UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported):
December 17, 2024

Tenaya Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**001-40656**	**81-3789973**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

171 Oyster Point Boulevard, Suite 500
South San Francisco, CA 94080
(Address of principal executive offices, including zip code)

(650) 825-6990
(Registrant's telephone number, including area code)

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of exchange on which registered
Common Stock, par value $0.0001 per share	TNYA	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On December 17, 2024, Tenaya Therapeutics, Inc. (the "Company") issued a press release announcing early data from the first cohort of patients in the MyPEAK-1 clinical trial of TN-201 gene therapy. The press release is attached hereto as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

On December 17, 2024, the Company also posted a presentation to the Investors section of its website (https://investors.tenayatherapeutics.com/). A copy of the presentation is furnished as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

The information in this Item 7.01, including Exhibits 99.1 and 99.2 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

On December 17, 2024, the Company reported early data from the first cohort of patients in the MyPEAK-1 clinical trial of TN-201 gene therapy. TN-201 is being developed for the potential treatment of MYBPC3-associated hypertrophic cardiomyopathy (HCM), a condition caused by insufficient levels of myosin-binding protein C (MyBP-C).

Preliminary data from three patients in the first dose cohort of 3E13 vg/kg (Cohort 1) showed that TN-201 was generally well tolerated, with readily detectable vector DNA in the heart, evidence of transgene RNA expression, and increasing TN-201 mRNA and MyBP-C protein levels over time. Circulating biomarkers of cardiac muscle strain and injury remained largely stable, and other clinical markers of disease showed stability or directional improvement in the first two individuals dosed, though longer-term data are needed to characterize TN-201's activity. Tenaya will continue to follow these first three patients with additional data readouts from Cohort 1 and the higher dose Cohort 2 anticipated in 2025.

Interim Phase 1b/2 My-PEAK-1 Results

Data reported today focus on changes over time in the first three patients to receive TN-201 gene therapy. Patients were dosed sequentially with TN-201 via a one-time intravenous infusion of a 3E13 vg/kg dose. Patients enrolled in Cohort 1 were required to be symptomatic adults with MYBPC3-associated nonobstructive HCM at sufficiently high risk of sudden cardiac death to warrant an implantable cardiac defibrillator device (ICD). An assessment of Patient 1 at Week 52, Patient 2 at Week 40 and safety data for Patient 3 at 12 weeks are included in this first readout. All three had objectively severe disease at the time of enrollment with mild to moderate heart failure symptoms that limited the activities of daily living as measured by New York Heart association (NYHA) classification.

TN-201 was generally well tolerated with a manageable safety profile.

- No cardiac toxicities, complement activation-associated adverse effects, or thrombotic microangiopathy (TMA)-related events were observed.
- All three patients experienced isolated elevations in liver enzymes associated with TN-201 treatment. These were not associated with other signs or symptoms of liver damage and were well managed with the administration of corticosteroids, per protocol. Liver enzyme elevations are a known side effect associated with AAV-based gene therapies.
    - One patient experienced asymptomatic and mild (Grade 1) enzyme elevation that was designated as an SAE due to the administration of a corticosteroid bolus in the hospital setting.
- On-study adverse events were primarily mild, transient or reversible. The majority of observed side effects were typical of those observed with use of adeno-associated viral vector (AAV)-based gene therapies or immunosuppressive (IS) regimens.
    - Two serious adverse events (SAEs) occurred that were not related to TN-201.
- Patients 1 and 2 have successfully tapered off immunosuppressives and all three patients remain on study.

TN-201 achieved robust transduction into cardiomyocytes and measurable transgene RNA expression. TN-201 RNA expression and levels of MyBP-C protein increased over time.

Cardiac biopsy samples were collected for analysis at Week 8 for Patients 1 and 2 and Week 52 for Patient 1 to confirm and characterize transduction of TN-201 DNA in the heart, the presence of TN-201 transgene mRNA, and changes in MyBP-C protein. Baseline biopsies have been added to the MyPEAK-1 protocol, beginning with Patient 3 to provide further insights into the changes in MyBP-C protein levels over time.

- At Week 8, Patients 1 and 2 achieved evidence of robust cardiac transduction at levels that were above those that were effective in preclinical knockout mouse models of disease and perform favorably to published levels for other clinical-stage AAV gene therapy agents for genetic cardiomyopathies.
- At Week 8, Patients 1 and 2 achieved TN-201-derived mRNA at levels similar to those of other clinical-stage cardiac gene therapies, though lower than those observed in preclinical studies. TN-201 mRNA expression increased by 50% at the Week 52 biopsy for Patient 1, offering early evidence of anticipated durability of expression.
- Total levels of MyBP-C protein were quantified and demonstrated a 3% increase from Weeks 8 to 52 in Patient 1. This increase, combined with the increase observed in TN-201 mRNA expression, suggest that TN-201 gene therapy is successfully being transcribed and expressed after reaching target cells. As TN-201 generated MyBP-C and endogenous MyBP-C are indistinguishable via assay, baseline biopsies will further elucidate protein level changes.

Clinical measures of HCM mostly remained stable or improved from baseline.

- Circulating biomarkers of heart muscle strain (measured via NT-proBNP) remained stable overall. Cardiac troponin I, a biomarker of heart muscle injury normalized in Patient 2.
- Improvement or stabilization from baseline was observed in some clinical endpoints, including improvements in NYHA classification for Patients 1 and 2, while other measures were not yet available, interpretable or were mixed.
- The overall clinical picture is anticipated to become clearer with time, more follow-up, and more patients.

Forward-Looking Statements

This Current Report on Form 8-K contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Statements in this report that are not purely historical are forward-looking statements. Words such as “will,” “anticipated,” “believe,” “look forward,” “potential,” and similar expressions are intended to identify forward-looking statements. Such forward-looking statements include, among other things, the planned timing to report additional data from 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. The forward-looking statements contained herein are based upon the Company’s current expectations and involve assumptions that may never materialize or may prove to be incorrect. These forward-looking statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, including but not limited to: availability of MyPEAK-1 data at the referenced time; 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; Tenaya’s 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; the Company’s continuing compliance with applicable legal and regulatory requirements; the Company’s ability to raise any additional funding it will need to continue to pursue its product development plans; the Company’s reliance on third parties; the Company’s manufacturing, commercialization and marketing capabilities and strategy; the loss of key scientific or management personnel; competition in the industry in which the Company operates; the Company’s ability to obtain and maintain intellectual property protection for its product candidates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section titled “Risk Factors” in Tenaya’s Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2024 and other documents that the Company files from time to time with the Securities and Exchange Commission. These forward-looking statements are made as of the date of this report, and the Company assumes no obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release, dated December 17, 2024
99.2	Presentation, dated December 17, 2024
104	Cover Page Interactive Data File (embedded within the Inline XBRL documents)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

TENAYA THERAPEUTICS, INC.

By: /s/ Jennifer Drimmer Rokovich
Jennifer Drimmer Rokovich
General Counsel and Secretary

Date: December 17, 2024

Exhibit 99.1

Tenaya Therapeutics Reports Promising Early Data from MyPEAK™-1 Phase 1b/2 Clinical Trial of TN-201 for Treatment of *MYBPC3*-Associated Hypertrophic Cardiomyopathy

TN-201 Well Tolerated at 3E13 vg/kg Dose

AAV9 Capsid Demonstrated Robust Delivery of TN-201 Transgene to Heart Muscle Cells Resulting in Increasing RNA Expression and an Increase in Protein Levels Observed at One Year

Circulating Biomarkers and Other Clinical Measures Mostly Remained Stable or Improved from Baseline

Tenaya Management to Host a Webcast Conference Call Today at 8:00 a.m. ET

SOUTH SAN FRANCISCO, Calif., December 17, 2024 – Tenaya Therapeutics, Inc. (NASDAQ: TNYA), a clinical-stage biotechnology company with a mission to discover, develop and deliver potentially curative therapies that address the underlying causes of heart disease, today reported encouraging early data from the first cohort of patients in the MyPEAK-1 clinical trial of TN-201 gene therapy. TN-201 is being developed for the potential treatment of *MYBPC3*-associated hypertrophic cardiomyopathy (HCM), a condition caused by insufficient levels of myosin-binding protein C (MyBP-C).

Preliminary data from three patients in the first dose cohort of 3E13 vg/kg (Cohort 1) showed that TN-201 was generally well tolerated, with readily detectable vector DNA in the heart, evidence of transgene RNA expression, and increasing TN-201 mRNA and MyBP-C protein levels over time. Circulating biomarkers of cardiac muscle strain and injury remained largely stable, and other clinical markers of disease showed stability or directional improvement in the first two individuals dosed, though longer-term data are needed to characterize TN-201's activity. Tenaya will continue to follow these first three patients with additional data readouts from Cohort 1 and the higher dose Cohort 2 anticipated in 2025.

"The initial patients enrolled in the MyPEAK-1 Phase 1b/2 clinical study are like many we see in our clinic: relatively young adults whose HCM is keeping them from having an adequate quality of life, including being able to perform activities of daily living and whose disease is progressing in spite of treatment interventions, putting them at significant risk of dire complications," said Milind Desai, M.D., M.B.A, Haslam Family Endowed Chair in Cardiovascular Medicine, Vice Chair, Heart Vascular Thoracic Institute, Director of the Hypertrophic Cardiomyopathy Center and at the Cleveland Clinic, and an investigator for the MyPeak-1 Phase 1b/2 clinical trial. "The goal of gene therapy is to halt or even reverse the steady decline in *MYBPC3*-associated HCM by addressing the underlying genetic cause of disease. Initial data from this first-in-human clinical trial of TN-201 demonstrate tolerability and early evidence of protein expression support additional investigation to build on these findings."

"TN-201's emerging safety profile, excellent uptake into cardiomyocytes, and evidence of transgene RNA and protein expression provide important de-risking of the program as we proceed with enrollment of the higher dose cohort," said Whit Tingley, M.D., Ph.D., Tenaya's Chief Medical Officer. "In addition, we have observed encouraging early hints of disease stability and improvement among certain clinical measures of disease, offering further reason to believe in TN-201's promise. Longer-term follow up for all patients in the lower dose cohort and results from the higher dose cohort will further inform our understanding of TN-201 gene therapy's potential in *MYBPC3*-associated HCM."

Interim Phase 1b/2 MyPEAK-1 Results

Data reported today focus on changes over time in the first three patients to receive TN-201 gene therapy. Patients were dosed sequentially with TN-201 via a one-time intravenous infusion of a 3E13 vg/kg dose. Patients enrolled in Cohort 1 were required to be symptomatic adults with *MYBPC3*-associated nonobstructive HCM at sufficiently high risk of sudden cardiac death to warrant an implantable cardiac defibrillator device (ICD). An assessment of Patient 1 at Week 52, Patient 2 at Week 40 and safety data for Patient 3 at 12 weeks are included in this first readout. All three had objectively severe disease at the time of enrollment with mild-to moderate heart failure symptoms that limited the activities of daily living as measured by New York Heart association (NYHA) classification.

TN-201 was generally well tolerated with a manageable safety profile.

- No cardiac toxicities, complement activation-associated adverse effects, or thrombotic microangiopathy (TMA)-related events were observed.
- All three patients experienced isolated elevations in liver enzymes associated with TN-201 treatment. These were not associated with other signs or symptoms of liver damage and were well managed with the administration of corticosteroids, per protocol. Liver enzyme elevations are a known side effect associated with AAV-based gene therapies.
    - One patient experienced asymptomatic and mild (Grade 1) enzyme elevation that was designated as an SAE due to the administration of a corticosteroid bolus in the hospital setting.
- On-study adverse events were primarily mild, transient or reversible. The majority of observed side effects were typical of those observed with use of adeno-associated viral vector (AAV)-based gene therapies or immunosuppressive (IS) regimens.
    - Two serious adverse events (SAEs) occurred that were not related to TN-201.
- Patients 1 and 2 have successfully tapered off immunosuppressives and all three patients remain on study.

TN-201 achieved robust transduction into cardiomyocytes and measurable transgene RNA expression. TN-201 RNA expression and levels of MyBP-C protein increased over time.

Cardiac biopsy samples were collected for analysis at Week 8 for Patients 1 and 2 and Week 52 for Patient 1 to confirm and characterize transduction of TN-201 DNA in the heart, the presence of TN-201 transgene mRNA, and changes in MyBP-C protein. Baseline biopsies have been added to the MyPEAK-1 protocol, beginning with Patient 3 to provide further insights into the changes in MyBP-C protein levels over time.

- At Week 8, Patients 1 and 2 achieved evidence of robust cardiac transduction at levels that were above those that were effective in preclinical knockout mouse models of disease and perform favorably to published levels for other clinical-stage AAV gene therapy agents for genetic cardiomyopathies.
- At Week 8, Patients 1 and 2 achieved TN-201-derived mRNA at levels similar to those of other clinical-stage cardiac gene therapies, though lower than those observed in preclinical studies. TN-201 mRNA expression increased by 50% at the Week 52 biopsy for Patient 1, offering early evidence of anticipated durability of expression.
- Total levels of MyBP-C protein were quantified and demonstrated a 3% increase from Weeks 8 to 52 in Patient 1. This increase, combined with the increase observed in TN-201 mRNA expression suggest that TN-201 gene therapy is successfully being transcribed and expressed after reaching target cells. As TN-201 generated MyBP-C and endogenous MyBP-C are indistinguishable via assay, baseline biopsies will further elucidate protein level changes.

Clinical measures of HCM mostly remained stable or improved from baseline

- Circulating biomarkers of heart muscle strain (measured via NT-proBNP) remained stable overall. Cardiac troponin I, a biomarker of heart muscle injury normalized in Patient 2.
- Improvement or stabilization from baseline was observed in some clinical endpoints, including improvements in NYHA classification for Patients 1 and 2, while other measures were not yet available, interpretable or were mixed.
- The overall clinical picture is anticipated to become clearer with time, more follow-up, and more patients.

“Taken together, the TN-201 data reported today are in line with our overall expectations at this early juncture in the study. The high levels of cardiac transduction and early evidence of increasing transgene expression support our confidence in TN-201’s potential at this early stage. We look forward to building on these results over time,” said Faraz Ali, Tenaya’s Chief Executive Officer. “We deeply appreciate the support we are receiving from the larger community of HCM clinicians and affected families, and we are especially grateful to our study investigators and to the first three patients in Cohort 1 without whom the promise and potential of TN-201 could not be explored.”

Investor and Analyst Conference Call and Live Webcast

Tenaya management will host a conference call and webcast today beginning at 8:00 am. ET/5:00 AM PT to discuss the initial MyPEAK-1 results. Investors and analysts may access the call here. A live webcast of the conference call, including an accompanying slide presentation, will be available on the Investors section of Tenaya’s website. A replay of the webcast, and accompanying slides, will be available on the Tenaya website for approximately 90 days following the call.

About the MyPEAK-1 Phase 1b/2 Clinical Trial

The MyPEAK-1 Phase 1b/2 clinical trial (Clinicaltrials.gov ID: NCT05836259) is an ongoing, multi-center, open-label, dose-escalating study designed to assess the safety, tolerability and clinical efficacy of a one-time intravenous infusion of TN-201 gene replacement therapy. The trial is enrolling symptomatic (New York Heart Association Class II or III) adults who have been diagnosed with *MYBPC3*-associated HCM. MyPEAK-1 is testing doses of 3E13 vg/kg and 6E13 vg/kg in two cohorts of three patients each. MyPEAK-1 may enroll up to 24 *MYBPC3*-associated HCM adults with either nonobstructive or obstructive forms of HCM in planned dose expansion cohorts.

To learn more about gene therapy for HCM and participation in the MyPEAK-1 study, please visit HCMStudies.com.

About *MYBPC3*-Associated Hypertrophic Cardiomyopathy Variants in the Myosin Binding Protein C3 (*MYBPC3)* gene are the most common genetic cause of hypertrophic cardiomyopathy (HCM), accounting for approximately 20% of the overall HCM population, or 120,000 patients, in the United States alone.(1) *MYBPC3*-associated HCM is a severe and progressive condition affecting adults, teens, children and infants. Mutations of the *MYBPC3* gene result in insufficient expression of a protein, called MyBP-C, needed to regulate heart contraction. The heart becomes hypercontractile and the left ventricle thickens, resulting in symptoms such as chest pain, shortness of breath, palpitations and fainting. Patients whose disease is caused by *MYBPC3* mutations are more likely than those with non-genetic forms of HCM to experience earlier disease onset and have high rates of serious outcomes, including heart failure symptoms, arrhythmias, stroke and sudden cardiac arrest or death.(2) There are currently no approved therapeutics that address the underlying genetic cause of HCM.

About TN-201

TN-201 is an adeno-associated virus serotype 9 (AAV9)-based gene therapy designed to deliver a working *MYBPC3* gene to heart muscle cells via a single intravenous infusion, increasing MyBP-C protein levels to address the underlying cause of *MYBPC3*-associated HCM with the aim of halting or even reversing disease after a single dose. The U.S. Food and Drug Administration has granted TN-201 Fast Track, Orphan Drug and Rare Pediatric Drug Designations. TN-201 has also received orphan medicinal product designation from the European Commission.

About Tenaya Therapeutics

Tenaya Therapeutics is a clinical-stage biotechnology company committed to a bold mission: to discover, develop and deliver potentially curative therapies that address the underlying drivers of heart disease. Tenaya employs a suite of integrated internal capabilities, including modality agnostic target validation, capsid engineering and manufacturing, to generate a portfolio of genetic medicines aimed at the treatment of both rare genetic disorders and more prevalent heart conditions. Tenaya’s pipeline includes TN-201, a gene therapy for *MYBPC3*-associated hypertrophic cardiomyopathy (HCM), TN-401, a gene therapy for PKP2-associated arrhythmogenic right ventricular cardiomyopathy (ARVC), TN-301, a small molecule HDAC6 inhibitor intended for heart failure with preserved ejection fraction (HFpEF), and multiple early-stage programs in preclinical development. For more information, visit www.tenayatherapeutics.com.

(1) Sedaghat-Hemedani, et al., *Clinical Research Cardiology*, 2017
(2) Ho, et al., *Circulation* 2018

Forward Looking Statements

This press release contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Statements in this press release that are not purely historical are forward-looking statements. Words such as "will," "anticipated," "believe," "look forward," "potential," and similar expressions are intended to identify forward-looking statements. Such forward-looking statements include, among other things, the planned timing to report additional data from 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; 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; and statements made by Tenaya's Chief Medical Officer and Chief Executive Officer and investigator for MyPEAK-1. The forward-looking statements contained herein are based upon Tenaya's current expectations and involve assumptions that may never materialize or may prove to be incorrect. These forward-looking statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, including but not limited to: availability of MyPEAK-1 data at the referenced time; 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; Tenaya's 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; Tenaya's continuing compliance with applicable legal and regulatory requirements; Tenaya's ability to raise any additional funding it will need to continue to pursue its product development plans; Tenaya's reliance on third parties; Tenaya's manufacturing, commercialization and marketing capabilities and strategy; the loss of key scientific or management personnel; competition in the industry in which Tenaya operates; Tenaya's ability to obtain and maintain intellectual property protection for its product candidates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section titled "Risk Factors" in Tenaya's Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2024 and other documents that Tenaya files from time to time with the Securities and Exchange Commission. These forward-looking statements are made as of the date of this press release, and Tenaya assumes no obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Contact

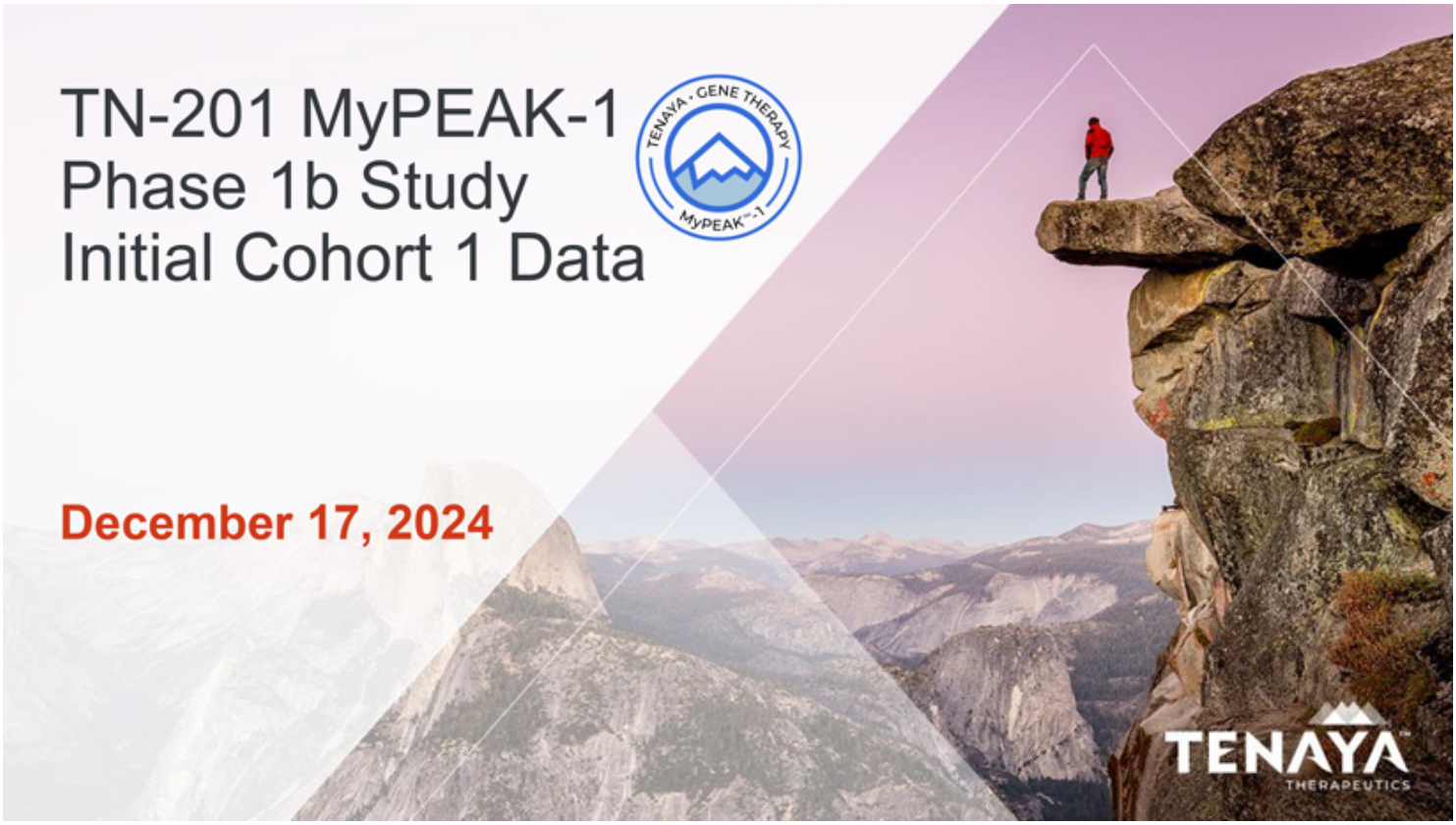
Michelle Corral
VP, Corporate Communications and Investor Relations
IR@tenayathera.com

Investors

Anne-Marie Fields
Precision AQ (formerly Stern Investor Relations)
annemarie.fields@precisionaq.com

Media

Wendy Ryan
Ten Bridge Communications
wendy@tenbridgecommunications.com


TN-201 MyPEAK-1
Phase 1b Study
Initial Cohort 1 Data
TENAYA · GENE THERAPY
MyPEAK-1
December 17, 2024
TENAYA
THERAPEUTICS

Today's speakers

Faraz Ali, MBA
Chief Executive Officer

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

Whit Tingley, M.D., PhD
Chief Medical Officer

Michelle Corral
Vice President, Corporate Communications and Investor Relations

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.

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

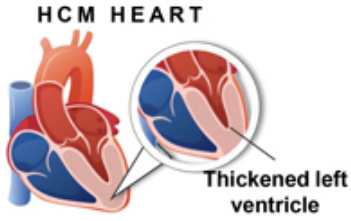
AAV9 = adeno-associated virus serotype 9 | DSMB = data safety and Monitoring Board | mRNA = messenger ribonucleic acid |

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

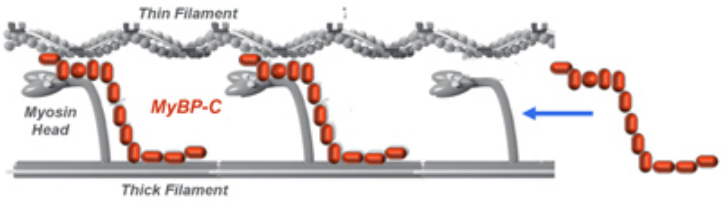
HCM = Hypertrophic cardiomyopathy | MYBPC3 = myosin binding protein C3

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

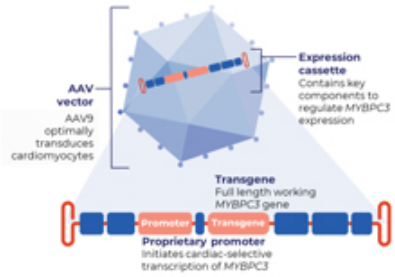
Underlying Problem

- 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

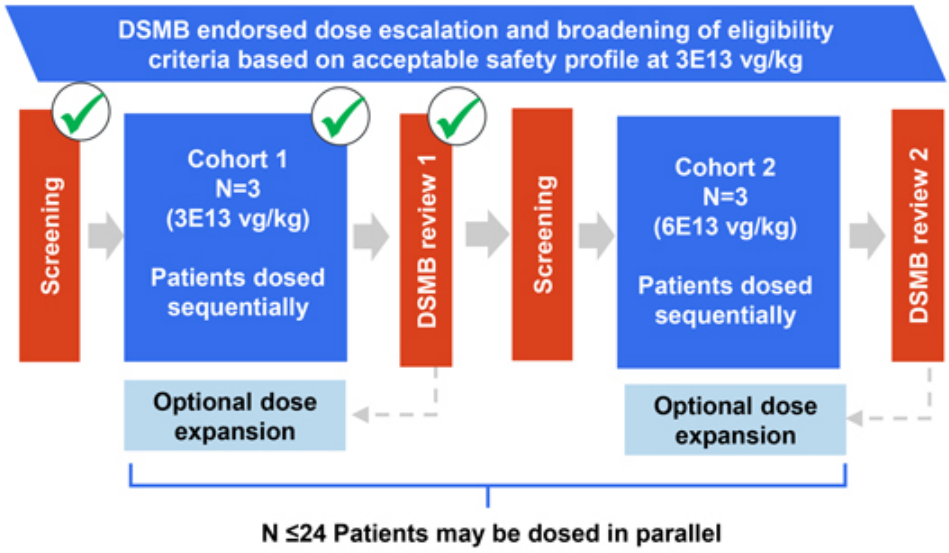
Open-label, multi-center dose escalation and expansion trial

Study objectives

- Safety, tolerability
- Dose-finding
- Pharmacodynamics

Design

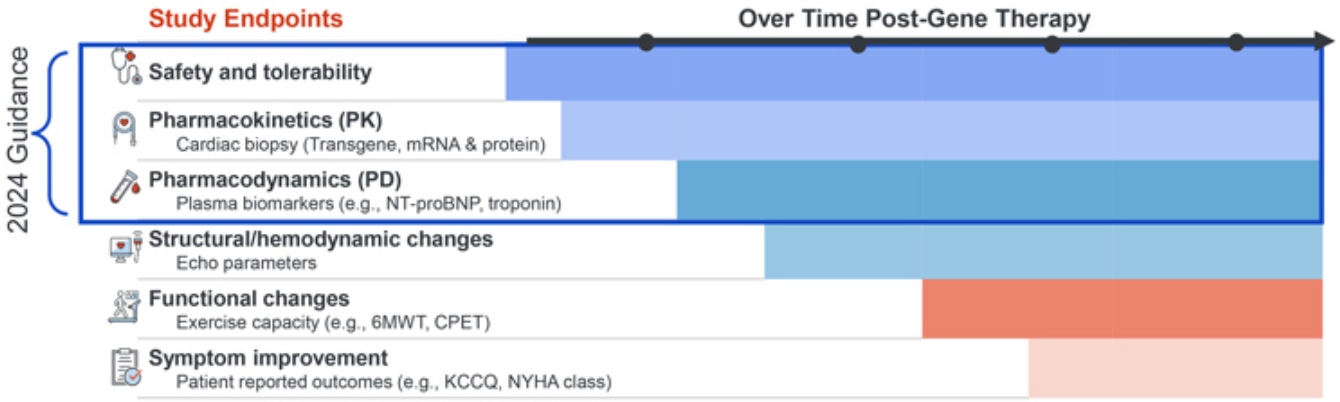
- Open-label, multi-center, dose-escalation and dose-expansion
- 52-week trial period with four-year safety and efficacy follow-up
- Cardiac biopsies at baseline, post-dose and ~52 weeks (effective with Cohort 1, patient 3)



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

TENAYA THERAPEUTICS

[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

TENAYA™ THERAPEUTICS

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

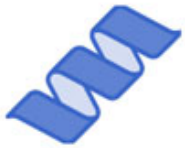
1 DELIVERY: Transduction (DNA)

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

2 EXPRESSION: Transcription (RNA)

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

3 EXPRESSION: Translation (Protein)



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

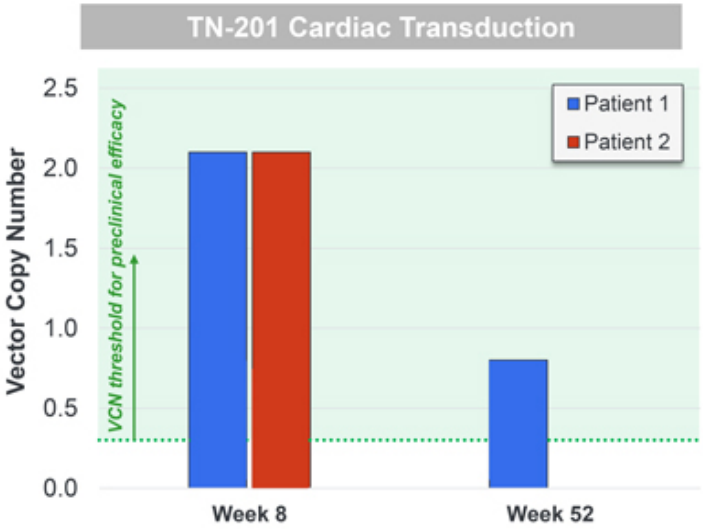
Overview of initial biopsy findings

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

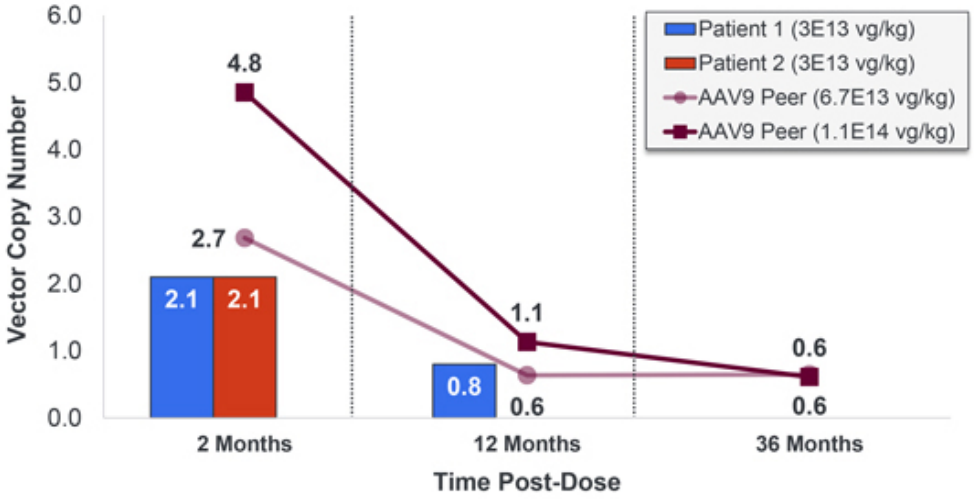
- Consistently high VCN >2.0 vg/dg at Week 8 for P1 and P2
- Expected drop of VCN to 0.8 vg/dg at Week 52 for P1

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.

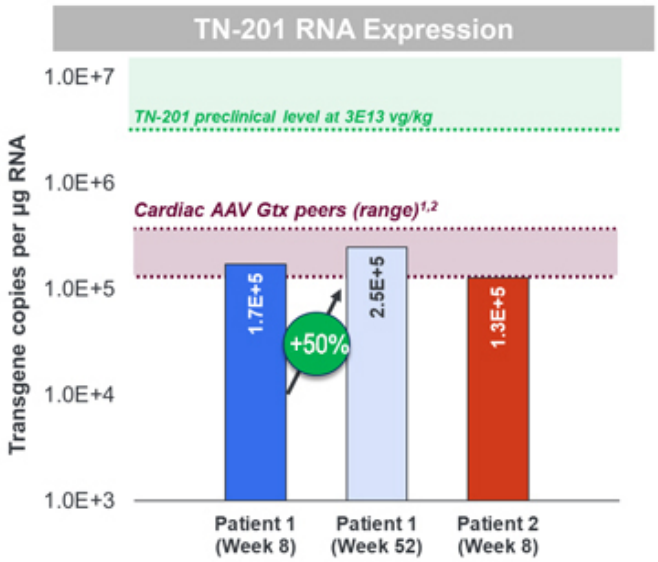
[1]Greenberg, NEJM 2024
*Peer values represented as means for given timepoint

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

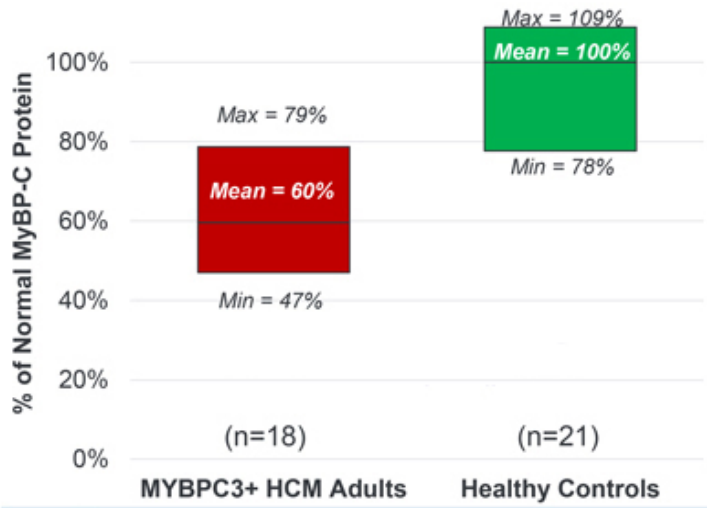
- mRNA expression at 3E13 vg/kg dose was lower in humans than achieved in preclinical models (Expected based on species-to-species variability)
- Magnitude of expression similar to peers' clinical data[1,2]

[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.

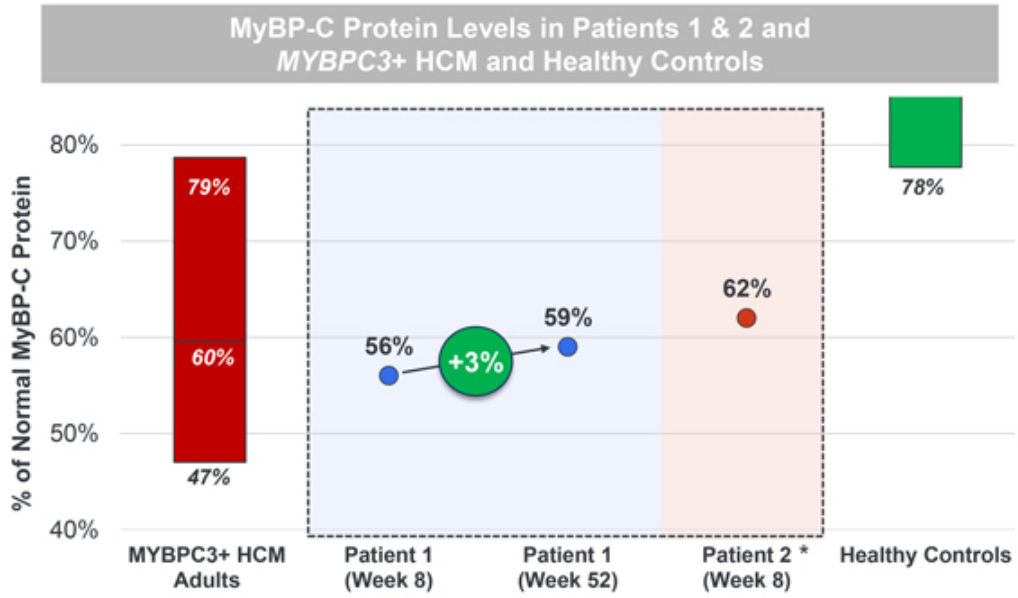
Modest restoration has achieved measurable benefit in other cardiac gene therapy clinical trials.

[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

TENAYA THERAPEUTICS

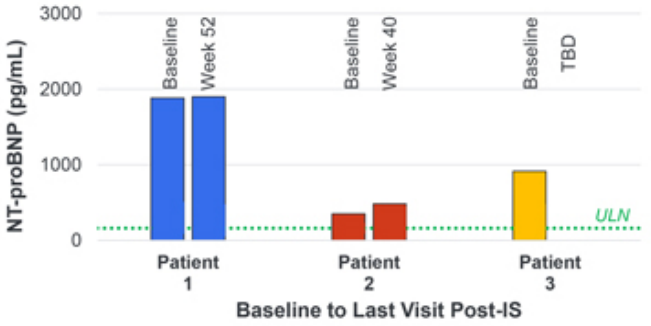
* Patient 2 52-week biopsy not yet taken

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

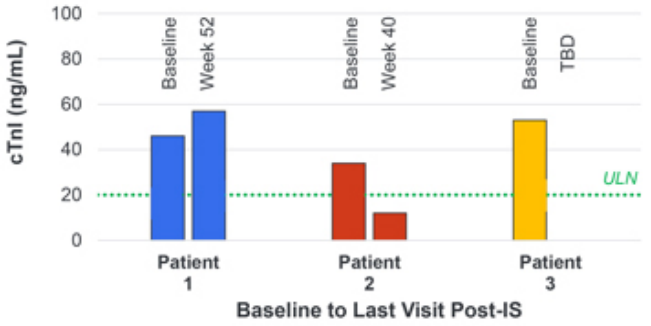
Circulating biomarker levels overall stable at this early time point

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

Domain		Clinical Snapshot: Patient 1 at Week 52	Clinical Snapshot: 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