ACC.26

Safety and Preliminary Efficacy of AAVrh.10hPKP2 (LX2020) Gene Therapy in *PKP2*-Arrhythmogenic Cardiomyopathy

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On behalf of the HEROIC-PKP2 investigators

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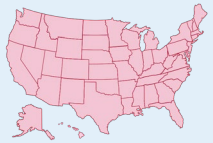
Arrhythmogenic Cardiomyopathy Caused by Mutations in the *PKP2* Gene: Devastating Genetic Heart Disease With Clearly Defined Mechanism

PKP2-ACM is a **rare, genetic cardiac disease** caused by loss of function variants in the *PKP2* gene and is the most common cause of ACM

Progressive replacement of cardiac muscle with fatty fibrotic tissue, with an **increased risk of ventricular arrhythmias and sudden cardiac death (SCD)**[1][2]

Approximately 23% of individuals present with **SCD.** Patients suffer from symptomatic arrhythmia, significant **anxiety and reduced quality of life**[3][4]

ICDs are common, but ongoing arrhythmias, appropriate and inappropriate shocks necessitate escalating anti-arrhythmic therapies. There are **no proven medical therapies** that reverse or halt progression the of ACM to end stage arrhythmia or heart failure[2][3]



~60,000

individuals affected by PKP2-ACM in the U.S.

23%

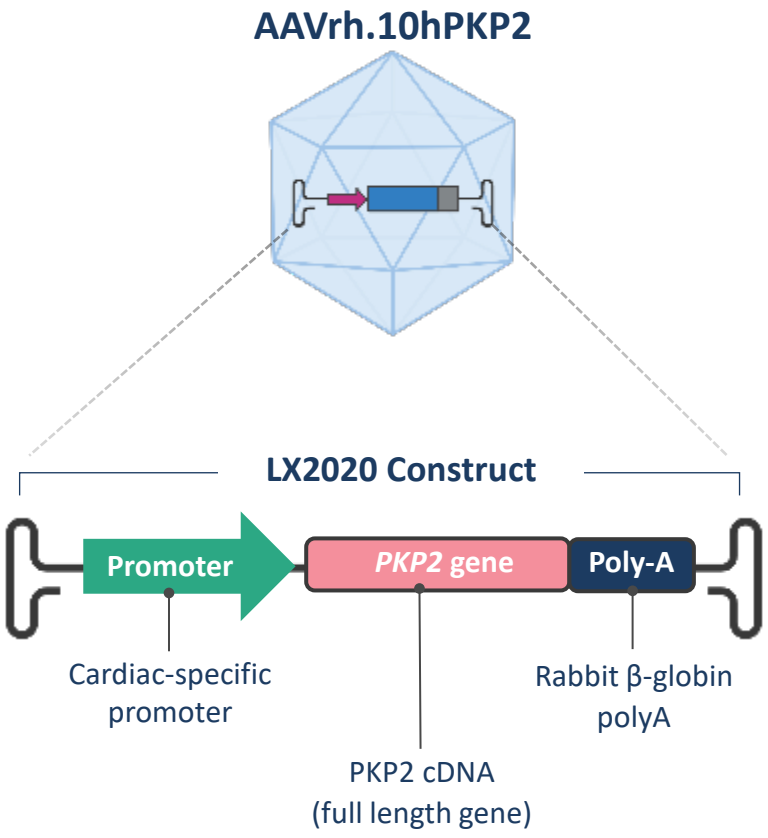
individuals present with SCA/D

Current management methods do not halt or reverse the progression of ACM

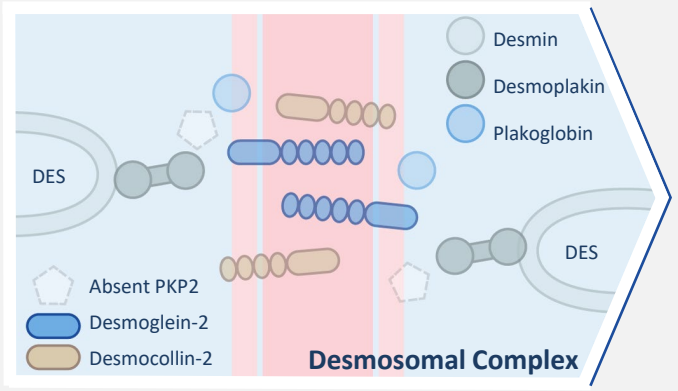
ACM, arrhythmogenic cardiomyopathy; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; ICD implantable cardioverter defibrillator; SDC sudden cardiac death.

(1) Cedars-Sinai ARVC overview. (2023). (2) Corrado et al. (2017). (3) Dalal et al. (2005). (4) Day, Circulation: Cardiovascular Genetics (2012).

LX2020 Delivers a Full-Length *PKP2* to Cardiomyocytes, Restoring the Desmosome

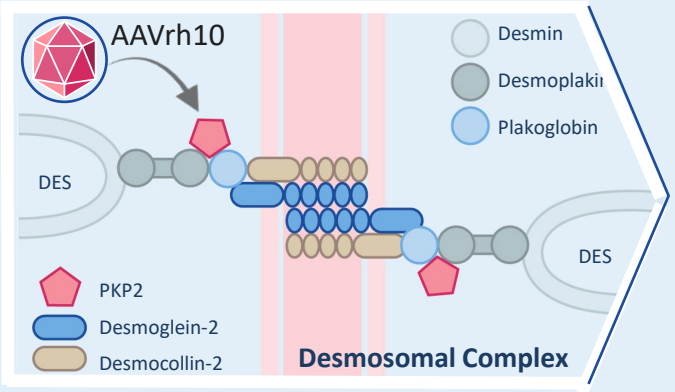


PKP2-ACM



Absence of PKP2 results in impairment of cardiac desmosomes, leading to slow conduction, abnormal cardiac rhythms (arrhythmias) and onset of cardiac dysfunction

LX2020 Mechanism



PKP2 expression **is expected to restore the balance of desmosomal proteins** by scaffolding adjacent cell-cell junctional proteins

The restoration of PKP2 may lead to **improvement in cardiac electrical and mechanical function** as well as **prevent further structural damage**

Phase 1/2 Study of LX2020 for *PKP2*-ACM: *HEROIC-PKP2*

1 Study Design & Objective

Design:
52-week open-label study with a **4-year** long term follow up

Objective:
To assess the **safety** and **efficacy** of LX2020 in individuals with PKP2-ACM

52-Week

Cohort 1
n=3
2.0x10^{13} vg/kg
Fully Enrolled

Cohort 2
n=3
6.0x10^{13} vg/kg
Fully Enrolled

Cohort 3
n=4
6.0x10^{13} vg/kg
Fully Enrolled

2 Key Inclusion Criteria

- Adults (18-65 years)
- Diagnosis of ACM with documented *PKP2* mutation
- Existing ICD that is MRI compatible and minimum threshold of PVCs / 24-hr
- Neutralizing anti-AAVrh.10 titer cutoff

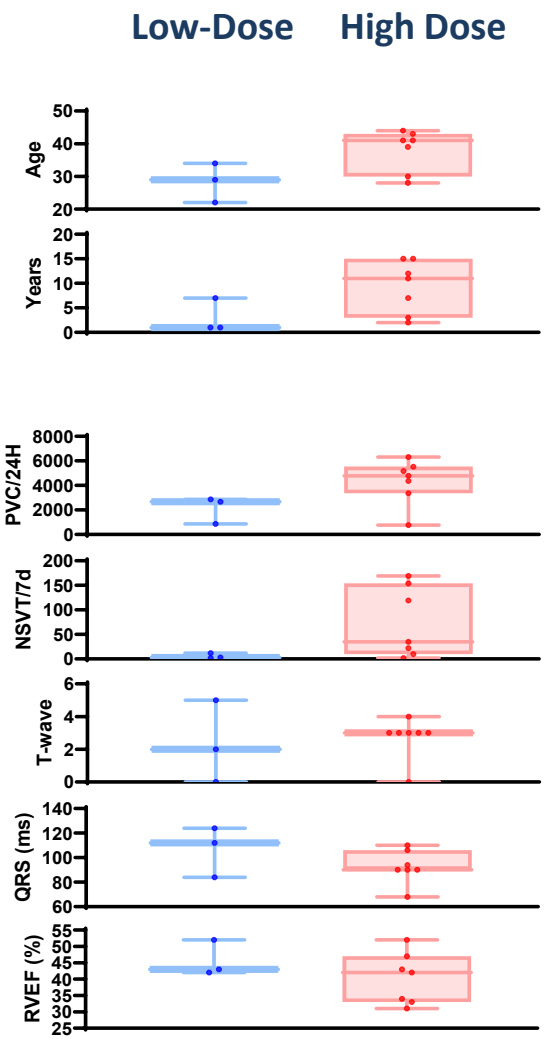
3 Key Measurements

- Ventricular arrhythmias and associated measures (PVC, VT, QRS, T-wave inversion)
- Cardiac Structure & Function (EF, EDV, ESV)
- Change in Symptoms (NYHA Class and PROs)
- Vector Transduction / Expression (VCN, mRNA, quantitative WB)

ICD, implantable cardioverter defibrillator; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; NYHA, New York Heart Association; PROs, patient reported outcomes; VCN, vector copy number; WB, western blot.
Note: LX2020 is administered systemically; participants receive immune suppression with prednisone and sirolimus on the day prior to treatment through ~12 weeks following LX2020 dosing.

Baseline Participant Characteristics: More Advanced Disease in High-Dose Cohorts

Characteristic	Statistic	Low-Dose Cohort 1 $2.0x10^{13}$ vg/kg, N=3	High Dose Cohorts 2 and 3 $6.0x10^{13}$ vg/kg, N=7
Age, years	Mean (SD) Min, Max	28 (6) 22, 34	38 (6.4) 28, 44
Years since diagnosis	Mean (SD) Min, Max	3 (3.5) 1, 7	9 (5.4) 2, 15
Male	N (%)	3 (100%)	3 (43%)
PVC, mean count per 24 hours	Mean (SD) Min, Max	2130 (1103) 861, 2859	4329 (1819) 774, 6309
NSVT, total / 7 days	Mean (SD) Min, Max	6 (5.2) 2, 12	73 (71.6) 2, 169
T-wave inversion, leads	Mean (SD) Min, Max	2 (2.5) 0, 5	3 (1.2) 0, 4
QRS duration, milliseconds	Mean (SD) Min, Max	107 (20.5) 84, 124	93 (13.6) 68, 110
RV Function (%)	Mean (SD) Min, Max	46 (5.5) 42, 52	40 (7.9) 31, 52
NYHA class	Class I (%) Class II (%)	2 (67%) 1 (33%)	7 (100%) 0 (0%)



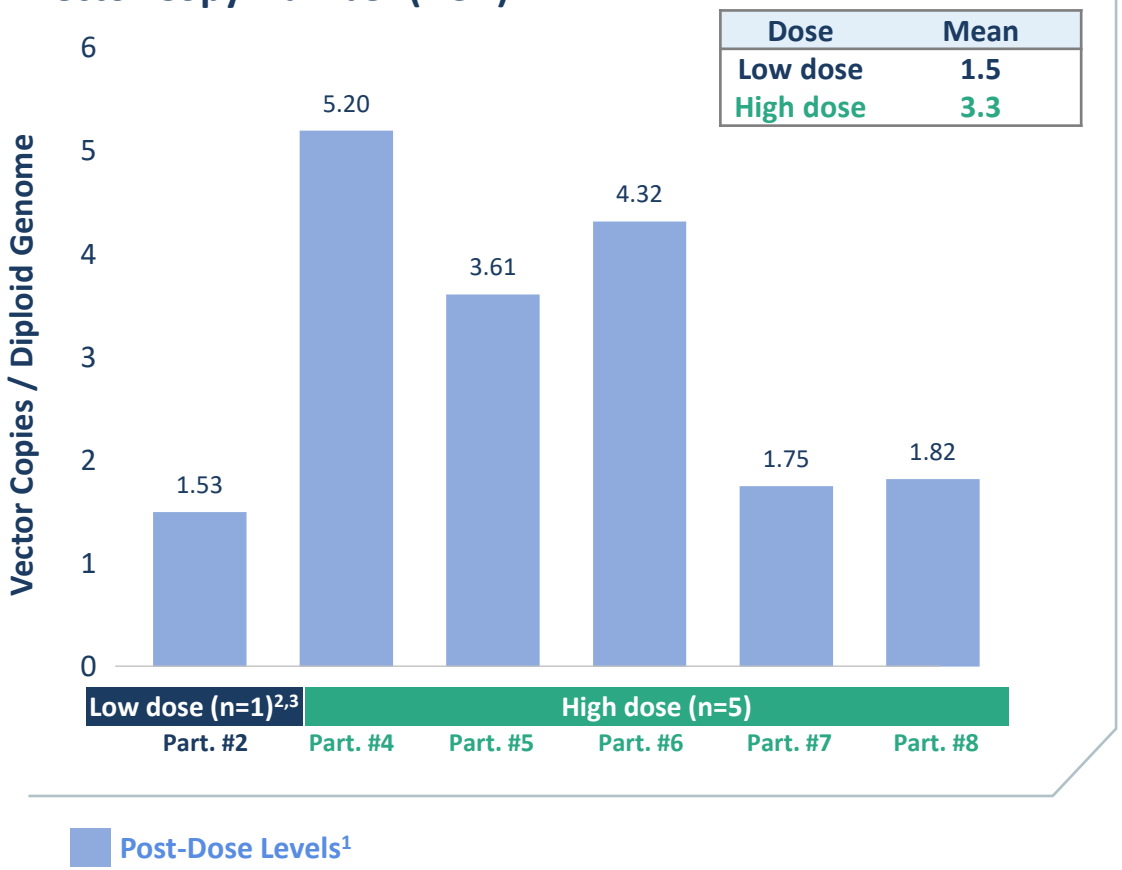
Treatment with LX2020 Well-Tolerated

10 Participants Dosed

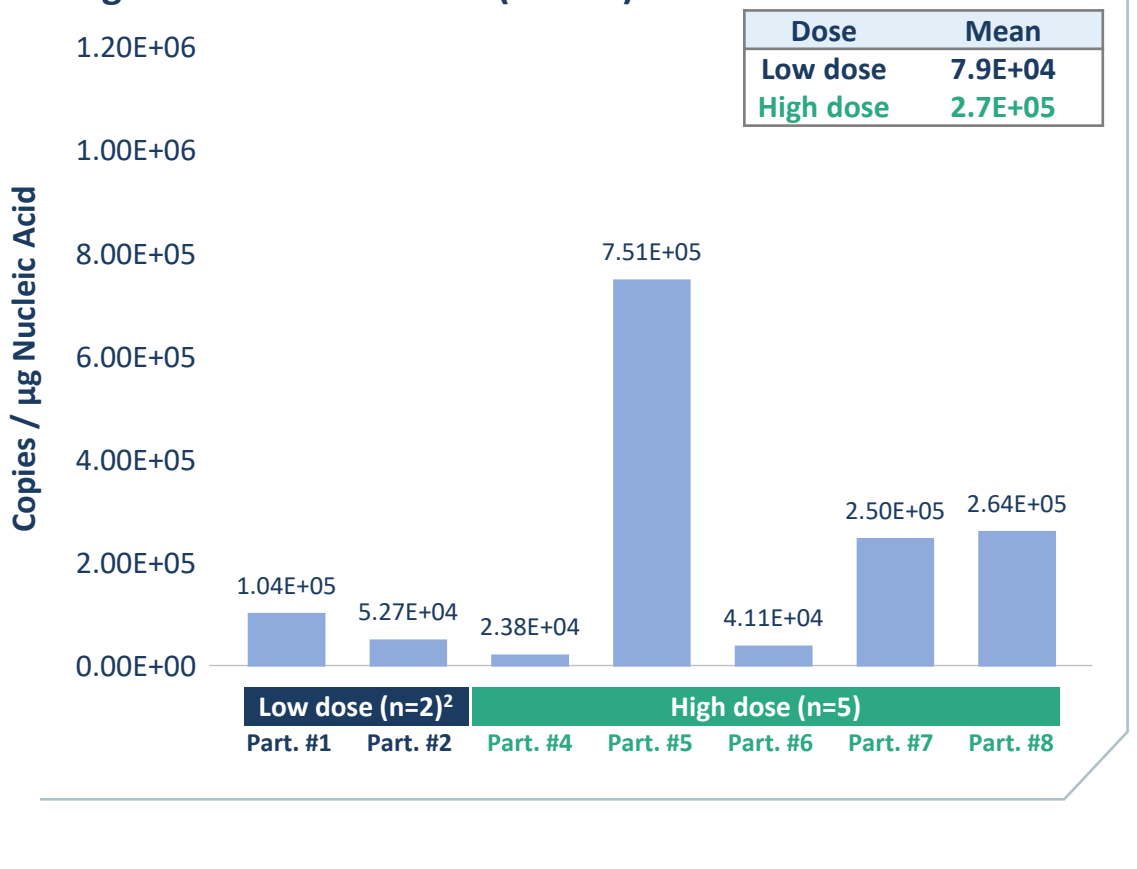
- No clinically significant complement activation
- Elevations in **liver function tests (LFT)** observed in 7 participants at the high-dose
  - **Treated successfully** with modified immunosuppression per the trial protocol
    - 5 elevations followed steroid tapering resolved with re-introduction of low-dose prednisone
    - 2 elevations occurred prior to steroid tapering and resolved with increased prednisone and sirolimus doses
- No participants discontinued from study
- One previously disclosed Grade 3 serious adverse event
  - Sustained VT 3 months after dosing in 1 participant in high dose cohort, assessed as possibly treatment related
  - Participant was successfully treated with anti-arrhythmic medication and discharged with no additional intervention required

LX2020 *PKP2* Payload Delivery Observed in All Participants

Vector Copy Number (VCN)



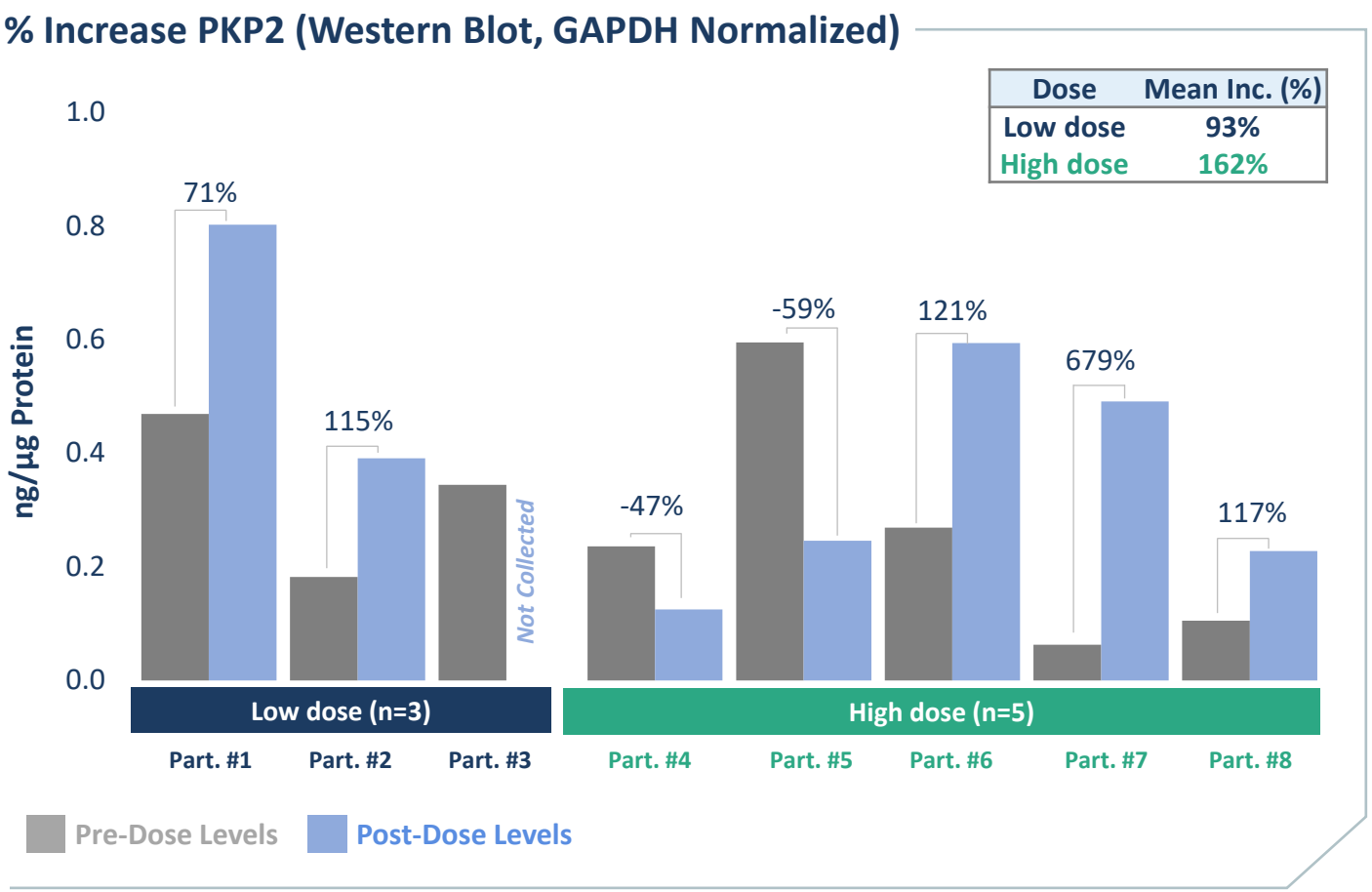
Exogenous PKP2 Increase (mRNA)



Post-Dose Levels[1]

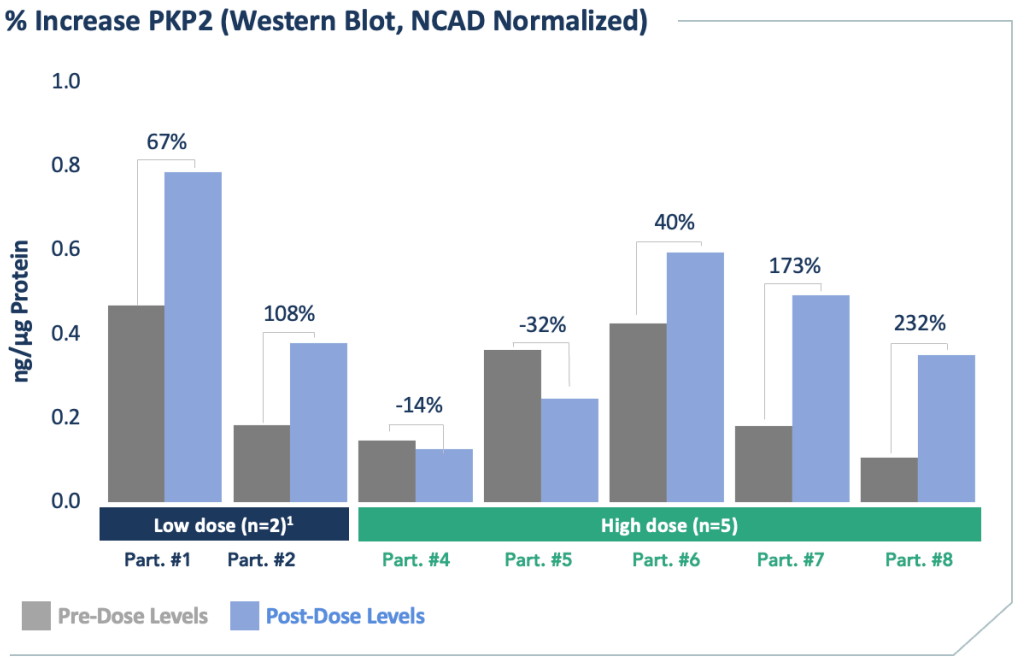
LX2020 not detected in pre-dose VCN or mRNA samples as expected.
Participant 3 elected not to undergo a post-treatment biopsy.
Participant 1 VCN not performed due to insufficient remaining cardiac biopsy tissue following other analyses.

Increased PKP2 Protein Observed Across Participants



- PKP2 expression increased across participants with greater mean response at high dose
- Heterogeneity of cardiac tissue composition may impact biopsy results

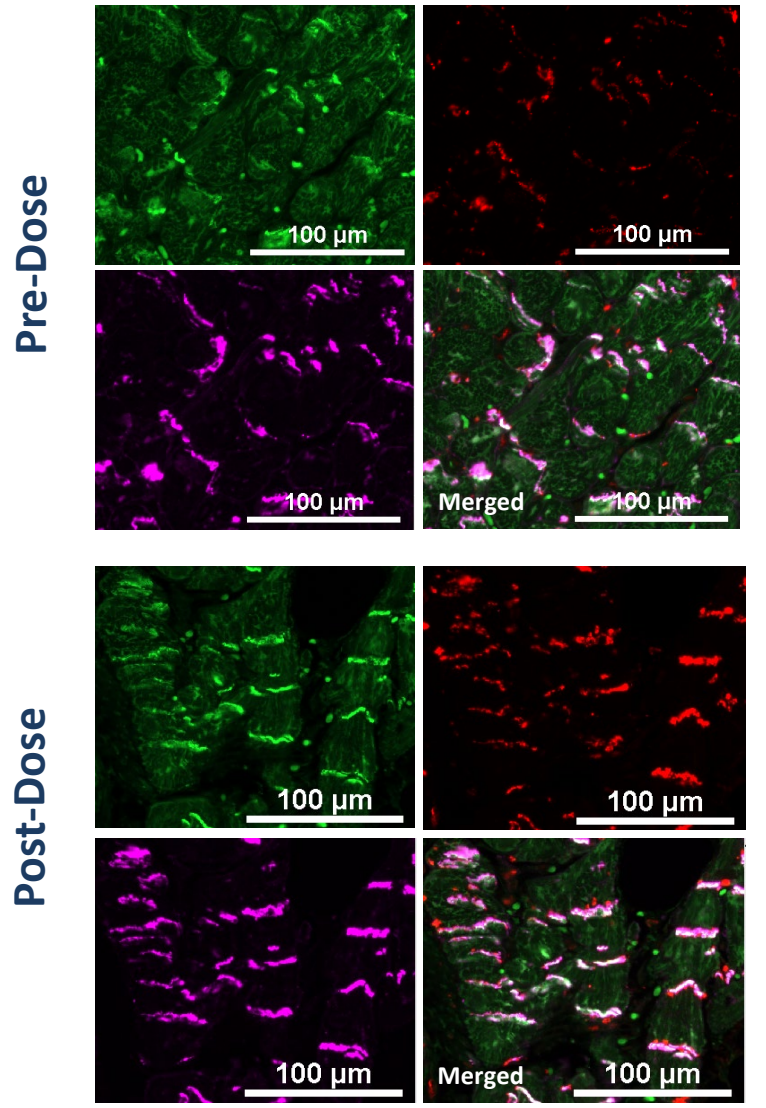
Cardiac-specific normalization reduces variability across samples; Appropriate intracellular localization of PKP2 protein



1. Participant 3 elected not to undergo a post-treatment biopsy.

Normalization to a cardiac-specific intercalated disc marker (NCAD) reduces variability of change in PKP2 protein level

Participant 4



PKP2 protein localizes appropriately to the desmosome in cardiomyocytes

Clinical outcomes at most recent follow up

Cohort	Part. #	Latest Visit (months)	Δ PVC / 24H Baseline → LV	Δ NSVT/7d Baseline → LV	Δ RVEF[2] Baseline → LV	Δ PGIC Scale[3] Baseline → LV
Cohort 1 (2E13 vg/kg)	#1 (M)	**12**	**861 → 345** -60%	**2 → 2** 0%	**43 → 42** -2%	**3 → 3**
	#2 (M)	**12**	**2859 → 3569** +25%	**3 → 1** -63%	**52 → 49** -6%	**3 → 3**
	#3 (M)[1]	**12**	**2669 → 4795** +80%	**12 → 20** +69%	**42 → 41** -2%	**3 → 4**
	Mean		**+36%**	**+35%**	**-3%**	**2/3 no change**
Cohort 2 & Cohort 3 (6E13 vg/kg)	#4 (M)	**9**	**4788 → 5601** +17%	**169 → 44** -74%	**31 → 40** +29%	**3 → 2**
	#5 (F)	**9**	**3362 → 3451** +3%	**22 → 18** -18%	**34 → 33** -3%	**3 → 2**
	#6 (F)	**6**	**5176 → 4814** -7%	**119 → 199** +67%	**33 → 32** -3%	**3 → 2**
	#7 (F)[1]	**6**	**4362→4163** -5%	**154 → 98** -36%	**42→ 40** -5%	**3 → 3**
	#8 (F)	**6**	**6309 → 2532** -60%	**2 → 4** +100%	**52→ 47** -10%	**3 → 1**
	Mean		**-14%**	**-22%**	**+2%**	**4/5 improved**

RVEF assessed by cardiac MRI at 6- and 12-months only; RVEF data for participants 4 and 5 from 6-month visit.
Patient Global Impression of Change (PGIC) 5-point scale, patient-reported outcome; 3 represents no change from baseline, 1 represents significant improvement, 5 represents significant worsening per patient perception.

Summary of Results and Next Steps for LX2020

- LX2020 generally well tolerated with resolved elevations in LFTs
- One episode of sustained VT three months post therapy expected in this ACM population
- Robust LX2020 transduction and dose-dependent increases in PKP2 mRNA and protein expression at 3 months after dosing
- Clinical signal at most recent follow up in high-dose cohort is encouraging
  - NSVT reduced or stable in majority of participants
  - PVCs and EKGs with no clinically significant changes across participants
  - Symptoms overall improved
- Complete 1 year follow up data for cohorts 2 and 3 projected to be available Q4 2026

Thank You

- **Patients and families** whose participation made this research possible
- The **HEROIC-PKP2 investigators and study teams** at each participating institution