

# RIDGE-1 Phase 1b/2 Clinical Trial of TN-401 gene therapy for the potential treatment of *PKP2*-Associated ARVC

May 15, 2026



  
**TENAYA**<sup>TM</sup>  
THERAPEUTICS

# Forward-looking statement

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# Today's speakers and agenda



**Faraz Ali, MBA**  
Chief Executive Officer



**Kathy Ivey, Ph.D.,**  
Senior Vice President,  
Research



**Whit Tingley, M.D., PhD**  
Chief Medical Officer



**Guest Speaker**  
**John Giudicessi, M.D., PhD**  
Mayo Clinic

## **Agenda**

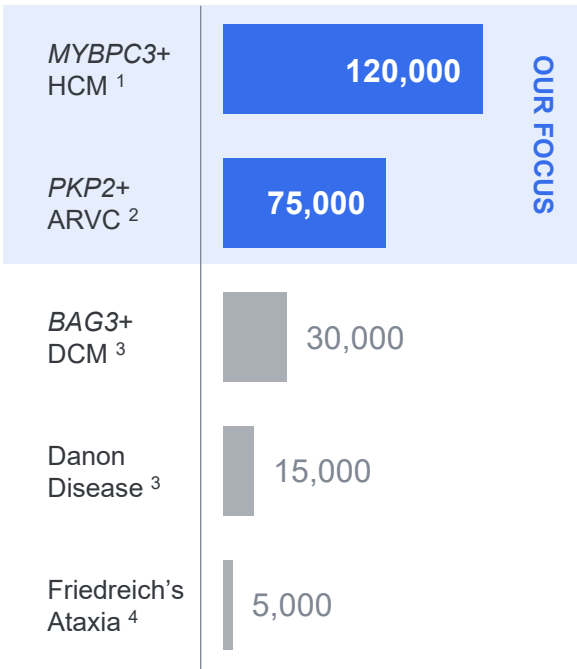
Introductory remarks	Faraz Ali
RIDGE-1 objectives	Whit Tingley
Clinical findings	Whit Tingley
Biopsy results	Kathy Ivey
Safety findings	Whit Tingley
<i>Clinician perspective</i>	
Q&A with guest expert	John Giudicessi
Closing remarks	Faraz Ali
Q&A	

IMMEDIATE OPPORTUNITY:

# Advancing TN-201 and TN-401 towards pivotal studies

## Large market potential in rare disease setting

### Addressable populations in the U.S.



## Early evidence of clinically meaningful benefit



**TN-201** improved multiple measures of disease (biomarkers, hypertrophy, symptom relief)



**TN-401** achieved meaningful reductions in electrical instability

## Planned data readouts offer multiple de-risking catalysts in 2026



Increase in protein levels vs. baseline



Decrease in key markers of disease



### TN-201

- Interim MyPEAK-1 data for Cohort 2 and updates from Cohort 1 (1H)
- **One-year Cohort 2 data and two-year Cohort 1 data (2H)**



### TN-401

- **One-year data for Cohort 1 and initial Cohort 2 data (1H)**
- Interim Cohort 2 data (2H)

## Seeking regulatory clarity on approvable endpoints and pivotal trial design



Updates expected in 2H'26

## HIGHLIGHTS

# Interim RIDGE-1 Cohort 1 & 2 Data



- 1 CLINICAL:** All patients on study achieved consistent and meaningful reductions in arrhythmia burden that were sustained up to 1 year for Cohort 1
- 2 BIOPSY:** TN-401 is reaching cardiomyocytes and achieving expression
- 3 SAFETY:** TN-401 was well tolerated at both doses

## SUBSTANTIAL UNMET NEED

# PKP2-associated ARVC is estimated to affect >70,000 people in the U.S.<sup>(1)</sup>

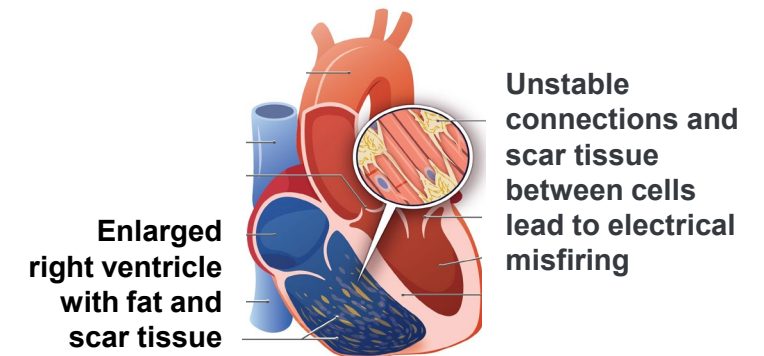
## ARVC is a severe and progressive genetic heart disease lacking therapeutic treatment options

**>15%** of heart-related deaths in patients < 35 are due to ARVC<sup>(1)</sup>

**~40%** Of those diagnosed with ARVC carry pathogenic PKP2 mutations<sup>(2)</sup>

**90%** have >500 PVCs/day, despite standard of care<sup>3</sup>

### ARVC HEART



- Early symptoms include palpitations, lightheadedness, fainting<sup>(1)</sup>
- Significant impact on quality of life due to arrhythmias, ICD shocks and restrictions on physical exertion<sup>(1)</sup>

TRACY | AGE 45  
AVA | AGE 14  
Living with genetic ARVC



# RIDGE-1 Interim Data Readout: Trial Objectives

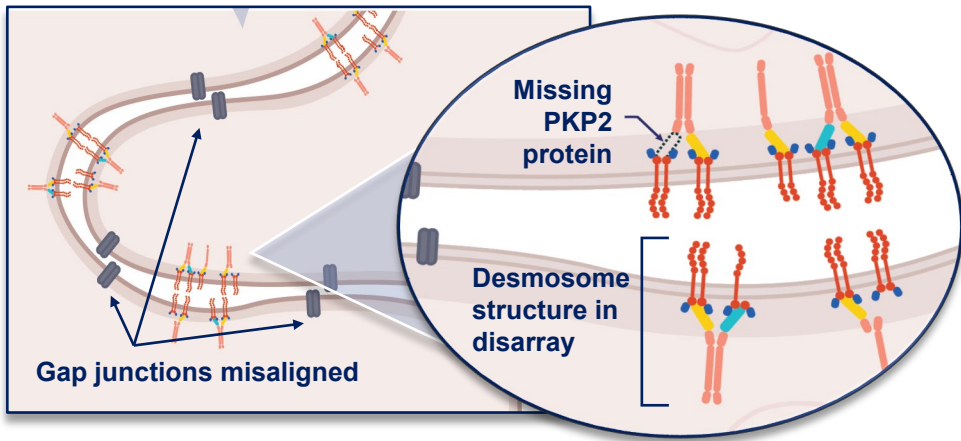


## MECHANISM

# TN-401 gene therapy for *PKP2*-associated ARVC

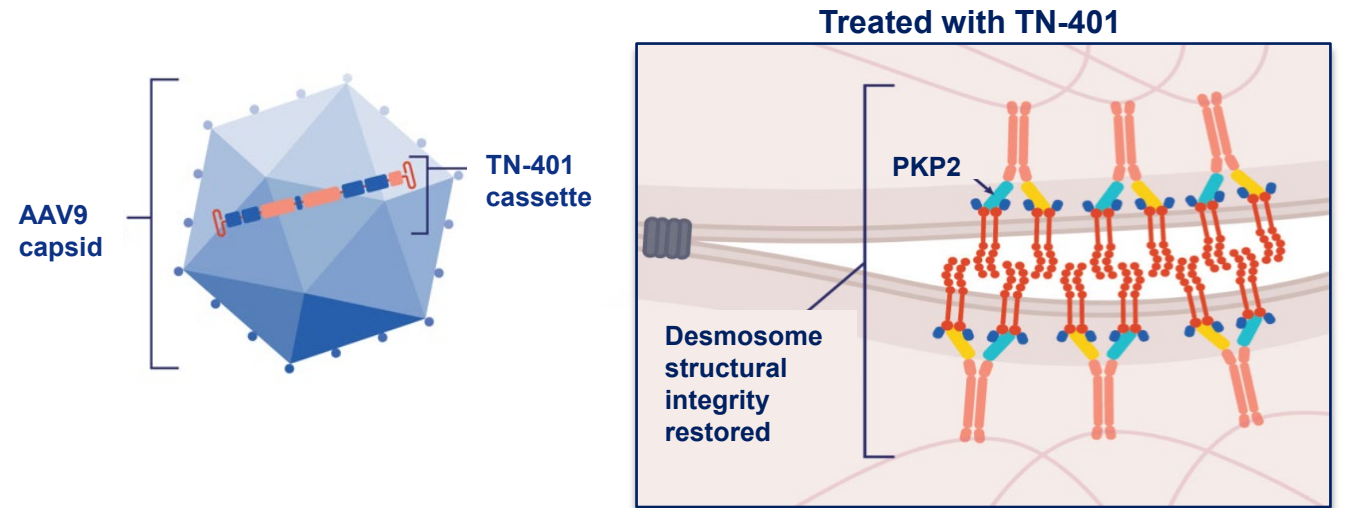
## *PKP2*+ Pathophysiology

### Desmosome and Gap Junctions in *PKP2*-associated ARVC Heart



- Mutations of the *PKP2* gene lead to lower levels of PKP2 protein<sup>(1)</sup> resulting in
  - Weakened cell-to-cell adhesion
  - Abnormal electrical activity

## TN-401 Mechanism of Action



- TN-401 targets the underlying genetic cause of disease by delivering a full-length *PKP2* gene to cardiomyocytes via an AAV9 capsid
- An increase in PKP2 protein levels is expected to restore desmosome function, with the potential to halt disease progression, reverse symptoms, improve patient quality of life and prevent SCA

# RIDGE-1 Phase 1b/2 clinical trial



Treatment goal: demonstrate reduction in arrhythmic events

## Study Objectives

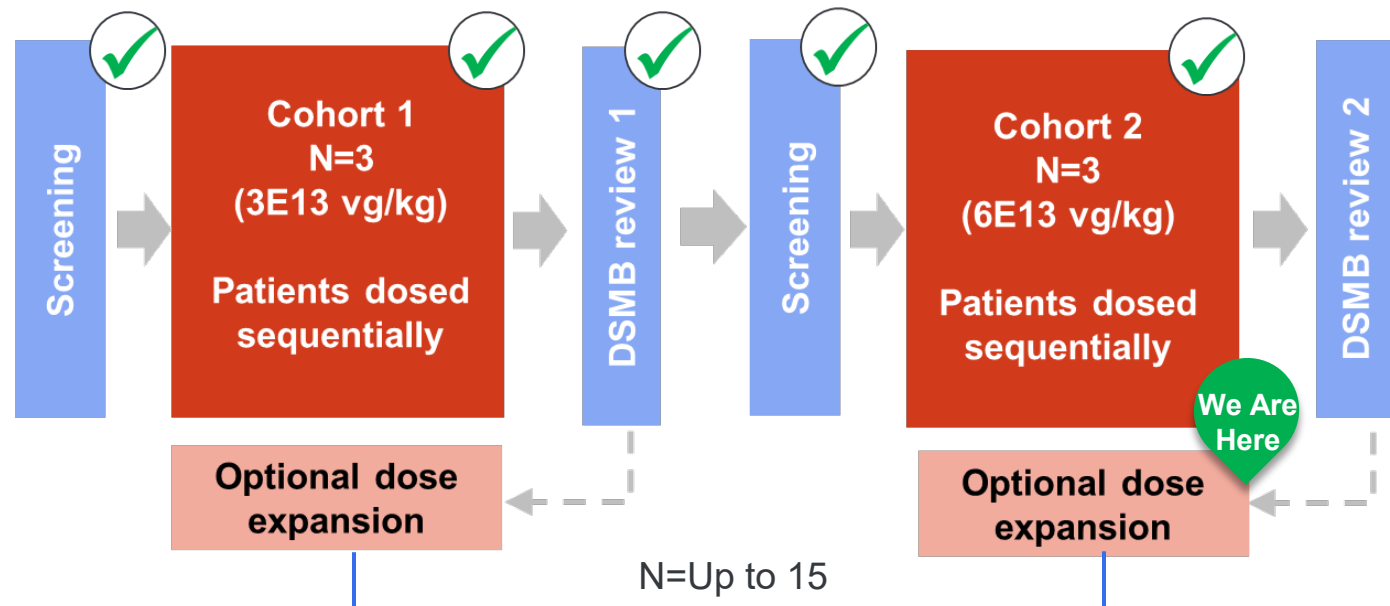
- Safety and tolerability
- Dose-finding
- Pharmacodynamics

## Design

- Open-label, multi-center dose-escalation and dose-expansion
- 52-week study period with four-year follow-up
- Cardiac biopsies at baseline, post-dose and week 52

## Endpoints

- Safety and tolerability
- Transgene uptake and expression
- Changes in PVC and NSVT counts
- ICD shock and VT frequency
- Structural/hemodynamic changes
- Plasma biomarkers
- Patient-reported outcomes



# RIDGE-1 patients' arrhythmia burden more severe than broader *PKP2*+ population

	Average <i>PKP2</i> + patient <sup>1</sup>	Cohort 1 (3E13 vg/kg)			Cohort 2 (6E13 vg/kg)		
		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Follow-Up	-	52 weeks	52 weeks	40 weeks	32 weeks	26 weeks	20 weeks
Gender	Male (62%)	Male	Male	Male	Male	Male	Male
Age at Dosing (y)	-	41	37	56	40	31	27
Age at ARVC Dx (y)	34	26	16	53	20	16	17
PVC Count (#/24h)	2,480	2,462	618	2,666	1,571	7,819	8,634
NYHA Class	Class I (74%)	Class I	Class I	Class I	Class I	Class I	Class I
% ICD & Age (y)*	100%, 35	26	16	53	20	16	17
Severe VA**	No (61%)	Yes; 7x	Yes; 5x	No	No	Yes; 11x	Yes; 3x
VT Ablation	No (54%)	Yes; 2x	Yes	No	Yes	No	Yes; 2x
RV Dysfunction	Yes (54%)	Yes	Yes	Yes	Yes	Yes	Yes
Background meds	Yes (88%)	Yes	Yes	Yes	Yes	Yes	Yes

\*RIDGE Natural History Study of *PKP2*+ ARVC patients required ICD. Published estimates suggest 35-80% have ICD<sup>2</sup>

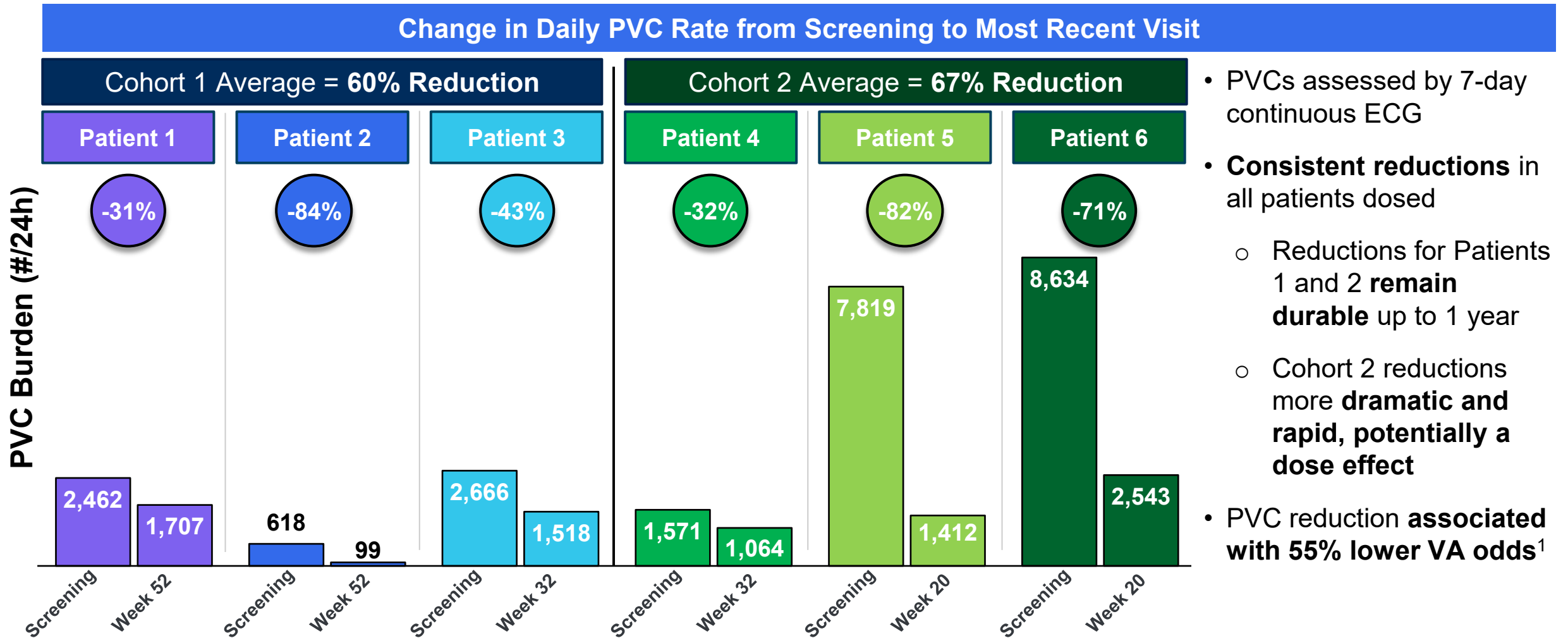
\*\*Severe VAs include sustained VT, VF, and appropriate ICD therapy

**More severe vs. average**



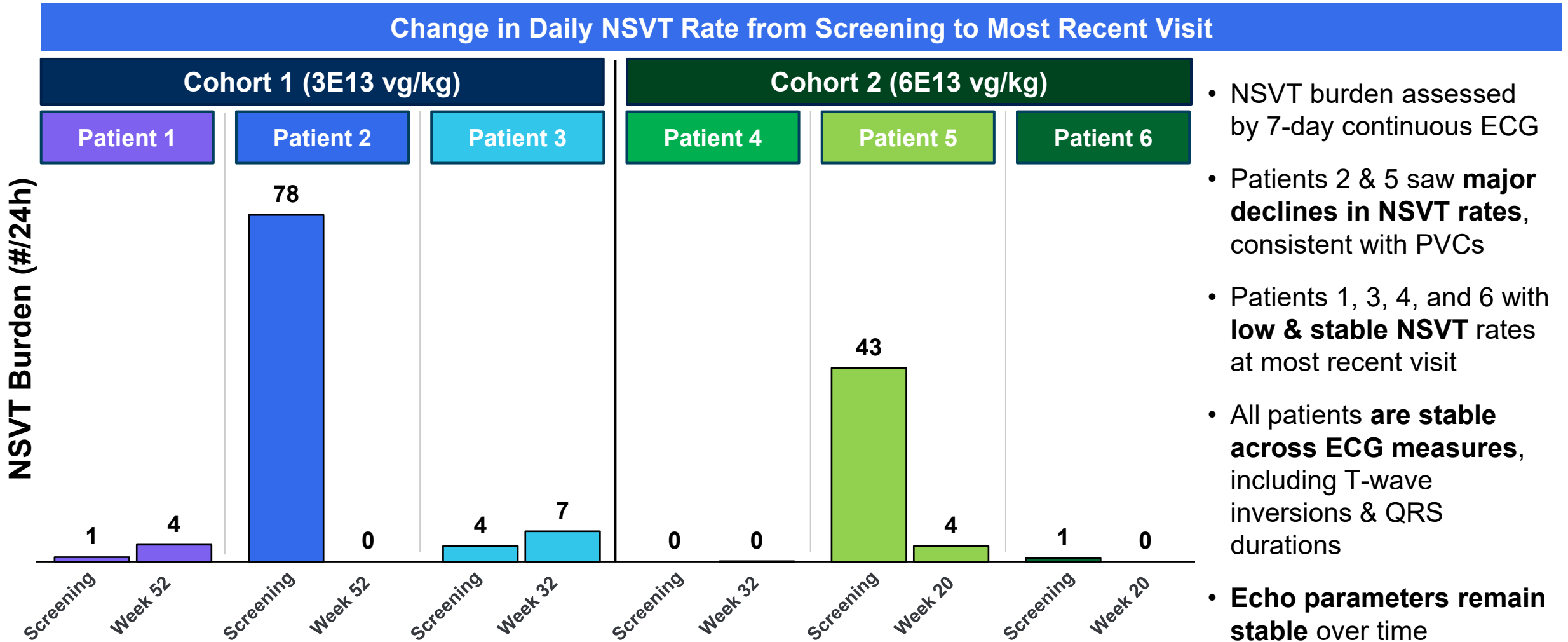
# RIDGE-1 Readout TN-401's Impact on Arrhythmia Burden

# All patients had meaningful reductions in PVC burden post-TN-401



- PVCs assessed by 7-day continuous ECG
- **Consistent reductions** in all patients dosed
  - Reductions for Patients 1 and 2 **remain durable** up to 1 year
  - Cohort 2 reductions more **dramatic and rapid, potentially a dose effect**
- PVC reduction **associated with 55% lower VA odds<sup>1</sup>**

# Patients with high NSVT burden had dramatic reductions over time



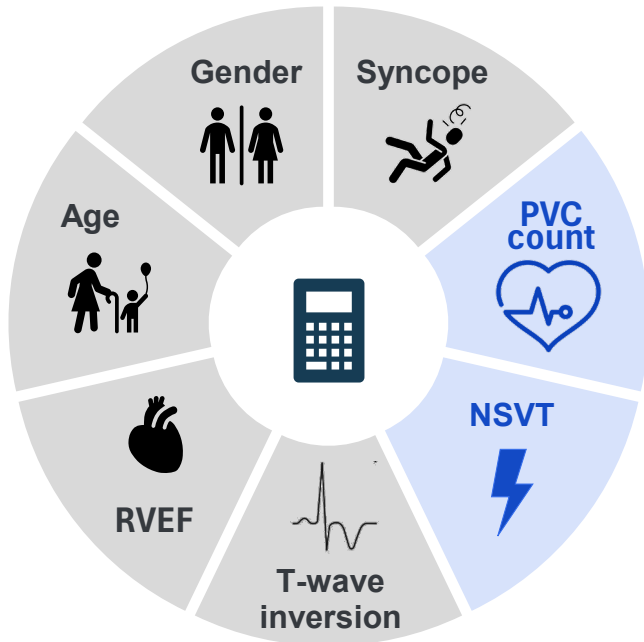
# PVC and NSVT burden are key indicators of electrical instability and risk of life-threatening events

Frequency

Severity

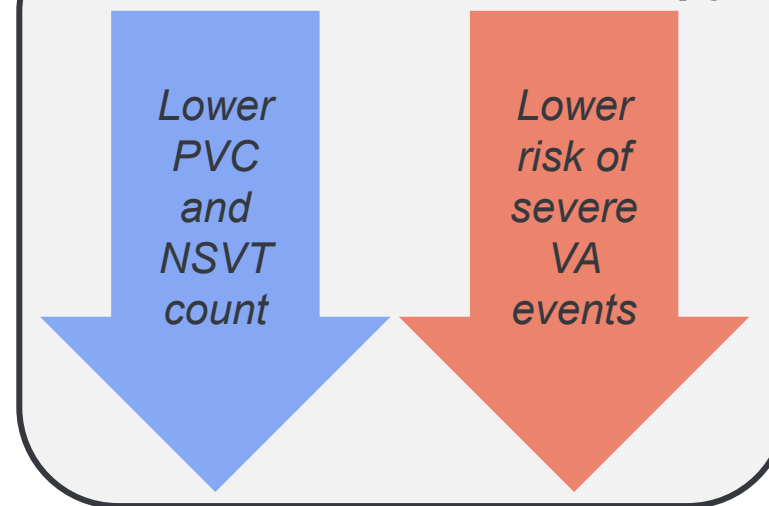


ARVC Risk Stratification Calculator



- PVCs are hallmark of PKP2+ ARVC and indicate electrical instability<sup>(1)</sup>
- Higher PVC counts are a recognized clinical predictor of higher 5-year risk of life-threatening VAs<sup>(2)</sup>
- PVC burden utilized as risk assessment tool for ICD placement<sup>(3)</sup>

## Goal of TN-401 Gene Therapy



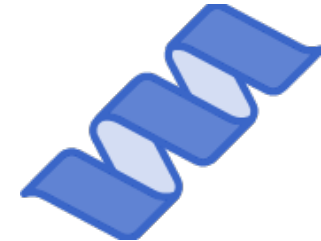
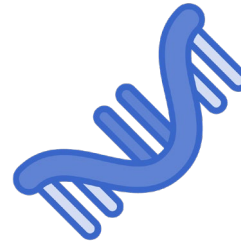
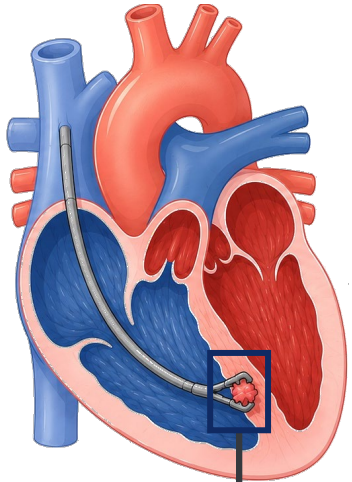
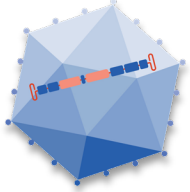


# RIDGE-1 Readout TN-401 Heart Biopsy Findings



# Tracking gene therapy's delivery to the heart

TN-401  
Upon Infusion



TN-401 enters cardiomyocytes. Healthy copy of *PKP2* gene forms stable episome in cell

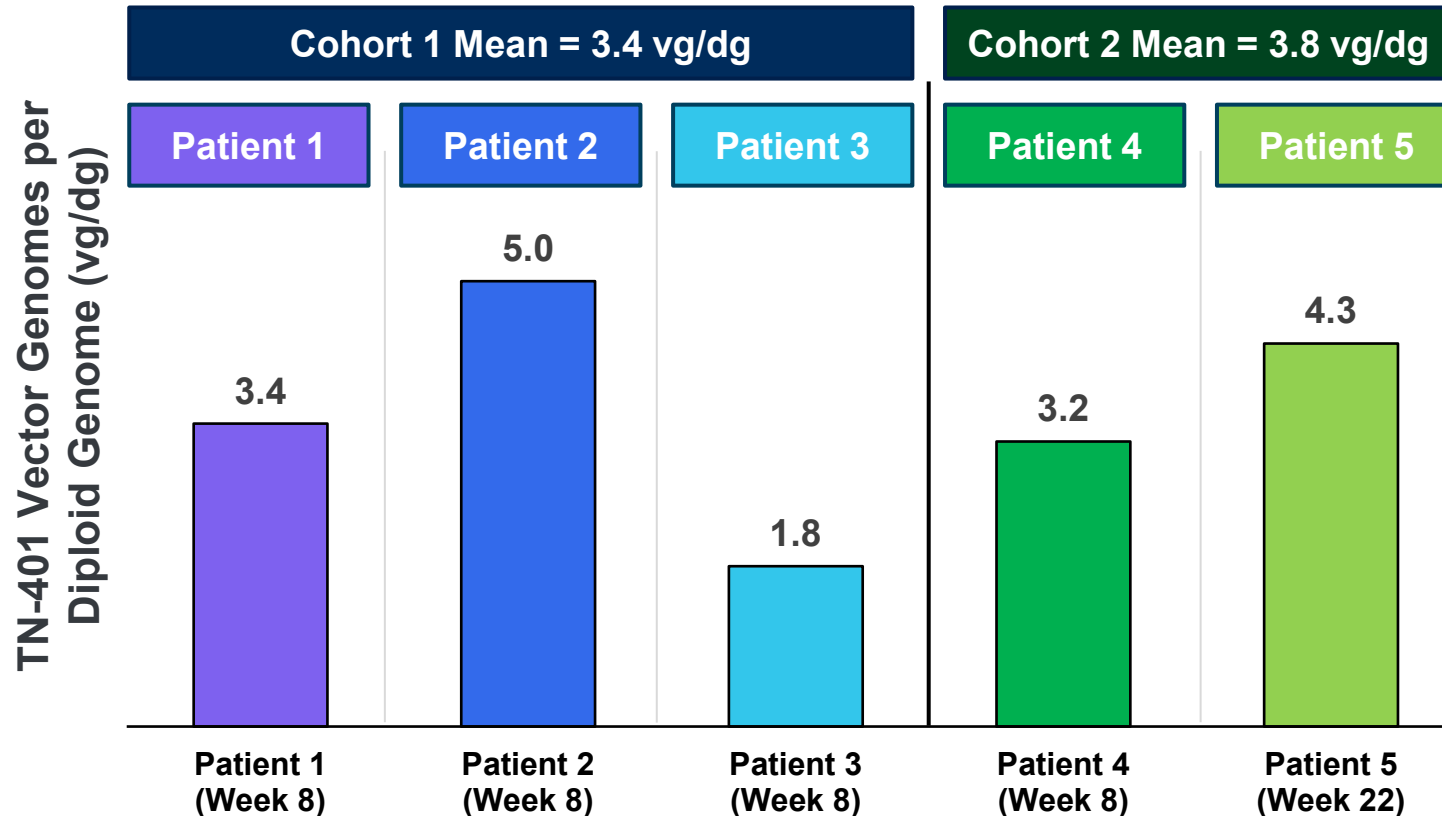
TN-401's healthy copy of *PKP2* gene is transcribed by cell's machinery to produce messenger RNA

TN-401 mRNA is then converted to PKP2 protein

5-7 biopsies of right ventricular septum, each sample analyzed separately for DNA or RNA or protein

# TN-401 DNA levels show robust cardiac transduction across both doses

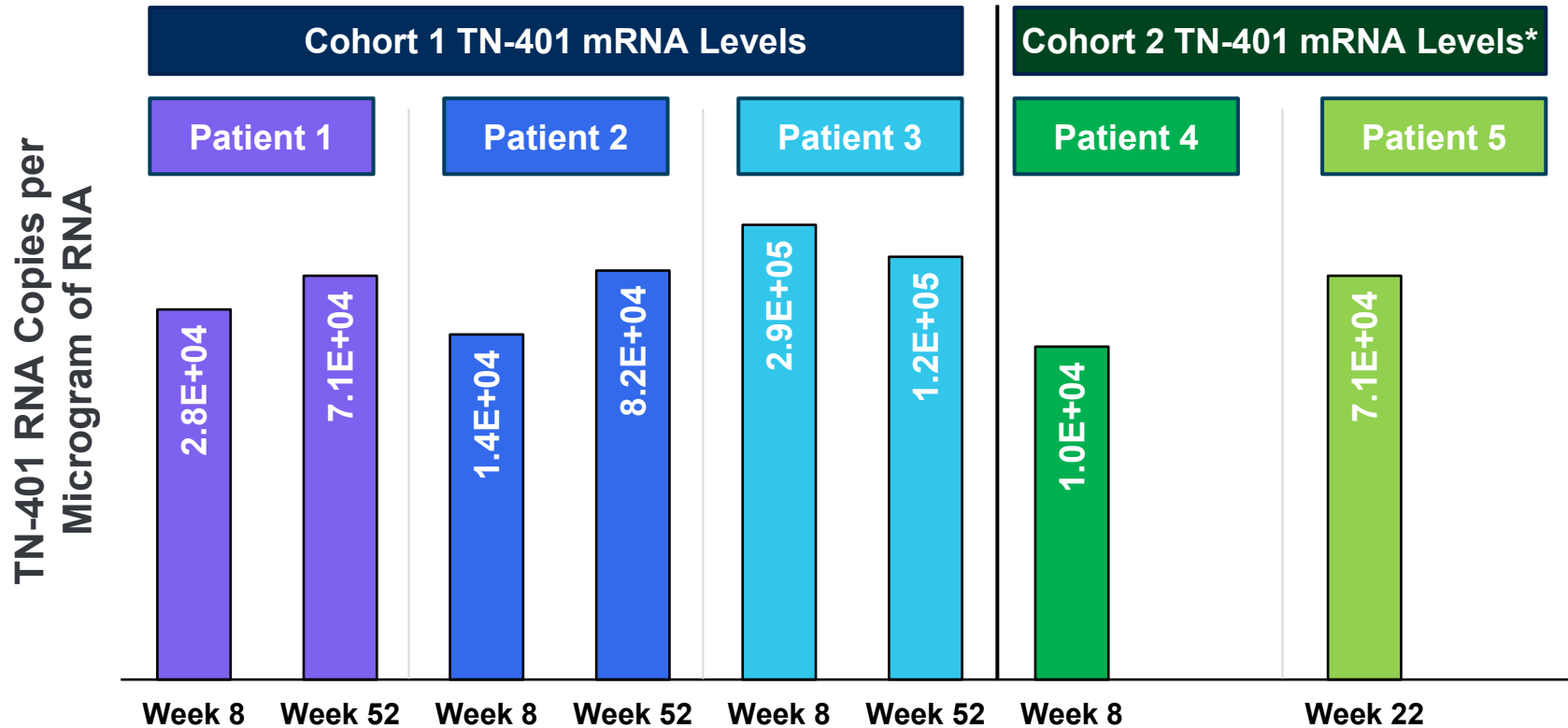
Post-Dose TN-401 DNA Levels by Patient 2



- Assay for assessing DNA levels specific to TN-401 vector genome
- TN-401 DNA levels detectable early and throughout follow-up
- **Expect durable presence of TN-401 DNA in cardiomyocytes**

# TN-401-specific RNA levels demonstrate PKP2 expression in all patients

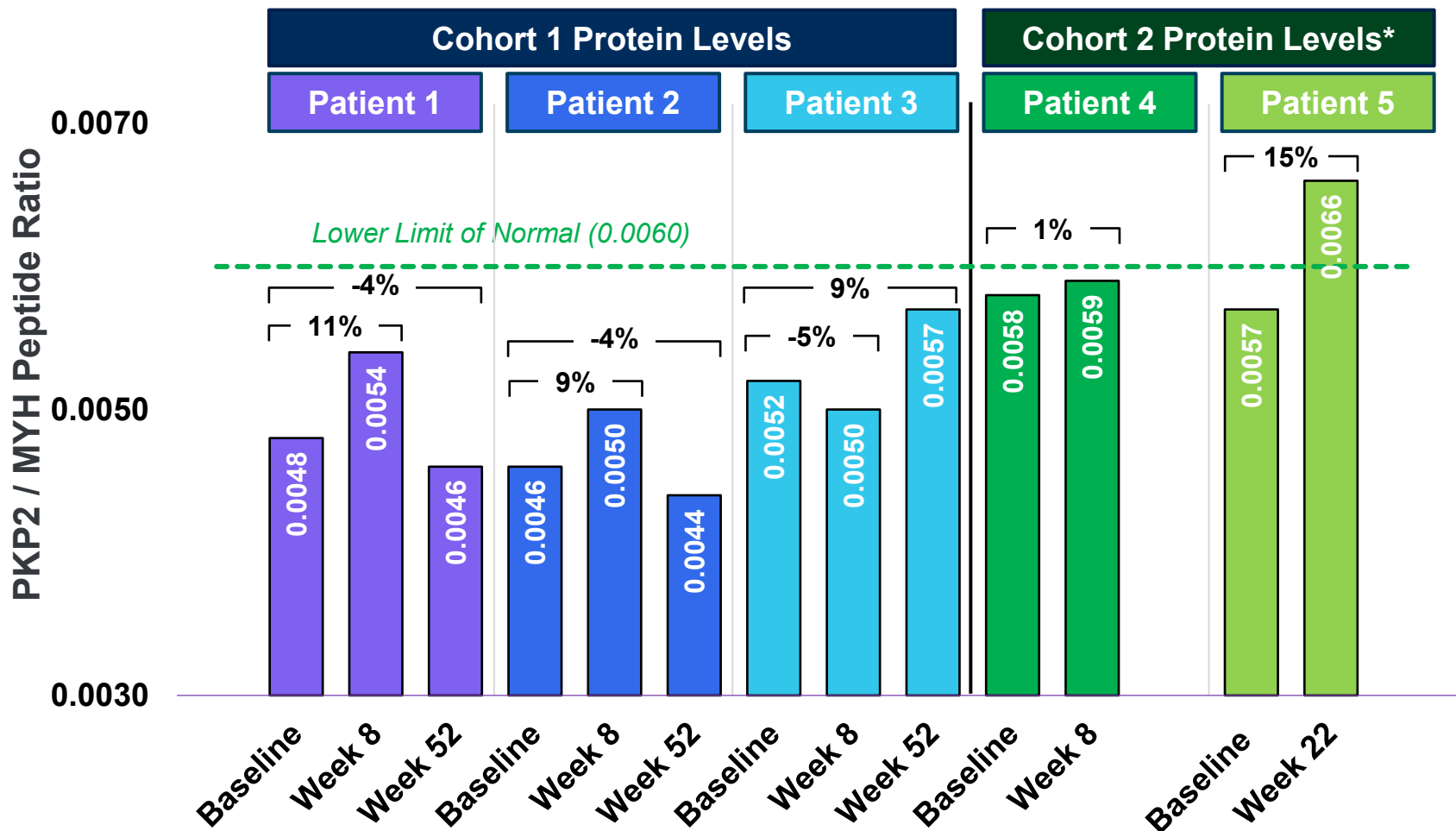
Post-Dose TN-401 RNA Levels by Patient



- Assay for TN-401 RNA is specific to TN-401 (vs. endogenous)
- TN-401 promoter drives **expression in cardiomyocytes**
- **Durable expression** 52 weeks after the single dose of TN-401
- **Clear evidence of RNA expression of TN-401 transgene in target cells** despite variable cellular composition (e.g., myocytes vs. fibroblasts) in small heart biopsy samples

# Assessment of TN-401 protein expression

PKP2 Protein Levels Over Time in Cohorts 1 and 2



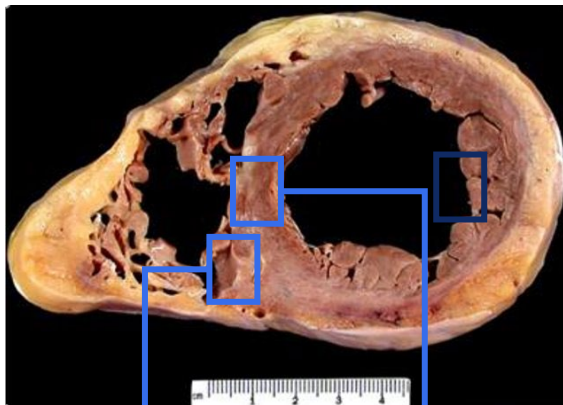
- Measured LC-MS assay for PKP2 protein (normalized to MYH protein)
- Variability is exacerbated across and within patients due to extent of fibrofatty infiltrate in myocardium
- **Totally of biopsy data**, including transduction, expression, and localization (not shown), **support TN-401 pharmacodynamic effect**

# Variability of biopsy samples from ARVC hearts creates methodological challenges to quantify PKP2 protein

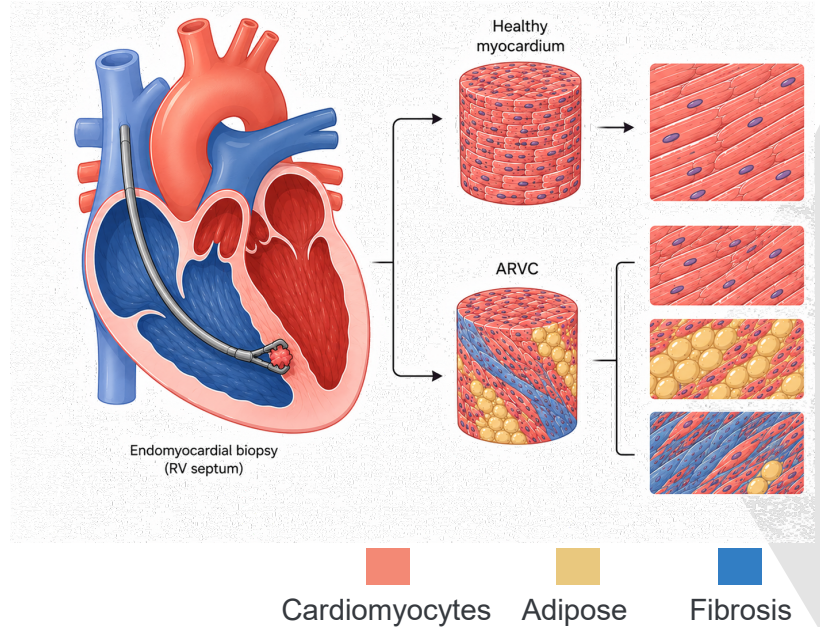
**PKP2-associated ARVC patients have fibrofatty replacement and fibrosis spread across the myocardium**

**Biopsy composition of each patient can vary significantly from pinch-to-pinch**

Image of an ARVC Heart<sup>1</sup>



Sample #1      Sample #2



\*Biopsy tissue pieces approx. by circles (~1-2 mm<sup>3</sup>)

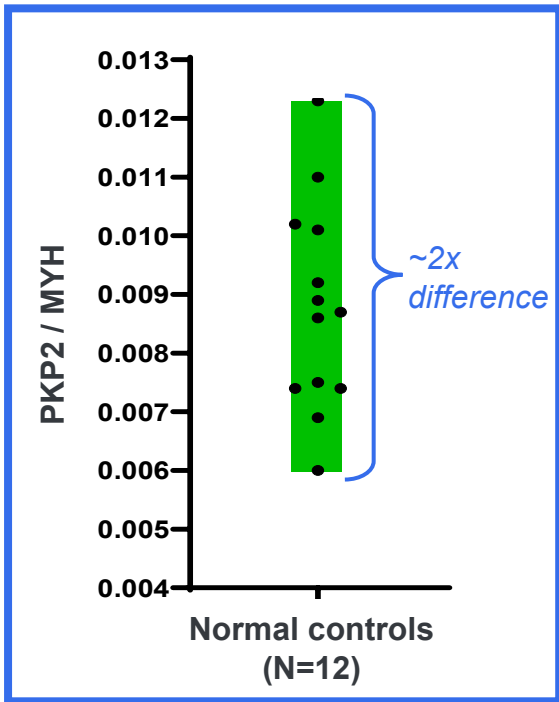
One sample has higher % cardiomyocytes vs fibrofatty infiltrates → higher PKP2 RNA and protein levels

Another sample has lower % cardiomyocytes vs fibrofatty infiltrates → lower PKP2 RNA and protein levels

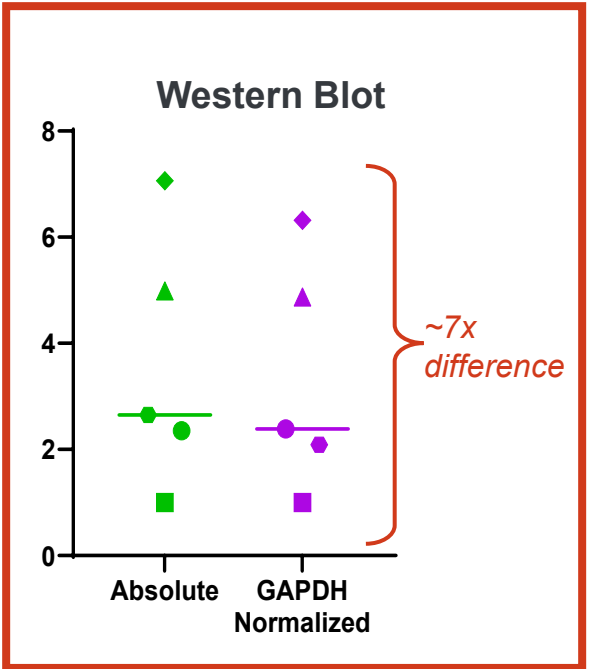
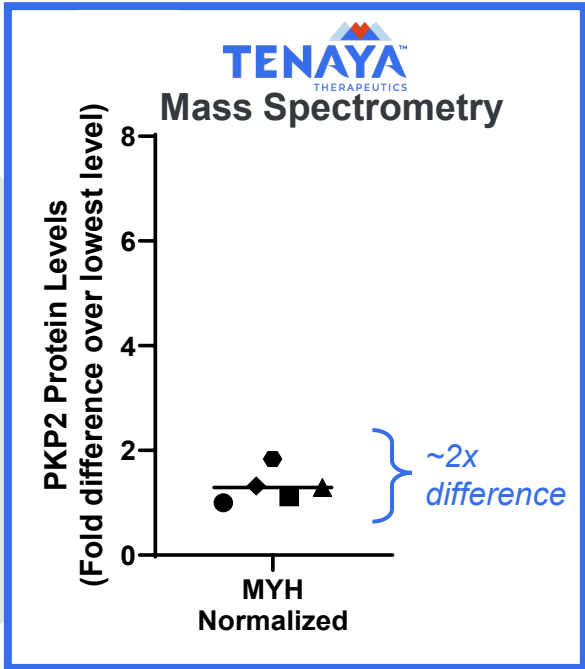
# Tenaya approach to quantifying changes in PKP2 protein levels selected to reduce variability

**PKP2 protein levels vary greatly across individuals<sup>1</sup> complicate interpretation and comparisons**

- PKP2 protein may be found in different tissue types, including fat cells
- Wide variance of PKP2 levels observed in samples collected from healthy donors – even when PKP2 protein measurement is normalized to a cardiomyocyte-restricted protein



**Use of LC-MS + normalizing to myosin heavy chain reduces variable factors**



- Head-to-head comparison of PKP2 levels from the same 5 healthy donors illustrates less variability with Tenaya methods



# RIDGE-1 Readout TN-401 Safety and Tolerability



# Both TN-401 doses equally well tolerated

Majority of TN-401-related AEs mild, asymptomatic and manageable

Relevant Adverse Event	Cohort 1* (3E13 vg/kg; n=3)				Cohort 2 (6E13 vg/kg; n=3)			
	Gr 1	Gr 2	Gr 3	Total	Gr 1	Gr 2	Gr 3	Total
Liver enzyme elevation	3	-	-	3	1	-	1**	2**
Troponin elevation	2	-	-	2	1	-	-	1
Thrombocytopenia†	-	-	-	0	-	-	1**	1**

\*Previously disclosed, no new AEs since December 2025 release

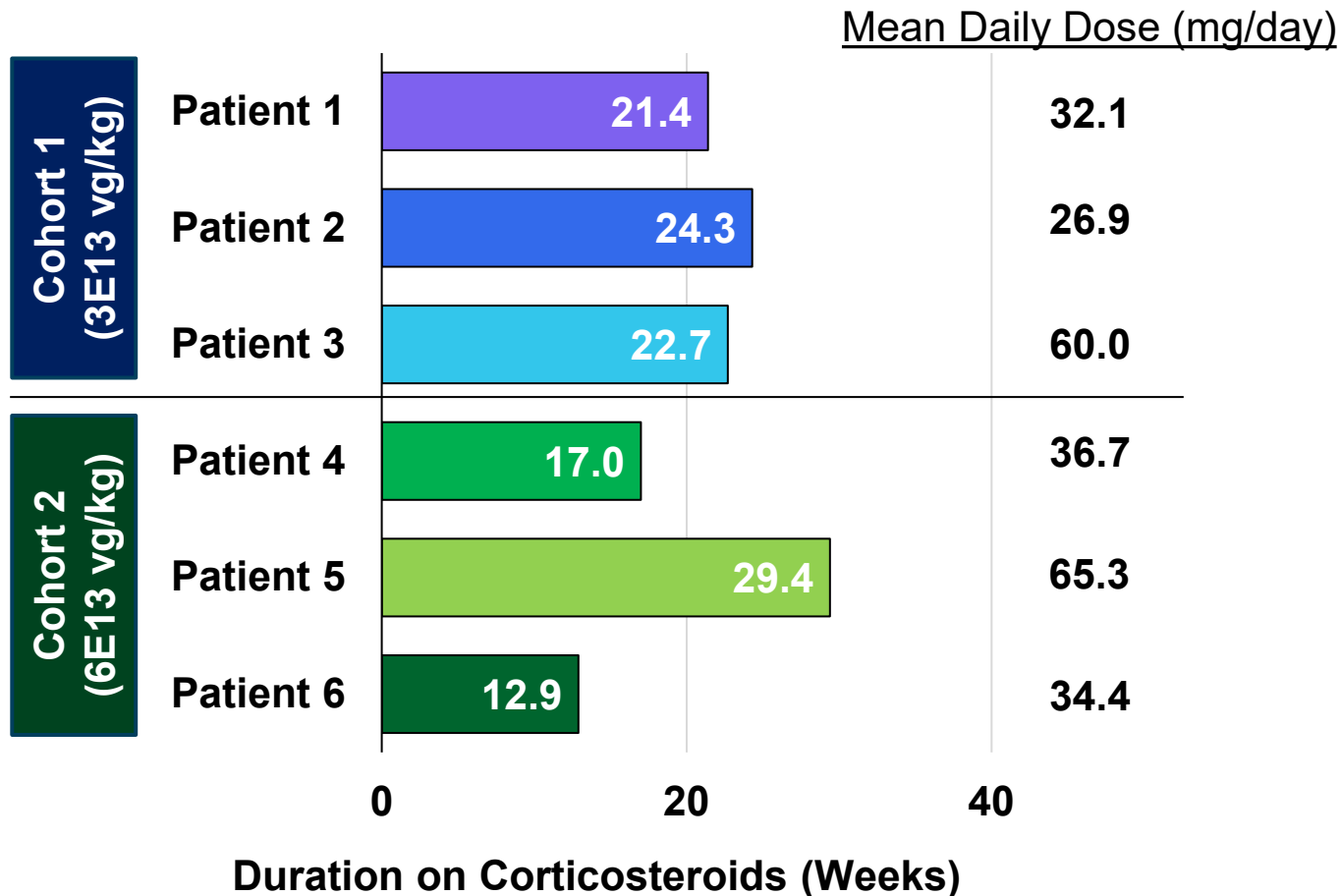
\*\*Event attributed to or associated with immunosuppression medication error

†Unrelated to TN-401

- Cohort 1 AEs **previously disclosed**
- Cohort 2 AEs include two grade 3 AEs in the same patient due to a **medication error**:
  - 1 Grade 3 AE of liver enzyme elevation associated with medication error resulting in steroid interruption
  - 1 Grade 3 SAE of thrombocytopenia due to medication error with sirolimus overdose (serum level 40.4 ng/mL [target level 4-8 ng/mL])
- **No** clinical thrombotic microangiopathy
- **No** sustained VT, VF, or ICD therapy related to TN-401. No other cardiotoxicities observed
- **DSMB endorsed expansion** for both cohorts

# Immunosuppression regimen successfully managed immune response at both doses

## Duration & Mean Daily Corticosteroid Dose



- Prophylactic prednisone and sirolimus successful in managing immune responses across both doses
- Duration and level of immunosuppression comparable across both doses
- All six patients have successfully weaned off all immunosuppression



# RIDGE-1 in Context Clinician Conversation





# Closing remarks



# Acknowledgments

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RIDGE™ -1

- RIDGE-1 patients and their families
- Drs. John Giudicessi, Vasanth Vedantham, Matthew Taylor, Andreas Barth and other RIDGE-1 investigators
- Members of the DSMB: Dr. Barry Greenberg, Dr. Gary Lipshutz, Ena Bromley, PhD, and Dr. James Lewis
- Michael Previs, PhD, and the University of Vermont team for PKP2 protein analysis
- Dr. Wojciech Zareba and the team at the University of Rochester Electrocardiogram Core Laboratory
- SADS Foundation and the broader ARVC community for their support
- The California Institute for Regenerative Medicine (CIRM) for their financial support in the development of TN-401

# RIDGE™ the largest natural history study of PKP2+ ARVC in the world

Largest Ever PKP2+ ARVC Natural History Study...



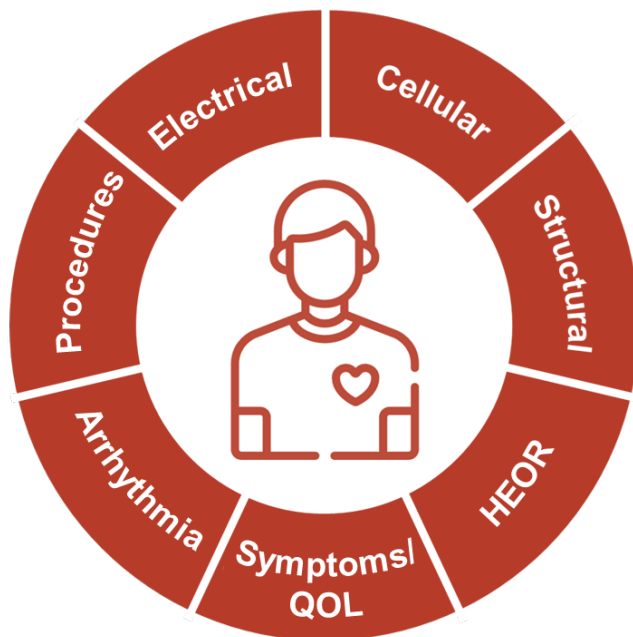
>185 Patients

>2,500 Years of Follow-Up

21 Sites

6 Countries

...Collecting Data Across Domains...



...Directly Feeding RIDGE-1 Trial



- All RIDGE-1 participants to date were identified through RIDGE
- RIDGE informed RIDGE-1 design, including eligibility criteria and endpoints
- Complements trial results by demonstrating natural history without gene therapy
- Supports discussions with health authorities about potential approvable endpoints, pivotal trial design

~70% of RIDGE patients eligible for RIDGE-1

# 2026 anticipated program milestones

## TN-201 for *MYBPC3*-associated HCM

- 1H**
- Enroll 6E13 vg/kg expansion cohort
  - MyPEAK-1 interim Cohort 2 data

- 2H**
- MyPEAK-1 ~2-year Cohort 1 and ~52-week Cohort 2 data
  - Continue MyPEAK-1 enrollment
  - Pursue regulatory alignment on pivotal plans

## TN-401 for *PKP2*-associated ARVC

- 1H**
- Conduct Cohort 2 DSMB
  - Enroll RIDGE-1 expansion cohort
  - RIDGE-1 ~52-week Cohort 1 and initial Cohort 2 data

- 2H**
- RIDGE-1 interim Cohort 2 data
  - Continue RIDGE-1 enrollment
  - Pursue regulatory alignment on pivotal plans

# Q&A

