Tenaya Therapeutics Reports Positive Interim Data from Cohort 1 of RIDGE™-1 Phase 1b/2 Clinical Trial of TN-401 Gene Therapy for Adults with PKP2-associated ARVC

December 11, 2025

TN-401 was Well Tolerated at 3E13 vg/kg dose

Robust Transduction and Demonstrated Increases in PKP2 Protein Levels in First Two Patients at Week 8

Clinically Meaningful Reductions in Arrhythmia Burden Observed in First Two Patients with More Than Six Months of Follow-Up

Tenaya Management to Host a Webcast Conference Call Thursday, December 11 at 5:00 pm ET to Review Preliminary Results

SOUTH SAN FRANCISCO, Calif., Dec. 11, 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 the ongoing RIDGE™-1 Phase 1b/2 clinical trial of TN-401 gene therapy for the potential treatment of adults with arrhythmogenic right ventricular cardiomyopathy (ARVC), a form of arrhythmogenic cardiomyopathy (ACM) that primarily impacts the right ventricle, caused by mutations in the plakophilin-2 gene, *PKP2*.

Data reported today include safety, biopsy and arrhythmia results from three patients who received TN-401 at a dose of 3E13 vg/kg. Patient follow-up at the time of data cut off ranged from 20-40 weeks post-dose. TN-401 was well tolerated, increased PKP2 protein expression from baseline in two of three patients and demonstrated evidence of meaningful improvements in arrhythmia burden as measured by premature ventricular contractions (PVCs) and non-sustained ventricular tachycardias (NSVTs) for those patients with greater than six months follow up.

“We are excited by the strength of the data for TN-401 at this relatively early timepoint in the RIDGE-1 trial. Less than a year after dosing, initial data indicate a promising safety profile, consistent transduction of the gene therapy in cardiomyocytes and RNA and protein expression, and meaningful reductions in PVCs and NSVTs, well-established risk factors for dangerous sustained arrhythmias,” said Whit Tingley, M.D., Ph.D., Tenaya’s Chief Medical Officer. “These findings are an important milestone in TN-401’s development and we’re eager to build on this momentum as we continue monitoring patients in Cohort 1 and Cohort 2.”

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 address the underlying cause of disease by delivering a functional *PKP2* gene into heart muscle cells using an adeno associated virus serotype 9 (AAV9) capsid. The RIDGE-1 clinical trial designed to assess the safety, tolerability and activity of a one-time dose of TN-401 at two dose levels, 3E13 vg/kg and 6E13vg/kg. To date, Tenaya has dosed three patients at the 3E13 vg/kg dose level (Cohort 1). Initial results reported today focus on interim data for Cohort 1 as of an October 2025 data cut off. Key findings include:

- **TN-401 was well tolerated at the3E13 vg/kg dose and no dose-limiting toxicities were observed**
    - Adverse events (AEs) were generally mild, asymptomatic and manageable and deemed unrelated to TN-401 treatment.
    - Among those AEs related to treatment, there was a transient, asymptomatic Grade 1 event of elevated cardiac troponin levels categorized as a serious AE (SAE) only due to inpatient monitoring.
    - No incidents of thrombotic microangiopathy (TMA) or cardiotoxicities were observed.
    - To date, no implantable cardioverter-defibrillator (ICD) shocks or arrhythmias associated with TN-401 have occurred
    - All patients have tapered off immunosuppressive medicines.

Enrollment and dosing of three patients at the 6E13 vg/kg dose (Cohort 2) is complete with no new SAEs related to TN-401 reported in the cohort to date.

- **Biopsies demonstrate robust transduction and expression detected in all patients within first eight weeks**
    - Patients 1 and 2 provided consistent evidence that TN-401 transduced the heart (3.4 vg/dg and 5.0 vg/dg). A biopsy analysis of TN-401 DNA for Patient 3 was not available at the time of data cut off.
    - Consistently high TN-401 mRNA expression, ranging from $1.4x10^4$ - $2.9x10^5$ copies per microgram of RNA, were detected for all three patients in Cohort 1 as early as eight weeks.
    - Post-treatment protein levels of PKP2 increased significantly in Patients 1 and 2 by a mean of 10% from baseline to Week 8
        - These data are based on rigorous methods to measure protein increases using liquid chromatography–mass spectrometry (LC-MS) normalized to myosin heavy chain, a motor protein in the sarcomere found exclusively in cardiomyocytes.
        - Change from baseline in PKP2 protein levels for Patient 3 fell within the standard deviation of these methods despite having

the highest levels of TN-401 mRNA expression across Cohort 1, which may be due to the inherent variability in sampling biopsies. A second post-dose biopsy will be collected and analyzed from Week 52 per protocol.

- The changes in PKP2 protein levels were also apparent using multiplexed immunofluorescent imaging, which provided visual evidence of protein level increases and colocalization of other proteins associated with intracellular stability and electrical signaling.

- **Clinically meaningful improvements in electrical instability were observed in the first two patients with greater than 6 months follow-up after TN-401 dosing**

  - Patient 1 PVC counts decreased by 46% as of their most recent (Week 40) visit, while Patient 2 PVC counts decreased by 89% by their most recent visit (Week 32).
  - Patient 2 also had a substantial NSVT burden of 78 counts per 24-hour period at baseline that dropped all the way to zero and remained stable by Week 32. Patient 1 had low NSVT count at baseline which remained low at Week 40.
  - For Patient 3, meaningful changes in PVCs or NSVTs were not expected nor observed as of the data cut off, which was less than six months following treatment with TN-401.
  - Other measures of clinical response including QRS duration, T wave inversions, heart function and New York Heart Association (NYHA) class were in the normal range or remained stable for all three Cohort 1 patients during the post-dose follow-up period.

"We extend our heartfelt gratitude to the patients and investigators involved in the RIDGE-1 clinical trial and our RIDGE natural history study of *PKP2*-associated ARVC. Their continued support and dedication have been instrumental in achieving the substantial progress we've made thus far," continued Dr. Tingley.

Webcast Conference Call
Tenaya management will host a conference call on Thursday, December 11, 2025, at 5:00 pm ET/2:00 pm PT to discuss the TN-401 data shared today. The webcast conference call, including an accompanying slide presentation, can be accessed from the Investor section on the "Events and Presentations" page of the Tenaya website at www.tenayatherapeutics.com.

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), occurring in 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. TN-401 has received Orphan Drug and Fast Track Designations from the U.S. Food and Drug Administration. Tenaya's development of TN-401 is supported in part by a grant from the California Institute for Regenerative Medicines (CIRM).

The RIDGE-1 Phase 1b/2 clinical trial of TN-401 in patients with *PKP2*-associated ARVC is a multi-center, open-label, dose escalation study being conducted in the U.S. and UK. RIDGE-1 is intended to 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 ICD and are at increased risk for arrhythmias as determined by premature ventricular count (PVC) during screening.

To learn more about gene therapy for ARVC and the RIDGE-1 clinical trial, 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's pipeline includes clinical-stage candidates TN-201, a gene therapy for *MYBPC3*-associated hypertrophic cardiomyopathy (HCM) and TN-401, a gene therapy for *PKP2*-associated arrhythmogenic right ventricular cardiomyopathy (ARVC). Tenaya has employed a suite of integrated internal capabilities, including modality agnostic target validation, capsid engineering and manufacturing, to generate a portfolio of novel medicines based on genetic insights, including TN-301, a clinical-stage small molecule HDAC6 inhibitor for the potential treatment of heart failure and related cardio/muscular disease, and multiple early-stage programs in preclinical development aimed at the treatment of both rare genetic disorders and more prevalent heart conditions. 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," promising," "look forward," "continue," "encouraging," "anticipated," "suggest," and similar expressions are intended to identify forward-

looking statements. Such forward-looking statements include, among other things, the planned timing to report additional data from RIDGE-1; the clinical, therapeutic and commercial potential of, and expectations regarding the safety and efficacy of TN-401; the value of additional RIDGE-1 data to inform the potential of TN-401; the inferences regarding transduction, translation and expression of TN-401; statements regarding the continued development TN-401 and TN-401 clinical outcomes, which may materially change as more patient data become available; 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: availability of RIDGE-1 data at the referenced time; the timing and progress of RIDGE-1; the potential failure of TN-401 to demonstrate safety and/or efficacy in clinical testing; the potential for any RIDGE-1 clinical trial results to differ from preclinical, interim, preliminary or expected results; the potential for the U.S. Food and Drug Administration and/or other regulatory agencies to conclude at any time that TN-401 may not have an appropriate risk/benefit profile; Tenaya's ability to enroll and maintain patients in clinical trials, including RIDGE-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 Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2025 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.

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

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

Media
Wendy Ryan
Ten Bridge Communications
wendy@tenbridgecommunications.com