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RESEARCH LETTER

First-in-human study of TN-201, an AAV9 gene replacement therapy in *MYBPC3*-associated hypertrophic cardiomyopathy: initial safety, pharmacodynamic, and imaging results from MyPEAK-1

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This brief report details the initial findings from a Phase 1b/2 trial of TN-201, an adeno-associated virus serotype 9 (AAV9) gene therapy for *MYBPC3*-associated hypertrophic cardiomyopathy (HCM), a condition with significant morbidity, increased risk of mortality, and no approved therapy for the majority of patients. TN-201 was well tolerated, and changes to the management of potential immune responses resulted in a shorter period of immunosuppression. These results show consistent transduction and expression of TN-201 in cardiomyocytes, corresponding with increases in MyBP-C levels, reductions or stabilization of cardiac biomarkers, and reductions in key measures of left ventricular (LV) hypertrophy.

1. Introduction

MYBPC3-associated HCM is a progressive disease, potentially leading to heart failure, arrhythmia, and death. Pathogenic/likely pathogenic (P/LP) variants in *MYBPC3*, the gene coding for myosin-binding protein C (MyBP-C), result in insufficient levels of MyBP-C in the heart.[1,2] MyBP-C regulates heart contraction and relaxation by modulating actin-myosin cross-bridge formation, integrating beta-adrenergic signals to match circulatory demands.[3,4] Its deficiency yields worse outcomes compared to genotype-negative HCM patients, underscoring the need for effective therapies.[3-5] Moreover, 70% of patients have non-obstructive HCM (nHCM), for which there are no approved therapies, with the largest trial in symptomatic nHCM failing to meet its primary endpoints.[6] TN-201 is an adeno-associated virus serotype 9 (AAV9)-based gene replacement therapy designed to deliver *MYBPC3* to cardiomyocytes (*Figure 1A*). In preclinical studies, TN-201 restored MyBP-C levels, improved hypertrophy and cardiac function, and extended survival in homozygous mice, and normalized calcium handling and relaxation defects in heterozygous human induced pluripotent stem cell-derived cardiomyocytes.[7]

MyPEAK-1 (NCT05836259) is a first-in-human trial to assess the safety and efficacy of TN-201 in symptomatic adults with *MYBPC3*-associated HCM (*Figure 1A*). This Phase 1b/2 multi-centre, open-label, dose-escalation trial enrolled symptomatic HCM patients at three centres between October 2023 and April 2025. Adult patients (18–75 years) with a P/LP truncating variant in *MYBPC3*, anti-AAV9 neutralizing antibody titre of ≤1:40, LV wall thickness ≥15 mm, LV ejection fraction (LVEF) ≥ 45%, New York Heart Association (NYHA) Class of II/III, and N-terminal pro-

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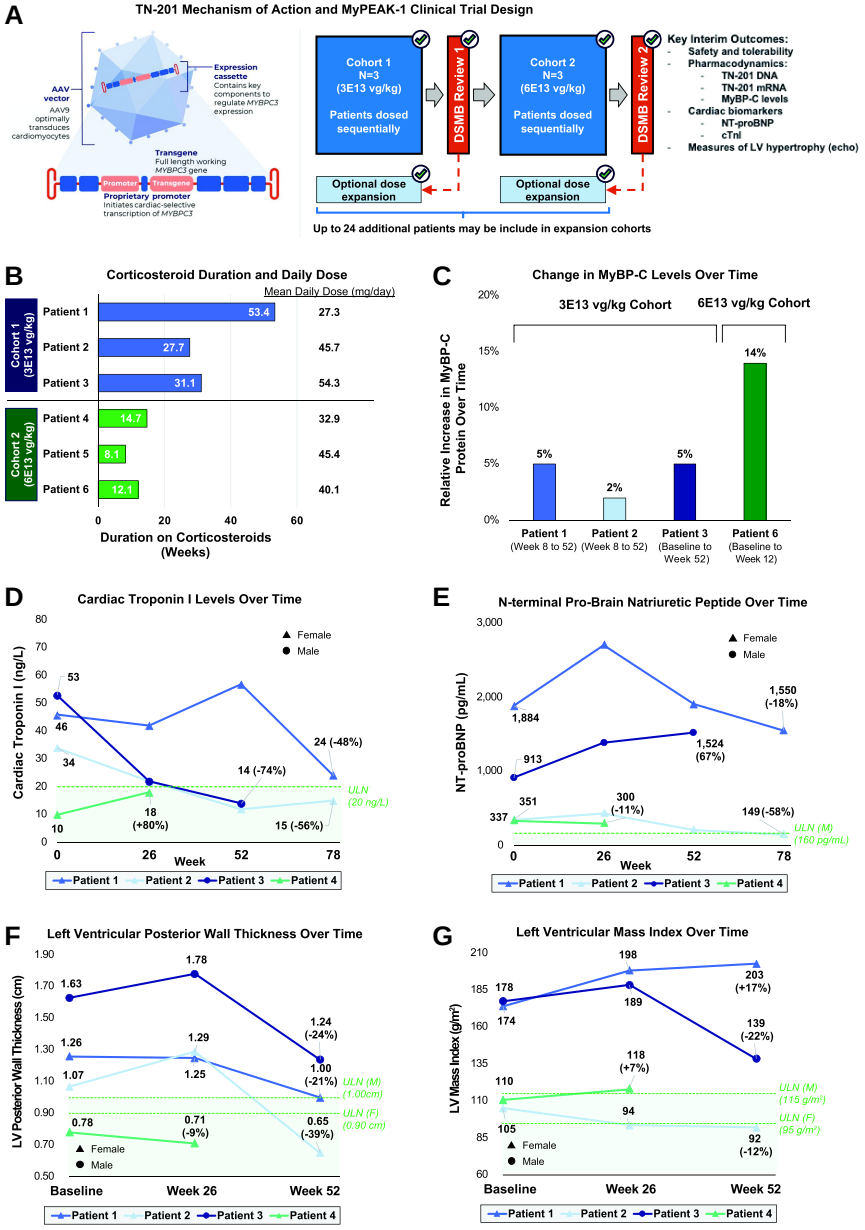

Figure 1 TN-201 mechanism of action and immunosuppression, efficacy of TN-201 in *MYBPC3*-associated HCM. (*A*) Visual depiction of TN-201, an AAV9-based *MYBPC3* gene replacement therapy: investigational therapy utilizes AAV9 serotype—a capsid known for cardiomyocyte tropism—as well as the expression cassette contained therein. The cassette contains two key elements—a copy of the *MYBPC3* gene and a cardiac-selective promoter to enhance expression in the target cell. Additionally, a schematic of the Phase 1b/2 trial (MyPEAK-1), depicting the dose cohorts, DSMB review process, and interim outcomes assessed in the trial. (*B*) Corticosteroid duration and mean daily dose: patients in Cohort 2 were consistently on corticosteroids for much shorter periods than Cohort 1, despite comparable mean daily doses of corticosteroids and the two-fold higher dose of TN-201. Biomarker and echocardiographic assessments may have occurred while patients were on immunosuppression; the effect of those agents on those assessments can be mapped for each patient using their respective immunosuppression duration and the values for their assessments displayed in other panels. (*C*) MyBP-C protein normalized to myosin was measured in serial heart biopsies by LC–TMS and expressed as percent difference between time points. Baseline biopsies were not collected for Patients 1 and 2 but were for Patients 3 and 6. Patients 4 and 5 had yet to have post-treatment endomyocardial biopsies at the time of the July 2025 data cut. (*D*) Serum hs-cTnI was abnormally elevated at baseline in Cohort 1 and decreased to normal or near-normal levels. The patient in Cohort 2, with 26 weeks of follow-up, remains within normal range. Episodes of elevated hs-cTnI were not associated with evidence of clinical myocarditis by ECG or echocardiography. (*E*) NT-proBNP levels were elevated at baseline and rose during prophylactic immunosuppression. Upon completion of the prednisone taper, three of four patients returned to baseline or saw slight decreases in NT-proBNP levels. (*F*) All patients in Cohort 1 had reductions in LV posterior wall thickness, with two of three reaching the normal range of healthy adults. The Cohort 2 patient had a slight decrease in thickness at Week 26. (*G*) Two of three Cohort 1 patients had reductions in LVMI by Week 52, and one Cohort 2 patient remains stable. Figures *C*–*G* show values at each visit and relative changes from baseline to last visit. Patients 5 and 6 had not completed their Week 26 visits as of the July 2025 data cut and therefore did not contribute to cardiac biomarker or echocardiography analyses.

brain natriuretic peptide (NT-proBNP) ≥ 160 pg/mL were included. Institutional review board approval was obtained and subjects provided informed consent. The investigation conformed to the principles outlined in the Declaration of Helsinki. Exclusion criteria included: coronary artery disease; septal reduction therapy or uncontrolled atrial fibrillation within 6 months of screening; use of cardiac myosin inhibitors; and conditions that could be exacerbated following AAV-based gene therapy or immunosuppression. The study was divided into two cohorts of three patients at each dose of TN-201, either 3E13 vector genomes per kilogram of body weight (vg/kg) (Cohort 1) or 6E13 vg/kg (Cohort 2). Dosing of patients was sequential and a safety review occurred after the third patient was dosed in each cohort to determine if expansion of the dose cohort or escalation to the next dose was warranted. Prophylactic prednisone and sirolimus were used to reduce potential immune responses. Prednisone was initiated 1 day prior to TN-201 dosing at 1 mg/kg/day orally and tapered for 3 weeks thereafter. The starting prednisone dose was capped at 80 mg daily but reduced to 60 mg for Cohort 2. A sirolimus loading dose (6 mg once orally) was followed by 2 mg/day, adjusted to maintain a trough level of 4–8 ng/mL. Sirolimus was initiated 3 days before dosing in the first two patients and 7 days prior in all subsequent patients, continuing until 1 week after prednisone completion. An independent data safety monitoring board provided safety oversight.

The primary objective was to assess the safety and tolerability of TN-201 through Week 52 (Stage 1), with future long-term follow-up to be scheduled through Year 5 (Stage 2). Exploratory efficacy endpoints include changes over time in: TN-201 vg (DNA), transgene messenger ribonucleic acid (mRNA), and MyBP-C levels in endomyocardial right ventricular biopsies; serum NT-proBNP and high-sensitivity cardiac troponin I (hs-cTnI); and LV mass, LV wall thickness, and LVEF by echocardiography. The initial protocol required biopsies collected at Weeks 8 and 52. Prior to the enrolment of the third patient in Cohort 1, the protocol was amended to collect biopsies at baseline (1–4 weeks before TN-201 dosing) and Weeks 12 and 52. TN-201-specific DNA and mRNA were measured by droplet digital polymerase chain reaction and reverse transcriptase-quantitative PCR, respectively. MyBP-C was measured by liquid chromatography-tandem mass spectrometry (LC–TMS).[8] Quantification of DNA, mRNA, protein, safety laboratory assessments, cardiac biomarkers, and echocardiograms were analysed by independent core laboratories. The authors had full study data access and reviewed, edited, and approved the manuscript. All statistical analyses are descriptive in nature.

2. Results

Enrolment was completed in both cohorts: three patients received TN-201 3E13 vg/kg (Patients 1–3) and three received 6E13 vg/kg (Patients 4–6). Patients ranged from 27 to 63 years of age; all were nonobstructive ($n = 6$). Five patients were female, with one male patient in Cohort 1. Five patients were NYHA Class II, with one Class III patient in Cohort 1. All patients had an ICD. All three patients in Cohort 1 had septal myectomies, compared to one patient in Cohort 2. Other baseline cohort differences include Cohort 1 with directionally higher NT-proBNP (1049 vs. 605 pg/mL) and hs-cTnI (44 vs. 15 ng/L) levels than Cohort 2, as well as more hypertrophy per LV mass index (LVMI) (152 vs. 130 g/m^2). As of July 2025, Cohort 1 patients had completed at least 52 weeks and up to 78 weeks of follow-up, while Cohort 2 patients had completed 12–26 weeks.

TN-201 has been well tolerated at both doses. Nausea was the most common treatment-emergent adverse event (AE) ($n = 5$), and transaminase elevation was the most common treatment-related AE (five events in three patients in Cohort 1 and one event in Cohort 2)—all reversible, asymptomatic, and without abnormal bilirubin or synthetic liver function. All treatment-related AEs were mild-moderate in severity, except one Grade 3 elevated transaminase. There were two treatment-related serious AEs—one in Cohort 1 of Grade 2 liver enzyme elevation on Day 26 that responded to intravenous prednisolone and resolved within 2 days; and another in Cohort 2 of Grade 1 asymptomatic elevated complement sC5b-9 on Day 6, resolving within several days without additional treatment. There were no AEs due to declines in LVEF, clinical myocarditis, ventricular arrhythmias, or study discontinuation or death. Adjustments to immune monitoring and immunosuppression during Cohort 1 to shorten the course of immunosuppression resulted in faster tapers and lower cumulative corticosteroid doses in Cohort 2, despite the higher TN-201 dose (*Figure 1B*). Mean patient sirolimus trough levels were similar between Cohorts 1 and 2 during prophylactic immunosuppression (7.2 and 7.4 ng/mL, respectively).

MyBP-C increased in all Cohort 1 patients by an average of 4% from the first biopsy taken (either from baseline for Patient 3 or Week 8 for Patients 1 and 2) to Week 52 (*Figure 1C*). The first Cohort 2 patient had an increase of 14% in MyBP-C from baseline to Week 12. MyBP-C abundance for the two patients with baseline biopsies was lower compared to donor hearts, consistent with published data. The distribution of MyBP-C peptides across the protein demonstrated full-length MyBP-C, rather than truncated peptides, suggesting haploinsufficiency as the mechanism, not dominant negative poison peptides.[7] TN-201 DNA (2.1 vg/diploid genome at Week 8 for Cohort 1 and 4.7 at Week 12 in Cohort 2) and mRNA (ranging from 1.17E5 at Week 8 in Patient 2 to 1.31E6 copies per microgram RNA at Week 52 for Patient 3) were detected in all post-dose biopsies, supporting the observed increase in MyBP-C levels.

All Cohort 1 patients had abnormal cTnI at baseline, which declined by up to 74% at their most recent visit (absolute change of −19 to −39 ng/L) (*Figure 1D*). NT-proBNP levels increased from baseline in all patients through up to 26 weeks following TN-201 administration, likely due to prednisone-related volume increase; levels were either below or at baseline levels at their most recent visit (*Figure 1E*). All patients had reductions in LV posterior wall thickness ranging from 21 to 39% by Week 52 (absolute change of −2.6 to −4.2 mm), with two of three within the normal range (*Figure 1F*). In two of three patients in Cohort 1, LVMI declined by >10% by Week 52 (absolute change of −13 and −39 g/m^2 in Patients 2 and 3) (*Figure 1G*).

3. Discussion

Results from Cohort 1 show increased MyBP-C levels and an even larger relative increase in protein levels in Cohort 2. Increased protein expression over 1 year was consistent with reports from other AAV-based cardiac gene therapies.[9] Decreases of cTnI and reductions in LV wall thickness were observed in Cohort 1. TN-201 was well tolerated at both doses in this first-in-human study of AAV9 gene replacement therapy in *MYBPC3*-associated HCM patients. Adjustments to safety monitoring and the immunosuppression regimen enabled a reduction in the total dose and duration of corticosteroids and were effective in managing potential immune responses.[10] Patients had advanced *MYBPC3*-associated HCM, with elevated LV mass and symptoms, despite prior myectomy in four patients. Directional changes in troponin and echocardiographic parameters are encouraging, as elevated cTnI and LV posterior wall thickness are independent predictors of cardiovascular AEs and death, respectively, in HCM patients.[11,12]

MYBPC3-associated HCM patients have limited treatment options. TN-201 is the first investigational therapy designed to address the underlying genetic cause of *MYBPC3*-associated HCM. Direct effects on MyBP-C levels and cardiac remodelling without declines in LV function potentially support broader expansion of clinical investigation of TN-201. However, the current open-label study requires longer-term follow-up to assess efficacy and durability of clinical benefit.

4. Conclusion

Single administration of TN-201, a first-in-human AAV gene replacement therapy in *MYBPC3*-associated HCM patients, was well-tolerated with immunogenicity successfully managed. Increases in MyBP-C, decreases in circulating biomarkers, and a reduction in LV hypertrophy were observed

during follow-up. Results support continued evaluation of TN-201 in the treatment of symptomatic *MYBPC3*-associated HCM.

Authors' contributions

This trial was sponsored by Tenaya Therapeutics, Inc. (South San Francisco, CA). The authors were responsible for reviewing and editing the manuscript and made the decision to submit the manuscript for publication. The final version of the manuscript was approved by all authors. The final decision on content was reserved for the first author, who vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

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Conflict of interest: M.Y.D. is a consultant for and has research agreements with Tenaya Therapeutics, Bristol Myers Squibb, Edgewise, Viz-AI, and Cytokinetics. J.R.G. is a consultant for Avidity Therapeutics, Citizen Health, and Nuevocor Therapeutics. J.R.G. and Mayo Clinic have an equity/licensing agreement with Prolaio. S.F.N. has no conflicts of interest. D.K. has no conflicts of interest. M.J.P., F.V., N.S.-P., R.P., B.M., L.T., W.G.H., L.Y., G.A., L.M.L., K.N.I., and W.G.T. are employees and stockholders of Tenaya Therapeutics, Inc.

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Data safety monitoring board

Patient safety and data integrity oversight were provided by members of the Data and Safety Monitoring Board: Barry H. Greenberg, MD (Chair), Gerald S. Lipshutz, MD, Ena Bromley, PhD, and James H. Lewis, MD.

Data availability

The interim data that support this manuscript come from an ongoing clinical trial sponsored by Tenaya Therapeutics, Inc. In accordance with company policy and applicable regulatory requirements, data will be made available to qualified researchers upon reasonable request only after the trial and associated analyses are completed.

References

1. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, Bezzina CR, Biagini E, Blom NA, de Boer RA, De Winter T, Elliott PM, Flather M, Garcia-Pavia P, Haugaa KH, Ingles J, Jurcut RO, Klaassen S, Limongelli G, Loeys B, Mogensen J, Olivotto I, Pantazis A, Sharma S, Van Tintelen JP, Ware JS, Kaski JP. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–3626.
2. Ommen SR, Ho CY, Asif IM, Balaji S, Burke MA, Day SM, Dearani JA, Epps KC, Evanovich L, Ferrari VA, Joglar JA, Khan SS, Kim JJ, Kittleson MM, Krittanawong C, Martinez MW, Mital S, Naidu SS, Saberi S, Semsarian C, Times S, Waldman CB. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology joint committee on clinical practice guidelines. *Circulation* 2024;**83**:2324–2405.
3. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM, Olivotto I. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe). *Circulation* 2018;**138**:1387–1398.
4. Bennett JS, Wood PT, Dominic KL, Moravec CS, Campbell KS, Stelzer JE. Functional analysis of a homozygous MYBPC3 null allele in human pediatric patients. *Circ Res* 2025;**137**:1226–1228.
5. Helms AS, Thompson AD, Glazier AA, Hafeez N, Kabani S, Rodriguez J, Yob JM, Woolcock H, Mazzarotto F, Lakdawala NK, Wittekind SG, Pereira AC, Jacoby DL, Colan SD, Ashley EA, Saberi S, Ware JS, Ingles J, Semsarian C, Michels M, Olivotto I, Ho CY, Day SM. Spatial and functional distribution of MYBPC3 pathogenic variants and clinical outcomes in patients with hypertrophic cardiomyopathy. *Circ Genom Precis Med* 2020;**13**:396–405.
6. Desai MY, Owens AT, Abraham T, Olivotto I, Garcia-Pavia P, Lopes RD, Elliott P, Fernandes F, Verheyen N, Maier L, Meder B, Azevedo O, Kitaoka H, Wolski K, Wang Q, Jaber W, Mitchell L, Myers J, Rano T, Gong Z, Zhong Y, Carter-Bonanza S, Florea V, Aronson R, Nissen SE. Mavacamten in symptomatic nonobstructive hypertrophic cardiomyopathy. *N Engl J Med* 2025;**393**:961–972.
7. Greer-Short A, Greenwood A, Leon EC, Qureshi TN, von Kraut K, Wong J, Tsui JH, Reid CA, Cheng Z, Easter E, Yang J, Ho J, Steltzer S, Budan A, Cho M, Chandrakumar R, Cisne-Thompson O, Feathers C, Chung TW, Rodriguez N, Jones S, Alleyne-Levy C, Liu J, Jing F, Prince WS, Lin J, Ivey KN, Tingley WG, Hoey T, Lombardi LM. AAV9-mediated MYBPC3 gene therapy with optimized expression cassette enhances cardiac function and survival in MYBPC3 cardiomyopathy models. *Nat Commun* 2025;**16**:2196.
8. O'Leary TS, Snyder J, Sadayappan S, Day SM, Previs MJ. MYBPC3 truncation mutations enhance actomyosin contractile mechanics in human hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2019;**127**:165–173.
9. Greenberg B, Taylor M, Adler E, Colan S, Ricks D, Yarabe P, Battiprolu P, Shah G, Patel K, Coggins M, Carou-Keenan S, Schwartz JD, Rossano JW. Phase 1 study of AAV9.LAMP2B gene therapy in Danon disease. *N Engl J Med* 2025;**392**:972–983.
10. Mucke MM, Fong S, Foster GR, Lillicrap D, Miesbach W, Zeuzem S. Adeno-associated viruses for gene therapy—clinical implications and liver-related complications, a guide for hepatologists. *J Hepatol* 2024;**80**:352–361.
11. Kubo T, Kitaoka H, Yamanaka S, Hirota T, Baba Y, Hayashi K, Iiyama T, Kumagai N, Tanioka K, Yamasaki N, Matsumura Y, Furuno T, Sugiura T, Doi YL. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2013;**62**:1252–1259.
12. Sun D, Schaff HV, Nishimura RA, Geske JB, Dearani JA, Ducharme MT, Ommen SR. Posterior wall thickness associates with survival following septal myectomy for obstructive hypertrophic cardiomyopathy. *JACC Heart Fail* 2022;**10**:831–837.