Cytokinetics®

EMPOWERING

muscle

EMPOWERING

lives

Vi, diagnosed with HCM
Avonne, diagnosed with HCM
John, diagnosed with heart failure

Forward-Looking Statements

This presentation contains forward-looking statements for purposes of the Private Securities Litigation Reform Act of 1995 (the "Act"). Cytokinetics disclaims any intent or obligation to update these forward-looking statements and claims the protection of the Act's Safe Harbor for forward-looking statements. Examples of such statements include, but are not limited to, statements express or implied related Cytokinetics' research and development and commercial readiness activities, including the initiation, conduct, design, enrollment, progress, continuation, completion, timing and results of clinical trials, projections regarding growing prevalence, low survival rates and market opportunity in heart failure, hypertrophic cardiomyopathy (HCM) or heart failure with preserved ejection fraction (HFpEF); projections regarding the size of the addressable patient population for *aficamten*, *omecamtiv mecarbil,* CK-136, CK-586 or any of our other drug candidates; Cytokinetics' commercial readiness for *aficamten* or *omecamtiv mecarbil*; our ability to submit a new drug application for *aficamten* with FDA in the third quarter 2024 or a marketing authorization application with EMA in the fourth quarter 2024, the likelihood and/or timing of regulatory approval for our planned new drug application for *aficamten*, *omecamtiv mecarbil* or any future new drug application for any of our other drug candidates or the anticipated timing of any interactions with FDA, EMA or any other regulatory authorities in connection thereto; the timing of our commencement of a new phase 3 clinical trial of *omecamtiv mecarbil*, the timing of completion of MAPLE-HCM, ACACIA-HCM, CEDAR-HCM, or any of our other clinical trials, the efficacy or safety of aficamten, *omecamtiv mecarbil*, CK-136, CK-586 or any of our other drug candidates, our ability to fully enroll or to announce the results of any of our clinical trials by any particular date; the properties, potential benefits and commercial potential of *aficamten*, *omecamtiv mecarbil*, CK-136, CK-586 or any of Cytokinetics' other drug candidates, our ability to satisfy the conditions for disbursement of additional capital/loans under our agreements with Royalty Pharma, or Royalty Pharma's decision to opt-in to the further development of CK-586 for additional funding. Such statements are based on management's current expectations; but actual results may differ materially due to various risks and uncertainties, including, but not limited to, potential difficulties or delays in the development, testing, regulatory approvals for trial commencement, progression or product sale or manufacturing, or production of Cytokinetics' drug candidates that could slow or prevent clinical development or product approval, including risks that current and past results of clinical trials or preclinical studies may not be indicative of future clinical trial results, patient enrollment for or conduct of clinical trials may be difficult or delayed, Cytokinetics' drug candidates may have adverse side effects or inadequate therapeutic efficacy, the FDA or foreign regulatory agencies may delay or limit Cytokinetics' ability to conduct clinical trials, and Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; Cytokinetics may incur unanticipated research, development and other costs or be unable to obtain financing necessary to conduct development of its products; standards of care may change, rendering Cytokinetics' drug candidates obsolete; and competitive products or alternative therapies may be developed by others for the treatment of indications Cytokinetics' drug candidates and potential drug candidates may target. These forward-looking statements speak only as of the date they are made, and Cytokinetics undertakes no obligation to subsequently update any such statement, except as required by law. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission (the "SEC"). This presentation concerns drug candidates that are under clinical investigation, and which have not yet been approved by the U.S. Food and Drug Administration. These are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

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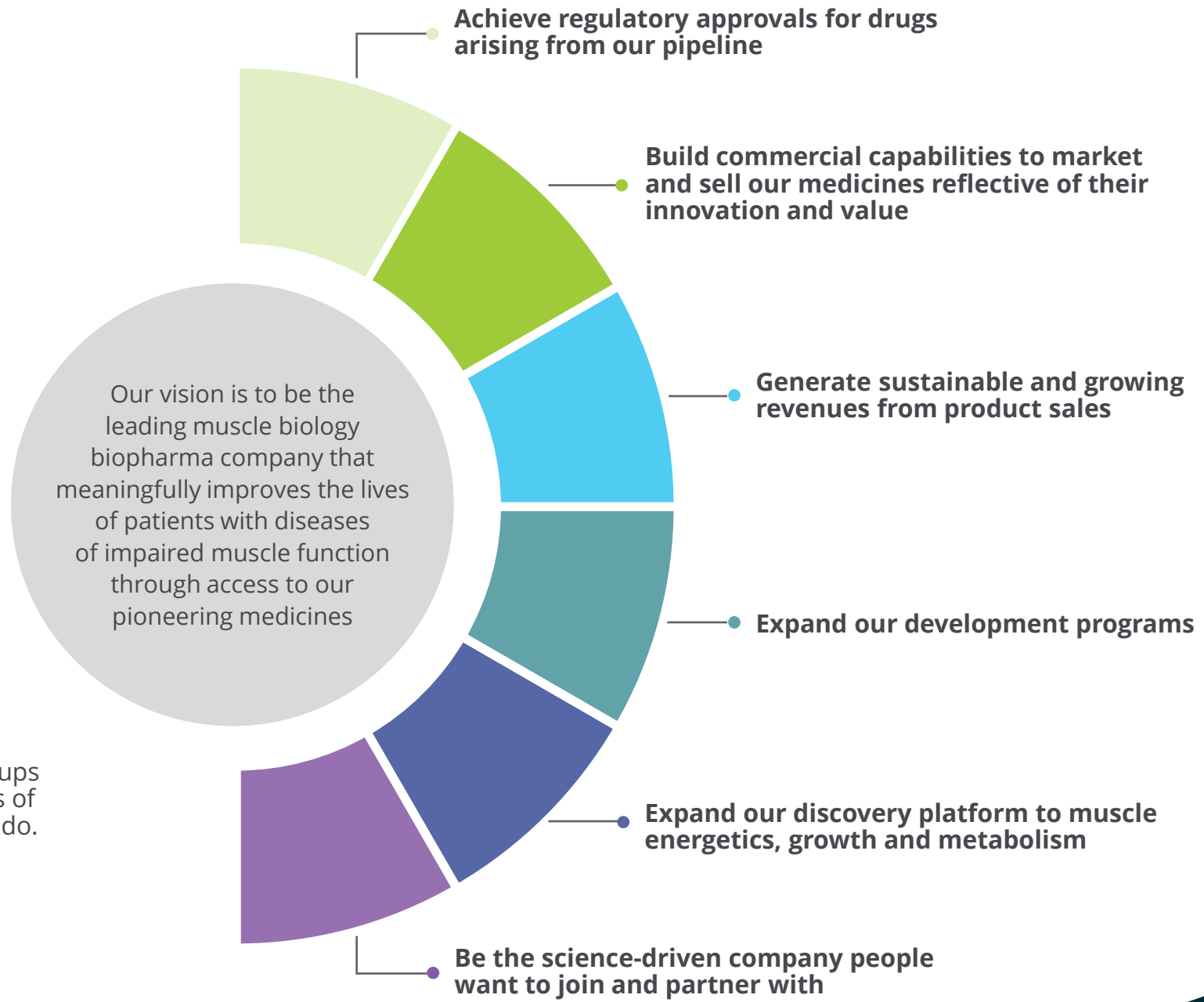
Our Mission

To bring forward new medicines to improve the healthspan of people with devastating cardiovascular and neuromuscular diseases of impaired muscle function.

VISION 2025

Leading with Science, **Delivering for Patients**

As always, we will support disease advocacy groups elevating the patient voice and live by our values of integrity, fairness and compassion in all that we do.



Cytokinetics®

A Great Place to Work; Uncommon Continuity of Team

VALUES

patients are our North Star

science is in our soul

we > me

make it happen

AWARDS

FORTUNE BEST WORKPLACES IN BIOPHARMA™ 2022

FORTUNE BEST WORKPLACES IN THE BAY AREA™ 2023

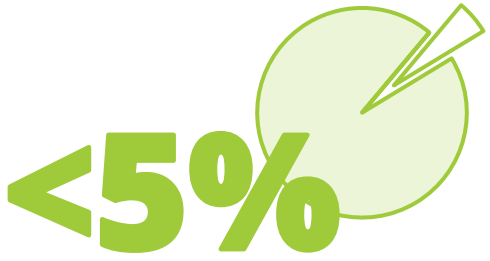
Great Place To Work. Certified FEB 2024-FEB 2025 USA

San Francisco Business Times · Silicon Valley Business Journal — BPtW — BEST PLACES TO WORK 2023

FAST COMPANY — BEST WORKPLACES FOR INNOVATORS 2023 — SCIENCE & TECHNOLOGY — CYTOKINETICS

Winner in Wellness 3rd — SAN FRANCISCO BUSINESS TIMES — Out of 25 Large Companies

RETENTION

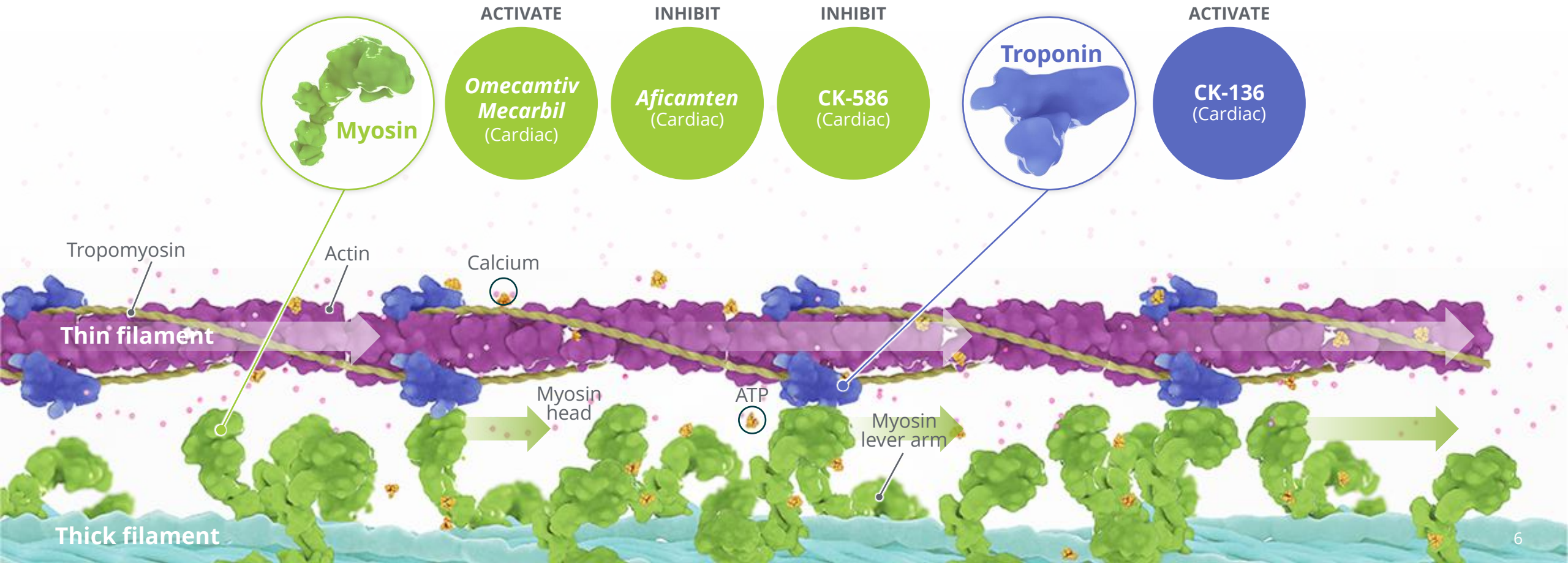


Turnover rate of leadership; low attrition

Average tenure of leadership; high continuity

Sarcomere Directed Drug Development

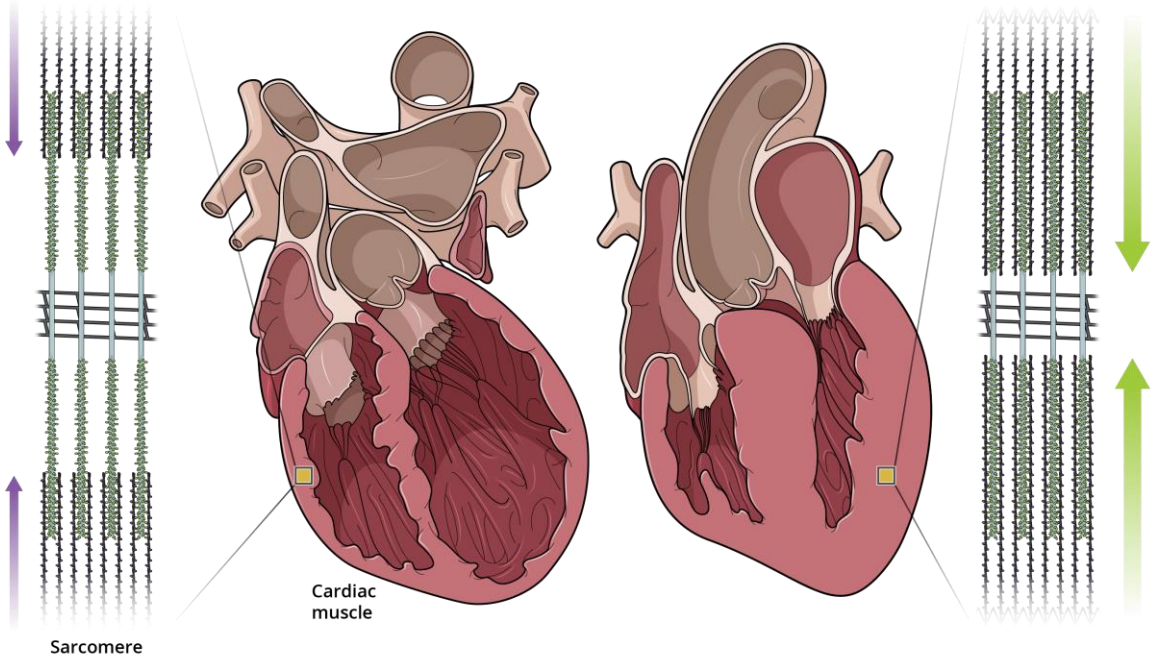
The sarcomere is a molecular structure found in skeletal and cardiac muscle that enables myocytes to contract and generate force



Contractile Dysfunction Underlies Cardiac Diseases

Decreased Cardiac Contractility

- Heart Failure with Reduced Ejection Fraction (HFrEF)
- Genetic Dilated Cardiomyopathy
- Pulmonary Hypertension with Right Ventricular Heart Failure



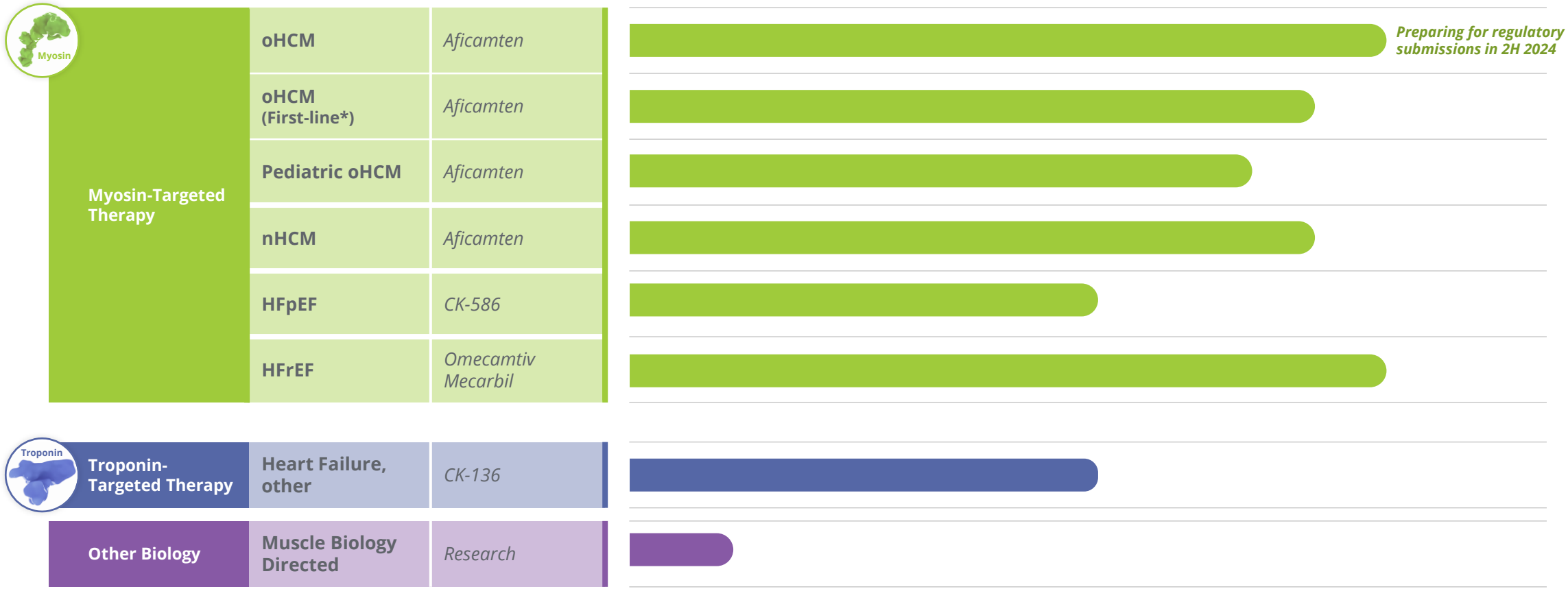
Increased / Preserved Cardiac Contractility

- Non-obstructive Hypertrophic Cardiomyopathy (nHCM)
- Obstructive Hypertrophic Cardiomyopathy (oHCM)
- Heart Failure with Preserved Ejection Fraction (certain HFpEF subsets)

A Commitment to Muscle-Directed Cardiac Medicines

Building a specialty cardiology franchise anchored by *aficamten*

Protein Target	Therapeutic Area	Drug Candidate
Myosin-Targeted Therapy	oHCM	*Aficamten*
	oHCM (First-line*)	*Aficamten*
	Pediatric oHCM	*Aficamten*
	nHCM	*Aficamten*
	HFpEF	*CK-586*
	HFrEF	*Omecamtiv Mecarbil*
Troponin-Targeted Therapy	Heart Failure, other	*CK-136*
Other Biology	Muscle Biology Directed	*Research*



**Pending results from MAPLE-HCM, an ongoing Phase 3 clinical trial evaluating for the potential superiority of aficamten as monotherapy compared to metoprolol as monotherapy in patients with obstructive HCM.*

All drug candidates above are investigational products and are not approved as safe or effective for any indication.

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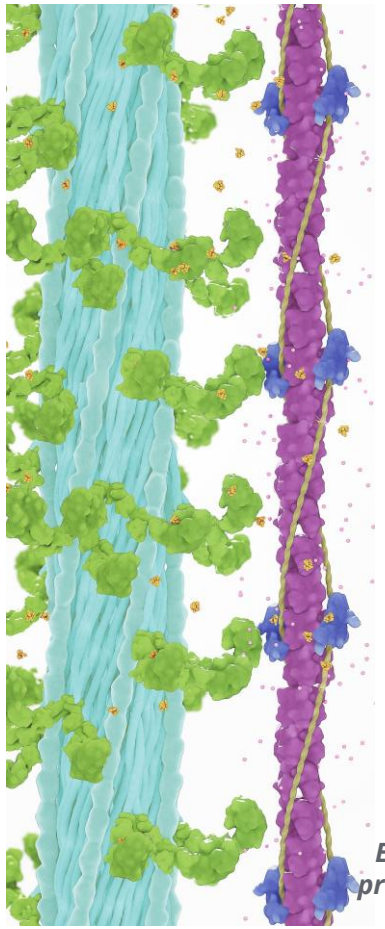
Building a Specialty Cardiology Franchise Anchored by *Aficamten*

Potential patient market for specialty cardiology franchise strategy



Estimated prevalence in US only

Myosin-Targeted Therapies

Troponin-Targeted Therapies

450-700K[1,2]
oHCM patients in 2025-2026

Aficamten

oHCM
SEQUOIA-HCM
First potential indication

250-400K[1,2]
nHCM patients in 2027

Aficamten

oHCM
MAPLE-HCM
Potential to expand to first-line treatment

Aficamten

nHCM
ACACIA-HCM
Potential to expand into nHCM

800K[3]
HFpEF + EF ≥ 65% in 2030

CK-586

HFpEF
With nHCM as a proxy, potential to expand into HFpEF

Omecamtiv Mecarbil

HFrEF
Potential in HFrEF in Europe

CK-136

Heart failure
Potential to expand to subsets of heart failure

All drug candidates above are investigational products and are not approved as safe or effective for any indication.

1. Cardiovascular Research Group: CVrg Market Strategies: Heart Failure, p 48, Q4 2022; Maron BJ: et al: Prevalence of Hypertrophic Cardiomyopathy In A General Population of Young Adults, Circulation 1995;92;785-789; Semsarian C. et al: New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy, J. Am, Coll. Cardiol. 2015; 65: 1249-1254;
2. Lu DY et al: Clinical Outcomes in Patients With Nonobstructive, Labile, and Obstructive Hypertrophic Cardiomyopathy. J. Am. Heart Assoc. 2018;7:1-11
3. Dunlay et al (2012) Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30.

Cytokinetics®

Aficamten

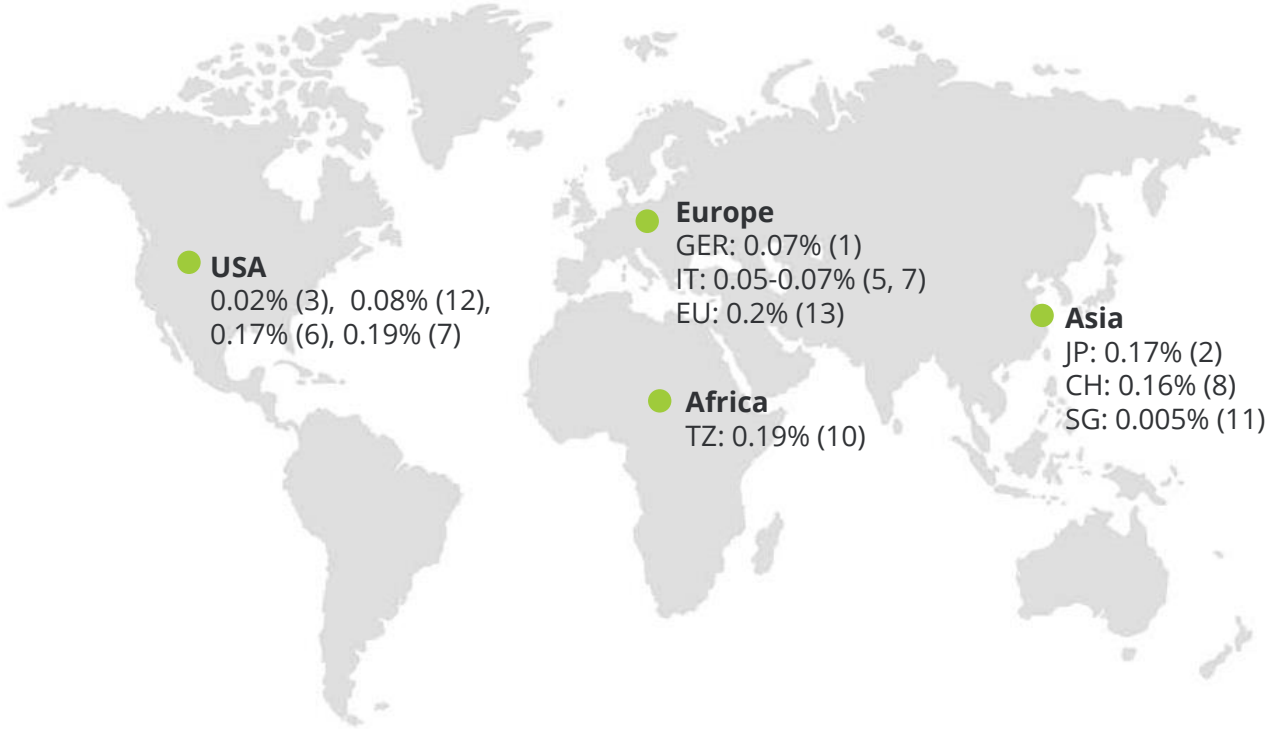
Cytokinetics®

Aficamten is an investigational agent and has not been approved for use by the U.S. Food & Drug Administration (FDA) or any regulatory agency. The safety and effectiveness of this product has not been established.

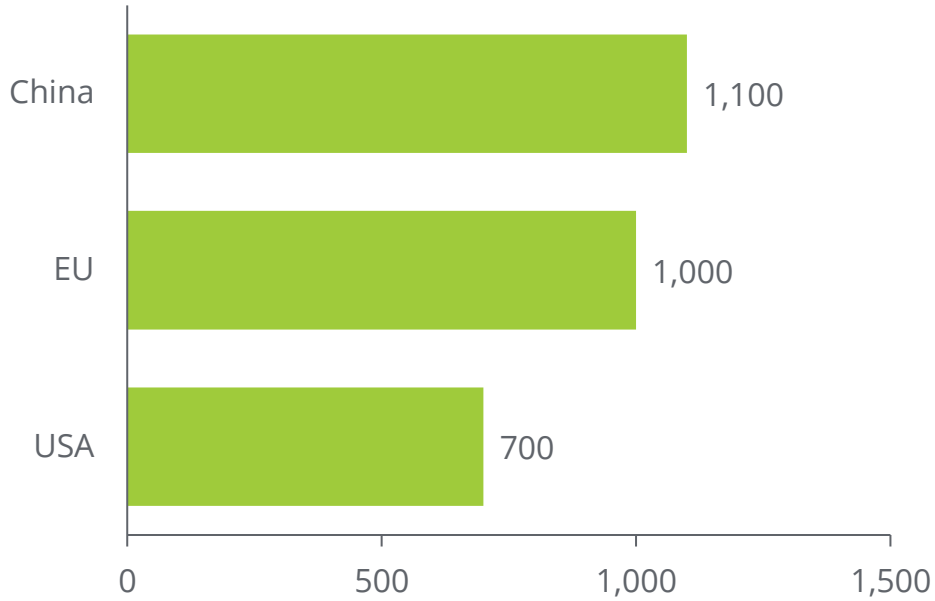
HCM Prevalence: Significant and Growing Globally

HCM prevalence estimates vary across geography and over time

Estimated HCM Prevalence Rates

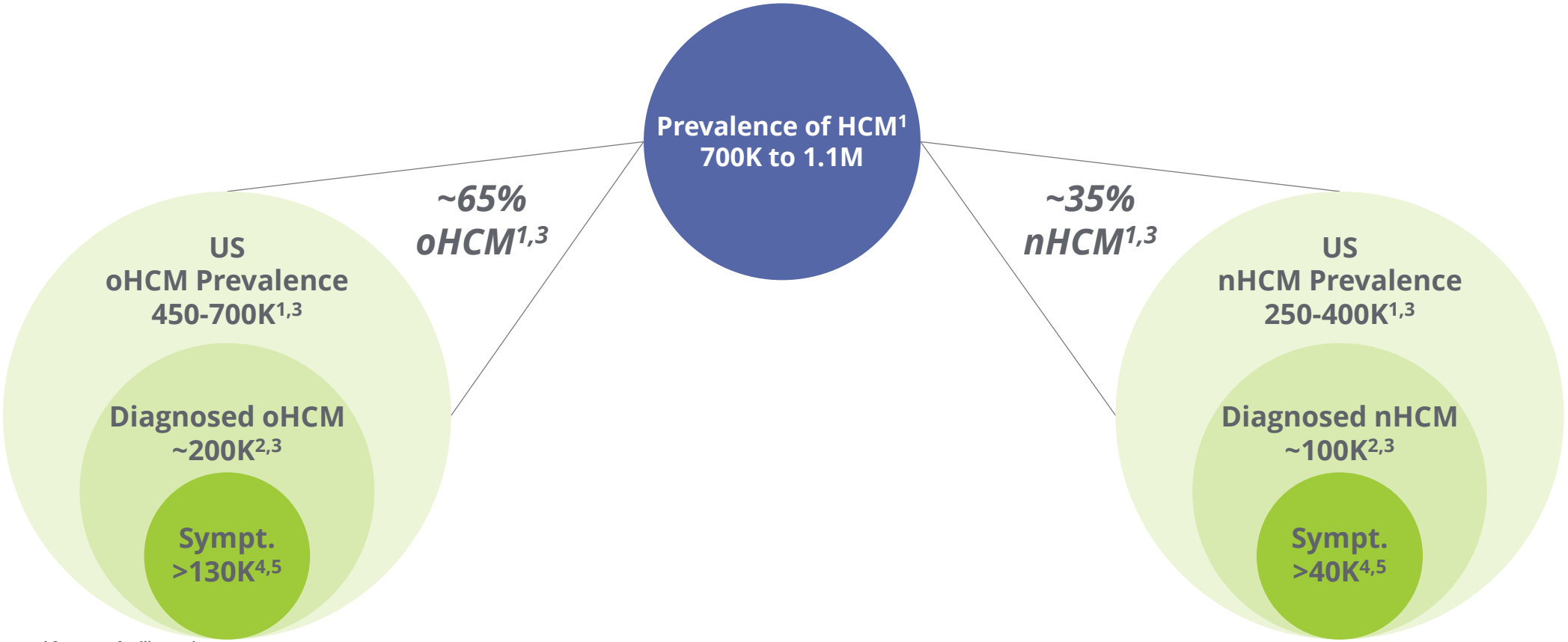


HCM True Patient Prevalence (Est. 2021)



Sources: 1. Husser et al 2018 doi.org/10.1371/journal.pone.0196612; 2. Hada et al 10.1016/s0002-9149(87)80107-8; 3. Codd 1989 10.1161/01.cir.80.3.564; 4. Maron et al 1995 10.1161/01.cir.92.4.785; 5. Corrado et al 1998 10.1056/NEJM199808063390602; 6. Maron et all 1999 10.1001/jama.281.7.650; 7. Nistri et al 2003 10.1016/s0002-9149(03)00132-2; 8. Zou et al 2004 10.1093/aje/kwh090; 9. Maron 2004 https://doi.org/10.1016/j.amjmed.2003.10.012; 10. Maro 2006 10.1258/004947506778604904; 11. Ng et al 2011 10.1093/europace/eur051; 12. Butzner et al 2021 10.1016/j.amjcard.2021.08.024; 13. Cardim et al 2011 10.1016/j.repc.2011.09.005

Opportunity for CMIs in Diagnosed, Symptomatic HCM Patients

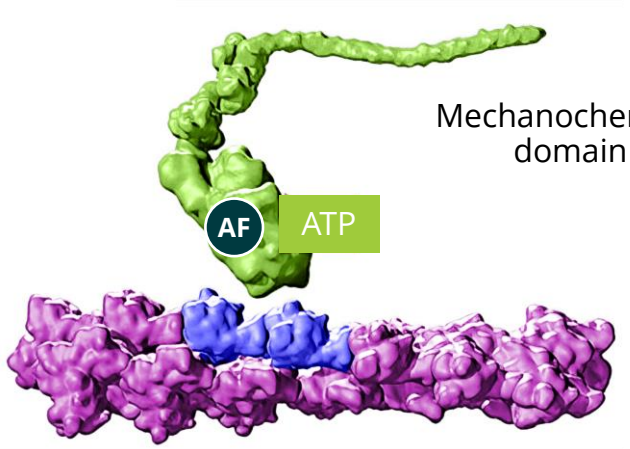


Projections and forecasts for illustration.

1. Cardiovascular Research Group: CVrg Market Strategies: Heart Failure, p 48, Q4 2022; Maron BJ: et al:: Prevalence of Hypertrophic Cardiomyopathy In A General Population of Young Adults, Circulation 1995;92;785-789; Semsarian C. et al: New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy, J. Am, Coll. Cardiol. 2015; 65: 1249-1254;
2. DoF: SHA; Symphony PTD (Patient Transaction Data): Includes patients diagnosed since 2016 and having any HC transaction in the claims data universe in the last year June 2022-May 2023);
3. Lu DY et al: Clinical Outcomes in Patients With Nonobstructive, Labile, and Obstructive Hypertrophic Cardiomyopathy. J. Am. Heart Assoc.2018;7:1-11
4. DoF: SHA Symphony PTD (Patient Transaction Data) includes any patients with symptoms in the last 2 years: angina, dyspnea, fatigue, palpitations, syncope, tachycardia; and/or treatments in the past 2 years: bb, ccb, dyso, ralo, Camzyos;
5. DoF Primary market research: 443 HCPs treating HCM - % of nHCM patients not considered under control with current SOC.

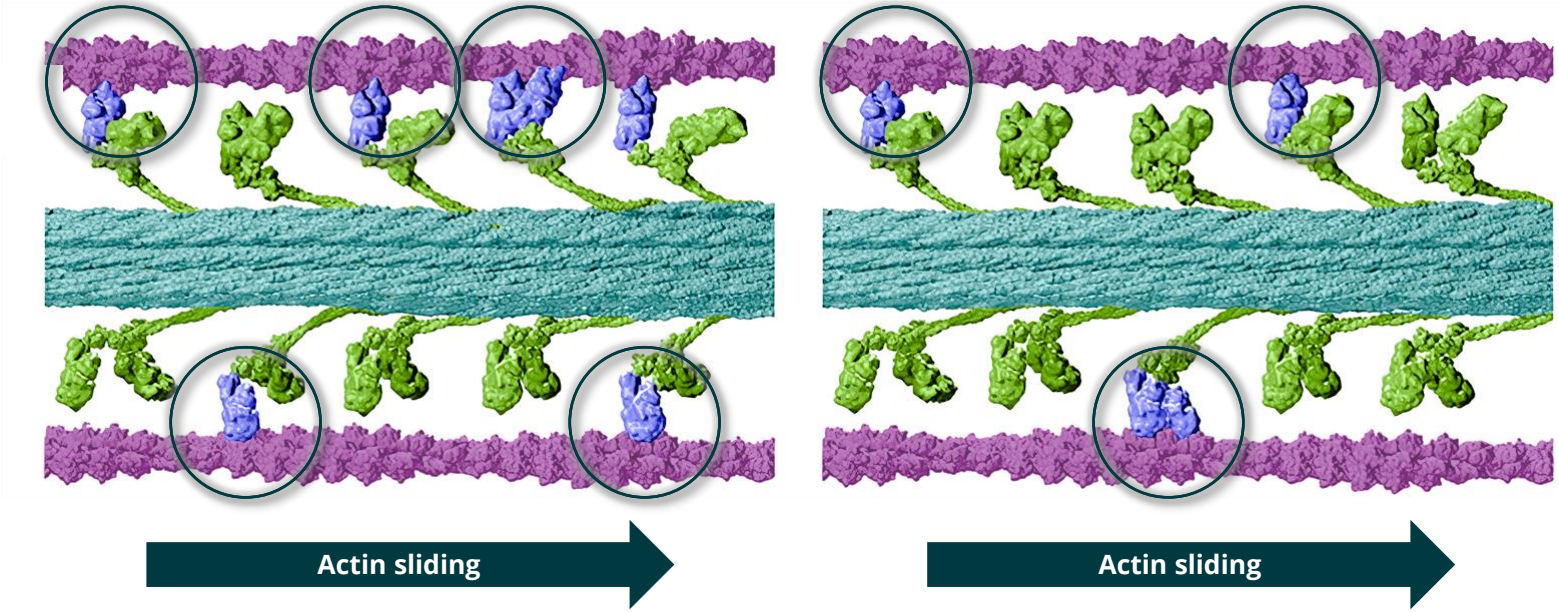
Aficamten: Mechanism of Action

Aficamten **stabilized myosin in the released post-powerstroke state unable to hydrolyze ATP**



Post-Powerstroke State

"Fewer hands pulling on the rope"



Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

Aficamten: Aspirational Target Profile

Potential next-in-class cardiac myosin inhibitor

Rapid onset

Rapid reversibility

Speed to optimal dose

Predictable dose response

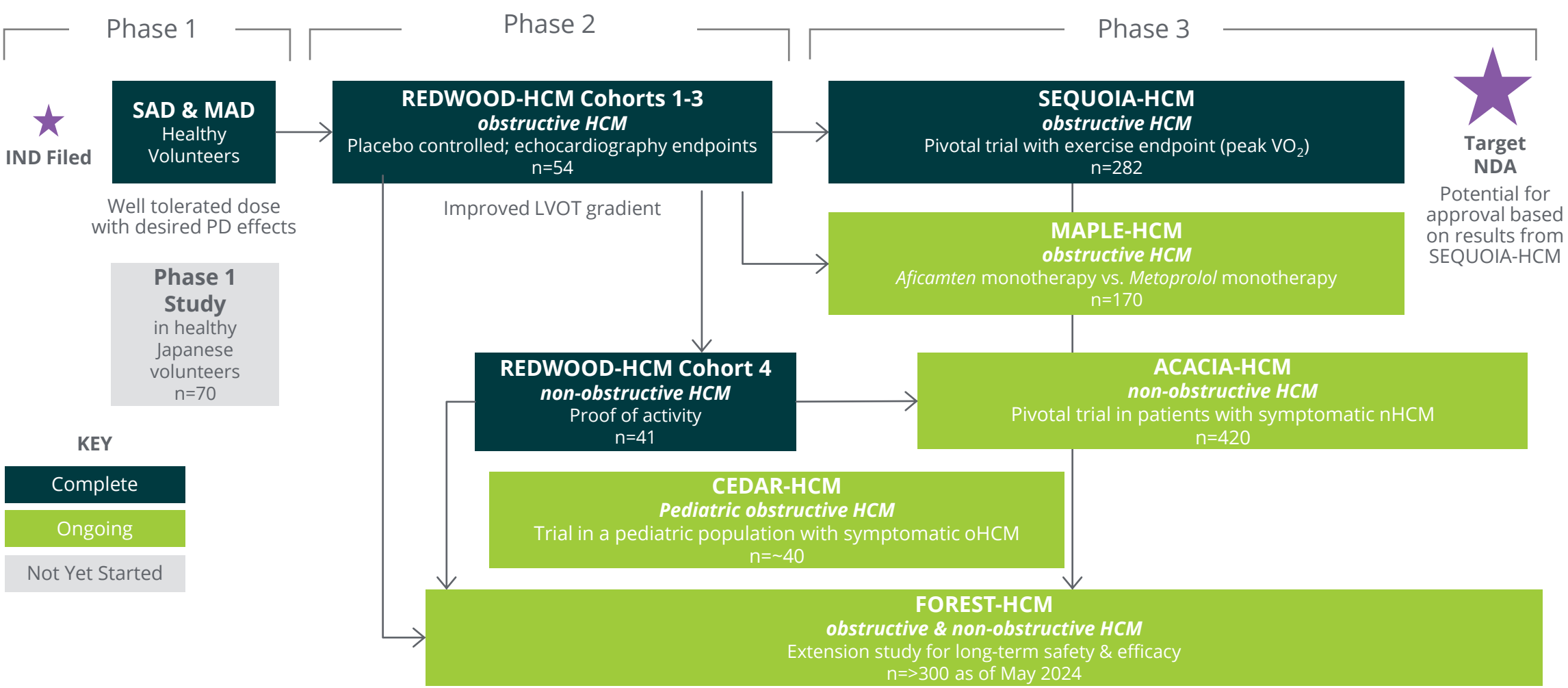
No teratogenicity

No clinically meaningful P450 liabilities

Aspirational information. Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

Aficamten: Clinical Development Plan for HCM



Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

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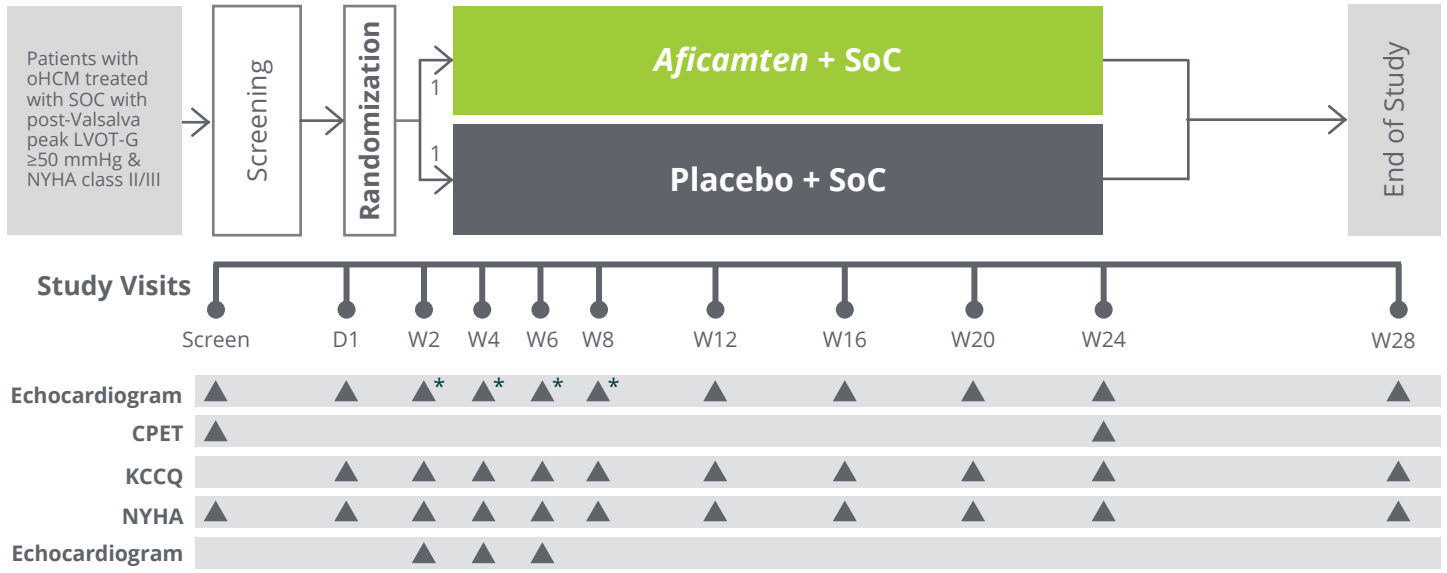
SEQUOIA-HCM: Phase 3 Trial

Primary endpoint: **Change in pVO_2 by CPET from baseline to Week 24**

Secondary objectives include measuring **change in KCCQ & improvement in NYHA class at week 12 and 24**

Enrolled 282 patients treated with standard of care with:
- **resting LVOT-G ≥30 mmHg,**
- **post-Valsalva LVOT-G ≥50 mmHg,**
- **NYHA Class II or III,**
- **exercise performance <80% predicted**

Individualized dose up-titration based on echocardiography: LVEF ≥55%, post-Valsalva LVOT-G ≥30 mmHg



Dose Options (Dose optimization completed by Week 8)

5 mg QD	10 mg QD	15 mg QD	20 mg QD

SOC: standard of care
** Focused echocardiogram*

SEQUOIA-HCM: Baseline Characteristics

Baseline characteristics reflect highly symptomatic patient population with reduced exercise capacity

- Significant **symptom burden** despite background therapy
- 61% of patients on **beta-blockers**
- Baseline pVO_2 reflects patient population with **reduced exercise capacity**

	Aficamten n=142	Placebo n=140
Age, y	59.2 ± 12.6	59.0 ± 13.4
Female sex, n (%)	56 (39.4)	59 (42.1)
Race, n (%)		
White	108 (76.1)	115 (82.1)
Geographic region, n (%)		
North America	49 (34.5)	45 (32.1)
China	24 (16.9)	22 (15.7)
Europe and Israel	69 (48.6)	73 (52.1)
Medical history, n (%)		
Hypertension	75 (52.8)	70 (50.0)
Paroxysmal atrial fibrillation	21 (14.8)	20 (14.3)
Permanent atrial fibrillation	2 (1.4)	1 (0.7)
CPET		
pVO_2 (mL/kg/min)	18.5 (4.5)	18.6 (4.5)
Percent of predicted pVO_2 (%)	58 (13)	57 (12)

	Aficamten n=142	Placebo n=140
Background HCM therapy, n (%)		
Beta-blocker	86 (60.6)	87 (62.1)
Calcium channel blocker	45 (31.7)	36 (25.7)
Disopyramide	16 (11.3)	20 (14.3)
None	19 (13.4)	22 (15.7)
KCCQ-CSS	76 ± 18	74 ± 18
NYHA FC, n (%)		
II	108 (76.1)	106 (75.7)
III/IV	34 (23.9)	34 (24.3)
Median NT-proBNP (IQR), pg/mL	818 (377–1630)	692 (335–1795)
Median hs-cTnI (IQR), ng/L	12.9 (7.6–33.6)	11.5 (7.7–25.0)
Echocardiographic parameters		
Valsalva LVOT-G, mmHg	82.9 ± 32	83.3 ± 33
Resting LVOT-G, mmHg	54.8 ± 27	55.3 ± 32
LVEF, %	74.8 ± 5.5	74.8 ± 6.3
Maximal LV wall thickness, mm	20.7 ± 3.0	21.0 ± 3.0

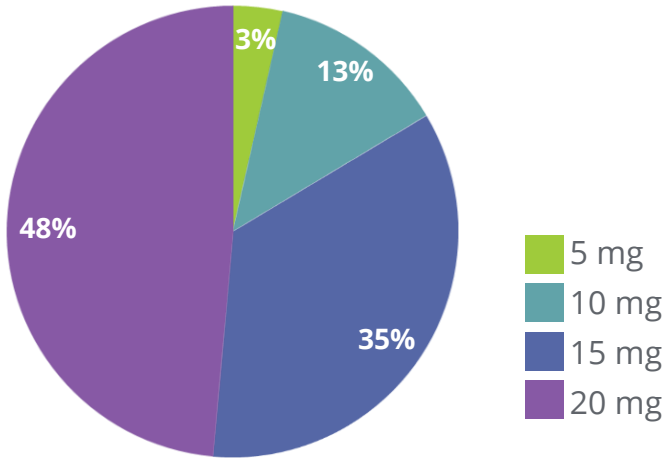
Values are the mean ± SD unless otherwise indicated.

Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Maron M. "Aficamten for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

SEQUOIA-HCM: Dosing

Aficamten dose at Week 8 (end of titration)



There were no differences in age, sex, ethnicity, body mass index, or comorbidities (diabetes, hypertension or AF) between dose groups

Mean ± SD, n (%), or median (IQR)	Placebo n=140	5 mg n=5	10 mg n=18	15 mg n=49	20 mg n=68
% per treatment group	100%	3.5%	12.7%	34.5%	47.9%
Background HCM therapy					
Beta-blocker	87 (62.1)	5 (100.0)	10 (55.6)	31 (63.3)	40 (58.8)
Calcium channel blocker	36 (25.7)	1 (20.0)	3 (16.7)	17 (34.7)	24 (35.3)
Disopyramide	20 (14.3)	1 (20.0)	5 (27.8)	3 (6.1)	7 (10.3)
Baseline study assessments					
KCCQ-CSS	74 ± 18	68 ± 26	75 ± 19	77 ± 20	75 ± 17
NYHA class II	106 (75.7)	3 (60.0)	16 (88.9)	33 (67.3)	54 (79.4)
NT-proBNP, pg/mL	692 (335, 1795)	1133 (992, 1475)	338 (283, 674)	871 (428, 1505)	962 (511, 2085)
hs-cTnI, ng/L	12 (8, 25)	12 (6, 234)	10 (5, 17)	13 (7, 24)	16 (8, 38)
pVO_2, mL/kg/min	18.6 ± 4.5	18.7 ± 2.9	18.6 ± 3.9	18.2 ± 4.1	18.3 ± 4.9
Echocardiographic parameters (core laboratory)					
LVEF at baseline, %	75 ± 6	71 ± 12	76 ± 5	75 ± 5	75 ± 5
Peak LVOT-G at rest	55 ± 32	29 ± 13	45 ± 21	56 ± 24	58 ± 30
Peak LVOT-G post-Valsalva	83 ± 33	51 ± 24	71 ± 29	84 ± 26	88 ± 35
Left ventricular MWT, cm	2.10 ± 0.30	2.42 ± 0.74	1.94 ± 0.22	2.04 ± 0.26	2.11 ± 0.28

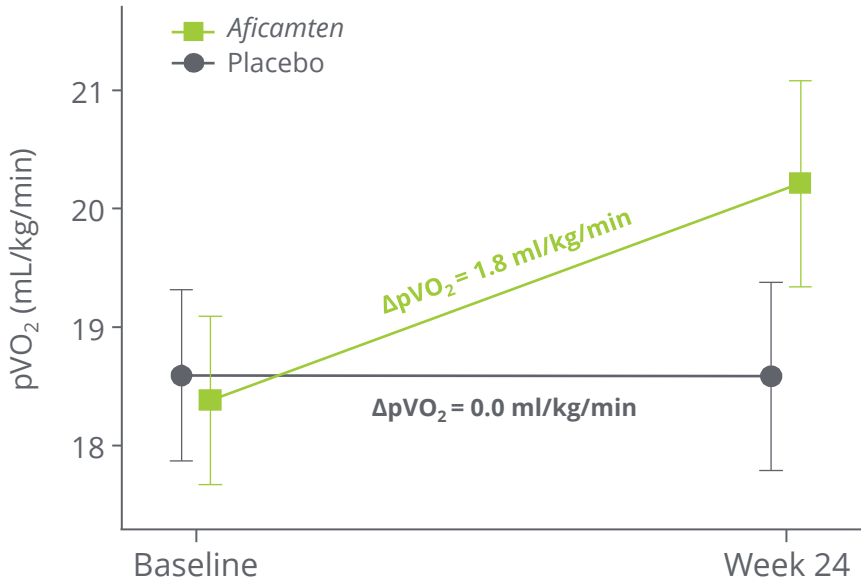
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
hs-cTnI, high-sensitive cardiac troponin; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary score; MWT, maximal wall thickness; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association.
Coats CJ. "Dosing and Safety Profile of Aficamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

SEQUOIA-HCM: Primary Endpoint

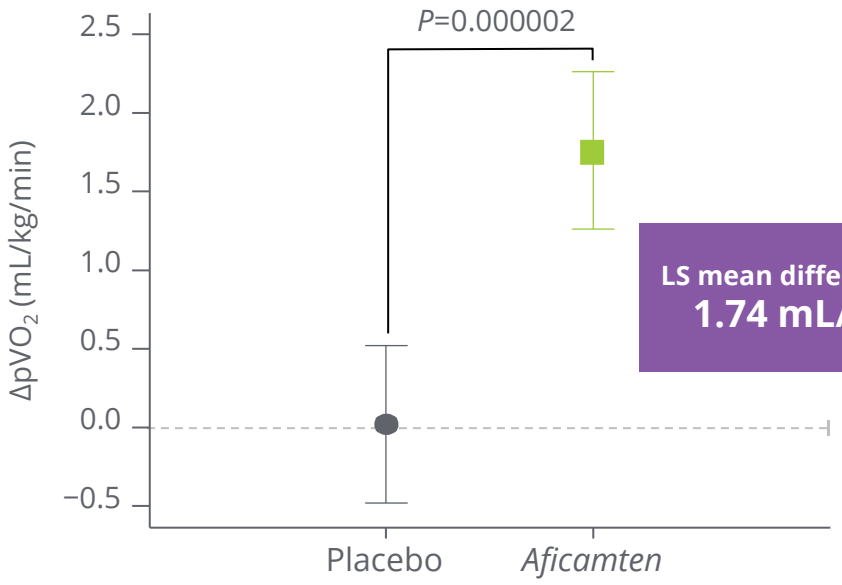
Significant improvement in exercise capacity compared to placebo

Results presented at Heart Failure 2024 and published in *NEJM*

Absolute Change from Baseline to Week 24



LS mean Change from Baseline to Week 24



Data are mean and 95% CI

LS mean difference (SE) vs placebo:
1.74 mL/kg/min (0.36)

Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Maron M. "*Aficamten* for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

SEQUOIA-HCM: Subgroup Analysis

Results consistent across all prespecified subgroups including patients receiving or not receiving background beta-blockers

	n (Afi/Plb)	*Aficamten* LS mean	Placebo LS mean	Mean difference (95% CI)
Age				
<65 y	85/84	2.4	0.4	2.0 (1.1, 2.8)
≥65 y	57/56	0.9	−0.5	1.4 (0.3, 2.5)
Sex				
Male	86/81	2.5	0.7	1.8 (0.9, 2.7)
Female	56/59	0.6	−0.8	1.4 (0.4, 2.5)
Baseline BMI				
<30 kg/m^2	97/94	1.9	0.1	1.8 (1.0, 2.7)
≥30 kg/m^2	45/46	1.4	−0.2	1.6 (0.3, 2.8)
Baseline Median LVEF				
≤75.6%	73/68	1.9	0.0	1.8 (0.8, 2.8)
>75.6%	69/72	1.7	0.0	1.6 (0.6, 2.6)
Baseline NYHA FC				
Class II	108/106	2.0	0.3	1.7 (0.9, 2.5)
Class III /IV	34/34	1.0	−0.9	1.9 (0.5, 3.3)
Baseline Median KCCQ-CSS				
≤78.1	67/75	1.7	−0.1	1.8 (0.8, 2.8)
>78.1	75/65	1.8	0.1	1.7 (0.7, 2.6)

Interaction *P* values were >0.05 for all prespecified subgroups

Favors Placebo — Favors Treatment

	n (Afi/Plb)	*Aficamten* LS mean	Placebo LS mean	Mean difference (95% CI)
Baseline NT-proBNP (median)				
≤ 788 pg/mL	66/73	2.2	0.6	1.7 (0.7, 2.7)
> 788 pg/mL	73/65	1.4	−0.6	2.0 (1.0, 2.9)
CPET Modality				
Treadmill	78/77	2.5	0.2	2.3 (1.4, 3.2)
Bicycle	64/63	0.9	−0.1	1.0 (−0.0, 2.1)
Baseline Median pVO_2				
≤18.4 mL/kg/min	74/67	1.5	−0.1	1.6 (0.6, 2.5)
>18.4 mL/kg/min	68/73	2.0	0.1	1.9 (1.0, 2.9)
Baseline Beta-Blocker Use				
Yes	86/87	1.4	−0.2	1.6 (0.7, 2.5)
No	56/53	2.2	0.2	1.9 (0.8, 3.1)
Baseline Resting LVOT (median)				
≤51.1 mmHg	72/69	1.8	0.5	1.3 (0.3, 2.3)
>51.1 mmHg	70/71	1.7	−0.4	2.1 (1.2, 3.1)
Genotype				
Positive	20/22	1.6	−1.0	2.6 (0.9, 4.2)
Negative	71/70	1.4	−0.1	1.4 (0.5, 2.3)

Favors Placebo — Favors Treatment

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Maron M. "*Aficamten* for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

SEQUOIA-HCM: Secondary Endpoints

Statistically significant improvements in all 10 pre-specified secondary endpoints

Endpoints	P value
Primary Endpoint	
pVO_2 change from baseline to Week 24	**<0.0001**
Secondary Endpoints	
1. KCCQ-CSS change from baseline to Week 24	**<0.0001**
2. NYHA Class Improvement by at least 1 class at Week 24	**<0.0001**
3. Valsalva LVOT-G change from baseline to Week 24	**<0.0001**
4. % Valsalva LVOT-G <30 mmHg at Week 24	**<0.0001**
5. Duration of SRT Eligible during 24 Weeks of Treatment	**<0.0001**
6. KCCQ-CSS change from baseline to Week 12	**<0.0001**
7. NYHA Class Improvement by at least 1 class at Week 12	**<0.0001**
8. Valsalva LVOT-G change from baseline to Week 12	**<0.0001**
9. % Valsalva LVOT-G <30 mmHg at Week 12	**<0.0001**
10. Total workload change from baseline to Week 24	**<0.0001**

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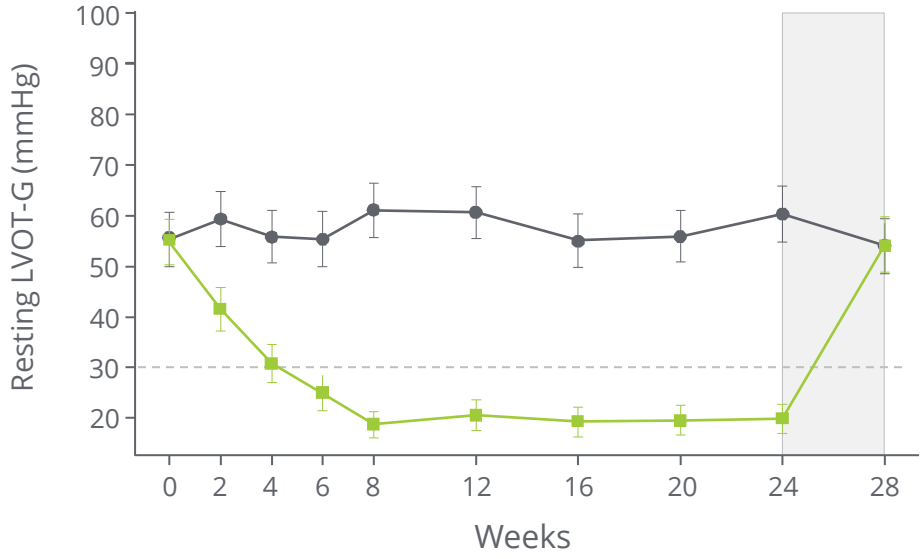
SEQUOIA-HCM: Secondary & Exploratory Endpoints

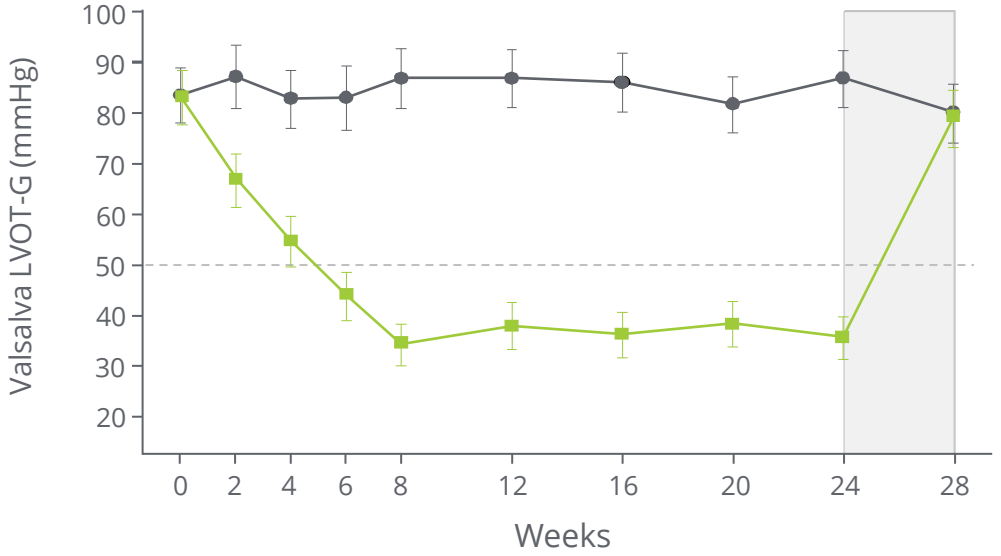
Significant improvement in post-Valsalva left ventricular outflow tract gradient (LVOT-G)

LS mean difference:
- 50 mmHg

Resting LVOT-G



Valsalva LVOT-G



Aficamten
Placebo
Washout

Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
Error bars are 95% CI
Maron M. "*Aficamten* for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

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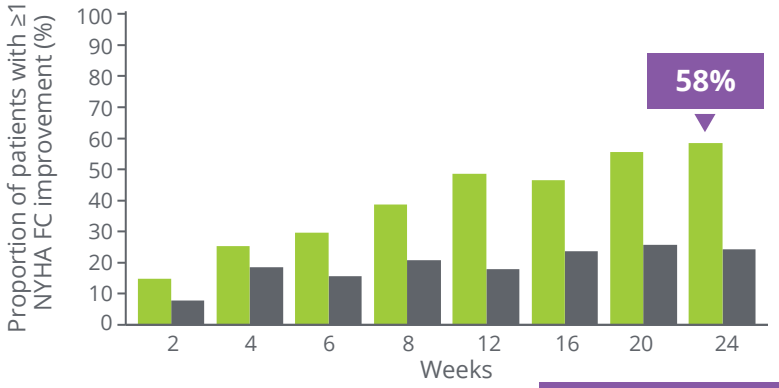
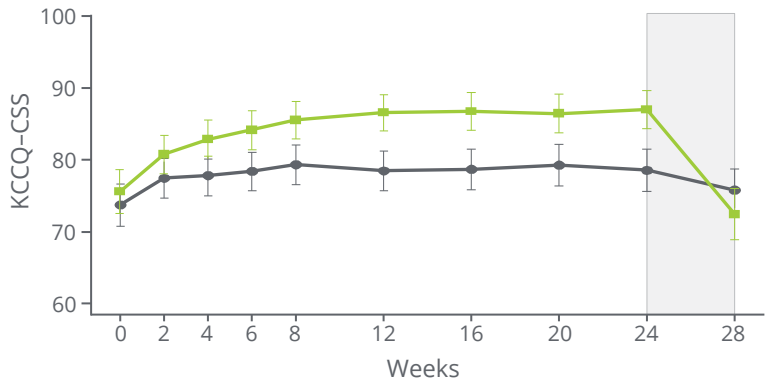
SEQUOIA-HCM: Secondary & Exploratory Endpoints

≥1 NYHA FC Improvement



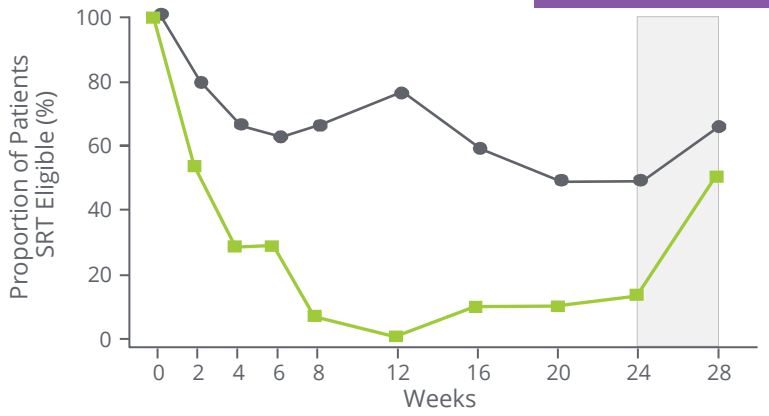
KCCQ-CSS

LS mean difference: 7 points



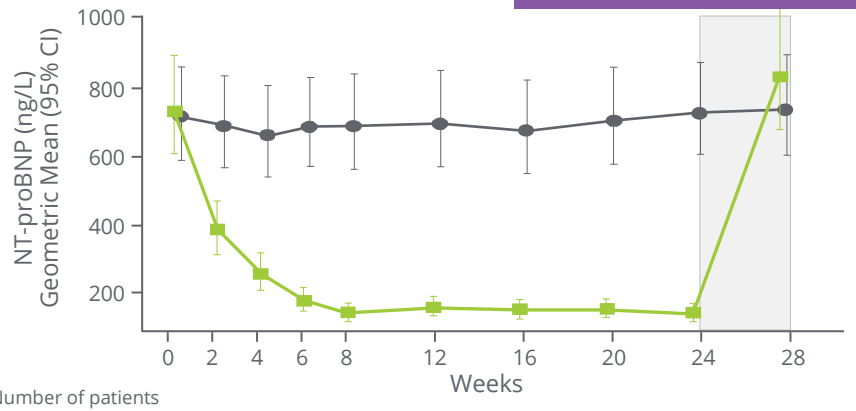
Guideline Eligibility for SRT

78 fewer days spent SRT-eligible



NT-proBNP

80% reduction from baseline to Wk 24



Aficamten
Placebo
Washout

Number of patients

Aficamten	139	141	141	139	139	139	137	139	136	135
Placebo	138	138	139	136	137	135	135	137	134	135

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Error bars are 95% CI
Maron M. "*Aficamten* for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

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SEQUOIA-HCM: Responder Analysis

Significant improvement in exercise capacity and symptoms in composite responder endpoint

	Aficamten n=142	Placebo n=140
≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA FC improvement *or* ≥3.0 mL/kg/min increase in pVO_2 and no worsening of NYHA FC, n (%)	60 (42)	19 (14)
≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA class improvement	44 (31)	9 (6)
≥3.0 mL/kg/min increase in pVO_2 and no worsening of NYHA class	37 (26)	13 (9)
Both ≥3.0 mL/kg/min increase in pVO_2 and ≥1 NYHA class improvement	21 (15)	3 (2)
Common rate difference vs placebo (95% CI)	**28.7** (18.8, 38.6)	
***P* value**	<0.0001	

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SEQUOIA-HCM: Safety Data

AEs with ≥5% incidence

There were no serious adverse cardiovascular events associated with *aficamten* treatment in SEQUOIA-HCM

Event, n (%)	Placebo (n=140)	*Aficamten* (n=142)
Overall AEs	99 (70.7)	105 (73.9)
Headache	10 (7.1)	11 (7.7)
Hypertension	3 (2.1)	11 (7.7)
Palpitations	4 (2.9)	10 (7.0)
Upper respiratory infection	12 (8.6)	9 (6.3)
COVID-19	9 (6.4)	8 (5.6)
Dyspnea	8 (5.7)	8 (5.6)
SAEs	13 (9.3)	8 (5.6)
Cardiac AEs	21 (15.0)	24 (16.9)
Discontinuations	4 (2.9)	5 (3.5)
New-onset AF	1 (0.7)	1 (0.7)
Appropriate ICD shock	1 (0.7)	0
LVEF <50% by core laboratory[a]	1 (0.7)	5 (3.5)
Dose reduction based on site-read LVEF <50%	1 (0.7)	7 (4.9)

[a] 1 placebo- and 1 *aficamten-treated* patient overlap with dose reduction based on site-read LVEF <50%.

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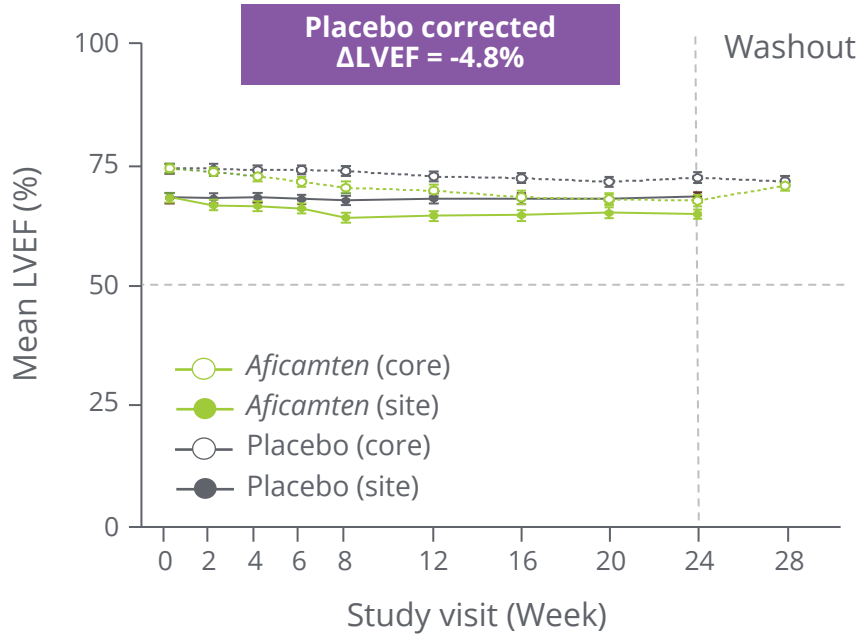
AE, adverse event; SAE, serious adverse event.
Coats CJ. Dosing and Safety Profile of *Aficamten* in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.

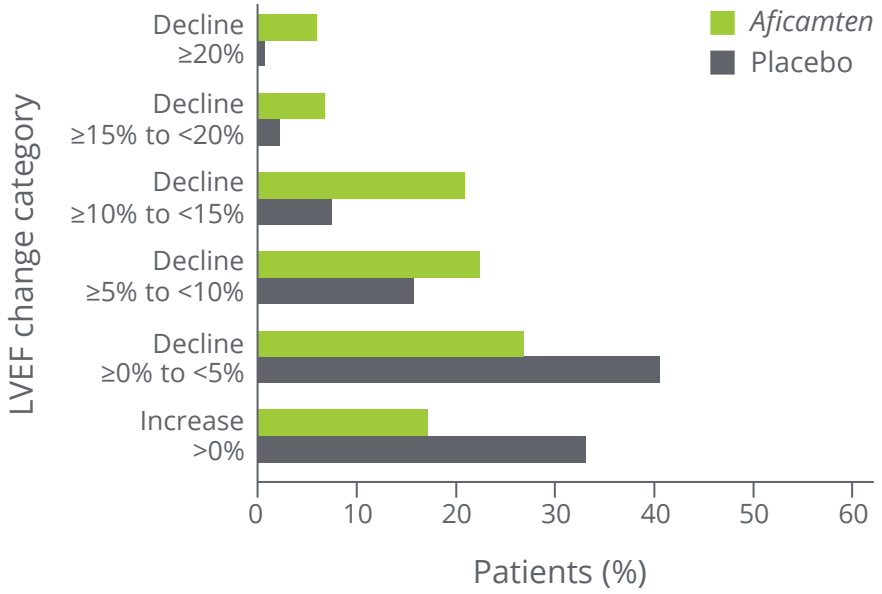
SEQUOIA-HCM: Change in LVEF

Modest reduction in LVEF in patients on *aficamten* resulted in large reductions in LVOT-G

Mean Change in Core Laboratory LVEF Over 24 Weeks



Distribution of Categorical Changes in Core Laboratory LVEF from Baseline to Week 24



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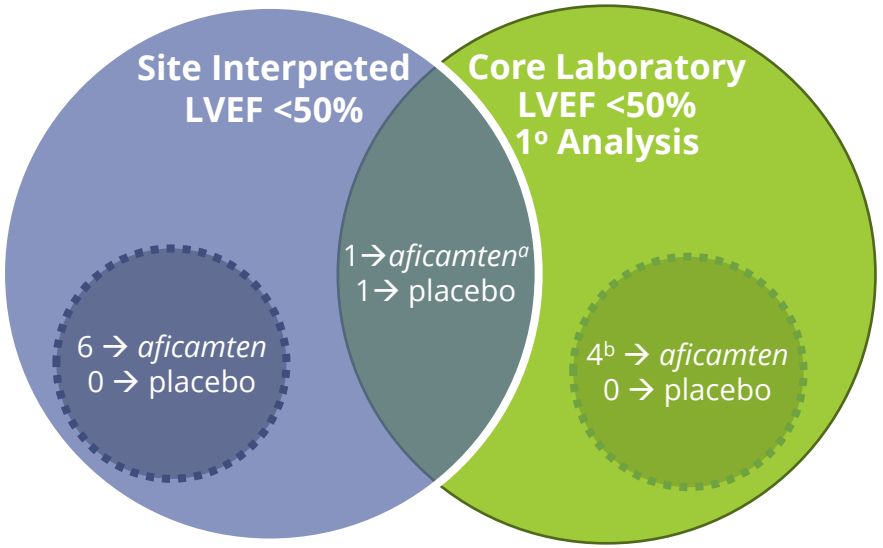
Coats CJ. Dosing and Safety Profile of *Aficamten* in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.

SEQUOIA-HCM: Low Incidence of LVEF <50%

5 (3.5%) of patients on *aficamten* had LVEF <50% determined by the core laboratory



a COVID-19 infection preceded LVEF <50% based on both core and site laboratory assessments.
b Did not undergo dose adjustment (3.5%)

- **No treatment interruptions** occurred
- **No heart failure** was experienced by any *aficamten*-treated patient with LVEF <50% by either core laboratory or site interpreted
- All *aficamten* patients with LVEF <50% were **reversible**

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Coats CJ. Dosing and Safety Profile of *Aficamten* in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.

SEQUOIA-HCM: Low Overall Incidence of LVEF <50%

Core lab LVEF was prespecified source for statistical analyses

LVEF <50% assessed at 3.5% by core lab and 4.9% by site

Prespecified Analysis

Core Lab Only LVEF <50%
4 *aficamten* patients

Age, y, Sex	*Aficamten* Dose, mg/d	BL Core LVEF, %	Study Week With Lowest Core LVEF	Lowest Core LVEF %	Matching Site LVEF %	NYHA Class	KCCQ-CSS	NT-proBNP, Change from BL, ng/dL	Down-Titration, mg	Next Visit LVEF Core	Matching Site LVEF %
30 M	20	65	8	48	62	1	+21	−535	N/A	56	65
57 F	5	56	24	46	60	2	+14	−372	N/A	51	NR
72 F	15	80	20	48	52	1	+5	−403	N/A	52	51
57 F	20	84	16	43	59	1	+12	−921	N/A	72	68

Both Core & Site-Read LVEF <50%
1 *aficamten* patient
1 placebo patient

75 F	Placebo	53	6	48	45	3	+29	−291	N/A	50	51
72 F *	15	63	16	34	49	2	+14	111	15 to 10	55	51

Site-Read Only LVEF <50%
6 *aficamten* patients

Age, y, Sex	*Aficamten* Dose, mg/d	BL Core LVEF, %	Study Week With Lowest Site LVEF	Lowest Site LVEF %	Matching Core LVEF %	NYHA Class	KCCQ-CSS	NT-proBNP, Change from BL, ng/dL	Down-Titration, mg	Next Visit LVEF Core	Matching Site LVEF %
41 M	20	70	16	47	59	2	+2	−1597	20 to 15	54	50
52 M	20	69	16	46	51	1	+25	−712	20 to 15	60	50
76 F	15	87	16	48	53	3	+22	−44	15 to 10	52	50
59 M	15	77	12	48	70	2	+10	−1482	15 to 10	60	55
54 M	15	76	8	49	72	1	+31	−162	15 to 10	60	54
66 M	20	76	20	45	53	3	+8	−83	20 to 15	61	60

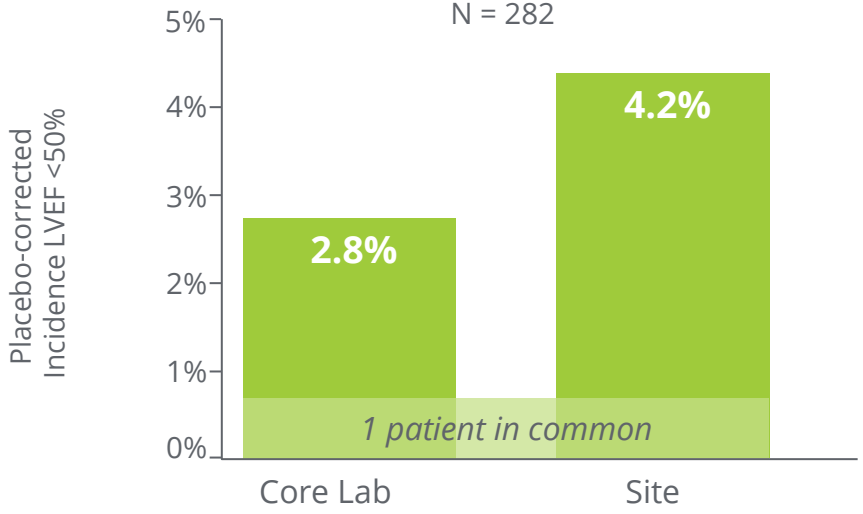
* COVID-19 infection preceded LVEF <50% based on both core and site laboratory assessments.
NR = not recorded, site LVEF were not obtained following Week 24 per protocol
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
Coats CJ. Dosing and Safety Profile of *Aficamten* in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.

Implementation of Dosing in Real-World Setting (FOREST-HCM)

Low incidence of LVEF <50% in patients with oHCM treated with *aficamten*

SEQUOIA HCM

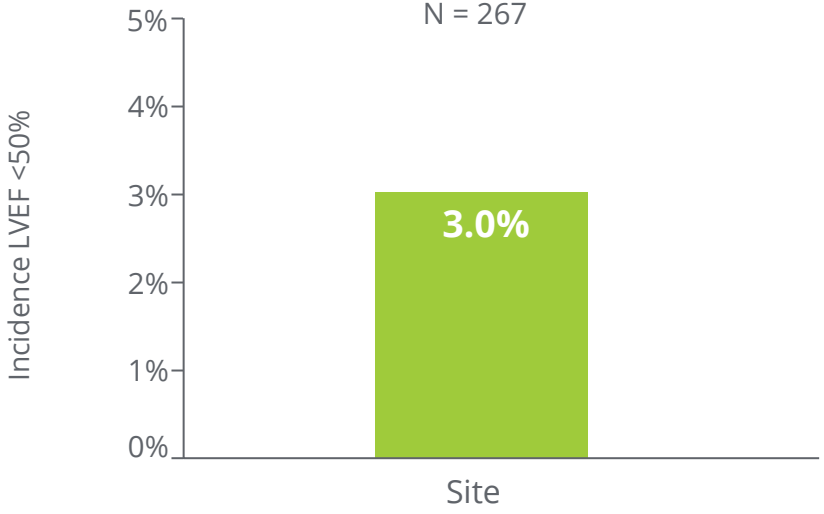
N = 282



- ✓ No treatment interruptions
- ✓ No heart failure events
- ✓ All reversible
- ✓ Great majority of patients on highest doses

FOREST HCM

N = 267



- ✓ No treatment interruptions
- ✓ No heart failure events
- ✓ All reversible
- ✓ Great majority of patients on highest doses

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SEQUOIA-HCM Source: Coats CJ. Dosing and Safety Profile of *Aficamten* in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.

FOREST-HCM Source: Data on file – data cut 15 Apr 24

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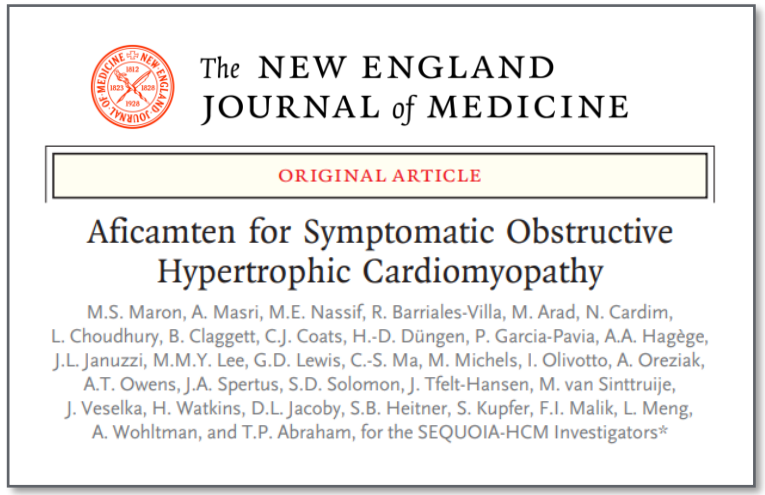
SEQUOIA-HCM: Conclusions

Trial underscores potential clinical efficacy & safety of *aficamten* in patients with symptomatic oHCM

- Patients treated with *aficamten* observed to have:
  - **Clinically meaningful improvements in exercise capacity (pVO_2), consistent across all prespecified subgroups**
  - **Significant reduction in the burden of limiting symptoms** based on improvement in KCCQ-CSS and NYHA Functional Class
- ***Aficamten* was generally well-tolerated with low frequency of LVEF <50%,** all asymptomatic, with no treatment interruptions and no instances of worsening HF
- **Functional & symptomatic improvements associated with benefits as early as 2 weeks; remained consistent & durable throughout treatment period:**
  - Substantial relief from resting and provocable LVOT obstruction observed
  - Large reductions in cardiac biomarker NT-proBNP observed
  - Considerable reduction in the number of patients eligible for SRT observed
- **Treatment effects were reversible within the 4-week washout period**


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

M.S. Maron, A. Masri, M.E. Nassif, R. Barriales-Villa, M. Arad, N. Cardim, L. Choudhury, B. Claggett, C.J. Coats, H.-D. Düngen, P. Garcia-Pavia, A.A. Hagège, J.L. Januzzi, M.M.Y. Lee, G.D. Lewis, C.-S. Ma, M. Michels, I. Olivotto, A. Oreziak, A.T. Owens, J.A. Spertus, S.D. Solomon, J. Tfelt-Hansen, M. van Sinttruije, J. Veselka, H. Watkins, D.L. Jacoby, S.B. Heitner, S. Kupfer, F.I. Malik, L. Meng, A. Wohltman, and T.P. Abraham, for the SEQUOIA-HCM Investigators*

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Maron M. "*Aficamten* for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.
Coats CJ. Dosing and Safety Profile of *Aficamten* in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.
Lewis G. Enhancing Exercise Response in Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.

Preparing for Regulatory Submissions to FDA, EMA

SEQUOIA HCM

Positive Results from SEQUOIA-HCM

2024

- Participated in **two meetings with FDA** in Q1 2024
- **Type B meeting with FDA** to occur in Q2 2024
- **Meetings with EMA** in Q2 2024
- **Expect to submit NDA to FDA** in Q3 2024 and **MAA to EMA** in Q4 2024: development of all modules underway and manufacturing activities on track

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Aspirational Profile of *Aficamten* & Results from SEQUOIA-HCM Inform Potential Risk Mitigation

REMS Existing Challenges	*Aficamten* Aspirational Profile
Echo frequency →	• Rapid onset • Rapid reversibility • Speed to optimal dose • SEQUOIA-HCM: No treatment interruptions due to low LVEF • SEQUOIA-HCM: No instances of worsening HF
Dosing window →	• Predictable dose response • Stable over time
DDI monitoring →	• No teratogenicity • No clinically meaningful P450 liabilities • All background therapies & combinations have been tested in clinical trials • No QTc liability

Potential Unique REMS

Potential for:

Echo monitoring during titration as **early as 2 weeks**, enabling titration to max dose of 20 mg in 6 weeks

Up-titration after each echo based on clinical judgement

Flexible **echo window** for dose titration and maintenance

Few Dose Reductions Occurred During Maintenance

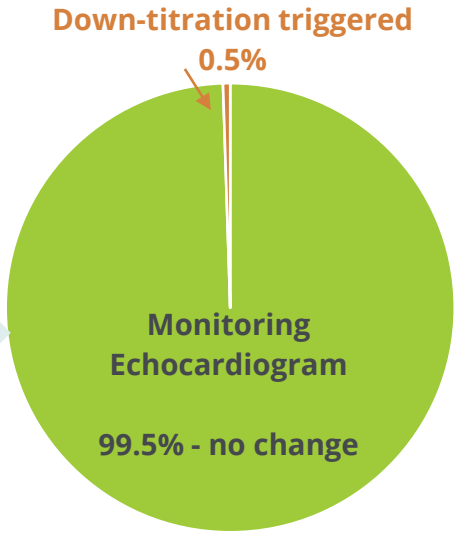
FOREST-HCM data cut as of September 15, 2023

Dose Titration Phase

- **No treatment-related LVEF <50% during the titration period**
- Of the 94 patients having completed the titration period, ~**2/3 are receiving 15 and 20 mg qd**
- Approximately 30% of patients have **reduced doses or discontinued background therapy** at the discretion of the treating physician and/or request from the patient

Maintenance Phase

- **579 monitoring echocardiograms completed* in oHCM patients**
- **None with LVEF <40%** requiring treatment interruption
- 3 patients (0.5%) with LVEF <50%
  - Two asymptomatic patients (LVEF of 47% and 49%) resulting in per-protocol dose reduction
  - One patient with atrial fibrillation (unrelated) and LVEF of 47%
  - All 3 patients are currently receiving *aficamten* with apparent relief from obstruction, symptoms & improved biomarkers



Target dose defined as achieved if Valsalva LVOT-G ≤ 30 mmHg or no dose change for 2 consecutive visits

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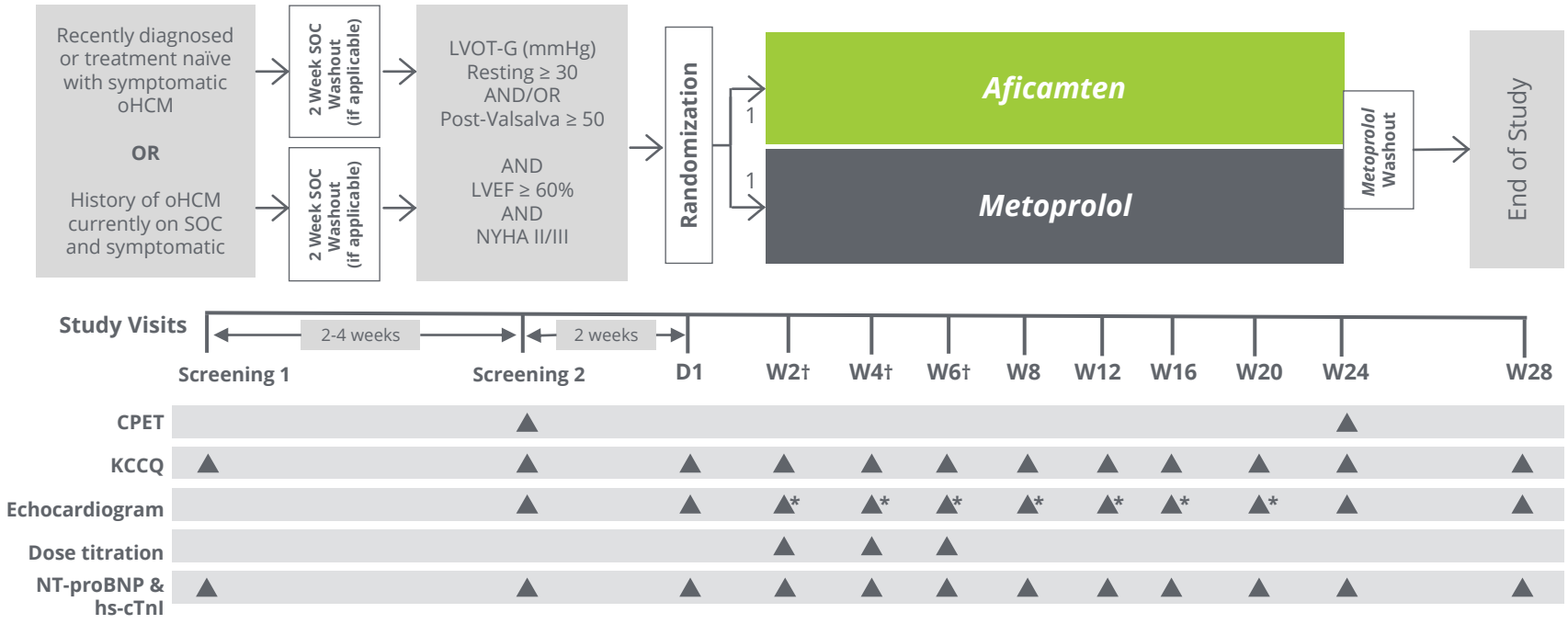
MAPLE-HCM: Phase 3 Monotherapy Trial

Currently enrolling

Active-comparator trial of *aficamten* as monotherapy vs. *metoprolol* in patients with oHCM

- Trial to enroll approximately **170 patients**
- Primary endpoint: **change in peak VO_2, assessed by CPET from baseline to Week 24**
- Secondary endpoints: **change in NYHA class, KCCQ, NT-proBNP, and measures of structural remodeling**



SOC: standard of care
**Focused echocardiogram*
***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

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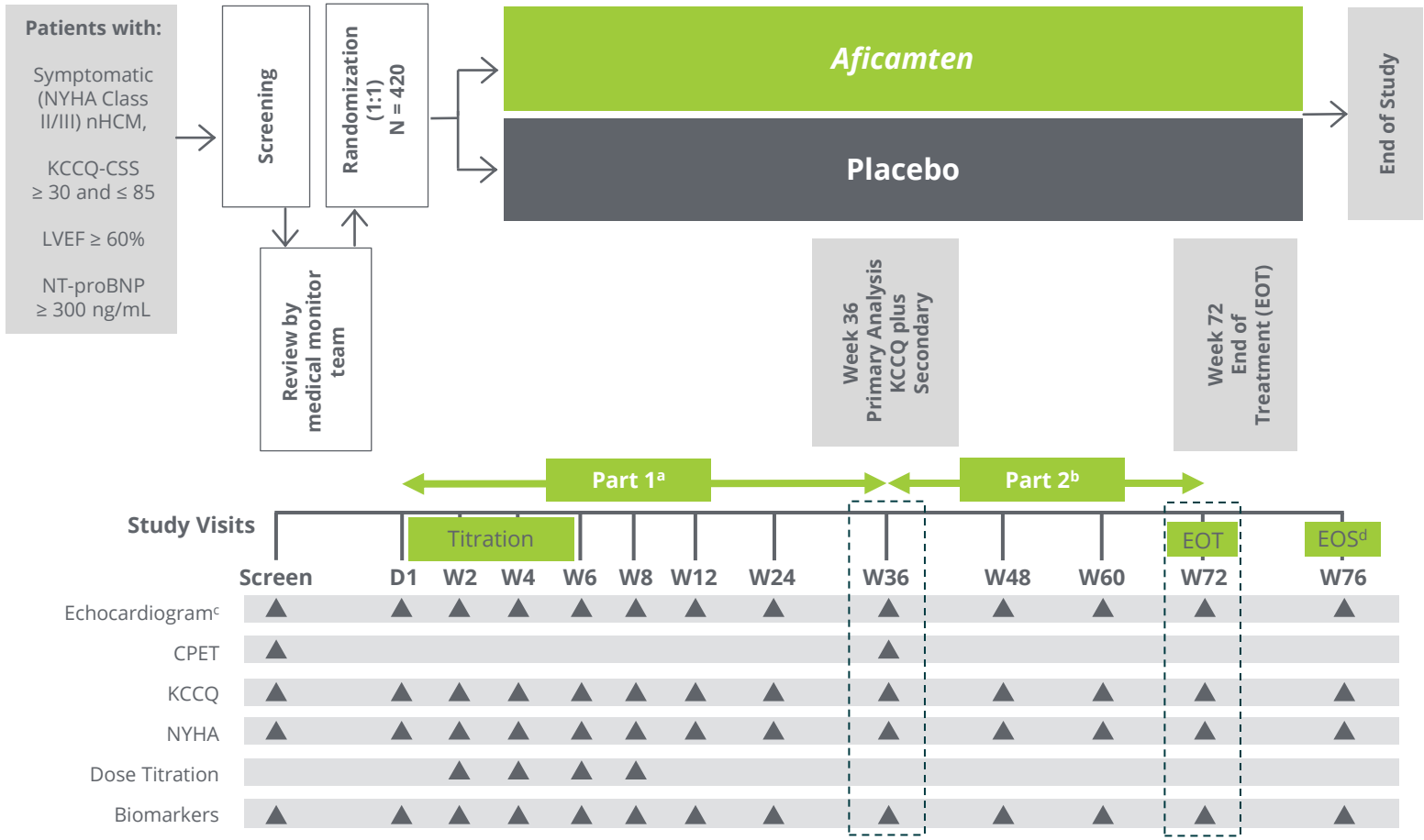
ACACIA-HCM: Pivotal Phase 3 Trial in nHCM

Currently enrolling

- Trial to enroll approximately **420 symptomatic nHCM patients**
- Primary endpoint: **change in KCCQ Clinical Summary Score** from baseline to Week 36
- **5-20 mg doses**; 6-week titration period
- Secondary endpoints:
  - Change in pVO_2, Ve/VCO_2,
  - Left atrial volume index (LAVI)
  - NT-proBNP
  - Proportion of patients with ≥1 class improvement in NYHA from baseline to Week 36
  - Time to first cardiovascular event



[a] Part 1: All participants followed until week 36
[b] Part 2: Participants completing Week 36 continue until either Week 72 (followed by EOS at Week 76) OR the last randomized participant in Part 1 completes Week 36.
[c] Site-read focused echocardiogram for titration visit (sole criterion). *Aficamten* dose range 5-20 mg.
[d] 4-week follow up after last dose

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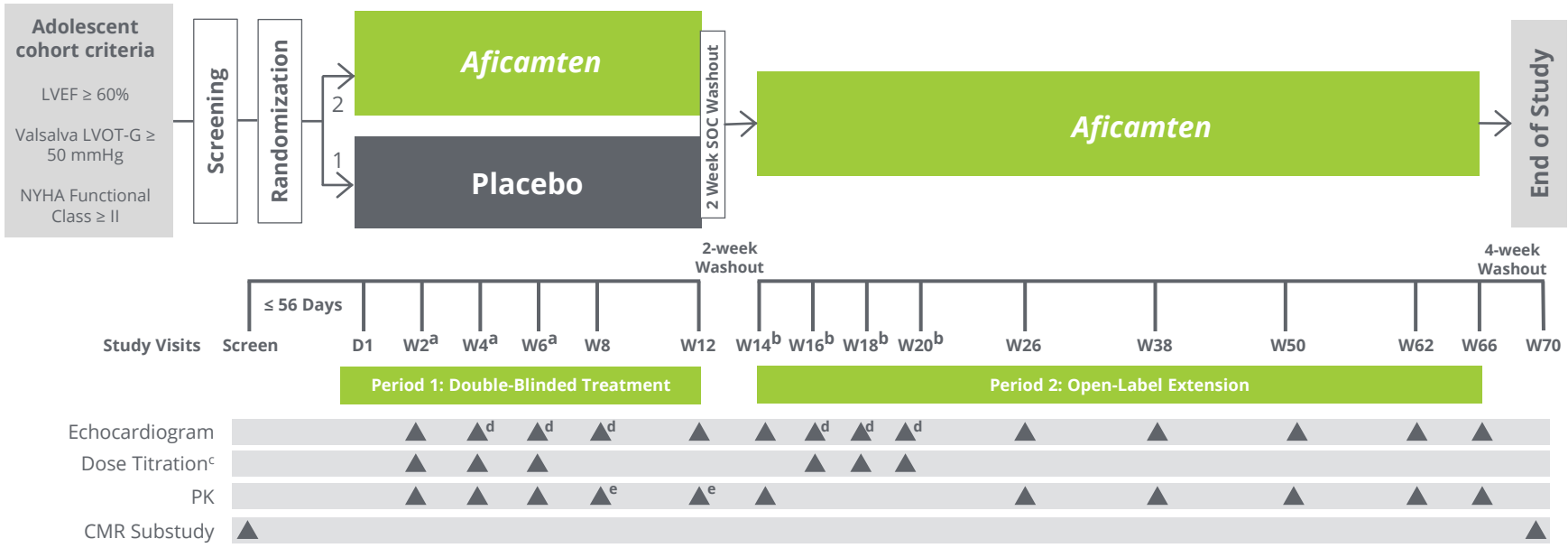
CEDAR-HCM: Clinical Trial in Pediatric Population

Currently enrolling

- Expected to enroll initial cohort of ~**40 adolescent patients aged 12 to 17**
- Data from adolescent patients will support decision to enroll **cohort of ~8 to 10 patients aged 6 to 11**
- **5-20 mg doses**; 6-week titration period
- Primary endpoint: **change in LVOT-G** from baseline to Week 12
- Secondary endpoints: **change in resting LVOT-G, NYHA Functional Class, pharmacokinetics & cardiac biomarkers**



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a Up-titration to the next dose in Period 1 will be managed by the IRT system and will only occur if Valsalva LVOT-G is ≥ 30 mmHg and biplane LVEF is ≥ 55%

b In Period 2, participants will start dosing with aficamten at the lowest dose (5 mg) and up-titration to the next dose (10, 15, or 20 mg) will be managed by the Principal Investigator or designee if Valsalva LVOT-G is ≥ 30 mmHg and biplane LVEF is ≥ 55%. Up-titrations may occur no more frequently than every 2 weeks

c Additional ad hoc titrations after Week 20 may occur at ad hoc titration visits (at least 2 weeks apart) or during a planned visit (ie, Weeks 26, 38, 50, or 62). A titration follow-up visit is required 2 weeks after any titration occurring after Week 20

d Focused echocardiogram (LVOT-G and LVEF only)

e Intensive PK substudy may occur at Week 8 or Week 12

Cytokinetics®

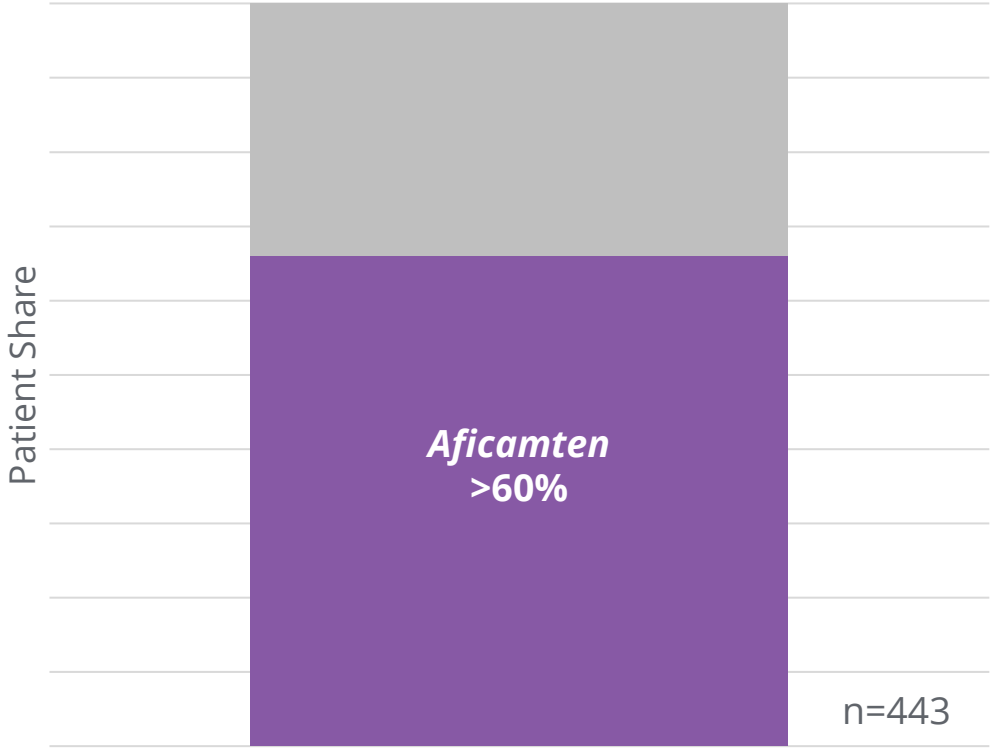
Cytokinetics Poised to Compete in the Specialty Cardiology Business

Potential for high return on investment

	Broad Cardiology	Specialty Cardiology
Example Therapies	Heart failure, cholesterol, blood thinner	**HCM, TTR amyloidosis**
Prescribers	*Broad*: Cardiologists, PCPs (50K+)	***Concentrated*: Subset of cardiologists (~10K)**
ROI / Prescriber	Limited	**High**
Distribution	Retail	**Limited, specialty distributor**
Customer-Facing Reps	Entry level	**Highly experienced**
Support Services	*Standard*: Affordability / copay	***High-touch*: Financial, education, journey**
Managed Care	Competitive/high rebates	**Managed to label**
Diagnosis	High awareness and diagnosis rate	**Limited awareness with high % undiagnosed**
HCP – Rep Interactions	Brief features/benefits	**Comprehensive broad-based discussion**

Market Research Shows *Aficamten* May Achieve High Share & Grow Category

oHCM CMI Preference Shares in Eligible Patient Population*



Survey results are based on the aspirational profile of *aficamten* and if approved, the actual profile could vary materially.

- Potential target product profile for *aficamten* interest creates **share opportunity** in newly treated CMI patients
- *Aficamten* could also be **expected to expand the total CMI market**
- Key attributes that may drive preference include the potential for:
  - LVOT gradient reduction
  - Change in NYHA Functional Class
  - Pharmacodynamics/LVEF maintenance
  - Change in KCCQ
  - Absence of DDI

Source: *Aficamten* Impact of Product Attributes on Product Preference Share n=443 cardiologists, Quantitative research including conjoint - Cogent

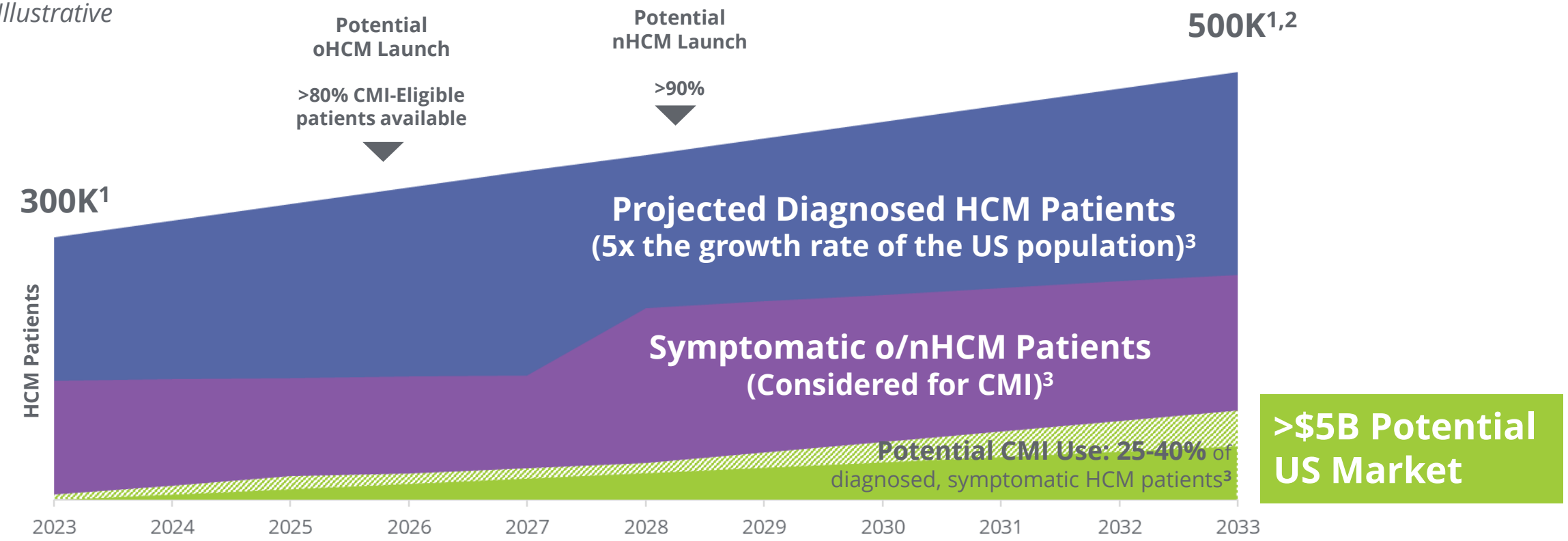
***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

If *Aficamten* is Approved, Expect Majority of CMI-Eligible Patients Available at Launch

Diagnosis of HCM anticipated to grow 5x the rate of the general U.S. population

US HCM Patients (in '000)

Illustrative



1. DoF: SHA; Symphony PTD (Patient Transaction Data): Includes patients diagnosed since 2016 and having any HC transaction in the claims data universe in the last year June 2022-May 2023);
2. Butzner et al 2021 estimated a 8% growth rate in diagnosed HCM patients between 2013-2019 https://www.ajconline.org/article/S0002-9149(21)00783-9/fulltext; CYTK is forecasting an average growth rate of 5% over the coming decade;
3. Internal forecasts

***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

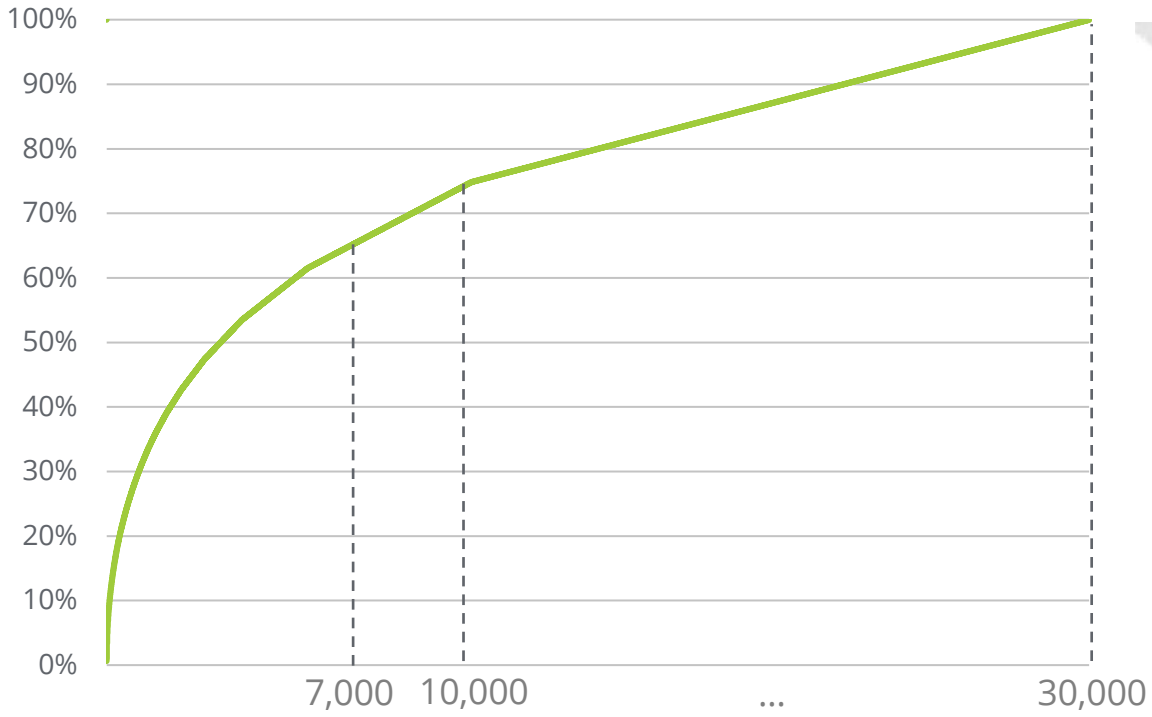
Projections and forecasts for illustration

Cytokinetics®

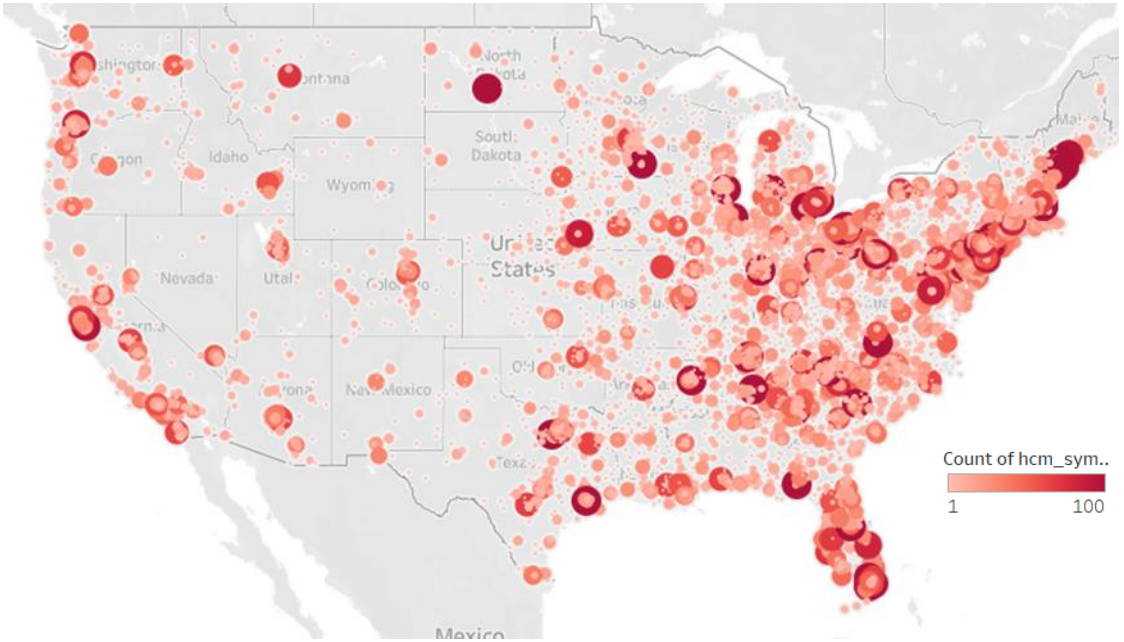
Cardiologists Located in Concentrated Geographic Clusters Across the US

~75% of the HCM patient volume is treated by ~10,000 cardiologists

HCM Patient Concentration by Cardiologist



Geographic Distribution of HCM Patients



Note: includes only patients who are treated by a cardiologist - not all patients see a cardiologist; sample of 67K HCM patients
Source: Symphony PTD (Patient Transaction Data); mapping of HCPs to HCOs using Definitive Healthcare Data 2023 and 7/2023 mapping; Patient volume by dominant Cardiologist Location 7/2023
***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

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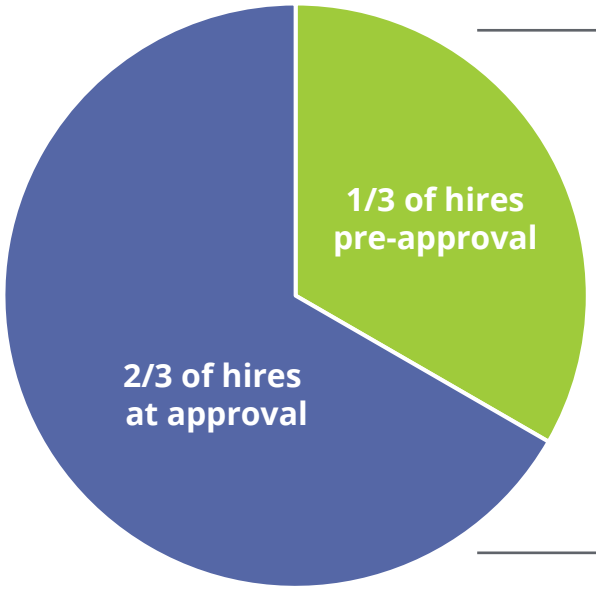
Gated Build of Commercial Infrastructure

Majority of spending to occur closer to potential approval in 2025

2/3 of hiring to occur at-approval



Commercial leadership
Marketing
HEOR
Patient services
Access & distribution
Field operations
Commercial learning & development
Sales team leadership

Sales representatives

Key activities after SEQUOIA-HCM readout

Continued insight generation
Market access strategy validation
Pricing strategy finalization
Distribution approach
Payer engagement
Brand strategy evolution
Customer account identification
Launch campaign development
Customer Experience
Payer Pre-approval Information Exchange
Sales force planning
Data & Technology Infrastructure build
Omnichannel execution
Market development rollout

Initiated upon FDA approval

Media purchases
Patient support programs
Peer to peer engagement
HCP Omnichannel launched

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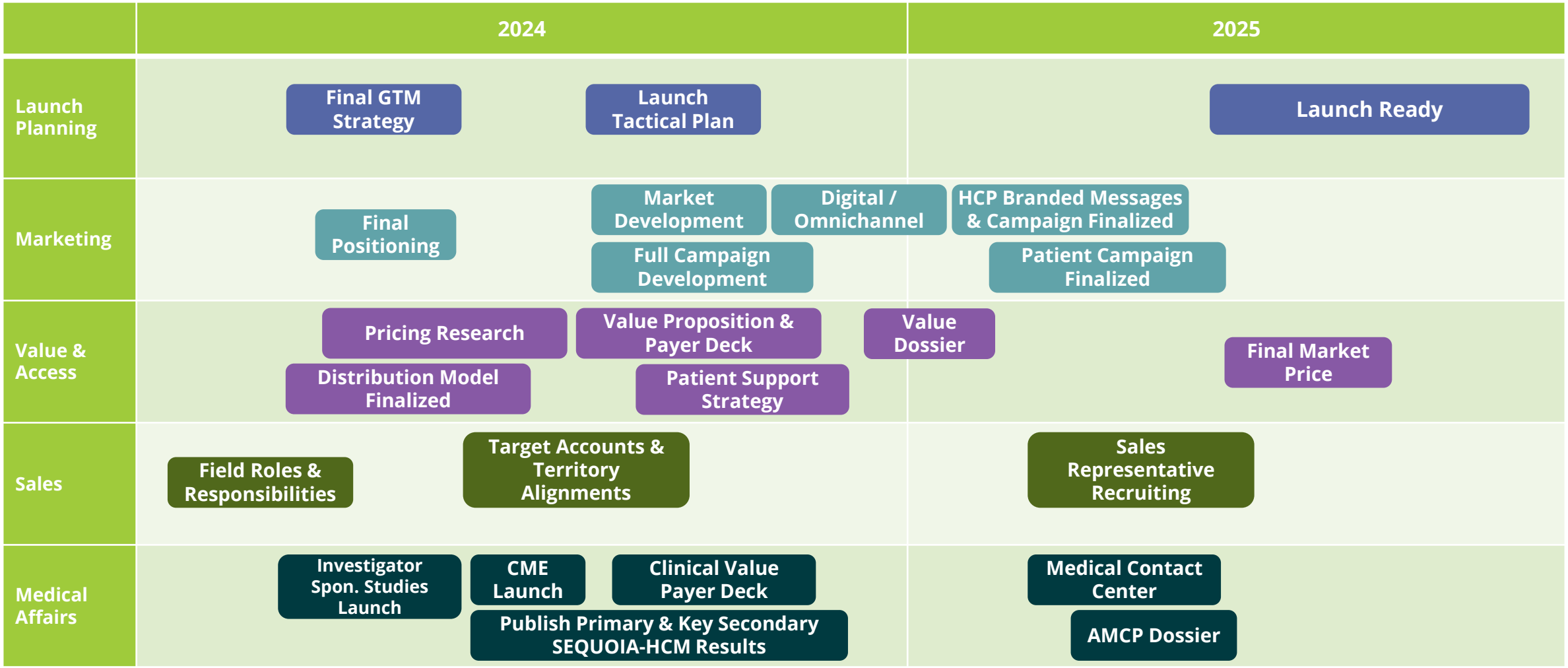
US Commercial Readiness Milestones for *Aficamten*

2024-2025



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Omecamtiv Mecarbil

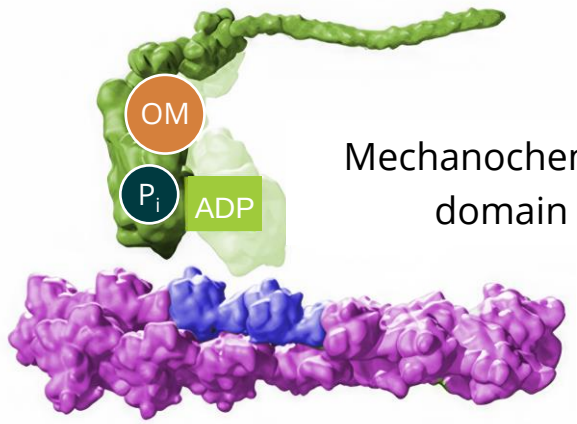
Cytokinetics®

Omecamtiv mecarbil is an investigational agent and has not been approved for use by the U.S. Food & Drug Administration (FDA) or any regulatory agency. The safety and effectiveness of this product has not been established.

Omecamtiv Mecarbil: Mechanism of Action

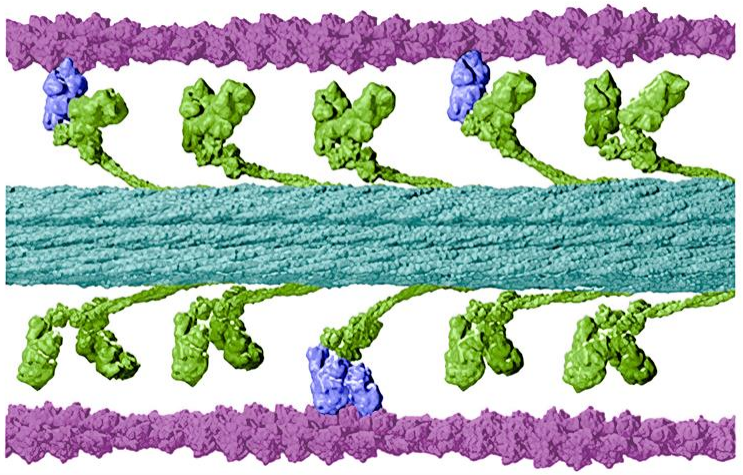
Omecamtiv mecarbil shifted equilibrium in favor of the pre-powerstroke state

"More hands pulling on the rope"



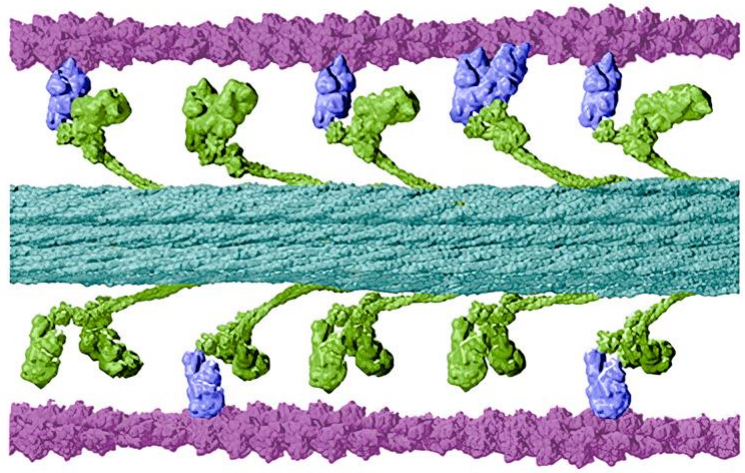
Pre-Powerstroke State

Before *Omecamtiv Mecarbil*



Actin sliding

After *Omecamtiv Mecarbil*



Actin sliding

Malik, et al. Science 2011; 1439-1443
Planelles-Herrero, et al. Nature Comm 2017; 1-10
Shen et al, Circ HF, July 2010, 522-527
Teerlink, et al. JACC-HF 2020; 329-340

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Omecamtiv Mecarbil: Potential for High-risk Severe HF Patients Despite GDMT

Advancing efficient, pragmatic Phase 3 clinical trial

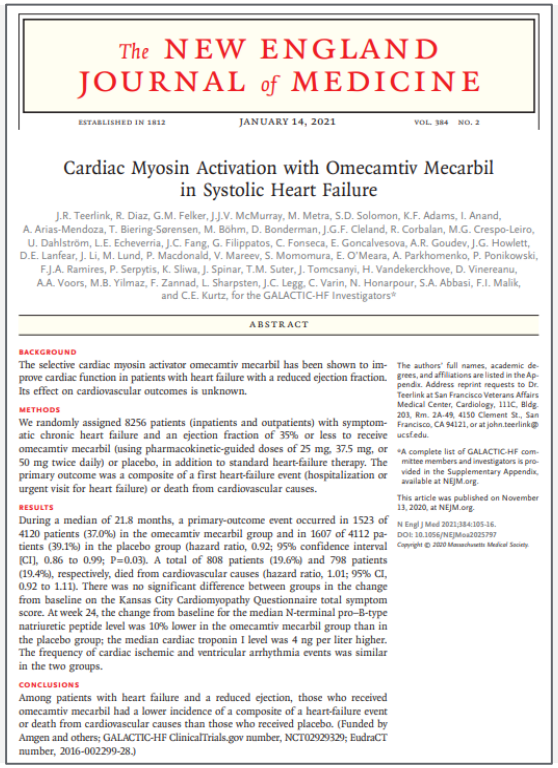
High Unmet Need

The large and growing heart failure population faces frequent hospitalizations, high mortality rates, comorbidities, and challenges staying on GDMT. Despite SGLT2 inhibitors, patients remain at significant risk.

Market Opportunity

18% of 7.1M patients with HFrEF have worsening heart failure (LVEF< <30%)

Estimated 8+ years of market exclusivity



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 14, 2021 VOL. 384 NO. 2

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

J.R. Teerlink, R. Diaz, G.M. Felker, J.J.V. McMurray, M. Metra, S.D. Solomon, K.F. Adams, I. Anand, A. Arias-Mendoza, T. Biering-Sørensen, M. Böhm, D. Bonderman, J.G.F. Cleland, R. Corbalan, M.G. Crespo-Leiro, U. Dahlström, L.E. Echeverria, J.C. Fang, G. Filippatos, C. Fonseca, E. Goncalvesova, A.R. Goudev, J.G. Howlett, D.E. Lanfear, J. Li, M. Lund, P. Macdonald, V. Mareev, S. Momomura, E. O'Meara, A. Parkhomenko, P. Ponikowski, F.J.A. Ramires, P. Serpytis, K. Sliwa, J. Spinar, T.M. Suter, J. Tomcsanyi, H. Vandekerckhove, D. Vinereanu, A.A. Voors, M.B. Yilmaz, F. Zannad, L. Sharpsten, J.C. Legg, C. Varin, N. Honarpour, S.A. Abbasi, F.I. Malik, and C.E. Kurtz, for the GALACTIC-HF Investigators*

ABSTRACT

BACKGROUND
The selective cardiac myosin activator omecamtiv mecarbil has been shown to improve cardiac function in patients with heart failure with a reduced ejection fraction. Its effect on cardiovascular outcomes is unknown.

METHODS
We randomly assigned 8256 patients (inpatients and outpatients) with symptomatic chronic heart failure and an ejection fraction of 35% or less to receive omecamtiv mecarbil (using pharmacokinetic-guided doses of 25 mg, 37.5 mg, or 50 mg twice daily) or placebo, in addition to standard heart-failure therapy. The primary outcome was a composite of a first heart-failure event (hospitalization or urgent visit for heart failure) or death from cardiovascular causes.

RESULTS
During a median of 21.8 months, a primary-outcome event occurred in 1523 of 4120 patients (37.0%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.86 to 0.99; P=0.03). A total of 808 patients (19.6%) and 798 patients (19.4%), respectively, died from cardiovascular causes (hazard ratio, 1.01; 95% CI, 0.92 to 1.11). There was no significant difference between groups in the change from baseline on the Kansas City Cardiomyopathy Questionnaire total symptom score. At week 24, the change from baseline for the median N-terminal pro–B-type natriuretic peptide level was 10% lower in the omecamtiv mecarbil group than in the placebo group; the median cardiac troponin I level was 4 ng per liter higher. The frequency of cardiac ischemic and ventricular arrhythmia events was similar in the two groups.

CONCLUSIONS
Among patients with heart failure and a reduced ejection, those who received omecamtiv mecarbil had a lower incidence of a composite of a heart-failure event or death from cardiovascular causes than those who received placebo. (Funded by Amgen and others; GALACTIC-HF ClinicalTrials.gov number, NCT02929329; EudraCT number, 2016-002299-28.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Teerlink at San Francisco Veterans Affairs Medical Center, Cardiology, 111C, Bldg. 203, Rm. 2A-49, 4150 Clement St., San Francisco, CA 94121, or at john.teerlink@ucsf.edu.

*A complete list of GALACTIC-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 13, 2020, at NEJM.org.

N Engl J Med 2021;384:105-16.
DOI: 10.1056/NEJMoa2025797
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Ph 3 clinical trial results in 8,000 patients point to important treatment benefit

Planning confirmatory Ph 3 trial, **n=~2,000, 2-3 years** to completion

Primary endpoint: time to CV death, HF events, transplant/LVAD, or stroke

Larger treatment benefit in patients with lower LVEF and other markers of advanced HF

Pragmatic design elements including EHR screening, limited monitoring visits, remove visits, and limited safety labs & AE reporting

Omecamtiv mecarbil is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

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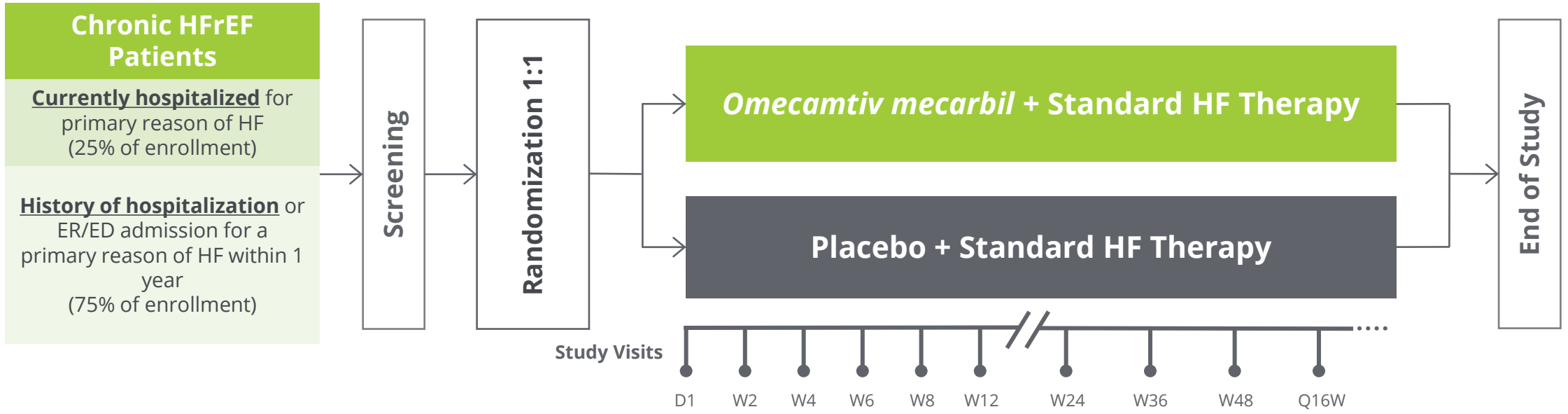
GALACTIC-HF: Clinical Trial Overview

Phase 3 clinical trial

Event-driven clinical trial; 8,256 patients randomized in 35 countries at 944 clinical trial sites



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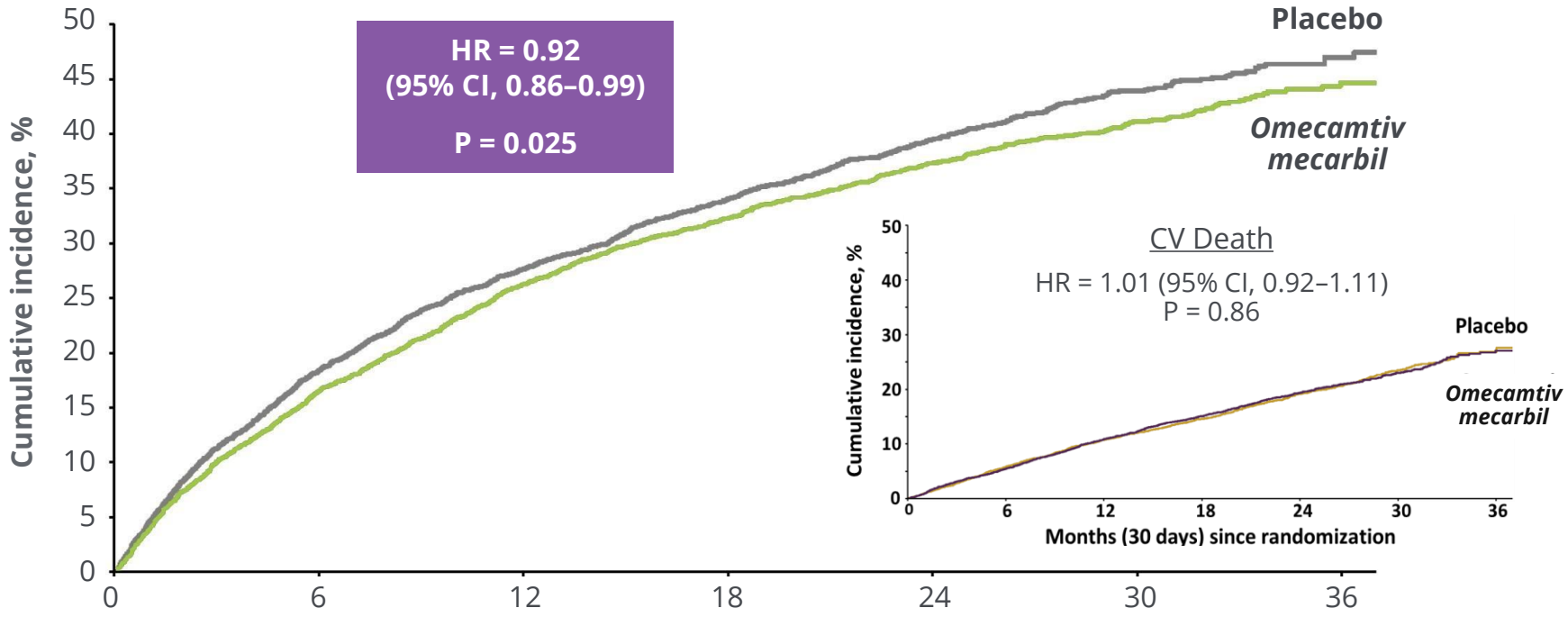
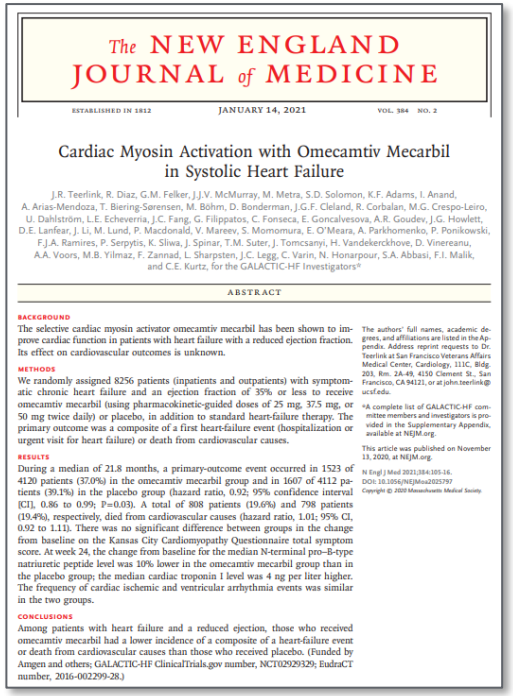
Primary Composite Endpoint



Patients at risk, n							
Placebo	4112	3310	2889	2102	1349	647	141
OM	4120	3391	2953	2158	1430	700	164



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Time to first HF event or CV death

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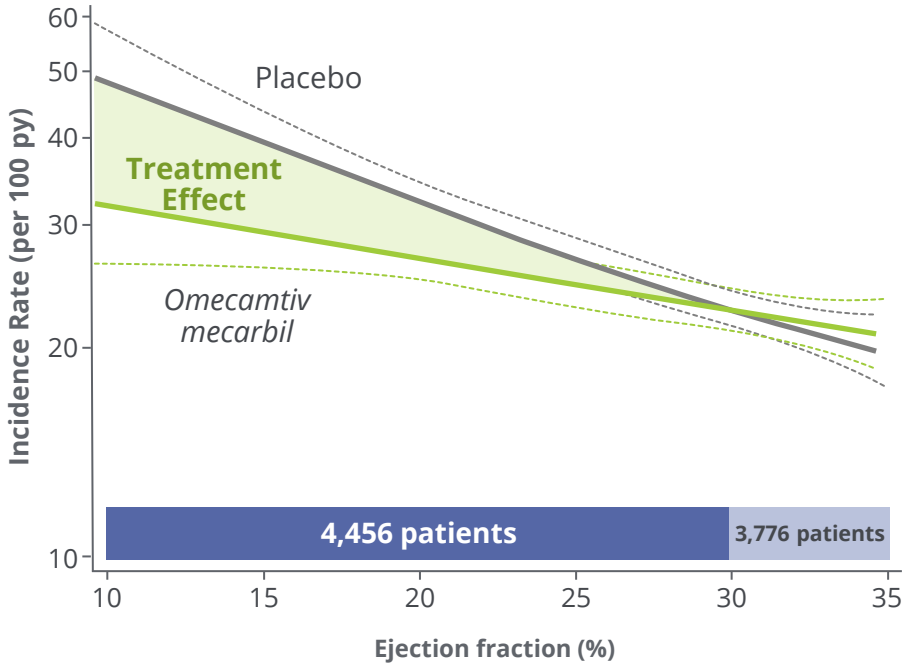
Benefit Observed to Increase as Baseline LVEF Decreased

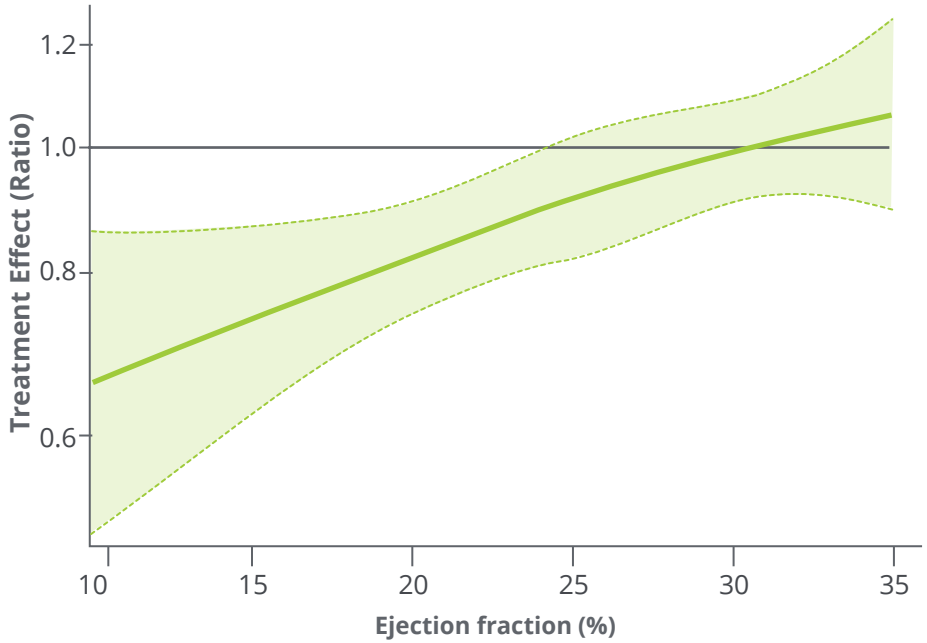
GALACTIC-HF

Incidence of Primary Composite Endpoint



Pre-specified Subgroup	Baseline LVEF	≤ median (28%)	0.84 (0.77, 0.92)
		> median (28%)	1.04 (0.94, 1.16)
	Interaction P-value = 0.004		

Relative Treatment Effect on Primary Endpoint



JACC

ORIGINAL INVESTIGATIONS

Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv Mecarbil in GALACTIC-HF

ABSTRACT

ARR = Absolute Risk Reduction. RRR = Relative Risk Reduction.
Teerlink JR., Diaz R., Felker GM., et al. Effect of Ejection Fraction on Clinical Outcomes in Patients treated with Omecamtiv Mecarbil in GALACTIC-HF. JACC. 2021
***Omecamtiv mecarbil* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

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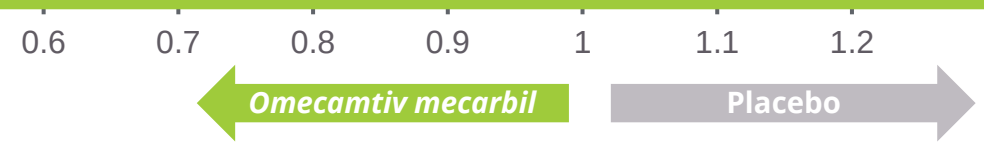
Large Treatment Effect in Easily Defined HF Population

GALACTIC-HF

	N	Hazard Ratio (95% CI)	Nom p-value	ARR
All Patients	8232		0.025	2.1
LVEF <30%	4704		<0.001	4.9
+ Hosp <3 mos	2836		<0.001	6.2
+ SBP <110	1881		0.004	7.2
+ Class III/IV	2249		<0.001	8.9
+ NT-proBNP ≥1000 pg/mL	2852		<0.001	8.8



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Treatment Effect in High-Risk Population with LVEF <30%

GALACTIC-HF

LVEF < 30% NTproBNP ≥ 1000 pg/mL Hospitalization within 12 mo	N	HR (95% CI)	Placebo Event Rate (%)	ARR (/100 p-y)	p-value
Primary Composite Endpoint **(CV death, HF event, LVAD/transplant, stroke)**	2852	0.78 (0.70, 0.86)	49.4	8.8	p < 0.001
CV Death		0.87 (0.75, 1.01)	25.5	1.8	p = 0.07
First HF Event		0.75 (0.66, 0.85)	38.1	7.5	p < 0.001

LVAD = left ventricular assist device, ARR = absolute risk reduction

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Cytokinetics®

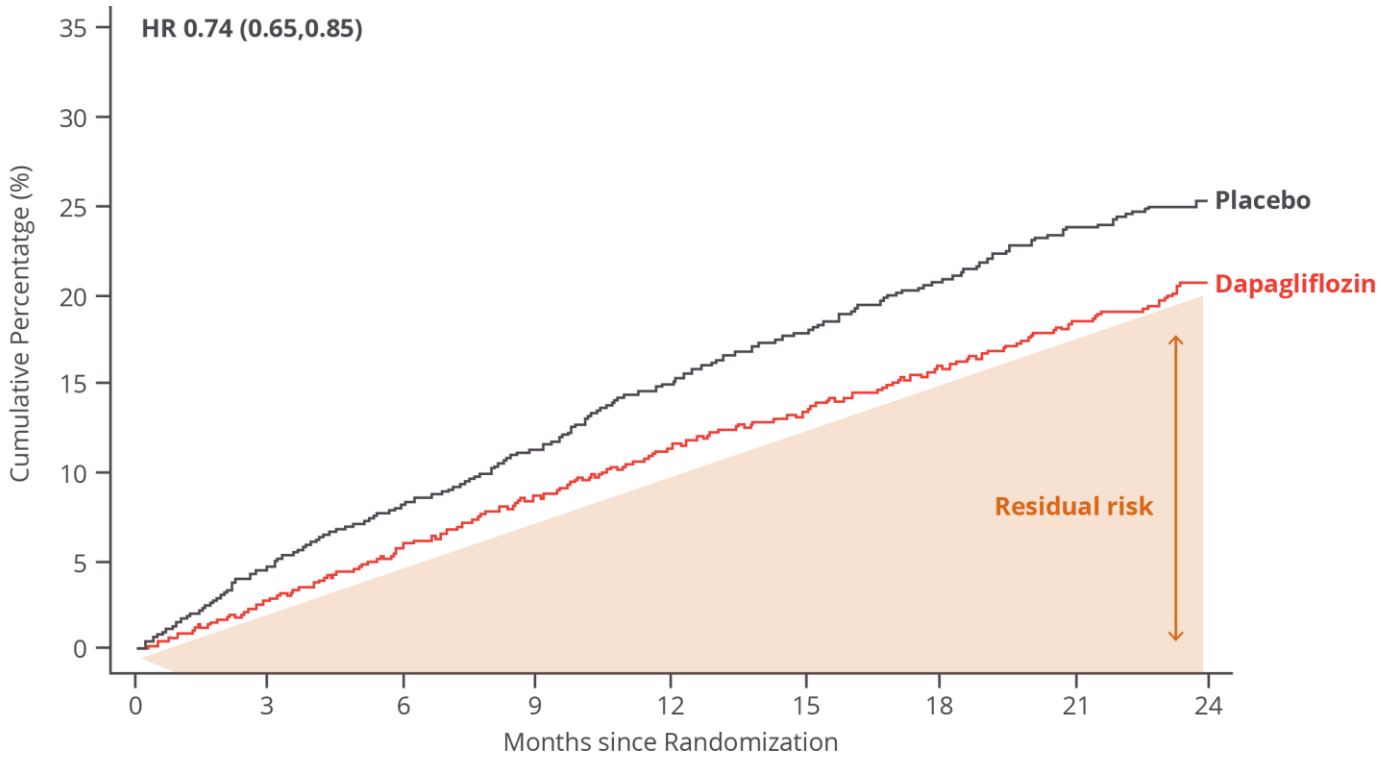
Residual Risk is High Despite Best Therapy

DAPA-HF Trial: Patients on GDMT including SGLT2-i

DAPA-HF trial
(dapagliflozin group)

- **Primary endpoint: CV Death/HF hospitalization/urgent HF visit**
- **4744 patients**
- Renin-angiotensin system blocker **94%**
- Beta-clocker **96%**
- Mineralocorticoid receptor (aldosterone) antagonist **71%**

DAPA-HF trial Residual Risk



Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

McMurray J et al, N Engl J Med. 2019;381:1995-2008

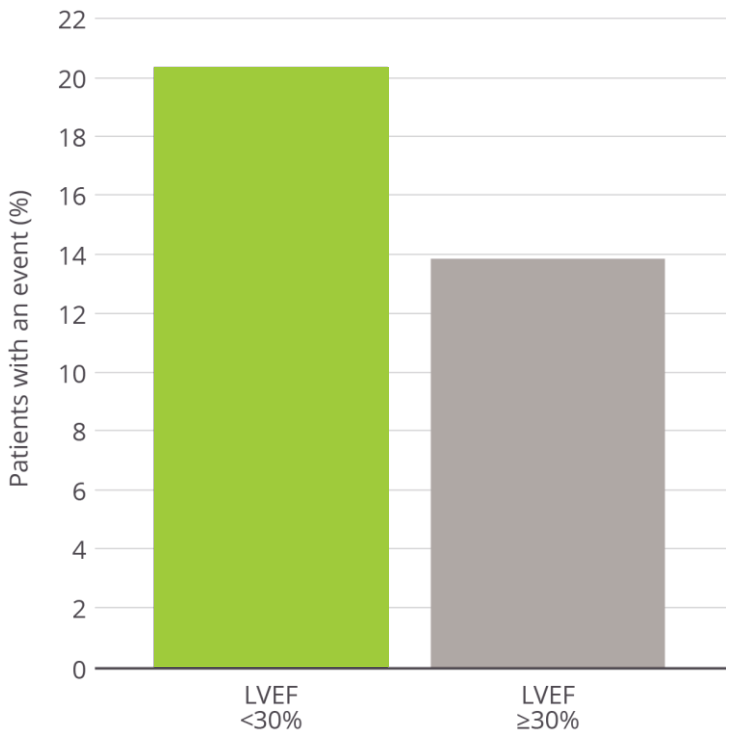
Cytokinetics®

Residual Risk is High Despite Best Therapy

DAPA-HF trial
(dapagliflozin group)

- **2373 patients**
- **Median follow-up 18.2 months**
- Renin-angiotensin system blocker **94%**
- Beta-blocker **96%**
- Mineralocorticoid receptor (aldosterone) antagonist **71%**
- SGLT2 inhibitor **100%**

Event rate according to LVEF (<30% vs. ≥30%)



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Safety in Low LVEF Subgroup Consistent with Overall Population

GALACTIC-HF

Incidences of SAEs, ventricular arrhythmias, & cardiac ischemic events were similar

Incidence of stroke was lower with *omecamtiv mecarbil*

	Overall Population		LVEF ≤28%	
	Omecamtiv Mecarbil N=4110 %	Placebo N=4101 %	***Omecamtiv Mecarbil*** N=2208 %	Placebo N=2236 %
Serious adverse events	57.7	59.4	58.8	61.9
Adverse events				
Ventricular tachyarrhythmia (narrow SMQ)	7.1	7.4	8.0	8.2
Torsade de pointes/QT prolongation (SMQ)	4.3	4.8	5.2	5.8
Serious adverse ventricular arrhythmia requiring Rx	2.9	3.1	3.4	3.6
Adjudicated major cardiac ischemic event	4.9	4.6	4.6	4.2
Myocardial infarction	3.0	2.9	3.0	2.9
Hospitalized for unstable angina	0.6	0.3	0.4	0.2
Coronary revascularization	2.8	2.9	2.6	2.5
Adjudicated stroke	1.6	2.8	2.1	2.6

GALACTIC-HF CSR Table 14.3.4.5.27

Omecamtiv mecarbil **is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

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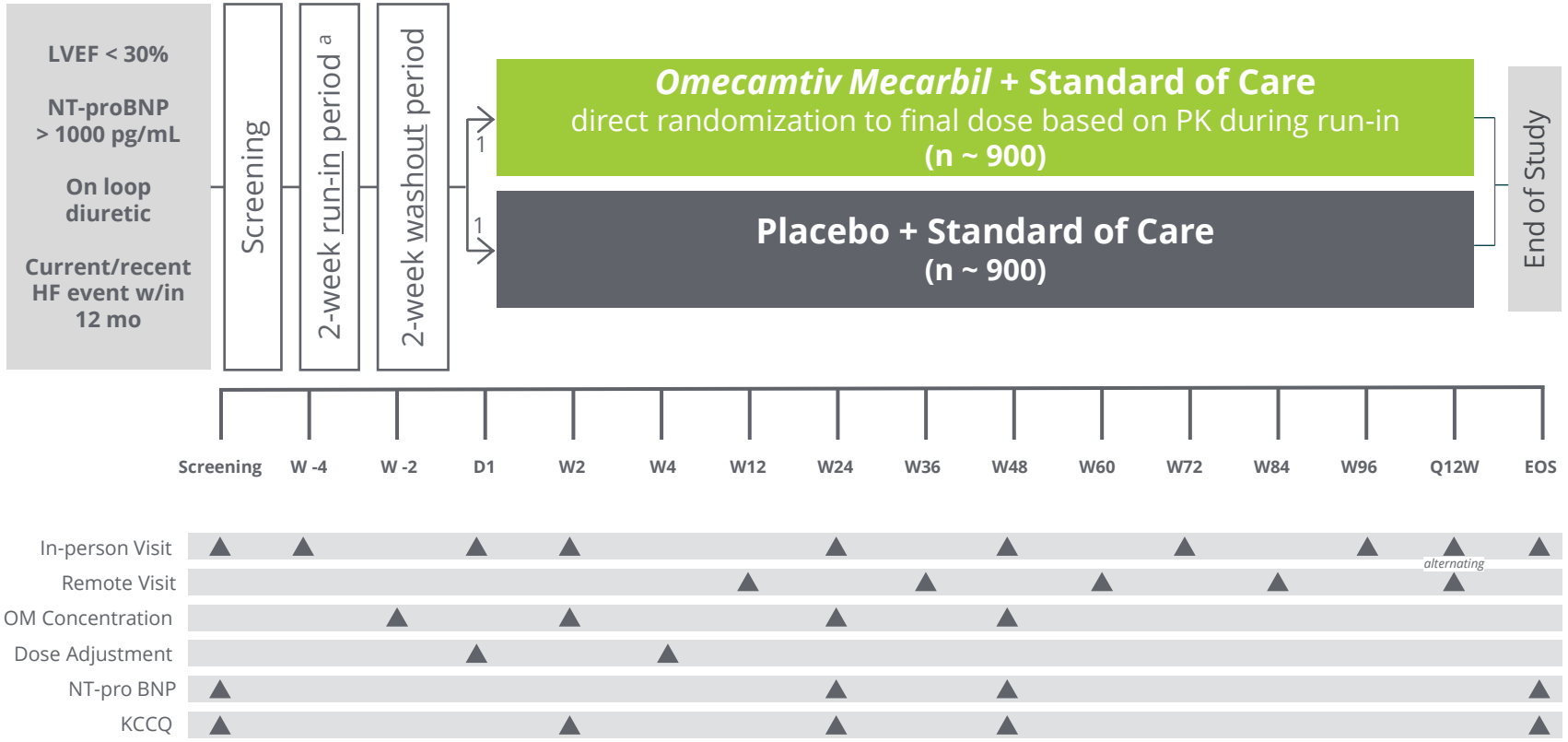
Phase 3 Confirmatory Anticipated Clinical Trial Design

Trial design to be finalized

- Primary endpoint: **time to CV death, HF events, transplant/LVAD, or stroke**
- **Enriched dosing for adherence**, with OM run-in period. Plan to randomize only those expected to land in therapeutic range
- **Pragmatic design elements:**
  - EHR screening
  - Limit monitoring visits
  - Remote visits
  - Limited safety labs & AE reporting



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Cytokinetics®

Omecamtiv Mecarbil: HFrEF Epidemiology

Circ Heart Fail. 2012;5:720-726
REAL HFrEF Study 2021
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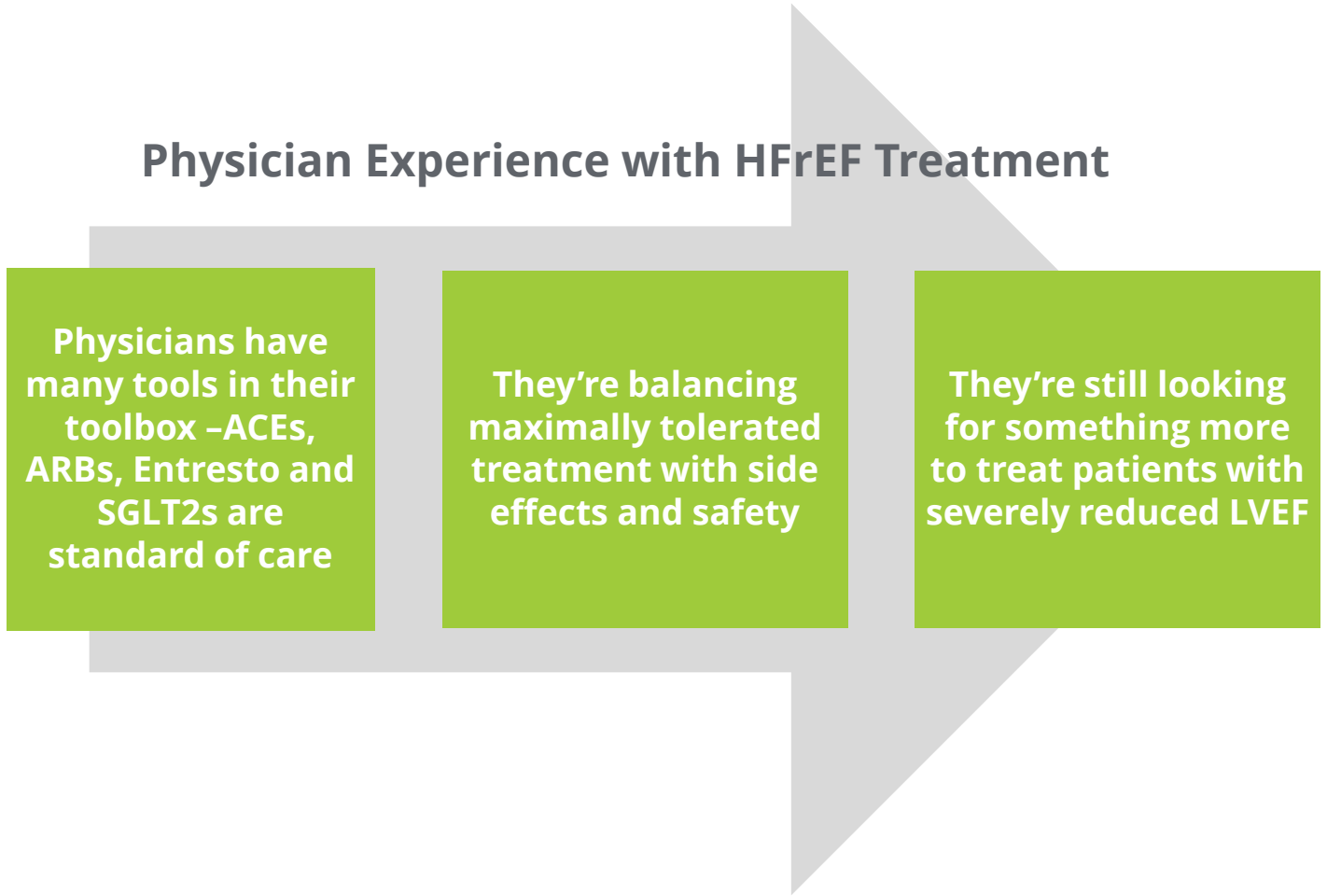
Omecamtiv Mecarbil: SOC Not Addressing Needs of Patients with EF <30%



Proposed Patient Type for *Omecamtiv Mecarbil*

- EF <30%
- Not responding to current treatment options, recently hospitalized
- Patients with renal insufficiency / hypotension / elevated NT-pro BNP
- Have contraindications limiting necessary SoC dose increases, e.g. low BP or renal dysfunction
- Higher NYHA grade

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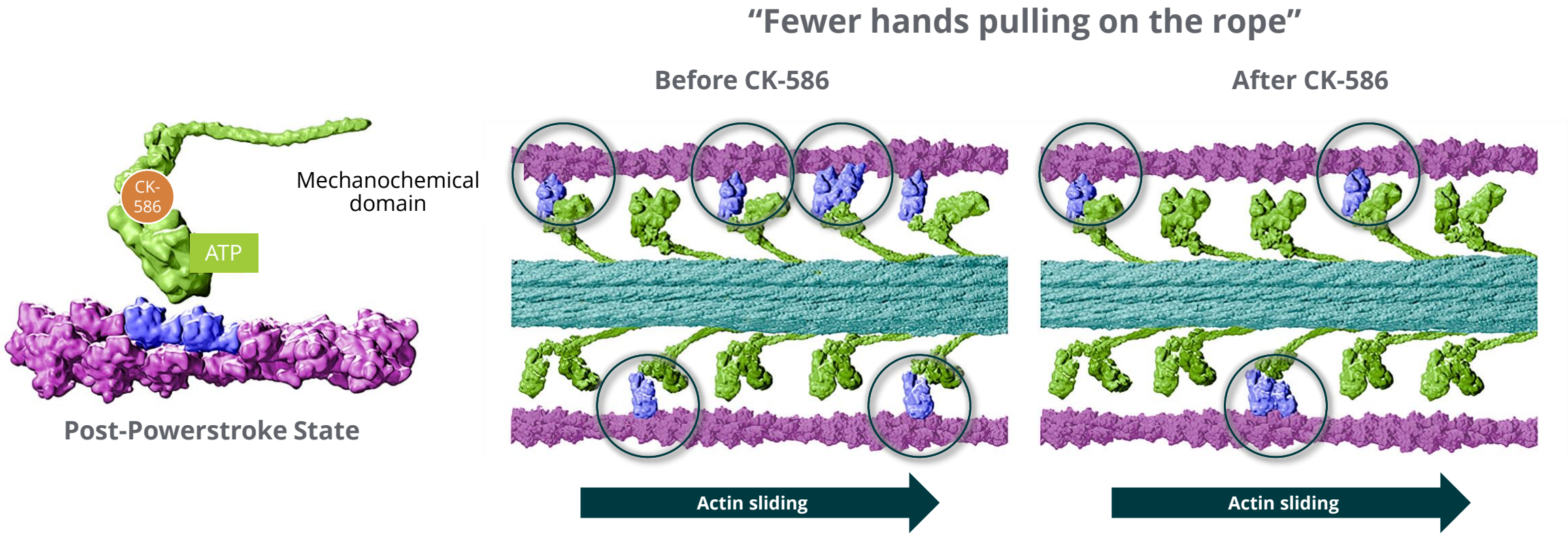
Cytokinetics®

CK-586

Cytokinetics®

CK-586 is an investigational agent and has not been approved for use by the U.S. Food & Drug Administration (FDA) or any regulatory agency. The safety and effectiveness of this product has not been established.

CK-586: Distinct Mechanism of Action from *Aficamten*



CK-586 is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Heart Failure with Preserved Ejection Fraction (HFpEF)

Despite broad use of standard treatments and advances in care, the prognosis for patients with heart failure is poor[1]

8.5 million

Americans will have heart failure by 2030[2]

~50%

HF patients have HFpEF[3] & prevalence of HFpEF is increasing[2,4]

~75%

HFpEF patients will die within five years of initial hospitalization[2]

~84%

HFpEF patients will be rehospitalized[2]

1. Jhund PS, MacIntyre K, Simpson CR, et al. Long-Term Trends in First Hospitalization for Heart Failure and Subsequent Survival Between 1986 and 2003. Circulation. 2009;119:515-523.
2. Bozkurt B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, Fonarow GC, Heidenreich P, Ho JE, Hsich E, Ibrahim NE, Jones LM, Khan SS, Khazanie P, Koelling T, Krumholz HM, Khush KK, Lee C, Morris AA, Page RL 2nd, Pandey A, Piano MR, Stehlik J, Stevenson LW, Teerlink JR, Vaduganathan M, Ziaeian B; Writing Committee Members. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. J Card Fail. 2023 Oct;29(10):1412-1451. doi: 10.1016/j.cardfail.2023.07.006. Epub 2023 Sep 26. PMID: 37797885; PMCID: PMC10864030.
3. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30. PMID: 22936826; PMCID: PMC3661289.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-e327.

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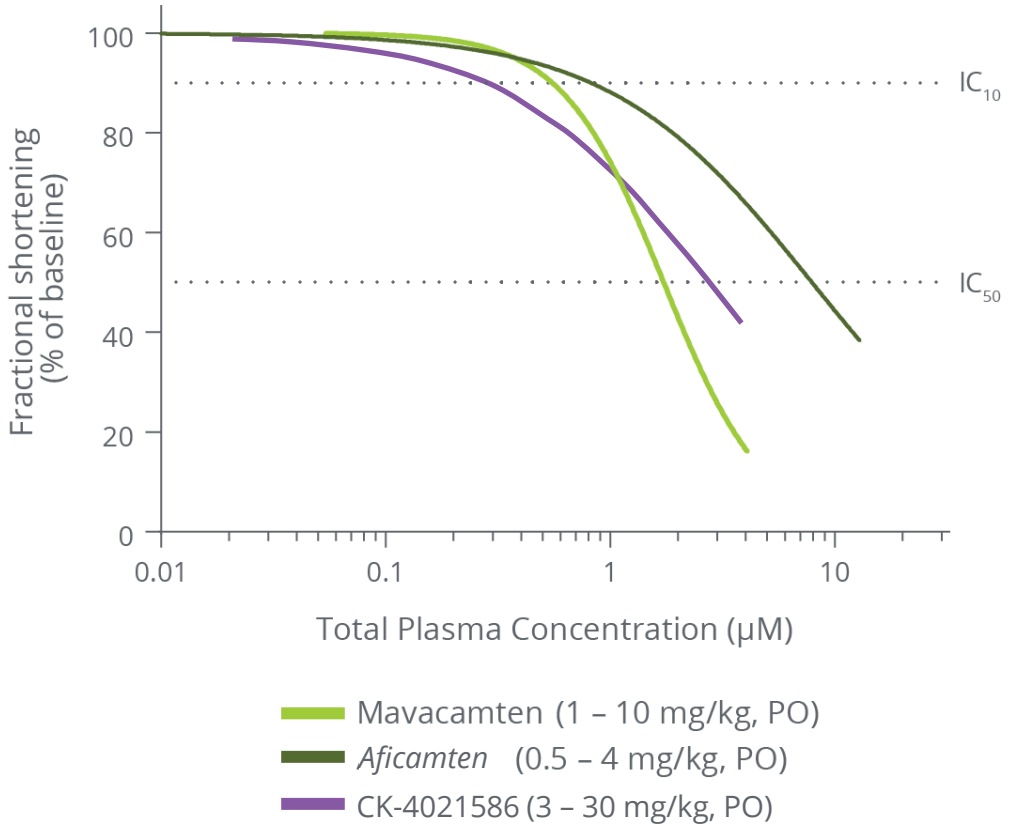
CK-586: Shallow *In Vivo* Concentration-Response

CK-586 will have a shorter half-life in humans than *aficamten*



Pharmacodynamic window Fractional shortening IC_{50} /IC_{10} ratio	
mavacamten	2.8x
aficamten	9.9x
CK-586	9.3x

IC_{10}: plasma concentration at 10% relative reduction in fractional shortening
IC_{50}: plasma concentration at 50% relative reduction in fractional shortening

Compound half-life in humans	Actual	Predicted
aficamten	~3 days	2.8 days
CK-586	~15 hours	15 hours

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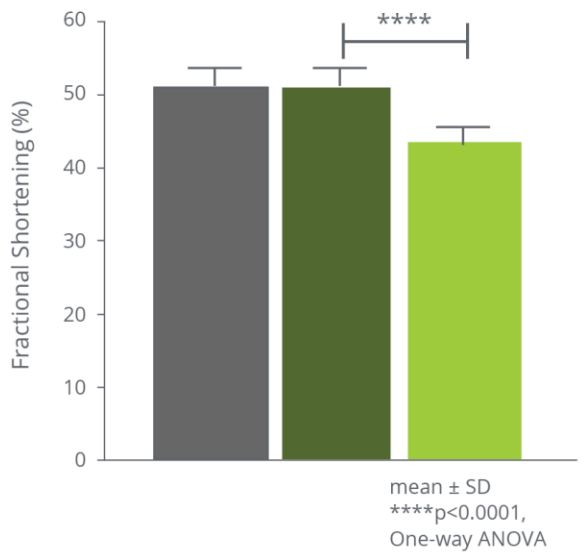
CK-586 is Efficacious in ZSF1 Obese Rat Model of HFpEF

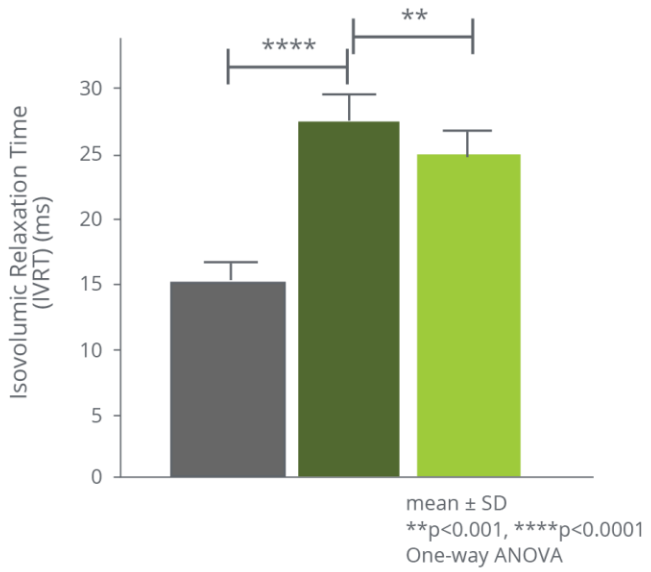
Model is representative of hypertensive, diabetic, metabolic aspects of HFpEF

10 weeks of treatment improved diastolic function and reduced cardiac fibrosis

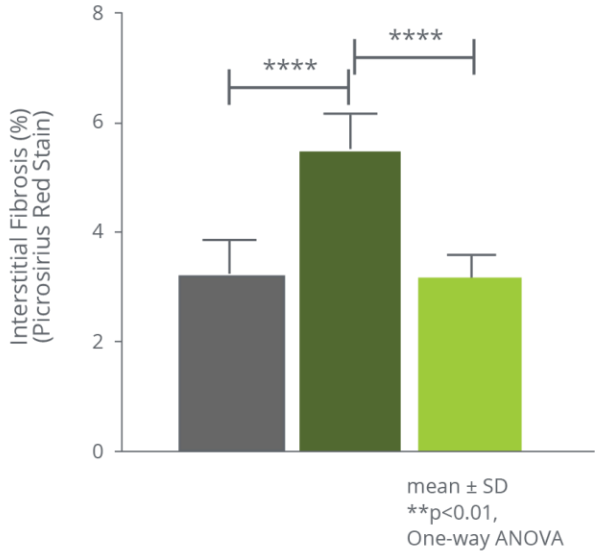
Reduced Fractional Shortening



Improved Diastolic Function



Reduced Fibrosis



ZSF1 Lean + Vehicle | ZSF1 Obese + Vehicle | ZSF1 Obese + CK-586 (10 mg/kg, PO QD)

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Phase 1 Data Support Advancement to Phase 2 Clinical Trial

Full data to be presented at a medical congress in 2H 2024

Phase 1 Design

- **7 SAD cohorts** (10 mg to 600 mg) comprised of 10 participants each
- **2 MAD cohorts** (100 and 200 mg once daily) comprised of 10 participants each

Key Findings

- Pharmacodynamics were evaluated using echocardiography and **consistent with expectations**
- CK-586 was generally **safe and well-tolerated** with **linear PK**
- **No serious adverse events** were observed
- **Stopping criteria were not met**

CK-586 is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

CK-136

Cytokinetics®

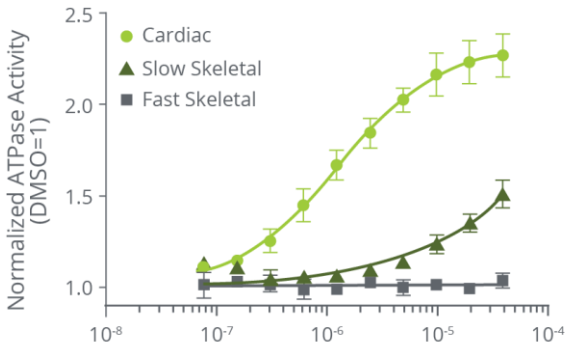
CK-136 is an investigational agent and has not been approved for use by the U.S. Food & Drug Administration (FDA) or any regulatory agency. The safety and effectiveness of this product has not been established.

CK-136: Mechanism of Action

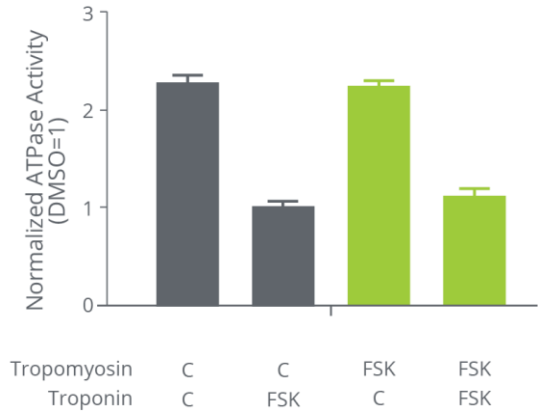
Key biochemical and cellular features

The first selective cardiac troponin activator

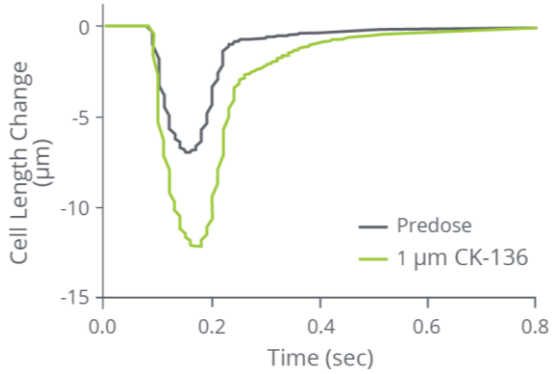
Greater ATPase Activity



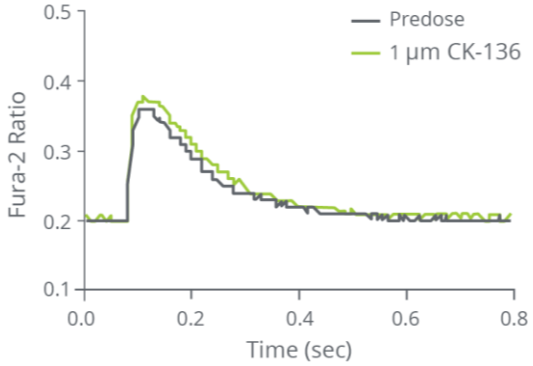
Greater ATPase Activity



Contractability Strongly Activated After Treatment



Calcium Transients Unchanged After Treatment



[1]PD Window = Maximum Tolerated Concentration (MTC) / 10% increase in Fractional Shortening (FS)

CK-136 is an investigational agent and has not been approved for use by any regulatory agency. Its safety and efficacy have not been established.

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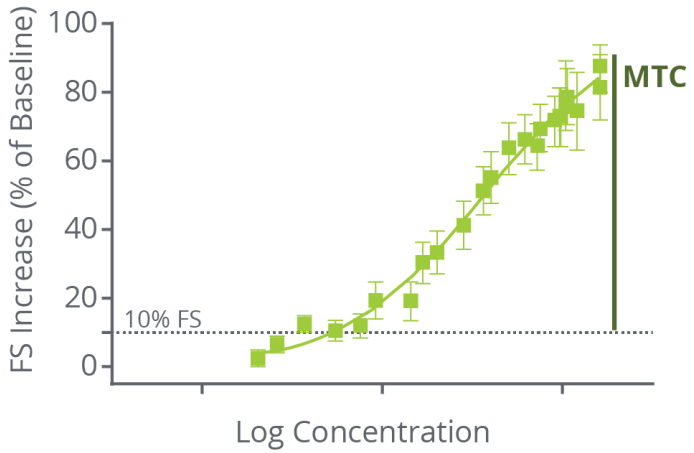
CK-136: Exposure Response Relationship

Exposure-response of troponin activator is shallower than myosin activator

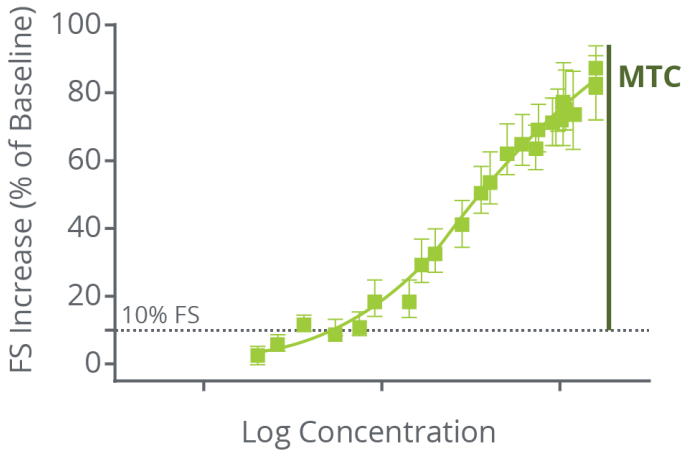
Completed Phase 1 study and have begun analyzing data

Animal Models of Cardiac Function

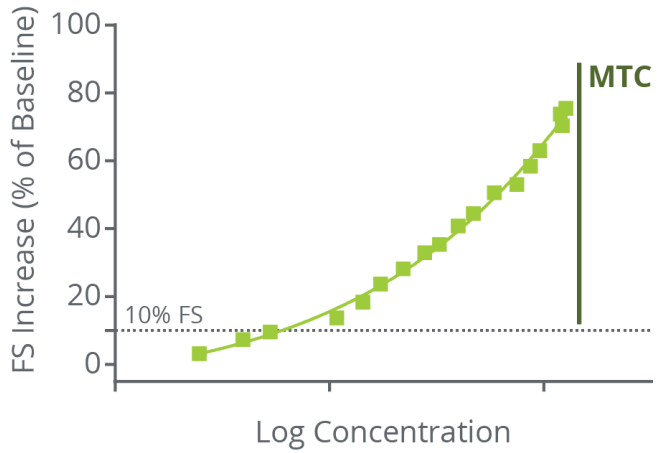
Healthy Rats PD Window[1]
≥15X



MI Rats PD Window[1]
≥15X



Healthy Dogs PD Window[1]
≥15X



[1]PD Window = Maximum Tolerated Concentration (MTC) / 10% increase in Fractional Shortening (FS)

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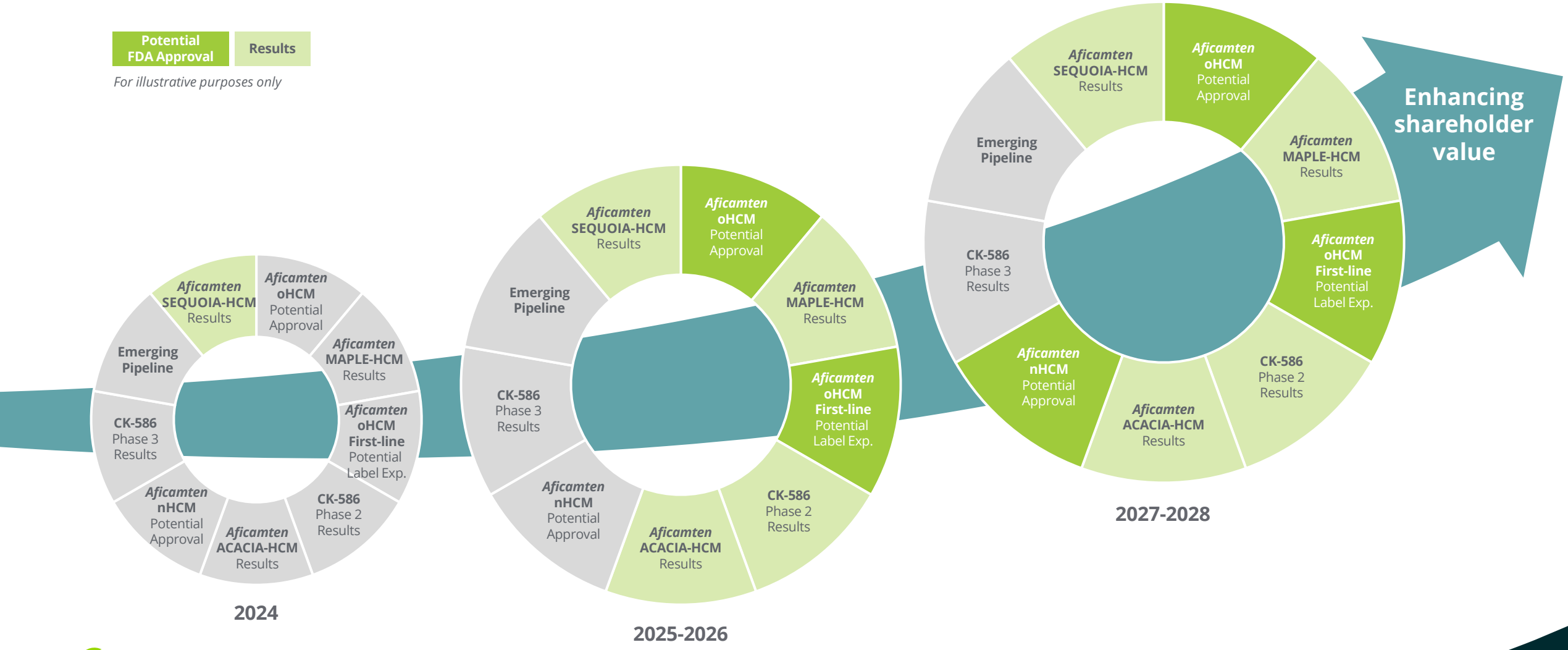
Corporate Profile

Myosin Platform Drives Multiple Data Milestones and Potential Approvals

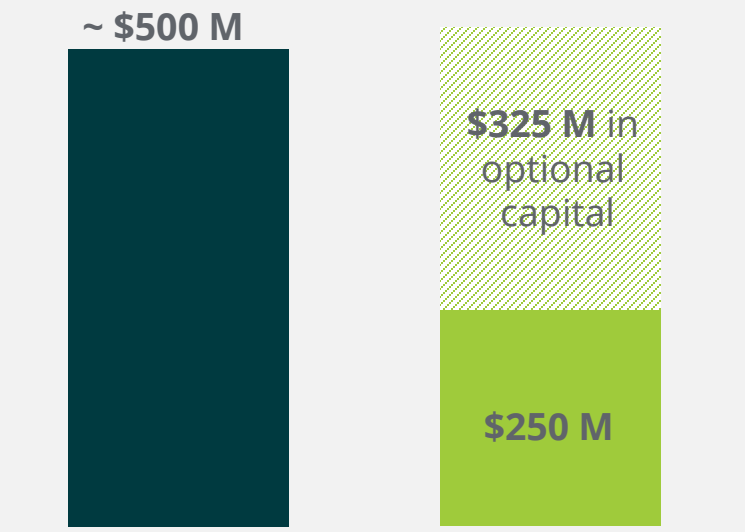


Cytokinetics®

Equity Financing, Royalty Pharma Fundraising

Well funded to enable our strategic priorities

Mix of equity, longer-term debt, and revenue sharing secured over **$1 billion** in capital, with ~**$740 million** in immediate cash



Strategic Priorities

Aficamten

- Global commercial launch of *aficamten* upon regulatory approvals
- Conduct additional label-expanding *aficamten* trials worldwide

Research & Development

Advance our pipeline, including:

- Confirmatory Phase 3 trial of *omecamtiv mecarbil*
- Phase 2 proof-of-concept trial of CK-586
- Potential Phase 3 registrational trial of CK-586

Aficamten, omecamtiv mecarbil and CK-586 are investigational drugs and are not approved by any regulatory agency. Their safety and efficacy have not been established.

Structured Financing Transaction with Royalty Pharma

Revenue sharing, royalty monetization, longer-term debt & equity investment

Four separate components providing $250M upon closing; up to $575M total

Broadens capital access to support prospective commercial launch and monetize myosin pipeline

Aficamten	*Aficamten*	*Omecamtiv Mecarbil*	CK-586	CK-586
$50M Upfront Capital for Future Commercial Launch	**Royalty**	**$100M Upfront Capital to Fund Ph 3 Trial**	**Phase 2 Trial Funding**	**Phase 3 Trial Funding**
• Eligible for additional **$175M** within 12 months of FDA approval for oHCM • Capital repayable over 10 years in quarterly installments (totaling 1.9x)	• Restructured to 4.5% up to $5B of annual net sales and 1% above $5B, compared to prior 4.5% up to $1B and 3.5% above $1B	• Positive Ph 3 and timely FDA approval yield RP a 1.0x milestone payment and 2% royalty on global sales • Otherwise, Cytokinetics repays loan quarterly (2.275x-2.375x) over 18 or 22 quarters starting in 2028 or 2030	• **$50M** Upfront Capital to Fund Ph 2 PoC trial • In exchange for 1.0% royalty on net sales of CK-586	• Option to invest up to an additional $150M for **Ph 3 development** • If RP opts into Ph 3, it may receive up to 0.75x milestone and 4.5% royalty on global sales • If RP opts out of Ph 3 funding, it gets a 1% royalty on global net sales

Royalty Pharma purchased $50M of Cytokinetics' stock

Aficamten, omecamtiv mecarbil and CK-586 are investigational drugs and are not approved by any regulatory agency. Their safety and efficacy have not been established.

Royalty Pharma Agreement: Efficient Fundraising for Next Wave of Innovation

Omecamtiv Mecarbil

Cytokinetics received **$100M** at a market-rate competitive cost of capital (low double-digit interest rate)

- **Cost effective Ph 3 trial:** $100M covers costs
- Clinical trial designed to confirm results from pre-specified sub-group in GALACTIC-HF
- Expected to start in Q4 2024

>$700m

Estimated peak sales in U.S. market

at least 8

Years of market opportunity in U.S. estimated

Highly Synergistic

Can leverage commercial infrastructure for *aficamten*

CK-586 Investment

Cytokinetics received **$50M** up-front and is eligible to receive an additional **$150M**

High Conviction

- RP made investment after having only seen Ph 1 data
- Initial investment covers entire Ph 2 POC trial
- RP has opt-in right to fund Ph 3 costs up to $150M

Shareholder Value

- RP entitled to 1% royalty on future net sales
- If opt-in is exercised, royalty rate increases to 4.5%
- RP receives 0.75x milestone upon approval

Omecamtiv mecarbil and CK-586 are investigational drugs and are not approved by any regulatory agency. Their safety and efficacy have not been established.

Balance Sheet & Financial Guidance

Approximately 2 years of cash runway based on 2024 guidance*

2024 Condensed Balance Sheet
As of 3/31/2024

in millions

	Total
Cash and investments	$634.3
Accounts receivable	$0.8
PPE	$68.0
Leased assets	$78.2
Other assets	$26.8
Total Assets	**$808.1**
Convertible Debt, net	$549.8
Liability related to sale of future royalties	$390.2
Lease liability	$136.8
Other liabilities	$127.4
Total Liabilities	**$1,204.2**
Working capital	$549.8
Accumulated deficit	($2,247.9)
Stockholders' deficit	($396.2)
Wtd Avg Basic Shares Outstanding (million)	**101.9**

2024 Financial Guidance

- **GAAP Operating (R&D and G&A) Expense:** $535 to $555 million
- **Non-cash expenses included in GAAP Operating Expense**:** $115 to $105 million
- Operating Expense (R&D and G&A) excluding non-cash expenses $420 to $450 million
- Expected Net Cash Utilization***: $390 to $420 million

** Including up to $175M we expect to be available to us under our loan agreement with Royalty Pharma, upon satisfaction of conditions.*
***Non-cash expenses included in GAAP Operating Expenses are comprised of stock-based compensation and depreciation. Non-cash expense is a non-GAAP financial measure that should be considered as supplemental information regarding our operations and should not be considered without also considering our results prepared in accordance with U.S. GAAP. It should not be considered as a substitute for, or superior to, our U.S. GAAP results. We believe non-cash expenses is a relevant and useful operational measure as our management uses it to budget and plan for the business and also useful to investors because similar measures are used by securities analysts, investors and others in their evaluation of companies in similar industries. Non-cash expense as we present it may not be comparable with similarly titled operational measures used by other companies. Our expectations regarding non-cash expenses are based on information currently available to us, but are forward-looking statements subject to change.*
****We define "Net Cash Utilization" as change in cash, cash equivalents and investments year over year.*

Planned 2024 Milestones

Aficamten

- **Submit NDA to FDA** in Q3 2024 and **MAA to EMA** in Q4 2024
- **Complete enrollment of MAPLE-HCM** in Q3 2024
- **Continue enrollment in ACACIA-HCM** in 2024
- **Continue enrollment of CEDAR-HCM** in 2024
- **Begin Phase 1 study of *aficamten* in healthy Japanese volunteers** in Q2 2024

CK-586

- **Share full data from Phase 1 study of CK-586** in 2H 2024
- **Initiate Phase 2 study of CK-586** in Q4 2024

Pre-Clinical Development & Ongoing Research

- **Initiate clinical development with another muscle-directed compound** in 2024

Aficamten **and CK-586 are investigational drugs and have not been approved.** ***Their*** **safety and efficacy have not been established.**

Cytokinetics®

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thank you

Vi, diagnosed with HCM
Avonne, diagnosed with HCM
John, diagnosed with heart failure