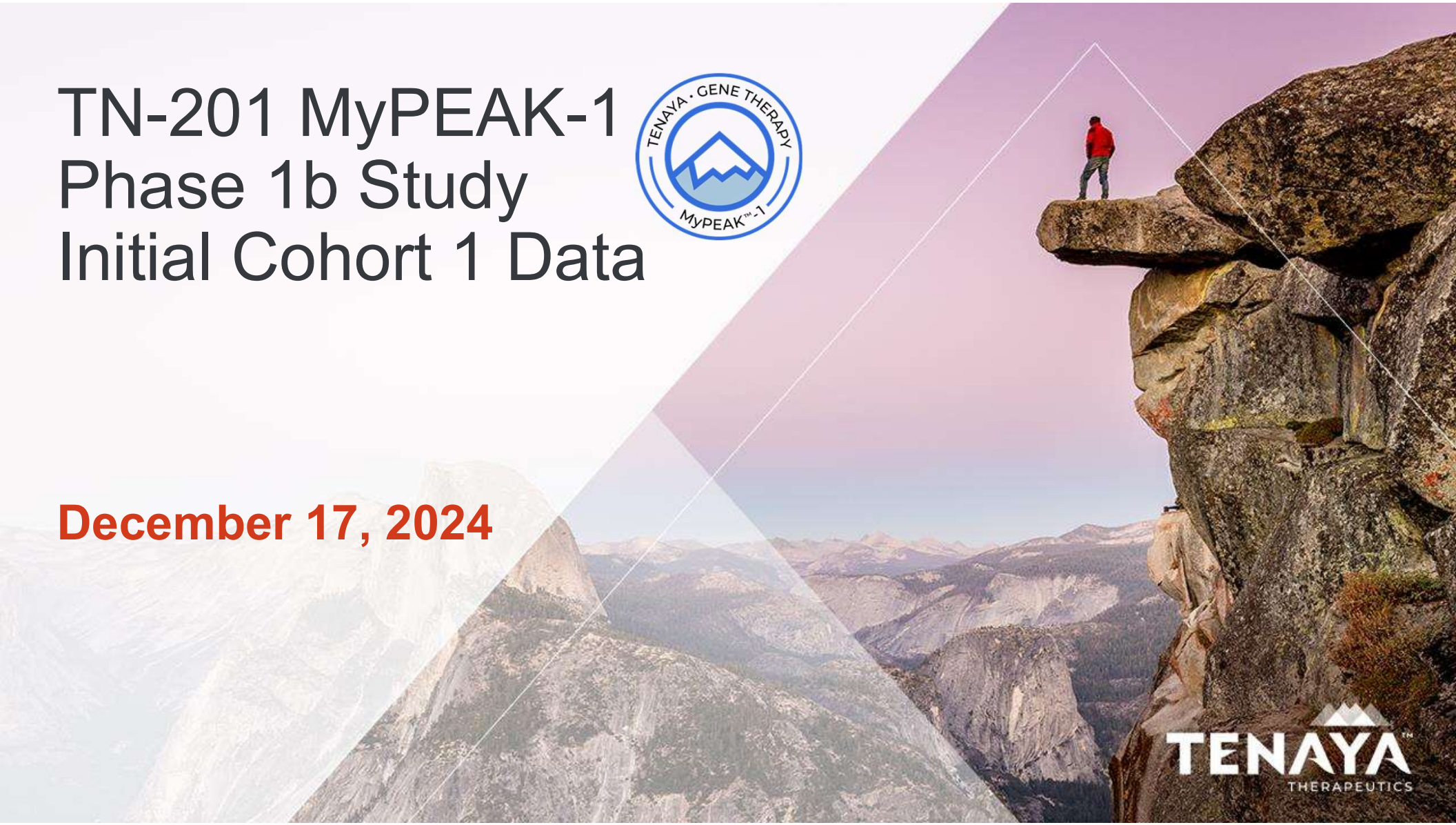
TN-201 MyPEAK-1 Phase 1b Study Initial Cohort 1 Data



December 17, 2024

Today’s speakers

Faraz Ali, MBA
Chief Executive Officer

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Haslam Family Endowed Chair in Cardiovascular Medicine,
Vice Chair, Heart Vascular Thoracic Institute, and
Director of the HCM Center at Cleveland Clinic

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Forward-looking statement

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, that are based on our management's beliefs and assumptions and on information currently available to our management. Forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified. All statements other than statements of historical facts contained in this presentation, including statements regarding the planned timing to report additional data from MyPEAK-1; the ongoing enrollment of patients in Cohort 2 of MyPEAK-1; the clinical, therapeutic and commercial potential of, and expectations regarding TN-201; the value of additional MyPEAK-1 data to inform the potential of TN-201; the inferences regarding MyBP-C protein and mRNA expression; and statements regarding the continued development TN-201 and TN-201 clinical outcomes, which may materially change as patient enrollment continues or more patient data become available, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "anticipated" "purpose," "focus," "believe," "expected," "look forward," "plan," "potential," "may," "future," "will," or the negative of these terms or other similar expressions. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions described in our filings with the SEC, including, but not limited to the section titled "Risk Factors" in our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2024, and other documents we have, or will file with the SEC. These filings, filed, are available on the SEC website at www.sec.gov. Such risks include, among other things: the availability of MyPEAK-1 data at the referenced times; the timing and progress of MyPEAK-1; the potential failure of TN-201 to demonstrate safety and/or efficacy in clinical testing; the potential for any MyPEAK-1 clinical trial results to differ from preclinical, interim, preliminary or expected results; our ability to enroll and maintain patients in clinical trials, including MyPEAK-1; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early stage company; our continuing compliance with applicable legal and regulatory requirements; our estimates of the number of patients who suffer from the diseases we are targeting and the number of patients that may enroll in our clinical trials; our ability to raise any additional funding it will need to continue to pursue its product development plans; our reliance on third parties; our manufacturing, commercialization and marketing capabilities and strategy; the loss of key scientific or management personnel; competition in the industry in which we operate; our ability to obtain and maintain intellectual property protection for its product candidates; general economic and market conditions; and other risks . These risks are not exhaustive. New risk factors emerge from time to time and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. The forward-looking statements made in this presentation relate only to events as of the date on which such statements are made. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

 This is showing as marked but we retained this from the original draft since the deck has patient population numbers. This is not included in the PR or 8-K.

Introductory comments

Faraz Ali, Chief Executive Officer

Initial MyPEAK-1 Cohort 1 data derisks safety; reaffirms AAV9 as capsid of choice

1 **Safety: TN-201 well tolerated; safety profile is consistent with other gene therapies**

- No cardiotoxicities
- Liver enzyme elevations manageable and reversible
- DSMB endorsed dose escalation

2 **Biopsy: TN-201 reaches heart cells and achieves expression**

- Robust cardiac transduction that exceeds expectations
- Durable and increasing mRNA expression over time
- Protein levels modestly higher from 8 to 52 weeks

3 **Clinical Endpoints: Encouraging, but early**

- Stability—and improvement—seen in certain parameters; further follow-up needed

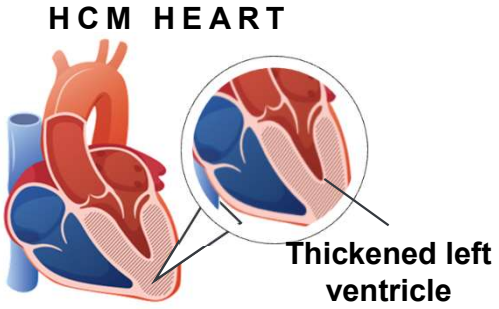
AAV9 = adeno-associated virus serotype 9 | DSMB = data safety and Monitoring Board | mRNA = messenger ribonucleic acid |

MYBPC3-associated HCM is estimated to affect 120,000 people in the U.S. alone(1)

A severe and progressive autosomal dominant condition affecting adults, teens, children and infants

~57% of identified genetic variants underlying familial HCM are *MYBPC3* mutations[1]

>30% of genetic variants underlying childhood-onset HCM are *MYBPC3* mutations[2]



- Significant functional impairment
- Social and psychological impacts
- Symptoms include shortness of breath, fainting, chest pain, fatigue, palpitations, arrhythmias
- Elevated risk of sudden cardiac death and heart failure

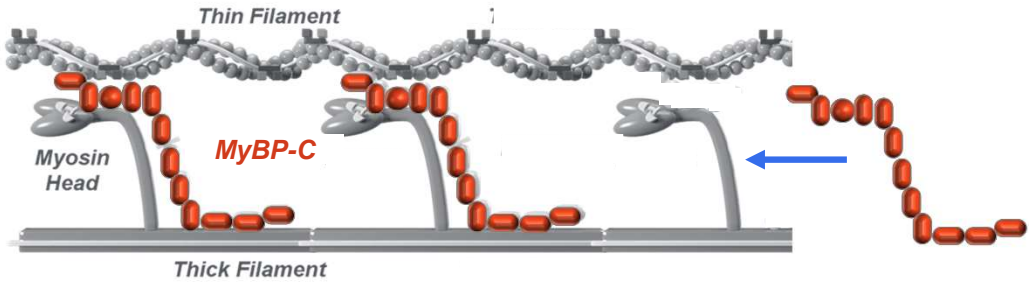
HCM = Hypertrophic cardiomyopathy | MYBPC3 = myosin binding protein C3

1. Ho, et al, *Circulation* 2018
2. Marston, et al, *Eur Heart Jrnl* 2021

TN-201 is the first gene therapy being developed for *MYBPC3*-associated HCM

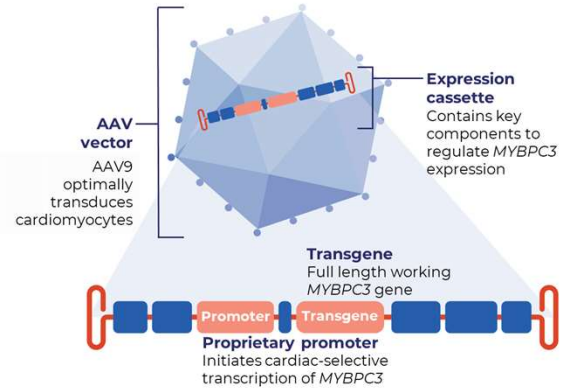
Underlying Problem

- Mutations of the *MYBPC3* gene lead to lower levels of myosin-binding protein C (MyBP-C)
- MyBP-C is an essential structural protein in the sarcomere required to regulate the binding of myosin to actin and modulate contraction
- Lower MyBP-C protein results in increased cardiac contractility (hypertrophy), thickening of left ventricle and impaired diastolic relaxation



Tenaya Approach

- Target the underlying genetic cause of disease
- Deliver a working *MYBPC3* gene utilizing AAV9 capsid
- Produce functional protein to increase MyBP-C levels to restore regulation of contraction and relaxation
- Potential to halt disease progression, reverse symptoms and improve patient quality of life



MyPEAK-1 Phase 1b/2 clinical trial

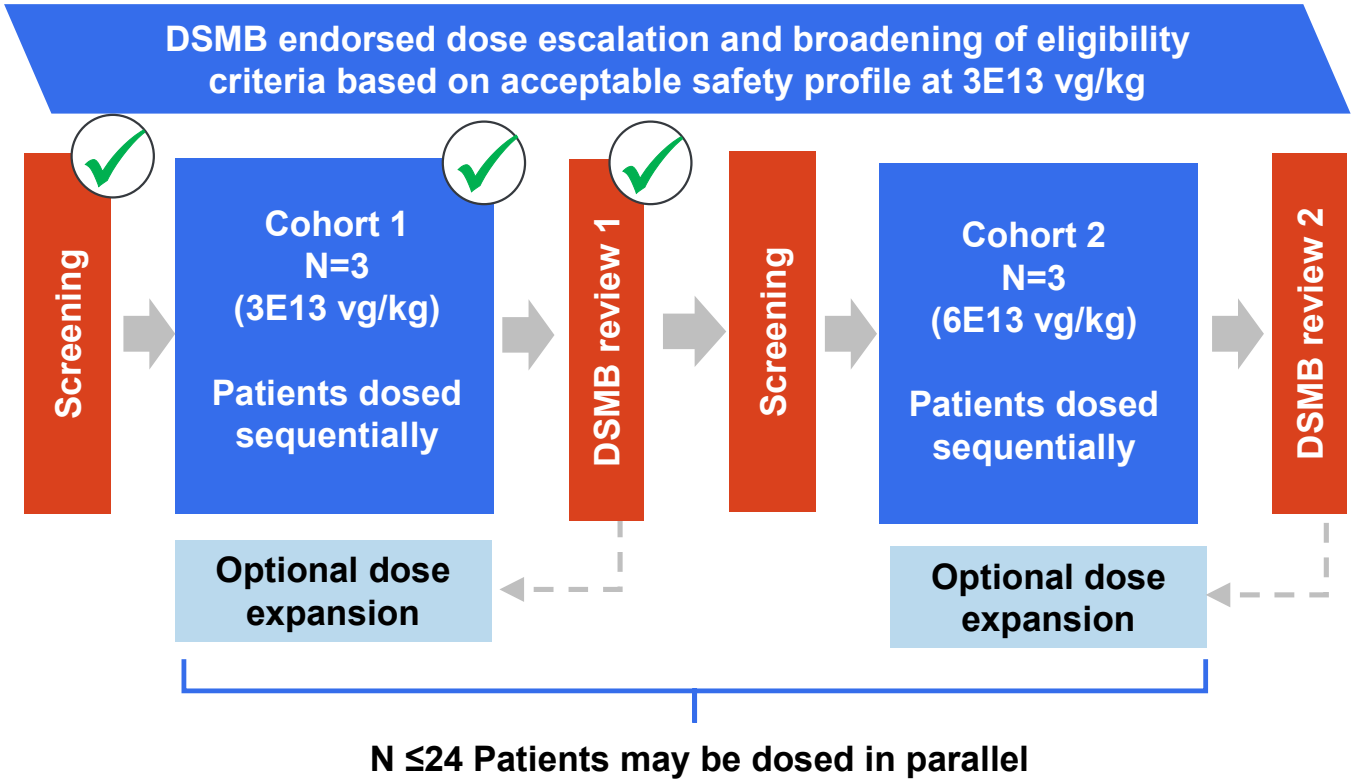
Open-label, multi-center dose escalation and expansion trial

Study objectives

- Safety, tolerability
- Dose-finding
- Pharmacodynamics

Design

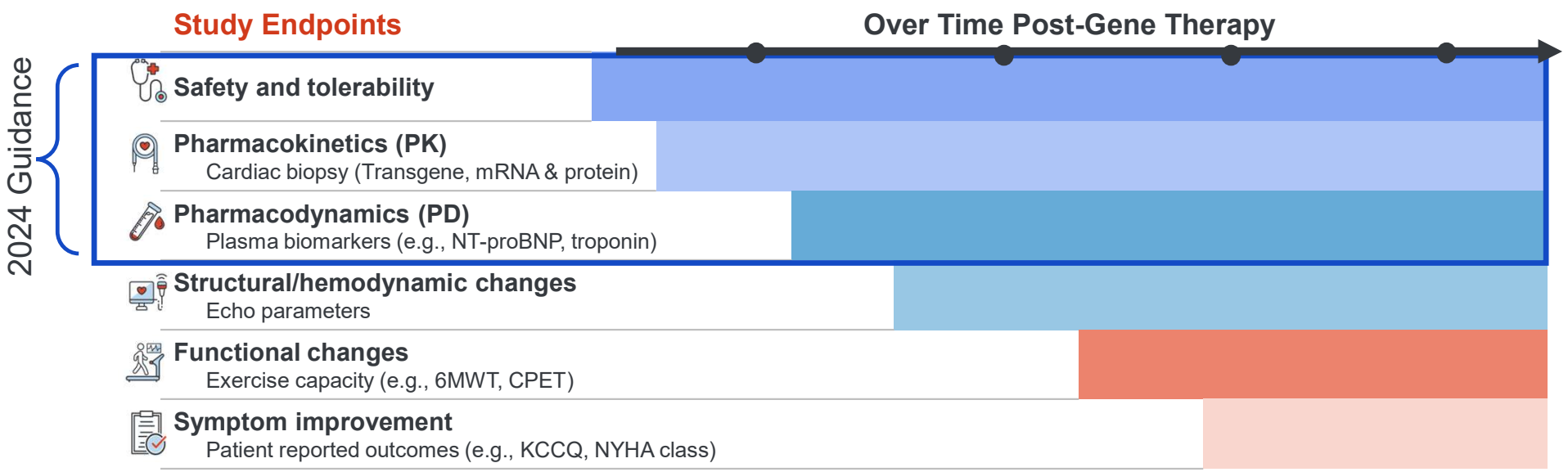
- Open-label, multi-center, dose-escalation and dose-expansion
- 52-week trial period with four-year safety and efficacy follow-up
- Cardiac biopsies at baseline, post-dose and ~52 weeks (effective with Cohort 1, patient 3)



Vg/kg: vector genomes per kilogram

MyPEAK-1 Phase 1b/2 clinical trial endpoints

Seeking directional consistency across multiple parameters over time



Today's dataset from Cohort 1 includes assessments for
Patient 1 at 52 weeks | Patient 2 at 40 weeks | Patient 3 at 12 weeks

NT-proBNP = N-terminal pro–B-type natriuretic peptide | CPET = Cardiopulmonary exercise testing |
6MWT = 6-minute walk test | KCCQ = Kansas City Cardiomyopathy Questionnaire | NYHA = New York Heart Association

Baseline characteristics and emerging safety profile

Dr. Milind Desai

Haslam Family Endowed Chair in Cardiovascular Medicine, Vice Chair, Heart Vascular Thoracic Institute, and Director of the Hypertrophic Cardiomyopathy Center at the Cleveland Clinic

MyPEAK-1 investigator

MyPEAK-1 patients younger and more severe across multiple parameters compared to average HCM patient

Typical for HCM	Abnormal for HCM	Very abnormal for HCM

	Average HCM Patient	Patient 1	Patient 2	Patient 3
Length of Follow-Up	-	12 months	9 months	3 months
Gender	Male (63%)[1]	Female	Female	Male
Current Age (years)	50[1]	27	43	47
ICD Implantation (years)	21% with ICD[1] Average age 38[2]	27	37	36
Myectomy Age (years)	18% with myectomy[3] Average age 54[4]	24	30	39
NT proBNP (pg/ml)	563[5]	1836	732	1229
Cardiac Troponin I (ng/L)	27[6]	46	34	53
LVMI (g/m^2)	Female: 89 | Male: 104[7]	174	105	177
NYHA Class	50% ≥ Class II[8]	II	III	II

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

ICD = implantable cardio defibrillator | LVMI = left ventricular mass index

TN-201 was generally well tolerated

Reported AEs are consistent with other AAV gene therapies and known effects of immunosuppression

TN-201 related-events

Reversible elevated liver enzymes occurred in all patients, normalized in response to steroid treatment

Patient 1	**Grade 3 AE at Week 15** Mitigated for subsequent patients by increased monitoring throughout IS tapering
Patient 2	**Grade 1 AE at Week 1**
Patient 3	**Grade 1 SAE at Week 2** Mild elevations classified as SAE because steroids administered in hospital
Patients 1 & 2 completed IS regimen; Patent 3 tapering	

Summary of TN-201 safety findings

- ✓ No thrombotic microangiopathy (TMA) or thrombocytopenia
- ✓ No signs of cardiotoxicities
  - No signs of myocarditis
  - No arrythmia-related adverse events
  - Stable ejection fraction
- ✓ No participants discontinued study

On study events deemed unrelated to TN-201

- ✓ Majority of treatment-emergent adverse events (TEAEs) were mild, transient or reversible
  - 2 SAEs unrelated to TN-201 occurred

DSMB cleared dose escalation to 6E13 vg/kg | All patients remain on study

TENAYA THERAPEUTICS

AE = adverse event | SAE = serious adverse event | IS = immunosuppression

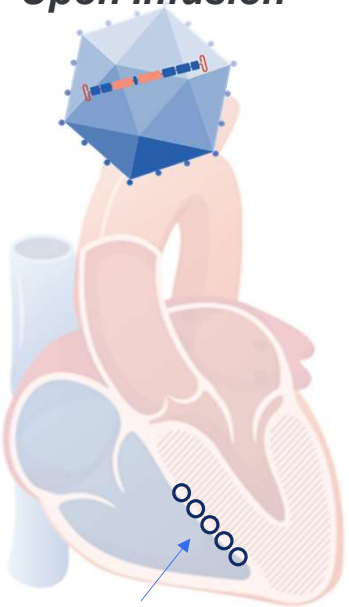
Biopsy Findings

Dr. Whit Tingley, Chief Medical Officer

TN-201 mechanism of action occurs in 3 stages within cardiomyocytes

TN-201 Mechanism of Action

TN-201 Upon Infusion



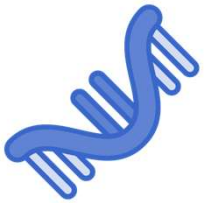
Biopsy samples

1 **DELIVERY: Transduction (DNA)**

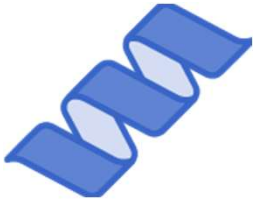
2 **EXPRESSION: Transcription (RNA)**

3 **EXPRESSION: Translation (Protein)**

TN-201 enters cardiomyocytes. Healthy copy of *MYBPC3* gene forms stable episome in cell

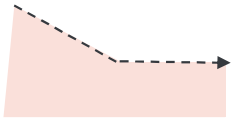
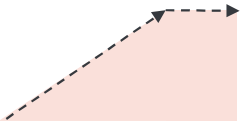
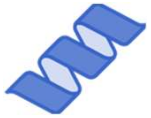
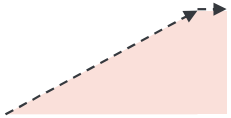


TN-201's healthy copy of *MYBPC3* gene is transcribed by cell's machinery to produce messenger RNA



TN-201 mRNA is then converted to MyBP-C protein and taken up into the sarcomere, filling empty slots

Cardiac biopsies are collected to quantify these leading indicators of TN-201 efficacy

Measurement assays	Anticipated result over time
 **TN-201 DNA is measured by ddPCR** Quantifies the number of TN-201 vector copies in heart tissue	 • Total VCN initially decreases as TN-201 DNA is cleared from non-CM cells • TN-201 DNA **delivered to CMs remains stable over time**
 ***TN-201 mRNA is measured by RT-qPCR*** Quantifies expression of TN-201 mRNA specifically (distinct from endogenous)	 • TN-201 **mRNA increases** as TN-201 DNA stabilizes and is transcribed in cardiomyocytes
 ***MyBp-C protein is measured by LCMS*** Quantifies abundance of total MyBP-C (normalized to myosin). LCMS cannot distinguish MyBP-C protein derived from TN-201 vs. patient's own gene.	 • Protein levels **increase from the patient's baseline** as TN-201 mRNA is translated into new MyBP-C that is incorporated into the sarcomere

ddPCR = digital droplet polymerase chain reaction | RT-qPCR = reverse transcriptase, quantitative polymerase chain reaction
LCMS = liquid chromatography – mass spectrometry| VCN = vector copy number | CMs = cardiomyocytes

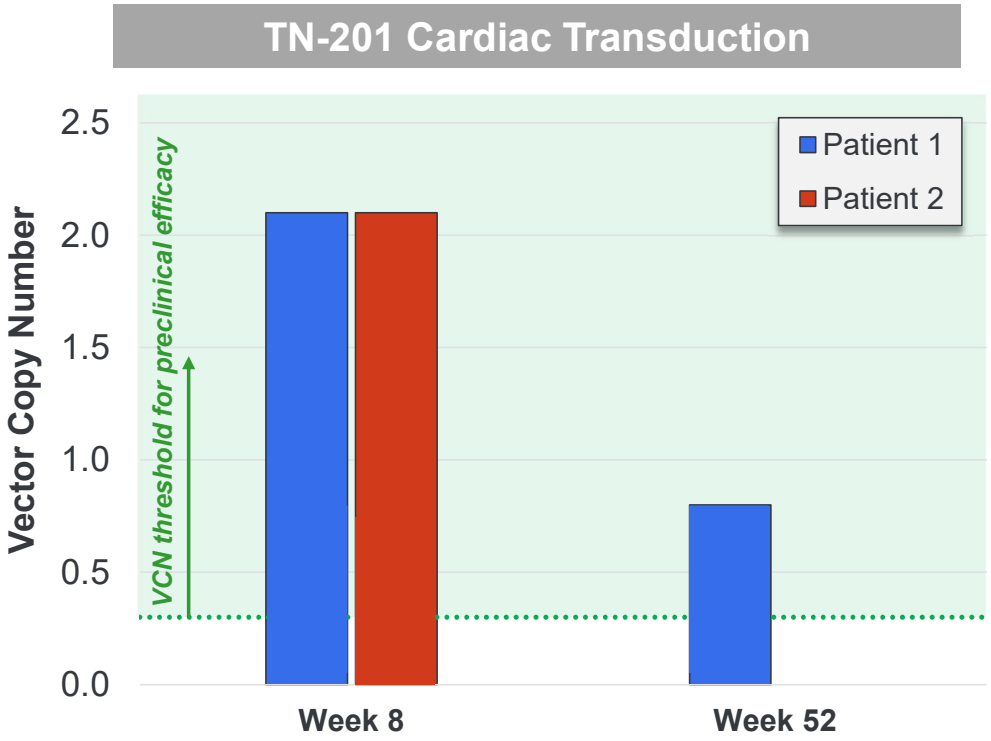
Overview of initial biopsy findings

TN-201 has been delivered to the heart with evidence of expression in Patients 1 & 2

Objective of Biopsy		*Is TN-201 DNA getting into the heart?*	*Is TN-201 DNA getting expressed in the heart?*	*Is TN-201 RNA translating into protein?*
Patient 1	☒ Baseline biopsy ☑ Week 8 biopsy ☑ Week 52 biopsy	✓	✓	✓
Patient 2	☒ Baseline biopsy ☑ Week 8 biopsy ☐ Week 52 biopsy	✓	✓	**To be confirmed with Week 52 biopsy**
Patient 3	☑ Baseline biopsy ☐ Week 26 biopsy ☐ Week 52 biopsy	**Baseline and Week 26 biopsy to be analyzed together**		

TN-201 demonstrates robust and durable levels of cardiac transduction at 3E13 vg/kg dose

Vector copy number (VCN) exceeds preclinical expectations



Cohort 1 results to date

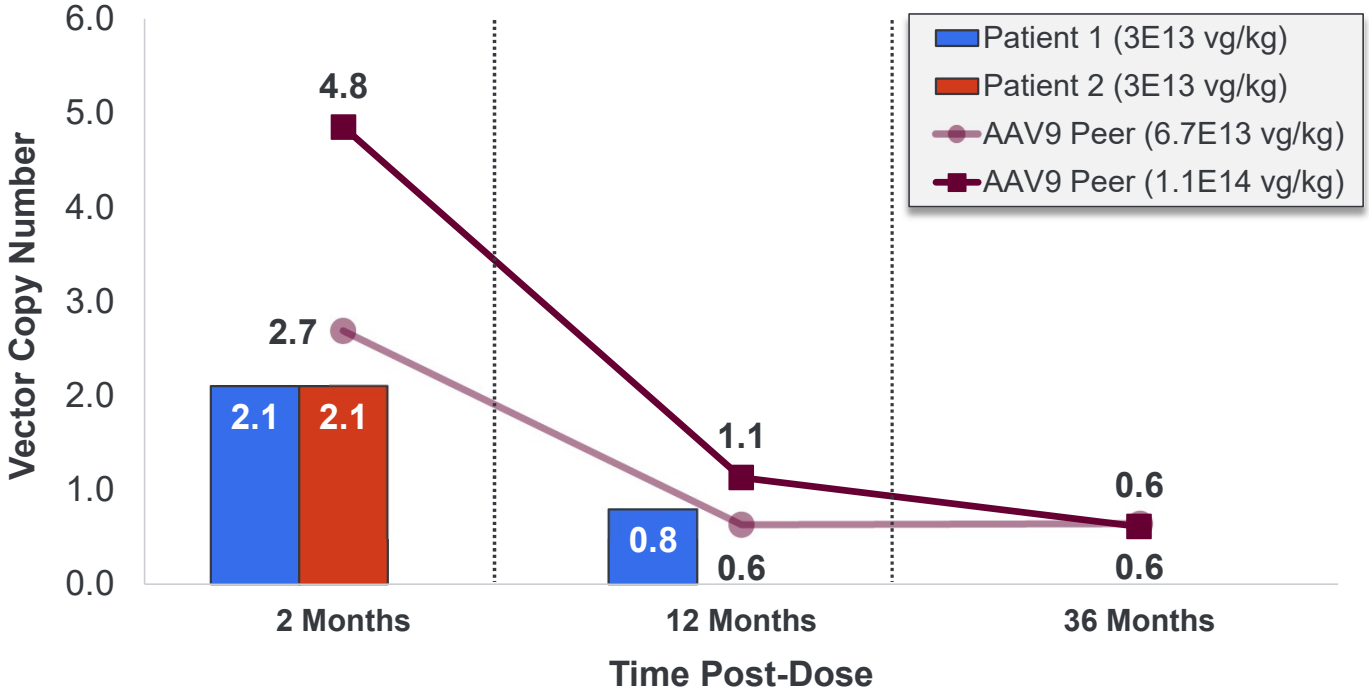
- Consistently high VCN >2.0 vg/dg at Week 8 for P1 and P2
- Expected drop of VCN to 0.8 vg/dg at Week 52 for P1

Preclinical comparison

- TN-201 VCN results in humans are within range associated with significant efficacy in preclinical studies in homozygous knock-out mouse model

TN-201 cardiac transduction compares favorably with clinical data from other cardiac gene therapies

TN-201 VCN and published results from peer cardiac GTx program[1*]



- Peer achieved higher VCN at a higher dose
- Peer VCN declines over first year, without loss of expression
- Peer VCN remains stable at least 3 years post-dose

Similar dose response and durability expected with TN-201.

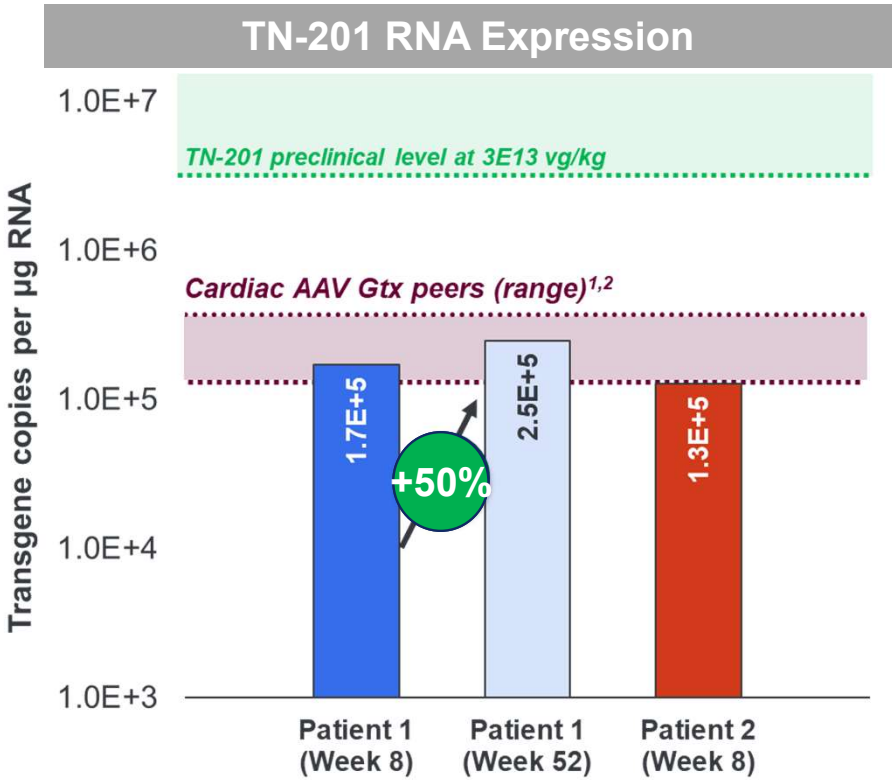
[1]Greenberg, NEJM 2024
*Peer values represented as means for given timepoint

GTx = gene therapy

Comparison with peer programs is not intended to indicate likelihood of TN-201 clinical benefit

TN-201 RNA expression in cardiomyocytes confirmed

TN-201 RNA expression increases over time; performs similarly to other sponsors' data



Cohort 1 results to date

- RT-qPCR assay is TN-201 specific
- P1 and P2 clearly show expression at Week 8
- P1 expression increased +50% from Week 8 → to Week 52

Contextual comparisons

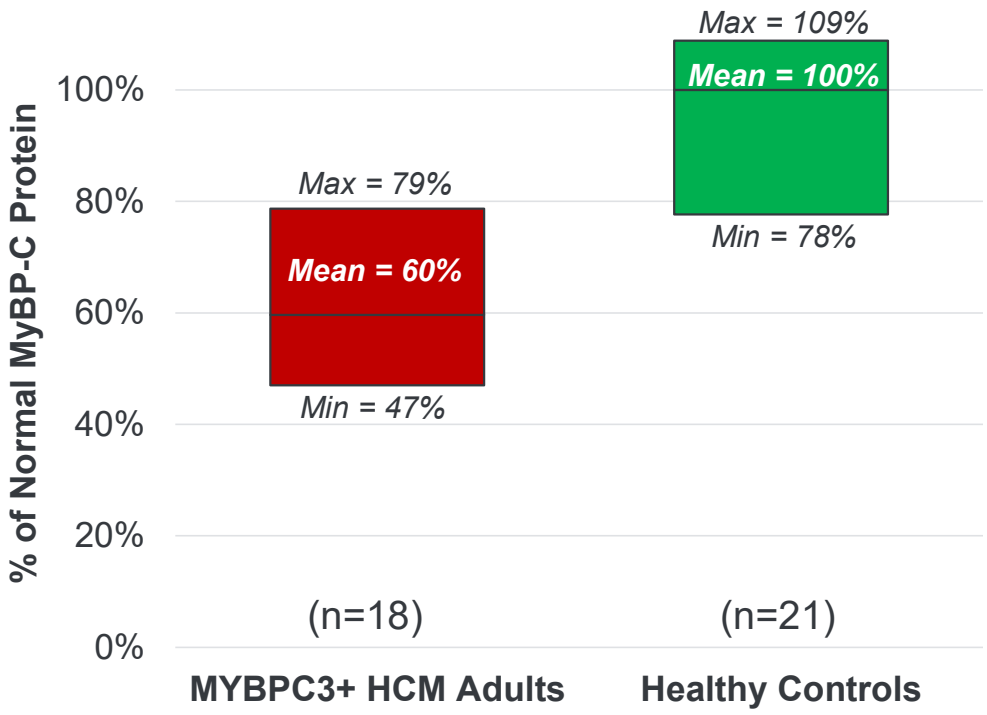
- mRNA expression at 3E13 vg/kg dose was lower in humans than achieved in preclinical models (Expected based on species-to-species variability)
- Magnitude of expression similar to peers' clinical data[1,2]

[1]Greenberg, NEJM 2024; median number of mRNA transcripts per µg RNA from 6.7E13 vg/kg and 1.1E14 vg/kg patients at latest timepoint
[2]Thomas, WORLD Symposium February 2024; n=1 patient at Week 26

Comparison with peer programs is not intended to indicate likelihood of TN-201 clinical benefit

MyBP-C protein levels vary between healthy and *MYBPC3*+HCM populations and between individuals

Range of MyBP-C protein levels in *MYBPC3*-associated HCM and healthy controls[1]



MyBP-C protein in *MYBPC3*-associated HCM

- *MYBPC3*-associated HCM patients exhibit ~40% lower MyBP-C protein levels on average vs. healthy controls
- No apparent correlation between MyBP-C protein level and markers of disease severity; suggests differing sensitivity to protein levels on an individual basis

Treatment goal with cardiac gene therapy: Increase each individual's protein levels from their own baseline.

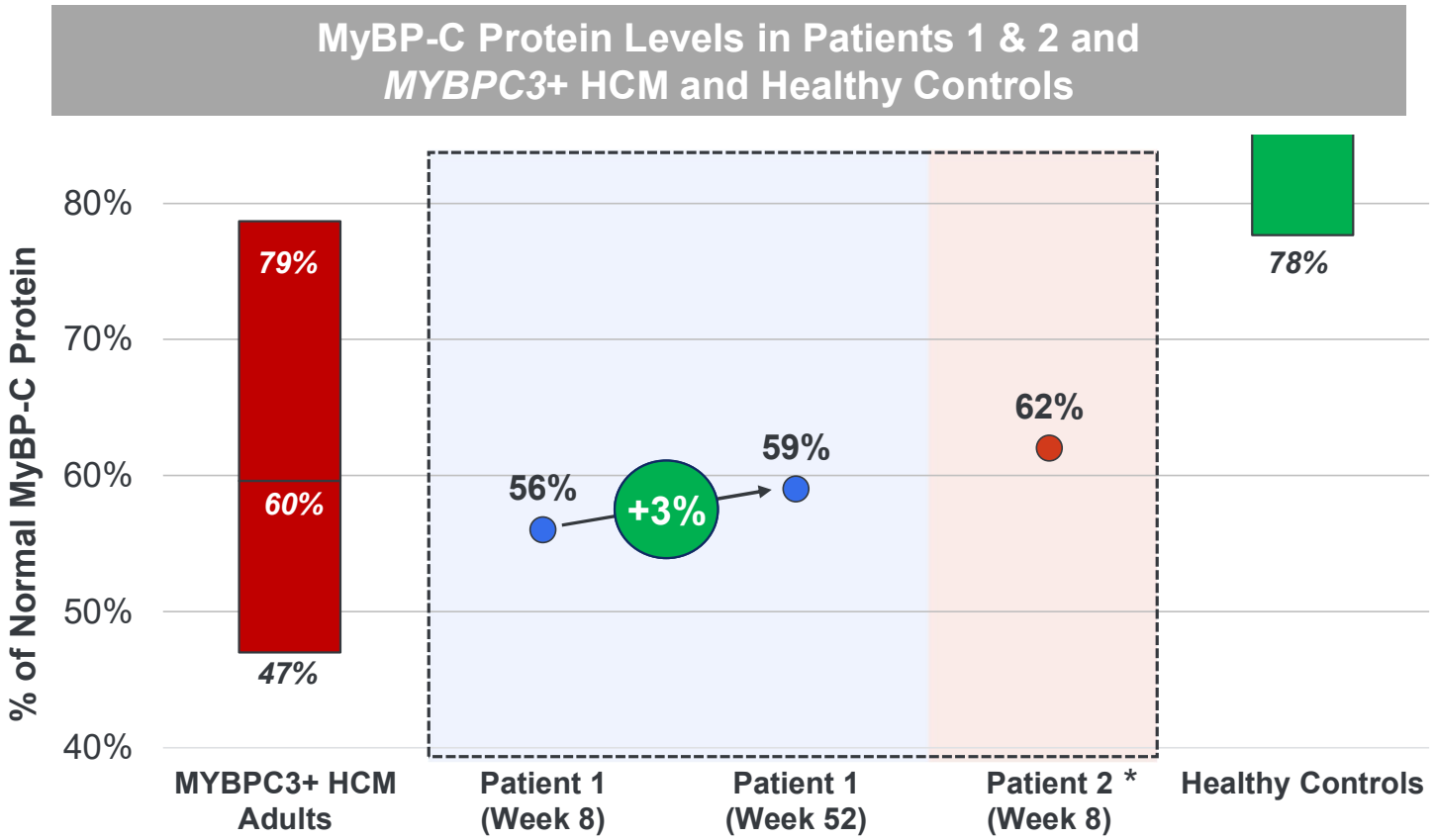
Modest restoration has achieved measurable benefit in other cardiac gene therapy clinical trials.

[1]O'Leary, et al; *J Mol Cell Cardiol* 2019 (updated)

Comparison with other GTx programs is not intended to indicate likelihood of TN-201 clinical benefit

Increase in MyBP-C protein levels observed in Patient 1

Changes in both mRNA and protein levels suggest TN-201 is being transcribed and expressed



Protein levels over time

- 3% increase may not represent total change in protein levels due to lack of baseline
- Baseline biopsies (plus post-dose and Week 52) are now in protocol starting with Patient 3
- Patients' clinical state anticipated to be sensitive to changes in protein over time

* Patient 2 52-week biopsy not yet taken

Biomarkers and clinical impressions

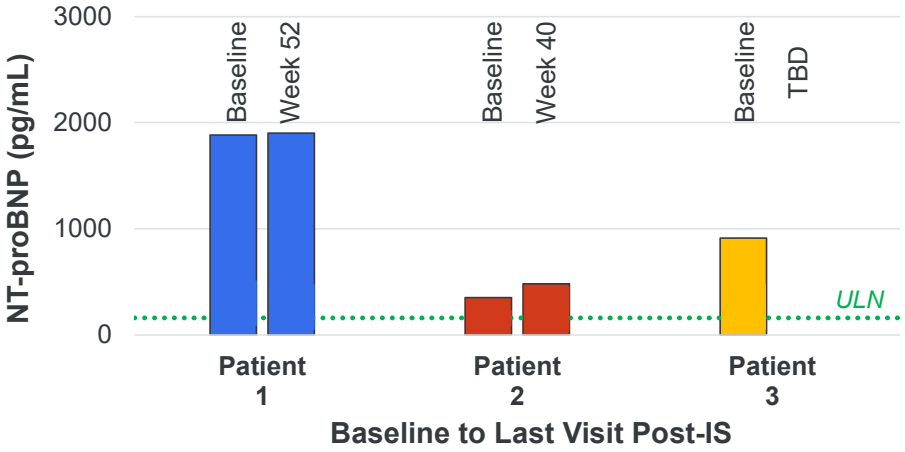
Dr. Milind Desai

Haslam Family Endowed Chair in Cardiovascular Medicine, Vice Chair, Heart Vascular Thoracic Institute, and Director of the Hypertrophic Cardiomyopathy Center at the Cleveland Clinic

MyPEAK-1 investigator

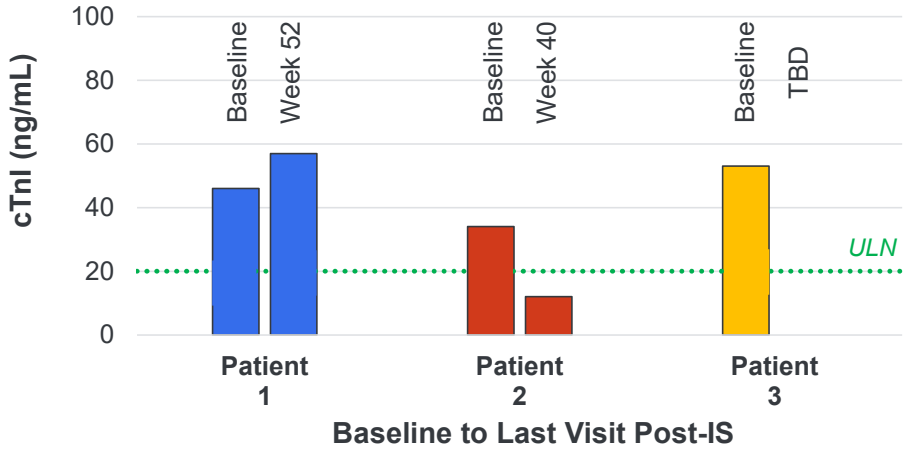
Circulating biomarker levels overall stable at this early time point

NT-proBNP Levels



- MyPEAK-1 baseline NT-proBNP levels are higher than levels in other nonobstructive HCM trials[1,2]
- Immunosuppression known to influence NT-proBNP levels; upon completion of IS regimen, levels return to baseline

Cardiac Troponin I Levels



- MyPEAK-1 baseline troponin I much higher than those in other nonobstructive HCM trials[1,2]
- Patient 1 remains elevated, however Patient 2 has normalized since TN-201 treatment

[1]Ho, et al; JACC 2020
[2]Masri, et al; JCF 2024

ULN = upper limit of normal (values per MyPEAK-1 central laboratory)

Encouraging early clinical signals

More follow-up, more patients, and data from higher-dose cohort needed

		Clinical Snapshot	
Domain		**Patient 1 at Week 52**	**Patient 2 at Week 40**
Biomarker	NT-proBNP		
	Troponin I		
Imaging	Hypertrophy		
	Diastolic Function		
Functional Capacity		*	
Symptoms	NYHA		
	KCCQ		*

Improved | **Stable** | **Mixed/Declined**

* Unavailable or confounded due to AEs unrelated to study drug

- Initial improvement and/or stabilization observed across several domains
- Seeking directional improvement in multiple parameters over time
- Overall clinical picture will become clearer with time, more follow-up, and more patients

Closing remarks and Q&A

Faraz Ali, Chief Executive Officer

Summary

- **Safety: TN-201's emerging safety profile is consistent with other AAV gene therapies and known effects of immunosuppressives**
  - Immunosuppressive regimen has been successful in preventing and managing immunologic reactions to TN-201
  - No cardiac AEs, including myocarditis or arrhythmia
  - Ejection fraction remained within the normal range
  - DSMB endorsed dose escalation; 6E13 vg/kg dose cohort now enrolling
- **Biopsy: Evidence of robust cardiac transduction and TN-201 RNA expression and protein level increase**
  - Vector copy numbers of TN-201 DNA are within range associated with significant efficacy in preclinical studies; compare favorably to published rates of other sponsors
  - TN-201 mRNA quantities increasing over time; expression levels at similar ranges as peers
  - Protein levels increase from Week 8 to Week 52 for Patient 1, consistent with mRNA changes
  - Relationship between dose, VCN, RNA and protein expression and clinical endpoints are not yet known for TN-201
- **Clinical parameters: Encouraging modest early signals in key parameters**
  - Circulating biomarkers stable overall
  - Improvements and/or stability observed in key measures of disease
  - More time and data points needed

Significant clinical progress coming in 2025

- **MyPeak-1 Study: Cohort 1 – Additional data anticipated in 1H 2025**
  - Patient 1: Ongoing clinical follow-up
  - Patient 2: Biopsy and clinical assessments at 1 year post dose
  - Patient 3: Biopsy and clinical assessments at 26 weeks post dose
- **MyPeak-1 Study: Cohort 2 – Initial data anticipated in 2025**
  - Enrollment ongoing
- **MyClimb Natural History: Initial data anticipated in 2025**
  - > 220 enrolled, additional enrollment ongoing

RIDGE-1: Cohort 1 – Initial data anticipated in 2025

Patient 1 dosed, enrollment ongoing

RIDGE Natural History Study: Additional data anticipated in 2025

> 100 enrolled, additional enrollment ongoing

Thank you