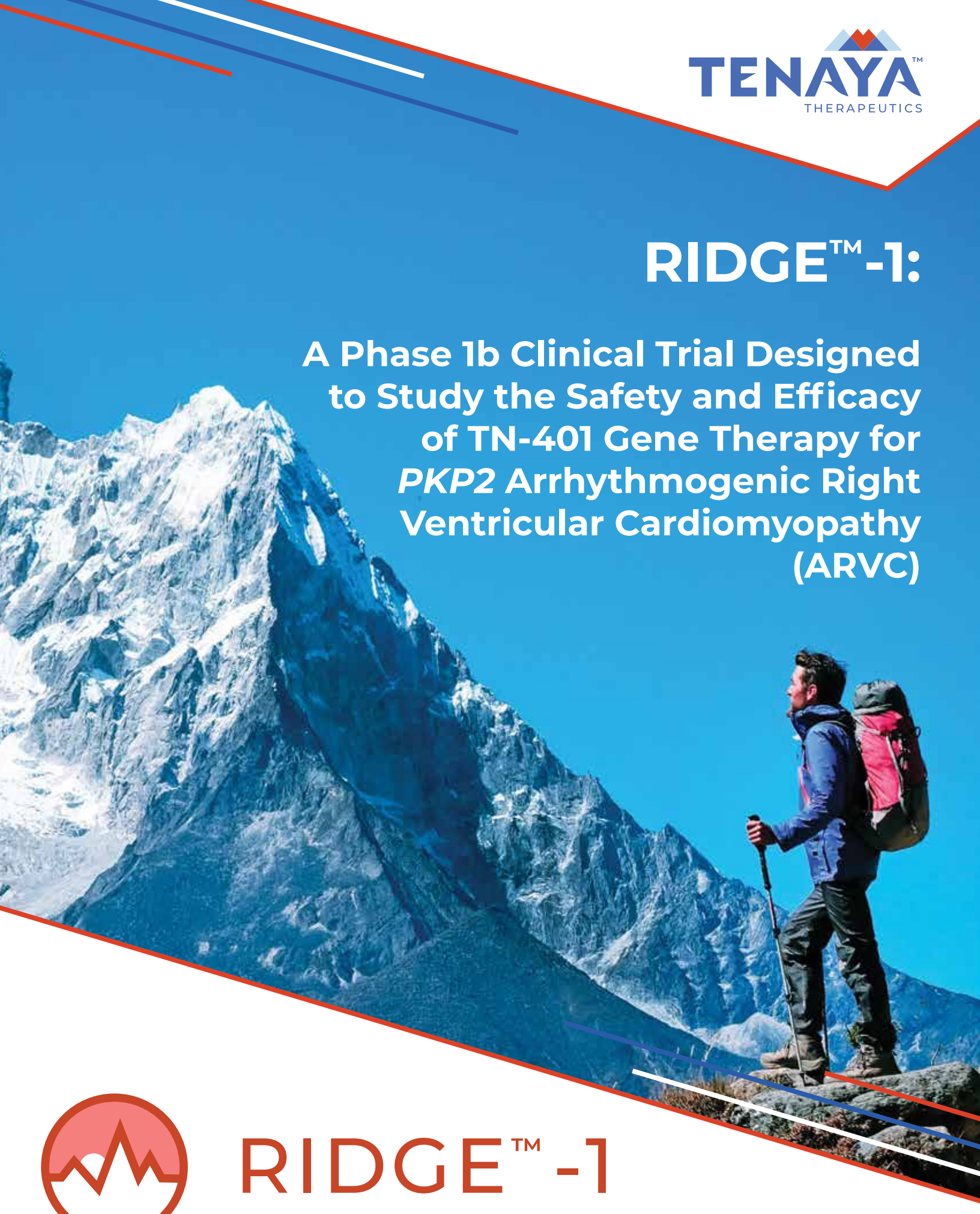
TENAYA™
THERAPEUTICS

RIDGE™-1:

A Phase 1b Clinical Trial Designed to Study the Safety and Efficacy of TN-401 Gene Therapy for *PKP2* Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)



RIDGE™ -1

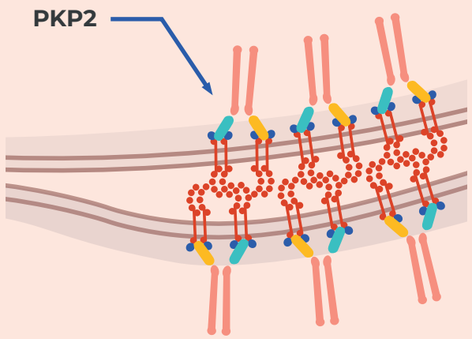
TN-401 investigational gene therapy is designed to address the underlying genetic cause of ARVC due to a plakophilin-2 (*PKP2*) mutation with a one-time infusion[1]

ARVC is a progressive genetic heart disorder associated with frequent ventricular arrhythmias (VAs) and high risk of sudden cardiac death[2]

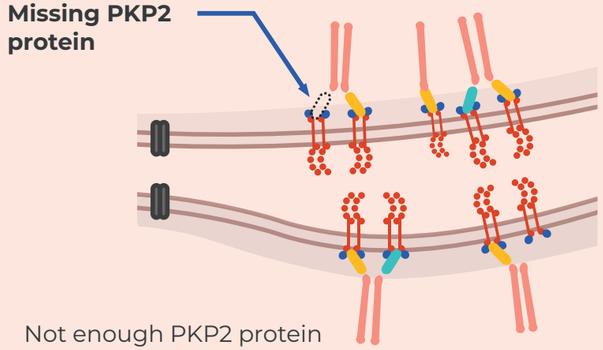
- *PKP2* is the most common gene associated with ARVC[3]
- ARVC is frequently underdiagnosed with typical onset before the age of 40[4,5]
- 50% of index cases present with sustained VAs. Palpitations, syncope, and death were the most common presenting symptoms in 27%, 26%, and 23%, respectively[6,7]
- Exercise restrictions, side effects from antiarrhythmic medications, and anxiety about implantable cardioverter-defibrillator (ICD) shocks have a significant impact on patient quality of life[5]
- Current treatments do not prevent disease onset or halt disease progression[5]

PKP2-associated ARVC is caused by mutations in the desmosome gene *PKP2*[8]

Healthy[9]



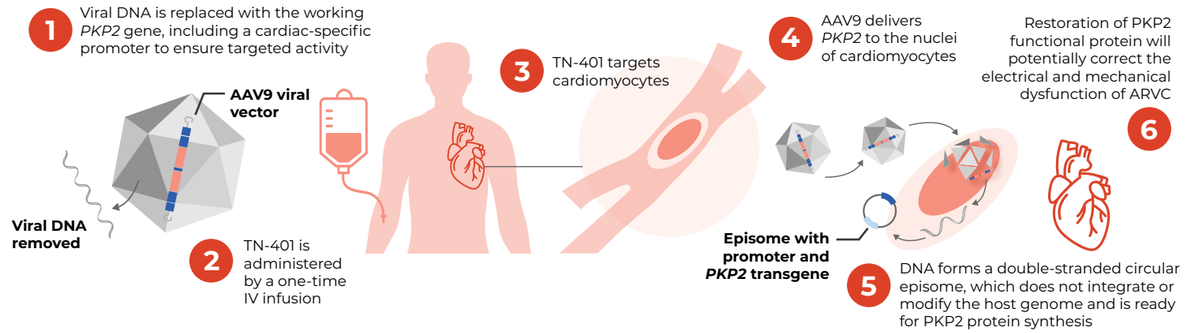
PKP2-associated ARVC[9]



Not enough PKP2 protein leads to reduced function of the desmosomes and gap junctions[8]

TN-401 is an AAV9-based *PKP2* gene therapy designed to deliver functional copies of *PKP2* directly to cardiomyocytes with a one-time IV dose[1,5,8,10]

AAV9 is a widely studied capsid and clinically validated gene therapy vector proven to transduce human cardiomyocytes to restore protein expression.[11,12]



After a single infusion of our AAV9-based *PKP2* gene therapy in a severe knockout mouse model of the disease, PKP2 protein levels were restored[13]

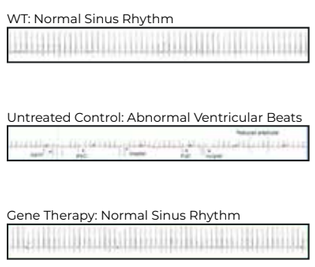
This led to

- Dose-dependent improvements in right ventricular dilation and ejection fraction
- Reductions in arrhythmia frequency and severity
- Prevention of adverse fibrotic remodeling

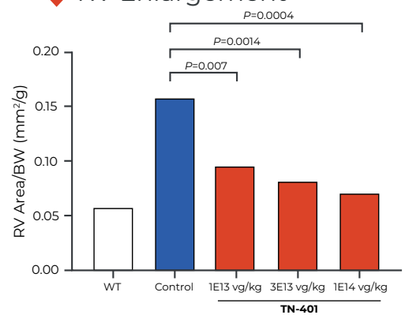
Near-maximal efficacy was achieved at the 3E13 vg/kg dose.

PKP2 knockout mouse model of disease treated with AAV9-based *PKP2* gene therapy[5,8]

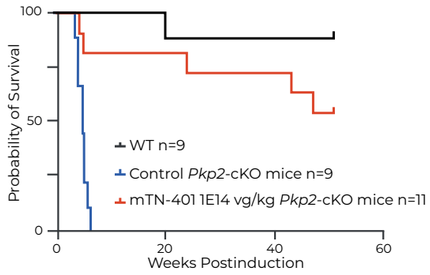
↓ Arrhythmia



↓ RV Enlargement



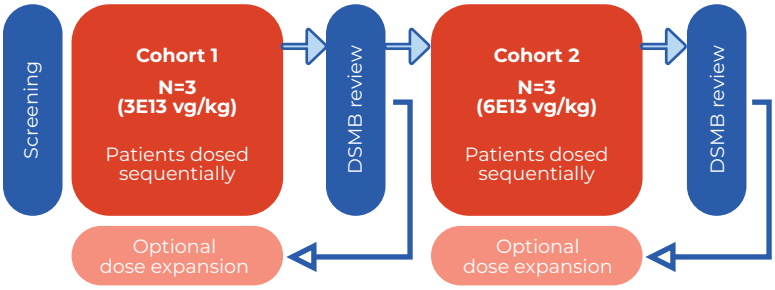
↑ Survival



By addressing the underlying genetic cause of disease, TN-401 has the potential to prevent disease onset and slow disease progression, by producing the PKP2 protein required to restore structural defects and electrical abnormalities.[8]

RIDGE™-1 is evaluating the safety and efficacy of TN-401 in adults with *PKP2*-associated ARVC[1]

RIDGE-1 is a Phase 1b study that will assess safety and explore efficacy endpoints at 52 weeks, with a 4-year follow-up[1]

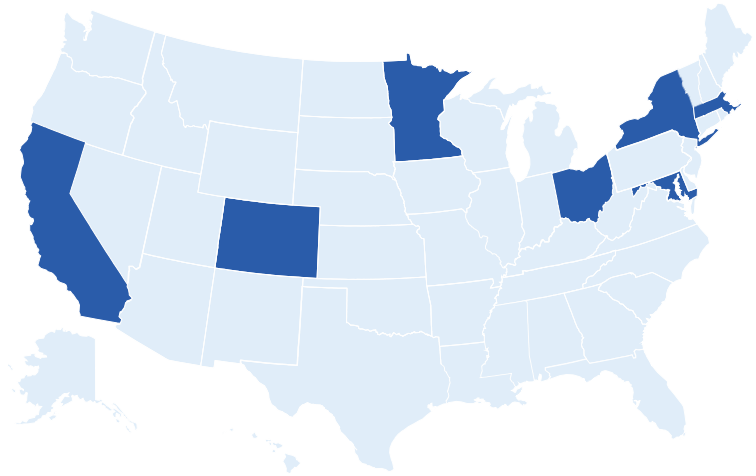


- Primary endpoint: safety and tolerability[1]
- Secondary endpoints[1]
  - Changes in daily PVC counts and NSVT from screening to Week 52
  - Changes in number of ICD therapies

Key eligibility criteria for your adult patients (18-65 years) include[1]

- An ARVC diagnosis due to P/LP mutation in *PKP2*
- A functioning ICD*
- LVEF ≥50%
- NYHA class I to III
- Seronegativity against AAV capsid (low AAV9 titer)
- Frequent PVCs

RIDGE-1 Clinical Trial Sites



If you have a patient interested in being referred to a RIDGE-1 study site, please contact us at our email **medaffairs@tenayathera.com**.

Visit **arvcstudies.com** or **clinicaltrials.gov/study/NCT06228924** for further information or to find a clinical trial site near you.

Active and planned study sites are included.

AAV9, adeno-associated virus 9; BW, body weight; DSMB, data and safety monitoring board; IV, intravenous; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; P/LP, pathogenic/likely pathogenic; PVC, premature ventricular contraction; RV, right ventricular; WT, wild type.

*With remote interrogation capabilities implanted ≥12 months prior to screening.[1]

1. Tenaya Therapeutics. Data on file [Protocol TN-401-0012 TN-401 Version 2.0, 07 Nov 2023]. 2. Marcus FI, et al. *Circulation*. 2010;121(13):1533-1541. 3. Jacob KA, et al. *Neth Heart J*. 2012;20(5):234-239. 4. Dexter KH. Arrhythmogenic right ventricular cardiomyopathy: a case of mistaken identity. December 12, 2022. Accessed February 9, 2024. https://www.clinicaladvisor.com/home/topics/cardiovascular-disease-information-center/arrhythmogenic-right-ventricular-cardiomyopathy-arvc-case/ 5. Wu I, et al. Session presented at: 2022 Heart Rhythm; April 29-May 1, 2022; San Francisco, CA. 6. Groeneweg JA, et al. *Circ Cardiovasc Genet*. 2015;8(3):437-446. 7. Dalal D, et al. *Circulation*. 2005;112(25):3823-3832. 8. Wu I, et al. *Commun Med (Lond)*. 2024;4(1):38. 9. MacRae CA, et al. *J Clin Invest*. 2006;116(7):1825-1828. 10. Tenaya Therapeutics. Data on file [Gene Therapy MOA 5 slides PKP2]. 11. Burdett T, Nuseibeh S. *Gene Ther*. 2023;30(3-4):323-335. 12. Zhang H, et al. *Front Cardiovasc Med*. 2022;9:952755. 13. Tenaya Therapeutics. Tenaya Therapeutics announces publication of TN-401 gene therapy preclinical data in Nature Communications Medicine. March 18, 2024. Accessed March 27, 2024. https://investors.tenayatherapeutics.com/news-releases/news-release-details/tenaya-therapeutics-announces-publication-tn-401-gene-therapy