

Assessing Seroprevalence to Adeno-Associated Virus Serotype 9 in Preparation for RIDGE™-1, a Phase 1b First-in-Human Study to Evaluate Safety and Efficacy of TN-401 Investigational Gene Therapy in Adults with **PKP2**-Associated Arrhythmogenic Right Ventricular Cardiomyopathy

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Introduction

- Recombinant adeno-associated viral vectors (rAAVs) are the primary method for therapeutic gene delivery. Preclinical data show that AAV9 enables significantly higher gene expression in cardiomyocytes compared to other parental capsids, such as AAVrh74 and AAVrh10.^{1,2} Moreover, rAAV9 is a clinically-validated serotype with a well-established clinical utility and safety record
- Exposure to wild-type AAV, a nonpathogenic virus, is common and potential patients may harbor pre-existing, neutralizing antibodies (NAbs) to epitopes on the rAAV capsid surface, potentially inhibiting rAAV transduction and limiting efficacy and/or increasing risk of inflammation³
- Seroprevalence studies to evaluate levels of NAbs to the vector serotype facilitate selection of participants for gene therapy and help to exclude individuals with high titers³
- Mutations in the gene encoding the desmosomal protein plakophilin 2 (*PKP2*) are the leading genetic cause of arrhythmogenic right ventricular cardiomyopathy (ARVC), representing nearly 40% of ARVC cases^{4,5}
- Current treatments for ARVC are palliative and fail to alter disease course.⁶ Tenaya Therapeutics has developed TN-401, an investigational AAV9-based gene therapy designed to restore the expression and function of *PKP2* in patients with *PKP2*-associated ARVC. The first-in-human phase 1b RIDGE-1™ (NCT06228924) is actively recruiting participants
- To date, no studies have assessed the seroprevalence of AAV9 in individuals with *PKP2*- associated ARVC. This poster describes interim results of an AAV9 seroprevalence study in this population

1. Cheng Z, et al. *ASGCT, Mol Ther* 2024;32(4S1).

2. Chen H. *World J Med Genet* 2015;5(3):28–45.

3. Mendell J, et al. *Mol Ther Methods Clin Dev* 2022;25:74–83.

4. James CA and Calkins H. *Annu Rev Med* 2019;70:1–18.

5. Krahn AD, et al. *AJACC Clin Electrophysiol* 2022;8:533–553.

6. Cadrin-Tourigny J, et al. *Eur Heart J* 2022;43:e1–e9.

Site Map of AAV9 Seroprevalence Study in individuals with PKP2-associated ARVC

Mayo Clinic,
Rochester, MN, USA

University of California,
San Francisco, CA, USA

University of Colorado,
Denver, CO, USA

Brigham and Women's Hospital, Boston, MA, USA

New York University, New York, NY, USA

Johns Hopkins University, Baltimore, MD, USA

The Cleveland Clinic, Cleveland, OH, USA

The Queen Elizabeth Hospital,
Glasgow, UK

St George's University Hospitals, NHS
Foundation Trust, London, UK

Royal Brompton & Harefield NHS Foundation
Trust, London, UK

Barts & The London NHS Trust,
London, UK

Hopital Louis Pradel, Bron, France

Istituti Clinici Scientifici Maugeri SpA, Pavia, Italy

Study Design

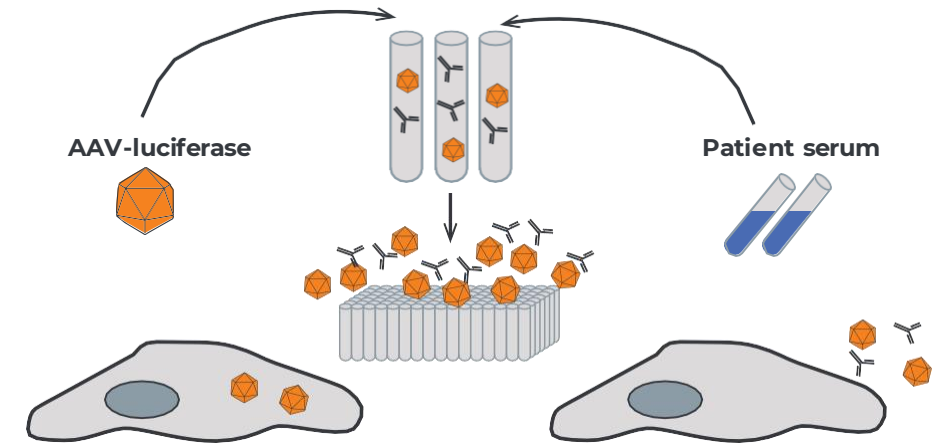
- Exploratory, multicenter AAV9 seroprevalence study (NCT06311708) enrolling participants with PKP2-associated ARVC across the US and Western Europe
- Sites collect demographic information, medical history, and serum from consented participants

Participant criteria

- Ages 14–65 years, inclusive, at the time of consent
- Pathogenic or likely pathogenic PKP2 gene mutation
- Diagnosed with ARVC and meets 2010 Modified Task Force Criteria for ARVC as affected
- Functioning implantable cardioverter defibrillator

AAV9 NAb Assay

- Locally collected blood samples were analyzed at a specialized central laboratory
- The AAV9 NAb assay utilised the AAV9 capsid containing a luciferase reporter (BioAgilytix, Durham, NC, USA)
- The custom vector was incubated with various dilutions of participant serum and inhibition of cell transduction was evaluated. The resulting luminescent signal was inversely proportional to the level of pre-existing AAV9 NAb in participant serum



The firefly luciferase reporter gene packaged in AAV9 capsid was exposed to cells, along with patient's serum. Inhibition of cell transduction by AAV9 NAb is detected as a reduction in luciferase reporter signal relative to controls.

Analyses

- Participants with titers $\leq 1:20$ were classified as having low pre-existing AAV9 NAb titers and being eligible for TN-401 therapy. This classification threshold is considered to be more conservative than most other AAV gene therapy clinical trials

Evaluation of Participants' Demographic and Medical History Characteristics

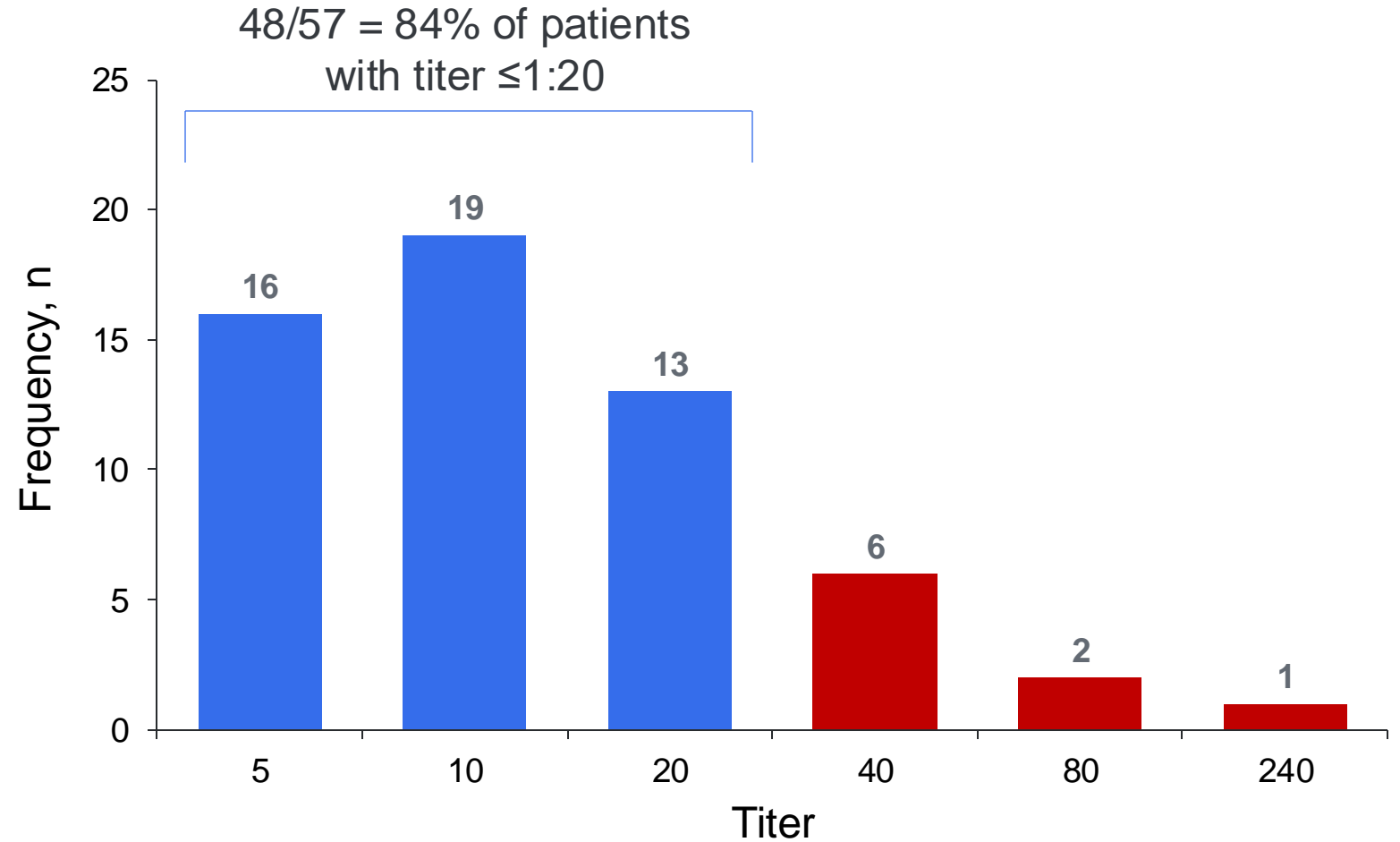
- Participants' age, sex, and race were collected as part of demographic data. Geographic location is assigned according to the location of the clinical trial site
- Parameters of interest included *PKP2* mutation status, New York Heart Association (NYHA) class and premature ventricular contraction rates
- Available data were summarised using descriptive statistics

Patient characteristics

| Characteristics | AAV9 NAb (N=57) |
|--|-----------------|
| Age, mean years (standard deviation) | 42.0 (13.4) |
| Sex, female, n (%) | 23 (40) |
| Race, n (%) | |
| White | 53 (93) |
| Black/African American | 2 (4) |
| Asian | 2 (4) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 56 (98) |
| Unknown ethnicity | 1 (2) |
| PKP2 Pathogenic/Likely Pathogenic variant, n (%) | |
| Yes | 56 (98) |
| No | 0 |
| Missing | 1 (2) |
| NYHA class, n (%) | |
| I | 39 (68) |
| II | 15 (26) |
| III | 3 (5) |
| Premature ventricular contractions per 24 hours, (n=44), median (Q1–Q3) | 1538 (385–2648) |

Seroprevalence data

- Interim analyses indicate that 48 of 57 (84%) of *PKP2*-associated ARVC participants had AAV9 NAb titers $\leq 1:20$ seroprevalence



Conclusions

- Results indicate that patients with *PKP2*-associated ARVC exhibited low levels of pre-existing immunity to AAV9. As a result, the majority of these patients may meet the titer eligibility requirement for participation in clinical trials involving TN-401
- Tenaya intends to expand this study to evaluate AAV9 seroprevalence in different ARVC patient populations, including in paediatric patients, through clinical development of TN-401
- Assessing potential titer requirement eligibility for TN-401 can be achieved through AAV9 NAb testing. Seroprevalence study sites are currently open and actively enrolling participants. For more information, including indicating interest in participating in this study, email clinicaltrials@tenayathera.com