MyPeak-1: A Phase 1b Study to Evaluate Safety and Efficacy of TN-201, an Adeno-Associated Virus Serotype 9 (AAV9) Investigational Gene Therapy, in Adults with MYBPC3-Associated Hypertrophic Cardiomyopathy (HCM)

Haroldson J,[1] Harrison W,[1] Lombardi L,[1] Argast G, Duclos Z, Nelson S, Sethi S, Tomlinson L, Paterson N,[1] Pollman M, Tingley W,[1] Robertson L[1]

[1]Tenaya Therapeutics, South San Francisco, CA, USA

MyPeak-1 is a Phase 1b clinical trial investigating TN-201, the first gene therapy for the treatment of MYBPC3-associated HCM

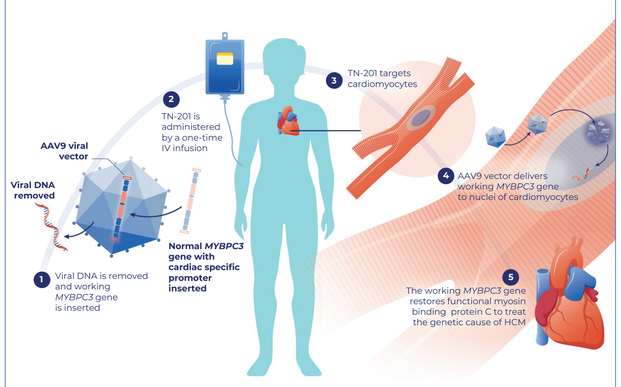
Unmet Need in *MYBPC3*-associated Nonobstructive HCM

- Mutations in the *MYBPC3* gene, which encodes cardiac myosin-binding protein C (MYBPC3), are the leading genetic cause of HCM, representing nearly half of all pathogenic/likely pathogenic HCM variants.
- Most pathogenic/likely pathogenic variants are loss-of-function, resulting in low MYBPC3 protein levels (~60% of normal), termed haploinsufficiency.
- Among patients with MYBPC3-associated HCM, 70% present with the nonobstructive form of the disease (nHCM), which is progressive, lacks an approved therapy and cannot be addressed through surgical intervention, representing a significant unmet need among the HCM population.
- Advances in gene therapy utilizing AAV enables *in vivo* gene delivery of a functional and working *MYPBC3* gene to potentially correct haploinsufficiency of the MYBPC3 protein.
- TN-201 utilizes adeno-associated virus serotype 9 (AAV9), a serotype with superior ability to deliver a working *MYPBC3* gene to the cardiac tissue and is administered as a one-time intravenous dose.
- MyPeak-1 is a Phase 1b clinical trial investigating TN-201, the first gene therapy for the treatment of *MYBPC3*-associated HCM. MyPeak-1 will initially enroll adult patients with nHCM.

TN-201 MOA and Nonclinical Studies Leading to IND Clearance

- TN-201 is an AAV9-based gene therapy designed to deliver the *MYBPC3* transgene to cardiomyocytes to restore MYBPC3 protein levels to ameliorate disease following a single IV infusion (**Figure 1**)
- Nonclinical studies conducted to evaluate the efficacy, biodistribution, and safety profile of TN-201 in a *Mybpc3-/-* knock out mouse model demonstrated its potential to improve survival, restore cardiac function, and reverse hypertrophy, all of which were durable out to 13 months, (the latest time point assessed) after a single dose.

Figure 1. TN-201 Construct Design and Mechanism of Action



TN-201 MOA and Nonclinical Studies Leading to IND Clearance (continued)

- Dose-response studies demonstrated that 3E13 vector genomes per kg body weight (vg/kg) yielded near maximal efficacy, transduced cardiomyocytes uniformly throughout the left ventricle, and restored wild-type MYBPC3 protein levels (**Figure 2**). 3E13 vg/kg was selected as a potentially fully effective starting dose for the MyPeak-1 study (**Figure 3**). This dose is lower than that of other FDA-approved AAV-based gene therapies.

Figure 2. Uniform transduction of cardiomyocytes, restoration of protein expression and maximal reduction in hypertrophy achieved with 3E13 vg/kg

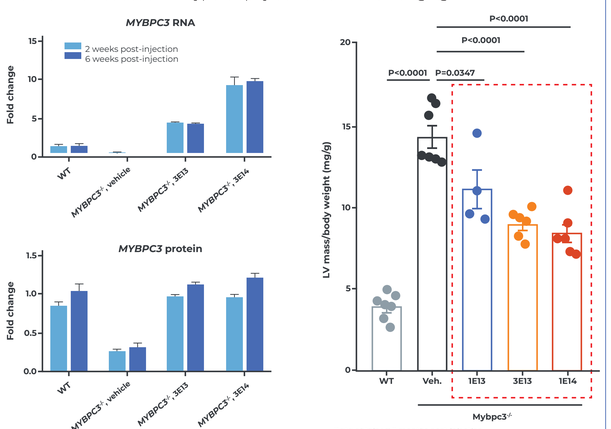
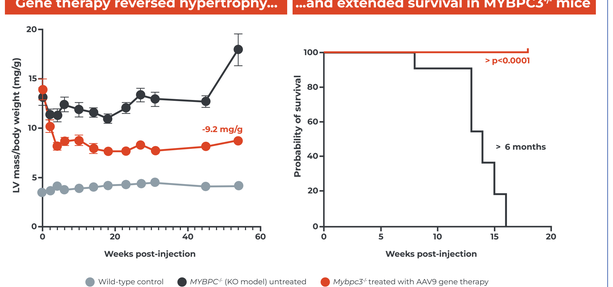


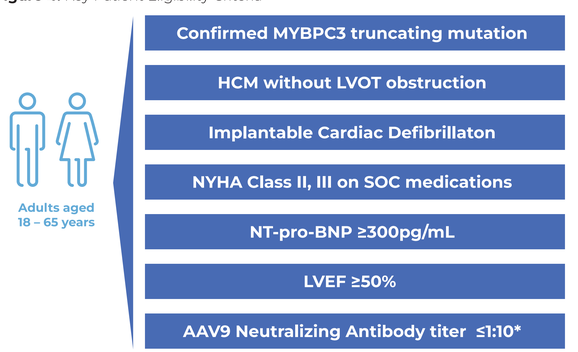
Figure 3. A Single dose of TN-201 Improves LV Mass and Extends Survival



MyPeak-1 Phase 1b Study Design

- MyPeak-1 (TN-201-0009) is an open-label, dose escalation Phase 1b study to evaluate the safety, tolerability, and pharmacodynamics of TN-201.
- MyPeak-1 will enroll 6 patients, ages 18-65 years. Key patient eligibility criteria are listed in **Figure 4**.

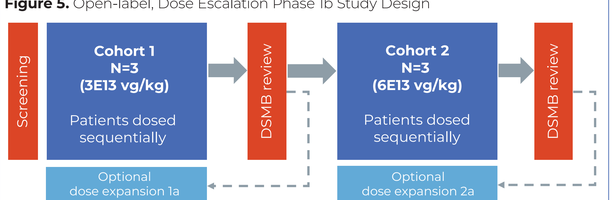
Figure 4. Key Patient Eligibility Criteria



*See Phase 0 seroprevalence poster also at HCMS 2023

- All participants will receive one of two doses of TN-201, 3E13 vg/kg and 6E13 vg/kg, delivered as a one-time IV infusion on Day 1. Cohort 1 includes 3 patients dosed sequentially with 3E13 vg/kg. Following Data Safety Monitoring Board (DSMB) review of Cohort 1, Cohort 2 may commence with 3 patients dosed sequentially with 6E13 vg/kg. There is an option for expansion cohorts at one or both dose levels (Cohorts 1a and 2a). (**Figure 5**)

Figure 5. Open-label, Dose Escalation Phase 1b Study Design



- Between each sequential patient in Cohorts 1 and 2, a Safety Review group (investigator, medical monitors from Sponsor and CRO, DSMB Chair and relevant consultants) will assess adverse events, safety, laboratory, and imaging data prior to determining whether to start the run-in period for the subsequent patient in that cohort.
- The ***primary objective*** of the MyPeak Phase 1b clinical trial is to assess the safety and tolerability of TN-201 (**Table 1**).

MyPeak-1 Phase 1b Study Design (continued)

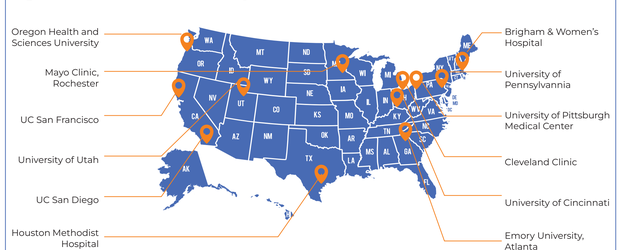
- The ***secondary objective*** will assess potential beneficial effects of TN-201 on patient reported outcomes (PROs) and will inform future dose selection. Specifically, improvements in KCCQ-CSS scores have been associated with improvements in clinical outcomes in symptomatic HCM patients. (**Table 1**)

Table 1. Study Endpoints

	Endpoints and Objectives
Primary	· Assess safety and tolerability of TN-201
Secondary and Exploratory	· Changes in health-related QOL as measured by KCCQ · Assess TN-201 cardiac transduction, expression of MYBPC3 transgene and MyBP-C protein · Evaluate changes in biomarkers (NT-proBNP, hs-cTnI) · ECHO (e.g. LV mass/thickness, LA and LV volumes, GLS) · Changes in NYHA functional class · Assess changes in functional improvement on CPET (pVO2)

- ***Exploratory endpoints*** include measures of TN-201 cardiac transduction and gene expression, cardiac biomarkers and function, as well as patient symptoms, exercise capacity and quality of life.
- Dosing and prophylactic immunosuppression (IS): Patients will begin IS 3 days prior to TN-201 infusion as prophylaxis for potential immune responses to AAV9. The one-time IV infusion of TN-201 and first 7 days of follow-up will occur in a hospital setting for daily laboratory and immune-monitoring assessments.
- To assess cardiac transduction and MYBPC3 expression in cardiomyocytes, heart biopsies will occur at weeks 8 and 52. Following the first stage of MyPeak-1 (52 weeks), stage two long-term follow up will occur through year (end of study).
- Multiple specialist centres are participating in MYPeak-1 across the United States (**Figure 6**)

Figure 6. Current and Planned MyPeak-1 Clinical Trial Sites



Future Implications of MyPeak-1

- MyPeak-1 is the first-in-human study of TN-201 and to our knowledge is the first clinical study of a gene therapy for sarcomeric HCM.
- Upon establishing a safe and effective dose of TN-201, Tenaya Therapeutics plans to assess TN-201 in a broader range of MYPC3-HCM patients, including younger participants and patients with obstructive HCM, in future studies.