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

Treatment goal: demonstrate reduction in arrhythmic events

Study Objectives

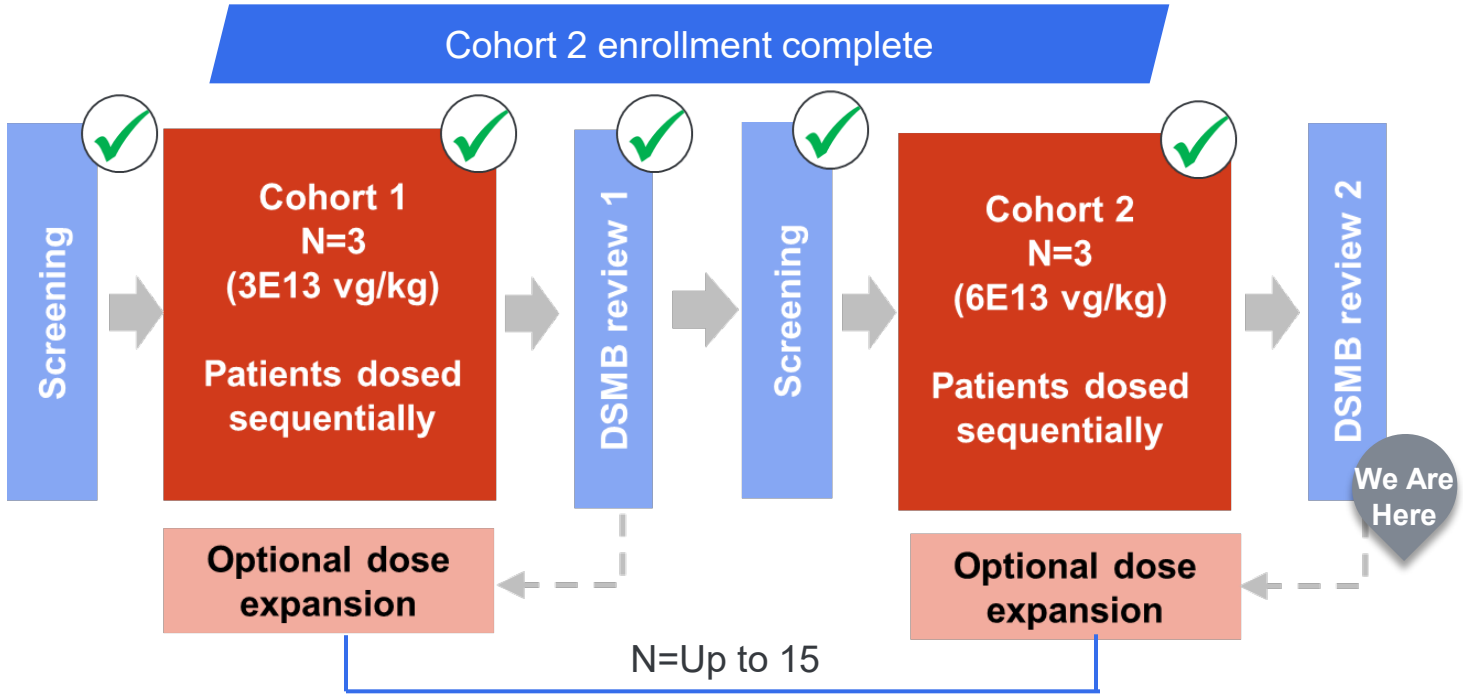
- Safety and tolerability
- Dose-finding
- Pharmacodynamics

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

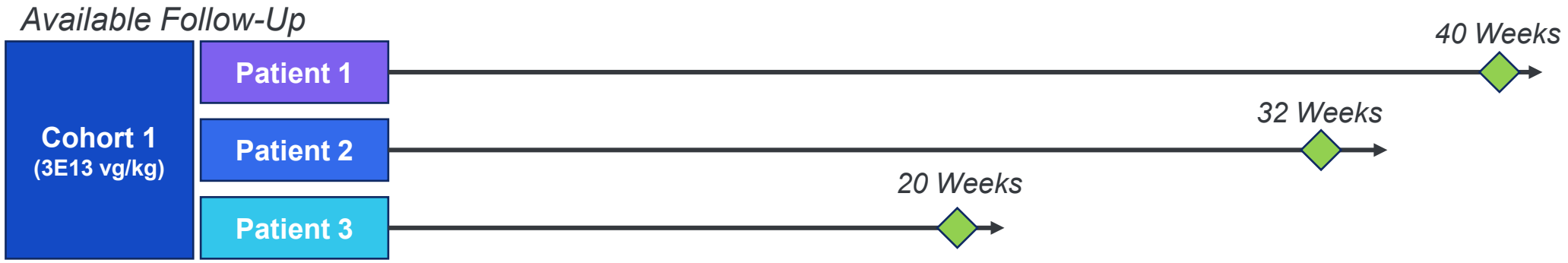
*** Patient 3 likely had prior VT, given history of VT ablation

Data cut as of October 2025

SoC = standard of care

VF = ventricular fibrillations

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

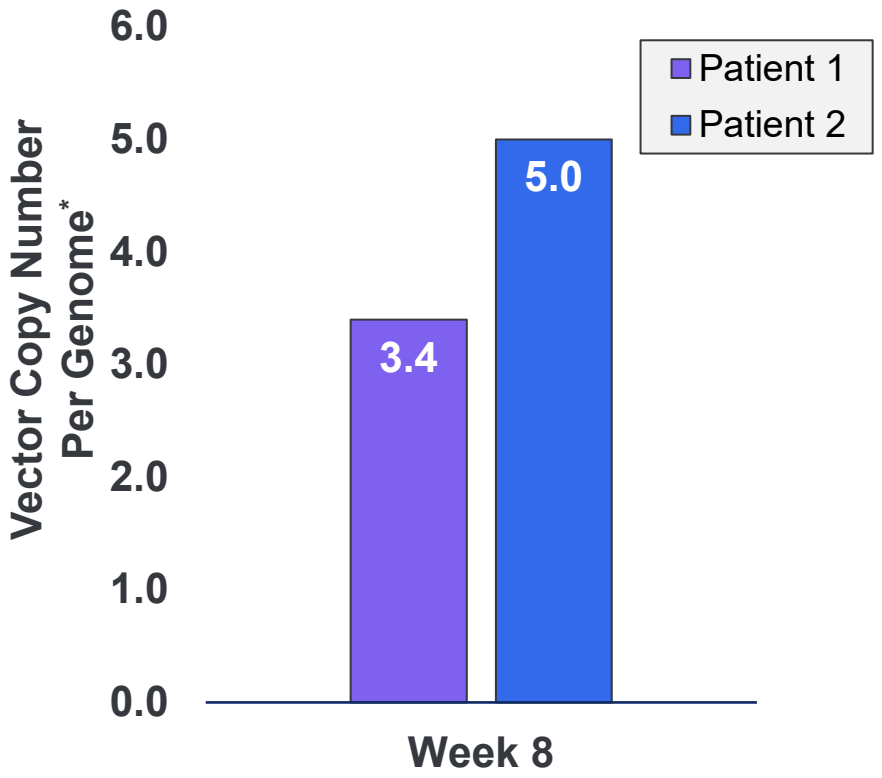
Cohort 2 (6E13 vg/kg) Preview

- ✓ 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

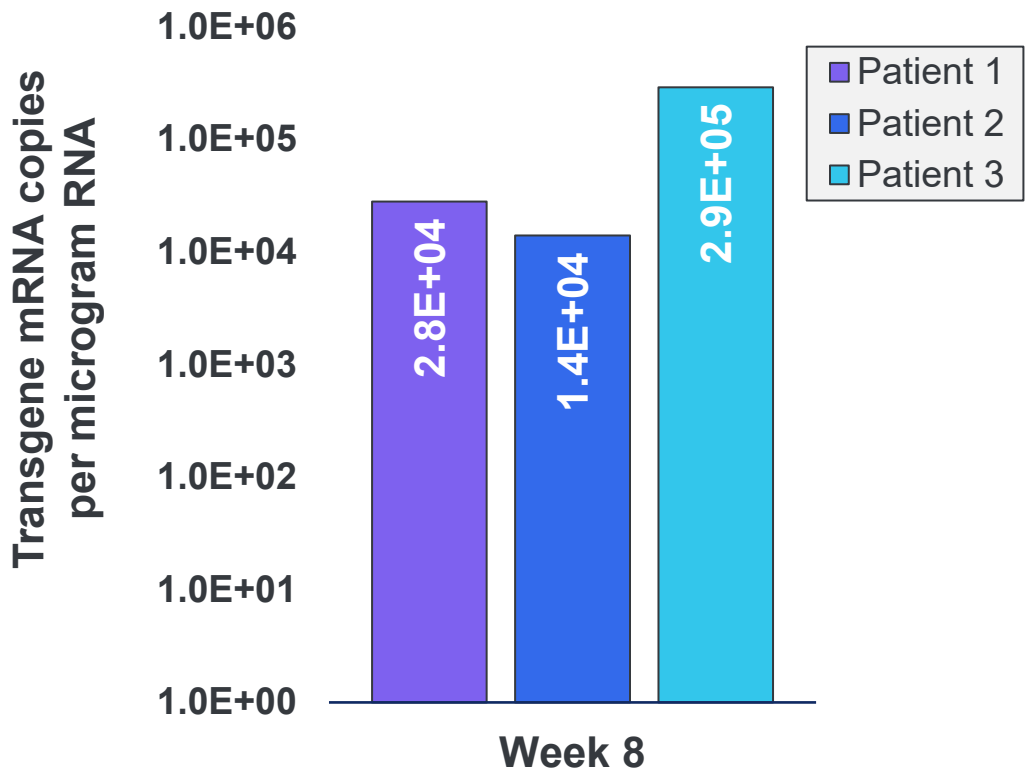
Robust transduction and consistent expression detected in all patients within first 8 weeks

Substantial Transduction at 3E13 vg/kg*



* Vector copy number from Patient 3 not yet available

Robust TN-401 mRNA Levels by 8 Weeks

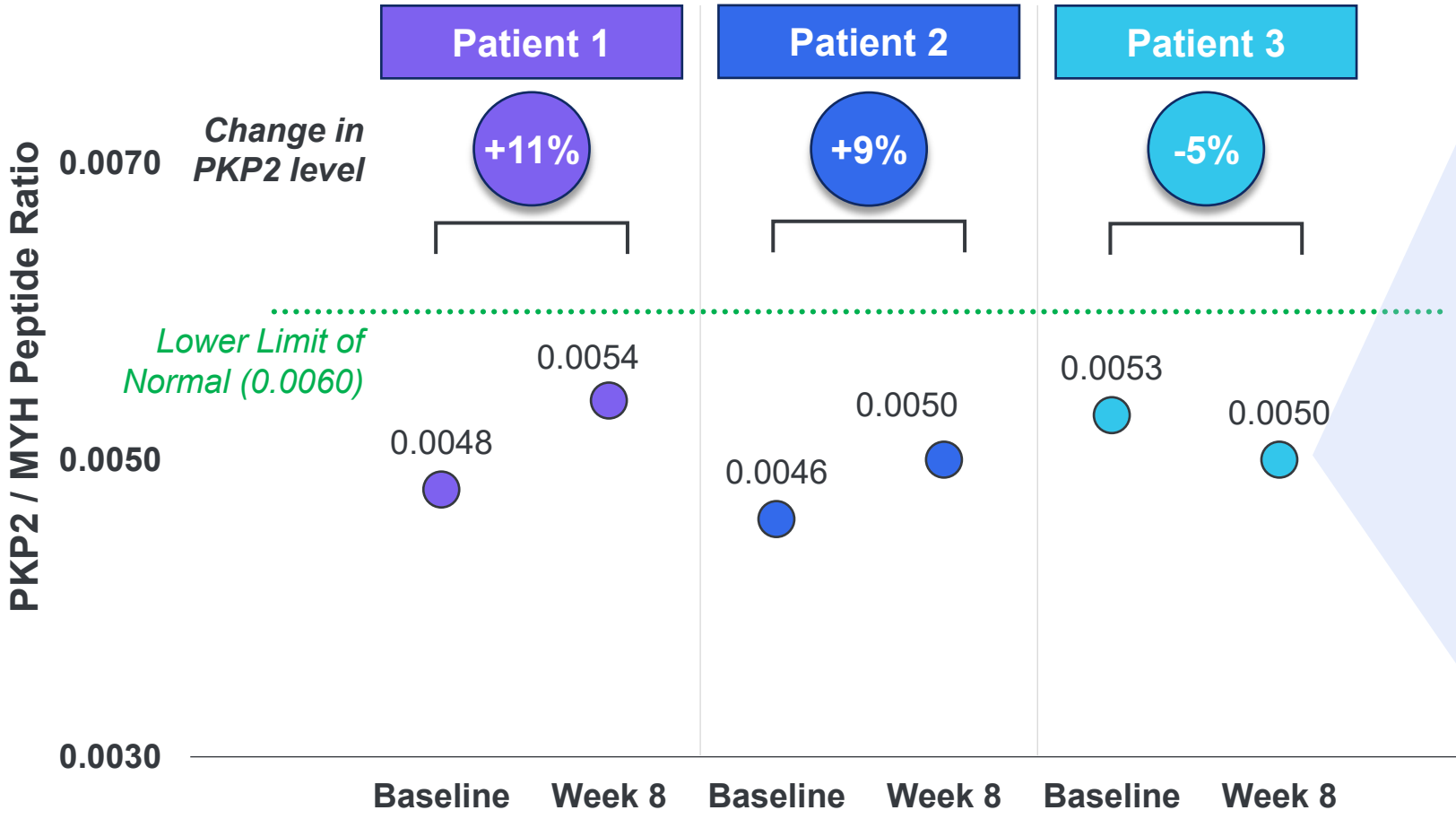


TN-401 DNA and mRNA were not detected in baseline biopsies before TN-401 administration, as expected

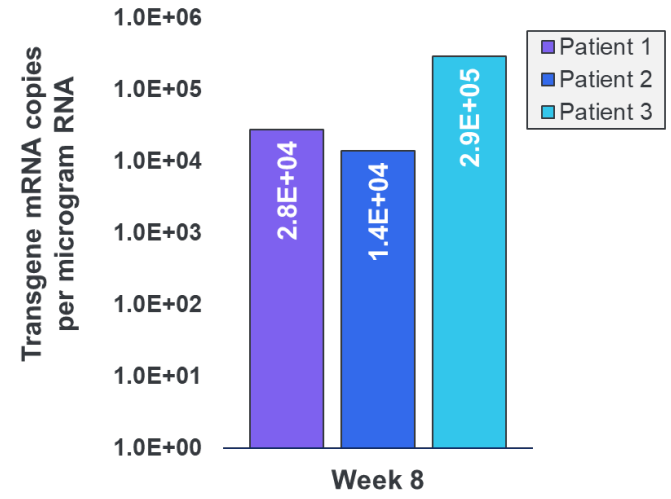
Data cut as of October 2025

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)



In mRNA sample, Patient 3 has highest level of expression



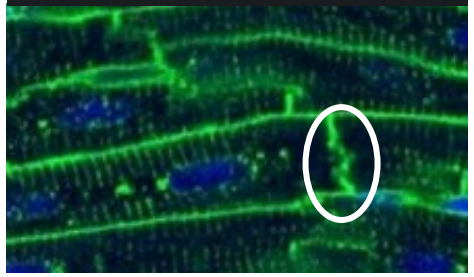
mRNA and protein analyses use tissue from separate biopsy samples

Data cut as of October 2025

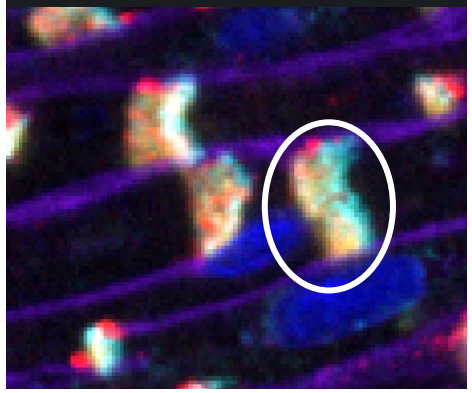
PKP2 localizes appropriately to intercalated discs after TN-401 administration

Healthy Donor Heart

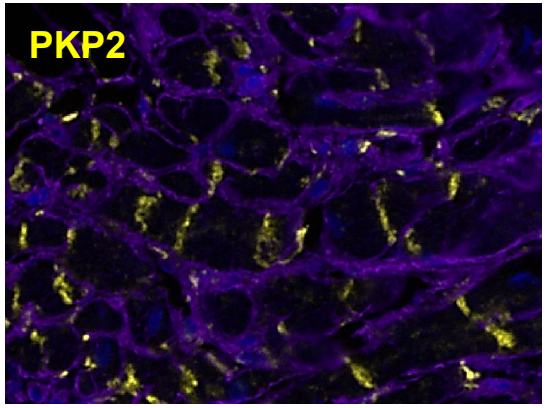
Intercalated disc

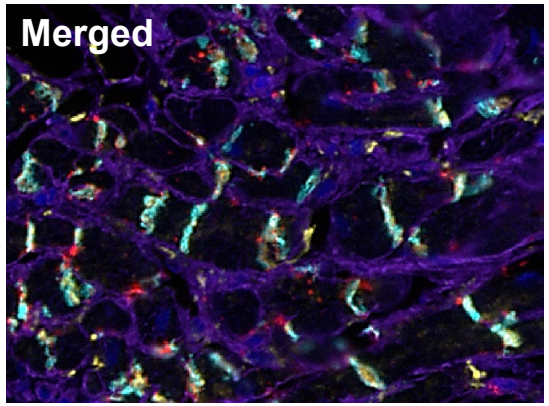


Merged image of PKP2, Cx43, & N-Cad

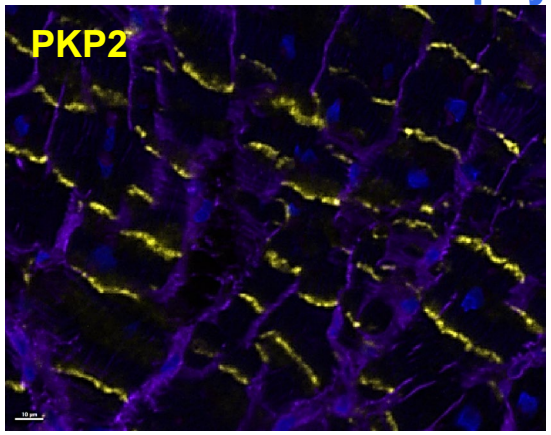


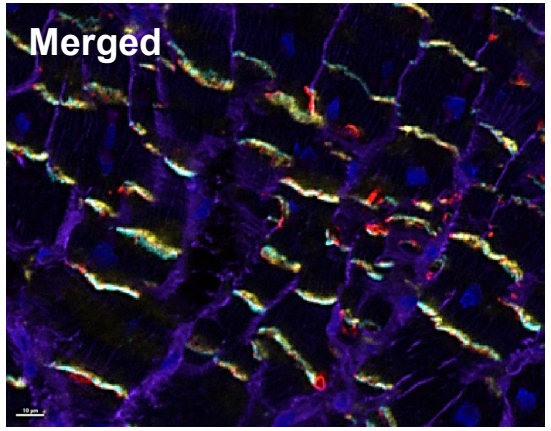
Patient 1: Baseline Biopsy





Patient 1 Week 8 Biopsy





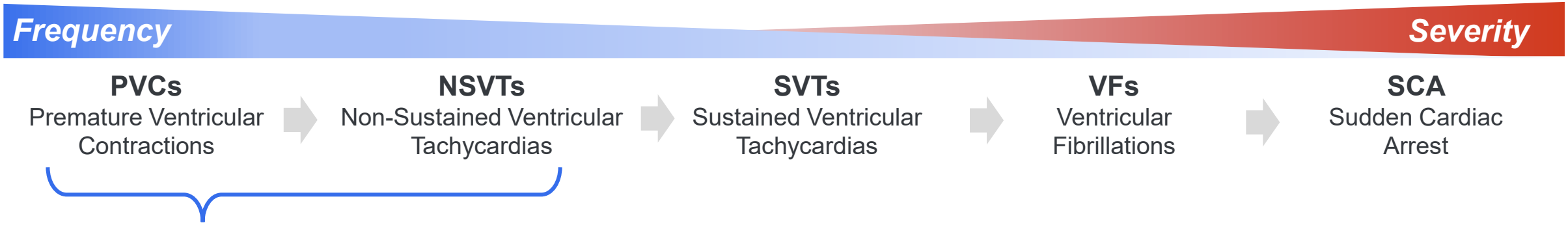
PKP2 protein colocalizes with gap junction (Connexin 43) and intercalated disc (N-Cadherin) proteins based on multiplexed immunofluorescence (mIF) imaging

PKP2
Connexin43
N-Cadherin
Membrane
Nucleus

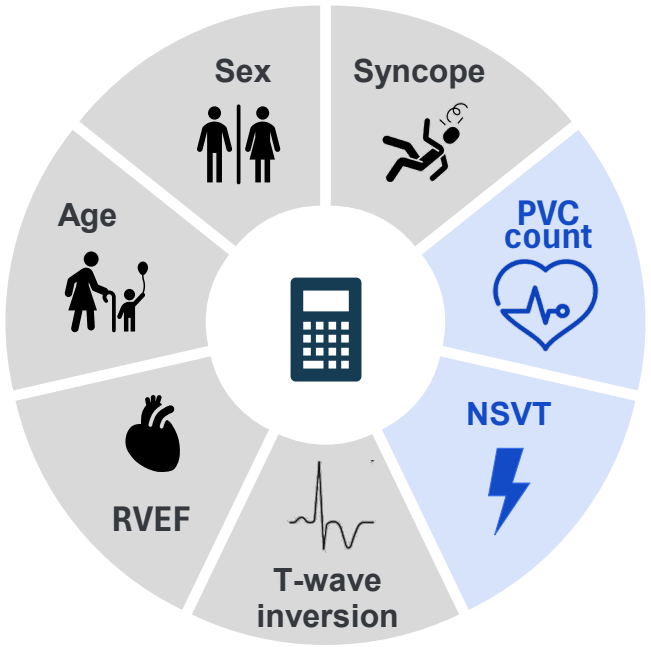
Data cut as of October 2025

Cx43 = Connexin 43
N-Cad = N-Cadherin

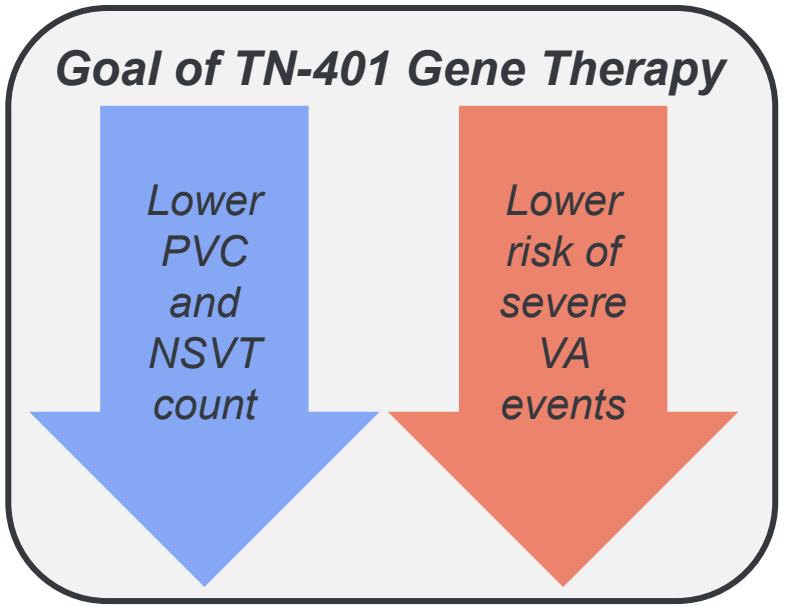
PVC and NSVT burden are key indicators of electrical instability and risk of life-threatening events



ARVC Risk Stratification Calculator



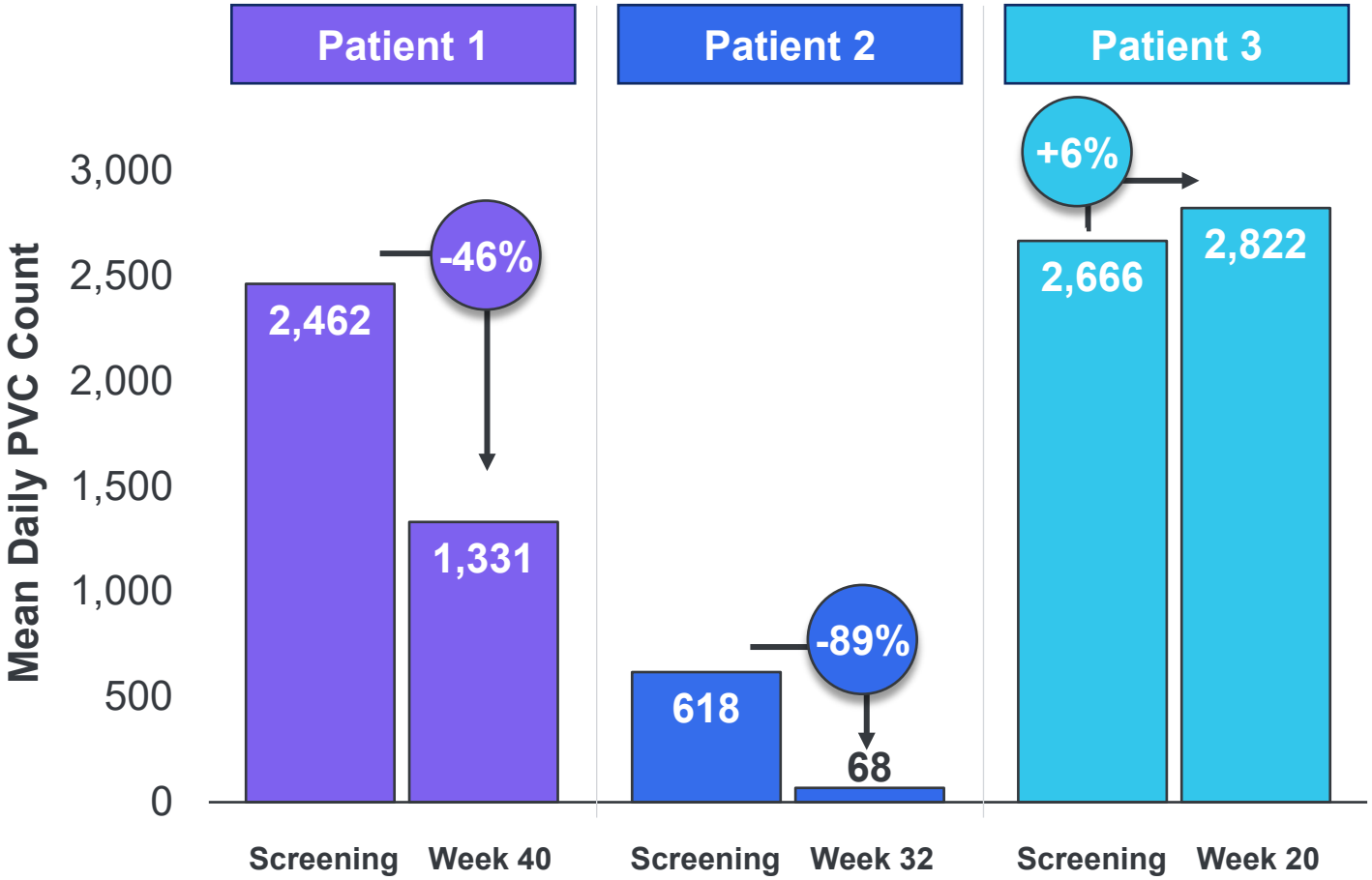
- PVCs are hallmark of PKP2+ ARVC and indicate electrical instability(1)
- Higher PVC counts are a recognized clinical predictor of higher 5-year risk of life-threatening VAs(2)
- PVC burden utilized as risk assessment tool for ICD placement(3)



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 translates to **lower odds by 67%** of a sustained VA event over the next 12 months[1]

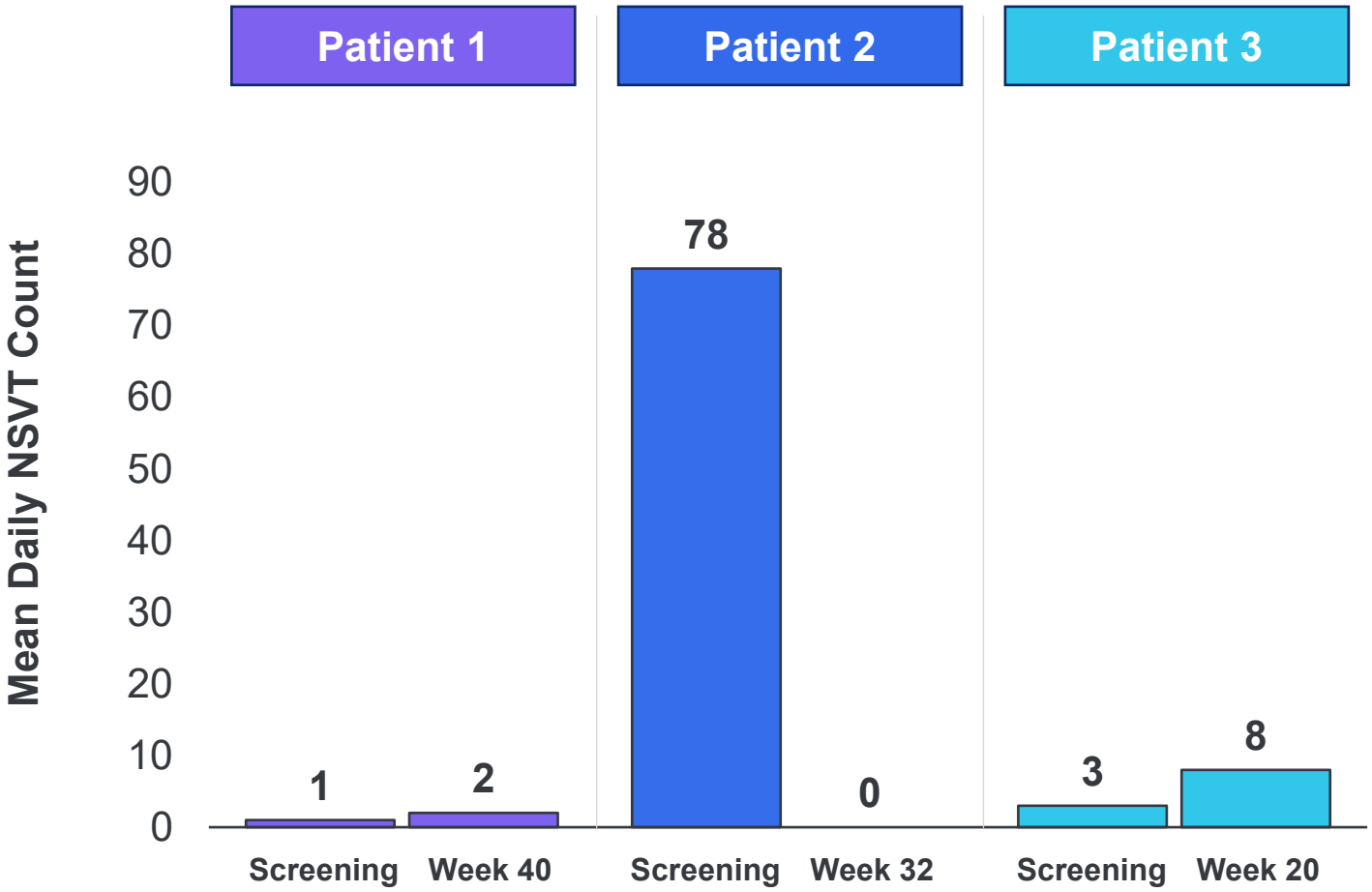
*PVC and NSVT rates calculated using counts over 7-day ambulatory monitoring period
Data cut as of October 2025

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

TENAYA THERAPEUTICS