Tenaya Therapeutics Presents Interim Data from RIDGE™ Natural History and Seroprevalence Study of Adults with PKP2-associated ARVC at Heart Rhythm 2025

April 24, 2025

RIDGE is Largest Natural History Study Conducted with More Than 175 Participants Enrolled to Date with Arrhythmogenic Right Ventricular Cardiomyopathy Due to Mutations in the PKP2 Gene

Patients Experience High Burden of Arrhythmias and Severe Disease Progression Despite Standard-of-Care Treatments

Large Majority of PKP2-associated ARVC Patients Appear Eligible for TN-401 Gene Therapy Based on Low Rates of Preexisting Immunity to AAV9 Antibodies

SAN DIEGO, April 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 interim data from its ongoing RIDGE (NCT06311708) natural history and seroprevalence study of adults with arrhythmogenic right ventricular cardiomyopathy (ARVC) caused by mutations in the *Plakophilin 2* (*PKP2*) gene will be presented at the Heart Rhythm Society's annual Heart Rhythm meeting taking place in San Diego, CA from April 24-27, 2025.

RIDGE is the largest non-interventional natural history and seroprevalence study of adults with *PKP2*-associated ARVC to date and was designed to collect and assess participants' clinical characteristics and medical history, as well as to test for preexisting neutralizing antibodies to AAV9. *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. Tenaya is developing TN-401 gene therapy as a potential treatment for *PKP2*-associated ARVC (also known as arrhythmogenic cardiomyopathy, or ACM). 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.

"Interim data from the RIDGE observational study bring into focus what we've long understood about *PKP2*-associated ARVC – the current treatment approaches such as ablation or prescribed medications are insufficient to address the high burden of arrhythmias or alter the progression of disease, placing patients at increased risk for life-threatening ventricular tachycardias," said Hugh Calkins, M.D., Catherine Ellen Poindexter Professor of Cardiology and Director, Johns Hopkins Hospital ARVD Program and an investigator for the RIDGE study. "I am encouraged by the potential of disease-modifying treatment approaches, such as TN-401 gene therapy, which is intended to alter the course of disease by delivering a functional *PKP2* gene to the heart."

The RIDGE study has enrolled more than 175 patients at approximately 20 clinical sites in the U.S., UK, France, Germany, Italy and Sweden. As of the February 2025 cut off, clinical data from 144 adults with *PKP2*-associated ARVC were analyzed.

Key findings being shared at Heart Rhythm 2025 include:

- Adults with *PKP2*-associated ARVC experience a high burden of arrhythmias despite treatments with standard of care medications including beta blockers and anti-arrhythmic medications such as flecainide, as well as surgical interventions such as ablation and implantable cardioverter-defibrillator (ICD) placement.
    - 83 percent (95 of 115) of participants with available Holter data had a premature ventricular contraction (PVC) count of 500 PVCs/day or greater, a threshold linked with increased risk of life-threatening ventricular arrhythmias.
    - 49 percent (56 of 115) of participants for whom Holter monitoring data was available had a history of ventricular tachycardia
- Current treatments appeared to do little to halt or prevent progressive structural changes to the heart that occur as a result of *PKP2* mutations. Study participants show evidence of progressive structural changes that occur as a result of *PKP2* mutations, in which the instability and disintegration of cellular structures in the desmosome results in fibrofatty scar tissue
    - 60 percent of patients with MRI data available showed disease progression, as indicated by measures of right and left ventricular function, and heart tissue health
- Electrocardiogram results affirmed that a majority of patients had T-wave inversions (an indicator of ventricular strain or myocardial injury). Both QRS prolongation, which can indicate a delay in electrical conduction, and terminal active duration (TAD) were not present in a majority of participants, potentially indicating that changes in fibrofatty replacement and conduction system develop more slowly than arrhythmia symptoms.
- 93 percent of patients show AAV9 neutralizing antibody titers ≤1:40
- A large majority of participants in the RIDGE study meet key eligibility criteria for participation in Tenaya's ongoing Phase 1b RIDGE-1 clinical trial of TN-401 gene therapy

Enrollment is also underway in Tenaya's Phase 1b clinical trial, known as RIDGE™-1, to assess the safety, tolerability and activity of a one-time dose of TN-401. Tenaya plans to report safety and biopsy data from the first cohort of RIDGE-1 patients in the second half of 2025.

“The RIDGE natural history study provides a rich source of data detailing the disease characteristics and burden for adults with ARVC. We extend our heartfelt gratitude to the patients and investigators involved in this important study. Their continued support has been instrumental in achieving the progress we've made thus far,” said Whit Tingley, M.D., Ph.D., Tenaya’s Chief Medical Officer. “As the largest collection of prospective and retrospective patient demographic and medical history data, RIDGE is expected to serve as a control arm to assess activity and efficacy of the interventional TN-401 study in determining meaningful clinical and surrogate endpoints for measuring gene therapy’s efficacy in the PKP2-associated ARVC indication, as well as serving as an important means of engaging with patients and clinical sites as we enroll our Phase 1b trial of TN-401.”

The interim data from RIDGE will be presented at Heart Rhythm 2025 on April 26, 2025 by Dr. Calkins during the Basic Translational Science session in a poster titled “*Determining Eligibility for RIDGE™-1, a Phase 1b Interventional Study to Evaluate Safety and Efficacy of TN-401 Gene Therapy in Adults with Plakophilin-2 (PKP2)-Associated Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): Interim Results of an Observational Study to Assess Seroprevalence to Adeno-Associated Virus Serotype 9 (AAV9)*”.

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 and the RIDGE-1 Clinical Trial

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. TN-401 has received Orphan Drug and Fast Track Designations from the U.S. Food and Drug Administration.

Tenaya is conducting the RIDGE-1 Phase 1b clinical trial of TN-401 in patients with *PKP2*-associated ARVC. 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. RIDGE-1 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 PVC count during screening.

To learn more about gene therapy for ARVC and participation in the RIDGE-1 study, please visit ARVCstudies.com or ClinicalTrials.gov (NCT06228924).

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 “potential,” “expected,” “plans, “will,” 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; expectation’s regarding the RIDGE data in support of determining meaningful clinical and surrogate endpoints for measuring gene therapy’s efficacy in the PKP2-associated ARVC indication; the planned timing to report initial data from RIDGE-1 and RIDGE; 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 potential failure of TN-401 to demonstrate safety and/or efficacy in clinical testing; actions and decisions of regulatory agencies; the timing and progress of RIDGE-1; availability of RIDGE-1 and RIDGE 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