Tenaya Therapeutics Announces FDA Clearance to Begin Clinical Testing of TN-401 Gene Therapy for the Treatment of PKP2-Associated Arrhythmogenic Right Ventricular Cardiomyopathy

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PKP2 Mutations Are the Leading Cause of ARVC, a Dangerous Condition Linked to Sudden Cardiac Arrest in Young People Estimated to Affect 70,000 People in the US

TN-401 Preclinical Studies Demonstrated Robust Reduction of Ventricular Arrhythmias and Extended Survival in Knockout Models of Disease After a Single Dose

SOUTH SAN FRANCISCO, Calif., Oct. 26, 2023 (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, announced today that the U.S. Food and Drug Administration (FDA) has provided clearance of the company's Investigational New Drug (IND) application to initiate clinical testing of TN-401.

TN-401 is Tenaya's adeno-associated virus serotype 9 (AAV9)-based investigational gene therapy product candidate for the treatment of arrhythmogenic right ventricular cardiomyopathy (ARVC) caused by mutations in the *plakophilin-2* (*PKP2)* gene. Based on this IND clearance, the company plans to initiate the RIDGE-1™ Phase 1b clinical trial of TN-401, 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 conducting the RIDGE™ global non-interventional natural history and serotype study of *PKP2*-associated ARVC.

ARVC, also known as arrhythmogenic cardiomyopathy (ACM), is a chronic, progressive, familial disease that typically presents before age 40. People with ARVC experience symptoms related to ventricular arrhythmias, including palpitations, lightheadedness and fainting, and are at increased risk of sudden cardiac death. *PKP2* mutations are the most common genetic cause of ARVC and result in a loss of key proteins needed to maintain the structural integrity and cell-to-cell signaling of heart muscle cells. TN-401 is designed to address the underlying cause of disease by delivering a fully functional *PKP2* gene to restore normal PKP2 protein levels and thereby slow disease progression and reverse the course of disease after a single dose.

"People with arrhythmogenic cardiomyopathy report high levels of fear and stress and must withstand burdensome physical and lifestyle restrictions in an effort to manage the frequent abnormal heart rhythms and constant risk of sudden cardiac arrest associated with their disease," said Whit Tingley, M.D., Ph.D., Tenaya's Chief Medical Officer. "TN-401 is intended to address the genetic mutation most frequently underlying ARVC. The initial dose for TN-401 in the RIDGE-1 study was associated with near maximal efficacy in our preclinical studies. With clinical site and patient community engagement well underway, we look forward to rapidly advancing TN-401 into the clinic."

In preclinical studies in a knock-out mouse model of disease, Tenaya's *PKP2* gene therapy administered at a dose of 3E13 vg/kg restored normal levels of PKP2 protein expression and demonstrated durable efficacy in preventing disease development and slowing or reversing disease progression after onset leading to long-term survival. AAV9 was selected as the vector for delivery of Tenaya's *PKP2* gene therapy based on its extensive clinical and commercial safety record in thousands of patients globally and its demonstrated ability in clinical studies to broadly distribute around the human heart and robustly express in heart muscle cells.

Tenaya has completed cGMP drug product manufacturing at the 1000-liter scale for TN-401 at the company's Genetic Medicines Manufacturing Center, with sufficient drug product produced to support the entire Phase 1b study.

TN-401 RIDGE-1 Phase 1b Protocol
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. The RIDGE-1 clinical trial will seek to enroll up to fifteen adults who have been diagnosed with *PKP2*-associated ARVC. Trial participants must have an implantable cardioverter defibrillator (ICD) and be at increased risk for arrhythmias as determined during screening by premature ventricular contraction (PVC) count.

The trial will be conducted in two stages, with dose administration and outpatient assessments through 52-weeks and a long-term follow-up segment for four-years thereafter. Enrollment will be divided into two dose cohorts, starting at a dose of 3E13 vg/kg, a dose associated with near-maximal efficacy in preclinical studies. Following dosing of the first three patients, a panel of independent safety reviewers will advise on plans to dose escalate and expand enrollment of the initial cohort.

The trial protocol includes assessments of safety, markers of cardiac transduction and transgene expression in right ventricular biopsy samples, changes in PVC, sustained or non-sustained ventricular tachycardia (VT or NSVT) occurrences, circulating plasma biomarkers, imaging biomarkers of disease as measured by echocardiogram and patient-reported outcomes.

About *PKP2*-Associated ARVC
Plakophilin-2 (*PKP2*) mutations are the most common genetic cause of arrhythmogenic right ventricular cardiomyopathy (ARVC), 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, though it frequently goes undiagnosed as sudden cardiac death is the first sign of disease in nearly one quarter of known cases. 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 adverse remodeling and 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 and the RIDGE Clinical Program

TN-401 is an investigational adeno-associated virus serotype 9 (AAV9)-based gene therapy being developed for the treatment of ARVC due to disease causing variants 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 normal levels of PKP2, normalized heart rhythms, improved right and left ventricular size and function and extended survival. 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 *PKP2* gene mutation carriers with ARVC. TN-401 has received Orphan Drug Designation 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 its integrated and interrelated Gene Therapy, Cellular Regeneration and Precision Medicine platforms and proprietary core capabilities, 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 Statement

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 "plans," "look forward," "will," and similar expressions are intended to identify forward-looking statements. Such forward-looking statements include, among other things, the plan to rapidly initiate RIDGE-1, a Phase 1b clinical trial of TN-401; the clinical and therapeutic potential of TN-401 as a treatment to address the genetic mutation most frequently underlying ARVC; enrollment targets for RIDGE-1; and clinical development plans for TN-401 and statements 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 impact of any future communications from the FDA regarding Tenaya's TN-401 IND; the costs of conducting clinical trials; Tenaya's ability to execute on its clinical development plans for TN-401; the potential failure of TN-401 to demonstrate safety and/or efficacy in clinical testing; the potential for RIDGE-1 initial clinical trial results to differ from preclinical or expected results; the timing, scope and likelihood of regulatory filings and approvals for TN-401; Tenaya's ability to successfully operate a manufacturing facility for clinical supply 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 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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