Determining Eligibility for RIDGE-1, a Phase 1b Interventional Study to Evaluate Safety and Efficacy of TN-401 Gene Therapy in Adults with Plakophilin-2 (PKP2)-Associated Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): Interim Results of an Observational Study to Assess Seroprevalence to Adeno-Associated Virus Serotype 9 (AAV9)

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Despite medication use (including flecainide, amiodarone) and VT ablation, the majority of patients experienced 24h PVC counts ≥500, which are recognized clinical predictors of life-threatening ventricular arrythmias. The majority of patients (93%) had AAV9 neutralizing antibody (NAb) titers ≤1:40, meeting eligibility criteria for TN-401 gene therapy.

INTRODUCTION

- Mutations in plakophilin 2 (*PKP2*) gene are the leading cause of arrhythmogenic right ventricular cardiomyopathy (ARVC), accounting for ~40% of cases[1]
- Current treatments for ARVC are palliative and fail to alter disease course[2,3]
- TN-401 is an investigational AAV9-based gene therapy designed to restore the expression and function of PKP2 protein in patients with *PKP2*-associated ARVC. The first-in-human phase 1b RIDGE-1™ (NCT06228924) is actively recruiting participants
- The objectives of this Natural History study (RIDGE™ (NCT06311708) is to understand the symptomatic patient population with high arrythmia burden and definitive ARVC diagnosis who might require *PKP2*-gene therapy treatment. It is the largest retrospective natural history study of patients with *PKP2*-associated ARVC to-date with a planned enrollment of up to 200 patients. This poster describes interim results of
  - Patients' clinical characteristics and medical history
  - AAV9 seroprevalence (preexisting AAV9 neutralizing antibody (NAb) and total antibody (TAb) titers in this population

METHODS

- This exploratory, natural history and AAV9 seroprevalence study enrolled participants with *PKP2*-associated ARVC across the US and Western Europe
- Sites collected demographics information, medical history (ablation and ICD procedures, Holter monitoring data, NYHA class, MRI features, medications for arrythmia), and serum (for AAV9 pre-existing antibody assessments) from consenting participants

Inclusion criteria

- Ages 14–65 years with pathogenic or likely pathogenic *PKP2* gene mutations
- A diagnosis of ARVC meeting 2010 Modified Task Force Criteria for ARVC[4] as affected
- Functioning implantable cardioverter defibrillator (ICD)

AAV9 Neutralizing Antibody (NAb) and Total Antibody (TAb) Assay

- AAV9 neutralizing antibodies (block AAV transduction) were measured using an *in vitro* assay, where cells were exposed to AAV9 vector containing a luminescent reporter
- AAV9 total antibodies (includes neutralizing) were measured using an immunoassay
- Participants with NAb titers ≤1:40 were classified as having low pre-existing AAV9 titer and seronegative; those with higher titers were deemed seropositive

Evaluation of Demographic and Medical History Characteristics

- Participants' demographic data were collected
- Medical history included medications for arrythmia, ablation and ICD procedures, Holter monitoring data, NYHA class and MRI features.

Statistical methods

- Correlation between NAb and TAb titer was evaluated using Spearman's rank correlation; 95% CI and *P*-values were estimated using Fisher transformation
- All statistical calculations were done using R 4.4.1

RESULTS

- As of February 2025, 144 participants enrolled in this seroprevalence study of whom 85 and 59 were enrolled in the US and ex-US sites respectively
- The median age of the overall population was 42.5 years (range, 21.0 – 65.0 years)
- The majority of enrolled patients were male (56%), White (87%) and identified as not Hispanic or Latino (94%)
- Baseline disease characteristics of participants are shown in **Table 1**

RESULTS (continued)

Table 1. Baseline Disease Characteristics in *PKP2*-Associated ARVC Participants

	Overall (N=144)	US (N=85)	Ex-US (N=59)
NYHA Class, n (%)			
Class I	90 (62.5)	57 (67.1)	33 (55.9)
Class II	38 (26.4)	21 (24.7)	17 (28.8)
Class III	2 (1.4)	2 (2.4)	0 (0)
Class IV	0 (0)	0 (0)	0 (0)
Missing	14 (9.7)	5 (5.9)	9 (15.3)
Any ablation, n (%)			
Yes	58 (40.3)	47 (55.3)	11 (18.6)

- Among patients with available Holter data, more than 80% had 24h premature ventricular contraction (PVC) counts ≥500 which is an established predictor for development of malignant ventricular arrythmias and half the patients experienced ventricular tachycardia (VT). PVC counts ≥500 is an inclusion criterion to RIDGE 1 interventional study (**Table 2**)

Table 2. Summary statistics of Holter data

	Overall (N=115)		Overall (N=115)
24h PVC count category, n (%)		**Ventricular tachycardia, n (%)**	
<350	9 (7.8)	Yes	56 (48.7)
350 to <500	2 (1.7)	No	46 (40.0)
≥500	95 (82.6)	Missing	13 (11.3)
Missing	9 (7.8)		

- About 60% of patients with available data had right ventricular (RV) global dysfunction, RV regional wall motion abnormality, or late enhancement, indicators of disease progression. Interestingly, left ventricular (LV) involvement was noted in 36% of the patients with the existing data. Severe RV dysfunction, an exclusion criterion for the RIDGE 1b study was apparent in 6% of patients (**Table 3**)

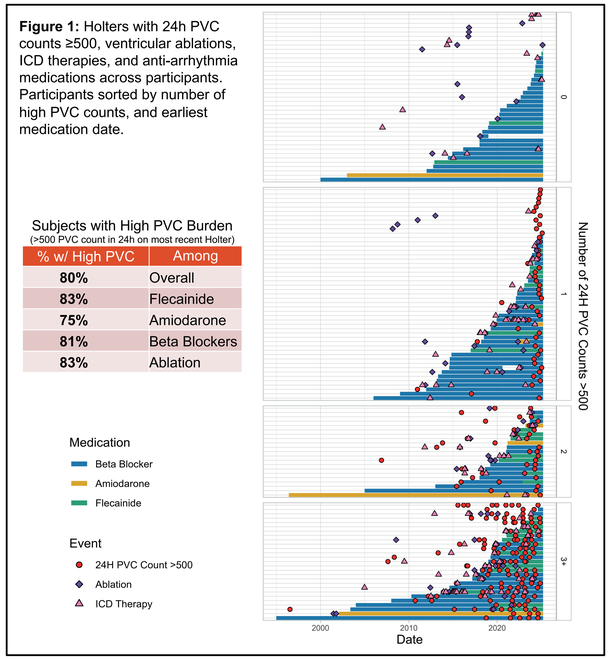
Table 3. MRI findings summary

	(N=91)		(N=91)
RV Global Dysfunction, n (%)		**Aneurysm, n (%)**	
Yes	46 (50.5)	Yes	6 (6.6)
No	30 (33.3)	No	72 (79.1)
Missing	15 (16.5)	Missing	13 (14.3)
RV Dysfunction Severity, n (%)		**RV Ejection Fraction (%)**	
No Dysfunction	30 (33.0)	Median [Q1, Q3]	43.0 [34.5, 50.0]
Mild	15 (16.5)	Missing	50 (54.9)
Moderate	15 (16.5)	**LV Involvement**	
Severe	6 (6.6)	Yes	33 (36.3)
Missing	25 (27.5)	No	7 (7.7)
		Missing	51 (56.0)
RV Regional Wall Motion Abnormality, n (%)		**RV or LV Late Enhancement, n (%)**	
Yes	53 (58.9)	Yes	26 (28.6)
No	25 (27.8)	No	23 (25.3)
Missing	13 (14.3)	Missing	42 (46.2)
Akinesia or dyskinesia, n (%)		**Fatty Infiltration, n (%)**	
Yes	34 (37.4)	Yes	19 (21.1)
No	44 (48.4)	No	42 (46.2)
Missing	13 (14.3)	Missing	30 (33.3)

RESULTS (continued)

- Despite medication use (including flecainide, amiodarone) and VT ablation, the majority of patients experienced 24h PVC counts ≥500, which are recognized clinical predictors of life-threatening ventricular arrythmias (**Fig 1**)

Figure 1: Holters with 24h PVC counts ≥500, ventricular ablations, ICD therapies, and anti-arrhythmia medications across participants. Participants sorted by number of high PVC counts, and earliest medication date.



- **T-wave inversions**, especially in V1–V3, are common (~65%), confirming repolarization abnormalities in this cohort. T-wave inversion in V4–V6 in 39% of patients confirm LV involvement which correlates with MRI findings. It's likely that the same 14 patients had both prolonged TAD and prolonged QRS, confirming fibrofatty replacement and conduction system disruption in these patients **(Table 4)**

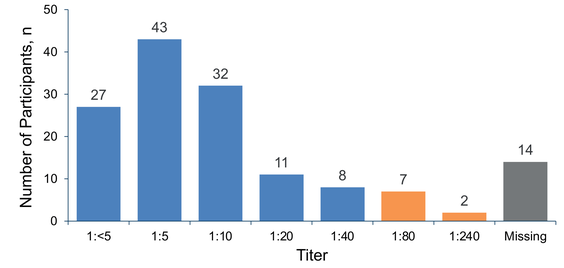
Table 4. Summary of ECG findings

	Overall (N=125)		Overall (N=125)
T-Wave Inversion in V1–V3		**Terminal Activation Duration ≥55 ms**	
Yes	81 (64.8%)	Yes	14 (11.2%)
No	21 (16.8%)	No	57 (45.6%)
Missing	23 (18.4%)	Missing	54 (43.2%)
T-Wave Inversion in V4–V6		**QRS Prolongation (≥110 ms)**	
Yes	49 (39.2%)	Yes	27 (21.6%)
No	53 (42.4%)	No	97 (77.6%)
Missing	23 (18.4%)	Missing	1 (0.8%)

RESULTS (continued)

- Interim analyses indicate that 121 of 130 (93%) of *PKP2*-associated ARVC participants had AAV9 NAb titers ≤1:40 seroprevalence (**Fig 2**)

Figure 2: Histogram of Participant Count by Pre-Existing AAV9 NAb titer



- TAb and NAb titer were strongly correlated (Spearman coefficient = 0.60; $P \leq 0.001$) supporting the utility of either assay as a reliable measure of pre-existing immunity

CONCLUSIONS

- **RIDGE** is the **largest natural history study** of patients with *PKP2*-associated ARVC, enrolling up to 200 participants
- **Interim data** reveal a **high burden of arrhythmias** on Holter monitoring and **progressive structural disease** on cardiac MRI, even with conventional therapies
- **80%** of patients have ≥500 PVCs per 24h, a threshold linked with increased risk of malignant ventricular arrhythmias despite **standard-of-care** including flecainide, amiodarone, VT ablation, and beta-blockers
- **AAV9 Seroprevalence**: 93% of patients show **AAV9 neutralizing antibody (NAb) titers ≤1:40**, meeting eligibility criteria for TN-401 gene therapy
- RIDGE study indicates that **67% of patients** with **PVC burden ≥500/24h and RV/LV structural abnormalities** (per 2010 Task Force Criteria) and **93% of patients** with **AAV9 NAb titers ≤1:40** are **potentially eligible** and may benefit from participation in the **RIDGE-1 trial** evaluating **TN-401**, an investigational AAV9-based gene therapy designed to restore PKP2 function

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