UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): October 19, 2023

Cytokinetics, Incorporated

(Exact name of Registrant as Specified in Its Charter)

Delaware	**000-50633**	**94-3291317**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

350 Oyster Point Boulevard **South San Francisco, California** **(Address of Principal Executive Offices)**	**94080** **(Zip Code)**

Registrant's Telephone Number, Including Area Code: (650) 624-3000

N/A
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value	CYTK	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

Cytokinetics, Incorporated is furnishing with this Current Report on Form 8-K a copy of a presentation, entitled New Horizons in Hypercontractility, that will be presented today at its virtual Investor and Analyst Day event. The information in these slides shall not be deemed "filed" for purposes of the Securities Exchange Act of 1934, as amended, nor shall it be incorporated by reference in any filing under the Securities Exchange Act of 1934, as amended, or the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d)

99.1 Investor and Analyst Day Presentation.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

CYTOKINETICS, INCORPORATED

Date: October 19, 2023

By: /s/ John O. Faurescu
John O. Faurescu, Esq.
Associate General Counsel & Corporate Secretary

Cytokinetics®

NEW HORIZONS IN HYPERCONTRACTILITY

An Investor & Analyst Day

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 related Cytokinetics' research and development and commercial readiness activities, including the initiation, conduct, design, enrollment, progress, continuation, completion, timing and results of clinical trials (including, but not limited to, SEQUOIA-HCM, MAPLE-HCM, and ACACIA-HCM), 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,* or CK-586; the Cytokinetics' commercial readiness for *aficamten* or *omecamtiv mecarbil*; the likelihood of approval and timing for regulatory approval of *aficamten*, *omecamtiv mecarbil* or any of our other drug candidates; the submission of a new drug application (NDA) to the FDA for *aficamten* in 2025, if ever; the timing of any potential commercial launch of our product candidates, if approved; commercial opportunities for our product candidates; the potential for *aficamten* to be first in line therapy for HCM; the potential REMS program for *aficamten* or any other differentiation from other therapies for HCM; Cytokinetics' cash runway, future cash balances and estimated cash expenditures; interactions with the FDA; the properties, potential benefits and commercial potential of *aficamten, omecamtiv mecarbil*, CK-586 and Cytokinetics' other drug candidates. 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").

Company Speakers

Robert Blum
President & CEO

Fady Malik, M.D., Ph.D.
EVP, Research & Development

Stuart Kupfer, M.D.
SVP, Chief Medical Officer

Steve Heitner, M.D.
VP, Clinical Research & Therapeutic Area Lead, Cardiovascular

Daniel Jacoby, M.D.
Senior Medical Director, Clinical Research Cardiovascular

Andrew Callos
EVP, Chief Commercial Officer

John Jacoppi
VP, US Marketing for *Aficamten*

Jeff Lotz
VP, US Sales & Operations

Diane Weiser
SVP, Corporate Communications & Investor Relations

Expert Speakers

Theodore Abraham, M.D., FACC, FASE
Meyer Friedman Distinguished Professor of Medicine, Division of Cardiology, University of California, San Francisco; Co-director, UCSF HCM Center of Excellence; Director, UCSF Adult Cardiac Echocardiography Laboratory

Caroline Coats, Ph.D.
Clinical Senior Lecturer, School of Cardiovascular & Metabolic Health, University of Glasgow

Carolyn Ho, M.D.
Associate Professor, Harvard Medical School, Medical Director of the Cardiovascular Genetics Center

Megan Link
Person Living with HCM

Actual patient who consents and agrees to appear.

Today's Agenda

Topic	Presenter
Welcome	Diane Weiser, SVP, Corporate Communications & Investor Relations
Building a Specialty Cardiology Franchise	Robert Blum, President & CEO
Cardiac Myosin Inhibition	Fady Malik, M.D., Ph.D., EVP, Research & Development
HCM Landscape	Andrew Callos, EVP, Chief Commercial Officer
***Aficamten*: Development Program**	Stuart Kupfer, M.D., SVP, Chief Medical Officer Steve Heitner, M.D., VP, Clinical Research & Therapeutic Area Lead, Cardiovascular Daniel Jacoby, M.D., Senior Medical Director, Clinical Research Cardiovascular
5 Minute Break	
HCM Patient Perspective	Diane Weiser, SVP, Corporate Communications & Investor Relations Megan Link, Person Living with HCM
***Aficamten*: Commercial Readiness**	John Jacoppi, VP, US Marketing for *Aficamten* Andrew Callos, EVP, Chief Commercial Officer Jeff Lotz, VP, US Sales & Operations
HCM KOL Panel	Fady Malik, M.D., Ph.D., EVP, Research & Development Theodore Abraham, M.D., FACC, FASE Caroline Coats, Ph.D. Carolyn Ho, M.D.
HFpEF Landscape & CK-586 Development Program	Stuart Kupfer, M.D., SVP, Chief Medical Officer
Q&A Session	Diane Weiser, SVP, Corporate Communications & Investor Relations
Closing Remarks	Robert Blum, President & CEO

Building a Specialty Cardiology Franchise

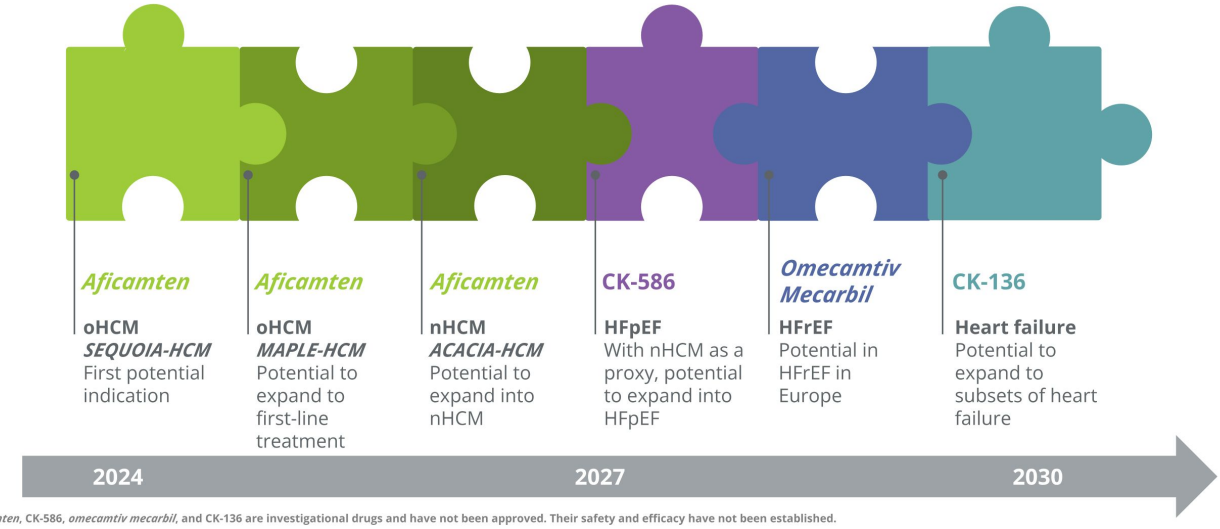
Robert Blum
President & CEO

Cytokinetics®

Building a Specialty Cardiology Franchise Anchored by *Aficamten*

Addressing severely ill and underserved populations in need of new therapies

Strategic expansion of clinical development program to various patient populations fuels leadership in cardiology

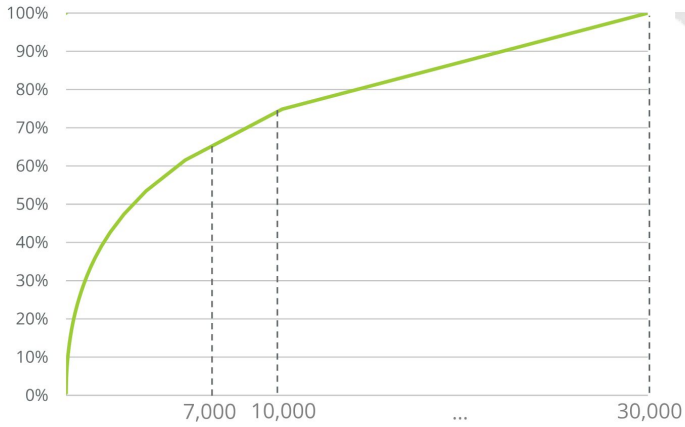


Aficamten, CK-586, *omecamtiv mecarbil*, and CK-136 are investigational drugs and have not been approved. Their safety and efficacy have not been established.

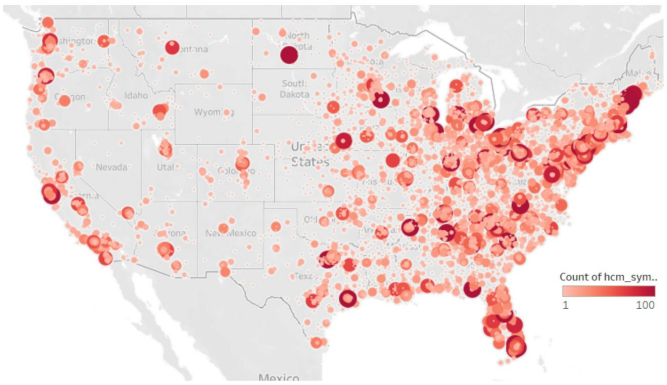
Cardiologists Located in Concentrated Geographic Clusters Across the US

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

HCM Patient Concentration by Cardiologist

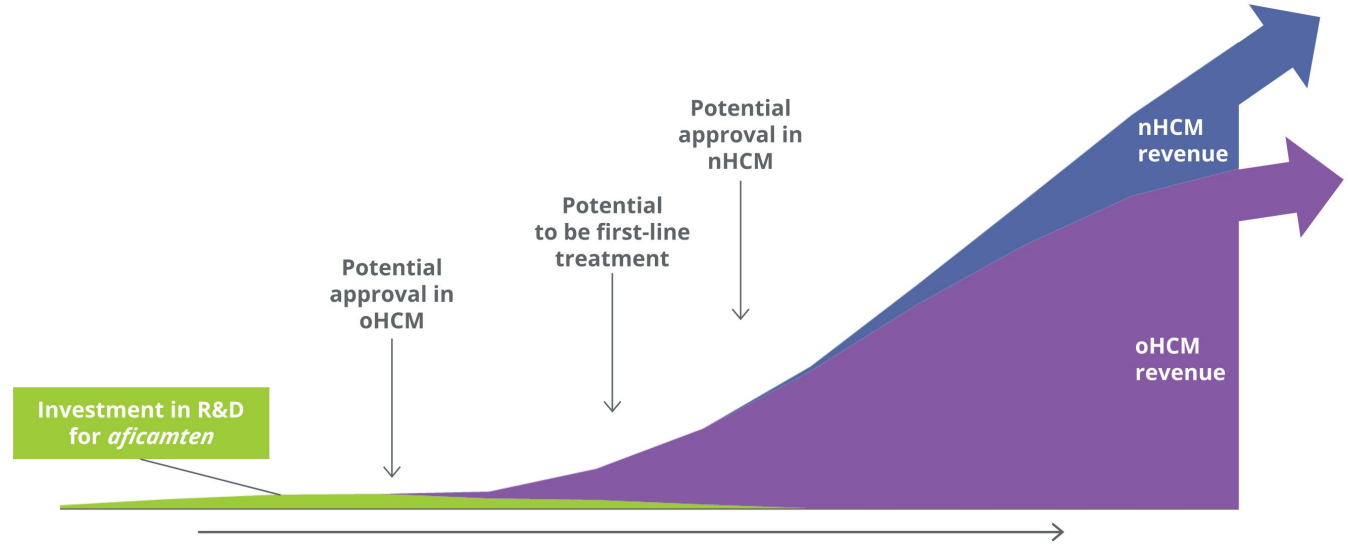


Geographic Distribution of HCM Patients



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

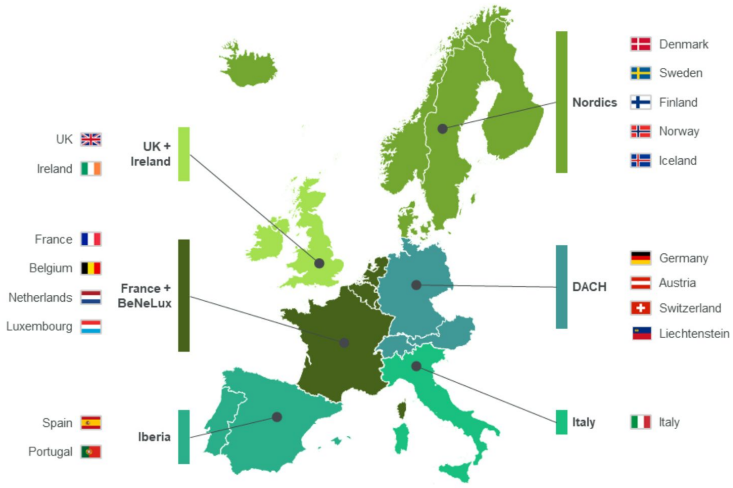
Investing in *Aficamten* to Achieve Sustainable, Growing Revenue



Projected forecast for illustration

Cytokinetics

Aficamten Supports Potential Go-To-Market in Europe



- **Opportunity is of sufficient scale** for standalone launch of *aficamten* and can support portfolio
- Plan is to launch across **6 country clusters** representing >95% of forecasted EU/UK revenue
- Minimal FTEs in 2024-2025, with **gradual build by country gated on regulatory progress and proximity to local reimbursement**

Cytokinetics

Unique Attributes of a Specialty Cardiology Company

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	**Minimal awareness with high % undiagnosed**
HCP – Rep Interactions	Brief discussion	**Scheduled meetings**

Cytokinetics: Uniquely Positioned for Success

Leadership
in muscle biology

Pioneer in CMI space

Multiple drug candidates arising from our research

Core research engine

Depth
in cardiology

Late-stage HCM program

HFrEF opportunity in Europe

Early-stage HFpEF research

Early-stage HF research

Relationships
with stakeholders

Seasoned commercial team

Strong existing payer relationships

Strong relationships with cardiologists and institutions

Access
to capital

Strong cash runway

Access to capital through Royalty Pharma transaction

CMI: cardiac myosin inhibitor

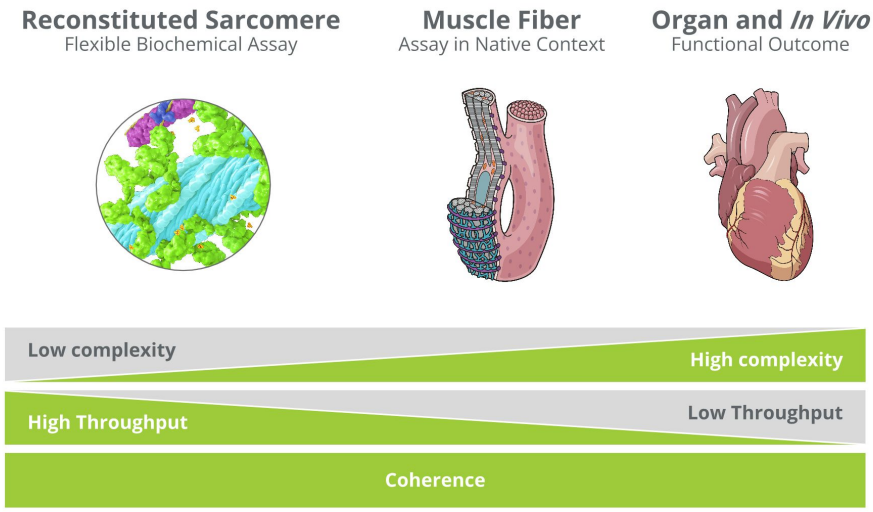
Cardiac Myosin Inhibition

Fady Malik, M.D., Ph.D.
EVP, Research & Development

Cytokinetics

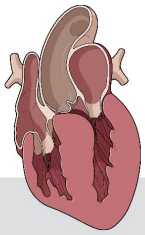
Pioneers in the Pharmacology of Muscle Contractility

- Novel molecular targets require novel assays
- Faithful representation of biological function from *in vitro* to *in vivo* setting
- Correlation of molecular findings with functional effects
- Purpose-built measurement technologies



Sarcomere Directed Drug Development

HCM = Hypercontraction



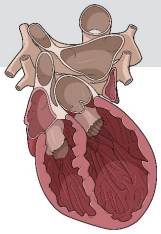
Inhibitors

Aficamten (Cardiac Myosin Inhibitor)

CK-586 (Cardiac Myosin Inhibitor)

Impaired cardiac muscle function → **Sarcomere Modulation**

HFrEF = Hypocontraction

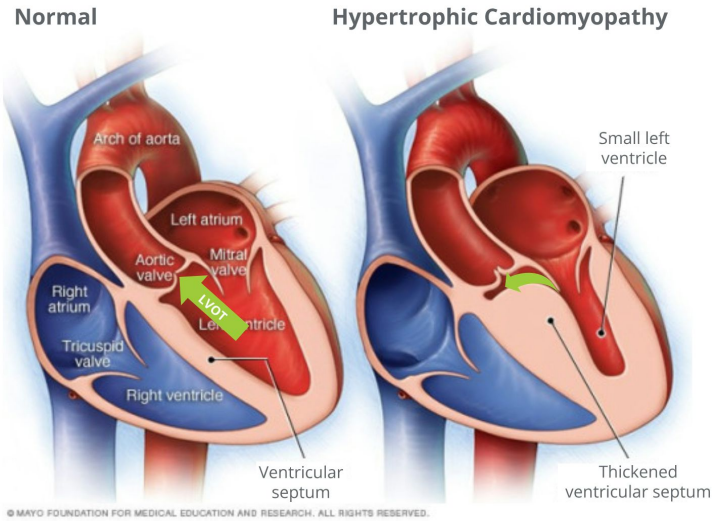


Activators

Omecamtiv mecarbil (Cardiac Myosin Activator)

CK-136 (Cardiac Troponin Activator)

Hypertrophic Cardiomyopathy



Phenotypically Defined

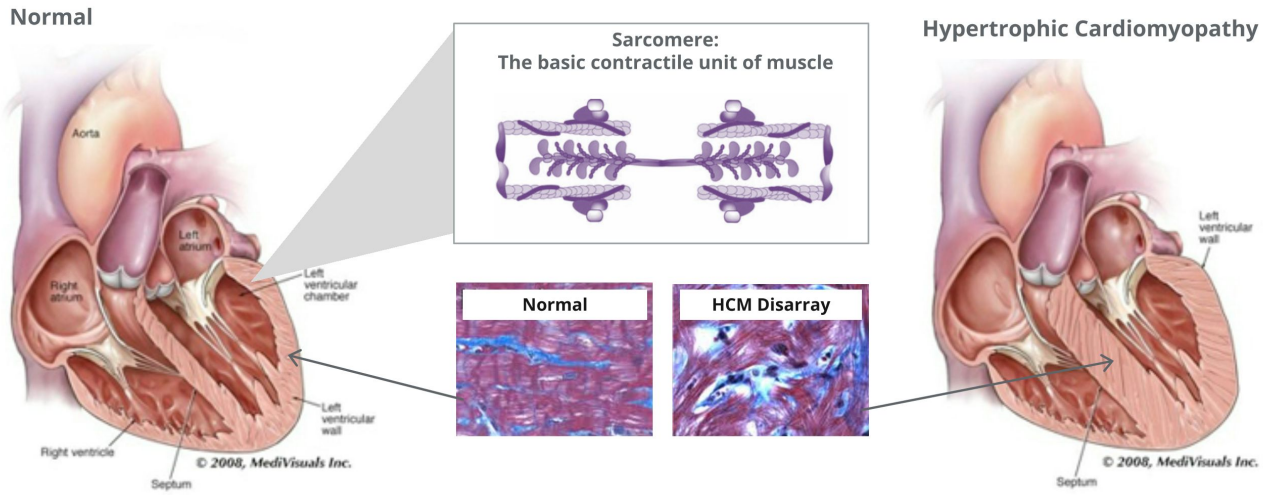
- Cardiac hypertrophy (increased wall thickness >15 mm) of left ventricle in the absence of another cardiac or systemic disease that could produce a similar magnitude of hypertrophy

Genetic Etiology

- Both monogenetic (30%) and polygenetic (70%) etiologies

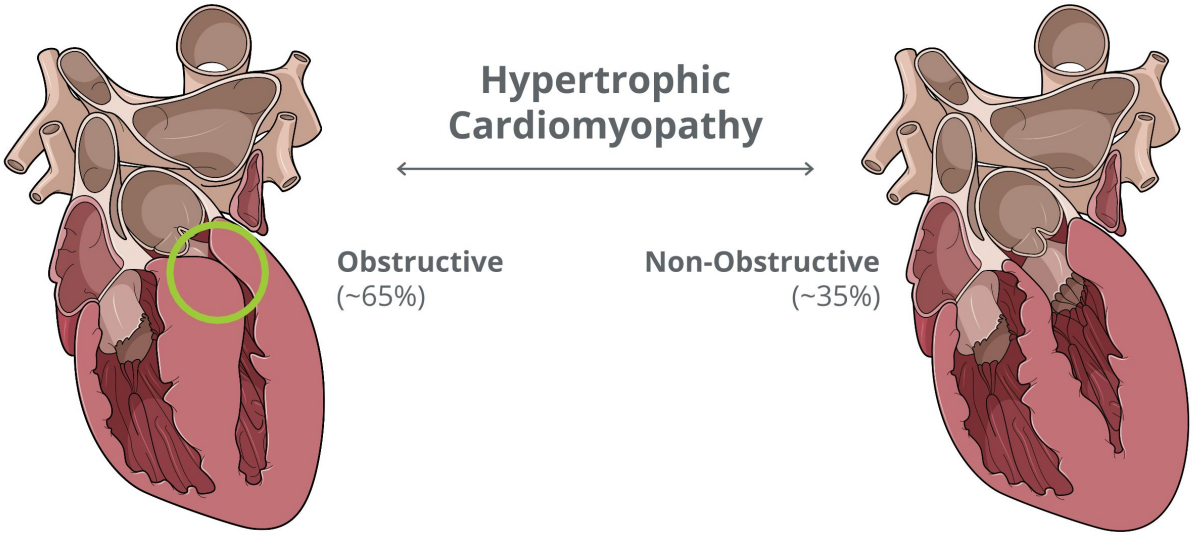
HCM: A Disease of the Sarcomere

Mutations in the sarcomere can cause hypercontraction, leading to abnormal growth (pathological hypertrophy) of the heart



Cytokinetics

Obstructive HCM is the Most Common Form of HCM



HCM: A Disease of the Sarcomere

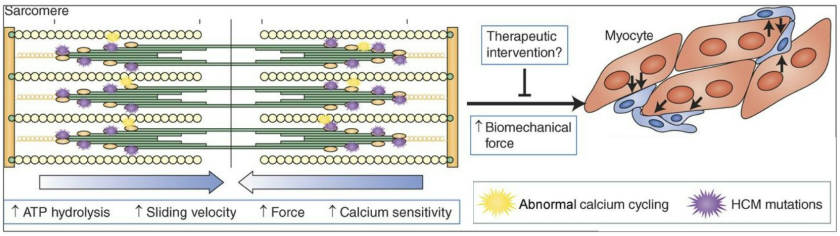
Therapeutic hypothesis

Addressing the underlying pathophysiology of HCM may lead to:

- Normalization of excessive crossbridge formation (2D-echo)
- Relief of obstruction of blood flow out of the LV (Doppler echo)
- Improvements in relaxation & high LV filling pressures (NT-proBNP)
- Positive remodeling of the heart (Cardiac MRI)

→

- Symptom Relief
- Increased Exercise Capacity
- Improved Functional Class
- Disease stabilization or regression?



Teekakirikul et al., JCB 2012

Cytokinetics

Cardiac Myosin Inhibitors: Aspirational Target Profile

Rapid Onset

Symptom relief as early as within 2 weeks initiation and dose adjustment possible biweekly if indicated

Precise Dosing

Echo guided dose titration allows both dose increases and decreases at the patient visit

Simplicity of Use

No off-target effects and use in combination with β-blockers, CCB, Disopyramide, and/or Ranolazine

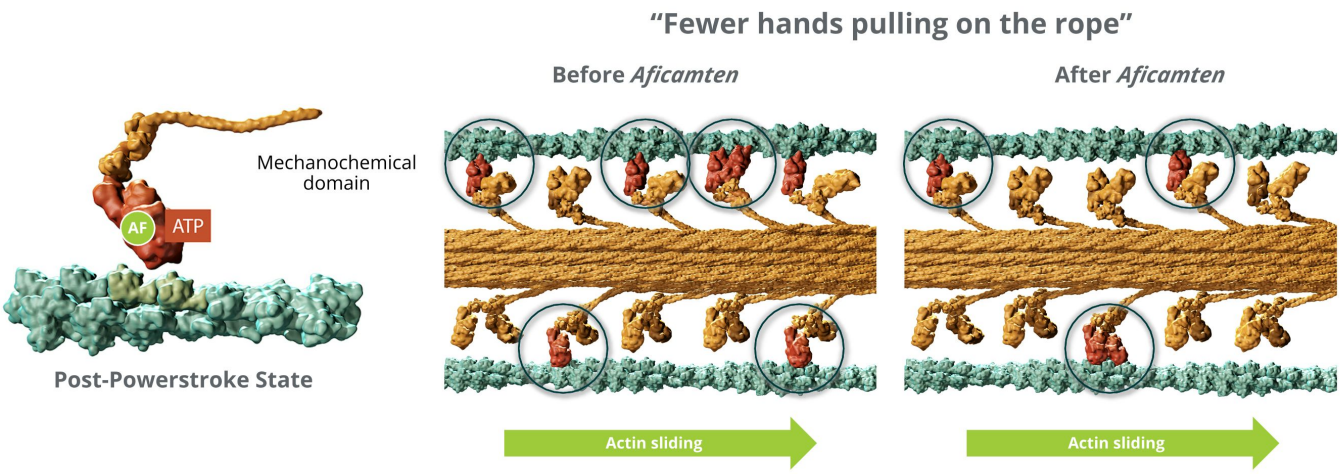
Rapid Reversibility

Down-titration to adjust dose or washout of pharmacodynamic effect within 2 weeks

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

Aficamten: Mechanism of Action

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



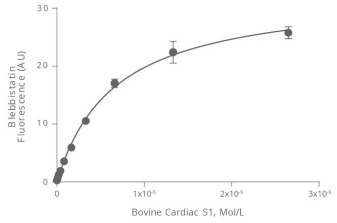
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Cytokinetics®

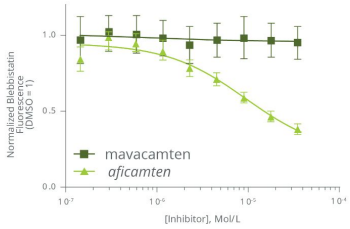
Aficamten: Binds to a Distinct Allosteric Site on Myosin

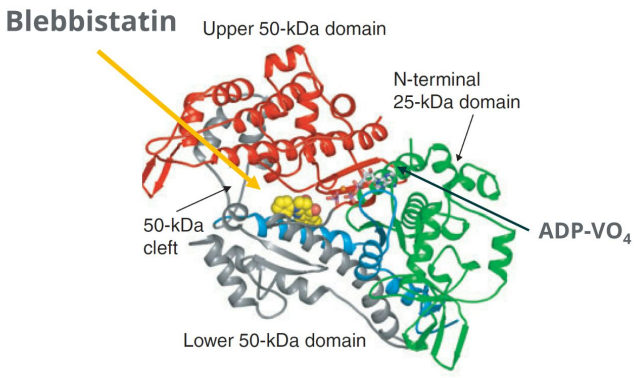
Different binding site of *aficamten* & *mavacamten* may underlie a difference in therapeutic index

Blebbistatin fluorescence increases when bound to cardiac S1



Fluorescence of blebbistatin/S1 decreases in the presence of increasing concentrations of *aficamten* (but not *mavacamten*)



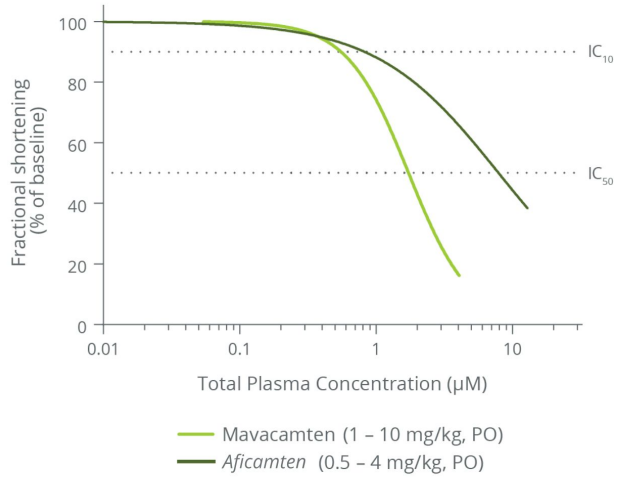


Blebbistatin chemical structure and binding site on MgADP-vanadate myosin II (Allingham, NSMB (2005))

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

Aficamten: Shallow Concentration-Response

Concentration-response relationship in Sprague-Dawley rat model of cardiac function



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

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

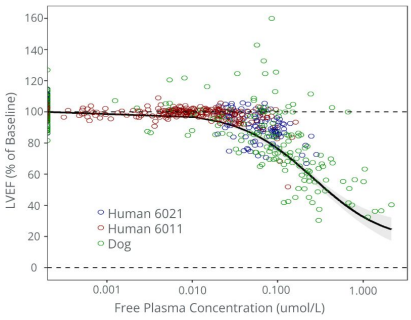
Compound half-life in humans	Actual	Predicted
aficamten	~3 days	2.8 days

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

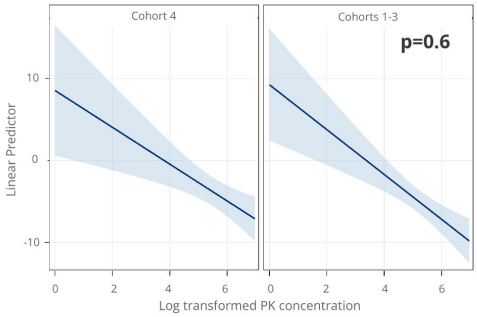
Aficamten: Concentration-Response Relationship

Shallow exposure response relationship appears to translate from animal to humans with HCM

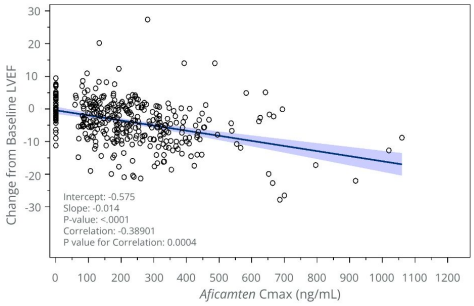
PK:PD Dog + Human (Ph1 and Ph2 oHCM)



Comparison of PK:PD Slope oHCM vs. nHCM



PK:PD Slope Human (P1 and P2 oHCM)



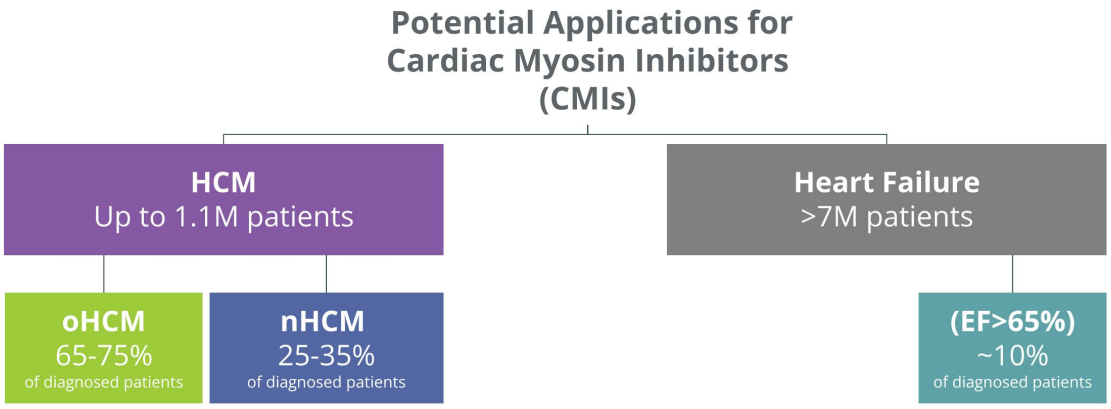
Aficamten **is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

HCM Landscape

Andrew Callos
EVP, Chief Commercial Officer

Cytokinetics®

CMIs May Offer Treatment Option for HCM & Heart Failure

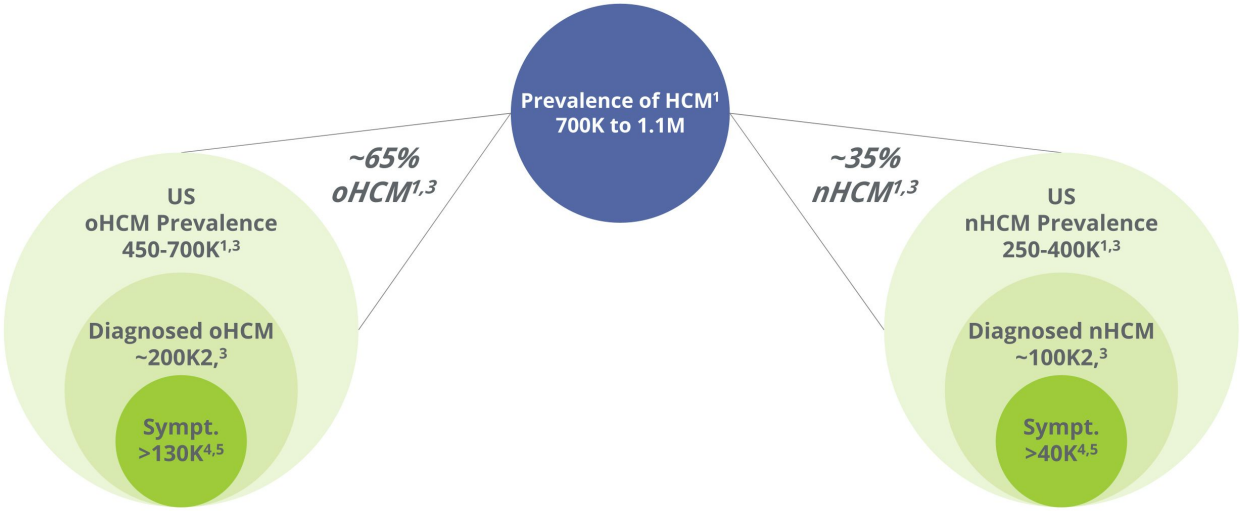


Projections and forecasts for illustration.

Cytokinetics®

Opportunity for CMIs in Diagnosed, Symptomatic HCM Patients

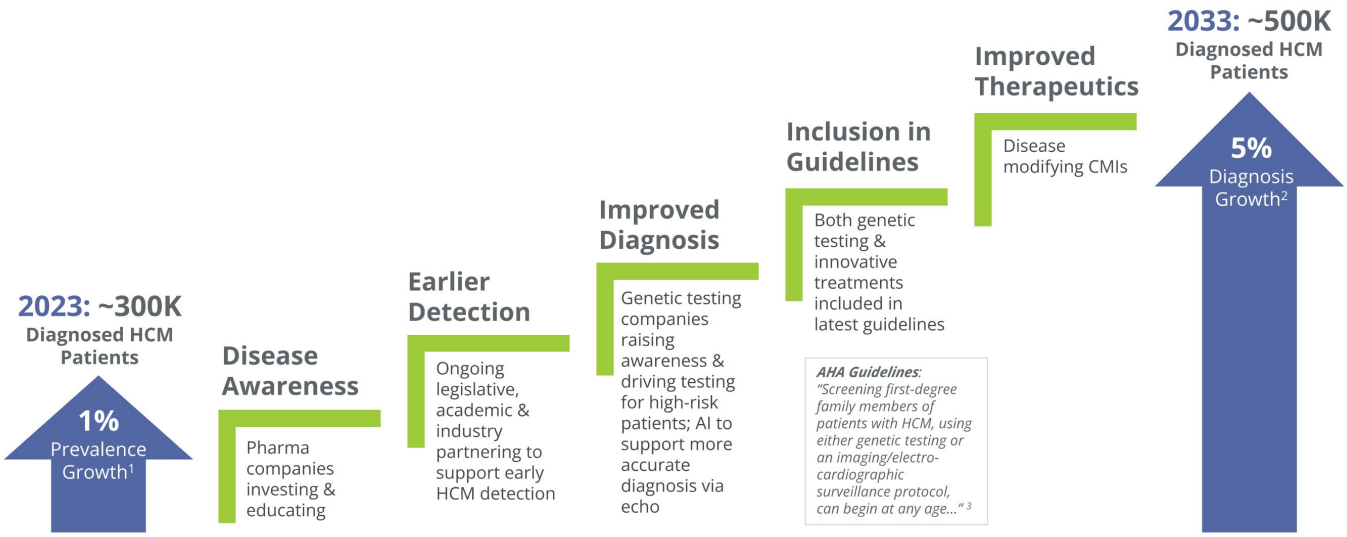
Potential for nearly 200K patients eligible for CMIs in 2025



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.

Diagnosis of HCM Anticipated to Grow 5x the Rate of the General Population



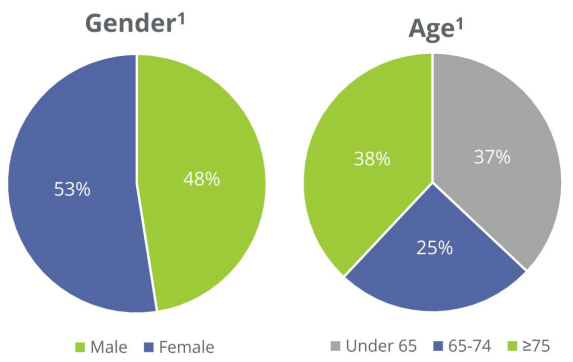
Source: 1) UN Population Projections: https://population.un.org/wpp/; 2) Butzner et al 2021 estimated a 8% growth rate in diagnosed HCM patients between 2013-2019 https://www.ajconline.org/article/S0002-9149(21)00783-9/fulltext; CYTK is forecasting an average growth rate of 5% over the coming decade; 3) Circulation. 2020;142:e558–e631. DOI: 10.1161/CIR.0000000000000937

Cytokinetics®

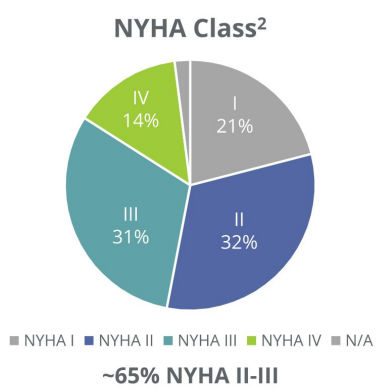
oHCM: High Unmet Need

oHCM patients tend to be older, NYHA Class II-III and symptomatic

Patient Demographics



Symptom Status

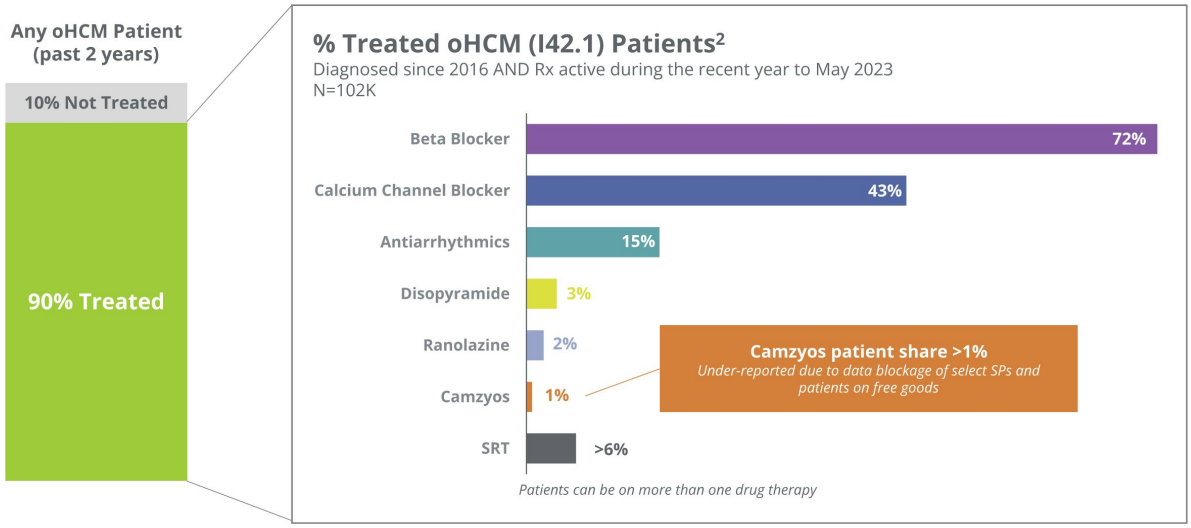


~65% NYHA II-III

1. SHA 2015-2023 DoF for patients ever diagnosed with I42.1
2. DoF Cogent MR October 2022; US data representative for 19,281 patients

Cytokinetics

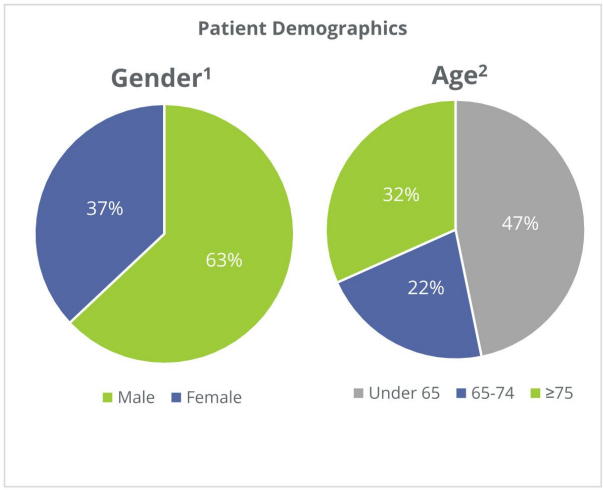
oHCM: 90% of Diagnosed Patients are Treated, Many Not Well-Controlled[1]

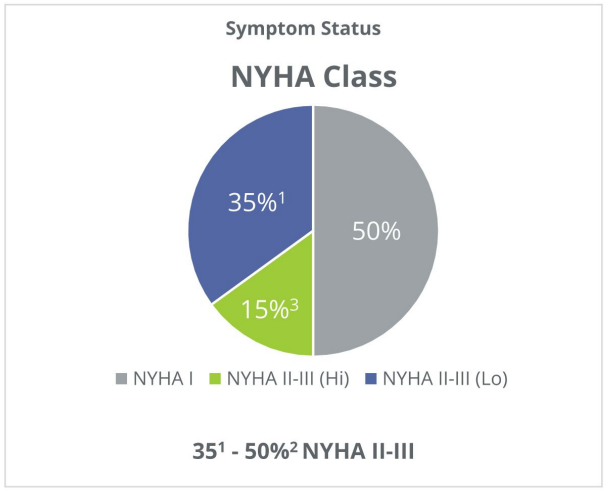


Note: Over a 2-year period, 90+% of oHCM patients receive treatment; ICD-10 code for oHCM is I42.1 (patients diagnosed since 2016 and active in claims data universe)
1. DoF Cogent MR October 2022; US data representative for 19,281 patients
2. Symphony PTD (Patient Transaction Data), only CVS & Optum SPs

nHCM: High Unmet Need

35-50% of patients are NYHA II-III, symptomatic



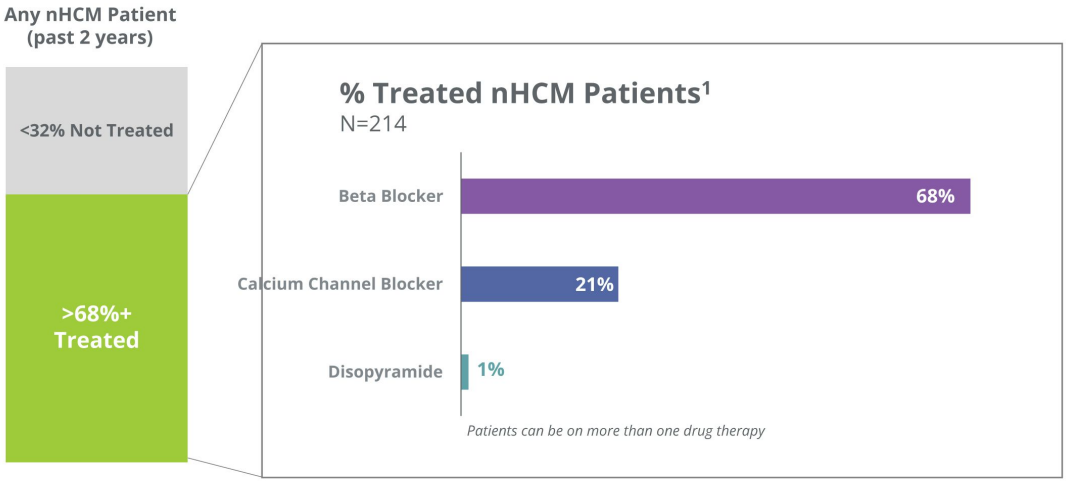


Note: Due to ICD-10 coding, claims analyses focusing on I42.2 includes both o/nHCM patients

1. Lu D. et al: "Clinical Outcomes in Patients With Nonobstructive, Labile, and Obstructive Hypertrophic Cardiomyopathy", JAHAVolume 7, Issue 5, March 2018
2. Symphony PTD (Patient Transaction Data 2015-2023; patients with any health care claims in 2023); Modelled age distribution of nHCM patients by using i.42.2 diagnosed HCM patients and separating out oCHM patients using the I42.1 age distribution and assuming a 70% oHCM patient proportion in i42.2.
3. Cogent MR October 2022; US data representative for 19,281 patients, 3) Masri, A et al. Evaluation of Aficamten in Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy: REDWOOD-HCM Cohort 4. Oral presentation at Heart Failure 2023, May 20-22, Prague, Czech Republic.

Cytokinetics®

nHCM: 68%+ of Diagnosed Patients are Treated

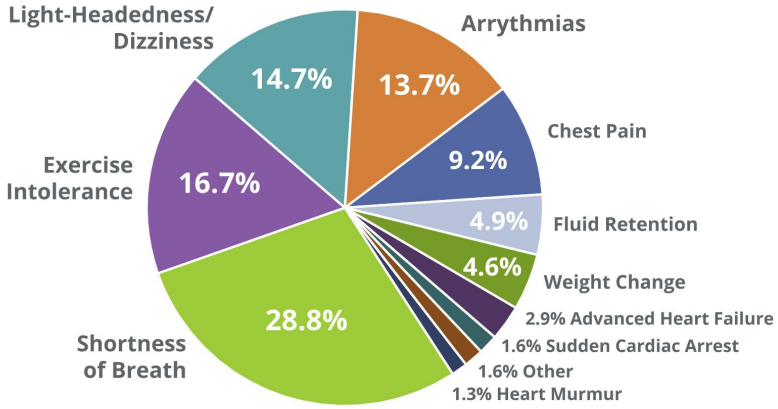


1. Lu D. et al: "Clinical Outcomes in Patients With Nonobstructive, Labile, and Obstructive Hypertrophic Cardiomyopathy", JAHA Volume 7, Issue 5, March 2018

Cytokinetics®

Symptoms Limiting Function Are Burdensome

Most Burdensome HCM-related Health Effects as Reported to FDA in a Patient-Focused Drug Development Meeting (% of patients)



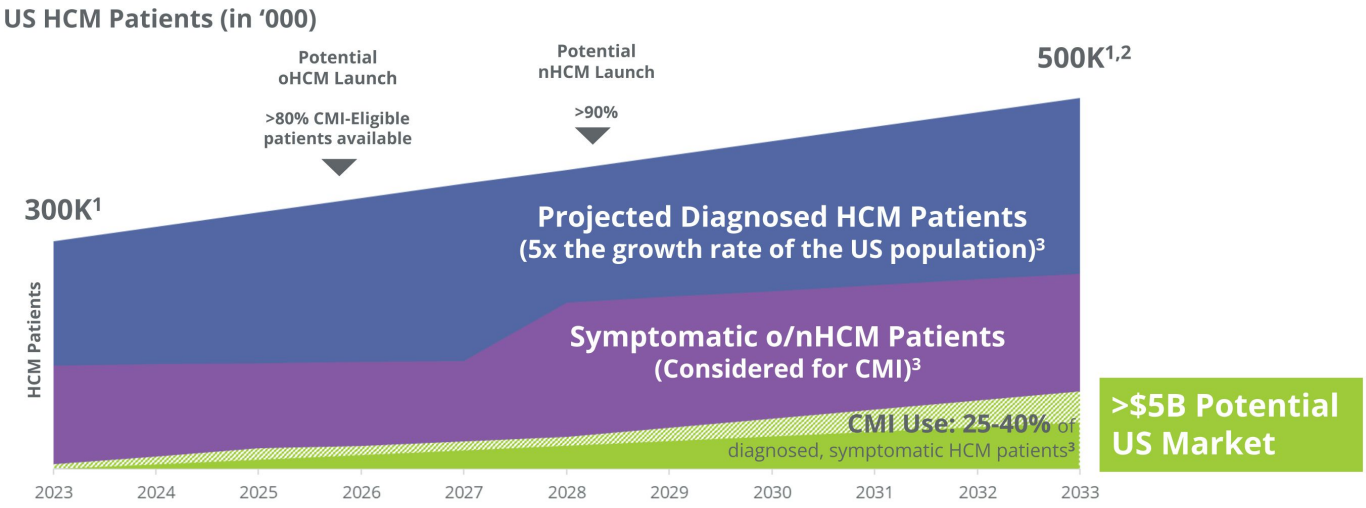
Polling question administered to participants in the FDA Voice of the Patient meeting and posted on HCMA website and social media 45 days following the event. This was not a scientifically validated study instrument.

"N" numbers not specified in the report.

Interpret data with caution.

Hypertrophic Cardiomyopathy Association. The Voice of the Patient report for hypertrophic cardiomyopathy (HCM). Proceedings from an externally led public Patient-Focused Drug Development meeting corresponding to the FDA's Patient-Focused Drug Development meeting. Held: June 26, 2020. Report submission: January 9, 2021. Accessed August 29, 2023. https://4hcm.org/wp-content/uploads/2021/06/Voice-of-the-HCM-patient-Report-final-January-9-2021.pdf

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



Projections and forecasts for illustration
Source: 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: Development Program

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

Cytokinetics®

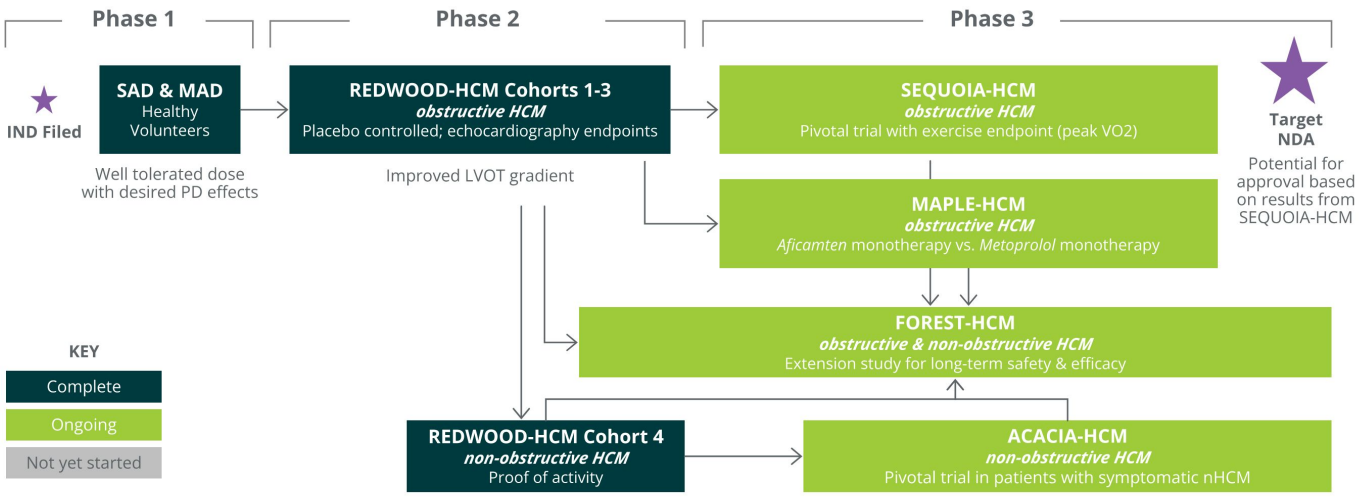
REDWOOD-HCM: oHCM

Stuart Kupfer, M.D.
SVP, Chief Medical Officer

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

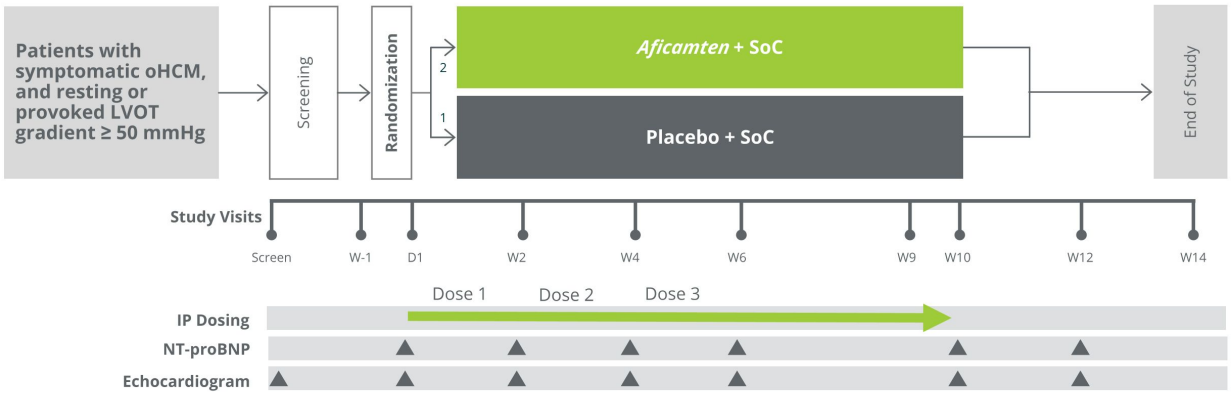


Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

REDWOOD-HCM: Cohorts 1 & 2

Patients with symptomatic oHCM on background therapy excluding *disopyramide*

Two sequential dose-finding cohorts



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

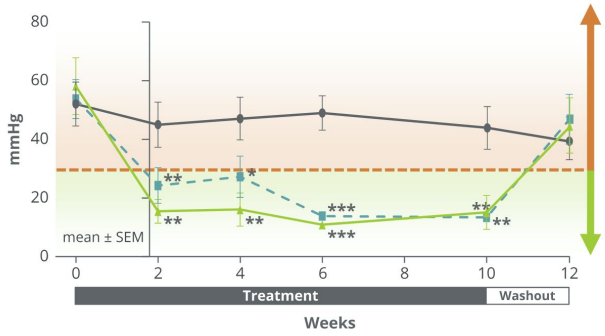
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

REDWOOD-HCM: Robust Reduction of LVOT Gradients

Cohorts 1 & 2

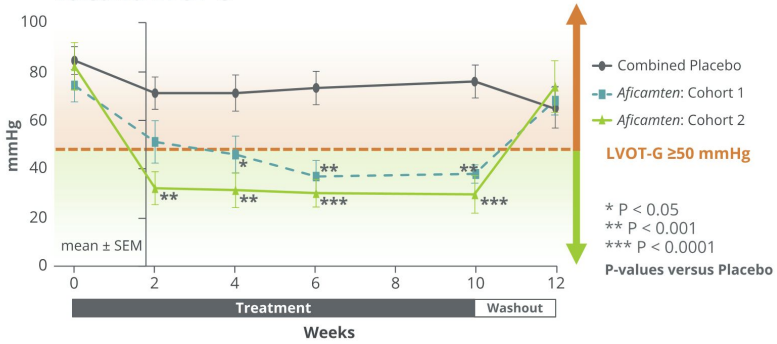
Consistent, **clinically meaningful reductions in LVOT gradients** within two weeks
No treatment interruptions or discontinuations
Reversibility of drug effect demonstrated

Resting LVOT-G



Dose finding study
Cohort 1 (n=21), Cohort 2 (n=20)

Valsalva LVOT-G

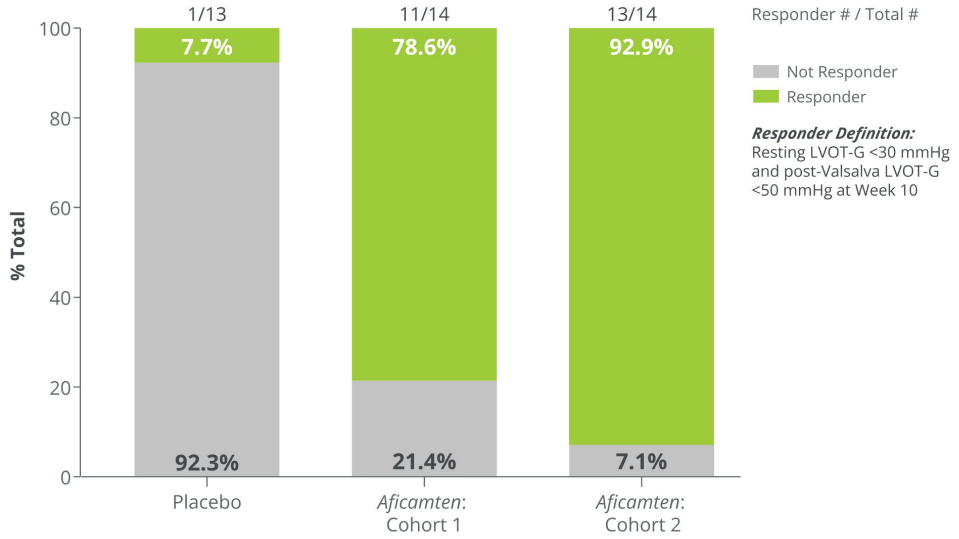


***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

Maron M, et. al. Phase 2 Study of *Aficamten* in Patients With Obstructive Hypertrophic Cardiomyopathy. JACC. January 2023.

High Proportion of Responders with *Aficamten*

Cohorts 1 & 2



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

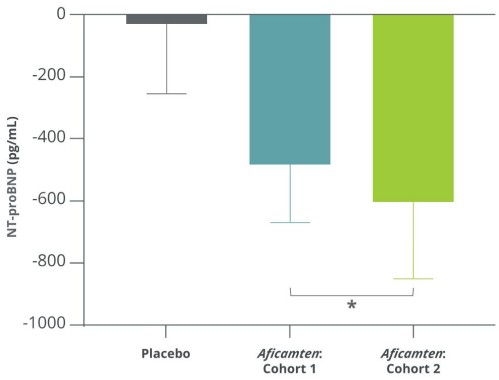
***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

Maron M, Abraham T, Masri A, et al. "REDWOOD-HCM: A Randomized, Double-blind, Placebo-controlled, Dose-finding Trial of the Cardiac Myosin Inhibitor, *Aficamten*, In Obstructive Hypertrophic Cardiomyopathy". HFSA 2021.

Improvements in NT-proBNP and NYHA Class

Cohorts 1 & 2

Change from Baseline NT-proBNP to Week 10

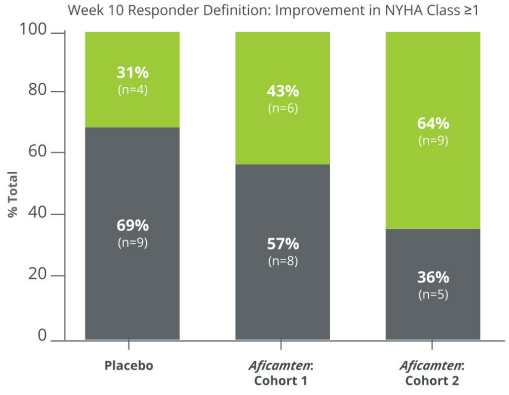


*** p = 0.003 for Pooled Cohort 1 & 2 vs. Placebo**

- Combined Placebo (N=13)
- *Aficamten*: Cohort 1 (N=14)
- *Aficamten*: Cohort 2 (N=14)

Improvement in Heart Failure Symptoms (NYHA Class)

Week 10 Responder Definition: Improvement in NYHA Class ≥1



Cohort 1 vs Placebo: p > 0.1
Cohort 2 vs Placebo: p = 0.08

- No Improvement in NYHA Class
- ≥1 NYHA Class Improvement

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

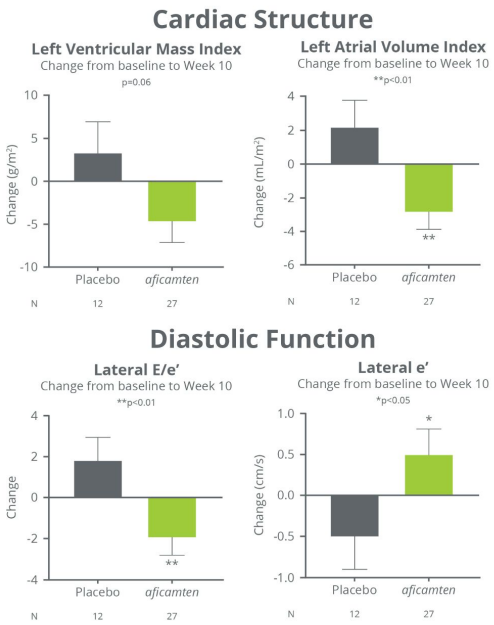
Maron M, Abraham T, Masri A, et al. "REDWOOD-HCM: A Randomized, Double-blind, Placebo-controlled, Dose-finding Trial of the Cardiac Myosin Inhibitor, *Aficamten*, In Obstructive Hypertrophic Cardiomyopathy". HFSA 2021.

Improved Cardiac Structure and Diastolic Function

Cohorts 1 & 2: Early signs of improvement in cardiac structure and myocardial relaxation

Treatment with *aficamten* for 10 weeks resulted in:

- **Significant reduction in left atrial volume index**
- Trend towards a **reduction in LV mass index**
- **Improved diastolic function**
  - reduction in lateral E/e' (p<0.01)
  - increase in lateral e' (p<0.05))



***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**
Abraham T. et al. "Early Cardiac Structural and Functional Reverse Remodeling in Obstructive Hypertrophic Cardiomyopathy after 10 Weeks of *Aficamten* Therapy: Analyses from REDWOOD-HCM". ASE 2022.

REDWOOD-HCM: Selected Safety Observations

Cohorts 1 – 3

- No treatment interruptions or discontinuations
- No patients met the "stopping criteria" of LVEF < 40%
- Transient and asymptomatic decrease in LVEF < 50% in 2 of 41 *aficamten*-treated patients in Cohort 2
- 2 SAEs in 41 *aficamten*-treated patients, neither related to *aficamten*
- No imbalance in treatment-emergent AEs between *aficamten* and placebo in Cohorts 1 & 2
- Similar safety profile for *aficamten* in combination with disopyramide in Cohort 3

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

FOREST-HCM

Steve Heitner, M.D.
VP, Clinical Research & Therapeutic Area Lead, Cardiovascular

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

Cytokinetics®

FOREST-HCM: Sustained Efficacy with *Aficamten*

Aficamten appears to result in sustained treatment effect in oHCM patients

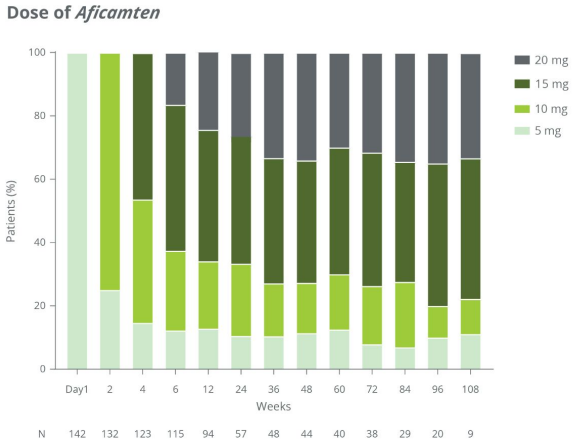
- **More than 200 patients are currently enrolled in FOREST-HCM**
- **143 patients were available for this analysis** (data cut Sept 15, 2023)
- **Almost all those eligible have chosen to participate**
- **Long-term data is available in some patients for greater than 2 years**
  - Sustained efficacy for duration of treatment
    - → Relief of symptoms
    - → Reductions in resting and Valsalva LVOT-G
    - → Improved cardiac biomarkers
    - → Most are longer eligible for invasive therapies per societal guidelines

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

FOREST-HCM: Baseline Characteristics

Baseline characteristics indicate substantial disease burden; ~2/3 patients achieving 15 or 20 mg

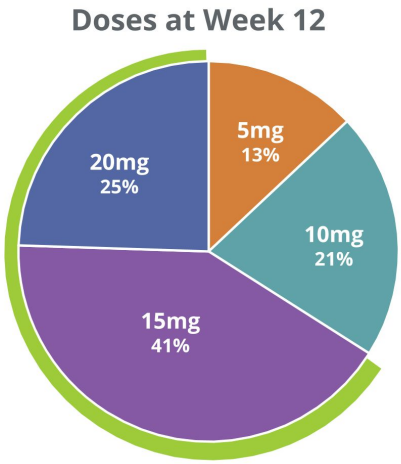
* Data cut Sept 15, 2023	FOREST-HCM oHCM N=143*
Age (Years), Mean (SD)	60.4 (13.2)
Female, n (%)	65 (45.5)
BMI (kg/m2), Mean (SD) [Range]	29.2 (4.5)
NYHA Class, n (%)	
Class II	82 (58)
Class III	60 (42)
Familial HCM, n (%)	40 (28.0)
Beta Blocker Use, n (%)	90 (62.9)
Calcium Channel Blocker Use, n (%)	14 (9.8)
Disopyramide Use, n (%)	27 (18.9)
LVEF* at Screening (%), Mean (SD)	69 (5)
LVOT-G*, Rest at Screening (mmHg), Mean (SD)	56.8 (33.2)
LVOT-G*, Valsalva at Screening (mmHg), Mean (SD)	93.1 (37.9)



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

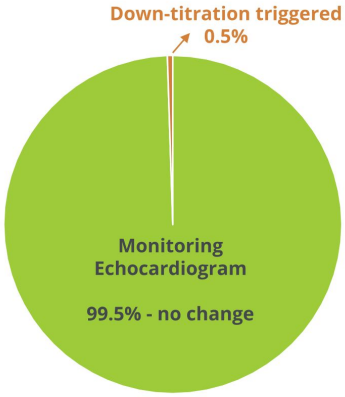
No Treatment Interruptions During Dose Titration

- **No patients had a 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



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

Dose Reduction During Maintenance Phase is Rare



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

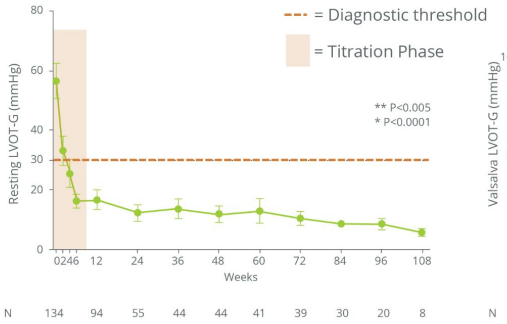
- **579 monitoring echocardiograms have been completed* in oHCM patients**
- **None with LVEF <40%** requiring treatment interruption
- 3 patients (0.5%) with LVEF <50%
  - Two asymptomatic patients (LVEF of 47% and 49%) resulting in per-protocol dose reduction
  - One patient with atrial fibrillation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

Aficamten **is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**
** As of Sept 15, 2023.*

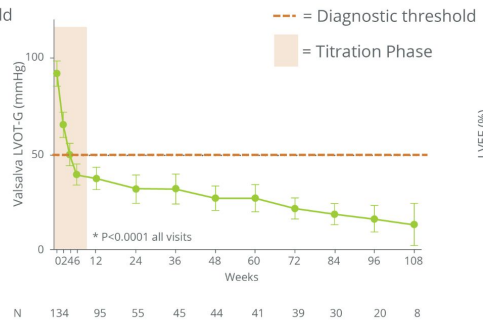
Durable Effects of *Aficamten* on LVOT-G & LVEF

Resting & provoked gradients remain below diagnostic threshold for >2 years, LVEF remains flat after titration

Resting LVOT Gradient



Valsalva LVOT Gradient



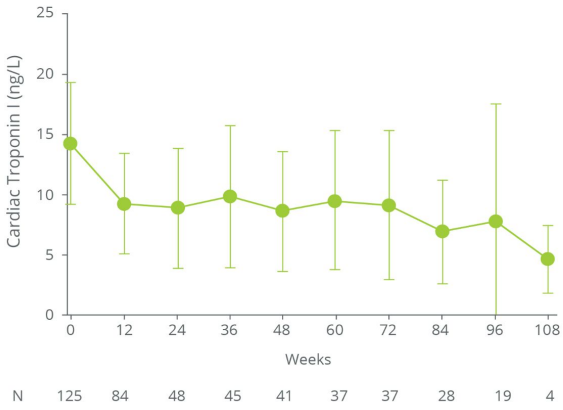
LVEF

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

Durable Effects of *Aficamten* on Biomarkers

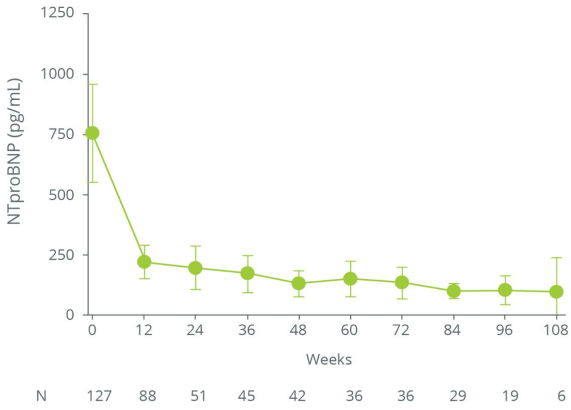
Sustained relative reductions in high-sensitivity Troponin I (~30%) & NT-proBNP (~70%) observed

High-Sensitivity Cardiac Troponin I



N	125	84	48	45	41	37	37	28	19	4

NT-proBNP



N	127	88	51	45	42	36	36	29	19	6

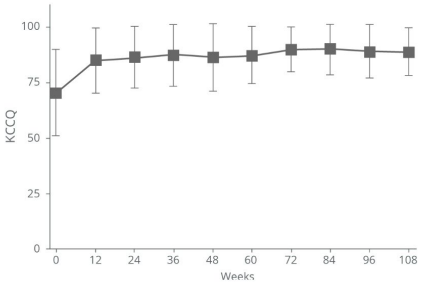
Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

Durable Effects of *Aficamten* on Clinical Endpoints

KCCQ-CSS

71% of patients had ≥ 5-point KCCQ-CSS increase

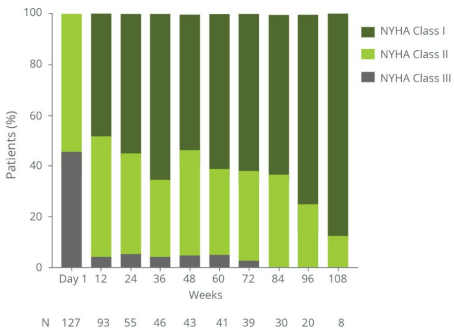
30% of patients had ≥ 10-point KCCQ-CSS increase



NYHA Class

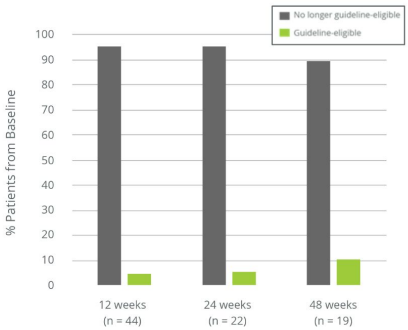
~50% of patients were asymptomatic at 1 year

>80% of patients improved ≥1 NYHA Class at every visit after initiation of *aficamten*



Guideline-Eligible for SRT

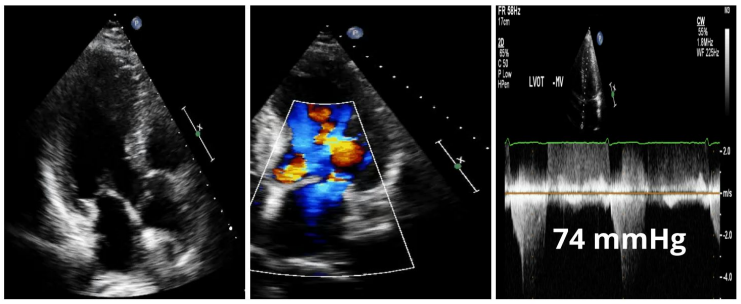
90% of SRT-eligible patients at baseline are no longer SRT-eligible



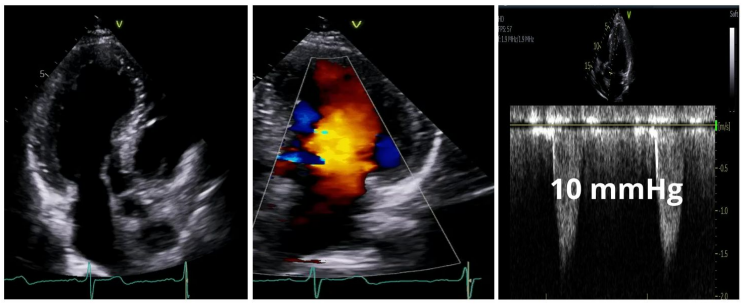
Aficamten **is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

64-year-old Man with a Family History of oHCM

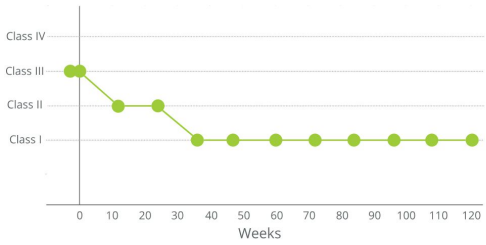
Baseline



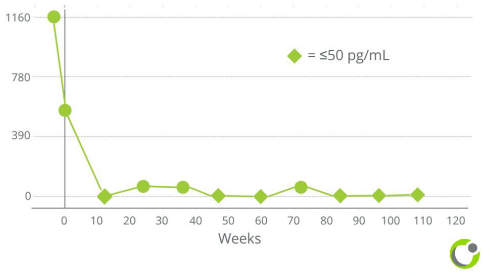
Week 2



NYHA Class



NT-proBNP



Cytokinetics®

Summary of Observations to Date

- **Almost all eligible patients choose to participate** in the OLE
- Echocardiography-guided dose titration of *aficamten* is **managed entirely by the treating physicians**
- 2/3 of patients achieve **higher doses;** no low LVEF events requiring treatment interruption
- 94 patients have **completed the titration period** - none have experienced LVEF <50%
- **99.5% of monitoring echocardiograms have not led to a dose reduction**
- Clinical, hemodynamic & biochemical markers of efficacy continue to indicate **sustained efficacy** following exposures for > 2-years
- Of the patients that are guideline-eligible for septal reduction therapies at baseline, **~90% are no longer eligible** after dose titration
- *Aficamten* has been **generally well-tolerated**, with 60% of patients experiencing at least one treatment emergent adverse event (TEAE) but there were no treatment-related serious adverse events (SAEs) as assessed by investigators, and no patient deaths

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

SEQUOIA-HCM

Daniel Jacoby, M.D.
Senior Medical Director, Clinical Research Cardiovascular

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

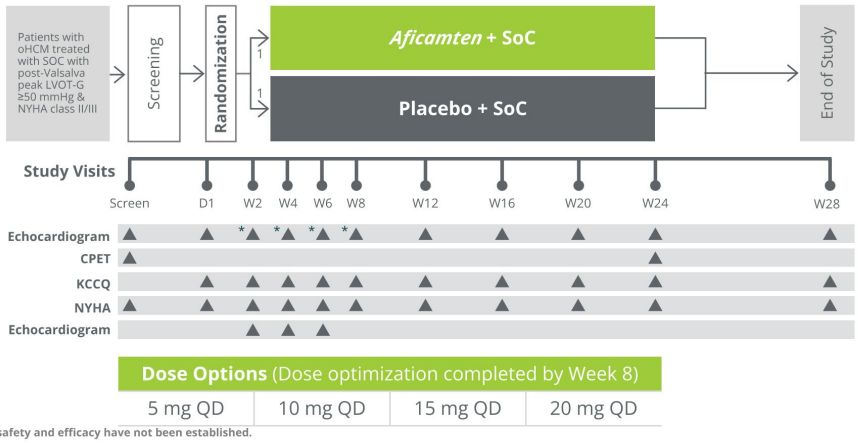
Completed enrollment; expect topline results by end of year

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

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

SEQUOIA-HCM: Enrollment Summary

North America
94 Enrolled

China
46 Enrolled

Europe + Israel
142 Enrolled

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

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 pVO2 reflects patient population with **reduced exercise capacity**

Baseline Characteristics (N=282)	n (%) or Mean (SD)[a]
Demographics	
Age, years	59.1 (12.9)
Female	114 (40.4)
Race/ethnicity[b]	
White	222 (78.7)
Black	3 (1.1)
Asian	53 (18.8)
Hispanic	9 (3.2)
Other	4 (1.4)
Region	
United States	94 (33.3)
China	46 (16.3)
Europe and Israel	142 (50.4)
Vital Signs	
Weight, kg	81.6 (15.7)
Body mass index, kg/m^2	28.1 (3.7)
Systolic blood pressure, mmHg	125.3 (16.1)
Diastolic blood pressure, mmHg	74.4 (10.6)
Heart rate, bpm	65.6 (11.2)
HCM History	
History of known HCM-causing gene mutation	48 (17.0)
Positive family history of HCM	71 (25.2)
Time since initial HCM diagnosis, median (IQR), years	5.9 (1.7 – 8.5)

Baseline Characteristics (N=282)	n (%) or Mean (SD)[a]
HCM Medical Therapies	
Beta-blocker	172 (61.0)
Non-dihydropyridine calcium channel blocker	75 (26.6)
Disopyramide	36 (12.8)
HCM Symptoms	
KCCQ-CSS	74.7 (18.0)
NYHA class II/III/IV	214 (75.9) 67 (23.8) 1 (0.4)
SRT guideline eligible	68 (24.1)
Comorbidities	
Hypertension[d]	136 (48.2)
Diabetes[e]	24 (8.5)
Permanent atrial fibrillation	1 (0.4)
Paroxysmal atrial fibrillation	40 (14.2)
CPET Metrics	
Treadmill	155 (55.0)
Peak VO_2, mL/kg/min	18.5 (4.5)
Peak VO_2, % of predicted maximum[f]	56.9 (11.8)
Total workload, watts	122.4 (41.2)
Biomarker	
hs-cTnI median (IQR), ng/L	21.1 (7.7 – 27.3)

a Unless otherwise indicated.
b >100% total due to overlap in ethnicity and race.
c NYHA FC III and any LVOTO ≥50 mmHg
d Combines hypertension and essential hypertension.
e Combines T2DM, T1DM, and DM
CCB, calcium channel blocker; DM, diabetes mellitus, including types 1 and 2; IQR, interquartile range

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

Cytokinetics®

SEQUOIA-HCM: Baseline Characteristics

SEQUOIA-HCM successfully met objectives for patient enrollment

Target population was successfully enrolled and representative of a broad group of oHCM patients seen in the clinic

- Diverse by race and sex
- Objective physical limitation demonstrated and a high degree of symptom burden
- Approximately equal split of CPET modality used (favoring treadmill)
- Allowed all currently available HCM therapies in North America and Europe
- Significant representation of patients not receiving background beta blocker therapy

All patients in SEQUOIA-HCM have passed through the dose-titration period and there have been no reports of LVEF <40% (reporting is mandatory as it triggers dose interruption)

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

Expected 2023 Milestones

Aficamten

- Expect **topline results from SEQUOIA-HCM** by end of year
- Continue enrollment of **MAPLE-HCM, second Phase 3 trial of *aficamten*** in oHCM
- Continue enrollment of **ACACIA-HCM, pivotal Phase 3 trial of *aficamten* in nHCM**

Omecamtiv Mecarbil

- Pursue **international approvals** for *omecamtiv mecarbil*

Emerging Pipeline

- Expect data from **Phase 1 study of CK-136** in 2H
- Continue Phase 1 study of **CK-586**

Aficamten, omecamtiv mecarbil, CK-586 and CK-136 are investigational drugs and have not been approved. Their safety and efficacy have not been established.

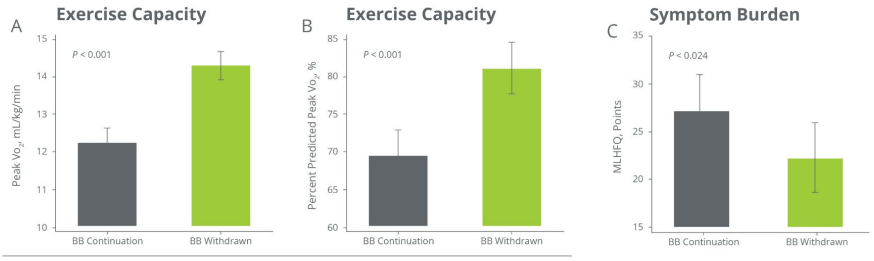
MAPLE-HCM

Daniel Jacoby, M.D.
Senior Medical Director, Clinical Research Cardiovascular

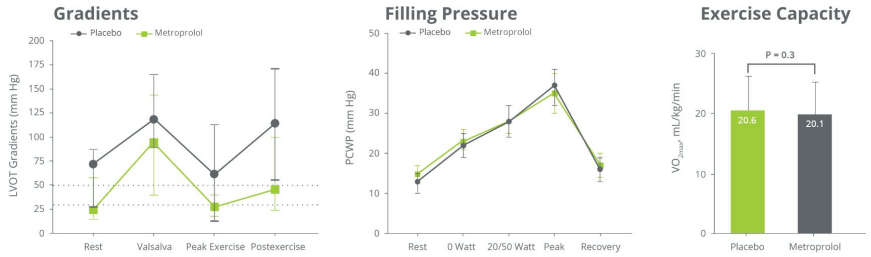
Aficamten **is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

Cytokinetics®

MAPLE-HCM: Rationale



(A) The change in peak oxygen consumption (peak VO_2) after β-blocker (BB) withdrawal was +2.1 ± 1.29 ($P < 0.001$).
(B) The increase in the percentage of predicted peak oxygen consumption (peak VO_2%) was +11.74 ± 2.32 ($P < 0.001$).



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

1. Palau et al. J Am Coll Cardiol. 2022 Mar 1;79(8):848.
2. Dybro, A. M. J et al. Am Coll Cardiol 78(25): 2505-2517.
3. Dybro, A. M., et al. J Am Coll Cardiol 79(16): 1565-1575.

Beta-blocker withdrawal in HFpEF **improves exercise capacity & symptoms**[1]

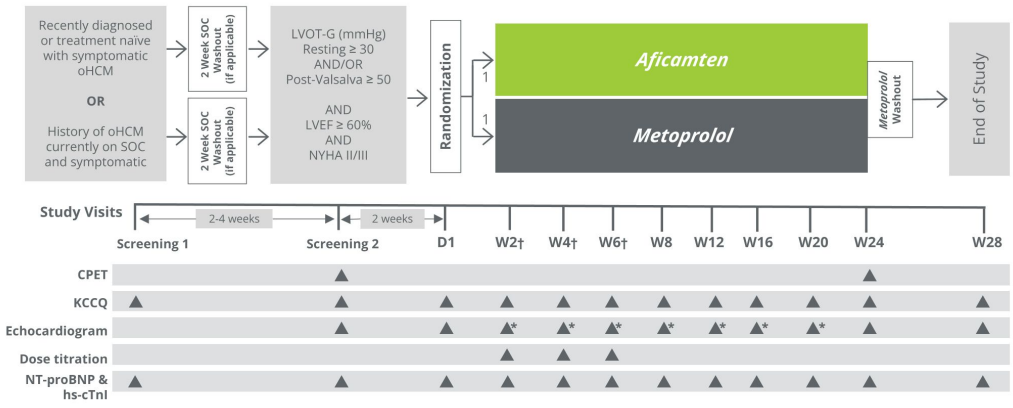
Beta blockers in oHCM improve symptoms & LVOT obstruction

BUT **do not improve exercise capacity**, filling pressures or NT-proBNP[2,3]

MAPLE-HCM: Phase 3 Monotherapy Trial

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**



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

MAPLE-HCM: Evolving the Treatment Paradigm

Pending favorable results, MAPLE-HCM has the potential to evolve the treatment paradigm by potentially:

- Supporting the rationale for **first-line use** in HCM treatment guidelines
- Demonstrating **efficacy in an earlier diagnosed** patient population
- Demonstrating **more favorable side effect profile** of *aficamten* vs. *metoprolol* in oHCM
- Demonstrating **structural remodeling** as a secondary endpoint (disease modification)

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

Expected 2023 Milestones

Aficamten

- Expect **topline results from SEQUOIA-HCM** by end of year
- Continue enrollment of **MAPLE-HCM, second Phase 3 trial of *aficamten*** in oHCM
- Continue enrollment of **ACACIA-HCM, pivotal Phase 3 trial of *aficamten* in nHCM**

Omecamtiv Mecarbil

- Pursue **international approvals** for *omecamtiv mecarbil*

Emerging Pipeline

- Expect data from **Phase 1 study of CK-136** in 2H
- Continue Phase 1 study of **CK-586**

Aficamten, omecamtiv mecarbil, CK-586 and CK-136 are investigational drugs and have not been approved. Their safety and efficacy have not been established.

REDWOOD-HCM: nHCM
ACACIA-HCM

Steve Heitner, M.D.
VP, Clinical Research & Therapeutic Area Lead, Cardiovascular

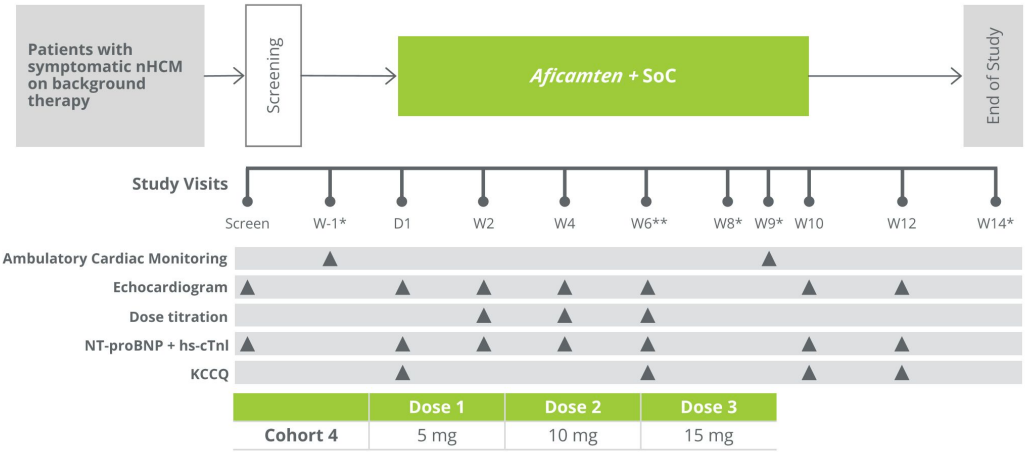
Aficamten **is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**

Cytokinetics®

REDWOOD-HCM: Cohort 4

Patients with symptomatic nHCM on background therapy

Results presented at ESC Heart Failure 2023



	Dose 1	Dose 2	Dose 3
Cohort 4	5 mg	10 mg	15 mg

Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.
*Telephone visits
**Patient can only be down-titrated at Week 6

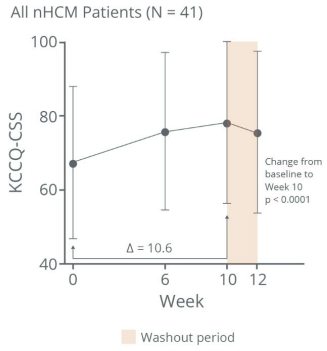
Significant Improvements in KCCQ & NYHA Class

Cohort 4

85% of patients achieved 15 mg dose; no discontinuations due to adverse events

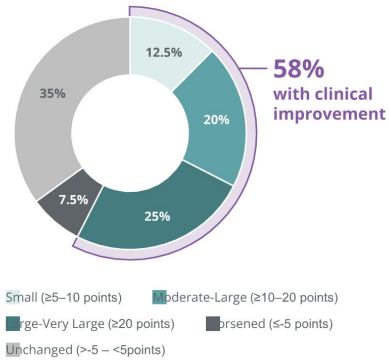
Kansas City Cardiomyopathy Questionnaire

Mean improvement in KCCQ of 10.6 points



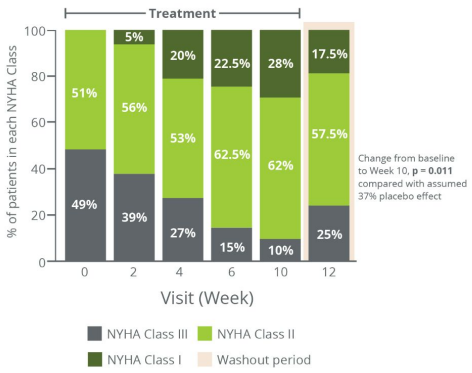
Data presented as mean and standard deviation

Categorical Changes at Week 10 in KCCQ-CSS



NYHA Functional Class

56% of patients improved by ≥1 NYHA class



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

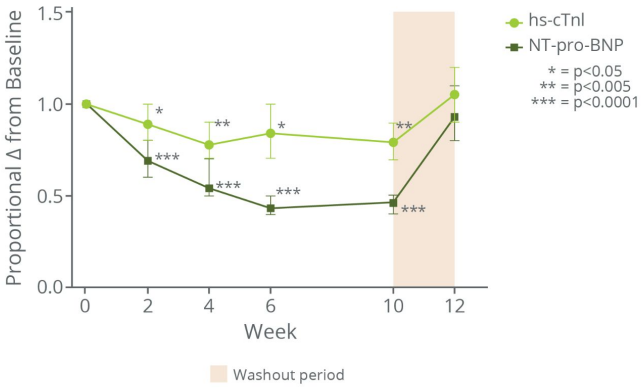
Masri A. et al. "*Aficamten* in Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (REDWOOD-HCM Cohort 4)". ESC HF 2023.

Change in Baseline in Biomarkers & Angina Frequency

Cohort 4

Proportional Change from Baseline in Cardiac Biomarkers

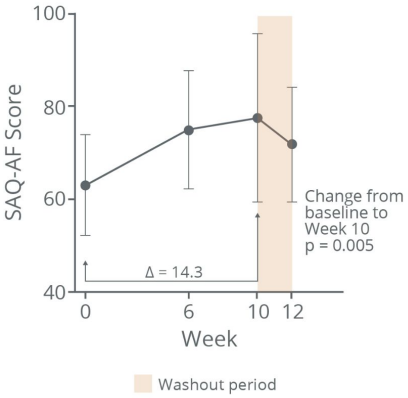
Mean reduction in high-sensitivity cardiac troponin of 21%
Mean reduction in NT-proBNP of 55%



Data presented as the mean proportional change and 95% CI

Seattle Angina Questionnaire Angina Frequency (SAQ-AF)

Reduction in frequency of angina from daily or weekly, to weekly or monthly



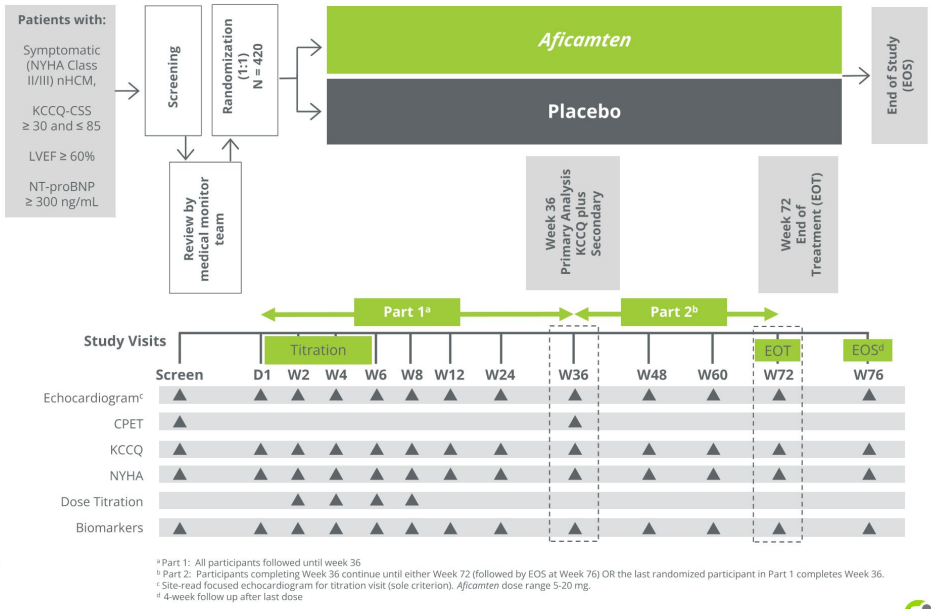
Data presented as mean and standard deviation

***Aficamten* is an investigational agent and is not approved by any regulatory agency. Its safety and efficacy have not been established.**
Masri A. et al. "*Aficamten* in Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (REDWOOD-HCM Cohort 4)". ESC HF 2023.

ACACIA-HCM: Pivotal Phase 3 Trial in nHCM

Planned to enroll patients at >150 global sites in 15-20 countries

- 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 pVO2, Ve/VCO2,
  - 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



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

[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

Expected 2023 Milestones

Aficamten

- Expect **topline results from SEQUOIA-HCM** by end of year
- Continue enrollment of **MAPLE-HCM, second Phase 3 trial of *aficamten*** in oHCM
- Continue enrollment of **ACACIA-HCM, pivotal Phase 3 trial of *aficamten* in nHCM**

Omecamtiv Mecarbil

- Pursue **international approvals** for *omecamtiv mecarbil*

Emerging Pipeline

- Expect data from **Phase 1 study of CK-136** in 2H
- Continue Phase 1 study of **CK-586**

Aficamten, omecamtiv mecarbil, CK-586 and CK-136 are investigational drugs and have not been approved. Their safety and efficacy have not been established.

5 Minute Break

The program will return shortly.

Cytokinetics®

HCM Patient Perspective

Megan Link, Person Living with HCM

Actual patient who consents and agrees to appear.

Cytokinetics®

Aficamten: Commercial Readiness

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

Cytokinetics®

New Market Research & Preliminary Positioning

John Jacoppi
VP, US Marketing for Aficamten

Cytokinetics

Patients Are Our North Star: Significant Impact of HCM

The most commonly reported impacts of HCM symptoms on patients' lives included limitations to physical activities (78%), emotional impacts, including feeling anxious or depressed (78%), and impacts on work (63%).

> My life was always unraveling, and after a while you get sick of being sick and weak. I could not even hold my husband's hand and walk on the boardwalk, because I could not keep up with him.
>
> – HCM Patient

> Patients make their world smaller and don't realize how symptomatic they have been until they feel well.
>
> – HCM Treater

Zaiser E, Sehnert AJ, Duenas A, Saberi S, Brookes E, Reaney M. Patient experiences with hypertrophic cardiomyopathy: a conceptual model of symptoms and impacts on quality of life. J Patient Rep Outcomes. 2020;4(1):102.

Our Planned Commercial Approach to *Aficamten*

Driven by a relentless focus on our North Star: the HCM patient

Learn	Design	Build
Leverage **deep understanding** of patients, HCPs, payers, and community	Engage with all stakeholders to design **an optimal customer experience**	Tap into deep functional experience to build **operational excellence** across launch functions

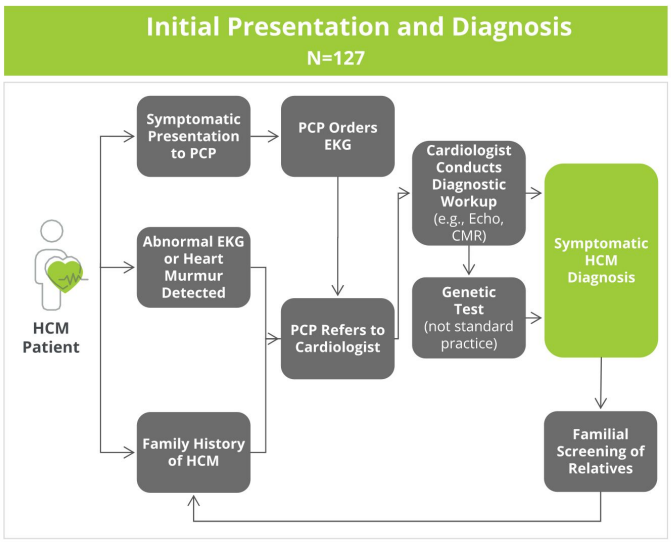
Our Focus to Date → **Our 2024 Focus**

Deep Understanding & Insights Gathered Over Last 18 Months

Cytokinetics has completed **14 primary market research projects with >831 HCPs**, including cardiologists, NP/PAs, and others

Cytokinetics has completed **5 primary market research projects with >163 HCM patients** & their loved ones

oHCM Patient Journey Includes Complex Diagnosis & Progression



Market Research Insights

- **Complex patient journey** due to non-specific symptomatology
- Underdiagnosis and misdiagnosis largely attributed to **limited oHCM disease awareness** and variable/inaccurate echocardiology practices in the community
- **Shared care workflows** between referring cardiologists and HCM specialists vary
- Patients receive **overwhelming amount of information & misinformation** along the way

Source: HCM Patient Journey, HCP Setting of Care Assessment: n=127 in-depth interviews- across 8 geographies; Cardiologists, PCPs, patients and pharmacists – includes Clearview data analysis using Symphony claims data and Compile affiliation data. Echocardiogram Landscape Assessment study with 15 Cards and 10 Payers.

HCM Patients Suffer Serious Complications & Debilitating Symptoms

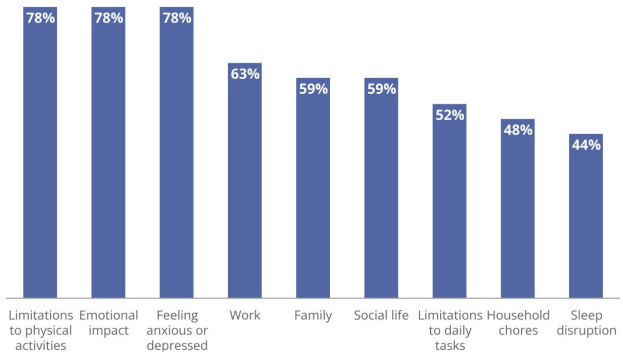
Some Consequences of HCM

- Atrial Fibrillation
- Heart Failure
- Emotional & Psychological Impact
- Sudden Cardiac Death

Sources: ACC, AHA, Elliott 2006, Harris 2016, Ommen 2009, Hamada 2014, Spirito 2017, Mayo Clinic, Bionest Partners

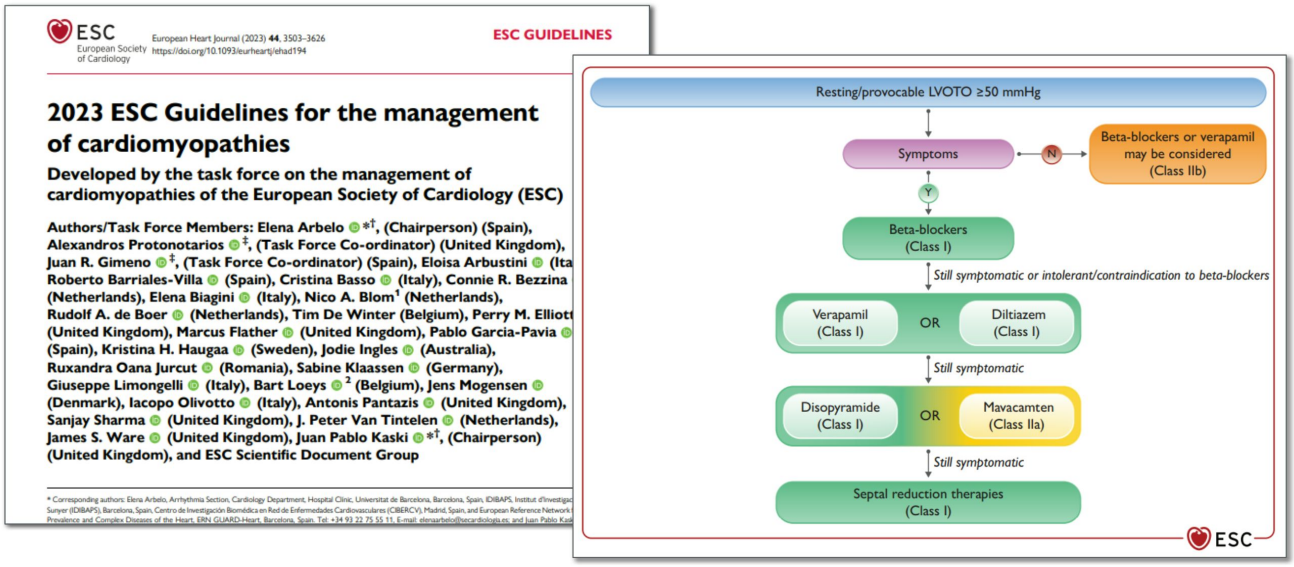
80% of Patients Experience Limitations on Daily Life

Interviews (N=27)



Source: Zaiser, et al. Patient experiences with hypertrophic cardiomyopathy: a conceptual model of symptoms and impacts on quality of life. J Patient Rep Outcomes 4, 102 (2020). https://doi.org/10.1186/s41687-020-00269-8

Cardiac Myosin Inhibitors are Entering Treatment Guidelines



ESC European Society of Cardiology

European Heart Journal (2023) 44, 3503–3626
https://doi.org/10.1093/eurheartj/ehad194

ESC GUIDELINES

2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

Authors/Task Force Members: Elena Arbelo *†, (Chairperson) (Spain), Alexandros Protonotarios ‡, (Task Force Co-ordinator) (United Kingdom), Juan R. Gimeno ‡, (Task Force Co-ordinator) (Spain), Eloisa Arbustini (Ita Roberto Barriales-Villa (Spain), Cristina Basso (Italy), Connie R. Bezzina (Netherlands), Elena Biagini (Italy), Nico A. Blom[1] (Netherlands), Rudolf A. de Boer (Netherlands), Tim De Winter (Belgium), Perry M. Elliott (United Kingdom), Marcus Flather (United Kingdom), Pablo Garcia-Pavia (Spain), Kristina H. Haugaa (Sweden), Jodie Ingles (Australia), Ruxandra Oana Jurcut (Romania), Sabine Klaassen (Germany), Giuseppe Limongelli (Italy), Bart Loeys[2] (Belgium), Jens Mogensen (Denmark), Iacopo Olivotto (Italy), Antonis Pantazis (United Kingdom), Sanjay Sharma (United Kingdom), J. Peter Van Tintelen (Netherlands), James S. Ware (United Kingdom), Juan Pablo Kaski *†, (Chairperson) (United Kingdom), and ESC Scientific Document Group

* Corresponding authors: Elena Arbelo, Arrhythmia Section, Cardiology Department, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain, IDIBAPS, Institut d'Investigac Sunyer (IDIBAPS), Barcelona, Spain, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain, and European Reference Network Prevalence and Complex Diseases of the Heart, ERN GUARD-Heart, Barcelona, Spain. Tel: +34 93 22 75 55 11. E-mail: elenaarbelo@ucardiologia.eu; and Juan Pablo Kas

Cytokinetics

CMIs Have Transformed Patients' Lives

> There was an incredible moment in clinic yesterday when I was able to tell a patient that her disease appeared to be "reversing". This is the first time in my life I have used those words. Cardiac myosin inhibitors for hypertrophic cardiomyopathy are game changing. – Dr. Euan Ashley, Stanford

Selected example for illustration

Cytokinetics

However, Opportunities Exist…

While CMIs offer strong efficacy, there are barriers to more widespread use

Key Benefits

- ✓ First non-interventional way to address underlying cause of oHCM
- ✓ Strong efficacy with few tolerability issues
- ✓ Few, if any, long-term concerns

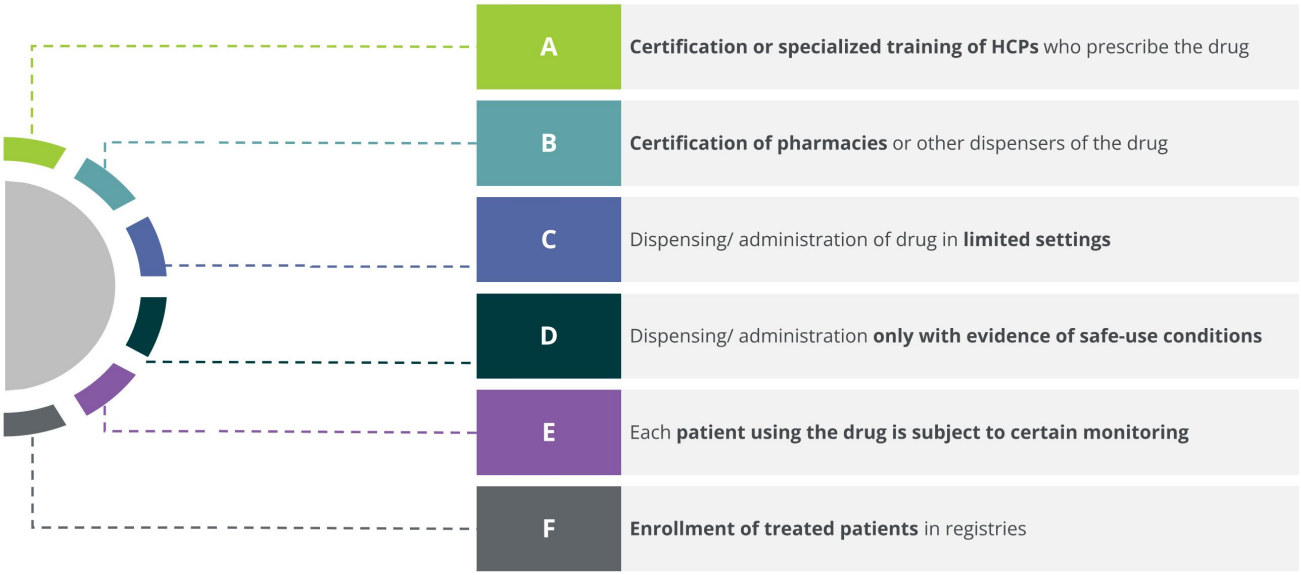
Key Challenges

- × Burden of required monitoring/echo frequency
- × Concerns about drug-drug interactions
- × Down titration challenges
- × Lack of treatment access/coverage for some
- × Lack of established office protocols

> It's revolutionary in my opinion… With myosin inhibitors, you're actually going to the problem of these HCM patients directly and **treating the underlying cause of disease**. It makes sense intuitively and mechanistically. I just **wish it wasn't so burdensome**. – Academic cardiologist

Sources: CMI Prescribing Process Research n=45 cardiologists, office staff and patients: Clearview, Echocardiogram Landscape Assessment n=25 cardiologists and payers; Putnam Associates, HCM Disease Treatment and Impact Study n=30 cardiologist; Hawk Partners, HCM HCP Emotive Insights n=24 cardiologists; BrandTrust

Elements of ETASU REMS



ETASU: Elements to Assure Safe Use. REMS: Risk Evaluation and Mitigation Strategies

Class May Not Necessarily Define Scope of REMS

Key Elements Noted in Market Research

REMS requirements impact all stakeholders, but greatest pain points include:

- Frequency & rigidity of **required echo monitoring**
- Stringency of **pharmacy certification** and dispensing requirements
- Significant **process complexity** and can lead to confusion for HCP & patients

Key Focus Areas to Potentially Reduce Burden

- **DDI profile** may lead to less burdensome requirements
- **Echo frequency & window**

Sources: CMI Prescribing Process Research n=45 cardiologists, office staff and patients: Clearview, Echocardiogram Landscape Assessment n=25 cardiologists and payers; Putnam Associates, HCM Disease Treatment and Impact Study n=30 cardiologist; Hawk Partners, HCM HCP Emotive Insights n=24 cardiologists; BrandTrust

Potential Profile for *Aficamten*

Possible key attributes

- 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.

Potential Target Patient for *Aficamten* Consistent with Anticipated Label

Potential Target Patient for *Aficamten*

- Symptomatic oHCM[1]
- NYHA Class II-III, LVEF ≥60%[1]
- Not well-controlled, contraindicated to, or cannot tolerate BB / CCB[2]

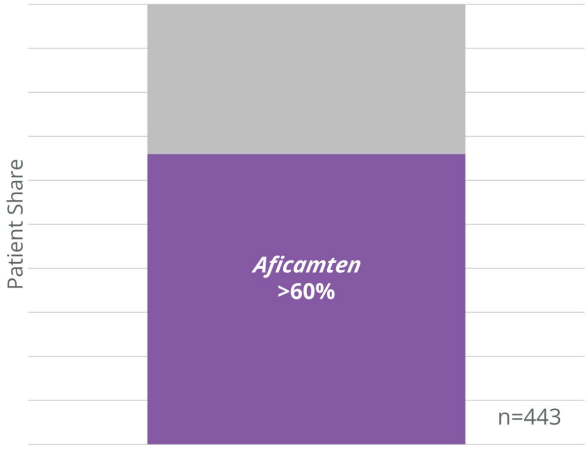
We **expect CMI penetration to be <20% of total addressable patient population** at expected launch of *aficamten*

Our primary focus will be on **patients that have already been diagnosed**

***Aficamten* is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.**
Sources: *Aficamten* Impact of Product Attributes on Product Preference Share n=443 cardiologists, Quantitative research including conjoint - Cogent, Internal advanced analytics using Symphony claims data and other secondary data sources
1. Aligned with indication statement based on SEQUOIA-HCM.
2. High dose single agent or combo; Aligns with anticipated payer coverage, which is expected to require BB/CCB use prior to CMI (in alignment with guidelines and trial criteria)

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

oHCM CMI Preference Shares in Eligible Patient Population*



- Potential target product profile for *aficamten* interest creates **share opportunity** in newly treated CMI patients
- *Aficamten* is **also 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

Our Brand Vision for *Aficamten*

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

Cytokinetics®

Our Commercial Path Forward

Learn	Design	Build
Leverage **deep understanding** of patients, HCPs, payers, and community	Engage with all stakeholders to design **an optimal customer experience**	Tap into deep functional experience to build **operational excellence** across launch functions

Our Focus to Date → **Our 2024 Focus**

- Patient-centric market development – on display this year at HFSA and AHA
- Continued insights gathering (listening to and learning from all our customer types)
- Once profile of *aficamten* is confirmed through SEQUOIA-HCM, plan to finalize go-to-market approach, including designing an optimal customer experience across stakeholders

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

Payer Landscape

Andrew Callos
EVP, Chief Commercial Officer

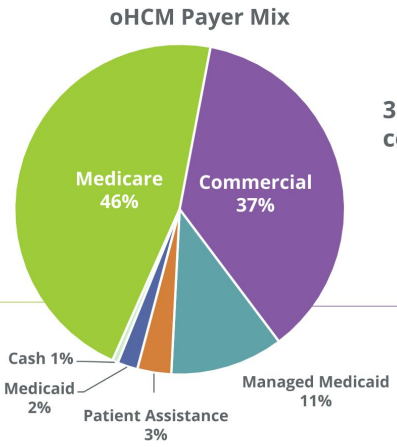
Cytokinetics

Most Patients Covered by Commercial or Medicare

Medicare and commercial volume will represent more than 80% of claims

4 Medicare PBM/Plans contract for 93%[3] of enrollment

1. CVS
2. OptumRx/United
3. Humana
4. ESI/Cigna/Prime



3 Commercial PBM/Plans contract for 95%[3] of enrollment

1. Ascent (ESI/Prime/Cigna)
2. Zinc (CVS)
3. OptumRx/United

1. Symphony Metys Data Jan 2023 to End of April 2023. Symphony does NOT provide full Camzyos data capture. A significant PBM has blocked their reporting
2. SHA Patient Level Claims Data 12/20-11/21; includes BB, ACE, CCB, Disopyramide.
3. MMIT enrollment data 10/1/23

Payer Research Covering >60% of Enrolled Lives Points to Broad Access

Payers consistently expressed low interest in managing or restricting branded HCM drug choice

Topline Beliefs of US Payers:

Recognize symptomatic obstructive HCM as a disease with **high criticality and continued unmet need**

> *Patients with HCM have a high symptom burden and need more effective treatment options than what's currently available.*
> *– Regional MCO 2023*

Anticipate **low overall budget impact and low management priority** due to disease prevalence

> *The juice is not worth the squeeze... Unless one drug is a fraction of the price, there is room for more than one CMI on our formulary.*
> *– National MCO 2023*

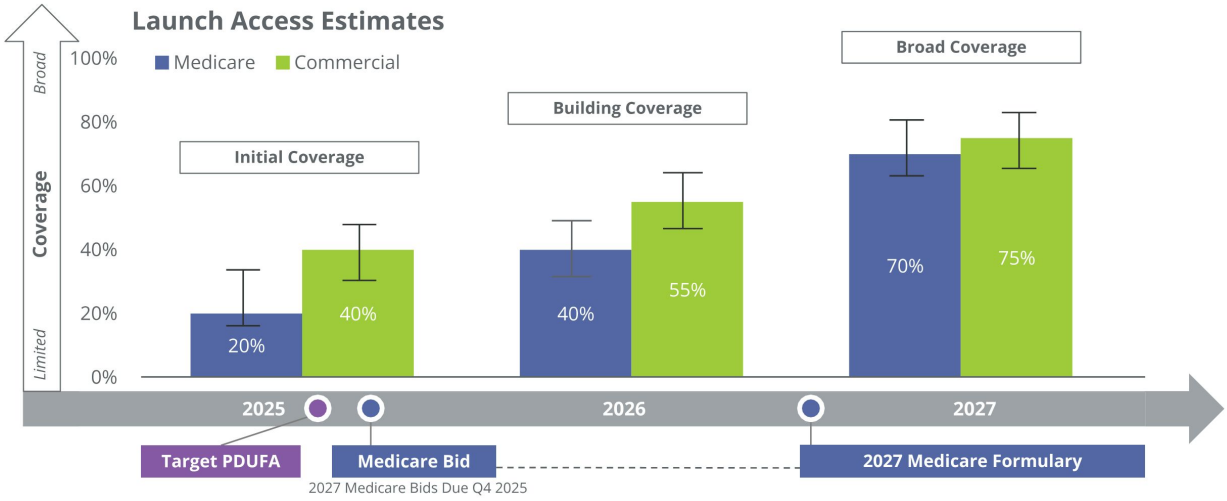
Expect coverage consistent with FDA label indication and clinical trial design

> *In addition to requiring adjunctive use, I'm going to manage with trial criteria and prior treatment in my PA [prior authorization].*
> *– National PBM 2023*

Source: 4 waves of US payer research 2019 through 2023 covering 190M to 250M lives. Most recent: Clearview HealthPartners qualitative interviews completed Mar 2023, n=15, Med-D lives = 41M, Comm Lives = 149M, Total lives ~190M; Market Access Transformation survey conducted Jul-Aug 2023, n=17, Med-D lives = 44M, Comm Lives = 193M lives

Medicare & Commercial Coverage Expectations

Medicare bid timing is a key driver of Medicare access; commercial access timing driven by individual payers



Cytokinetics

Experienced Market Access Team to Accelerate Access

Strong & extensive customer relationship experience

Average of **30+ Years** of experience per Account Director

Collectively, **~300 years** of payer/PBM relationship experience

~250 product launches, including **~100 CV products**

Health Economics Data to Support Value Proposition for *Aficamten*

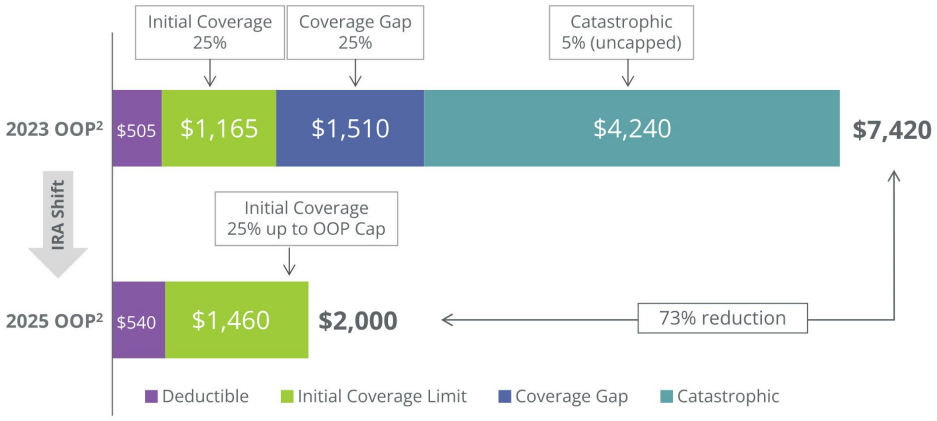
Platform	Objectives
1 **Potentially Leverage SEQUOIA-HCM Clinical Trial Data Read-out into Clear Value Articulation for Stakeholders**	• Improvement in exercise capacity (pVO_2), improvement in NYHA functional class and improvement in KCCQ-CSS lead to better health outcomes and cost savings • Sustained efficacy could delay cost and complication of SRTs
2 **Potentially Translate Potential Clinical Attributes of *Aficamten* into Value for Stakeholders**	• Minimal drug-drug interactions & rapid reversibility could result in broad usage of *aficamten,* potentially leading to improved health outcomes & cost savings • Stable PK/PD profile could lead to minimal treatment interruptions and improved health outcomes

↓

Multiple manuscripts and abstracts published with leading KOLs
Deliver fit for purpose value proposition and communicate to stakeholders

IRA Potentially Reduces Patient OOP Cost Burden

Illustration[1]: Shift of Total Annual Patient Cost Burden Due to IRA Comparing 2023 to 2025 Per WAC of $96,000 per year



Medicare patients are very sensitive to Rx OOP cost
>70% abandonment at $250+ monthly patient OOP

HCM/CMI patients will surpass the $2,000 OOP catastrophic threshold[3] and have *zero* cost exposure after

1. Illustration assumes a specialty drug with a WAC price of $96,000 per year. 2. OOP Out-of-Pocket Cost. Source: Adaptation of KFF report. https://www.kff.org/medicare/issue-brief/changes-to-medicare-part-d-in-2024-and-2025-under-the-inflation-reduction-act-and-how-enrollees-will-benefit/. 3. $2,000 OPP threshold includes total drug spending.

Innovative Therapies Can Have More Complex Patient Journeys

Focused investments in the customer experience required

Patients and providers can experience many hurdles getting on Rx therapy

Complex Patient Journey + Launch Coverage Delays + Payer Utilization Mgmt + Specialty Cost Sharing

Comprehensive patient support* is often provided to help address emotional, financial, and educational needs throughout the patient journey

Access & Reimbursement Support

- Navigating Prior Auths and Medical Exceptions
- Benefits Verification
- Free Trial/Bridge Programs

Affordability Programs

- Commercial Co-pay Programs
- Patient Assistance Programs
- Echo Reimbursement
- Foundation Support

Patient Journey Support

- REMS Support
- Nurse Support
- Transportation Services
- Mental Health Support

Education & Resources

- OOP and Coverage Education
- Disease State Education

*All patient support is informational only and within industry standards and regulatory requirements.

Planned Sales Strategy

Jeff Lotz
VP, US Sales and Operations

Cytokinetics®

Gated Build of Commercial Infrastructure

Majority of spending to occur closer to 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

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 FDA approval
Media purchases
Patient support programs

Initial HCM Customer Universe Includes 7-10K HCPs & ~500 Accounts

Current Understanding of Customer Universe

- **Initial lists of HCPs and HCOs were defined based on:**
  - Diagnosers: HCM patient volume
  - Treaters: BB/CCB, disopyramide claims, SRT, and *mavacamten* claims
  - HCM trial investigators/sites
  - HCM CoEs/Programs

Initial Insights

7-10K HCPs
represent ~75% of HCM patient volume

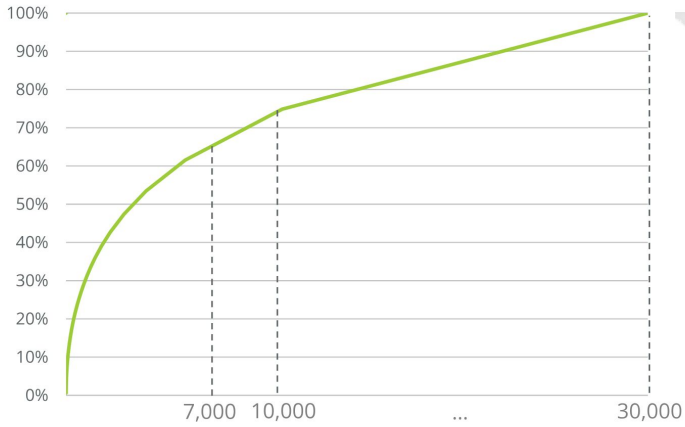
500-700 HCOs
represent ~75% of HCM patient volume

Source: Sales Ops team analysis as of 2H 2022

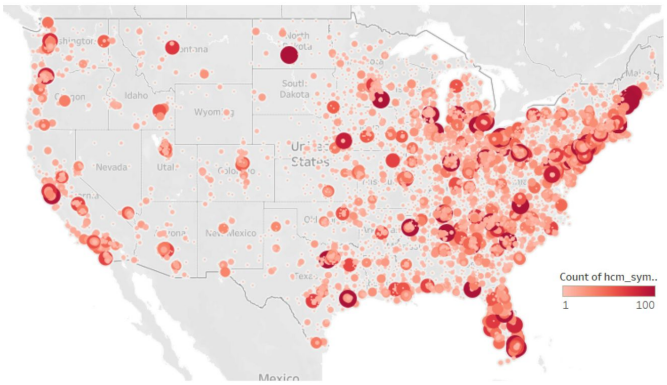
Cardiologists Located in Concentrated Geographic Clusters Across the US

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

HCM Patient Concentration by Cardiologist



Geographic Distribution of HCM Patients



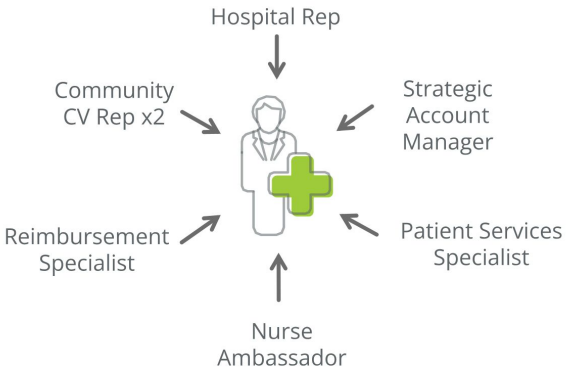
Note: includes only patients who are treated by a cardiologist - not all patients see a cardiologist; sample of 67K HCM patients
Source: Symphony PTD (Patient Transaction Data); mapping of HCPs to HCOs using Definitive Healthcare Data 2023 and 7/2023 mapping; Patient volume by dominant Cardiologist Location 7/2023

Sales Team Designed Based on Efficiency & Customer Feedback

Traditional Models

Several functions with very focused roles

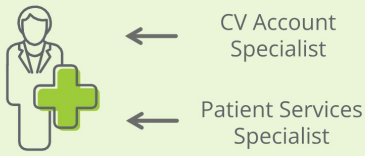
Overwhelmed customers, "It's too much"



Our Design Principles

Simple model creating quality experience

Hire team with deep experience in specialty



Cytokinetics

Highly Experienced Leadership Team

Sales leaders have extensive industry, leadership and cardiovascular experience

Our Leaders

- Average of ***22 years*** in industry
- Average of ***13 years*** in leadership
- Average of ***14 years*** in cardiovascular therapeutic area
- Nearly ***50% / 50%*** Big vs. Small Pharma
- ***100%*** have launch experience

Our Account Specialist Candidate Pipeline Will Be Recruited Using Same Criteria

- Pipeline is building
- Deep industry and cardiovascular experience
- Deep launch experience

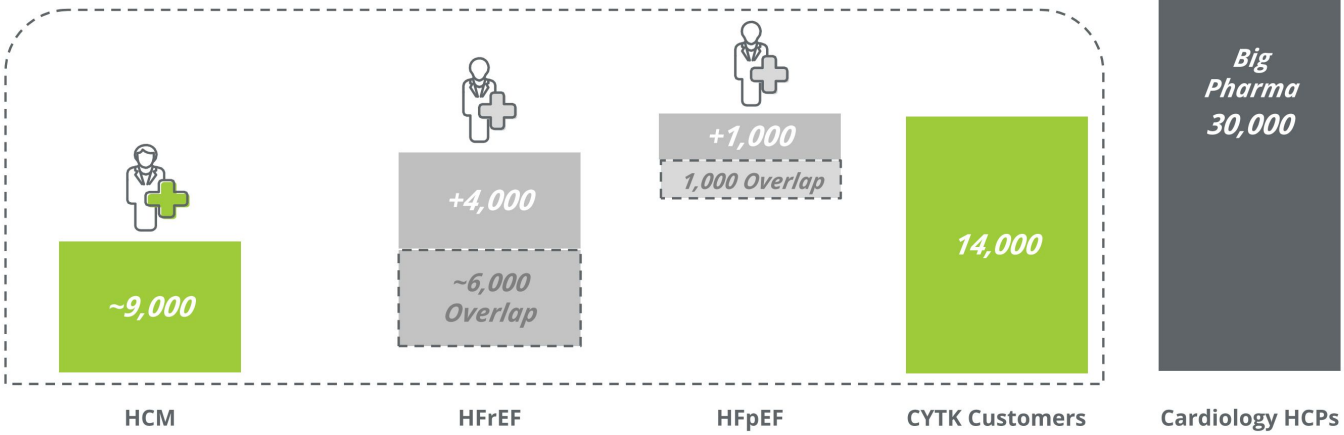
Customer Coverage Evolves With Specialty Cardiology Franchise

Building Today …

To optimize value capture for potential launch of *aficamten*

… To Lead Tomorrow

To support future launches and establish Cytokinetics as a CV leader



Cytokinetics

HCM KOL Panel

Cytokinetics®

HCM KOL Panel

Theodore Abraham, M.D., FACC, FASE
Meyer Friedman Distinguished Professor of Medicine, Division of Cardiology, University of California, San Francisco; Co-director, UCSF HCM Center of Excellence; Director, UCSF Adult Cardiac Echocardiography Laboratory

Caroline Coats, Ph.D.
Clinical Senior Lecturer, School of Cardiovascular & Metabolic Health, University of Glasgow

Carolyn Ho, M.D.
Associate Professor, Harvard Medical School, Medical Director of the Cardiovascular Genetics Center

MODERATED BY

Fady Malik, M.D., Ph.D.
EVP, Research & Development

HFpEF Landscape & CK-586

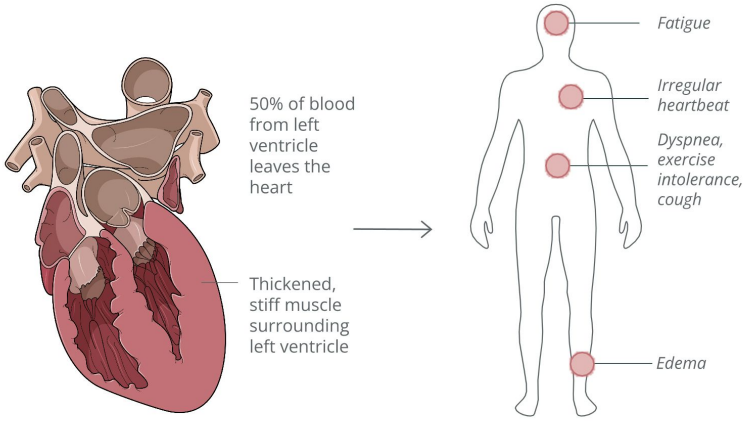
Stuart Kupfer, M.D.
SVP, Chief Medical Officer

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

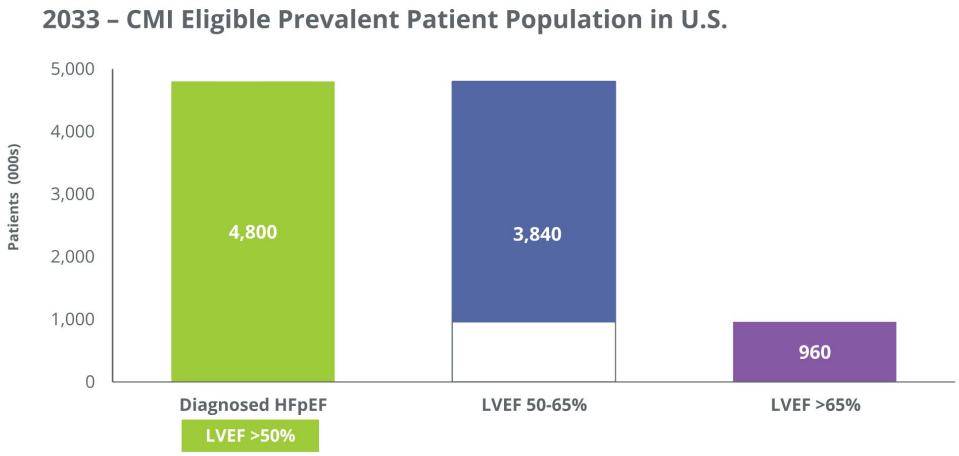
- Heart failure with preserved ejection fraction (HFpEF) is a condition where pumping of the heart is impaired despite **relatively normal ejection fraction** and can lead to heart failure
- HFpEF (LVEF >50) is a **heterogenous group of diseases**
- One clinically defined, more homogenous, and more severe subgroup is **HFpEF with LVEF ≥65%**



HFpEF Diagnosis Expected to Grow Faster than the General Population

CMI eligible patient population of LVEF ≥ 65% without severe comorbidities is ~770K

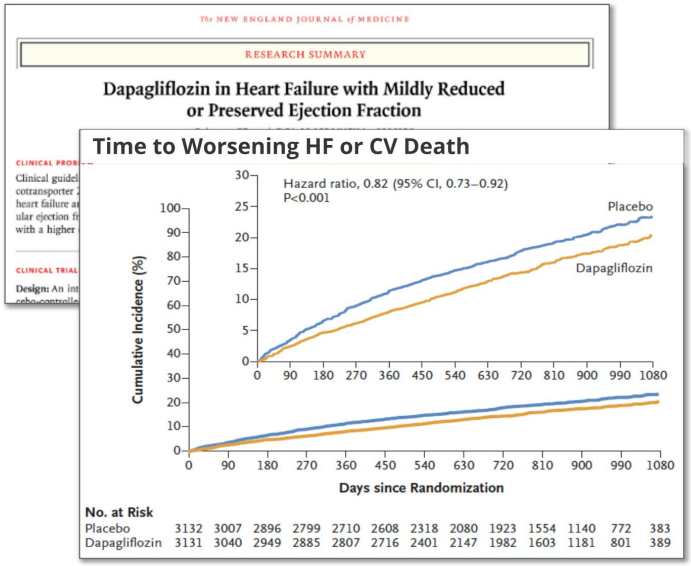
CAGR of HFpEF is 2.1% compared with 1% U.S. population growth



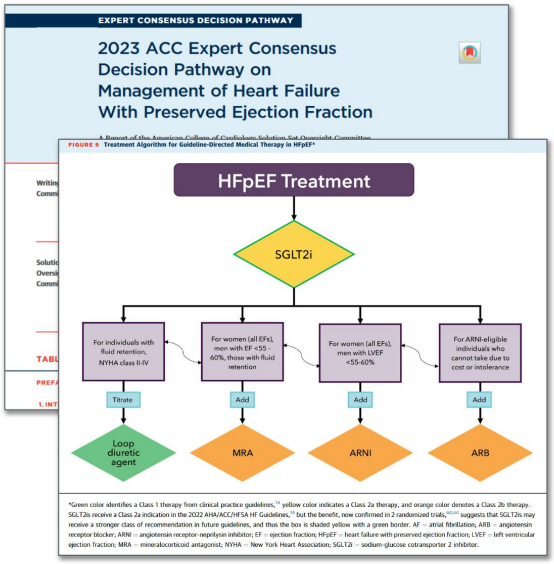
Source: DataMonitor, Rosano 2022 ESC Heart Fail, Bellanca 2023 BMC,Feldman 2020 Arch. Cardiovasc. Dis. Norhammar 2023 Heart, Delepaul 2016 ESC Heart Fail, Bhatt 2021 Eur J Heart Fail, Uijl 2021 NHJ.

High Residual Risk in HFpEF Despite Benefit of SGLT2 Inhibitor Therapy

30-40% of HFpEF without severe comorbidities are not well-managed by SoC & remain symptomatic



Source: Solomon SD et al., 2022 *NEJM*, 387:1089-98



Source: Journal of American College of Cardiology, April 19, 2023

nHCM is a Human Model of HFpEF Subgroup

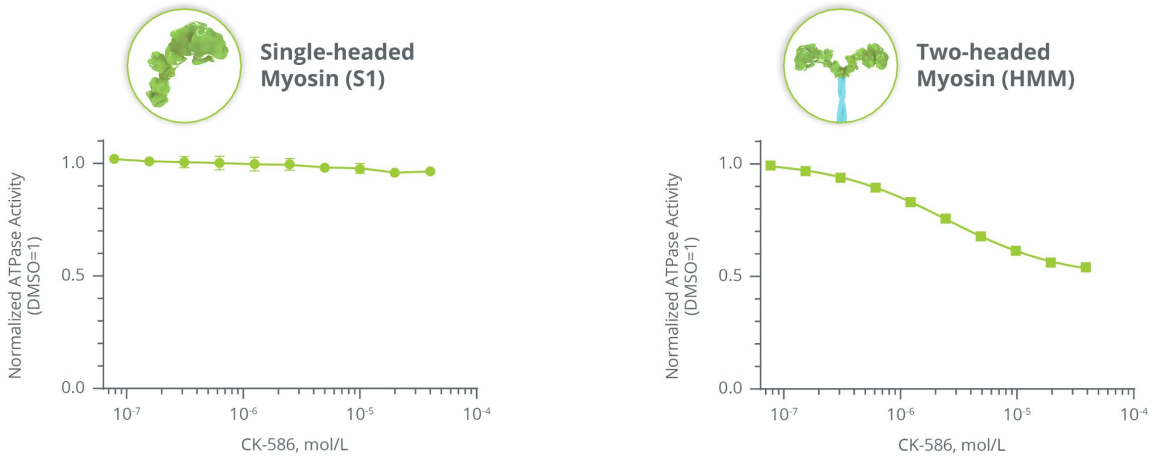
nHCM patients are similar to subgroups of HFpEF patients with hypercontractility

Symptoms and pathophysiology are similar in both conditions

Symptoms	Pathophysiology
Dyspnea	Increased Contractility
Exercise Capacity Diminished	Left Ventricular Hypertrophy
Peripheral Edema	Increased LV Filling Pressure
Fatigue	Diastolic Dysfunction

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

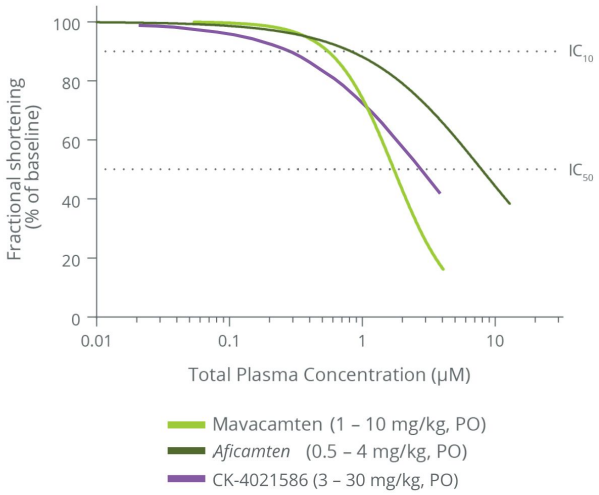
CK-586 inhibits actin-activated ATPase of HMM only; *aficamten* inhibits both S1 and HMM



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

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

CK-586 is predicted to 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	TBD	15 hours

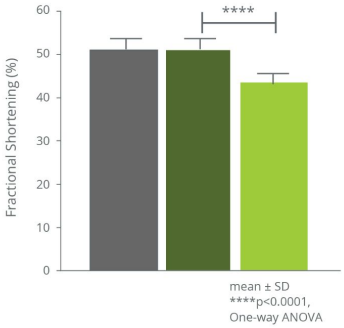
CK-586 is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

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

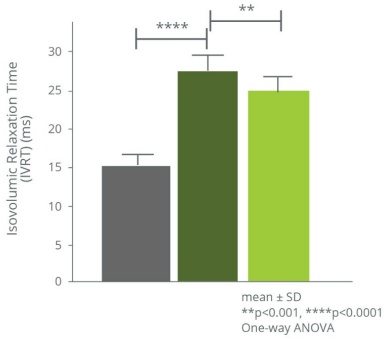
Model is representative of hypertensive, diabetic, metabolic aspects of HFpEF

10 weeks of treatment improved diastolic function and reduced cardiac fibrosis

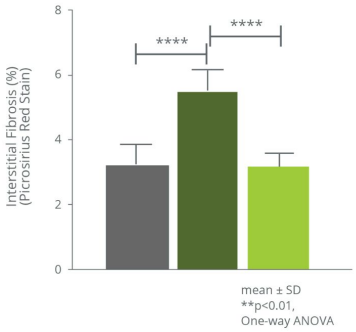
Reduced Fractional Shortening



Improved Diastolic Function



Reduced Fibrosis



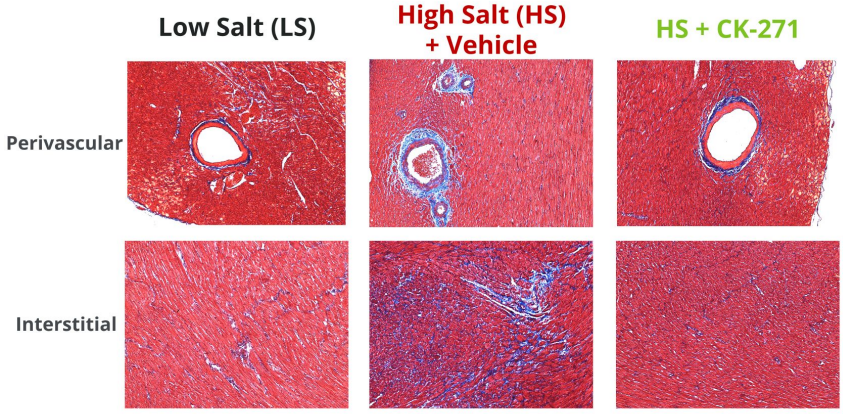
ZSF1 Lean + Vehicle ZSF1 Obese + Vehicle ZSF1 Obese + CK-586 (10 mg/kg, PO QD)

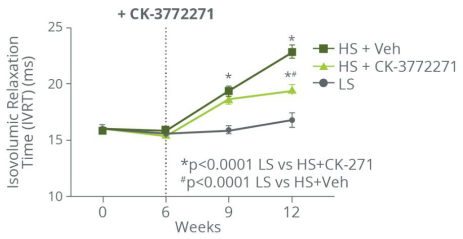
CK-586 is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

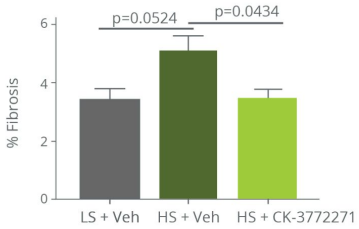
CK-271: Efficacious in Dahl Salt Sensitive (DSS) Rat Model of HFpEF

Model is characterized by hypertension, LV hypertrophy, and heart failure

Significant reduction in fibrosis in DSS rats on high salt diet in the absence of a change in blood pressure







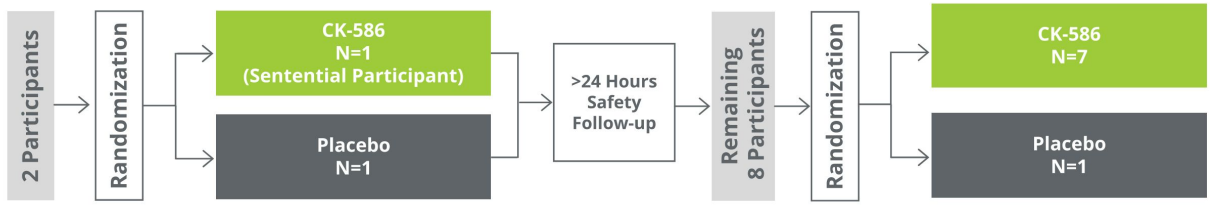
CK-271 is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

CK-586: First-in-Human Study Design

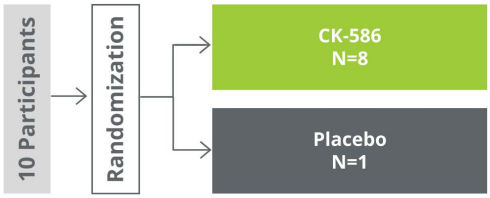
Single and multiple ascending doses in healthy participants

Recently completed SAD cohorts, progressing to MAD cohorts

Single Ascending Dose Cohorts

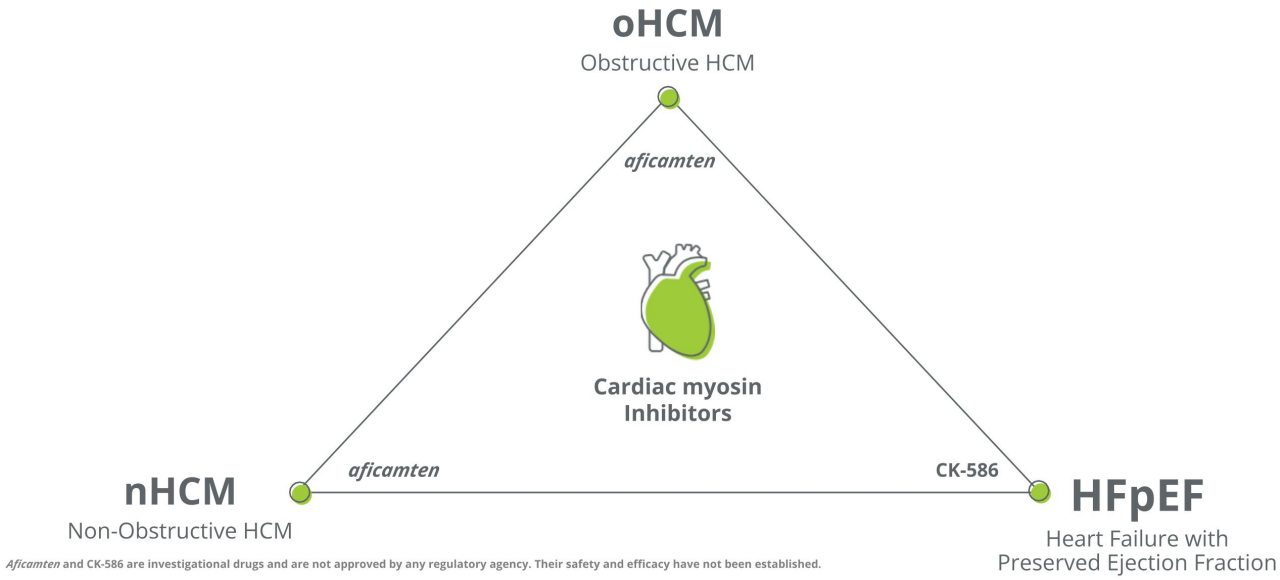


Multiple Ascending Dose Cohorts



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

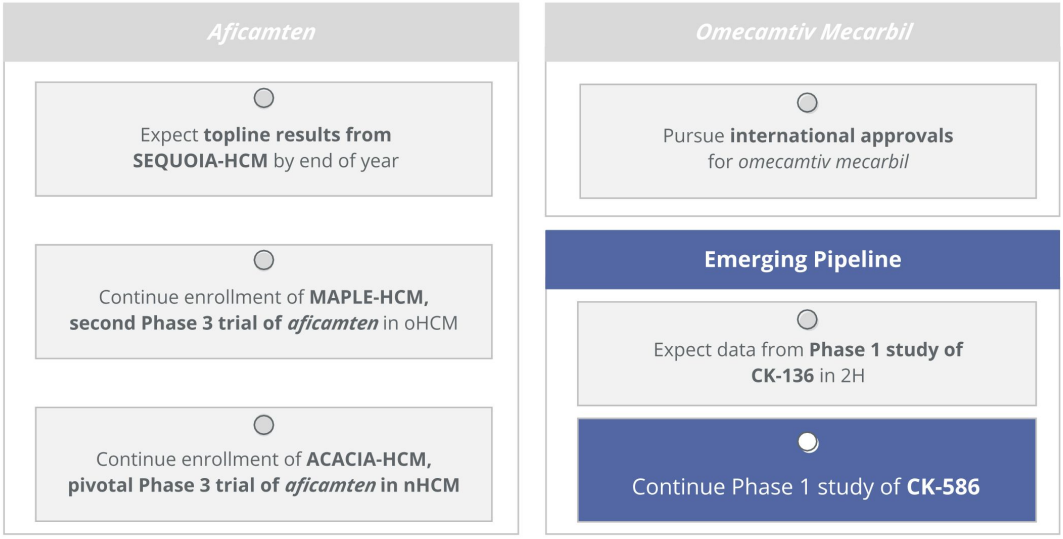
Cardiac Sarcomere Inhibition May Address Multiple Unmet Patient Needs



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

Cytokinetics®

Expected 2023 Milestones



Aficamten, omecamtiv mecarbil, CK-586 and CK-136 are investigational drugs and have not been approved. Their safety and efficacy have not been established.

Q&A

Cytokinetics

Closing Remarks

Robert Blum
President & CEO

Cytokinetics®

Key Takeaways

Cytokinetics is building a **specialty cardiology franchise**, led by *aficamten*, to address patient populations of high unmet medical need.

Topline Results from SEQUOIA-HCM Expected by EOY	*Aficamten* is progressing in a broad development program, with **topline results from SEQUOIA-HCM** expected by EOY. Baseline characteristics reflect a population with substantial deficit in exercise capacity & significant symptom burden despite background therapy.
Long-Term Data Support Safety and Efficacy of *Aficamten*	**New long-term data from FOREST-HCM** show treatment with *aficamten* results in sustained improvements in clinical efficacy endpoints and no treatment interruptions for low ejection fraction.
Commercial Readiness	Cytokinetics is engaging in **ongoing commercial readiness activities**, with market research revealing a symptomatic patient population in need of treatment with a potential next-in-class CMI.
Advancing CK-586	The company is **advancing CK-586, a second cardiac myosin inhibitor** for the potential treatment of patients with HFpEF.

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

Cytokinetics: Uniquely Positioned for Success

Leadership
in muscle biology

Pioneer in CMI space

Multiple drug candidates arising from our research

Core research engine

Depth
in cardiology

Late-stage HCM program

HFrEF opportunity in Europe

Early-stage HFpEF research

Early-stage HF research

Relationships
with stakeholders

Seasoned commercial team

Strong existing payer relationships

Strong relationships with cardiologists and institutions

Access
to capital

Strong cash runway

Access to capital through Royalty Pharma transaction

Solid Financial Foundation & Prudent Spending

Strong cash position

Access to additional capital

Gated spending

Expected 2023 Milestones

Aficamten

- Expect **topline results from SEQUOIA-HCM** by end of year
- Continue enrollment of **MAPLE-HCM, second Phase 3 trial of *aficamten*** in oHCM
- Continue enrollment of **ACACIA-HCM, pivotal Phase 3 trial of *aficamten* in nHCM**

Omecamtiv Mecarbil

- Pursue **international approvals** for *omecamtiv mecarbil*

Emerging Pipeline

- Expect data from **Phase 1 study of CK-136** in 2H
- Continue Phase 1 study of **CK-586**

Aficamten, omecamtiv mecarbil, CK-586 and CK-136 are investigational drugs and have not been approved. Their safety and efficacy have not been established.

Thank You

Cytokinetics®