Tenaya Therapeutics Presents Encouraging New Clinical and Preclinical Data from HDAC6 Inhibitor Program TN-301 for the Potential Treatment of Heart Failure with Preserved Ejection Fraction at the 2023 HFSA Annual Scientific Meeting

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TN-301 Demonstrates Tolerability, Potential for Once Daily Dosing, Target Engagement and Selectivity for HDAC6 in Phase 1 Clinical Trial of Healthy Participants

Combination of Tenaya's HDAC6 inhibitors with Empagliflozin Shows Additive Benefits in Preclinical HFpEF Model and Highlights Differentiated Mechanism of Action

SOUTH SAN FRANCISCO, Calif. and CLEVELAND, Oct. 09, 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, today released new data for TN-301 at the 2023 Heart Failure Society of America (HFSA) Annual Scientific Meeting. TN-301 is Tenaya's highly selective small molecule inhibitor of histone deacetylase 6 (HDAC6) being developed for the potential treatment of heart failure with preserved ejection fraction (HFpEF).

"TN-301 continues to generate promising early data as a differentiated candidate for the treatment of HFpEF, a form of heart failure with few treatment options and unacceptably low survival rates. The first-in-human data from our Phase 1 study of TN-301 demonstrated safety and tolerability in healthy participants with dose-proportional pharmacokinetics and robust target engagement," said Whit Tingley, M.D., Tenaya's Chief Medical Officer. "The attractive therapeutic profile seen in our Phase 1 trial of healthy participants and the additive benefits observed preclinically of HDAC6 inhibition in combination with empagliflozin support the potential for TN-301 to be utilized as a single agent or in combination with an emerging standard of care. Taken together, these data support continued development of TN-301 as a potential treatment to address the many HFpEF patients underserved by today's treatment options."

Phase 1 Results Demonstrate Safety, Target Engagement and Suitability for Once-Daily Dosing
Results from the Phase 1 clinical trial of TN-301 were presented in an ePoster, *Phase 1 Clinical Trial Of TN-301, A Highly Selective HDAC6 Inhibitor with Potential in HFpEF, Shows Target Engagement* (#417). Tenaya initiated the randomized, double-blind, placebo-controlled Phase 1 clinical trial in September 2022 to assess the safety and tolerability of escalating, oral doses of TN-301, as well as pharmacokinetics (PK) and pharmacodynamics (PD) measures. The Phase 1 trial enrolled a total of 72 healthy adult participants in two stages. In Stage 1, participants received single ascending doses (SAD) of either TN-301 at doses ranging from 1mg – 700mg or placebo. Tubulin acetylation was previously established as a relevant PD marker of HDAC6 inhibition in preclinical studies and utilized in the Phase 1 clinical trial to confirm target engagement. Upon achieving evidence of target engagement at single doses of 5mg, participants were enrolled in Stage 2 and received multiple ascending doses (MAD) of TN-301 at once daily doses of 25mg, 100mg and 300mg for 14 days.

Key Findings:

- TN-301 was generally well tolerated across the broad range of doses studied, with no dose-limiting toxicities or serious adverse events observed. The most common adverse events observed were related to gastrointestinal disturbances. These occurred with similar frequency among those who received placebo or TN-301 and did not increase with TN-301 dose. All participants completed the study.
- PK results showed overall dose proportionality in both the SAD and MAD stages of the study with a half-life supportive of once-daily dosing.
- Robust HDAC6 inhibition was observed and increasing doses and exposures with TN-301 correlated with increasing PD effects. Plasma exposure and target engagement observed in this healthy participant study met or exceeded those required for maximal efficacy in preclinical studies.
- There were no changes in histone acetylation with TN-301, underscoring the selectivity of TN-301 for HDAC6 and potentially reducing the risk of off target effects observed with less selective HDAC6 inhibitors or pan-HDAC inhibition.
- Future studies of TN-301 in HFpEF patients may evaluate a range of doses starting at approximately 25 mg and higher.

Additive Benefit Observed with Combination of Tenaya's HDAC6 inhibitor with Approved SGLT2 inhibitor in HFpEF Model
The ePoster titled, *Co-Administration of Inhibitors of HDAC6 and SGLT2 in Murine HFpEF Models Results in Additive Improvements in Cardiac Structural and Functional Measures* (#104), describes an effort by Tenaya researchers to examine the effect of combining TYA-018 (an HDAC6 inhibitor structurally and functionally similar to TN-301) with empagliflozin (a sodium-glucose cotransporter-2 (SGLT2) inhibitor) which is approved for the treatment of HFpEF) in the company's proprietary HFpEF mouse model. This study compared healthy controls with those treated with TYA-018 and empagliflozin administered alone or in combination vs. untreated HFpEF mice.

Key findings:

- Evidence of additive benefits at or nearing that of healthy controls were observed in all treatment groups at eight weeks, but more substantially with combination treatment, across multiple measures of diastolic function (E/e', E/A, end diastolic pressure) without negative consequences to ejection fraction.
- At a gene level, an extensive reversal of disease toward healthy controls was observed in TYA-018 and combination groups, but less so in the empagliflozin group. A gene set enrichment analysis of pathway and functional level HFpEF changes provided insights on the distinct impact of HDAC6 inhibition on disease pathophysiology compared to SGLT2 inhibition, with TYA-018 demonstrating a greater impact on improving metabolism, oxidative stress and inflammation.

About HFpEF and TN-301
HFpEF is characterized by a stiffening of the heart muscle resulting in an inability for the left ventricle to relax properly during normal heart rhythm, referred to as diastolic dysfunction. There are several cellular processes thought to underly the pathophysiology of HFpEF including increases in fibrosis and inflammation and defects in metabolism. Although HFpEF accounts for approximately 50 percent of all heart failures, there are few proven treatment options.

TN-301 is Tenaya's highly specific first-in-class small molecule histone deacetylase (HDAC) 6 inhibitor, initially being developed for the potential treatment of HFpEF. TN-301 has a multi-modal mechanism of action that includes modifying cytoskeletal and other proteins to coordinate cellular processes. In preclinical studies, TN-301 has been shown to reverse many of the signs and symptoms of HFpEF, with evidence of improved cardiac function and improved glucose tolerance and reduced inflammation and fibrosis.

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 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," 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-301 both alone or in combination with an emerging standard of care as a treatment for HFpEF. 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-301 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-301; the timing, scope and likelihood of regulatory filings and approvals for TN-301; 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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