Tenaya Therapeutics Publishes Preclinical Data Demonstrating TN-201 Enhances Cardiac Function and Survival in MYBPC3 Cardiomyopathy Models

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Robust Evidence of Disease Reversal in Severe Knock Out Mice Model Supports Tenaya's Clinical Development Plan to Evaluate TN-201 as a Potential Treatment for Patients with MYBPC3-associated Hypertrophic Cardiomyopathy

SOUTH SAN FRANCISCO, Calif., March 24, 2025 (GLOBE NEWSWIRE) -- 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 announced the publications of positive preclinical data for TN-201, the company's gene therapy candidate for *Myosin-Binding Protein C3 (MYBPC3)*-associated hypertrophic cardiomyopathy (HCM), in *Nature Communications*.

Variants in the *MYBPC3* gene resulting in insufficient levels of MyBP-C protein are the most common genetic cause of HCM. TN-201 is Tenaya's 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. Preclinical results published in *Nature Communications* show that Tenaya's *MYBPC3* gene replacement therapy achieved dose-dependent increases in MyBP-C protein, improving multiple parameters of cardiac function at protein levels well below wild-type with doses as low as $1x10^{13}$ vg/kg. Of note, treatment with Tenaya's *MYBPC3* gene therapy reversed left ventricular hypertrophy, a hallmark of HCM, as evidenced by decreases in posterior wall thickness relative to vehicle and normalization of left ventricular mass relative to body weight. TN-201 is currently being evaluated at doses of $3x10^{13}$ vg/kg and $6x10^{13}$ vg/kg in Tenaya's ongoing MyPEAK™-1Phase 1b/2 clinical trial for the treatment of *MYBPC3*-associated HCM.

"The extensive body of preclinical data published in *Nature Communications* highlights the engineering, production and thorough testing that support TN-201's clinical development and offers substantial evidence that our novel gene therapy approach to *MYBPC3*-associated HCM has the potential to change the treatment paradigm for patients suffering with this genetic heart condition," said Kathy Ivey, Ph.D., Senior Vice President of Research of Tenaya Therapeutics.

"We are encouraged by TN-201's consistency in achieving transduction and expression across our preclinical studies and the early findings from our first-in-human Phase 1b study of TN-201," added Whit Tingley, M.D., Ph.D., Tenaya's Chief Medical Officer. "The robust transduction and improvements in cardiac function observed in a model of severe disease, provide reason to believe in TN-201's potential to achieve similar improvements in key parameters of human disease over time. We look forward to presenting additional data from our first cohort of patients in the MyPEAK-1 clinical trial at the upcoming American College of Cardiology Scientific Sessions, as well as sharing initial data from our high-dose cohort in the second half of this year."

Key Preclinical Findings

The article, titled, "*AAV9-Mediated MYBPC3 Gene Therapy with Optimized Expression Cassette Enhances Cardiac Function and Survival in MYBPC3 Cardiomyopathy Models*," describes the results from *in vitro* and *in vivo* preclinical studies.

Studies conducted in human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) compared various cassette configurations and informed the final design of TN-201, which incorporates a full-length *MYBPC3* gene with a proprietary cardiac promoter that maintains high specificity for heart cells.

To test transduction and expression strength, additional analyses in human iPSC-derived cardiomyocytes showed transduction equivalent to 1 vector genome per diploid genome (vg/dg) resulted in near-wild type levels of *MYBPC3* RNA and MyBP-C protein at $3x10^{13}$ vg/kg. Researchers observed proportional increases in transgene RNA at doses of $3x10^{13}$ and $1x10^{14}$ vg/kg, while MyBP-C protein levels did not exceed wild type levels, indicating that RNA overexpression does not result in overexpression of protein, suggesting an attractive safety feature of *MYBPC3* gene therapy.

To measure the efficacy of TN-201, a mouse surrogate of TN-201 (mTN-201) was tested against vehicle in a homozygous *Mybpc3*-deficient murine model that mimics severe disease in humans. Treatment with mTN-201 in *Mybpc3* knock-out mice at the time of disease onset or in a more challenging model of advanced disease resulted in:

- Sustained increases in *Mybpc3* RNA and MYBPC3 protein expression
- Decreased cardiac biomarkers associated with fibrosis and heart failure
- Improved cardiac function, including improved ejection fraction and diastolic function
- Heart remodeling
- Extended survival

These results were dose dependent, with near-maximal efficacy achieved at doses of $3x10^{13}$ vg/kg, and durable, lasting out to 20 months post-treatment.

Additional experiments in human engineered heart tissue models that replicate the hypercontractility associated with *MYBPC3*-associated HCM

demonstrated:

- Resolution of calcium handling abnormalities
- Enhanced diastolic activity

The complete article can be accessed at *Nature Communications* and within the Publications and Presentations section of Tenaya Therapeutics' website.

About *MYBPC3*-Associated Hypertrophic Cardiomyopathy

Variants in the *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 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 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.

(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 "potential," "believe," "look forward," and similar expressions are intended to identify forward-looking statements. Such forward-looking statements include, among other things, the clinical, therapeutic and commercial potential of, and expectations regarding TN-201; the value of preclinical data to inform the potential of TN-201; the planned timing to report additional data from MyPEAK-1; statements regarding the continued development of TN-201; and statements made by Tenaya's Senior Vice President of Research and Chief Medical Officer. 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: 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; availability of MyPEAK-1 data at the referenced times; the timing and progress of MyPEAK-1; 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 Annual Report on Form 10-K for the year ended December 31, 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.

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