Tenaya Therapeutics Announces Publication of TN-401 Gene Therapy Preclinical Data in Nature Communications Medicine

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TN-401 AAV9-Based Gene Therapy Being Developed to Treat the Underlying Cause of PKP2-associated Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

PKP2 Gene Replacement Therapy Normalized Heart Rhythms, Reversed Disease Progression and Extended Survival in a Severe Mouse Model of Disease

Tenaya Anticipates Dosing First Patient in Phase 1b RIDGE™-1 Clinical Trial of TN-401 in Second Half of 2024

SOUTH SAN FRANCISCO, Calif., March 18, 2024 (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 publication of its preclinical research related to its gene therapy candidate, TN-401, in the current issue of *Nature Communications Medicine*.

TN-401 is an adeno-associated virus serotype 9 (AAV9)-based gene therapy being developed for the treatment of arrhythmogenic right ventricular cardiomyopathy (ARVC) caused by *Plakophilin-2* (*PKP2*) gene mutations. *PKP2* mutations are the most common genetic cause of ARVC, also known as arrhythmogenic cardiomyopathy (ACM), and result in a loss of key proteins needed to maintain the structural integrity and cell-to-cell electrical signaling of heart muscle cells. TN-401 is designed to deliver a functional *PKP2* gene to heart cells where it works to restore normal protein levels in order to halt or even reverse disease after a single dose.

“Following a single infusion of our AAV9-based *PKP2* gene therapy in a severe knock-out mouse model of the disease, PKP2 protein levels were restored. This led to dose-dependent improvements in right ventricular dilation and ejection fraction, reductions in arrhythmia frequency and severity, and prevention of adverse fibrotic remodeling, with near-maximal efficacy achieved at the 3E13 vg/kg dose.” said Tim Hoey, Ph.D., Chief Scientific Officer of Tenaya.

“ARVC can have a devastating effect on patients’ lives, putting them at risk of life-threatening arrhythmias and placing limitations on their quality of life,” said Whit Tingley, M.D., Ph.D., Chief Medical Officer of Tenaya. “These promising preclinical results show the potential of TN-401 to prevent, halt or even reverse the steady progression of *PKP2*-associated ARVC by addressing the underlying genetic cause, and offer hope to patients. We look forward to commencing dosing of TN-401 in patients with *PKP2*-associated ARVC in our Phase 1b RIDGE-1 clinical trial in the second half of this year.”

Tenaya’s RIDGE-1 Phase 1b clinical trial of TN-401 is a multi-center, open-label study to assess the safety, tolerability and clinical efficacy of a one-time intravenous infusion of TN-401. Tenaya is currently also conducting the RIDGE™ global non-interventional natural history and serotype study of *PKP2*-associated ARVC. Both studies are being conducted at leading centers for ARVC care.

Key Findings
The paper, titled “*AAV9:PKP2 improves heart function and survival in a Pkp2-deficient mouse model of arrhythmogenic right ventricular cardiomyopathy*,” describes results from preclinical studies in a *Pkp2*-deficient mouse model to understand gene therapy’s impact in both prevention mode before disease onset and in treatment mode after disease onset. A single dose of Tenaya’s AAV9:PKP2 gene therapy:

- Restored normal levels of PKP2 protein expression,
- Led to a highly coordinated and durable correction in structural genes encoding desmosome, sarcomere and calcium handling proteins with a role in maintaining cellular integrity and function,
- Reduced the frequency and severity of arrhythmias,
- Demonstrated durable efficacy in preventing disease development,
- Slowed or reversed disease progression after onset,
- Prevented fibrotic remodeling, and
- Improved long-term survival.

Tenaya selected AAV9 as the vector for delivery for TN-401 based on its extensive clinical and commercial safety record in thousands of patients globally and its demonstrated ability in clinical studies to broadly distribute in all regions of the human heart and to more robustly express the *PKP2* gene in cardiomyocytes as compared to other vectors.

About *PKP2*-Associated ARVC
Mutations in the desmosome gene *PKP2* are the most frequent cause of ARVC, with greater than 40% of those diagnosed estimated to carry pathogenic *PKP2* mutations. In the U.S. prevalence of *PKP2*-associated ARVC is estimated at more than 70,000, though the condition is frequently undiagnosed; in nearly one in four cases, sudden cardiac death is the first sign of disease.

Mutations of the *PKP2* gene result in insufficient expression of a protein needed for the proper functioning of the desmosomal complex that maintains physical connections and electrical signaling between heart muscle cells. As the desmosome structure degrades, cardiac muscle cells are replaced by fibrofatty tissue and electrical pulses in the heart become unstable, resulting in adverse remodeling and irregular heart rhythms. A progressive disease, ARVC is typically diagnosed before age 40 and symptoms may include arrhythmias, palpitations, lightheadedness, dizziness and fainting and sudden cardiac arrest. Current treatments include anti-arrhythmic medications, implantable cardioverter-defibrillators (ICDs) and ablation procedures, which do not address the underlying genetic cause of disease.

About TN-401 Gene Therapy and the RIDGE Clinical Program
TN-401 is an investigational AAV9-based gene therapy being developed for the treatment of ARVC due to mutations in the *PKP2* gene. Tenaya has received clearance from the FDA to initiate its first-in-human RIDGE-1 Phase 1b clinical trial of TN-401 in patients with *PKP2*-associated ARVC. To support TN-401's clinical development, the company is currently enrolling the RIDGE global non-interventional study to collect natural history and AAV9 antibody (seroprevalence) data among ARVC patients carrying *PKP2* gene mutations. TN-401 has received Orphan Drug and Fast Track Designations from the FDA.

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. Leveraging integrated proprietary core capabilities enabling target identification and validation, design of AAV-based genetic medicines and in-house manufacturing the company is advancing a pipeline of novel therapies with diverse treatment modalities for rare genetic cardiovascular disorders and more prevalent heart conditions. Tenaya's most advanced candidates include TN-201, a gene therapy for *MYBPC3*-associated hypertrophic cardiomyopathy (HCM), TN-401, a gene therapy for *PKP2*-associated arrhythmogenic right ventricular cardiomyopathy (ARVC), and TN-301, a small molecule HDAC6 inhibitor being initially developed for heart failure with preserved ejection fraction (HFpEF). Tenaya also has multiple early-stage programs progressing through preclinical development. For more information, visit www.tenayatherapeutics.com.

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 "anticipates," "promising," "potential," "look forward," "plan," 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 TN-401 as a treatment for *PKP2*-associated ARVC and the plan for initiation of patient dosing in RIDGE-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: the potential failure of TN-401 to demonstrate safety and/or efficacy in clinical testing; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating TN-401; the timing and progress of the RIDGE-1 clinical trial; the timing, scope and likelihood of regulatory filings and approvals for TN-401; 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 ability to develop, initiate or complete preclinical studies and clinical trials, and obtain approvals, for any of its product candidates; 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 business and 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 entitled "Risk Factors" in 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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