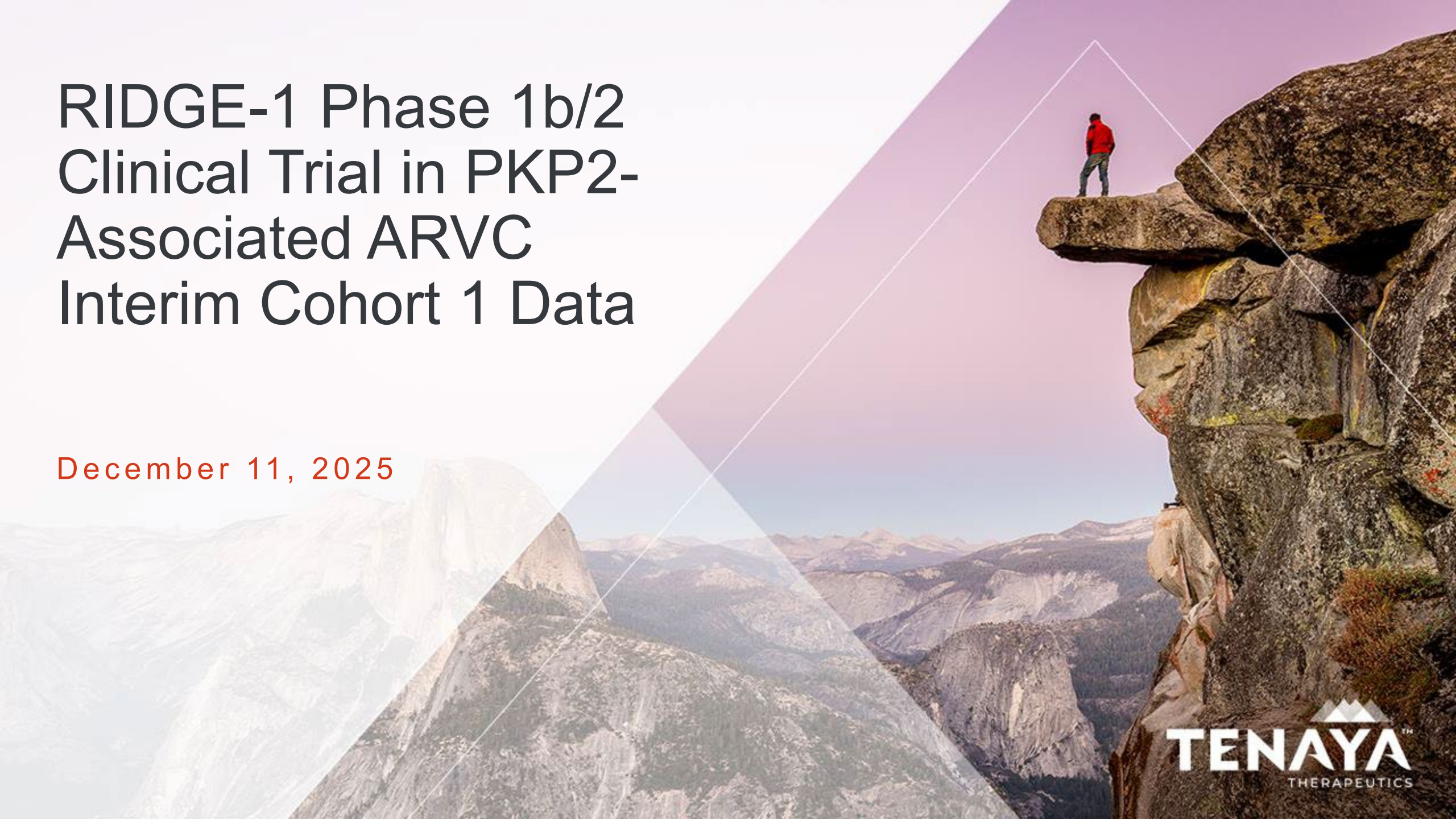
# RIDGE-1 Phase 1b/2 Clinical Trial in PKP2-Associated ARVC Interim Cohort 1 Data

December 11, 2025



# Forward-looking statement

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, that are based on our management's beliefs and assumptions and on information currently available to our management. Forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified. All statements other than statements of historical facts contained in this presentation, including statements regarding the ongoing enrollment of patients in Cohort 2 of RIDGE-1 and anticipated timing for completion of dosing; the clinical, therapeutic and commercial potential of, and expectations regarding TN-401; the value of RIDGE data to support future clinical development and regulatory plans for TN-401; the inferences regarding PKP2 protein and mRNA expression; and statements regarding the continued development TN-401 and TN-401 clinical outcomes; and the planned timing to report additional data from RIDGE-, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "estimated," "expected," "potential," "continues," "will," "goal," "promising," "next," "on track," "may," "future," or the negative of these terms or other similar expressions. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions described in our filings with the SEC, including, but not limited to the section titled "Risk Factors" in our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2025, and other documents we have, or will file with the SEC. These filings, filed, are available on the SEC website at www.sec.gov. Such risks include, among other things: the availability of RIDGE-1 data at the referenced times; the timing and progress of RIDGE-1; the potential failure of TN-401 to demonstrate safety and/or efficacy in clinical testing; the potential for any RIDGE-1 clinical trial results to differ from preclinical, interim, preliminary or expected results; our ability to enroll and maintain patients in clinical trials, including RIDGE-1; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early stage company; our continuing compliance with applicable legal and regulatory requirements; our estimates of the number of patients who suffer from the diseases we are targeting and the number of patients that may enroll in our clinical trials; our ability to raise any additional funding needed to continue to pursue our product development plans; our reliance on third parties; our manufacturing, commercialization and marketing capabilities and strategy; the loss of key scientific or management personnel; competition in the industry in which we operate; our ability to obtain and maintain intellectual property protection for its product candidates; general economic and market conditions; and other risks . These risks are not exhaustive. New risk factors emerge from time to time and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. 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# RIDGE™ -1 Cohort 1 Interim Data Highlights

| | |
|---|---|
| **SAFETY** | • Well tolerated at Cohort 1 (3E13 vg/kg dose)<br>• DSMB cleared dosing to Cohort 2 (6E13 vg/kg)<br>• Cohort 2 patients dosed, awaiting DSMB clearance for expansion |
| **BIOPSY** | • Robust transduction in cardiomyocytes and consistent expression of mRNA observed<br>• PKP2 protein levels increased by average of 10% in the first 2 patients |
| **CLINICAL** | • First 2 patients have ≥46% reduction in PVC count 6+ months post TN-401 dosing plus positive changes on NSVT |
| **NEXT STEPS** | • Continued follow-up of Cohort 1 and Cohort 2 patients<br>• Dosing patients following implementation of protocol changes<br>• Pursue regulatory feedback in 2026 on late-stage trial plans |

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Vg/kg = vector genome/kilogram
DSMB = Data safety monitoring board
PVC = Premature ventricular contraction
mRNA = messenger ribonucleic acid
*PKP2* = *Plakophilin 2* gene


# *PKP2*-associated ARVC is estimated to affect >70,000 people in the U.S.[1]

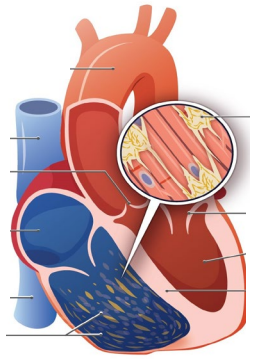
## ARVC is a severe and progressive genetic heart disease lacking therapeutic treatment options

**>15%** of heart-related deaths in patients < 35 are due to ARVC[1]

**23%** of ARVC patients present with sudden cardiac death[2]

**~40%** Of those diagnosed with ARVC carry pathogenic *PKP2* mutations [3]

**ARVC HEART**



**Enlarged right ventricle with fat and scar tissue**

**Unstable connections and scar tissue between cells lead to electrical misfiring**

- Early symptoms include palpitations, lightheadedness, fainting [1]
- Significant impact on quality of life due to arrhythmias, ICD shocks and restrictions on physical exertion [1]

1. SADS Foundation
2. Dalal, et al., Circulation 2005
3. Hermida, et al, Eur J Heart Failure, 2019

# Genetic subtypes in ARVC influence prognosis

## RIDGE Natural History Study provides distinct insights into *PKP2*-specific disease

### Stages of *PKP2*-associated ARVC Progression[1, 2]

**Concealed Stage** → **Overt Electrical Instability Stage** → **Structural Dysfunction Stage**

**60%**
of patients with cardiac arrest had no prior symptoms[2]

**>80%**
of patients have had >500 PVCs per day despite standard of care

**49%**
have history of ventricular tachycardia

**51%**
have RV dysfunction

**36%**
have LV involvement; fewer report HF symptoms

***Insights*[3] *from* RIDGE™**

**PKP2-specific finding**

***PKP2*+ patients are more likely to experience consequences of electrical instability than HF[3,4]**

***Risk of Sudden Cardiac Arrest / Death At Any Stage***

1. Adapted from Tadros, App of Clinical Genetics 2023
2. Shah, et al, Statpearls 2024
3. Calkins, HRS 2025
4. Biernacka, et al, J. Applied Genetics 2021

RV = right ventricular
LV = left ventricular
HF = heart failure

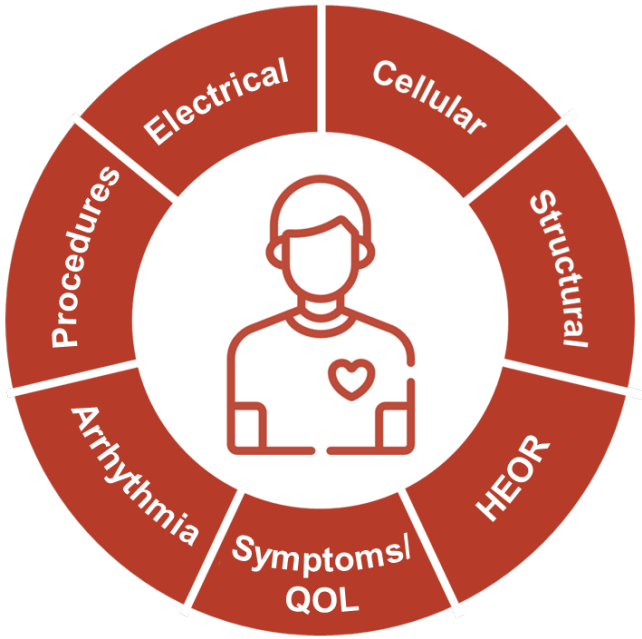
# Continue to gather unique disease insight from RIDGE, the largest natural history study for PKP2+ ARVC

## Largest *PKP2*+ ARVC Study Ever…

RIDGE™

| | |
|---|---|
| **>185** Patients | **>2,500** Years of Follow-Up |
| **21** Sites | **6** Countries |

## …Collecting Data Across Domains…




## …Directly Feeding RIDGE-1 Trial

RIDGE™-1

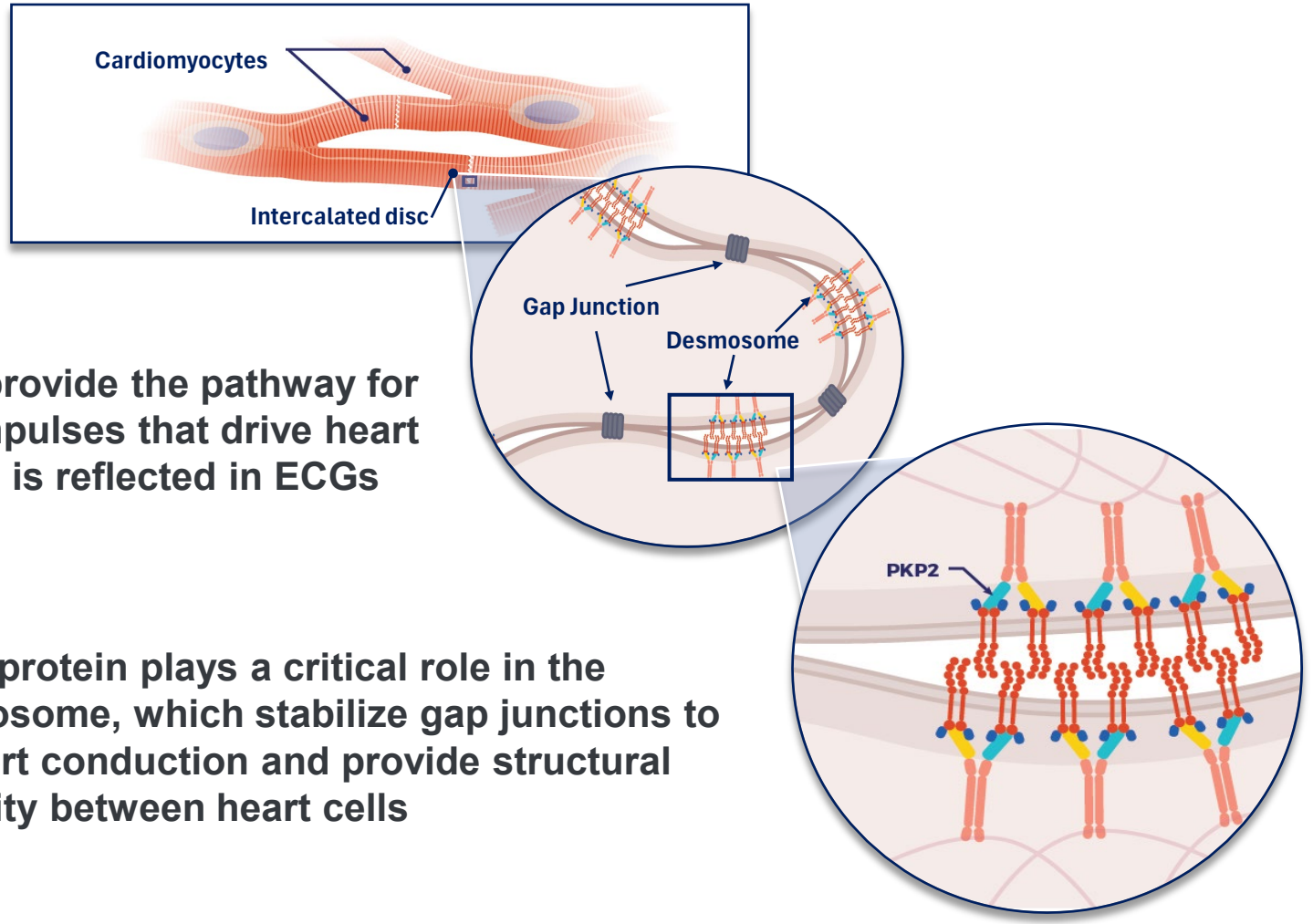
- All RIDGE-1 participants to date were identified through RIDGE
- RIDGE informed RIDGE-1 design, including eligibility criteria and endpoints
- Complements trial results by demonstrating natural history without gene therapy
- Supports potential pivotal trial & BLA

***~70% of RIDGE patients eligible for RIDGE-1***

BLA = Biologics license application

# PKP2 required for mechanical and electrical connections between cardiomyocytes

**Proteins in the intercalated disc form mechanical (e.g., desmosome) and electrical (e.g., gap junctions) connections**




**Gap junctions provide the pathway for the electrical impulses that drive heart contraction and is reflected in ECGs**

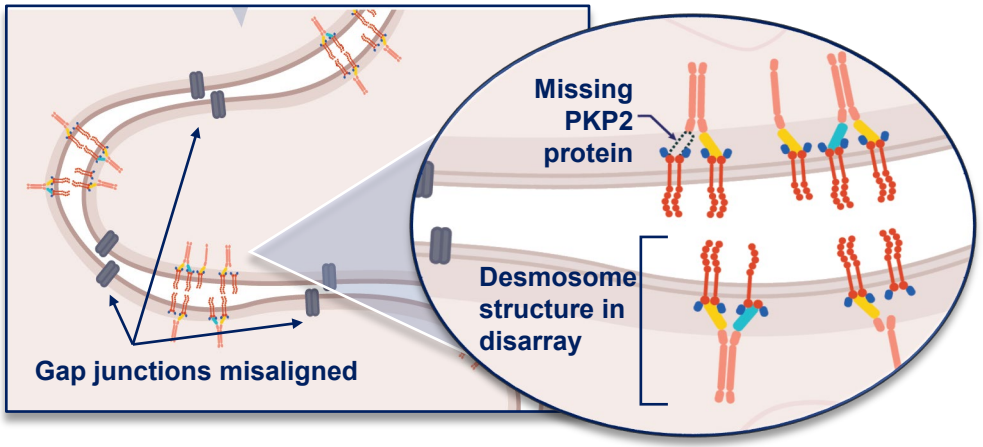
**PKP2 protein plays a critical role in the desmosome, which stabilize gap junctions to support conduction and provide structural integrity between heart cells**

ECG = electrocardiogram

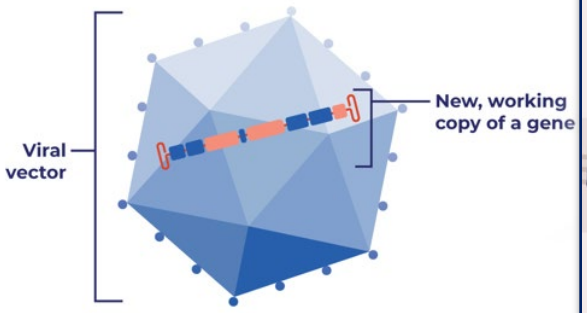
# TN-401 gene therapy for *PKP2*-associated ARVC

## *PKP2*+ Pathophysiology

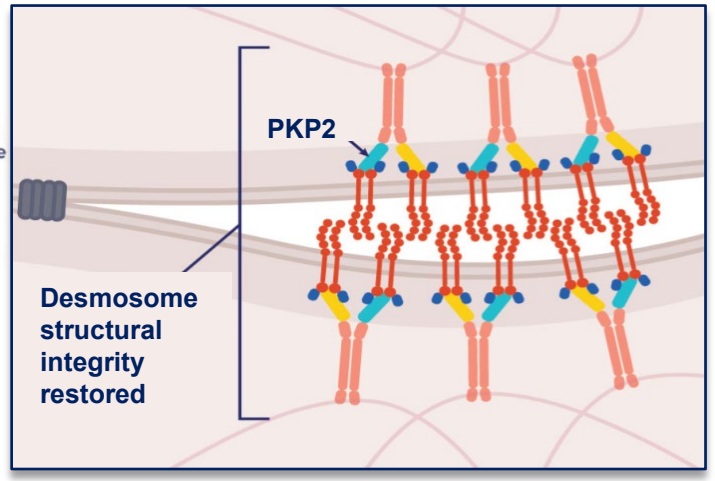
**Desmosome and Gap Junctions in *PKP2*-associated HCM Heart**




## TN-401 Mechanism of Action




**Treated with TN-401**




- Mutations of the *PKP2* gene lead to lower levels of PKP2 protein[1] resulting in
  - Weakened cell-to-cell adhesion
  - Abnormal electrical activity

- 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

1. van Tintelen, et al, Circulation 2006

SCA = Sudden cardiac arrest

# RIDGE-1 Interim Data Readout: Safety

# RIDGE-1 Phase 1b/2 clinical trial for *PKP2*-associated ARVC

**Treatment goal: demonstrate reduction in arrhythmic events**

## Study Objectives

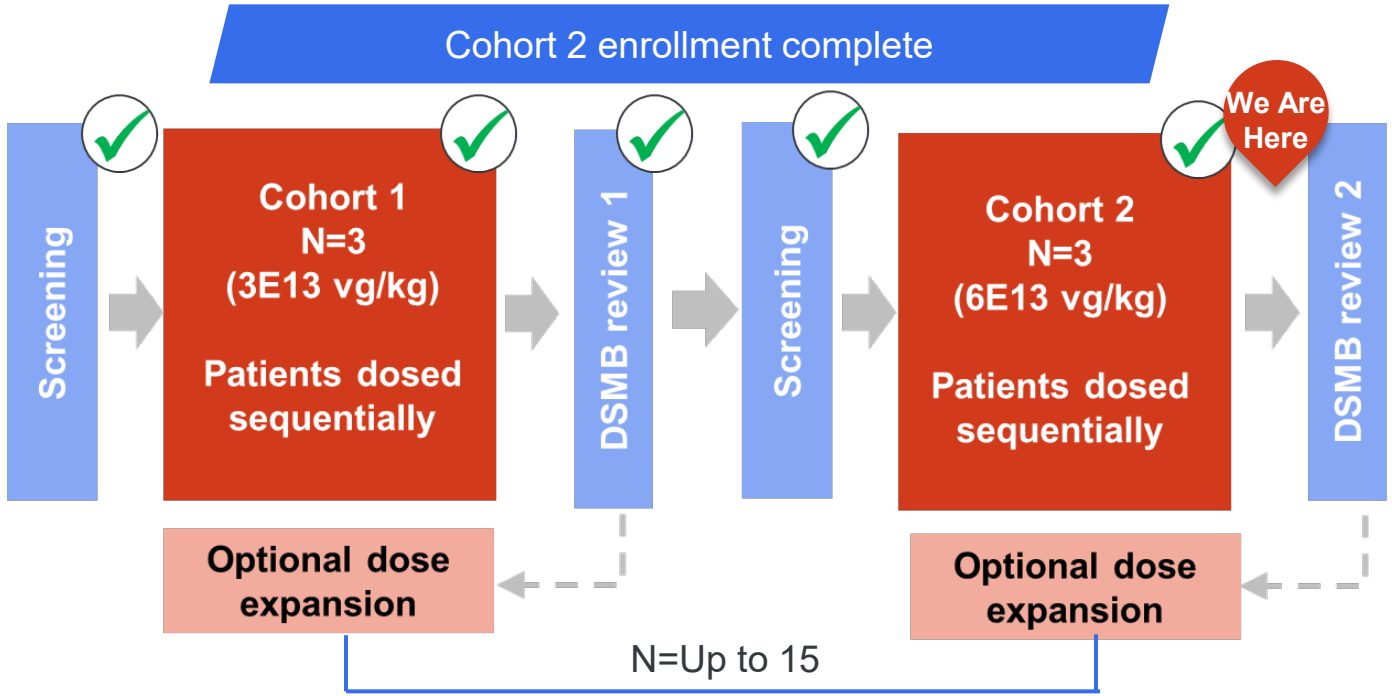
- Safety and tolerability
- Dose-finding
- Pharmacodynamics

## 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

## 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




NSVT = Non-sustained ventricular tachycardia

VT = ventricular tachycardia

# Cohort 1 patients all show signs of electrical instability resistant to SoC at baseline

**RIDGE-1 Cohort 1 Screening Characteristics**

| | Average Patient from RIDGE* | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|---|
| **Follow-Up** | - | 40 weeks | 32 weeks | 20 weeks |
| **Gender** | Male (62%) | Male | Male | Male |
| **Age at Dosing (y)** | - | 41 | 36 | 56 |
| **Age of ARVC Dx (y)** | 34 | 26 | 16 | 49 |
| **PVC Count (#/24h)** | 2,480 | 2,462 | 618 | 2,666 |
| **NYHA Class** | Class I (74%) | Class I | Class I | Class I |
| **% ICD & Age (y)** | 100%, 35 | 25 | 20 | 53 |
| **Severe VA**** | 39% | Yes; ≥4x | Yes; ≥6x | -*** |
| **VT Ablation** | 46% | Yes; twice | Yes | Yes |
| **Background meds** | ≥65% | Yes | Yes | Yes |

* Data from RIDGE as of September 2025

** Severe ventricular arrythmias include sustained VT, VF, and appropriate ICD therapy

*** Patient 3 likely had prior VT, given history of VT ablation

SoC = standard of care
VF = ventricular fibrillations

# Disease history and severity for each RIDGE-1 patient

## Gathered from RIDGE Natural History Study

| Domain | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
|  **Electrical Instability** | History of persistent electrical instability, including elevated PVCs, for >10 years | Stable until 5 years ago, now with elevated PVCs despite medication and ablation | Persistently high PVC (>500) count for 5 years |
|  **Medication Utilization** | Consistent beta blocker use and dose for >10 years | Flecainide and beta blocker since arrhythmias | Beta blockers (with & without flecainide historically) |
|  **Procedures** | Ablation >10 years ago | Ablation <5 years ago | Ablation >5 years ago |
|  **Lethal Arrhythmias** | Multiple instances of ICD shock and ATP, as recent as 2023 (despite therapy) | Cluster of ICD shocks and ATPs | No reported instances of ICD shock, ATP or lethal arrhythmias |

ATP = anti-tachycardia pacing

# Taking a comprehensive approach to safety

## CAPSID

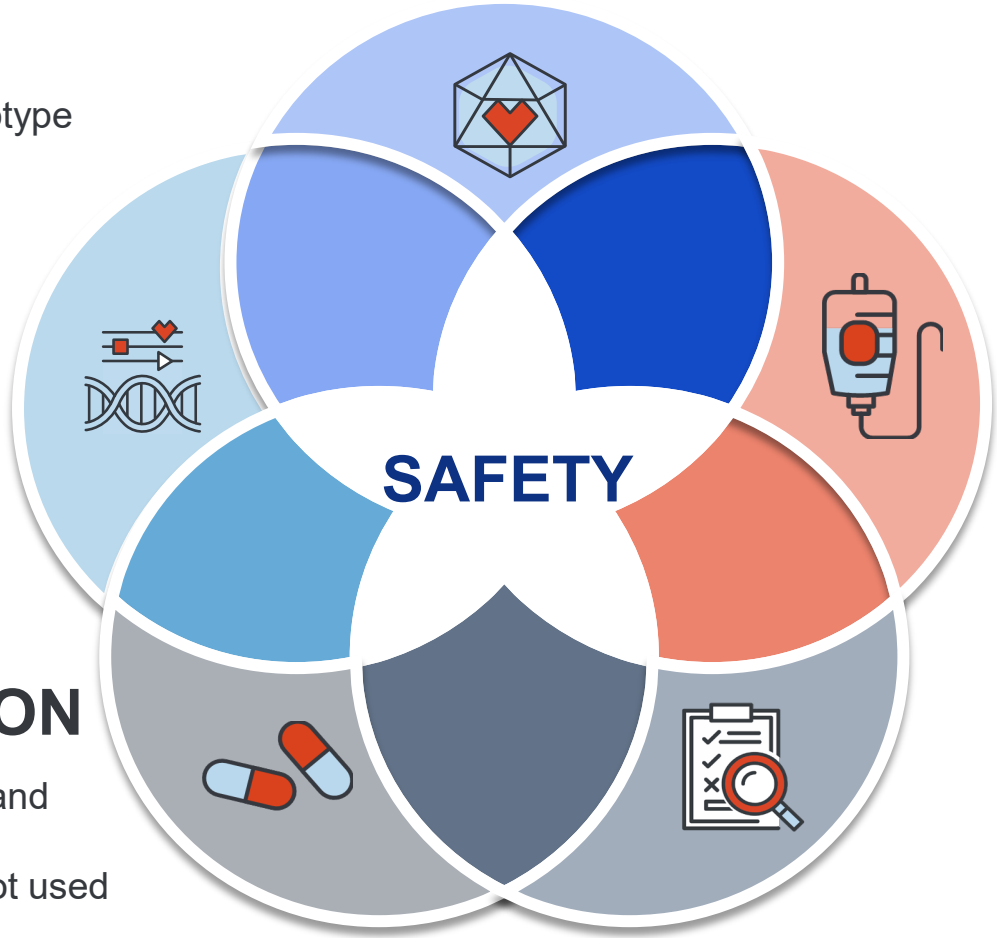
- AAV9 is the most widely used serotype worldwide >5000 patients dosed
- Preclinical studies indicate higher expression vs. other serotypes

## CASSETTE

- Ful-length copy of human gene
- Promoters and regulatory elements enable preferential expression in the heart

## IMMUNOSUPPRESSION

- Temporary prophylactic sirolimus and prednisone
- Complement inhibitor available (not used to date)




## DOSE

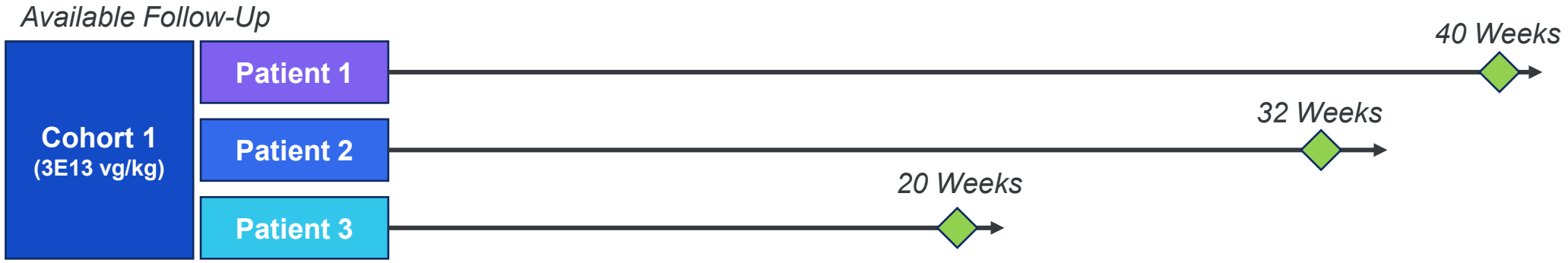
- Low-to-mid $10^{13}$ vg/kg purposefully chosen to optimize for safety and efficacy

## MONITORING

- In-hospital monitoring for one week after infusion
- Frequent lab assessments enable safe & personalized withdrawal of immunosuppressives
- Close oversight by DSMB of experts in cardiology, hepatology, immunology, and AAV therapy

AAV = Adeno-associated virus

# Cohort 1 safety: 3E13vg/kg dose has been well tolerated




- ✓ Majority of TN-401-related AEs have been **mild, asymptomatic, and manageable**
  - Most frequent AEs were transient elevations of transaminases or troponin requiring no additional treatment and with no sequelae
  - 1 Grade 1 SAE of troponin elevation (classified as "SAE" due to inpatient monitoring)
- ✓ **No TMA**
- ✓ **No cardiotoxicities**
  - No arrhythmias deemed related to treatment
  - No signs of myocarditis on echo, electrocardiography, histology or cardiac MRI
  - No ICD shocks or arrhythmias associated with TN-401 to date
- ✓ All patients **have tapered off immunosuppressive** medicines

**Cohort 2 (6E13 vg/kg) Preview**

- ✓ Dosing complete
- ✓ No TN-401-related SAEs reported to date

Data cut as of October 2025
AE = adverse events
SAE = serious adverse event
TMA = thrombotic microangiopathy
MRI = magnetic resonance imaging

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# Heart Biopsy

# TN-401 mechanism of action occurs in 3 stages within cardiomyocytes

***TN-401 Mechanism of Action***

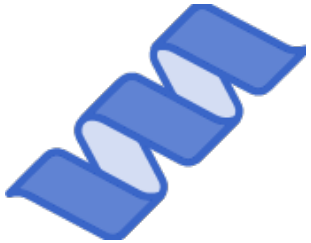
***TN-401 Upon Infusion***

***Biopsy samples***

1. **DELIVERY: Transduction (DNA)**
2. **EXPRESSION: Transcription (RNA)**
3. **EXPRESSION: Translation (Protein)**

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

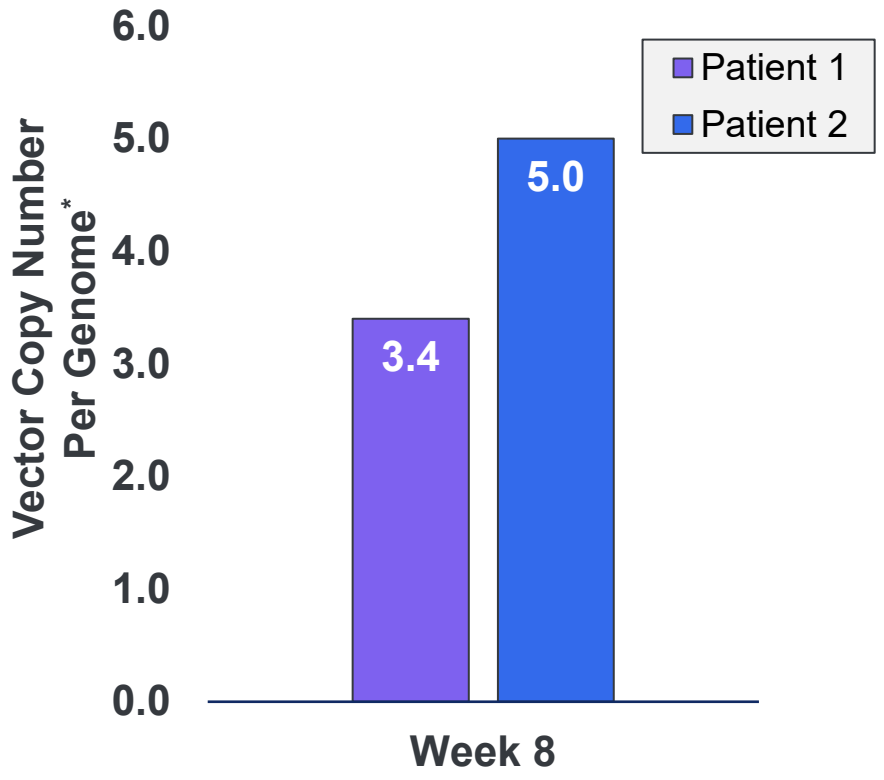
TN-401's healthy copy of *PKP2* gene is transcribed by cell's machinery to produce messenger RNA



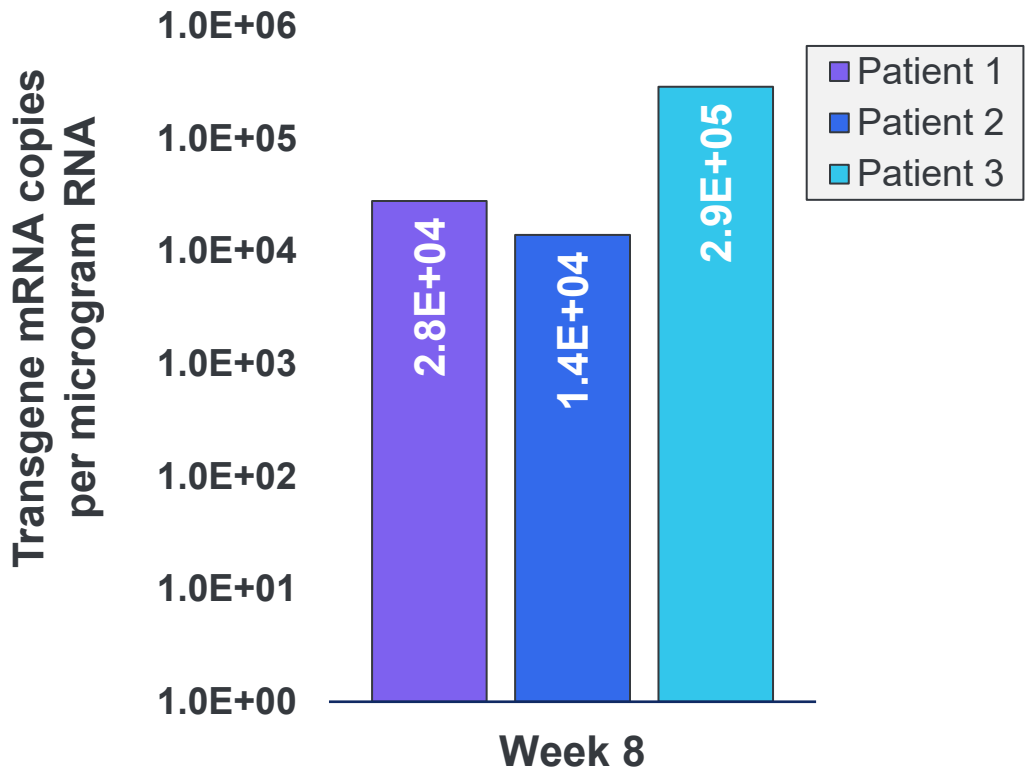
TN-401 mRNA is then converted to PKP2 protein

# Robust transduction and consistent expression detected in all patients within first 8 weeks

## Substantial Transduction at 3E13 vg/kg*




## Robust TN-401 mRNA Levels by 8 Weeks



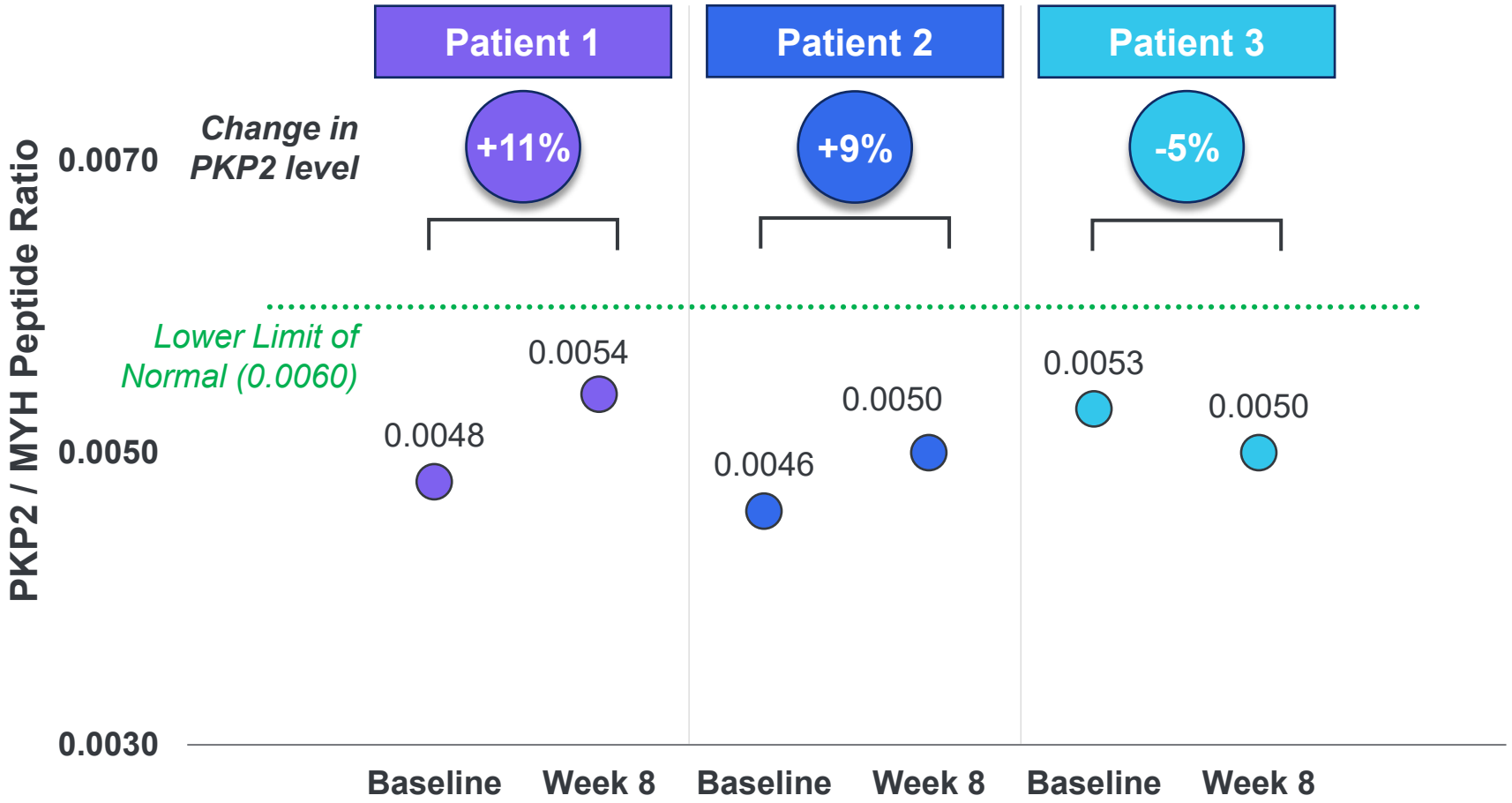

TN-401 DNA and mRNA were not detected in baseline biopsies before TN-401 administration, as expected

* Vector copy number from Patient 3 not yet available

Data cut as of October 2025

# Quantifiable increase in PKP2 protein expression in majority of Cohort 1 patients as early as Week 8

## PKP2 Protein Levels Over Time in Cohort 1 (3E13 vg/kg)



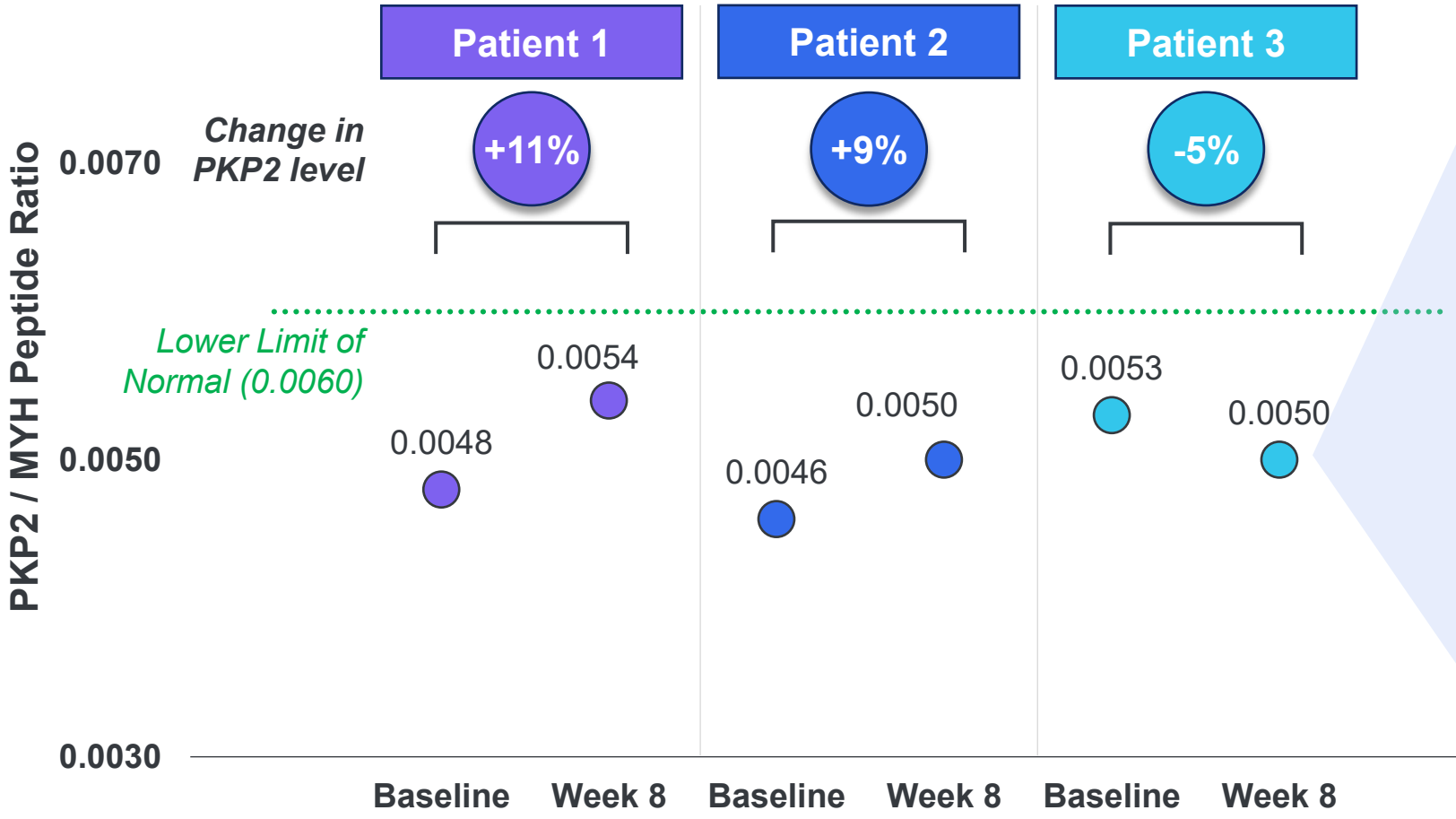

- PKP2 from TN-401 & endogenous gene are indistinguishable
- LC-MS assay quantifies total PKP2 protein level
- Baseline levels are below normal, consistent with *PKP2* haploinsufficiency
- Two of three patients show increases in PKP2 levels, above level of individual variability
- Preclinical and clinical data for AAV9 gene therapy indicate expression continues increasing over time [1],[2]

LC-MS = liquid chromatography mass spectrometry
MYH = myosin heavy chain

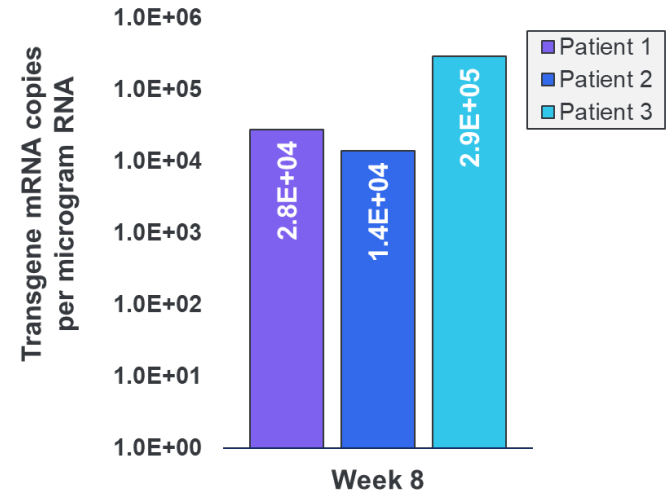

1. Desai, et al., *Circulation Research* 2025
2. Greenberg, et al., *NEJM* 2024

# Quantifiable increase in PKP2 protein expression in majority of Cohort 1 patients as early as Week 8

## PKP2 Protein Levels Over Time in Cohort 1 (3E13 vg/kg)




***In mRNA sample, Patient 3 has highest level of expression***



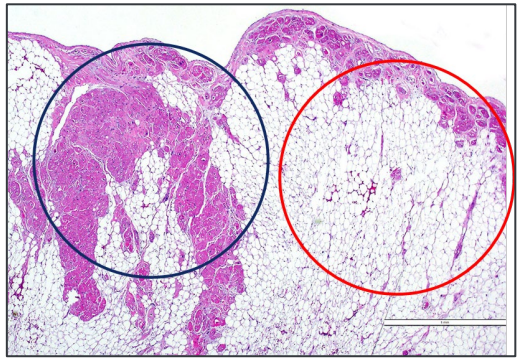

*mRNA and protein analyses use tissue from separate biopsy samples*

Data cut as of October 2025

# Mass spectrometry methodology chosen to reduce variability in quantifying PKP2 protein level changes

**Heart tissue from cardiomyopathy patients may have uneven composition of cardiomyocytes and fibrofatty infiltrates across samples**

**ARVC Donor Heart Tissue with Fibrofatty Replacement***



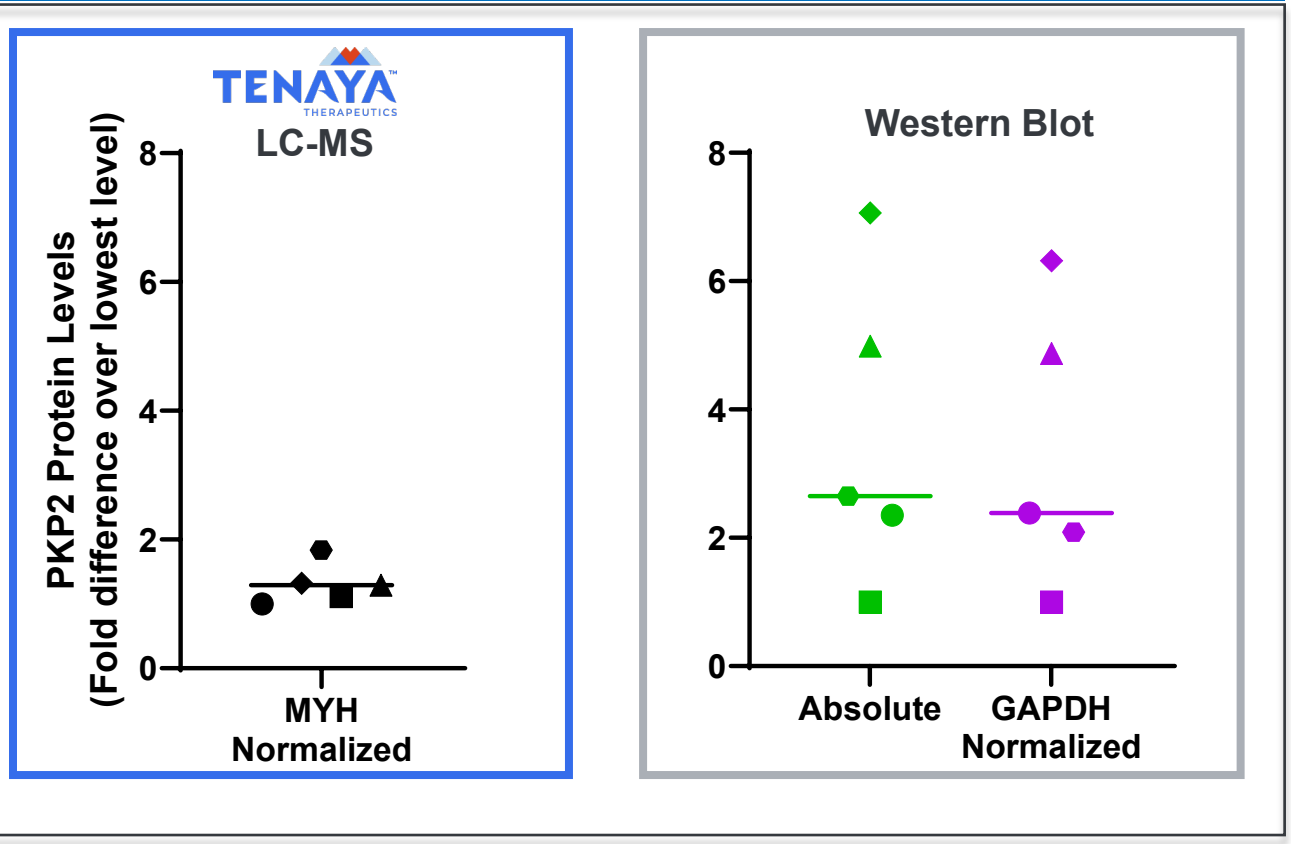
% cardiomyocytes > % fibrofatty infiltrates

% fibrofatty infiltrates > % cardiomyocytes

**Biopsy tissue pieces approx. by circles (~1-2 mm³)*

- PKP2 is primarily expressed in cardiomyocytes, so differences in cardiomyocyte composition in biopsy will affect PKP2 levels
- Normalizing PKP2 levels to a cardiomyocyte-restricted protein (e.g. MYH) and utilizing LC-MS corrects for variable cardiomyocyte composition between biopsies

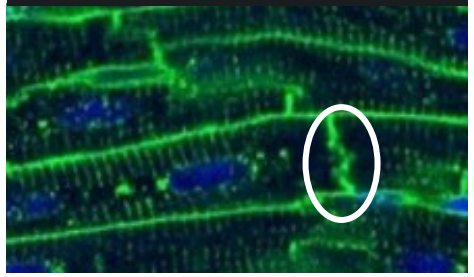
**Without MYH normalization, western blots show up to 7-fold difference between 5 normal donors. Variability may be further exacerbated in samples from diseased hearts.**



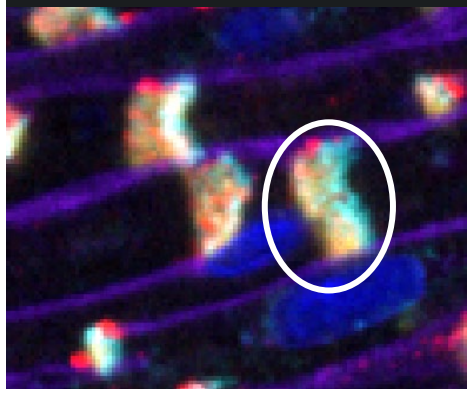
# PKP2 localizes appropriately to intercalated discs after TN-401 administration

## Healthy Donor Heart

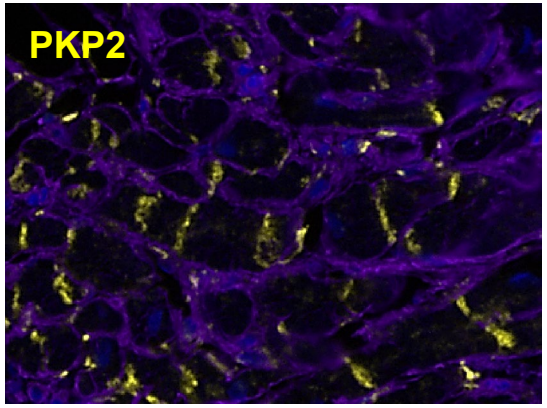
**Intercalated disc**

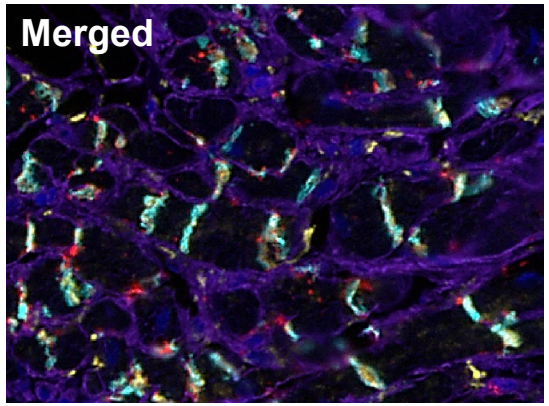


**Merged image of PKP2, Cx43, & N-Cad**

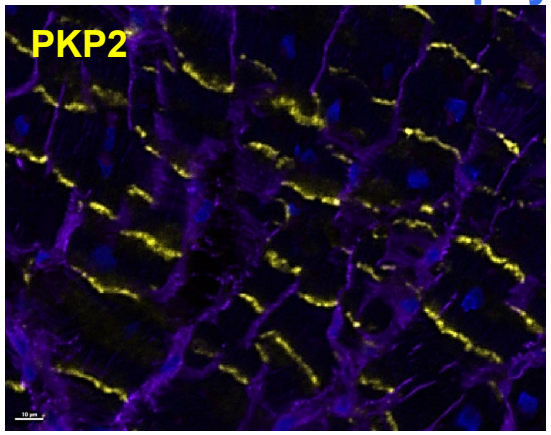


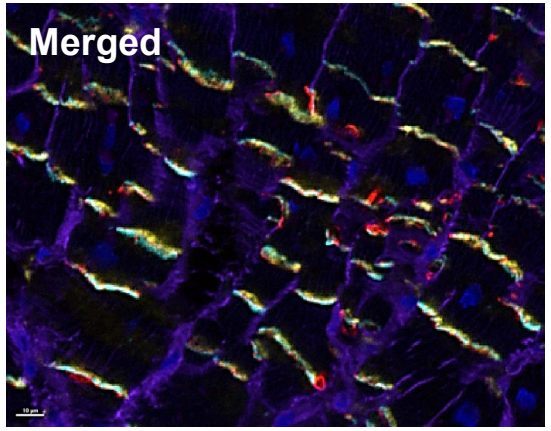
## Patient 1: Baseline Biopsy




## Patient 1 Week 8 Biopsy




PKP2 protein colocalizes with gap junction (Connexin 43) and intercalated disc (N-Cadherin) proteins based on multiplexed immunofluorescence (mIF) imaging

**PKP2**
**Connexin43**
**N-Cadherin**
**Membrane**
**Nucleus**

Cx43 = Connexin 43
N-Cad = N-Cadherin

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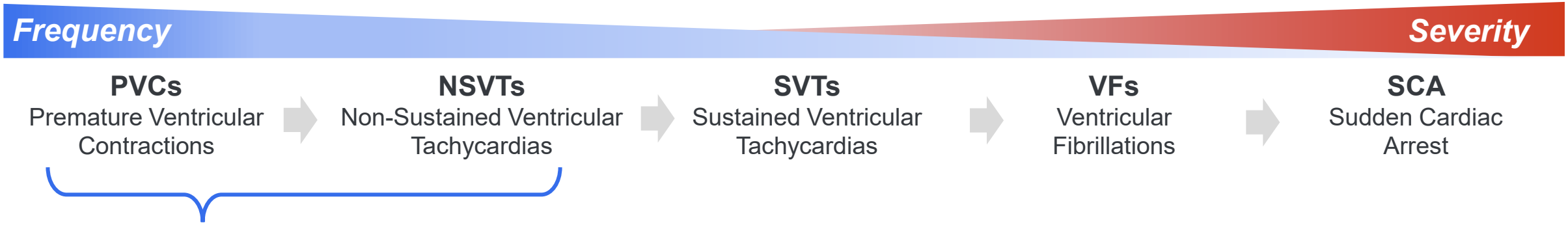
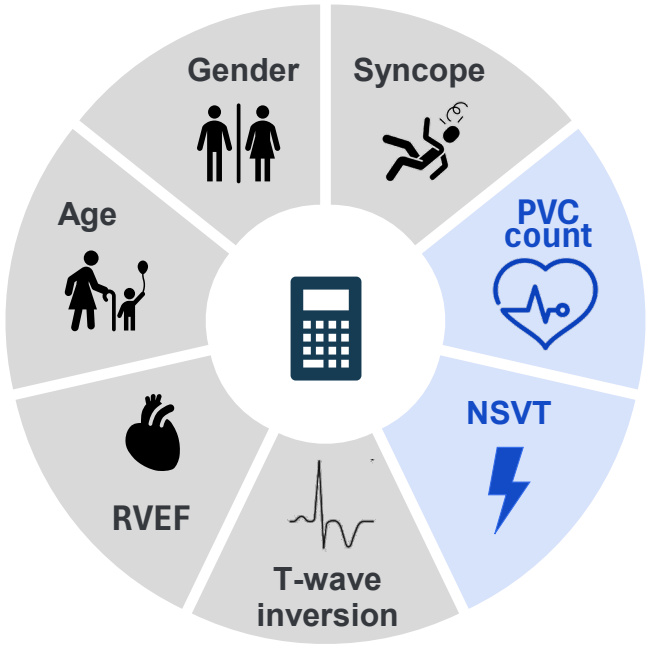
# Clinical

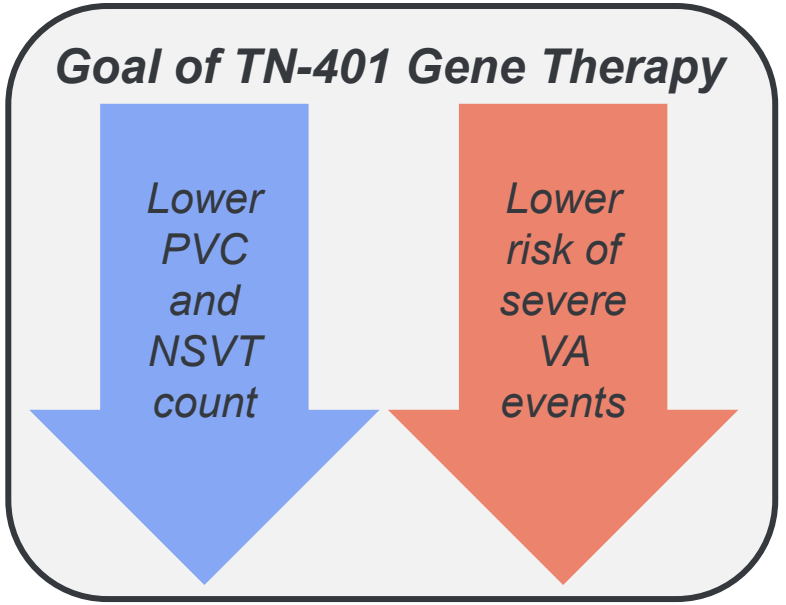
# PVC and NSVT burden are key indicators of electrical instability and risk of life-threatening events




**ARVC Risk Stratification Calculator**




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

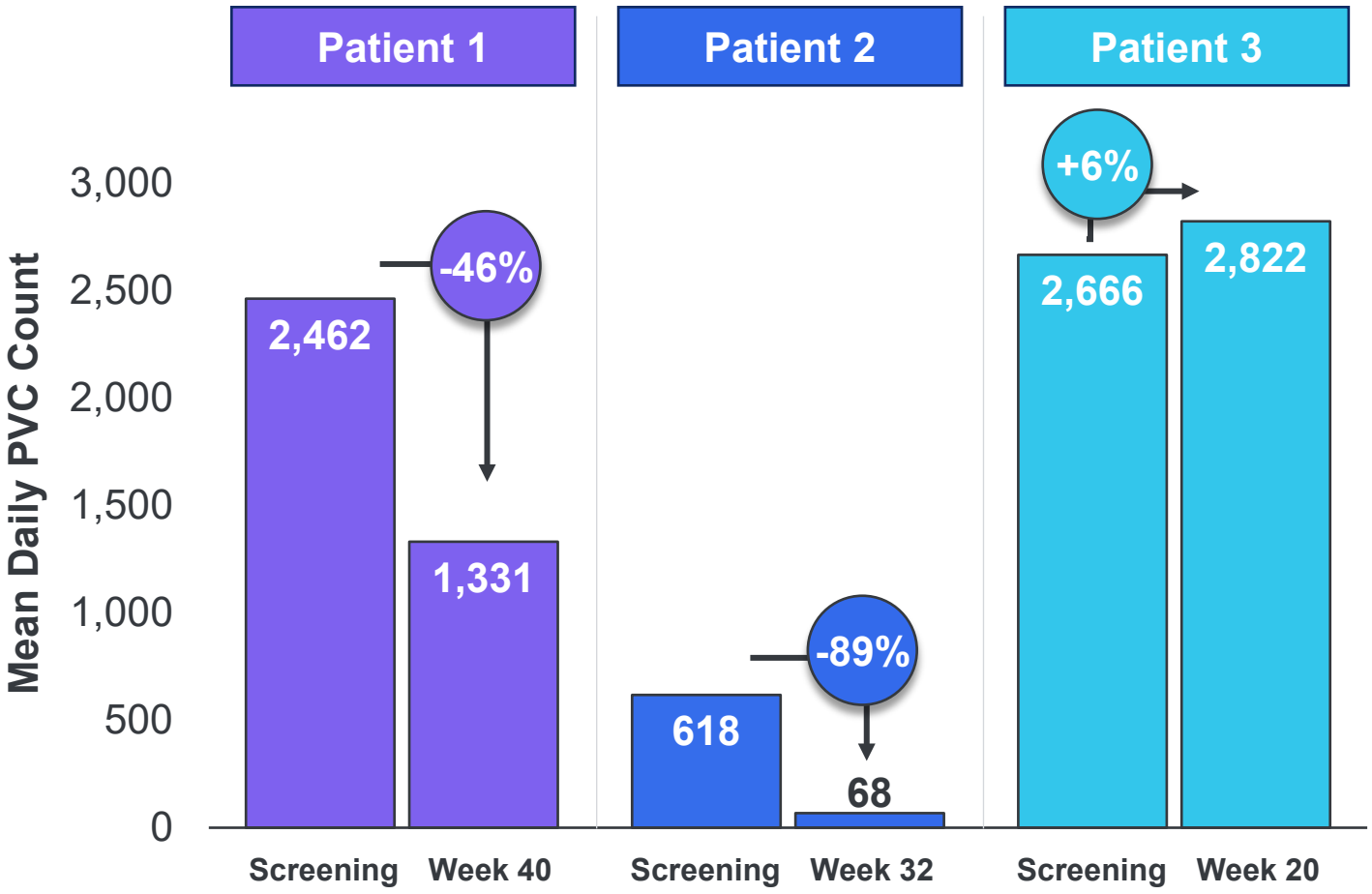




1. Calkins, et al, HRS 2025
2. Carrick, et al, Circ Arrhythm and Electrophysiol 2022
3. https://arvcrisk.com/

# Meaningful decline in PVC burden in first two patients with ≥6 months of follow-up after TN-401 treatment

## Change in Mean Daily PVC Rate in Cohort 1 (3E13 vg/kg)




- Daily PVC counts are the average of 7-day ambulatory ECG monitors used for baseline and post-dose arrhythmia quantification
- Among the two patients with ≥6 months of follow-up post-dose, mean **reduction of 67% in PVC count**
- A 67% decrease in daily PVC count **lowers odds of a sustained VA event by 67%** over the next 12 months[1]

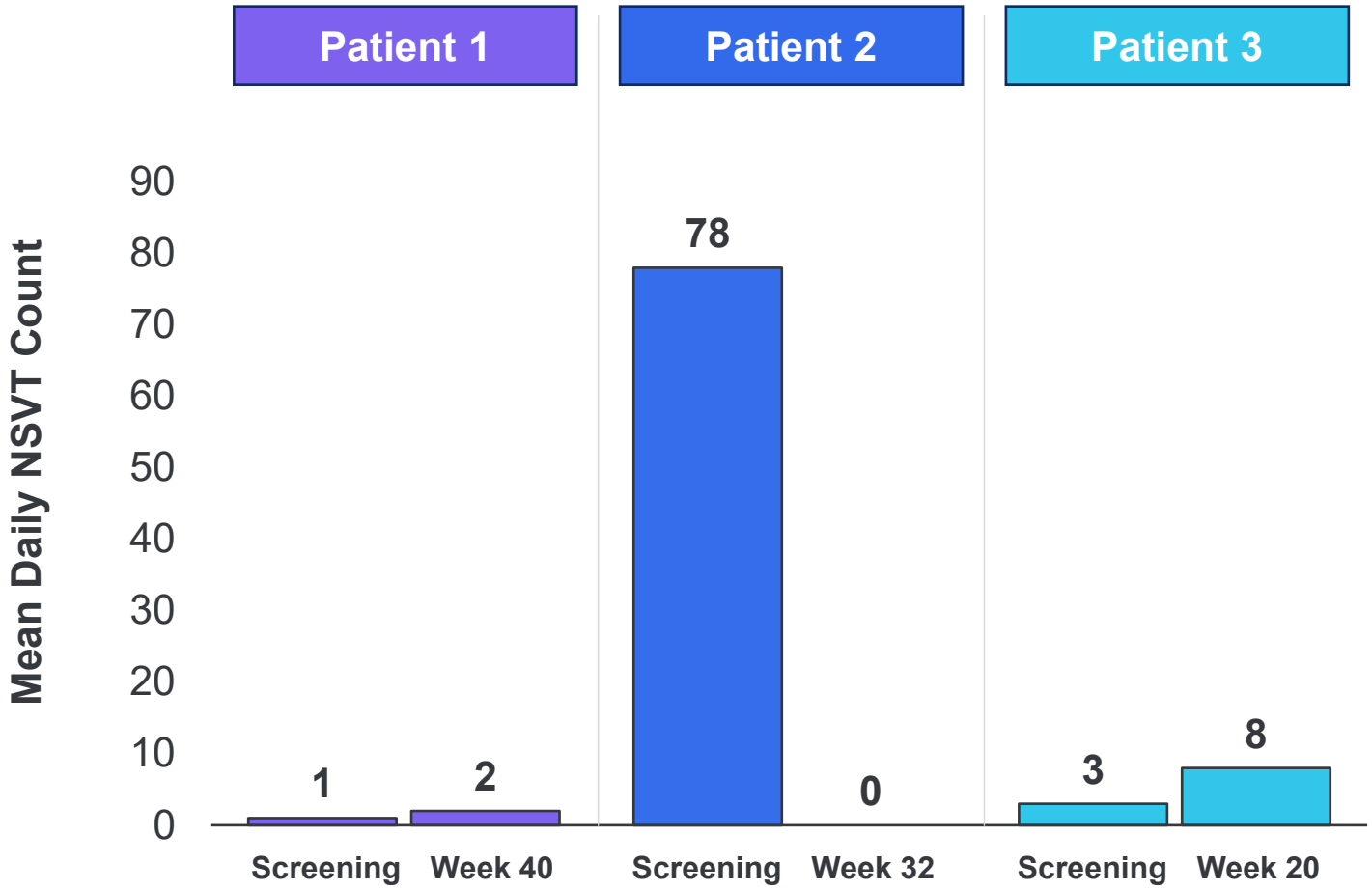
*PVC and NSVT rates calculated using counts over 7-day ambulatory monitoring period
Data cut as of October 2025

ECG = electrocardiogram

1. Gasperetti, *JAMA Cardiol* 2022

# NSVT burden was eliminated or stable in first two patients ≥6 months post-dose with TN-401

## Change in Mean Daily NSVT Count in Cohort 1 (3E13 vg/kg)

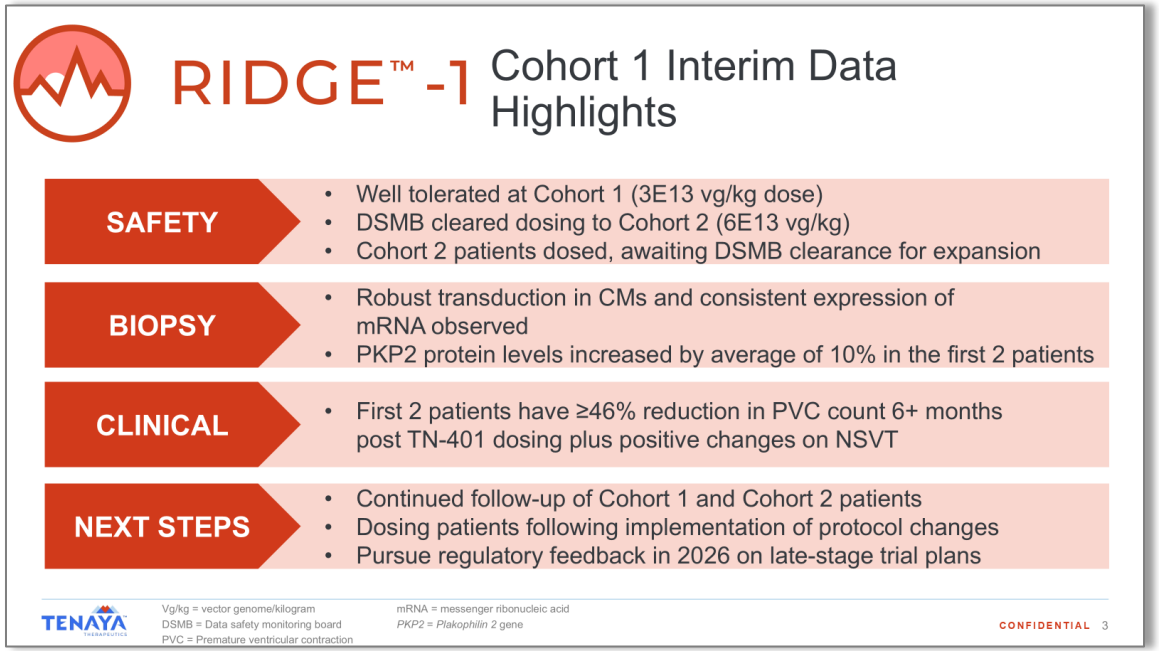



- Patient 1 had low NSVT count at baseline and **remains low**
- Patient 2 had **no NSVTs detected** at most recent visit vs. significant NSVT burden prior to treatment
- Patient 3 had slight increase in NSVTs at <6 months follow up
- Other measures of clinical response, including QRS duration, T-wave inversions, heart function, and NYHA class, were in the normal range or remained stable

*PVC and NSVT rates calculated using counts over 7-day ambulatory monitoring period
Data cut as of October 2025

# TN-401's promising initial Cohort 1 create a strong foundation for future milestones

## Summary of findings from Cohort 1




## TN-401 next steps in 2026

- Cohort 2 DSMB in Q1 '26
- 52-week Cohort 1 data in mid'26
- 20+-week Cohort 2 data in 1H'26
- Pursue regulatory alignment on pivotal program in 2026

***Tenaya would like to acknowledge the contributions of patients, clinical sites, researchers to this work.***
***RIDGE-1 is supported by a clinical grant from the California Institute for Regenerative Medicines (CIRM).***

CIRM
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# Anticipated 2025-26 milestones

| | 1H'25 | 2H'25 | Expected 2026+ |
|---|---|---|---|
| **TN-201** | | | |
| **MyPEAK-1** | ✓ **Present additional Cohort 1 data**<br>✓ Complete Cohort 2 enrollment | ✓ **Provide Cohort 1 data update & present initial Cohort 2 data** | • **1H'26: Present two-year Cohort 1 and one-year Cohort 2 data**<br>• Pursue regulatory alignment on pivotal studies<br>• Initiate pediatric pivotal study |
| **MyClimb** | ✓ Presented data at ESC Congress | | |
| **TN-401** | | | |
| **RIDGE-1** | ✓ Complete Cohort 1 enrollment<br>✓ Ex-US expansion | ✓ **Cohort 1 initial data**<br>✓ Cohort 2 and/or expansion cohort enrollment | • **1H'26: Present one-year Cohort 1 data and early Cohort 2 data**<br>• Pursue regulatory alignment on pivotal study |
| **RIDGE** | ✓ Presented data at Heart Rhythm Society | | |

Cash and equivalents expected to be sufficient to fund operations into 2H'26[1,*] – beyond planned longer-term data readouts for MyPEAK-1 and RIDGE-1 trials

1. Based on $56.3M cash, cash equivalents and investments as of 9/30/25
*Tenaya has not drawn on the SVB credit facility put in place in Q3'24

# Q&A &
# Closing remarks