Tenaya Therapeutics Doses First Patient in RIDGE™-1 Phase 1b Clinical Trial of TN-401 for the Treatment of PKP2-Associated Arrhythmogenic Right Ventricular Cardiomyopathy

November 25, 2024

TN-401 AAV9-based Gene Therapy Designed to Deliver Fully Functional PKP2 Gene with the Aim of Increasing Protein Levels to Address Underlying Disease

RIDGE-1 Currently Enrolling at Six Centers; Observational Natural History and Seroprevalence Study of PKP2-associated ARVC Adults Continues Enrollment at 20 Clinical Sites in the U.S., UK and Europe

Initial Clinical Data for RIDGE-1 Anticipated in 2025

SOUTH SAN FRANCISCO, Calif., Nov. 25, 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 that the first patient has been dosed with TN-401 gene therapy in the RIDGE-1 Phase 1b clinical trial at the University of California, San Francisco. Tenaya currently anticipates sharing initial data from the RIDGE-1 trial in 2025.

TN-401 is being developed for the treatment of arrhythmogenic right ventricular cardiomyopathy (ARVC, also known as arrhythmogenic cardiomyopathy or ACM) caused by mutations in the *plakophilin-2* (*PKP2)* gene. *PKP2* gene mutations result in insufficient levels of critical proteins needed to maintain the structural integrity and cell-to-cell signaling of heart muscle cells. TN-401 gene replacement therapy is designed to deliver a functional *PKP2* gene into heart muscle cells using an adeno associated virus serotype 9 (AAV9) capsid. In preclinical studies, the new, healthy *PKP2* gene was successfully integrated into heart cells where it produced the missing protein to slow or even reverse the course of disease. Compared to untreated *in vivo* knock-out models, TN-401 normalized heart rhythms, reversed disease progression and extended survival following a single dose.

“People living with ARVC frequently experience dangerous arrhythmias and are at risk for developing heart failure, cardiac arrest and sudden death. To minimize their risk, ARVC patients live with significant activity restrictions, take chronic medications, and require interventions that together negatively impact their quality of life but don’t address the underlying problem of a defective gene,” said Vasanth Vedantham, M.D., Ph.D., Professor of Medicine, Cardiac Electrophysiologist, Director of Cardiovascular Genetics at the University of California, San Francisco and an investigator for the RIDGE-1 Phase 1b clinical trial. “*PKP2* genetic mutations are the most common single gene cause of ARVC and unlike existing treatments for ARVC, TN-401 gene therapy seeks to directly address the underlying cause of disease by delivering a fully functional copy of *PKP2* to the heart.”

The RIDGE-1 Phase 1b clinical trial is a multi-center, open-label, dose escalation study being conducted in the U.S. and UK. RIDGE-1 will assess the safety, tolerability and preliminary clinical efficacy of a one-time intravenous infusion of TN-401. The trial will seek to enroll up to fifteen adults who have been diagnosed with *PKP2*-associated ARVC, have an implantable cardioverter defibrillator (ICD) and are at increased risk for arrhythmias as determined by premature ventricular contraction count during screening.

The first dose of TN-401 being assessed in the RIDGE-1 clinical trial is 3E13 vg/kg, a dose that was associated with near maximal efficacy in preclinical studies. The first three patients will be dosed on a sequential basis. Once three patients have been dosed at the 3E13 vg/kg level, a panel of independent safety reviewers will advise on plans to dose escalate and/or expand enrollment of the initial cohort dosing in parallel.

“Initiation of this first-in-human study of TN-401 is a significant milestone for Tenaya and we are grateful for the ongoing support received from our trial sites, advocacy organizations, patients and families in our efforts to advance a novel gene replacement therapy for PKP2-associated ARVC,” said Whit Tingley, M.D., Ph.D., Tenaya’s Chief Medical Officer. “We believe TN-401 has best-in-class potential due to its differentiated construct, which utilizes an AAV9 capsid to deliver a fully functioning *PKP2* gene directly to heart cells. We selected AAV9 capsid due to its extensive track record and in preclinical studies it outperformed other capsids and TN-401 restored PKP2 levels in a knockout model, leading to reductions in arrhythmia frequency and severity, and halted disease progression.”

The RIDGE-1 clinical trial is currently enrolling patients at six leading U.S. centers specializing in ARVC care. To learn more about gene therapy for ARVC and participation in the RIDGE-1 study, please visit ARVCstudies.com or ClinicalTrials.gov (NCT06228924). In 2022, Tenaya initiated a non-interventional global natural history and seroprevalence study of adults with *PKP2*-assocated ARVC (NCT06311708). The RIDGE study continues to enroll participants at more than 20 clinical sites in the U.S., UK, France, Germany, Italy and Sweden.

About *PKP2*-Associated ARVC
Plakophilin-2 (*PKP2*) mutations are the most common genetic cause of arrhythmogenic right ventricular cardiomyopathy (ARVC, also known as arrhythmogenic cardiomyopathy or ACM), estimated to represent approximately 40 percent of the overall ARVC population. The prevalence of *PKP2*-associated ARVC is estimated at more than 70,000 people in the U.S. alone.

In *PKP2*-associated ARVC, mutations of the *PKP2* gene results 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 irregular heart rhythms. ARVC symptoms include arrhythmias, palpitations, lightheadedness, dizziness and fainting. It is typically diagnosed before age 40, and sudden cardiac arrest due to life-threatening ventricular arrhythmias is frequently the first manifestation of disease. 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
TN-401 is an investigational AAV9-based gene therapy being developed for the treatment of ARVC due to mutations in the *PKP2* gene. AAV9 was selected as the vector for delivery of Tenaya's *PKP2* gene therapy based on its extensive clinical and commercial safety record and demonstrated ability to target heart muscle cells. In preclinical studies, Tenaya has shown that a single dose of TN-401 restored healthy levels of PKP2 protein, normalized heart rhythms, improved right and left ventricular size and function and extended survival.

Tenaya is conducting the 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. 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.

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," "will," "believe" 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-401; the planned timing to report initial data from RIDGE-1 and related focus of the data readout; and statements made by Tenaya's 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 timing and progress of RIDGE-1; the potential failure of TN-401 to demonstrate safety and/or efficacy in clinical testing; availability of RIDGE-1 data at the referenced time; the potential for any RIDGE-1 clinical trial results to differ from preclinical, interim, preliminary, topline or expected results; 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 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.

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

Investors
Anne-Marie Fields
Precision AQ
annemarie.fields@precisionaq.com

Media
Wendy Ryan
Ten Bridge Communications
wendy@tenbridgecommunications.com