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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.



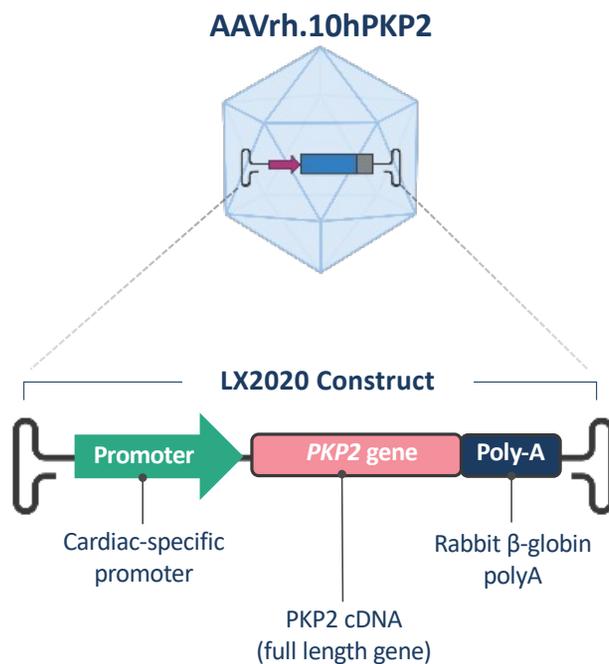
23%

individuals present
with SCA/D

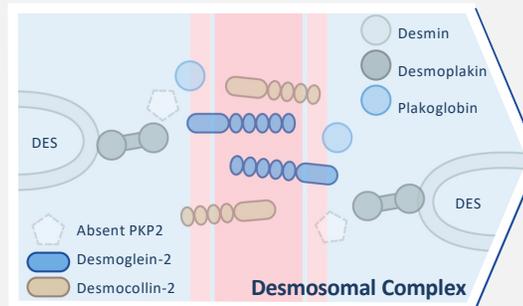
Current management methods do not halt or reverse the progression of ACM

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).

LX200 Delivers a Full-Length *PKP2* to Cardiomyocytes, Restoring the Desmosome

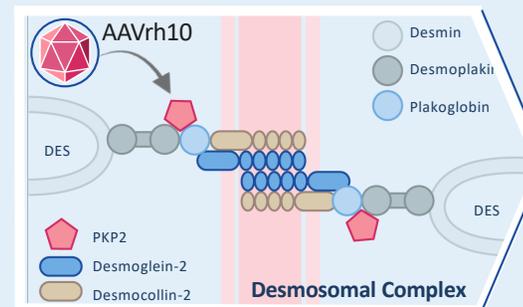


PKP2-ACM



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

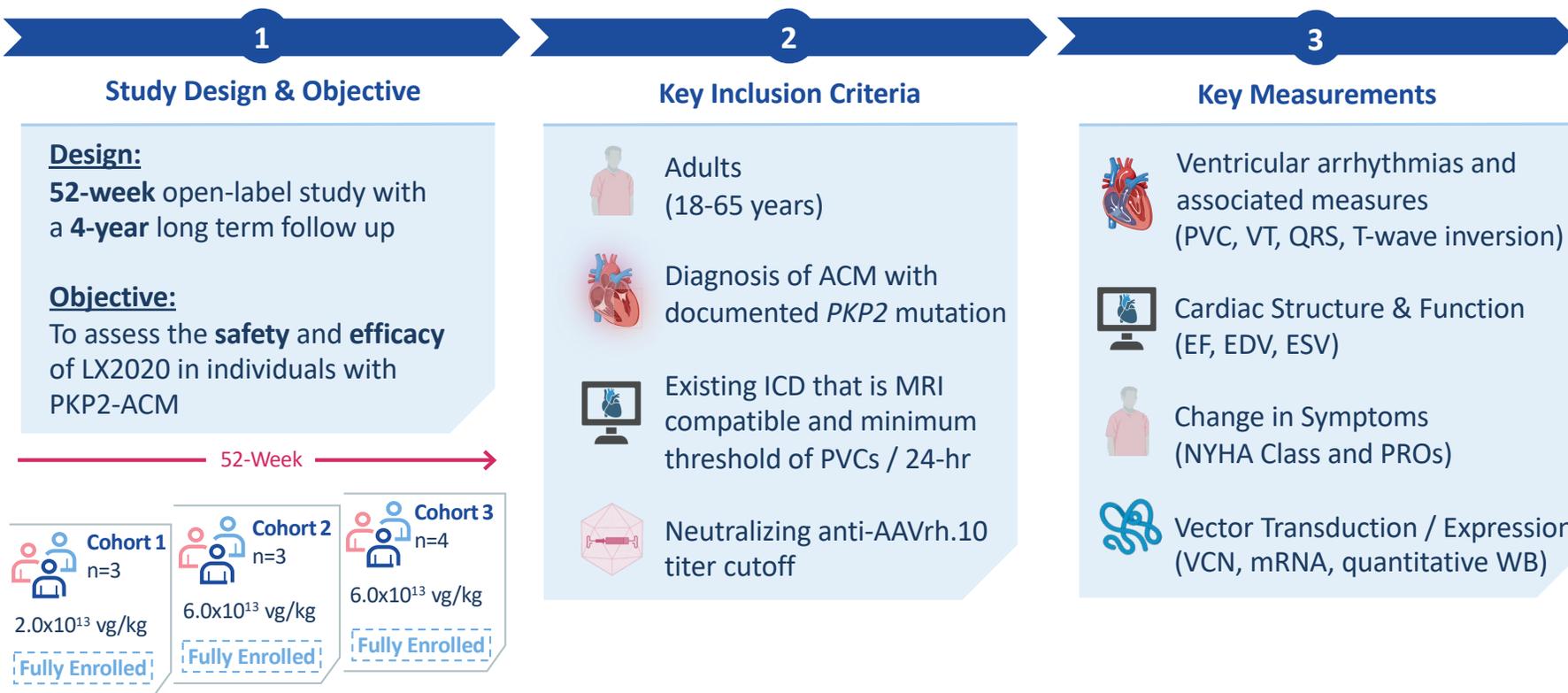
LX200 Mechanism



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**



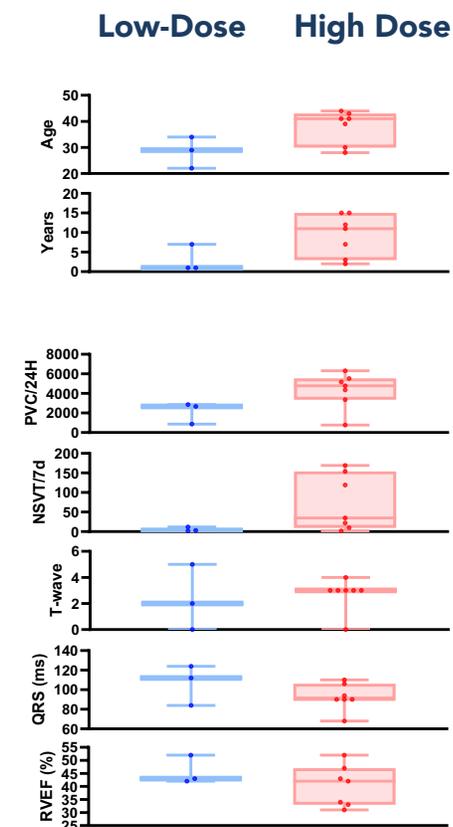
ICD, implantable cardioverter defibrillator; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; NYHA, New York Heart Association; PROs, patient reported outcomes; VCN, vector copy number; WB, western blot.

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%)



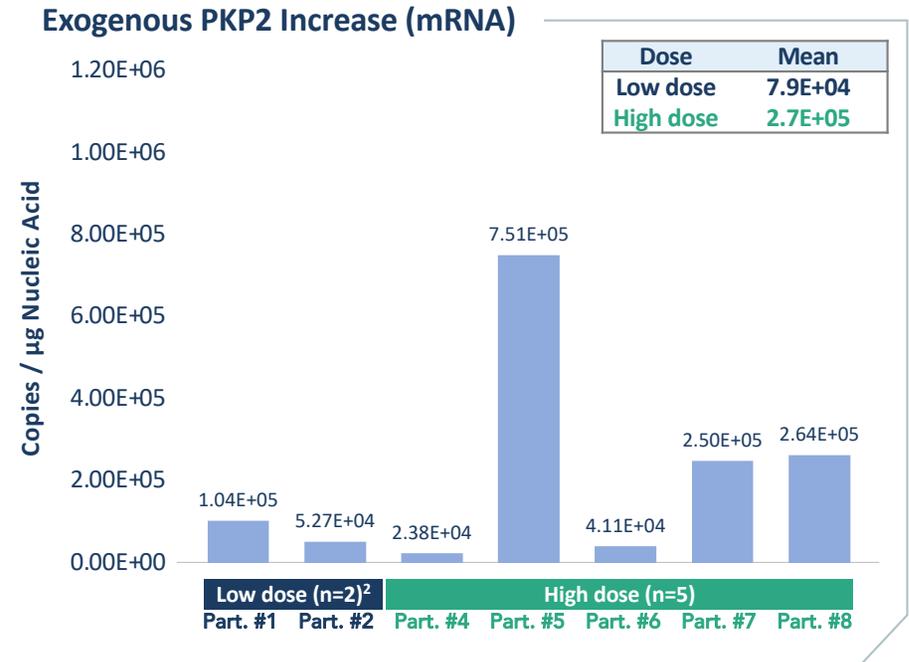
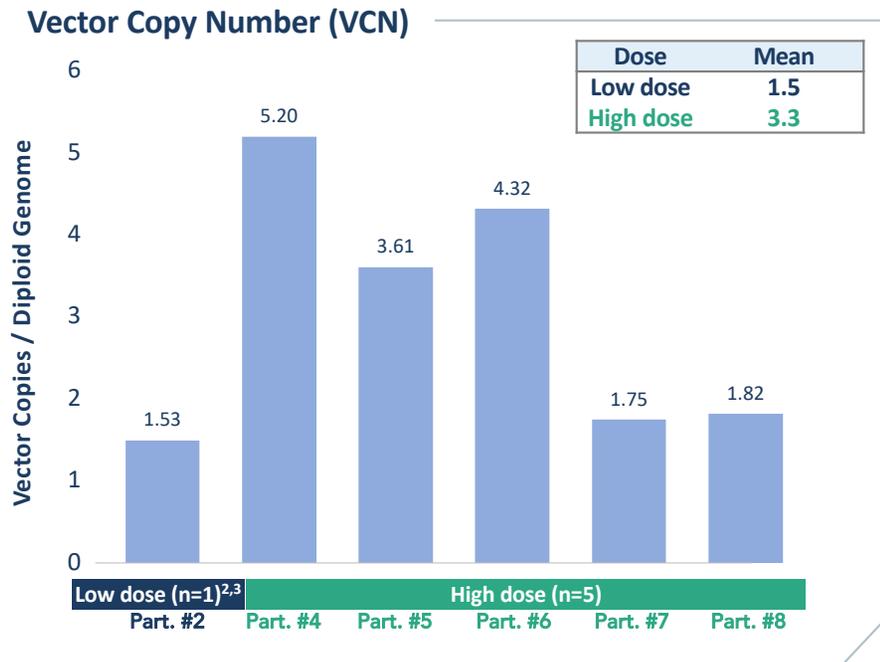
Treatment with LX2020 Well-Tolerated



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



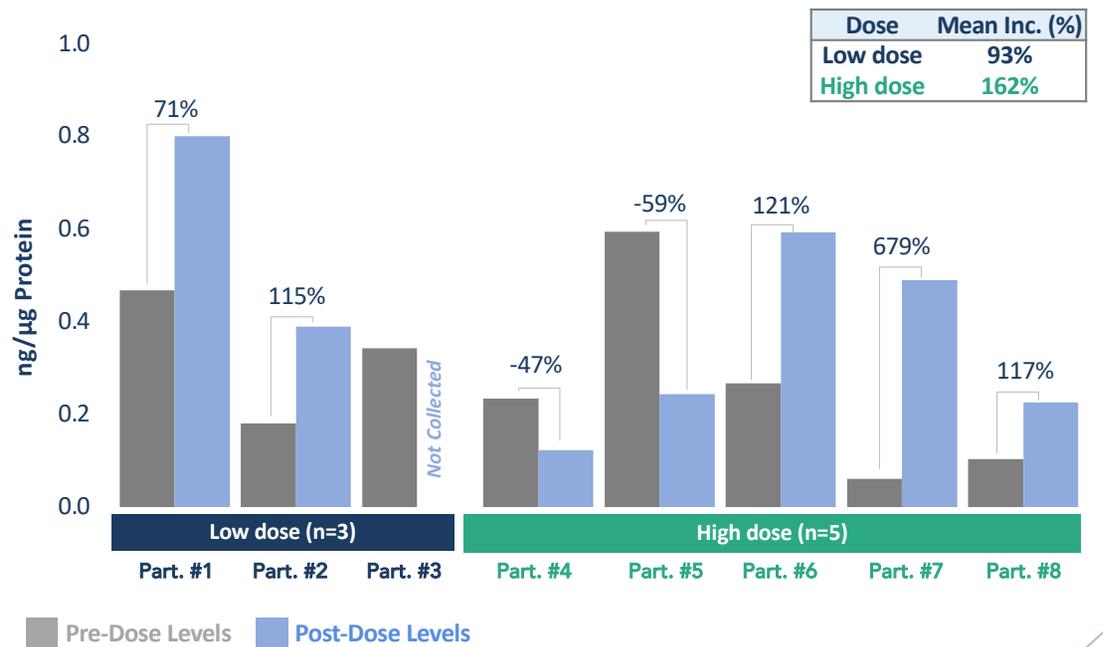
■ Post-Dose Levels¹

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

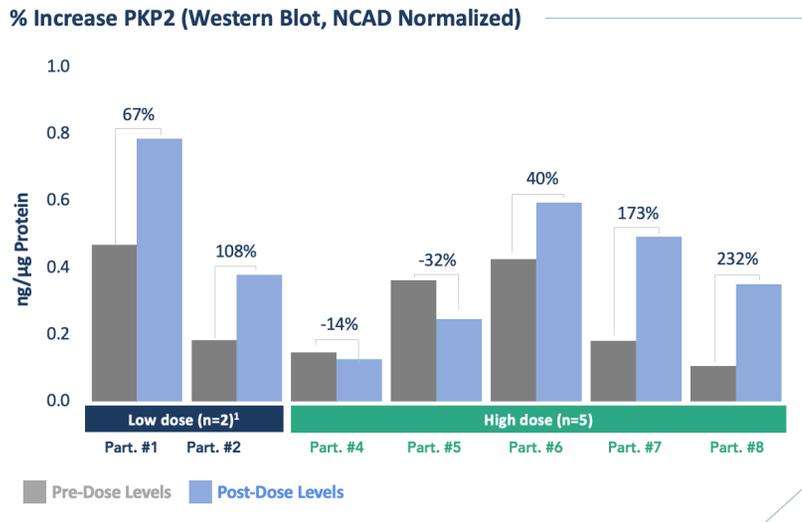


% Increase PKP2 (Western Blot, GAPDH Normalized)



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

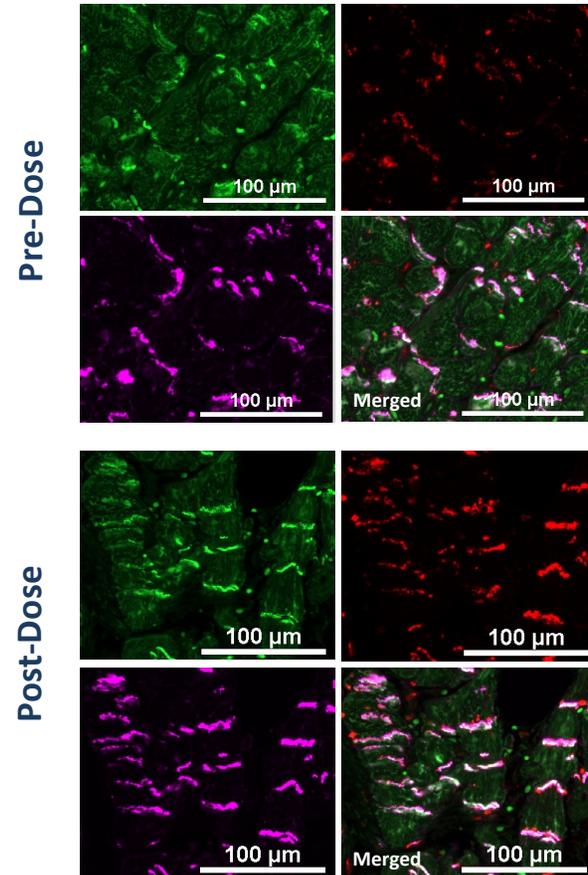
Cardiac-specific normalization reduces variability across samples; Appropriate intracellular localization of PKP2 protein



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



Plakophilin-2 (PKP2)
 Connexin 43 (Cx43)
 N-cadherin (Ncad)
 Merged

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

