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-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-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-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.

Disclaimer: The assumptions used in the preparation of this presentation, although considered reasonable by us at the time of preparation, may prove to be incorrect. You are cautioned that the information is based on assumptions as to many factors and that actual results may vary from the results projected and such variations may be material. Accordingly, you should not place undue reliance on any forward-looking statements contained herein or rely on them as predictions of future events.

The trademarks, trade names and service marks appearing in this presentation are the property of their respective owners. Certain information contained in this presentation relate to or are based on studies, publications and other data obtained from third-party sources as well as our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources.

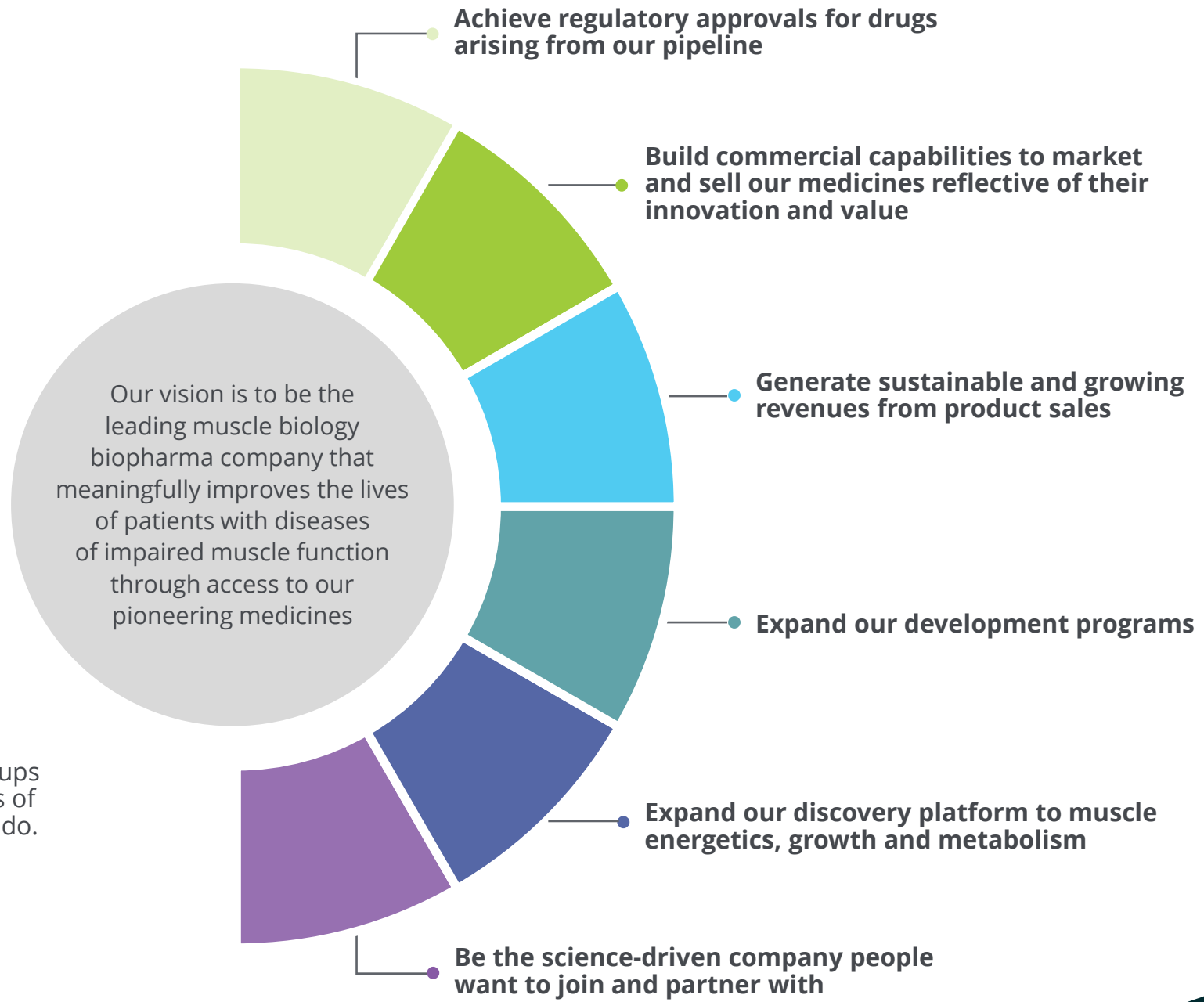
Our Mission

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**

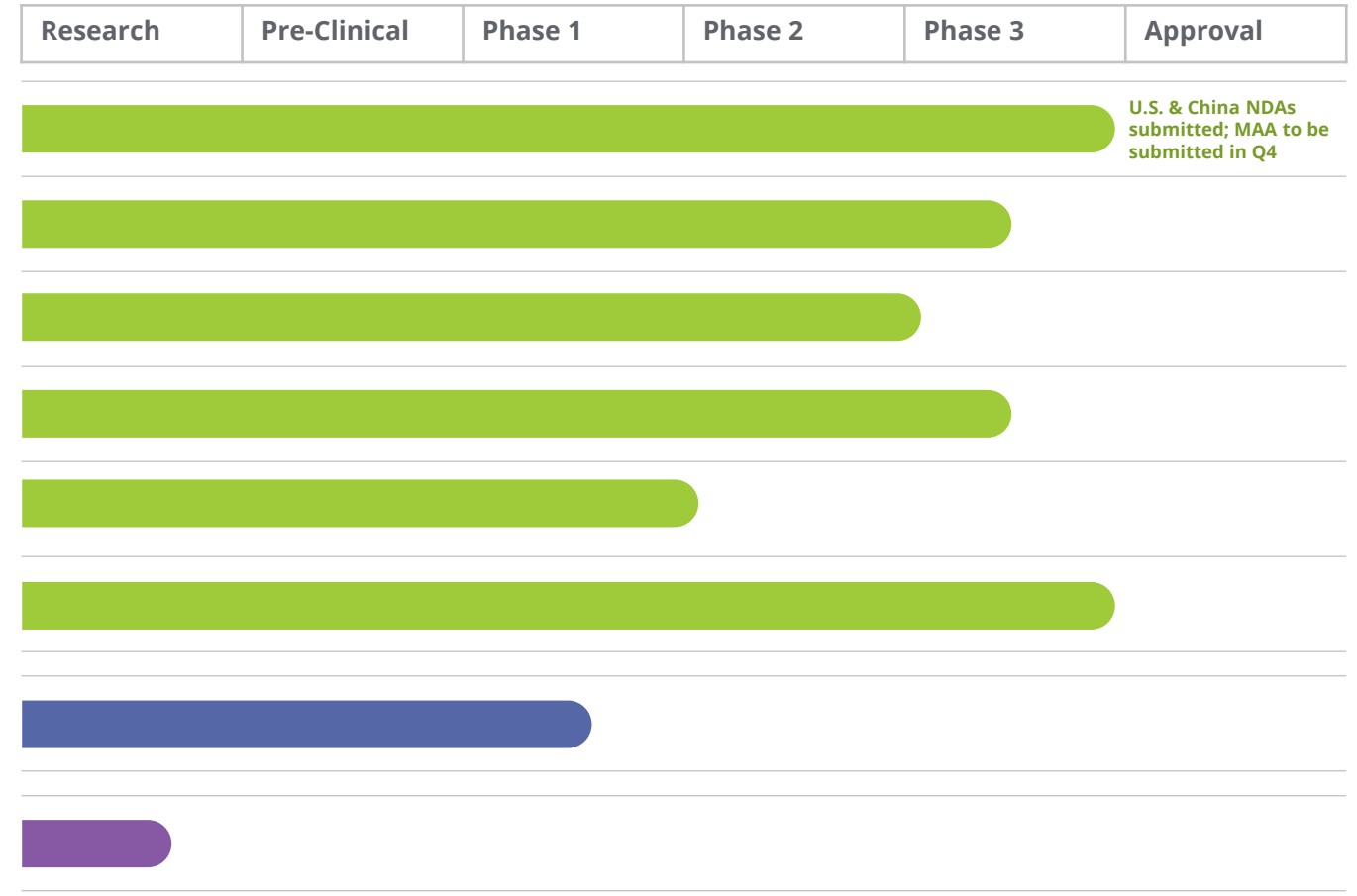
As always, we will support disease advocacy groups elevating the patient voice and live by our values of integrity, fairness and compassion in all that we do.



Cytokinetics®

A Commitment to Muscle-Directed Cardiac Medicines

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	Muscular Dystrophy, other	CK-089
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.

Cytokinetics®

Strong Financial Position

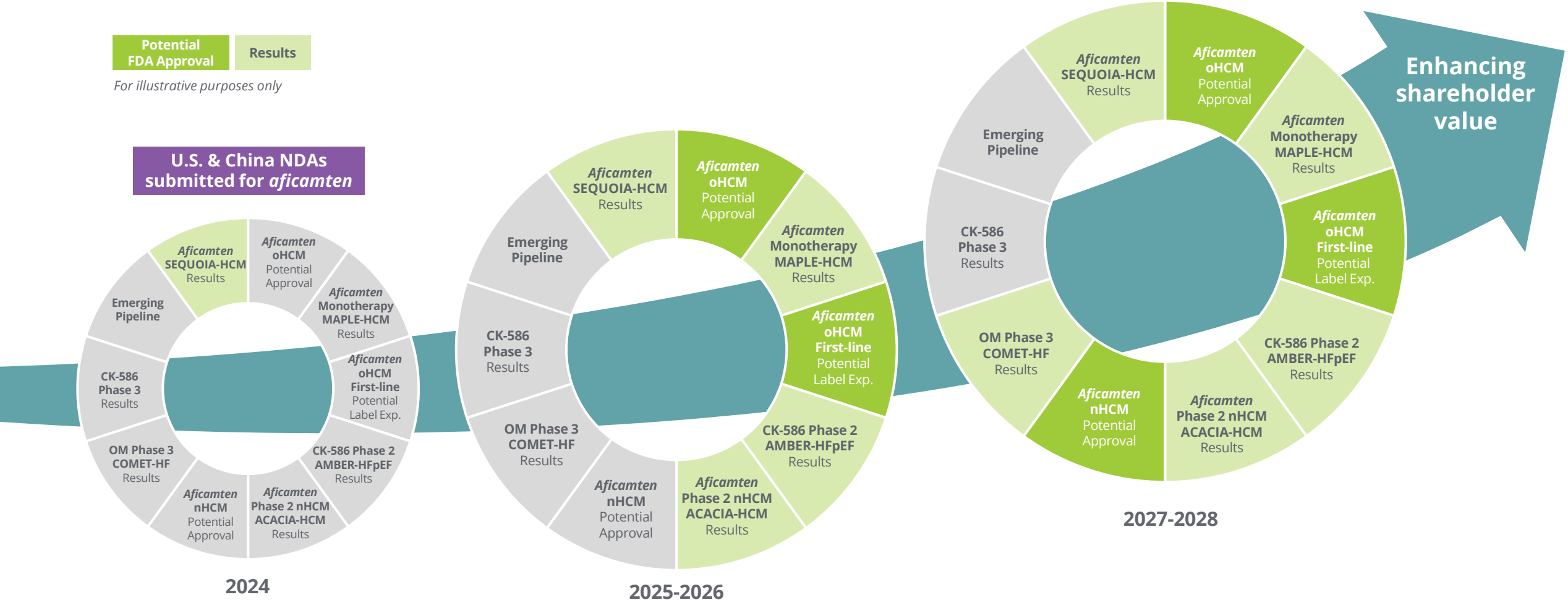
Strengthened balance sheet & access to capital to execute launch & advance R&D pipeline

September 30, 2024	**~$1.3B** in cash, cash equivalents and investments
Further access to capital through term loans with Royalty Pharma (RP)	Access up to $350M in term loans*
Potential further funding through RP opt-in	RP, at its option, can invest up to **$150M** in a Phase 3 trial of CK-586 in exchange for an additional*** 3.5% revenue participation interest in worldwide net sales of CK-586

Add'l $500M

**Term loans are comprised of Tranche 4 , 5, and 7 Loans*
Tranche 4: Cytokinetics is eligible to draw up to $75m by April 3, 2025. The minimum draw for tranche 4 is $50m.
Tranche 5: Cytokinetics, at its option, is eligible to draw up to $100m during the 1-year period following the acceptance of the NDA filing for aficamten in oHCM provided that the NDA filing is accepted on or prior to March 31, 2025.
Tranche 7: Cytokinetics, at its option, is eligible to draw up to $175m subject to conditions related to the approval of the NDA for aficamten in oHCM on or prior to December 31, 2025.
**** Royalty Pharma currently has a revenue participation interest of 1.0% of worldwide net sales of CK-586.*

Myosin Platform Fuels Multiple Milestones and Increased Value



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.

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**

Addressing Difficult to Treat Populations Within Heart Failure

Specialty cardiology franchise strategy applies to markets with similar characteristics

HCM

Opportunity for *aficamten* as the anchor

- ✓ Few available therapies
- ✓ Significant unmet need
- ✓ Concentrated market
- ✓ Tractable customer base
- ✓ Payers manage to label

HFrEF
Severely reduced EF

Expanding into adjacent population

- ✓ Few available therapies
- ✓ Significant unmet need
- ✓ Tractable customer base
- ✓ Payers manage to label

HFpEF
Supranormal EF

Addressing underserved segment of HF market

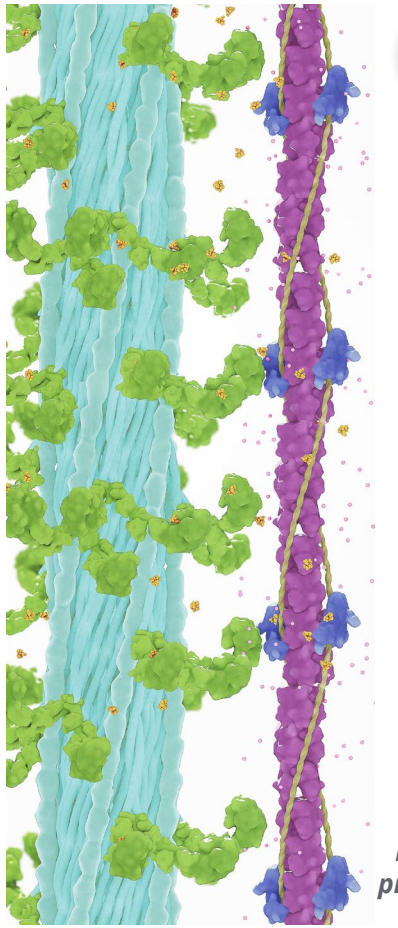
- ✓ Few available therapies
- ✓ Significant unmet need
- ✓ Concentrated market
- ✓ Tractable customer base
- ✓ Payers manage to label

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

Cytokinetics®

Building a Specialty Cardiology Franchise Anchored by *Aficamten*

Potential patient market for specialty cardiology franchise strategy



Estimated prevalence in US only

Myosin-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

~840K[3]
HFrEF + EF <30% in 2029

Omecamtiv Mecarbil

HFrEF
Potential in HFrEF

800K[4]
HFpEF + EF ≥ 65% in 2030

CK-586

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

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

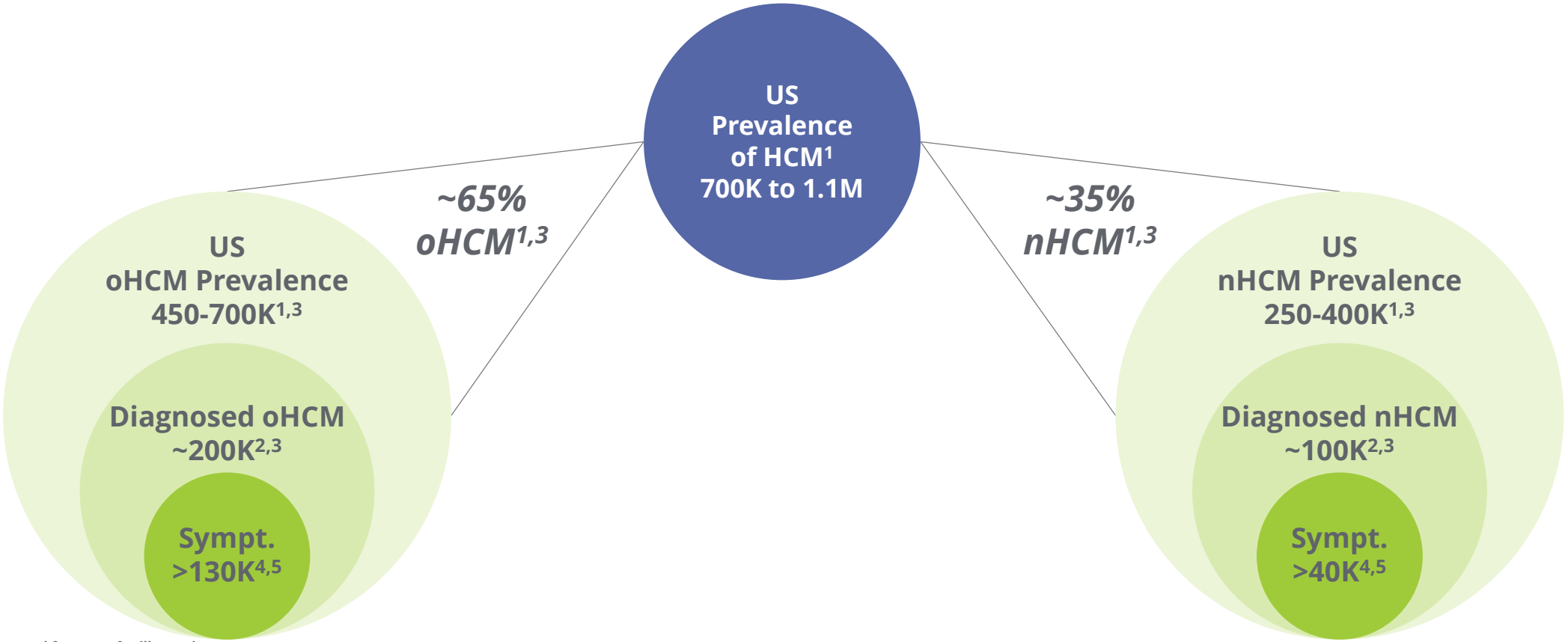
1. Cardiovascular Research Group: CVrg Market Strategies: Heart Failure, p 48, Q4 2022; Maron BJ: et al: Prevalence of Hypertrophic Cardiomyopathy In A General Population of Young Adults, Circulation 1995;92;785-789; Semsarian C. et al: New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy, 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. Greene et al JACC 2023; 81:413-424
4. Dunlay et al (2012) Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30.

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.

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: 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®

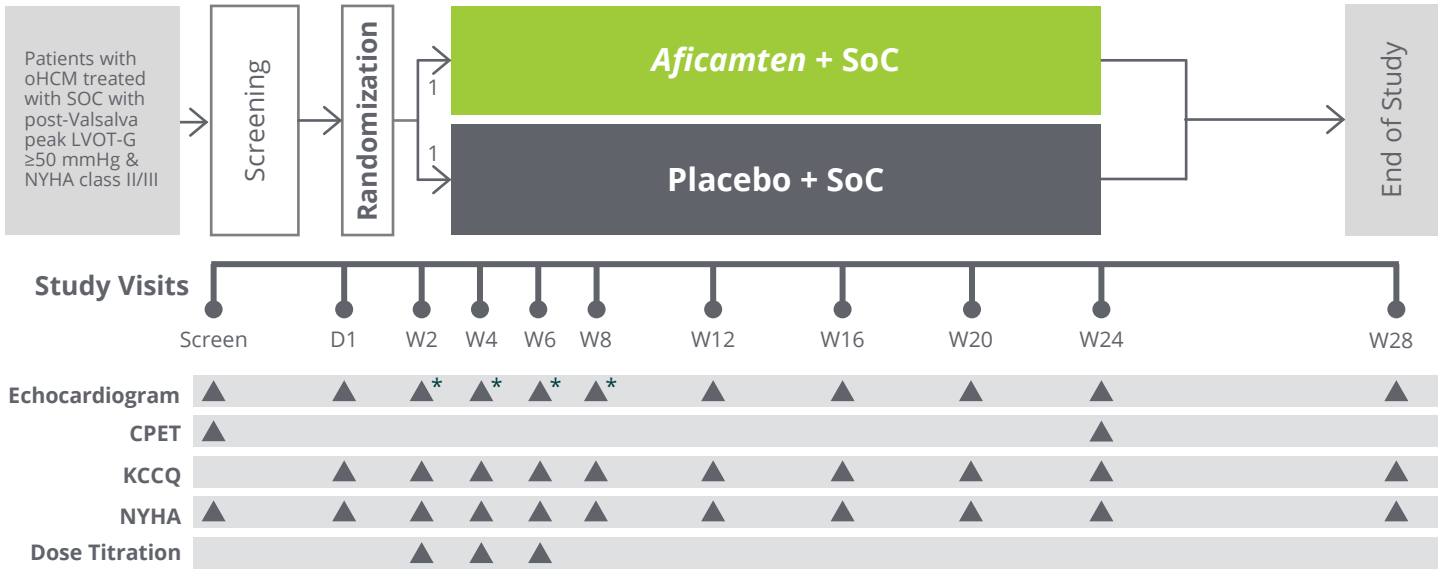
SEQUOIA-HCM: Phase 3 Trial

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.

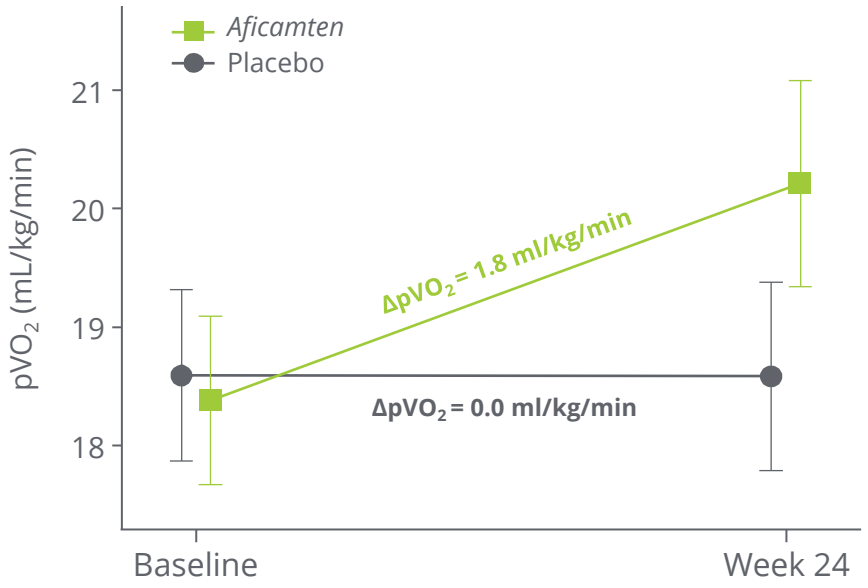
Maron M. "Aficamten for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

SEQUOIA-HCM: Primary Endpoint

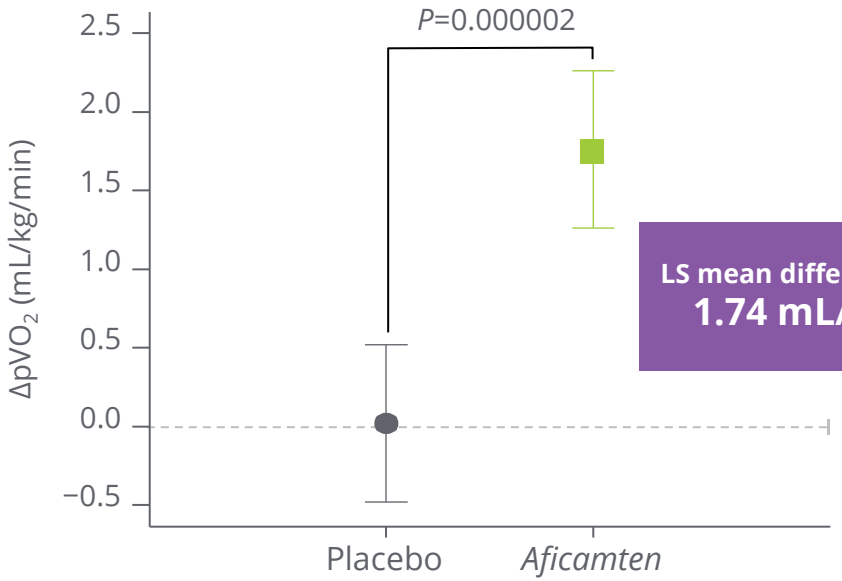
Significant improvement in exercise capacity compared to placebo

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)

	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)

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

Favors Placebo — Favors Treatment

Favors Placebo — Favors Treatment

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.

Cytokinetics®

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**

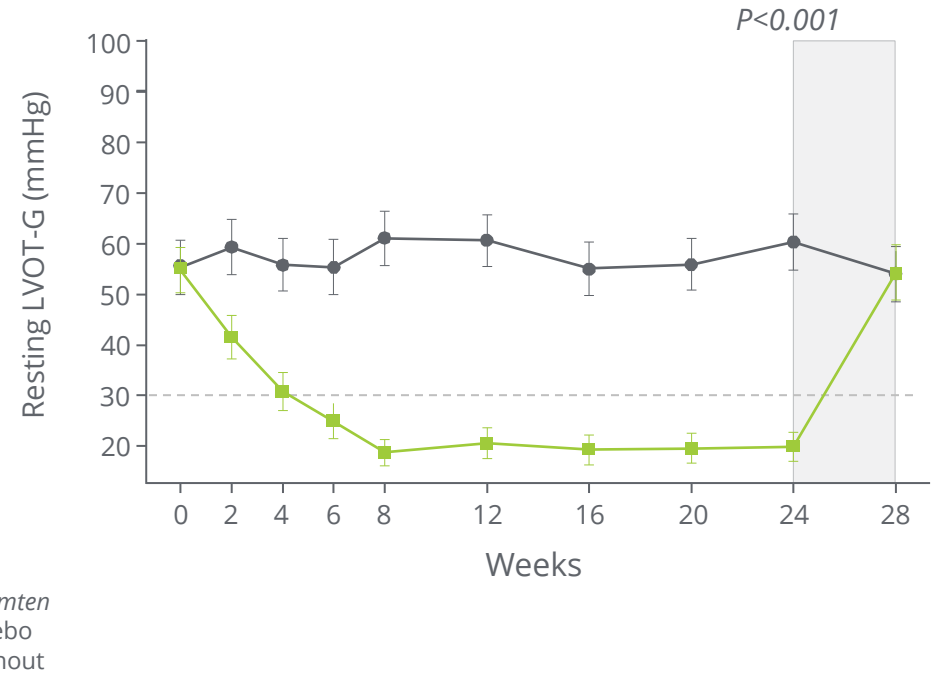
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
Maron M. "Aficamten for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.

SEQUOIA-HCM: Secondary & Exploratory Endpoints

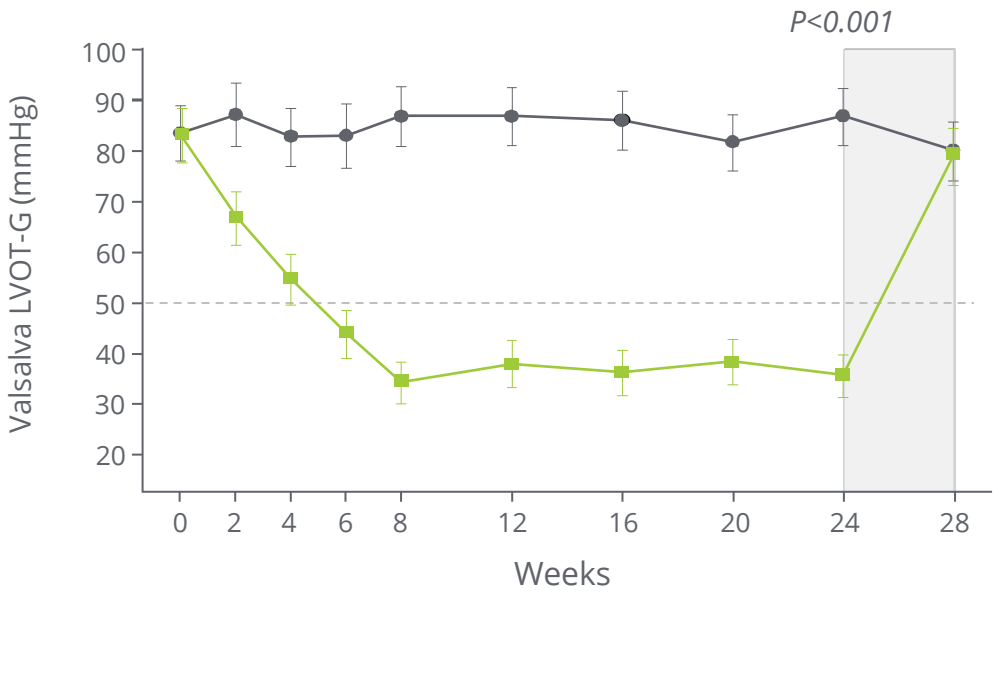
Significant improvement in gradients by ~60% with no significant adverse change in LVEF

LS mean difference: - 50 mmHg

Resting LVOT-G



Valsalva LVOT-G



Aficamten
Placebo
Washout

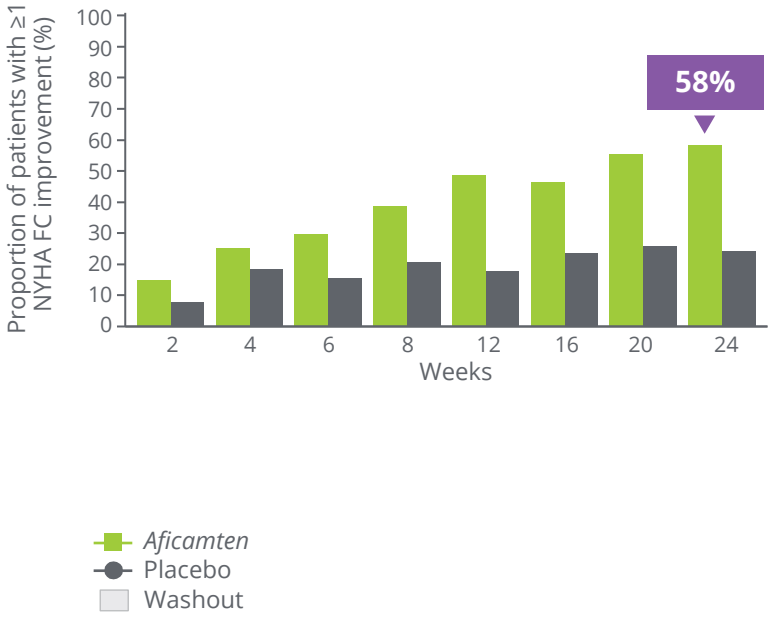
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
Error bars are 95% CI
Hegde S, et al. Impact of Aficamten on Echocardiographic Cardiac Structure and Function in Symptomatic Obstructive Hypertrophic Cardiomyopathy. JACC. 2024.

Cytokinetics®

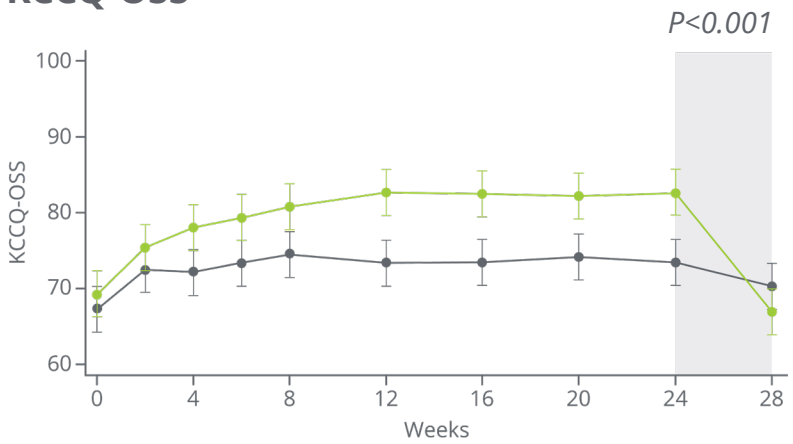
SEQUOIA-HCM: Secondary & Exploratory Endpoints

Significant improvement in patient symptom burden and quality of life

≥1 NYHA FC Improvement[1]



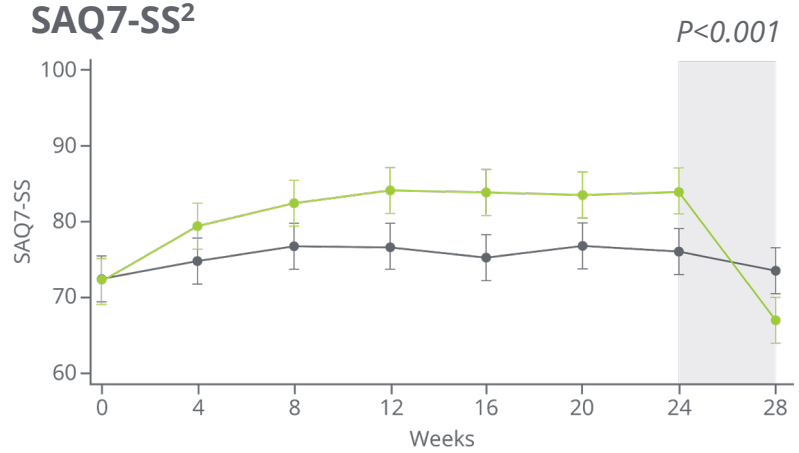
KCCQ-OSS[2]



Mean difference between *aficamten* & placebo = **7.9 points**

30% on *aficamten* vs. 12% on placebo had an improvement of ≥20 points

SAQ7-SS[2]



Mean difference between *aficamten* & placebo = **7.8 points**

31% on *aficamten* vs. 14% on placebo had an improvement of ≥20 points

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

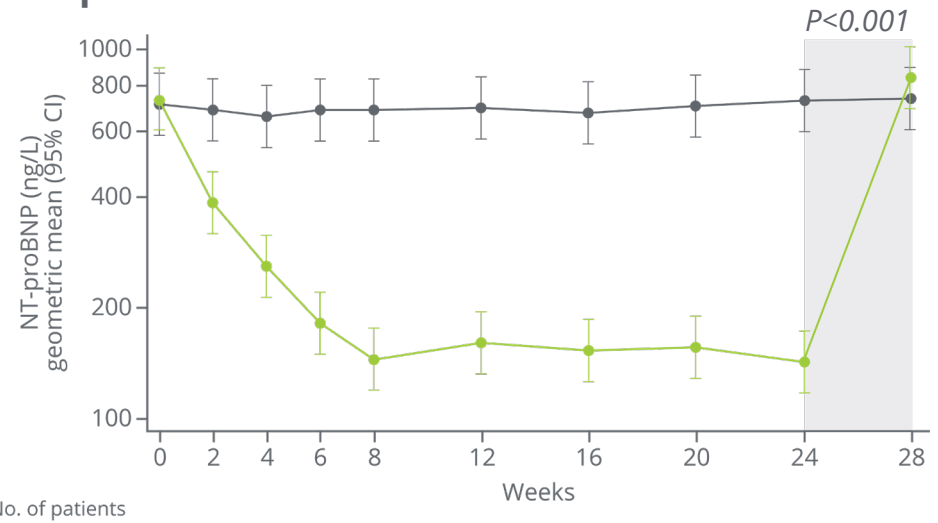
Maron M. "Aficamten for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy". ESC Heart Failure 2024.
Sherrod C, et al. Effect of Aficamten on Health Status Outcomes in Obstructive Hypertrophic Cardiomyopathy: Results from SEQUOIA-HCM. JACC. 2024.

SEQUOIA-HCM: Improvement in Biomarkers

Significant improvement in cardiac biomarkers indicative of cardiac wall stress & myocardial injury

Treatment with *aficamten* led to **80% reduction from baseline to week 24**

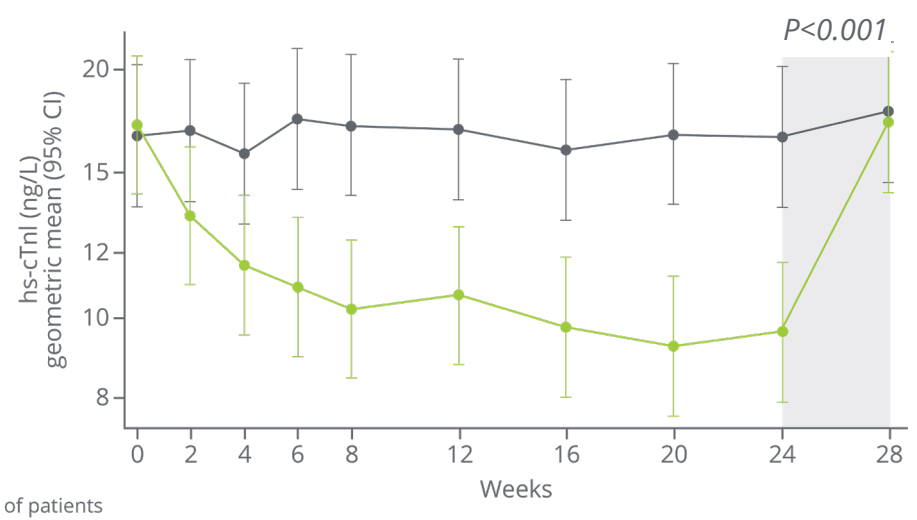
NT-proBNP



No. of patients										
Aficamten	139	141	141	139	139	139	137	139	136	135
Placebo	138	138	139	136	137	135	135	137	136	135

Treatment with *aficamten* led to **43% reduction from baseline to week 24**

hs-CTnI



No. of patients										
Aficamten	139	139	136	134	138	138	135	137	136	134
Placebo	131	129	134	132	133	131	131	134	134	134

Aficamten
Placebo
Washout

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

Coats CJ, et al. Cardiac Biomarkers and Effects of Aficamten in Obstructive Hypertrophic Cardiomyopathy: The SEQUOIA-HCM Trial. Eur Heart J. 2024

Cytokinetics®

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	

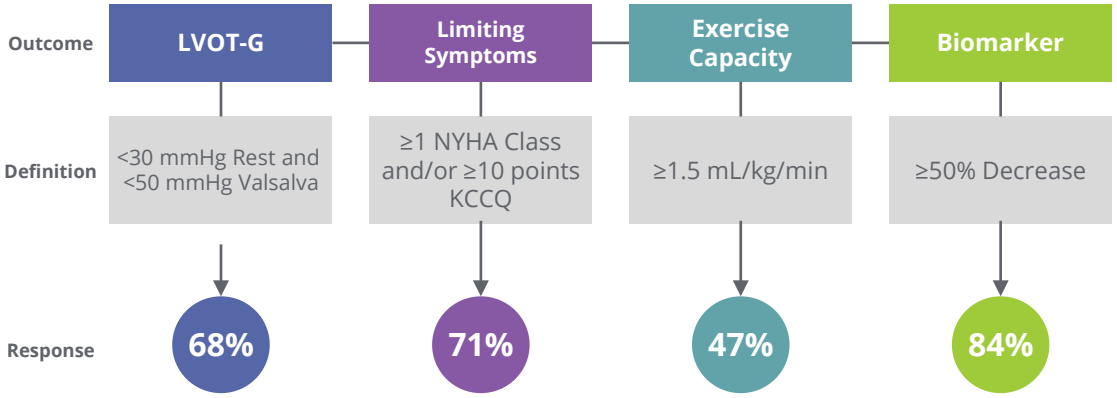
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

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

Clinically Relevant Improvements

2/3 patients achieved complete hemodynamic response in prespecified analyses

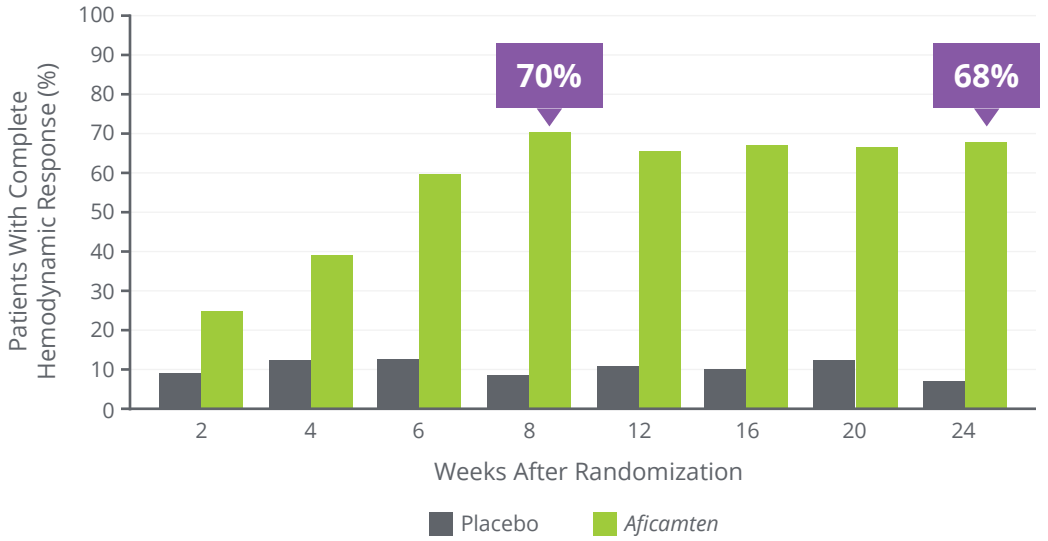
Responder Analysis: Achievement of 4 Clinically Relevant Assessments



P<0.002
vs. placebo

Complete Hemodynamic Response

Resting LVOT-G <30 mmHg & Valsalva LVOT-G <50 mmHg



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

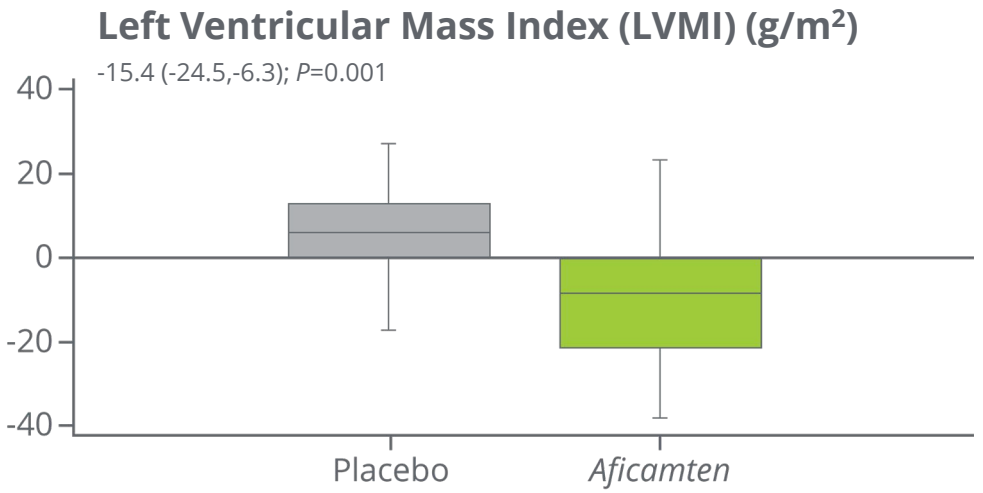
Maron MS, et al. "Impact of Aficamten on Disease and Symptom Burden in Obstructive Hypertrophic Cardiomyopathy: Results from SEQUOIA-HCM ." HFSA 2024.

SEQUOIA-HCM: CMR Sub-Study

Aficamten associated with favorable cardiac remodeling

Among 50 of the 284 eligible patients who opted to complete the CMR sub-study there was:

- **Significant improvement in LVMI**
- **Favorable cardiac remodeling** as demonstrated by reductions in:
  - **Left ventricular maximal wall thickness**
  - **Left atrial volume index (LAVI)**
  - **Extracellular volume mass index (ECVi)**



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

Masri A, et al. Effect of Aficamten on Cardiac Structure and Function in Obstructive Hypertrophic Cardiomyopathy: SEQUOIA-HCM CMR Substudy. JACC. 2024.

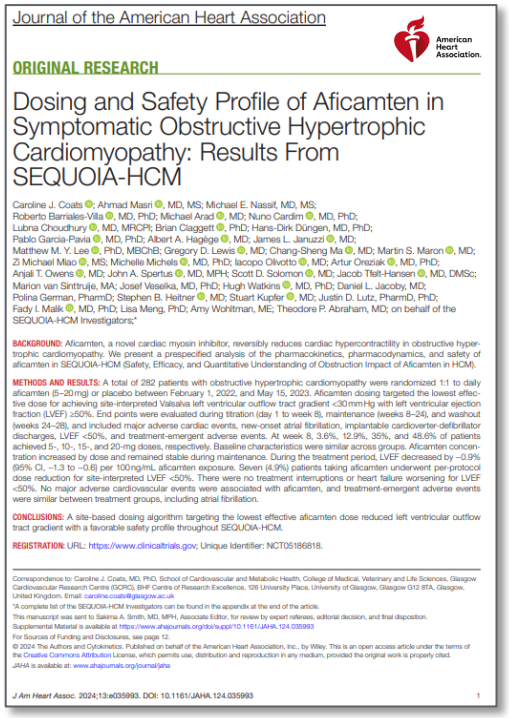
SEQUOIA-HCM: Safety Data

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%.



Journal of the American Heart Association

ORIGINAL RESEARCH

Dosing and Safety Profile of Aficamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results From SEQUOIA-HCM

Caroline J. Coats; Ahmad Masri, MD, MS; Michael E. Nassif, MD, MS; Roberto Barriales-Villa, MD, PhD; Michael Arad, MD; Nuno Cardim, MD, PhD; Lubna Choudhury, MD, MRCPI; Brian Claggett, PhD; Hans-Dirk Düngen, MD, PhD; Pablo Garcia-Pavia, MD, PhD; Albert A. Hagège, MD; James L. Januzzi, MD; Matthew M. Y. Lee, PhD, MBChB; Gregory D. Lewis, MD; Chang-Sheng Ma, MD; Martin S. Maron, MD; Zi Michael Miao, MS; Michelle Michels, MD, PhD; Iacopo Olivotto, MD; Artur Oreziak, MD, PhD; Anjali T. Owens, MD; John A. Spertus, MD, MPH; Scott D. Solomon, MD; Jacob Tfelt-Hansen, MD, DMSc; Marion van Sintruije, MA; Josef Veselka, MD, PhD; Hugh Watkins, MD, PhD; Daniel L. Jacoby, MD; Polina German, PharmD; Stephen B. Heitner, MD; Stuart Kupfer, MD; Justin D. Lutz, PharmD, PhD; Fady I. Malik, MD, PhD; Lisa Meng, PhD; Amy Wohltman, ME; Theodore P. Abraham, MD; on behalf of the SEQUOIA-HCM Investigators;*

BACKGROUND: Aficamten, a novel cardiac myosin inhibitor, reversibly reduces cardiac hypercontractility in obstructive hypertrophic cardiomyopathy. We present a prespecified analysis of the pharmacokinetics, pharmacodynamics, and safety of aficamten in SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM).

METHODS AND RESULTS: A total of 282 patients with obstructive hypertrophic cardiomyopathy were randomized 1:1 to daily aficamten (5–20 mg) or placebo between February 1, 2022, and May 15, 2023. Aficamten dosing targeted the lowest effective dose for achieving site-interpreted Valsalva left ventricular outflow tract gradient <30 mm Hg with left ventricular ejection fraction (LVEF) ≥50%. End points were evaluated during titration (day 1 to week 8), maintenance (weeks 8–24), and washout (weeks 24–28), and included major adverse cardiac events, new-onset atrial fibrillation, implantable cardioverter-defibrillator discharges, LVEF <50%, and treatment-emergent adverse events. At week 8, 3.6%, 12.9%, 35%, and 48.6% of patients achieved 5-, 10-, 15-, and 20-mg doses, respectively. Baseline characteristics were similar across groups. Aficamten concentration increased by dose and remained stable during maintenance. During the treatment period, LVEF decreased by −0.9% (95% CI, −1.3 to −0.6) per 100 ng/mL aficamten exposure. Seven (4.9%) patients taking aficamten underwent per-protocol dose reduction for site-interpreted LVEF <50%. There were no treatment interruptions or heart failure worsening for LVEF <50%. No major adverse cardiovascular events were associated with aficamten, and treatment-emergent adverse events were similar between treatment groups, including atrial fibrillation.

CONCLUSIONS: A site-based dosing algorithm targeting the lowest effective aficamten dose reduced left ventricular outflow tract gradient with a favorable safety profile throughout SEQUOIA-HCM.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique Identifier: NCT05186818.

Correspondence to: Caroline J. Coats, MD, PhD, School of Cardiovascular and Metabolic Health, College of Medical, Veterinary and Life Sciences, Glasgow Cardiovascular Research Centre (GCRC), BHF Centre of Research Excellence, 126 University Place, University of Glasgow, Glasgow G12 8TA, Glasgow, United Kingdom. Email: caroline.coats@glasgow.ac.uk

*A complete list of the SEQUOIA-HCM Investigators can be found in the appendix at the end of the article.

This manuscript was sent to Sakima A. Smith, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.035993

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

J Am Heart Assoc. 2024;13:e035993. DOI: 10.1161/JAHA.124.035993

Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
AE, adverse event; SAE, serious adverse event.
Coats CJ. Dosing and Safety Profile of Aficamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.

Integrated Safety Analysis

Analysis represents 206 patient-years* of exposure to *aficamten*

- **<4% of patients** experienced LVEF <50%
- **0 dose terminations** due to LVEF <40%
- **<1% of echocardiograms performed** led to a reduction in dose
- **No difference in atrial fibrillation** between placebo and *aficamten*

	Cumulative[a] *aficamten*-treated pool	Placebo-controlled pool[b]	
	Aficamten	***Aficamten***	**Placebo**
Number of participants	283	170	153
LVEF <50%[c], n (%)	11 (3.9)	9 (5.3)	1 (0.7)
LVEF <50% with clinical HF	0	0	1 (0.7)
Atrial fibrillation	12 (4.2)	4 (2.4)	5 (3.3)
New onset	5 (1.8)	1 (0.6)	3 (2.0)
Recurrent	7 (2.5)	3 (1.8)	2 (1.3)

[a] Parent and extension studies. [b] Placebo-controlled pool of REDWOOD-HCM and SEQUOIA-HCM. [c] Site read.

*Median exposure: 6-months, range of exposure: 0-32 months

Integrated Safety Analysis to reflect real world clinical application.

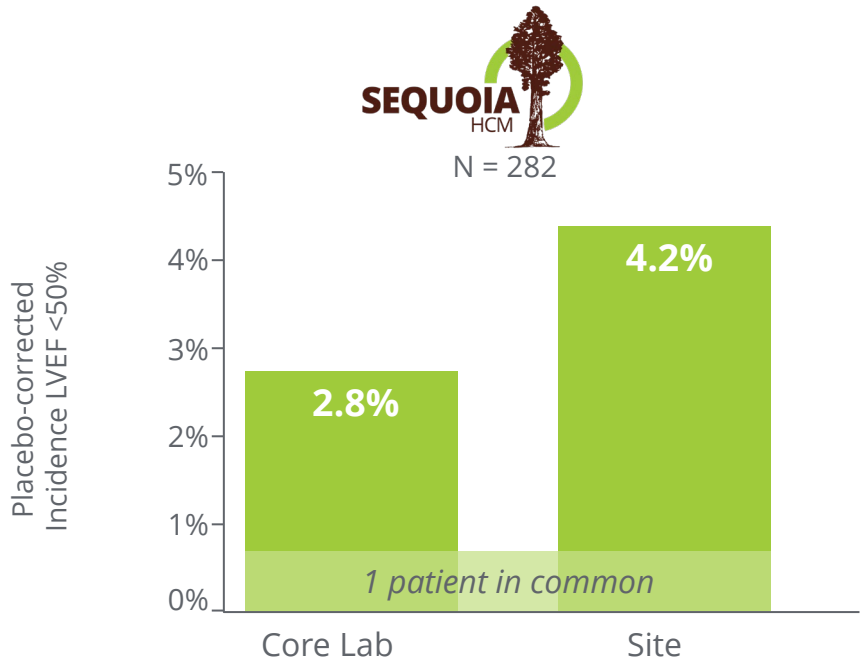
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

IMasri A. Aficamten in Patients with Obstructive Hypertrophic Cardiomyopathy: An Integrated Safety Analysis. ESC 2024.

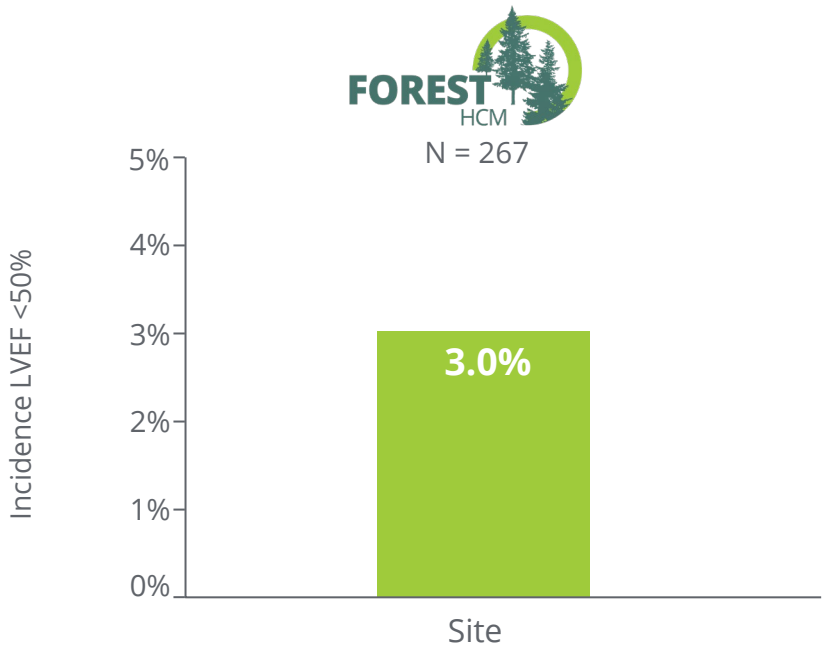
Cytokinetics®

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

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



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



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

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

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

Cytokinetics®

Submitted US NDA; Preparing for Ex-US Regulatory Submissions

Positive Results from SEQUOIA-HCM

2024

- Submitted NDA to U.S. FDA in Q3
- Corxel (*formerly Ji Xing Pharmaceuticals*) submitted NDA to the CDE of the NMPA in China; NDA was accepted
- **Expect to submit MAA to EMA in Q4 2024**

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

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

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

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

Ongoing Clinical Trials of *Aficamten*

Pivotal Phase 3 clinical trial of *aficamten* as monotherapy vs. metoprolol in oHCM

Enrollment Complete

Pivotal Phase 3 clinical trial in nHCM

Clinical trial in a pediatric population with oHCM

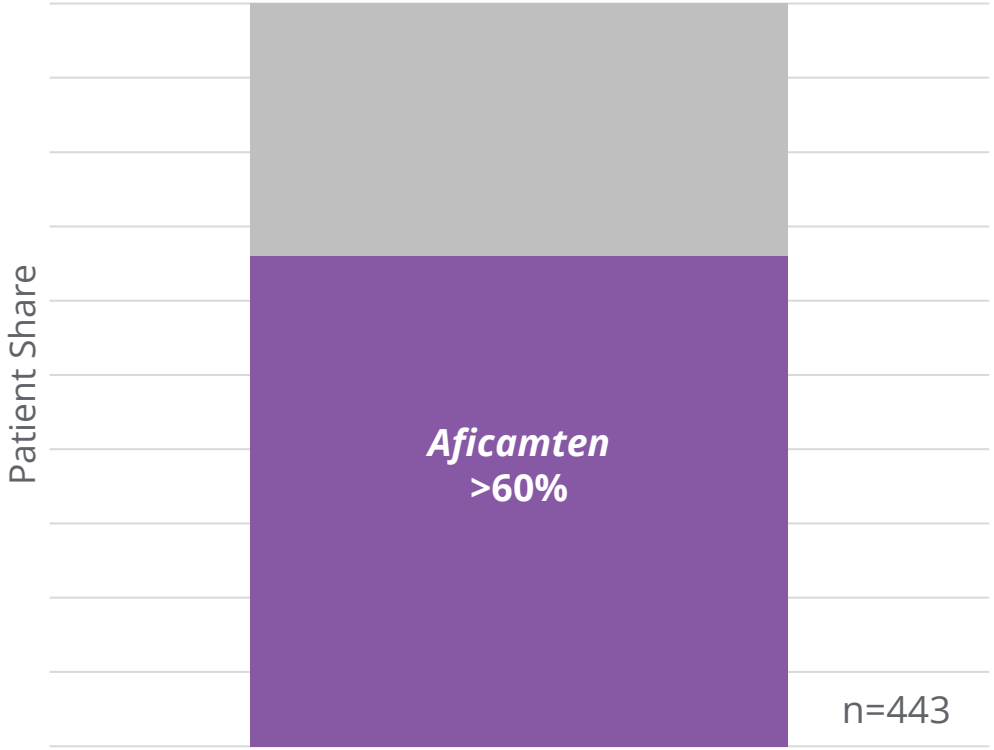
Open-label extension clinical study in HCM

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

Cytokinetics®

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

Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
Source: Aficamten Impact of Product Attributes on Product Preference Share n=443 cardiologists, Quantitative research including conjoint - Cogent

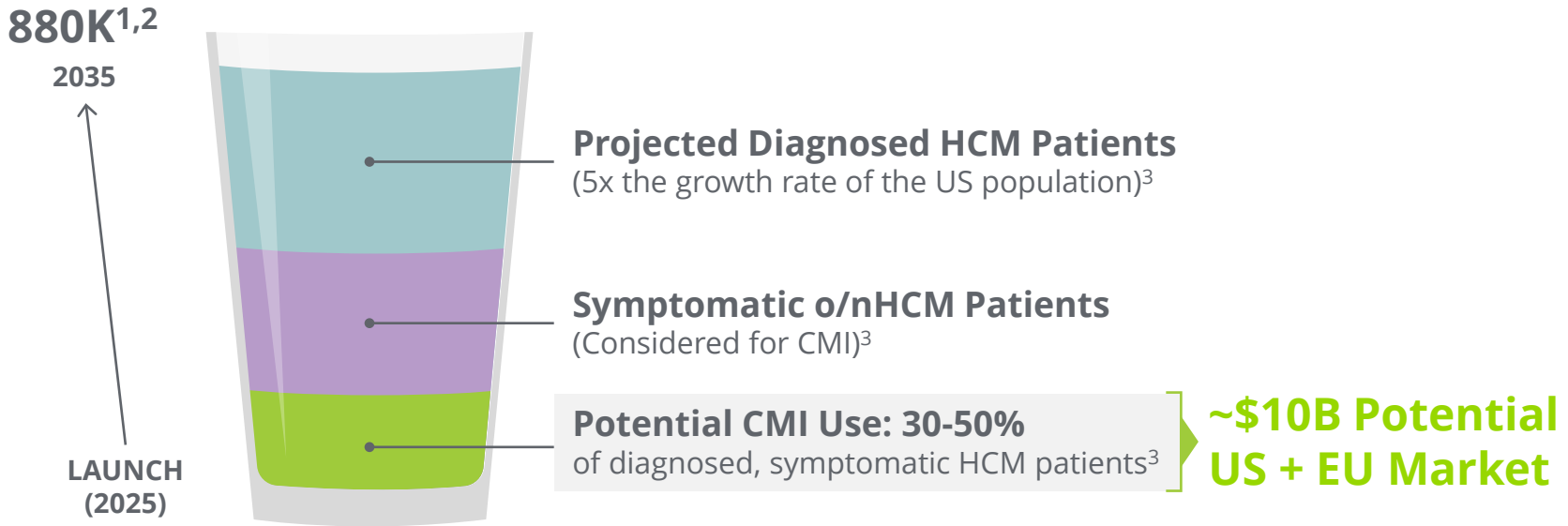
Cytokinetics®

$10B Potential Market of CMI-Eligible Patients, Majority Expected to be Available at Launch, if *Aficamten* is Approved

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

US and EU HCM Patients in 2035

Illustrative



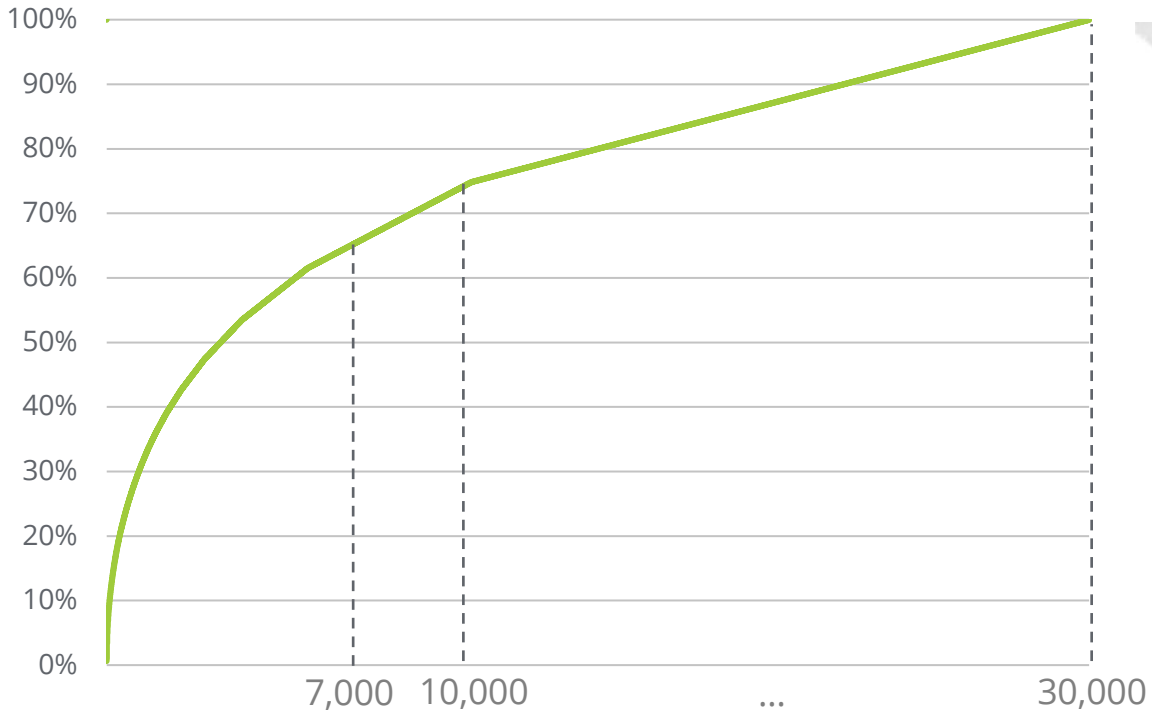
1. DoF: SHA; Symphony PTD (Patient Transaction Data): Includes patients diagnosed since 2016 and having any HC transaction in the claims data universe in the last year June 2022-May 2023);
2. Butzner et al 2021 estimated a 8% growth rate in diagnosed HCM patients between 2013-2019 https://www.ajconline.org/article/S0002-9149(21)00783-9/fulltext; CYTK is forecasting an average growth rate of 5% over the coming decade and a more conservative 4% growth rate in Europe due to a lack of growth of the overall population in EU5 countries.
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.**

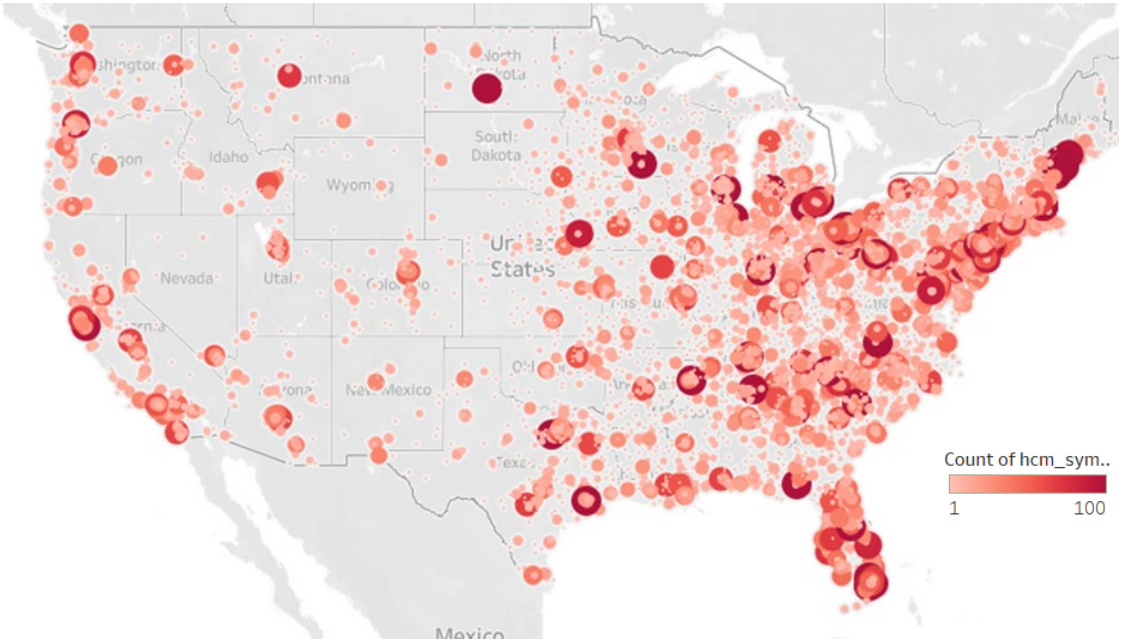
Cardiologists Located in Concentrated Geographic Clusters Across the US

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

HCM Patient Concentration by Cardiologist



Geographic Distribution of HCM Patients



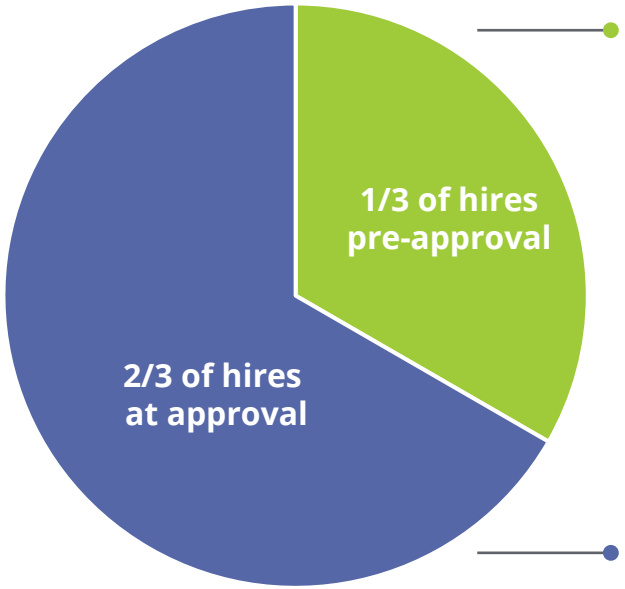
Note: includes only patients who are treated by a cardiologist - not all patients see a cardiologist; sample of 67K HCM patients
Source: Symphony PTD (Patient Transaction Data); mapping of HCPs to HCOs using Definitive Healthcare Data 2023 and 7/2023 mapping; Patient volume by dominant Cardiologist Location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

Cytokinetics®

Gated Build of Commercial Infrastructure

Sales representative hiring to occur in proximity to approval

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

Activities initiated upon key de-risking events

Underway before SEQUOIA-HCM readout
Market access strategy
Pricing strategy
Distribution approach
Payer engagement
Brand strategy
Customer account identification

Initiated after SEQUOIA-HCM readout
Launch campaign
Commercial training
Payer Pre-approval Information Exchange
Sales force planning
Technology build
Omnichannel execution
Market development

Initiated upon or in Proximity to FDA approval
Media purchases
Patient support programs

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

Cytokinetics®

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: Potential for High-Risk Severe HF Patients Despite GDMT

Advancing efficient, pragmatic Phase 3 clinical trial

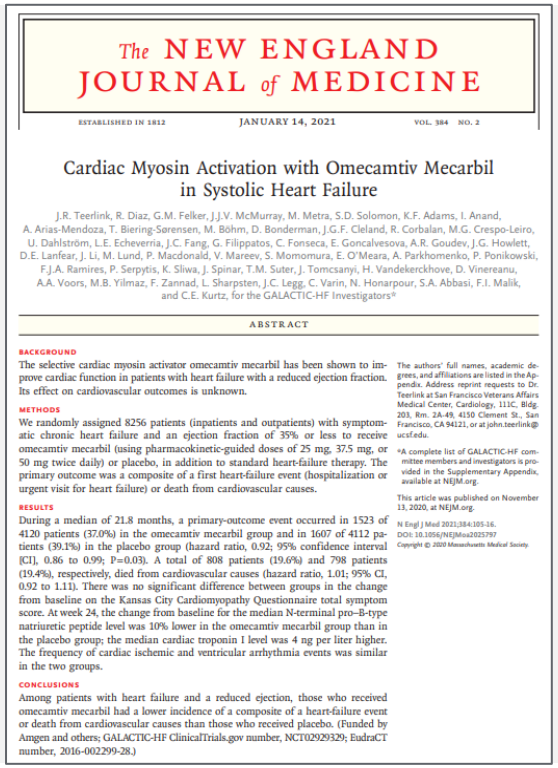
High Unmet Need

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
Copyright © 2020 Massachusetts Medical Society.

Ph 3 clinical trial results in 8,000 patients point to important treatment benefit

Planning confirmatory Ph 3 trial, **n= ~2,000, ~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

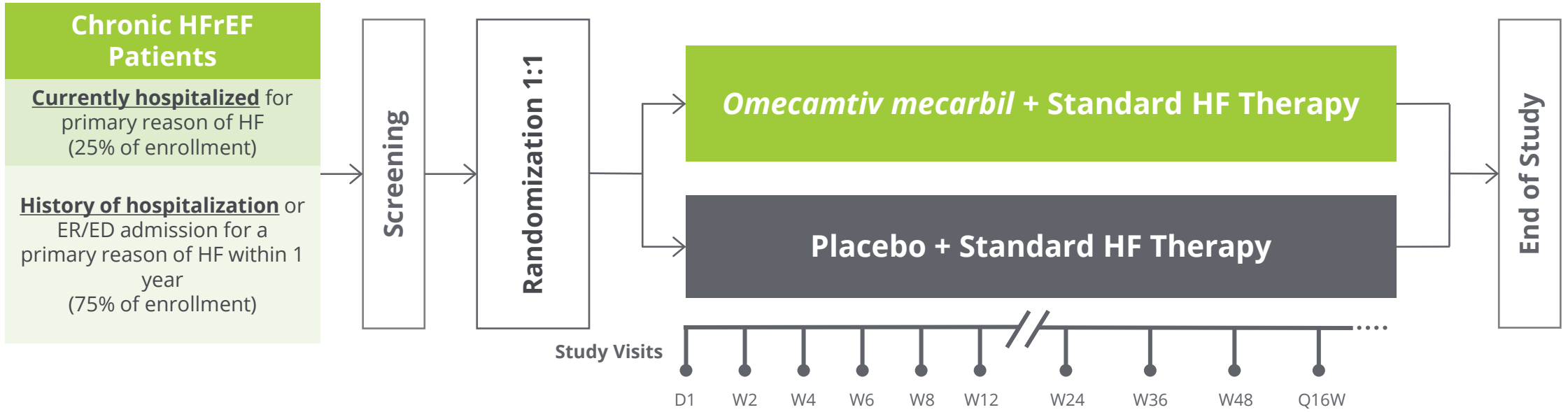
Omecamtiv mecarbil is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

GALACTIC-HF: Clinical Trial Overview

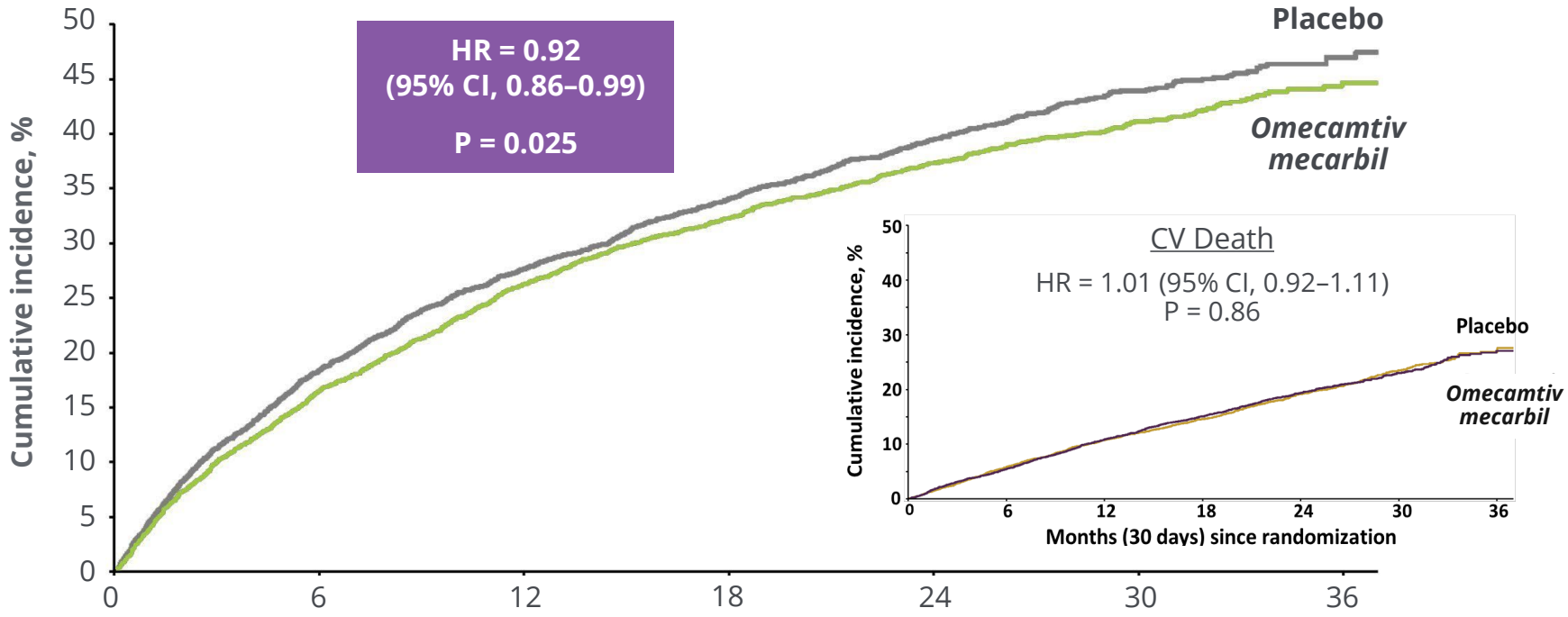
Phase 3 clinical trial

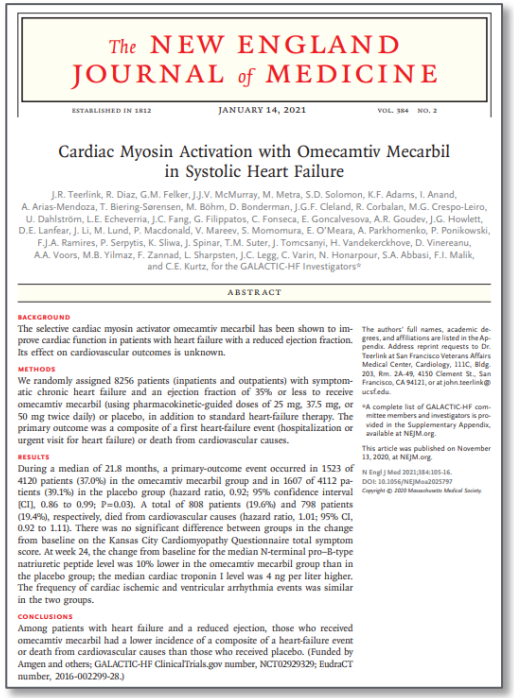
Event-driven clinical trial; 8,256 patients randomized in 35 countries at 944 clinical trial sites



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

Primary Composite Endpoint





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

Copyright © 2020 Massachusetts Medical Society.

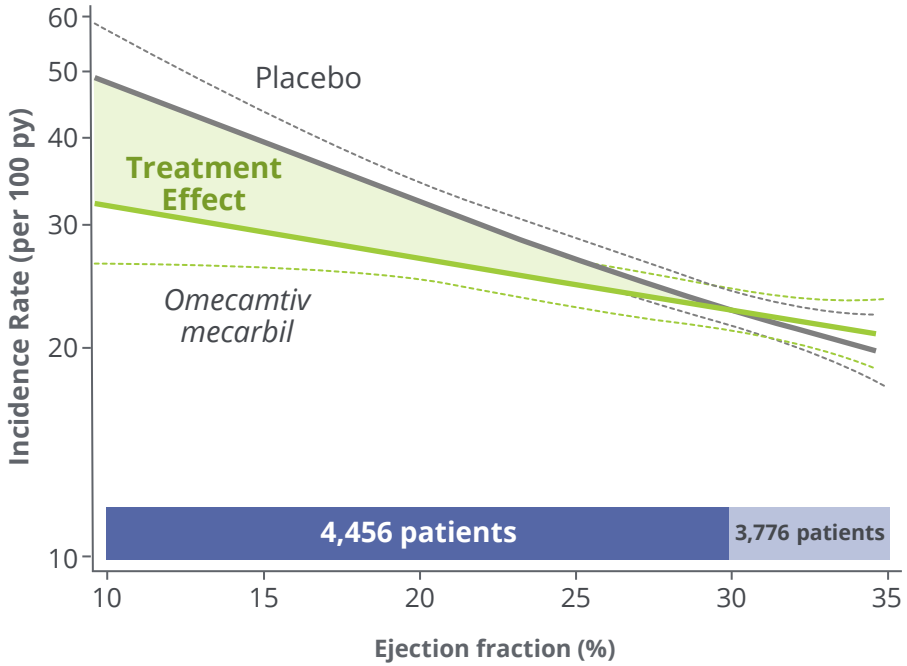
Patients at risk, n							
	Months (30 days) since randomization						
Placebo	4112	3310	2889	2102	1349	647	141
OM	4120	3391	2953	2158	1430	700	164

Time to first HF event or CV death

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

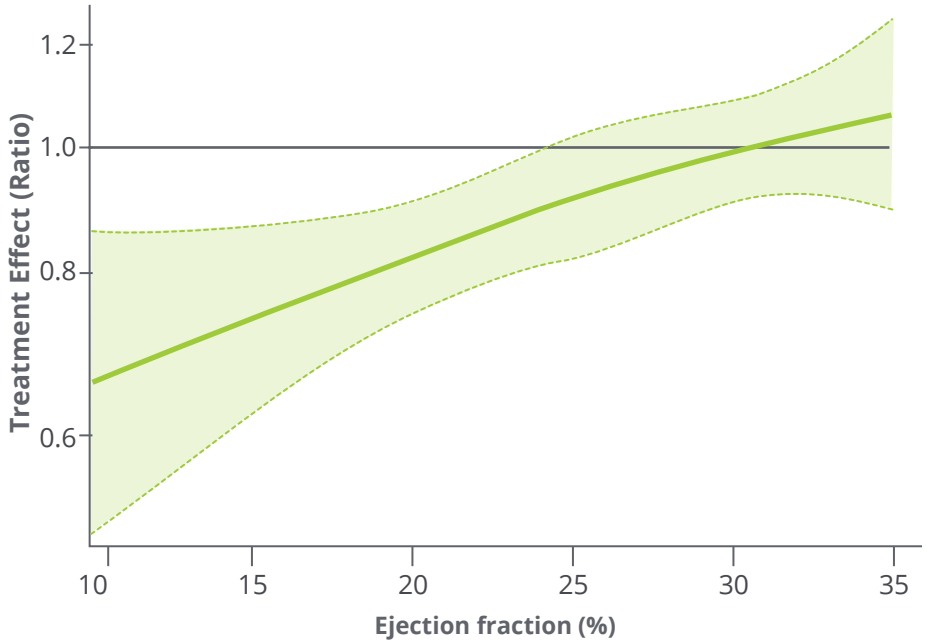
Benefit Observed to Increase as Baseline LVEF Decreased

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

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

ORIGINAL INVESTIGATIONS

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

John R. Teerlink, MD,[a] Rafael Diaz, MD,[b,c] G. Michael Felker, MD, MHS,[d] John J.V. McMurray, MD,[e] Marco Metra, MD,[f] Scott D. Solomon, MD,[g] Tor Biering-Sørensen, MD, PhD, MPH,[h] Michael Böhm, MD,[i] Ekaterina Bonderman, MD,[j] James C. Fang, MD,[k] David E. Lanfear, MD,[l] Mayanna Lamd, MD,[l] Shin-ichi Momomura, MD,[m] Eileen O'Meara, MD,[n] Piotr Ponikowski, MD, PhD,[o] Jindrich Spinar, MD, PhD,[p] Jose H. Flores-Arredondo, MD,[q] Brian L. Claggett, PhD,[r] Stephen B. Heitner, MD,[s] Stuart Kupfer, MD,[t] Siddique A. Abbasi, MD,[u] Fady I. Malik, MD, PhD,[v] on behalf of the GALACTIC-HF Investigators

ABSTRACT

BACKGROUND In GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) (n = 8,256), the cardiac myosin activator, omecamtiv mecarbil, significantly reduced the primary composite endpoint (PCE) of time to first heart failure event or cardiovascular death in patients with heart failure and reduced ejection fraction (EF) (≤35%).

OBJECTIVES The purpose of this study was to evaluate the influence of baseline EF on the therapeutic effect of omecamtiv mecarbil.

METHODS Outcomes in patients treated with omecamtiv mecarbil were compared with placebo according to EF.

RESULTS The risk of the PCE in the placebo group was nearly 1.8-fold greater in the lowest EF (≤22%) compared with the highest EF (>33%) quartile. Amongst the pre-specified subgroups, EF was the strongest modifier of the treatment effect of omecamtiv mecarbil on the PCE (interaction as continuous variable, p = 0.004). Patients receiving omecamtiv mecarbil had a progressively greater relative and absolute treatment effect as baseline EF decreased, with a 17% relative risk reduction for the PCE in patients with baseline EF ≤22% (n = 2,246; hazard ratio: 0.83; 95% confidence interval: 0.71 to 0.95) compared with patients with EF >33% (n = 1,750; hazard ratio: 0.99; 95% confidence interval: 0.84 to 1.16; interaction as EF by quartiles, p = 0.011). The absolute reduction in the PCE increased with decreasing EF (EF ≤22%; absolute risk reduction, 7.4 events per 100 patient-years; number needed to treat for 3 years = 11.8), compared with no reduction in the highest EF quartile.

CONCLUSIONS In heart failure patients with reduced EF, omecamtiv mecarbil produced greater therapeutic benefit as baseline EF decreased. These findings are consistent with the drug's mechanism of selectively improving systolic function and presents an important opportunity to improve the outcomes in a group of patients at greatest risk. (Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure With Reduced Ejection Fraction [GALACTIC-HF]; NCT02929329)

(J Am Coll Cardiol 2021;78:97–108) Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California San Francisco, San Francisco, California, USA; [b]Estudios Clínicos Latino América (ECLA), Rosario, Argentina; [c]Division of Cardiology, Duke University School of Medicine and Duke Clinical Research Institute, Durham, North Carolina, USA; [d]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [e]Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [f]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [g]Department of Cardiology, Herlev & Gentofte Hospital & Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [h]Imperial University, Klinik für Innere Medizin III (Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätskliniken des Saarlandes, Homburg, Germany; Medical University of

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2021.04.085

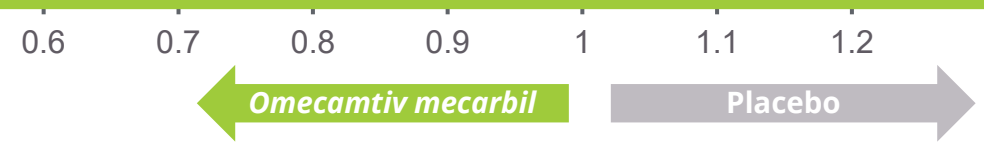
Omecamtiv mecarbil is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
ARR = Absolute Risk Reduction. RRR = Relative Risk Reduction.
Teerlink JR., Diaz R., Felker GM., et al. Effect of Ejection Fraction on Clinical Outcomes in Patients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

Cytokinetics®

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



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

Cytokinetics®

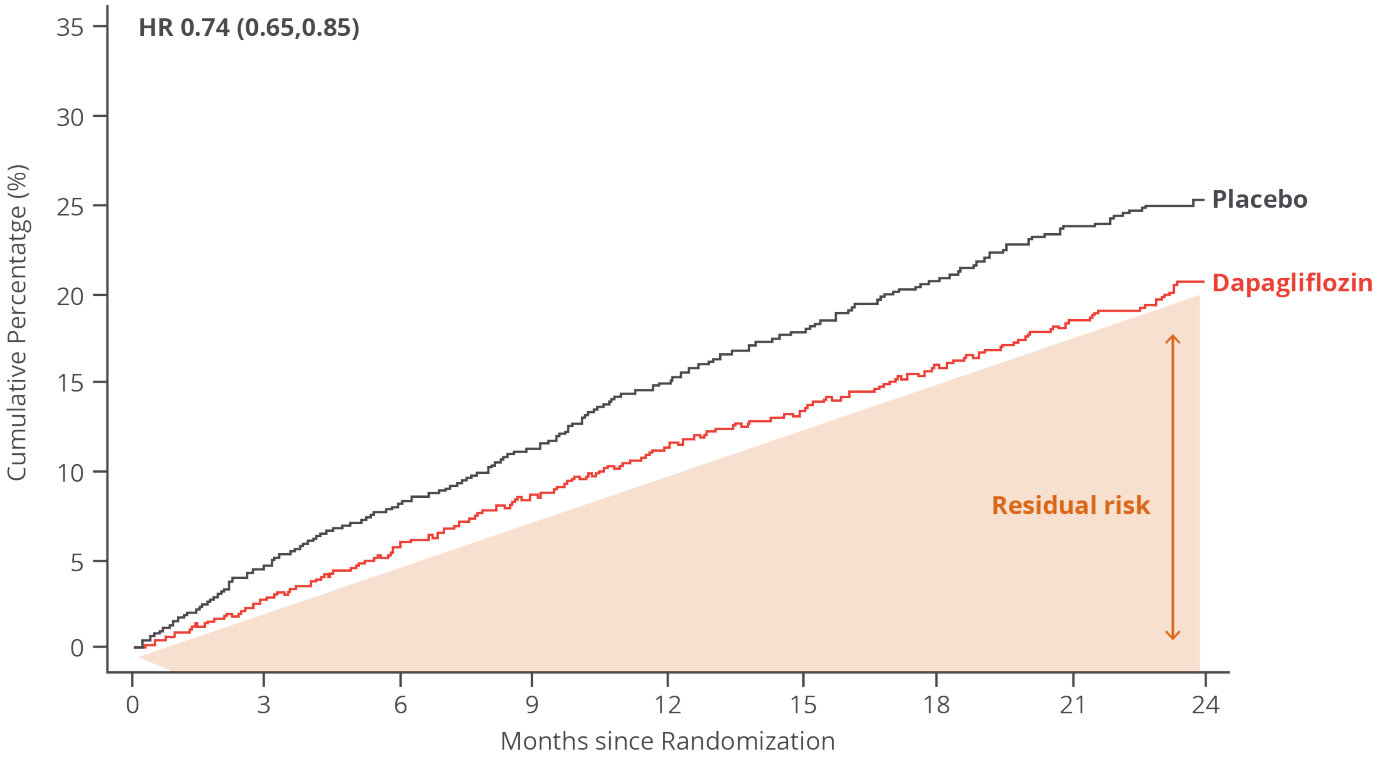
Residual Risk is High Despite Best Therapy

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%**
- Dapagliflozin **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

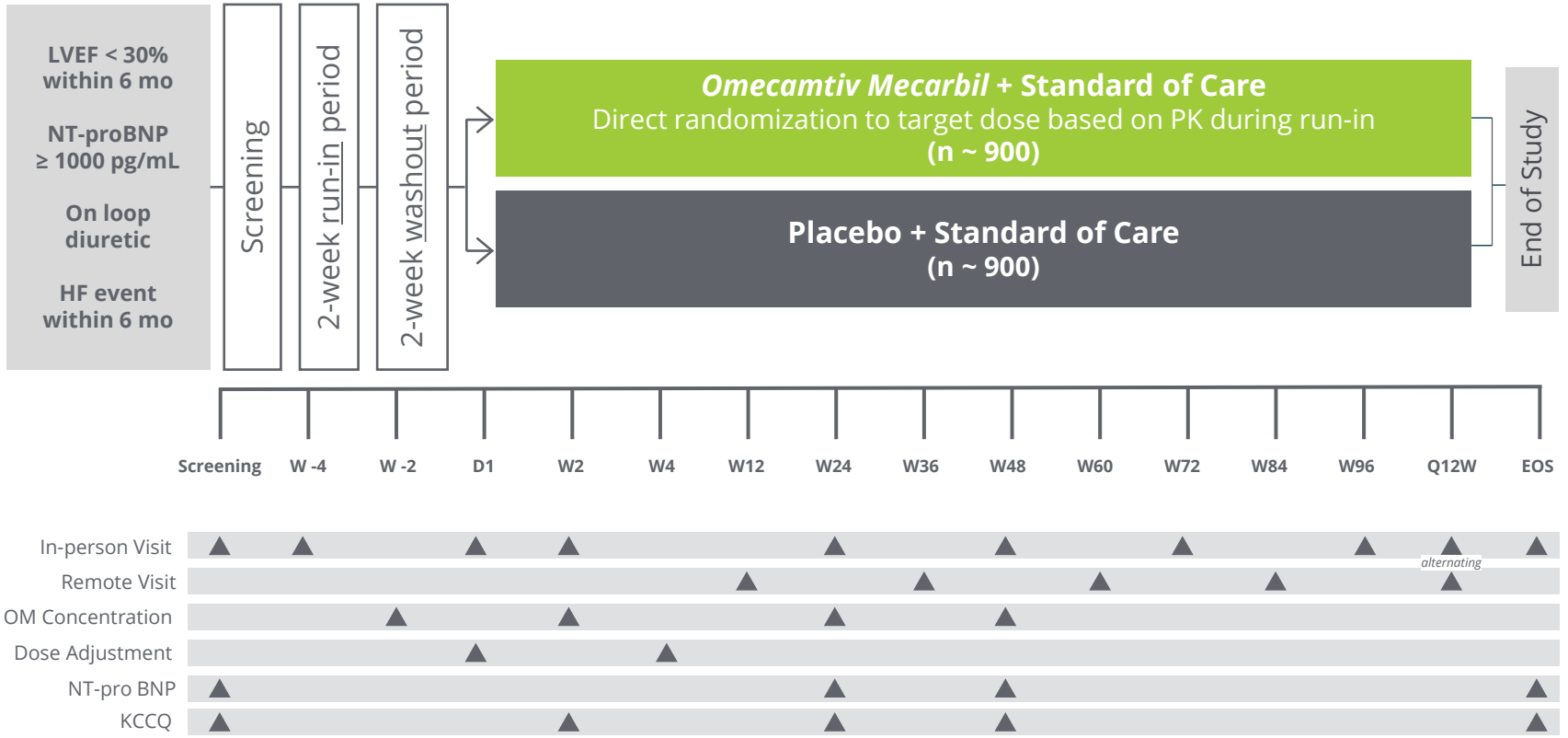
Cytokinetics®

Phase 3 Confirmatory Clinical Trial Design

COMET-HF expected to start in Q4 2024

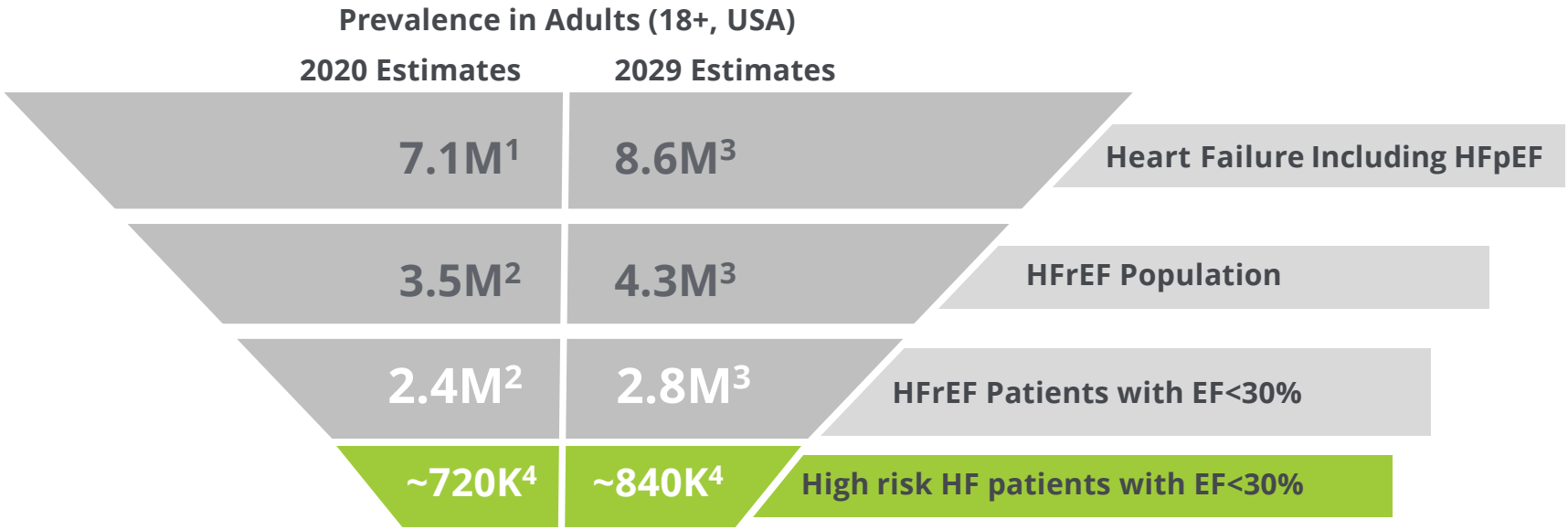
COMET-HF: Confirmation of *Omecamtiv Mecarbil* Efficacy Trial in Heart Failure

- Primary endpoint: **time to CV death, HF events, transplant/LVAD, or stroke**
- **Enriching population for adherence** with OM run-in period
- **Pragmatic design elements:**
  - Remote clinic visits
  - Limited safety labs & ECGs
  - Streamlined eligibility and study conduct
  - Streamlined AE reporting



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

Large and Growing Target Patient Population in US



Proposed
Omecamtiv Mecarbil
Target Patient

Patients treated with GDMT and still experiencing severely reduced EF and symptoms of heart failure

Cardiac Function

LVEF < 30%

+

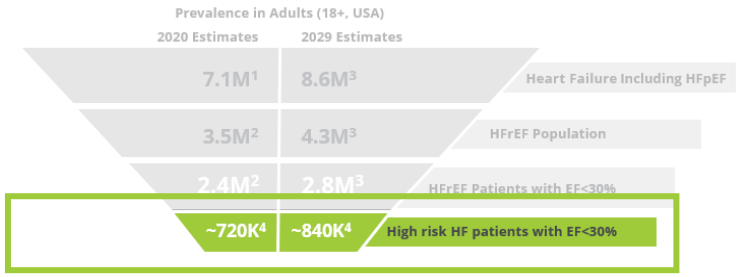
Markers of High-Risk HFrEF

- **HF Event* within the last 12 months**
- **Elevated NT-pro BNP**
- **Contraindications limiting GDMT, e.g. hypotension, renal dysfunction or hyperkalemia**

1. Tsao 2023, AHA. Racine 2022 CVrg. Bionest 2021.
2. 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.
3. 2.1% annual growth rate:1.9% annual growth rate of patient population 65+ (UN World Populations Prospects Nov 2019) and a 0.2% mortality impact of HF treatment (doi: 10.1136/bmj.l223 | BMJ 2019;364:l223)
4. Greene et al JACC 2023; 81:413-424
** HF Event: Urgent, unscheduled outpatient visit or hospitalization*
Omecamtiv mecarbil is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

Higher Event Rate & Costs in Patients with Severely Reduced EF



Accounts for **~60% of HFrEF hospitalizations**[5]

35% of patients with severely reduced EF **re-hospitalized within 1 year**[6]

$15,493 per HF re-hospitalization[7]

Direct costs from HF re-hospitalizations projected to increase from **$3.9 billion** in 2020 to **$4.6 billion** by 2029**

1. Tsao 2023, AHA. Racine 2022 CVrg. Bionest 2021.
** HF Event: Urgent, unscheduled outpatient visit or hospitalization **in terms of 2024 dollars*
2. 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.
3. 2.1% annual growth rate:1.9% annual growth rate of patient population 65+ (UN World Populations Prospects Nov 2019) and a 0.2% mortality impact of HF treatment (doi: 10.1136/bmj.l223 | BMJ 2019;364:l223)
4. Greene et al JACC 2023; 81:413-424
5. Extrapolated from Desai NR, Butler J, Binder G, Greene SJ. Prevalence and Excess Risk of Hospitalization in Heart Failure with Reduced Ejection Fraction. Poster presented at: Heart Failure Society of America (HFSA) Annual Scientific Meeting; 2022 Sep 30-Oct 3; Washington, DC.
6. Carnicelli AP, Clare RM, Hofmann P, Chiswell K, DeVore AD, Vemulapalli S, Felker GM, Kelsey AM, DeWald TA, Sarocco P, Mentz RJ. Clinical trajectory of patients with a worsening heart failure event and reduced ventricular ejection fraction. Am Heart J. 2022 Mar;245:110-116. doi: 10.1016/j.ahj.2021.12.003. Epub 2021 Dec 18. PMID: 34932997.
7. Urbich M, Globe G, Pantiri K, Heisen M, Bennison C, Wirtz HS, Di Tanna GL. A Systematic Review of Medical Costs Associated with Heart Failure in the USA (2014-2020). Pharmacoeconomics. 2020 Nov;38(11):1219-1236. doi: 10.1007/s40273-020-00952-0. PMID: 32812149; PMCID: PMC7546989.

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

Cytokinetics®

The Business Case for *Omecamtiv Mecarbil*

Significant clinical need, lack of treatments drives higher price potential in HF with severely reduced EF

		"Severely Reduced EF"
US Price Potential		Premium to market
Market Insights	**Disease Severity**	**Severely Reduced EF** LVEF <30
	Payer Positioning	**~1M patients** Post tolerated GDMT
	Therapeutic Choices	**Limited to no treatment options**, +50% patients share vs. ≤30 EF
Financials	**Improved Margin[1]**	+20% incremental improvement in brand margin*
	Cost Savings[1]	+70% cost avoidance driven by portfolio synergies*

** Based on internal analysis*
Financials compared to launching OM alone vs launching as second product following aficamten
Omecamtiv mecarbil is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

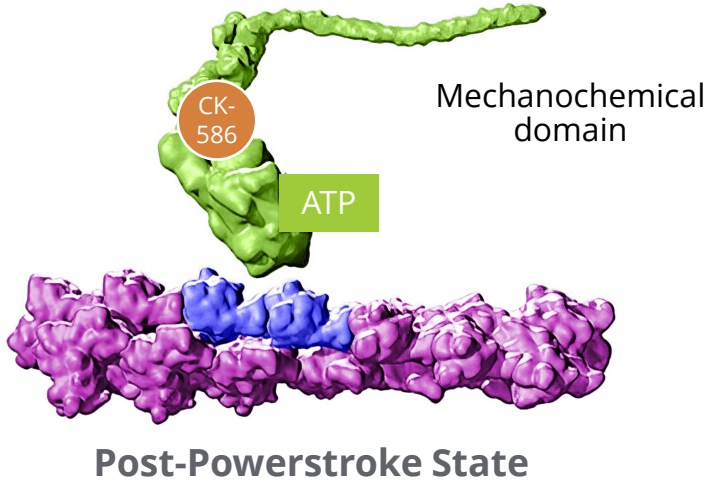
Cytokinetics®

CK-586

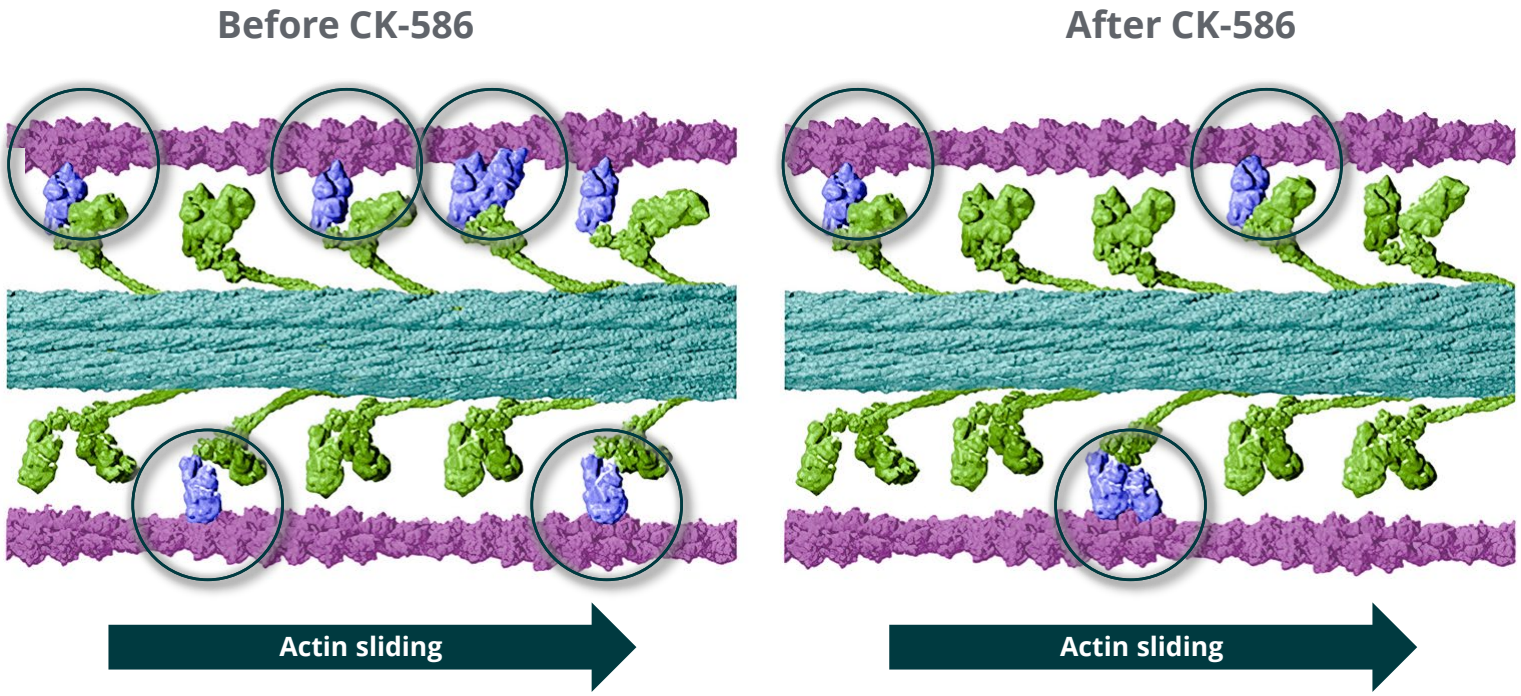
Cytokinetics®

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*



"Fewer hands pulling on the rope"

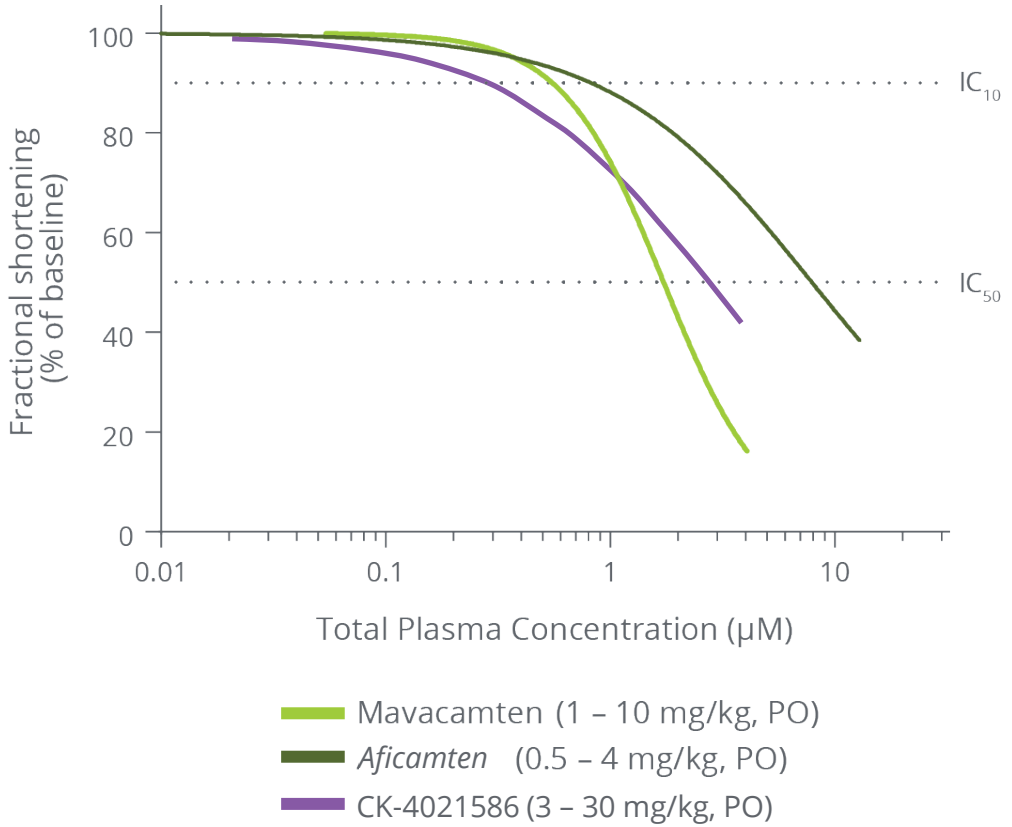


CK-586 is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

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

CK-586 has a shorter half-life 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

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

Cytokinetics®

Phase 1 Data Support Advancement to Phase 2 Clinical Trial

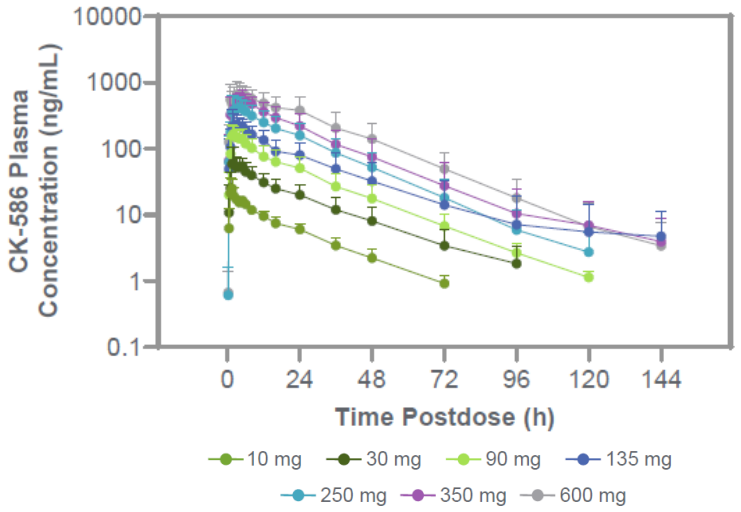
Phase 2 dose-finding trial in HFpEF expected to start in Q4 2024

Phase 1 study design: 7 SAD cohorts (10 mg to 600 mg) & 2 MAD cohorts (100 & 200 mg once daily), 10 participants each

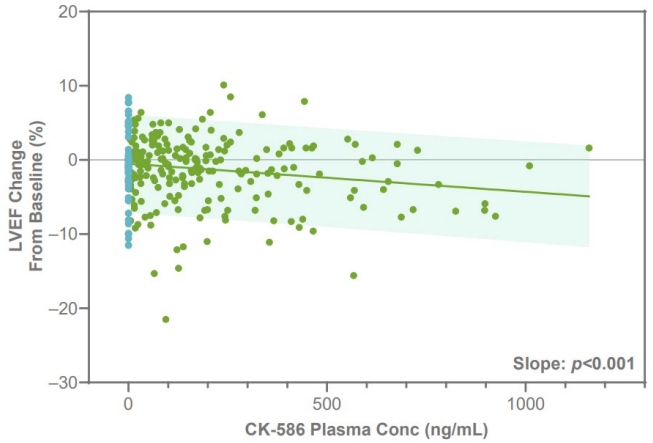
- **Less than 24-hour** half-life
- **Shallow and predictable** PK/PD relationship based on LVEF and LVFS
- **Well-tolerated** across all cohorts
- **No serious adverse events** were observed
- **Stopping criteria were not met**

Plasma Concentration

(mean [SD]) over time after single ascending doses of CK-586



Change in LVEF vs. CK-586 Plasma Concentration



PK/PD: pharmacokinetic/pharmacodynamic
LVEF: left ventricular ejection fraction
LVFS: left ventricular fractional shortening
Lutz JD., Simpkins T., Cheplo K., et al. A First-in-Human, Single and Multiple Ascending Dose Study of CK-4021586, a Novel Cardiac Myosin. Poster, American College of Clinical Pharmacology 2024
CK-586 is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

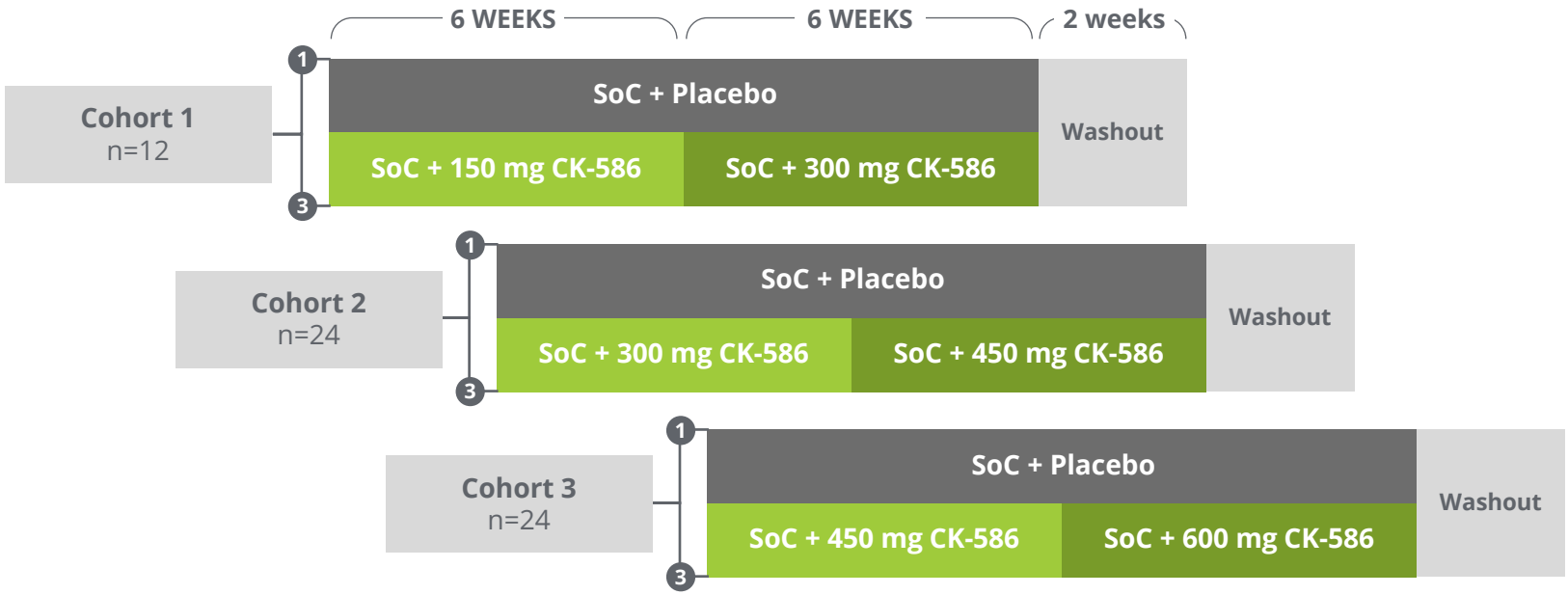
Phase 2 Study Schema

AMBER-HFpEF expected to start in Q4 2024

AMBER-HFpEF: Assessment of CK-586 in a **M**ulti-Center, **B**linded **E**valuation of Safety and Tolerability **R**esults in **HFpEF**

Enrolling HFpEF patients with:

- LVEF ≥ 60%
- Structural abnormality
- BMI < 40
- NYHA FC II or III
- NT-proBNP ≥ 300 (or ≥ 900 in AF)



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

Cytokinetics®

Heart Failure with Preserved Ejection Fraction (HFpEF)

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

~75%

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

~84%

HFpEF patients will be rehospitalized[2]

Subset of HFpEF patients with hypercontractility, ventricular hypertrophy, elevated biomarkers & HF symptoms **may benefit from a cardiac sarcomere inhibitor**

Significant increase in hospitalizations due to HFpEF, from 189,260 in 2008 to 495,095 in 2018 [6]

Lifetime healthcare costs for HFpEF are ~ $126,819 per patient[5], per-patient monthly cost for healthcare is $7,482, primarily, driven by **high rates of inpatient & outpatient visits**

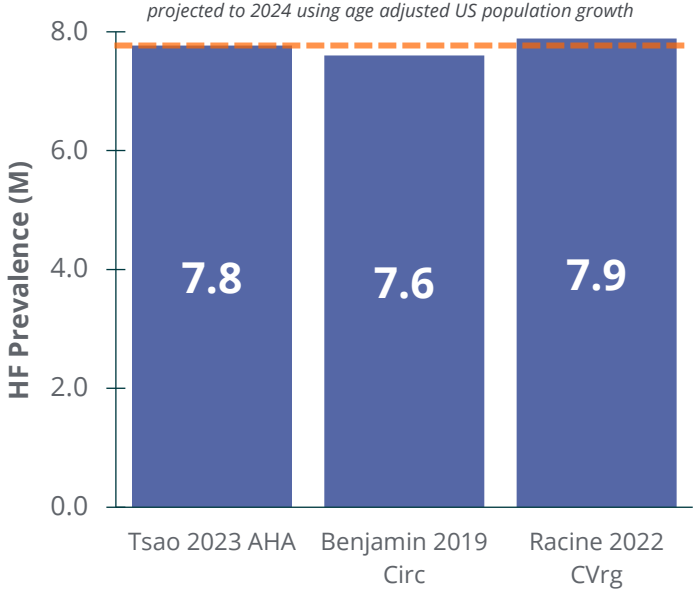
1. Jhund PS, MacIntyre K, Simpson CR, et al. Long-Term Trends in First Hospitalization for Heart Failure and Subsequent Survival Between 1986 and 2003. Circulation. 2009;119:515-523.
2. Bozkurt B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, Fonarow GC, Heidenreich P, Ho JE, Hsich E, Ibrahim 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.
5. Kapelios, Cardiac Failure Review 2023
6. Clark KAA, Reinhardt SW, Chouairi F et al (2022) Trends in heart failure hospitalizations in the US from 2008 to 2018. J Card Fail 28(2):171–180.
7. Lam CSP, Wood R, Vaduganathan M et al (2021) Contemporary economic burden in a real-world heart failure population with Commercial and Medicare supplemental plans. Clin Cardiol 44(5):646–655.

Cytokinetics®

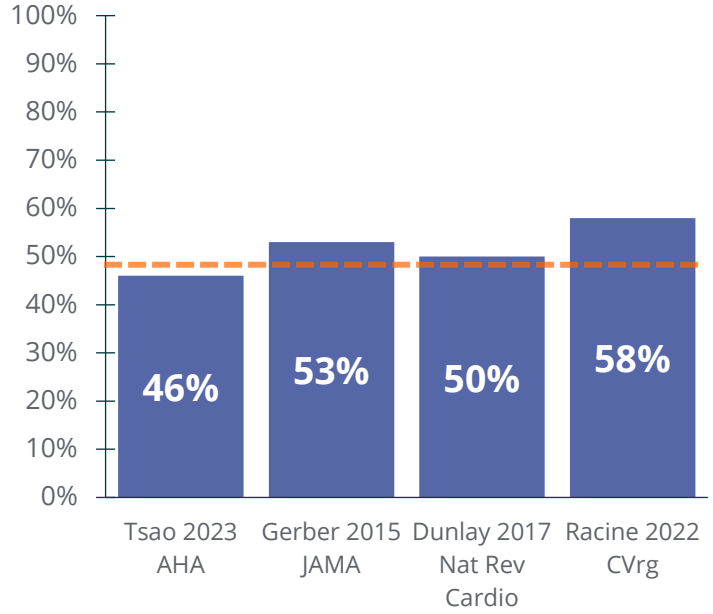
CK-586: Focusing on Patients with HFpEF and EF ≥ 60

7.9M
Heart Failure Prevalence in 2024, US

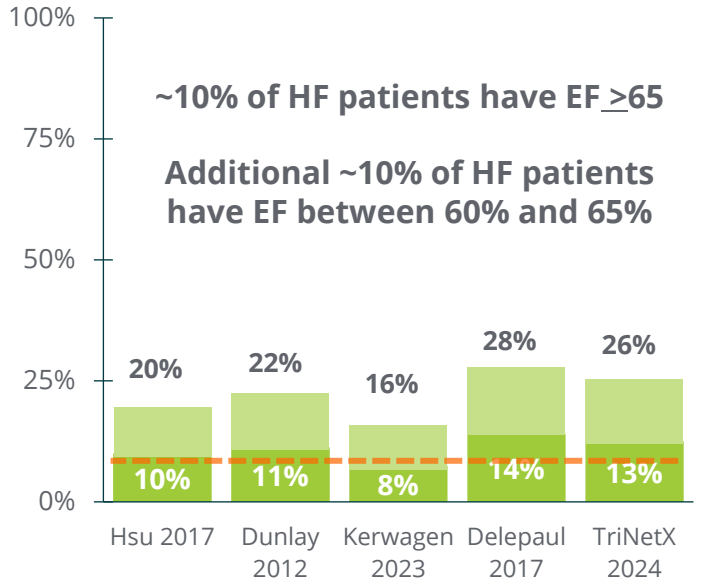
2024 prevalence calculated using published, historic estimate and projected to 2024 using age adjusted US population growth



4.0M (2024)
50% of HF with HFpEF (EF ≥ 50%)



1.0M (EF≥65) to 2.0M (EF ≥ 60)
~20% of HF with EF ≥ 60%



Source: Racine et al Heart Failure 2020-2029, CVrg March 2020 p 26; includes patients in long term care settings, which NHANES epi does not incorporate; Benjamin, E. et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the AHA Circulation Vol 139, Issue 10, 5 March 2019; Pages e56-e528 historic growth rate of HF 2009-2012 vs. 2013-2016: 2.1%; the population of 65+ year old is expected to grow at 1.9% according to the UN – mortality improvement of 0.2% per year.; Heidenreich P. at al: Forecasting the Impact of Heart Failure in the United States Circulation: Heart Failure Volume 6, Issue 3 May 2013; Tsao C., et al Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association, Circulation Volume 139, Issue 10 Mar 2019; UN Population Report Nov 2020; 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, Gerber 2015 JAMA, Hsu JJ, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: Clinical Implications and Future Directions. JACC Heart Fail. 2017 Nov;5(11):763-771. doi: 10.1016/j.jchf.2017.06.013. Epub 2017 Oct 11. PMID: 29032140; PMCID: PMC6668914. Kerwagen F, Koehler K, Vettorazzi E, Stangl V, Koehler M, Halle M, Koehler F, Störk S. Remote patient management of heart failure across the ejection fraction spectrum: A pre-specified analysis of the TIM-HF2 trial. Eur J Heart Fail. 2023 Sep;25(9):1671-1681. doi: 10.1002/ejhf.2948. Epub 2023 Jul 31. PMID: 37368507. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, Roger-Rollé A, Domain G, Delon C, Uzan C, Boudjellil R, Carrié D, Roncalli J, Galinier M, Lairez O. Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines? ESC Heart Fail. 2017 May;4(2):99-104. doi: 10.1002/ehf2.12131. Epub 2017 Jan 31. PMID: 28451445; PMCID: PMC5396039.

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

Cytokinetics®

CK-586 May Address Unmet Needs of HFpEF Patients

Proposed Mechanistic Benefits

- CK-586 may benefit cardiac relaxation during diastole
- CK-586 may reduce symptoms and improve functional capacity

Target Product Profile

- Statistically significant reduction in composite of mortality and hospitalization outcomes
- Oral QD tablet
- Minimal drug interactions
- Simple dose titration with biomarker monitoring

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

Financials & Milestones

Strong Financial Position

Strengthened balance sheet & access to capital to execute launch & advance R&D pipeline

September 30, 2024	**~$1.3B** in cash, cash equivalents and investments
Further access to capital through term loans with Royalty Pharma (RP)	Access up to $350M in term loans*
Potential further funding through RP opt-in	RP, at its option, can invest up to **$150M** in a Phase 3 trial of CK-586 in exchange for an additional*** 3.5% revenue participation interest in worldwide net sales of CK-586

Add'l $500M

**Term loans are comprised of Tranche 4 , 5, and 7 Loans*
Tranche 4: Cytokinetics is eligible to draw up to $75m by April 3, 2025. The minimum draw for tranche 4 is $50m.
Tranche 5: Cytokinetics, at its option, is eligible to draw up to $100m during the 1-year period following the acceptance of the NDA filing for aficamten in oHCM provided that the NDA filing is accepted on or prior to March 31, 2025.
Tranche 7: Cytokinetics, at its option, is eligible to draw up to $175m subject to conditions related to the approval of the NDA for aficamten in oHCM on or prior to December 31, 2025.
**** Royalty Pharma currently has a revenue participation interest of 1.0% of worldwide net sales of CK-586.*

2024 Financial Guidance

	Current Guidance Issued on Aug. 8, 2024
GAAP Operating Expense[1]	$555m to $575m
Non-cash Expense[2] Included in GAAP Operating Expense	$110m to $105m
Non-GAAP Operating Expense[3]	$445m to $470m
Net Cash Utilization[4]	$400m to $420m

The financial guidance does not include the effect of GAAP adjustments as may be caused by events that occur subsequent to publication of this guidance including but not limited to Business Development activities.

[1] GAAP operating expense comprised of R&D and G&A expenses.
[2] Non-cash operating expense comprised of stock-based compensation and depreciation.
[3] Non-GAAP operating expense comprised of R&D and G&A expenses but excludes non-cash operating expense.
[4] Net cash utilization is a non-GAAP financial measure that we define as our ending 2023 cash, cash equivalents, and investments balance of $655 million plus the net proceeds of $707 million received from the sale of common stock (through the at-the-market facility, public offerings, and stock purchase agreement with Royalty Pharma) plus proceeds of $200 million received from the structured financing agreement with Royalty Pharma announced on May 22, 2024 minus our projected ending 2024 cash, cash equivalents, and investments balance of between $1,142 million and $1,162 million.

Exclusive Licensing Collaboration with Bayer for *Aficamten* in Japan

Upfront payment, development & commercial milestone payments & tiered royalties

Collaboration leverages Bayer's regional capabilities & expertise in development & commercialization

Collaboration Financials:

- €50 million upfront payment
- Up to €90 million upon the achievement of milestones through commercial launch, €20 million of which are near-term payments
- Up to €490 million in commercial milestone payments upon the achievement by Bayer of certain sales milestones
- Tiered royalties ranging from the high teens to the low 30s on net sales of *aficamten* in Japan

Joint Development Program:

- Bayer will conduct a Phase 3 clinical trial in Japanese patients with oHCM
- Cytokinetics will expand ACACIA-HCM, the Phase 3 clinical trial of *aficamten* in patients with nHCM, and CEDAR-HCM, the study of *aficamten* in a pediatric population, into Japan

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

Robust Pipeline, Upcoming Commercial Launch & Solid Financial Position

Commercial

U.S. & China NDAs for *aficamten* submitted
U.S go-to-market strategies anchored in differentiated market access & patient experience

Plan to submit MAA to EMA in Q4 2024
European commercial readiness activities underway

Pipeline

Aficamten

SEQUOIA-HCM: Positive Phase 3 results
Ongoing clinical program with label-expanding opportunities including:
MAPLE-HCM: Phase 3 monotherapy
ACACIA-HCM: Phase 3 nHCM
CEDAR-HCM: Phase 2-3 in pediatric oHCM
FOREST-HCM: OLE in oHCM & nHCM

Omecamtiv mecarbil
Phase 3 confirmatory clinical trial **COMET-HF** starting in Q4 2024

CK-586
Phase 2 **AMBER-HFpEF** clinical trial starting in Q4 2024

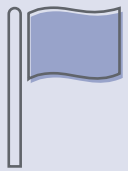
CK-089
Phase 1 study in healthy participants

Ongoing R&D
Additional research in muscle biology, energetics & metabolism

Foundation

R&D platform rooted in **myosin modulation**

Pioneers in muscle biology



$1.3B cash & investments* with further access to long-term capital, up to $500M**

**As of September 30, 2024*
** $500M comprised of $350 M in term loan facilities with Royalty Pharma, and $150M Royalty Pharma can, at its option, invest in a Phase 3 clinical trial of CK-586 in exchange for an additional 3.5% revenue participation interest in worldwide net sales 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.

Cytokinetics®

Upcoming Milestones

Aficamten

- **Submit MAA to EMA** in Q4 2024
- **Report topline results from MAPLE-HCM** in 1H 2025
- **Complete enrollment of ACACIA-HCM** in 2025
- **Continue enrollment of CEDAR-HCM** in 2024
- **Continue Phase 1 study of *aficamten* in healthy Japanese volunteers** in 2024

Omecamtiv Mecarbil

- **Initiate COMET-HF** in Q4 2024

CK-586

- **Initiate AMBER-HFpEF** in Q4 2024

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

Cytokinetics®

thank you

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