

Assessing clinically meaningful arrhythmias in PKP2 arrhythmogenic cardiomyopathy (ACM)

October 21, 2026



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PKP2-associated arrhythmogenic cardiomyopathy is a progressive genetic heart disease with significant unmet need



Disease overview

- Rare, genetic cardiac disease
- Caused by loss of function mutations in the *PKP2* gene
- Progressive replacement of cardiac muscle with fatty fibrotic tissue^{1,2}
- ~60,000 affected in the U.S.



Cardiac impact

- Disrupted electrical signaling → **ventricular arrhythmias and sudden cardiac death (SCD)**^{1,2}
- ~23% of individuals present with SCD^{3,4}
- Progressive disease associated with **reduced quality of life**^{3,4}



The unmet need

- **No therapies address the underlying genetic cause of ACM**
- Current management focuses on symptom control and SCD prevention (e.g., ICDs)^{2,3}
- Disease progression continues despite intervention

PKP2-ACM has a clearly defined genetic cause alongside progressive, potentially life-threatening cardiac consequences, with no disease-modifying therapy today

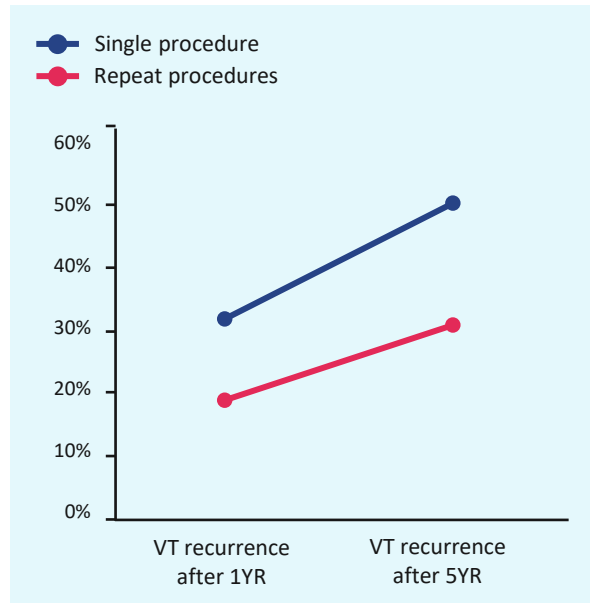
ACM, arrhythmogenic cardiomyopathy; ICD, implantable cardioverter defibrillator; PKP2, Plakophilin-2; SCD, sudden cardiac death.

Sources: (1) Cedars-Sinai, 2023, Accessed from: <https://www.cedars-sinai.org/health-library/diseases-and-conditions/a/arrhythmogenic-right-ventricular-dysplasia.html>.

(2) Corrado, D., et al. Cir Res, 2017;121:784-802; (3) Dalal, D. et al. Circulation, 2005;112:3823-3832. (4) Day, S.M., Circ: Cardiovasc Genet, 2012;5(1):2-4.

Current therapies may help manage arrhythmias, but limitations in durability, efficacy & tolerability leave a significant unmet need

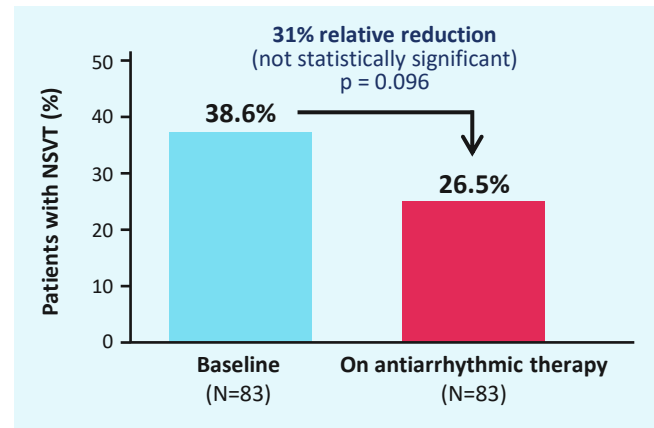
Severe arrhythmia recurrence common after ablation



50% VT recurrence reported within 5 years after a single procedure¹

Limited reduction in NSVT burden with available drugs

Effect of antiarrhythmic therapy flecainide on NSVT in PKP2-ACM population
Largest available dataset²



~39% of those with PKP2-ACM experienced NSVT prior to treatment, and ~27% continued to experience NSVT after treatment (31% relative reduction)

Safety and tolerability may limit long-term use of AADs*

- Flecainide may increase the risk of **proarrhythmia and conduction abnormalities**
- Amiodarone is associated with **pulmonary, thyroid, hepatic, ocular, and dermatologic toxicities**, particularly with long-term use
- Chronic use may require **ongoing safety monitoring and treatment modification**
- Existing therapies are not approved for ACM and are used off label

Existing therapies may reduce arrhythmia burden but overall efficacy in PKP2-ACM may be limited and certain AADs present tolerability concerns

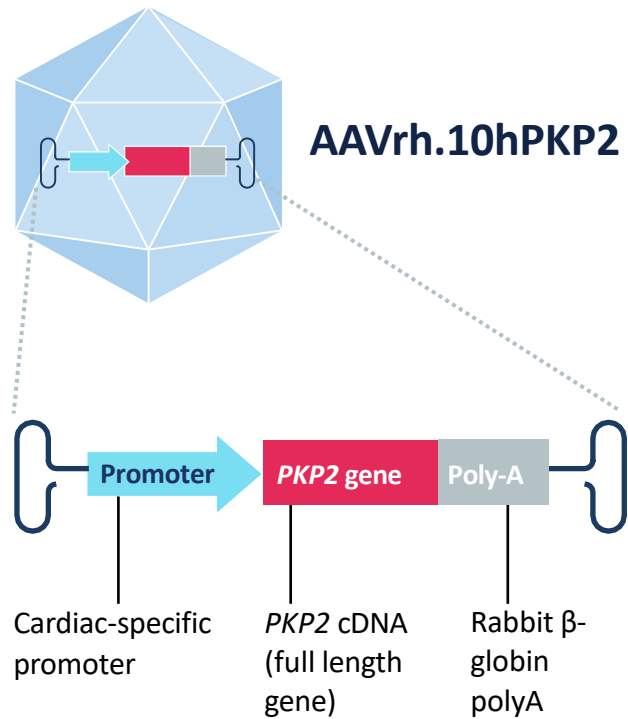
Importantly, no existing therapies address the underlying genetic cause of ACM; Disease progression continues despite intervention

*AAD = anti-arrhythmia drugs

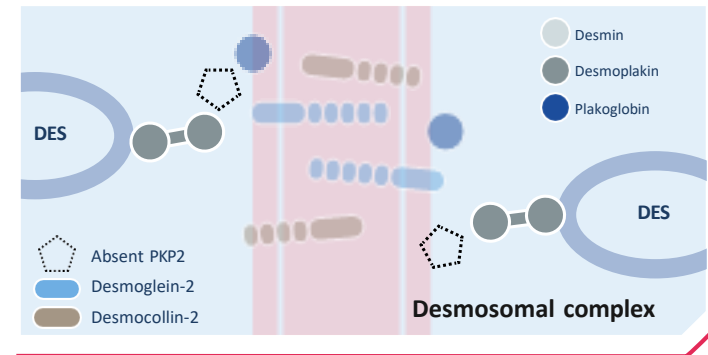
Sources: (1) Daimee et al 2021 n=166. (2) Gaine et al. 2025, N=83

LX200 delivers a full-length PKP2 gene to cardiomyocytes, restoring the desmosome

LX200 construct:

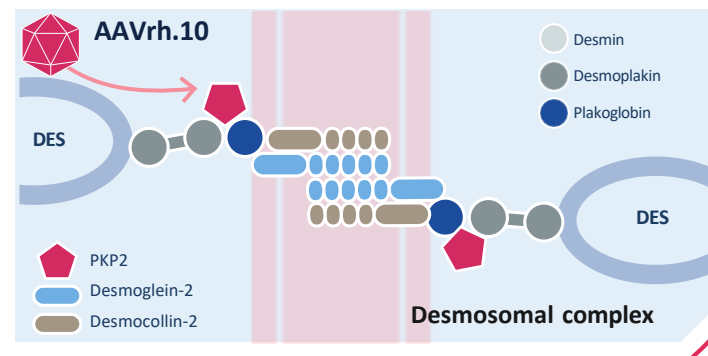


PKP2-ACM:



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

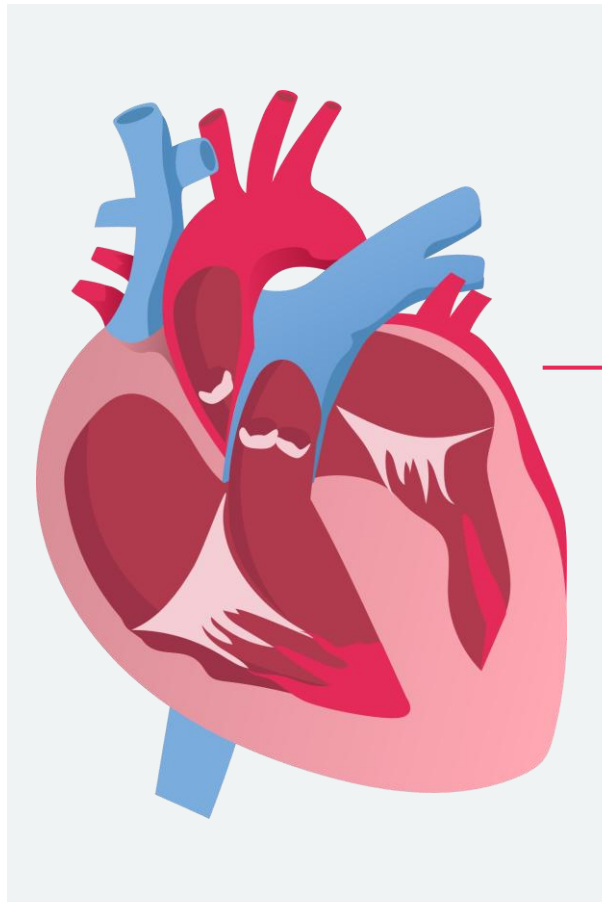
LX200 mechanism:



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 **inhibit further structural damage**

Treatment response in PKP2-ACM may be reflected across complementary measures of disease activity



Arrhythmic activity

- PVC burden
- NSVT burden
- Sustained VA / ICD shocks

May evaluate **duration, frequency and proportion of patients** experiencing events



Myocardial structure & function

- Right ventricular ejection fraction (RVEF)
- RV size and volumes
- Myocardial strain / contractility

Improvements in muscle contractility may precede RV functional improvements due to existing scar tissue



Patient & clinical burden

- Patient-reported outcomes
- Treatment escalation (changes in AADs, ablation, transplant)

Despite current care, significant negative impact on patient quality of life

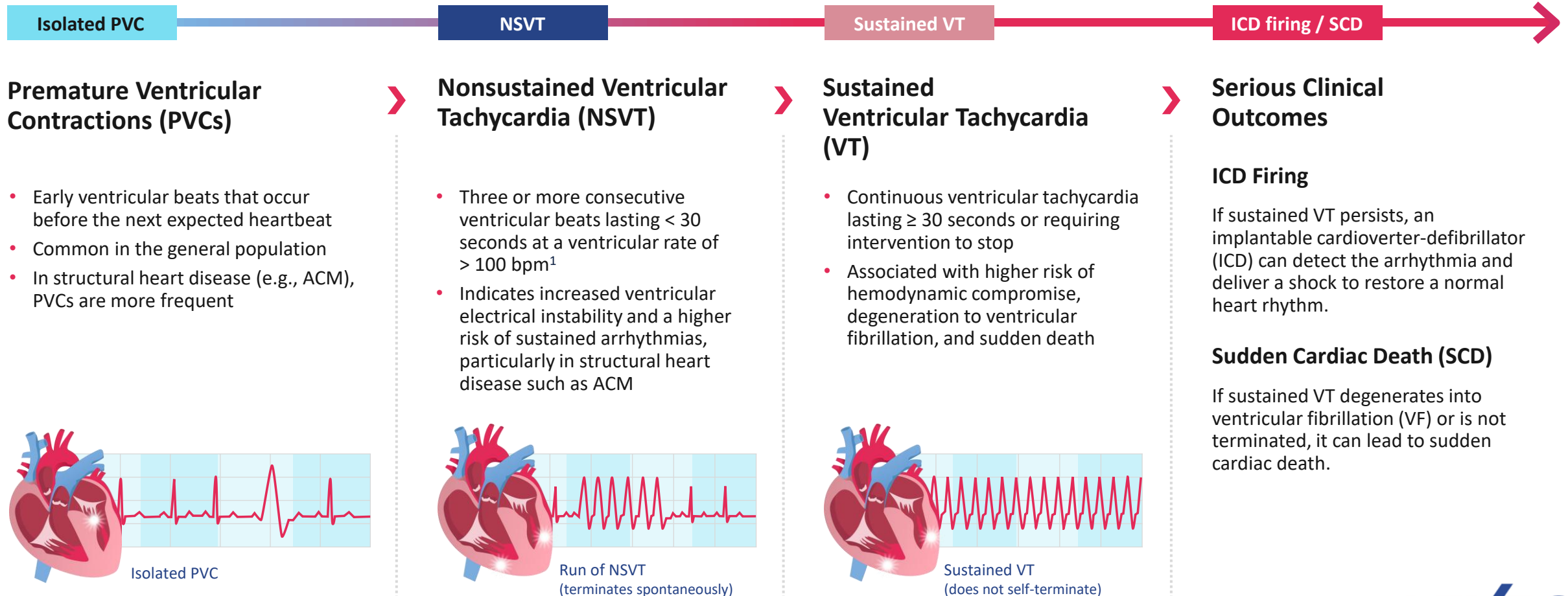
Measurements of arrhythmia and function have been assessed within individuals and across ACM populations

ACM, arrhythmogenic cardiomyopathy; ICD, implantable cardioverter defibrillator; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; RVEF, right ventricular ejection fraction; VA, ventricular arrhythmia.

Sources: (1) Cadrin-Tourigny J, et al. Eur Heart J. 2019;40(23):1850-1858. (2) Gasperetti A, et al. JAMA Cardiol. 2022;7(4):378-385; (3) Elias Neto J, et al. Arq Bras Cardiol. 2019;112(1):91-103; (4) Wang W, et al. Europace. 2019;21(1):9-21.

Ventricular arrhythmic activity exists along a spectrum of increasing complexity and clinical consequence

Increasing Arrhythmic Risk



PVC burden and NSVT provide complementary information

Attribute	PVC	NSVT
Represents ventricular electrical activity	●●	●●
More prevalent in patients with ACM	●●	●
Demonstrates presence and activation of a re-entrant circuit	—	●●
Reflects greater arrhythmic complexity	—	●●
Associated with clinical outcomes (ICD shocks, SCD) ¹	●	●●
Established role in ACM risk assessment	●	●●
Susceptible to external factors (exercise, caffeine, etc.)	●●	●
Binary assessment in literature; any presence is clinically meaningful	—	●●

●● Stronger or defining attribute ● Relevant attribute — Not the primary role

PVC burden is a hallmark of ACM disease, while NSVT is more closely linked to negative clinical outcomes and reflects greater disease severity and progression^{1,2,3}

8 ACM, arrhythmogenic cardiomyopathy; ICD, implantable cardioverter defibrillator; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; SCD, sudden cardiac death.
Sources: (1) Gasperetti A, et al. JAMA Cardiology, 2022; (2) Cadrin-Tourigny J, et al. Eur Heart J. 2022;43(32):e1-e9; (3) Towbin JA, et al. Heart Rhythm. 2019;16(11):e301-e372.

PVC burden and NSVT can diverge because they capture distinct aspects of ventricular electrical activity

PVC burden	
NSVT burden	Decreases
	Increases
Decreases	Both decrease • Why: Fewer ventricular triggers and less progression into clinically meaningful arrhythmia • Interpretation: Most consistent evidence of a broad reduction in arrhythmic activity
Increases	Measures diverge • Why: Ventricular triggers may persist or increase, while fewer progress into clinically meaningful arrhythmia • Potential contributors: PVC burden can be influenced by external factors, medications, etc. • Interpretation: May still indicate reduced arrhythmic complexity despite persistent electrical irritability
	Both increase • Why: More ventricular triggers accompanied by greater progression into complex arrhythmias • Interpretation: Most consistent evidence of increasing arrhythmic activity and disease worsening

**PVC burden measures the frequency of ventricular triggers;
NSVT reflects progression into more clinically meaningful arrhythmias**

NSVT is associated with serious outcomes, informs clinical management, and can be objectively assessed

1 Serious outcomes and longitudinal risk



2.53×

Any prior NSVT was associated with increased risk of life-threatening arrhythmic events, including sudden cardiac death¹



2.29 OR

Any NSVT detected during follow-up was associated with higher odds of sustained ventricular arrhythmia over the subsequent 12 months²



2.13 HR

Baseline NSVT independently predicted subsequent sustained ventricular arrhythmia³

2 Informs clinical management



Prompts monitoring and risk reassessment



May inform medication, ablation, and surveillance decisions



Contributes to ICD-related assessment

2022 ESC Guidelines identify NSVT as a key factor in arrhythmic risk assessment and ICD consideration in ACM, making changes in NSVT burden a clinically meaningful outcome

3

Objectively identifiable using standardized criteria in guidelines⁴

Detected through ambulatory rhythm monitoring using defined beat-count, rate, and duration criteria

≥3

consecutive
ventricular beats

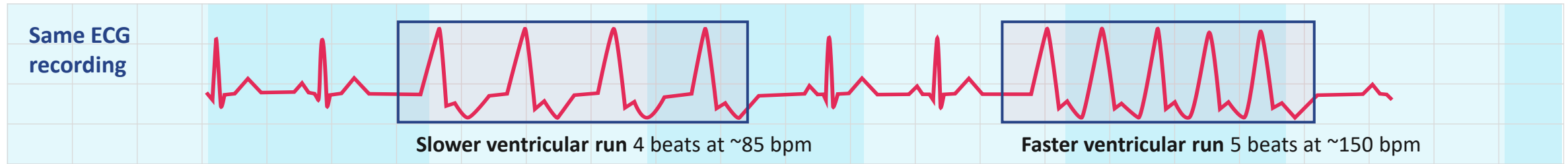
<30 sec
duration

>100 bpm
ventricular rate

OR = Odds Ratio; HR = Hazard Ratio

Sources: (1) Agbaedeng et al., 2022; (2) Gasperetti et al., 2022; (3) Carrick et al., 2022; (4) Al-Khatib SM, et al. Circulation. 2018;138(13):e272-e391.

Guideline-defined NSVT provides a standardized measure of clinically relevant ventricular runs



Total Ventricular Run

≥3 consecutive beats, any rate



Counted

(4 beats at ~85 bpm)



Counted

(5 beats at ~150 bpm)

= 2 NSVT events

Guideline-Defined NSVT

≥3 beats, <30 seconds, >100 bpm



Not counted

(≤100 bpm)



Counted

(5 beats at ~150 bpm)

= 1 NSVT events

Same underlying ECG data and disease biology; more clinically standardized classification



NSVT Classification

- Applied guideline-defined criteria: ≥3 beats, >100 bpm, <30 seconds
- Runs below the 100 bpm rate threshold no longer classified as NSVT



PVC Classification

- Application of guideline-based NSVT criteria resulted in minor changes to reported PVC burden due to event reclassification
- All changes remain within normal Holter measurement variability for PVC assessment

LX2020 baseline using guideline-defined NSVT criteria

Same disease biology, more standardized endpoint measurement

	Cohort 1 (2.0x10 ¹³ vg/kg)			Cohorts 2 & 3 (6.0x10 ¹³ vg/kg)						
Participant	1	2	3	4	5	6	7	8	9	10
Age, years	34	22	29	44	43	30	41	41	28	39
Gender	M	M	M	M	F	F	F	F	M	M
Baseline Data										
Total Ventricular Run (NSVT per 7 days)	2	3	12	169	22	119	154	2	13	19
Guideline-Defined NSVT (NSVT per 7 days)	1	3	2	31	8	13	24	1	5	8
Relevant Medical History Prior to Study	Sustained VT, ICD shock, ablation	Sustained VT, syncope, ICD shock	Sustained VT, syncope	Sustained VT, VT storm, ICD shock, ablation	Sustained VT, ICD shock		Sustained VT, near syncope	Sustained VT, syncope, ablation, stable use of flecainide at study start	Sustained VT, VT storm, ICD shock, ablation	Sustained VT, syncope

Use of guideline-defined NSVT criteria may slightly affect Holter-derived measures of arrhythmic activity, though assessments remain within normal measurement variability

Expectations for upcoming LX2020 readout



Meaningful reduction in arrhythmic burden

Improvement beyond the effect observed with current care would provide compelling evidence of treatment benefit



Sustained or deepening effect over time

Maintenance or deepening improvement over time would strengthen evidence of biologically meaningful treatment effect



Continued well-tolerated safety profile

Safety must remain supportive of the benefit-risk profile for a one-time gene therapy

We remain on track to provide a regulatory update concurrently with the data readout this quarter

Clinical perspective on PKP2-ACM



Dr. Gasperetti, M.D., Ph.D., is a physician scientist at the Cleveland Clinic specializing in inherited arrhythmia syndromes, cardiomyopathies, ventricular arrhythmias, and sudden cardiac death risk stratification.

His research focuses on improving diagnosis, risk assessment, and treatment strategies for patients with genetic and structural heart disease and has helped advance the understanding of the natural history of PKP2-ACM including disease progression, arrhythmic burden, clinical outcomes and treatment response under current standards of care.

Alessio Gasperetti, M.D., Ph.D.

Significant commercial potential for LX2020 given unmet need and global patient population

60K

Patients in the U.S.

Larger-rare, diagnosed population

>\$4-6B

Total addressable market opportunity

Significant commercial upside at peak



Global prevalence

Pivotal development feasible across: US, EU, Asia



Trial ready

Broad patient pool expected to support rapid recruitment



Manufacturing scale

Differentiated Lexeo process will enable rapid and cost-efficient supply



THANK YOU
