Cytokinetics

Sarcomere Directed Therapies

EMPOWERING MUSCLE EMPOWERING LIVES

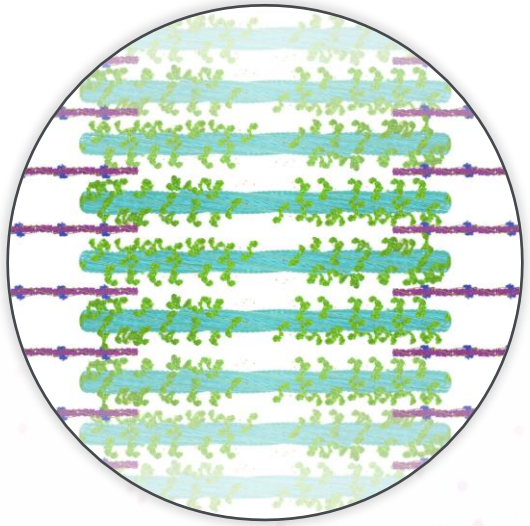
John, *diagnosed with heart failure*

Jillian, *diagnosed with HCM*

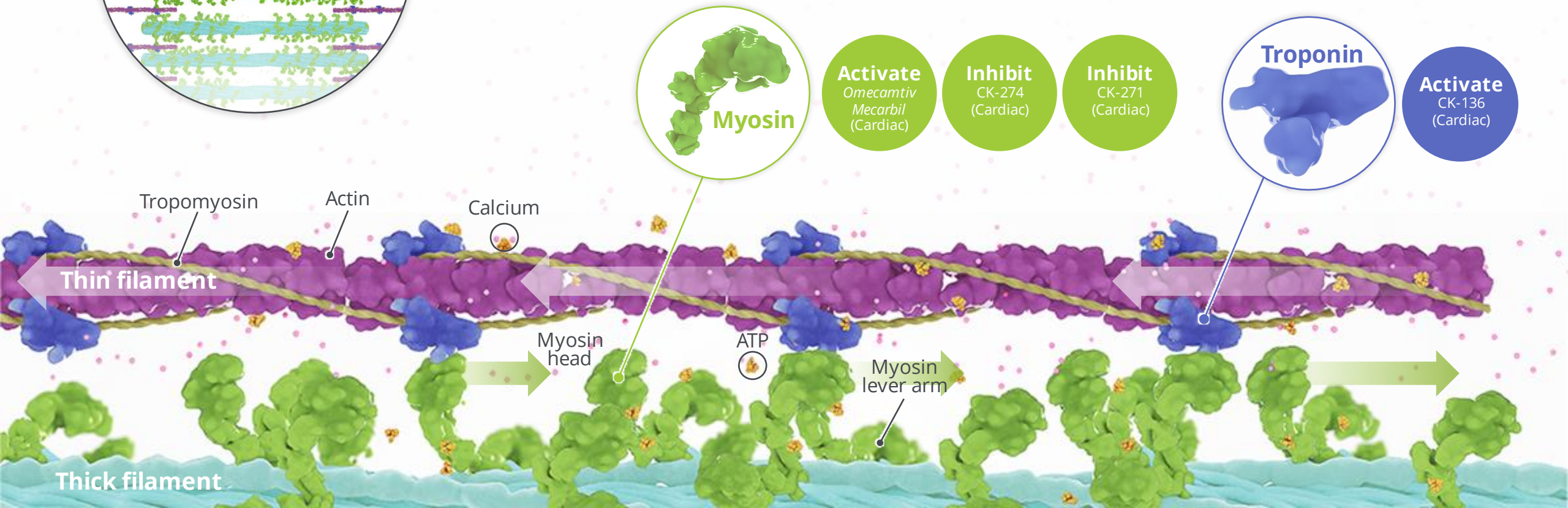
Chuck, *diagnosed with ALS*

Sarcomere Directed Drug Development

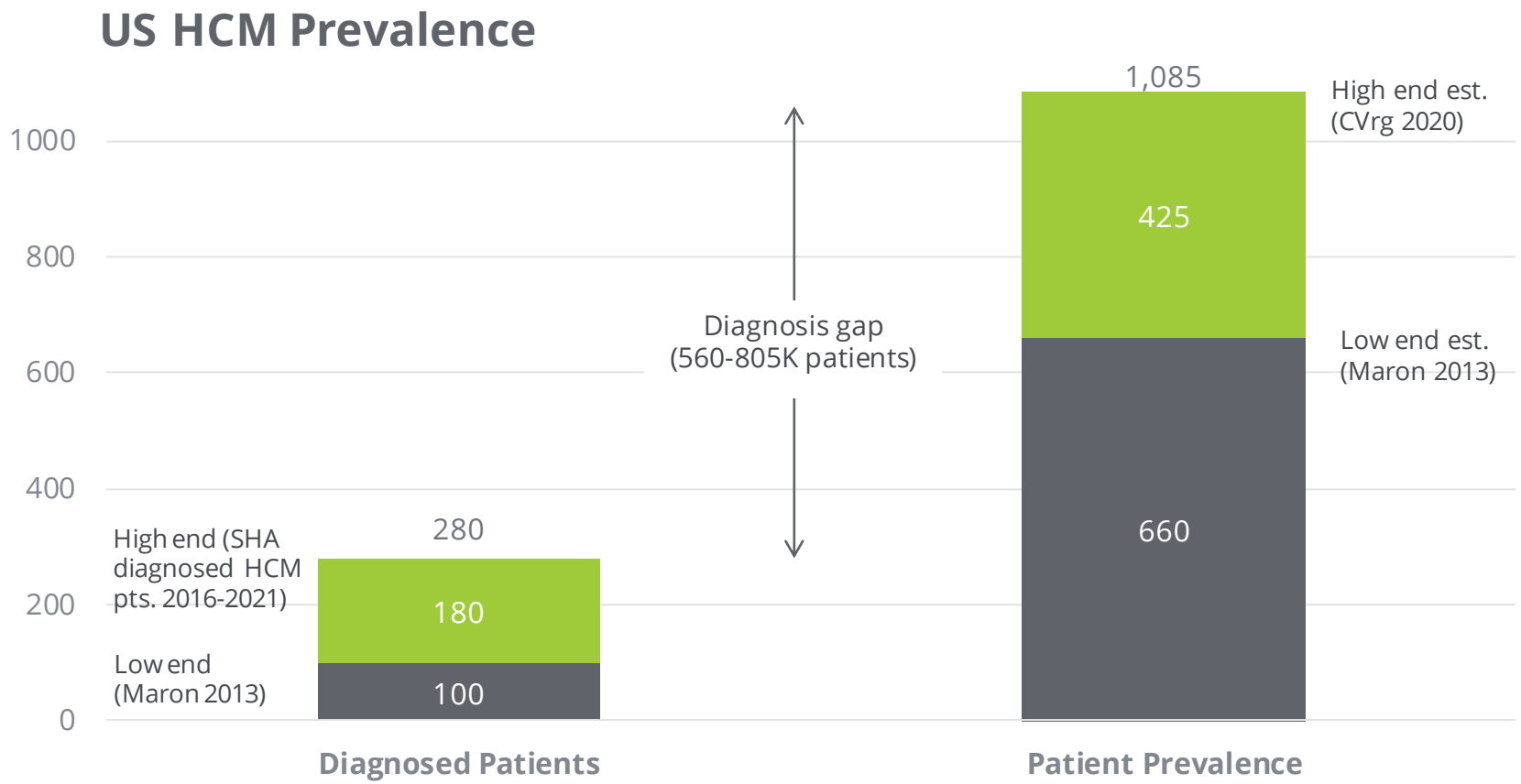
Cardiac muscle



The sarcomere is a molecular structure found in skeletal and cardiac muscle that enables cardiac myocytes to contract and generate force



Symptomatic HCM: Orphan Indication



Source: #26 SHA 2016-2021 Patient Claims Data; #20 Cogent HC 2020 DoF

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CK-274: Next-In-Class Cardiac Myosin Inhibitor

Potential treatment for patients with HCM

- Selective allosteric inhibitor of cardiac myosin discovered by company scientists independent of collaborations
- Potential *in vivo* pharmacodynamic advantages related to distinctive binding site
- Optimized for
  - Onset of action (reach steady state within two weeks)
  - Rapid reversibility of effect
  - Minimal drug-drug interactions
  - Favorable tolerability
  - Ease of titration for personalized dosing
- Clear pharmacokinetic/pharmacodynamic (PK/PD) relationship observed
- Shallow exposure-response relationship

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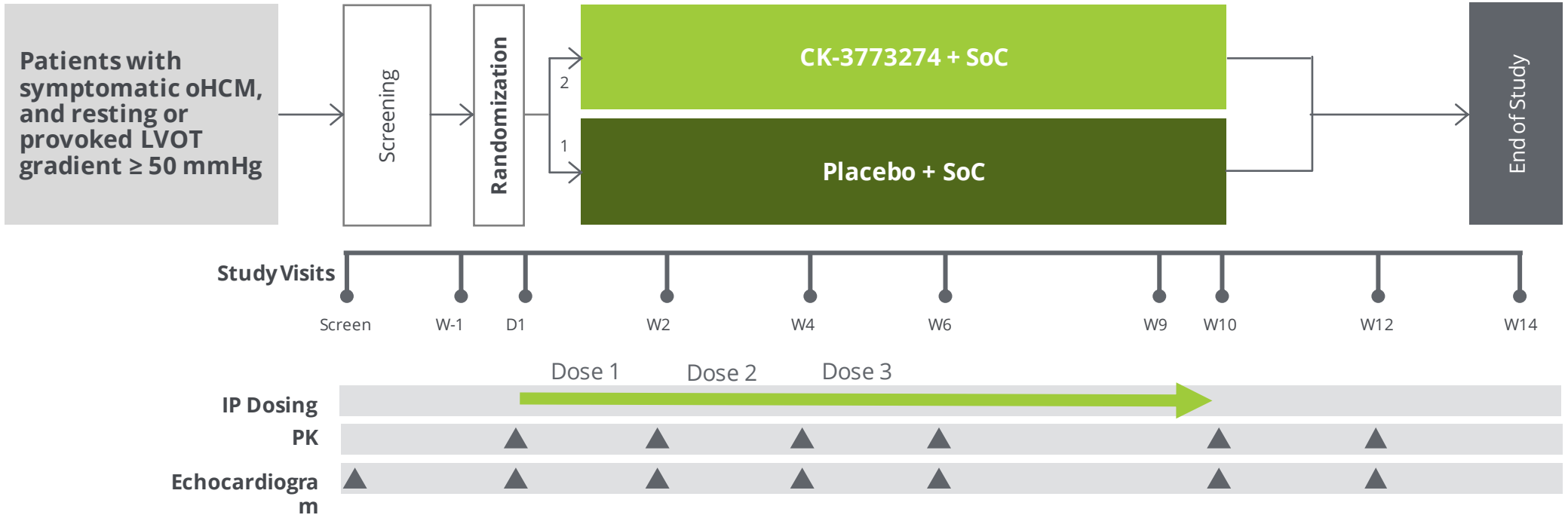
Phase 2 Clinical Trial Design

Two sequential dose-finding cohorts (with third cohort assessing patients on *disopyramide*)



	Dose 1	Dose 2	Dose 3
Cohort 1	5 mg	10 mg	15 mg
Cohort 2	10 mg	20 mg	30 mg

Patient Enrollment and Dosing

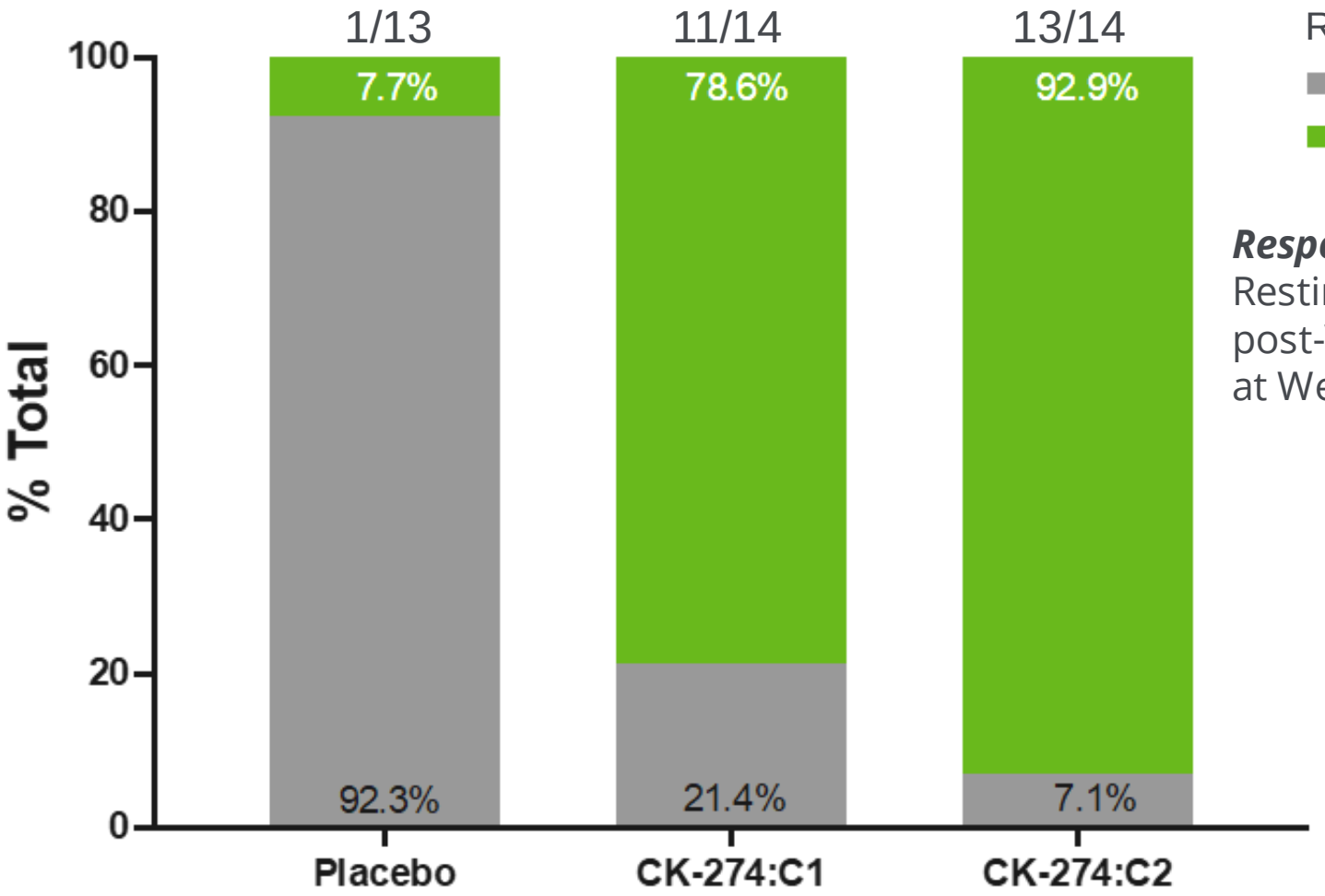
41 Total Enrolled Patients

	Final Dose Achieved (N)					
	Cohort 1			Cohort 2		
Placebo	5mg	10mg	15mg	10mg	20mg	30mg
13	4	5	5	9	4	1

Baseline Echocardiographic Data

Characteristic, mean	Baseline (Day 1 Pre-dose)		
	Placebo C1 + C2 Combined (N = 13)	CK-274	
		Cohort 1 (N = 14)	Cohort 2 (N = 14)
LVEF (%)	74.5	73.2	75.4
LVOT-G, Rest (mmHg)	52.1	53.8	58.2
LVOT-G, Valsalva (mmHg)	84.6	74.4	82.3

High Response Rates on Treatment with CK-274



Responder Definition:
Resting LVOT-G <30 mmHg and post-Valsalva LVOT-G <50 mmHg at Week 10

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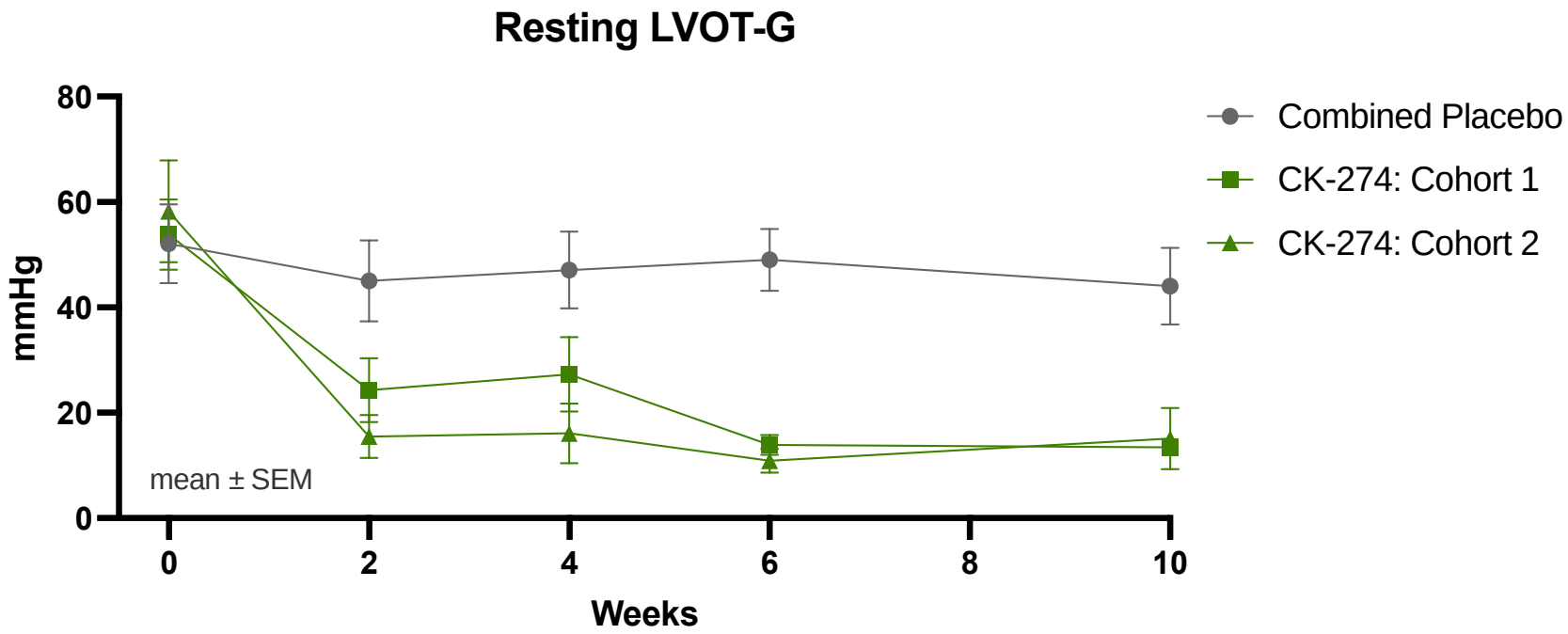
Resting Left Ventricular Outflow Tract Gradient



Mean ± SEM	Resting LVOT-G (mmHg)				
	Baseline	*Week 2*	*Week 4*	*Week 6*	*Week 10*
Placebo (n=13)	52.1	45.0	47.1	49.0	44.0
Cohort 1 (n = 14)	53.8	24.3	27.3	13.9	13.4
p-value vs placebo	-	0.007	0.025	<0.0001	0.0003
Cohort 2 (n = 14)	58.2	15.5	16.1	10.9	15.1
p-value vs placebo	-	0.0002	0.0006	<0.0001	0.0004

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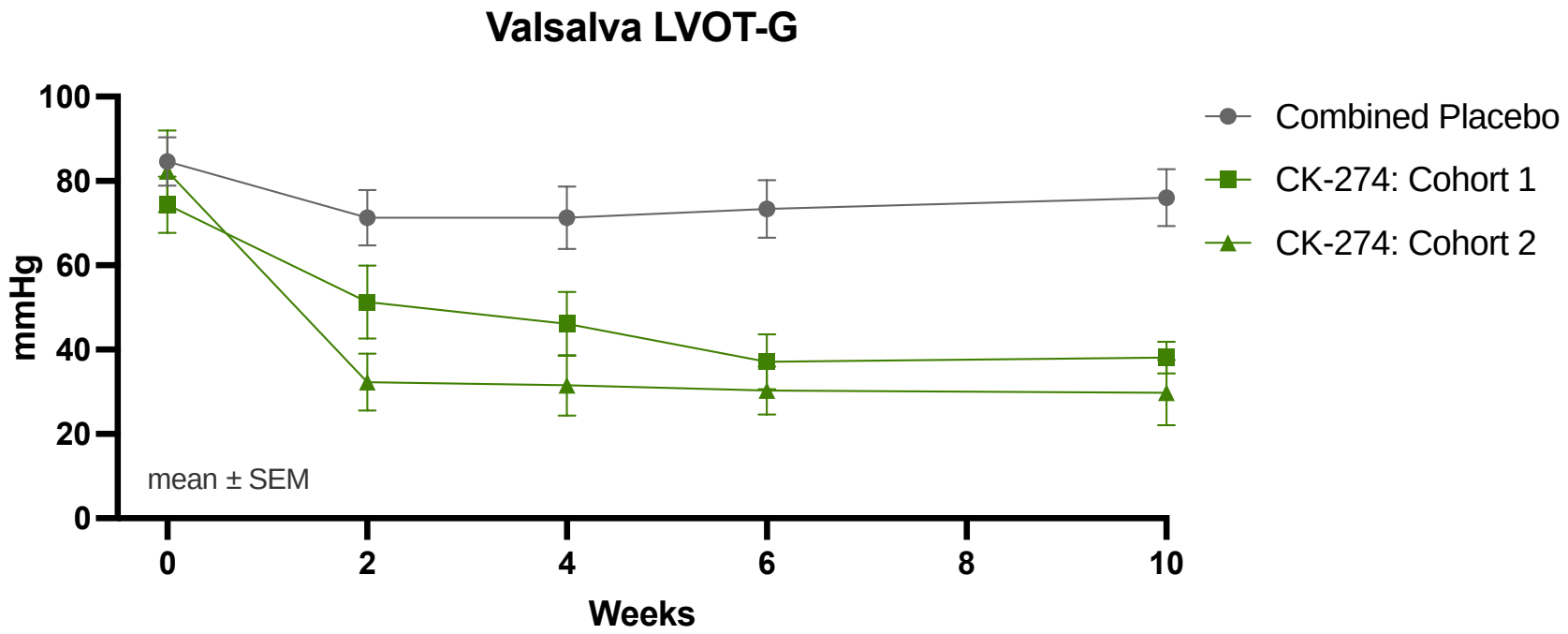
Post-Valsalva Left Ventricular Outflow Tract Gradient



Mean ± SEM	Valsalva LVOT-G (mmHg)				
	Baseline	*Week 2*	*Week 4*	*Week 6*	*Week 10*
Placebo (n=13)	84.6	71.3	71.3	73.4	76
Cohort 1 (n = 14)	74.4	51.3	46.1	37.1	38.1
p-value vs placebo	-	0.097	0.038	0.0003	0.001
Cohort 2 (n = 14)	82.3	32.3	31.5	30.3	29.8
p-value vs placebo	-	0.0005	0.0005	<0.0001	<0.0001

Safety Data

- Incidence of adverse events on CK-274 similar to placebo and mild or moderate
- There were no treatment related serious adverse events reported by investigators
- No patients who received CK-274 in Cohort 1 had an LVEF <50%
- In Cohort 2, one patient with LVEF at baseline of 58% was up titrated to 20 mg and experienced transient LVEF reduction to <50% (remaining above 40%) requiring down titration
- No interruptions or discontinuations of treatment with CK-274 occurred across both cohorts

Open Label Extension Trial

REDWOOD HCM OLE

REDWOOD-HCM OLE open for eligible patients who completed REDWOOD-HCM

- Primary endpoint: incidence of AEs & LVEF <50
- Secondary endpoints: measures of long-term effects of CK-274 on LVOT-G; assessments of steady-state pharmacokinetics.
  - Cardiac MRI sub-study to assess changes in cardiac morphology, function and fibrosis
- Individually optimized dose starts at lowest dose in prespecified range with echo-guided dose titration
- Initial dose and highest target dose informed by interim analyses from REDWOOD-HCM

OLE: Escalating doses based on echo-guided dose titration

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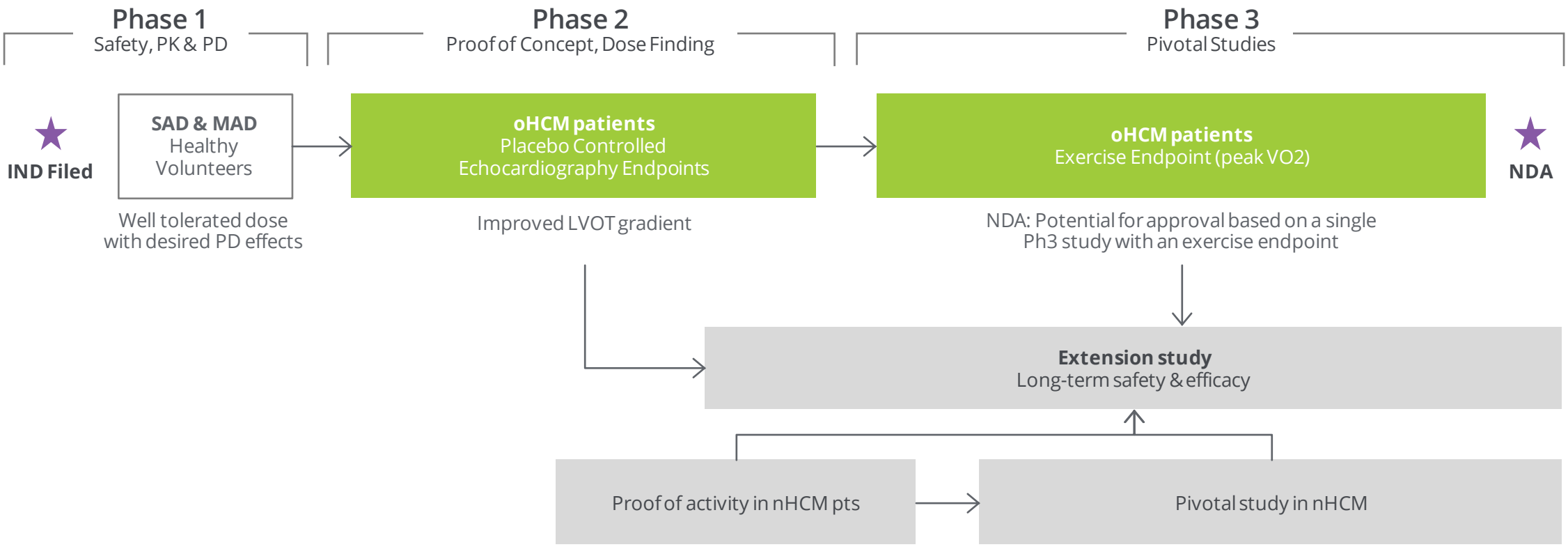
Engaging Regulatory Authorities to Inform Phase 3

- Type C meeting with FDA to review Phase 3 clinical trial design
- End of Phase 2 meeting to review final dose selection rationale for Phase 3

FDA U.S. FOOD & DRUG ADMINISTRATION

CK-274: Clinical Development Plan for HCM



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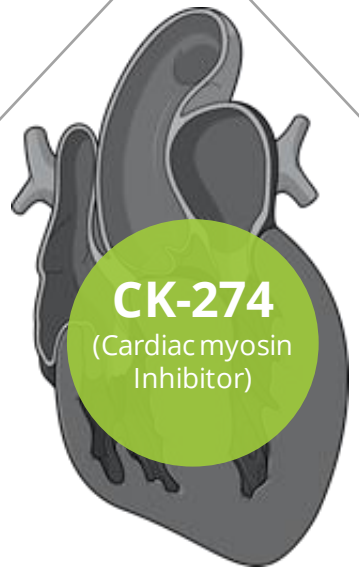
Novel Approach May Address Multiple Unmet Patient Needs

No FDA-approved therapies

Obstructive HCM

oHCM



CK-274
(Cardiac myosin Inhibitor)

nHCM

Non-Obstructive HCM

HFpEF

Heart Failure with Preserved Ejection Fraction

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Sarcomere Directed Therapies

THANK YOU

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