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# HEART*FORWARD*

Advancing Cardiac Myosin Modulation

# Forward-Looking Statements

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# Company Speakers

**Robert Blum**
President & Chief Executive Officer

**Sung Lee**
EVP, Chief Financial Officer

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

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

**Stephen Heitner, M.D.**
VP, Head of Clinical Research

**Daniel Jacoby, M.D.**
Executive Medical Director, Clinical Research Cardiovascular

**Punag Divanji, M.D.**
Medical Director, Clinical Research Cardiovascular

**Andrew Callos**
EVP, Chief Commercial Officer

**Joseph Dagher**
SVP, Head of Europe

**Daniel Kates, M.D., M.B.A.**
SVP, Medical Affairs

**Genie Dubuk**
VP, Customer Experience & Insights

**Sunil Karnawat, Ph.D.**
VP, Global Value, Access & Distribution

**John Jacoppi**
VP, US Marketing for *Aficamten*

**Jeff Lotz**
VP, US Sales & Operations

**Diane Weiser**
SVP, Corporate Affairs

# Expert Speakers

**G. Michael Felker, M.D., MHS, FACC, FAHA, FHFSA**
Professor of Medicine, Division of Cardiology, Duke Clinical Research Institute

**Mariko Harper, M.D., MS, FACC**
Medical Director, The Hypertrophic Cardiomyopathy Center, Virginia Mason Franciscan Health

**Shepard D. Weiner, M.D.**
Medical Director, Hypertrophic Cardiomyopathy Center and Associate Professor of Medicine, Columbia University Medical Center

***Outside experts have been contracted by Cytokinetics***

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# Today's Agenda

| Topic | Presenter |
|---|---|
| **Welcome** | **Diane Weiser**, SVP, Corporate Affairs |
| **Introduction** | **Robert Blum**, President & CEO<br>**Sung Lee**, EVP, Chief Financial Officer |
| ***Aficamten*: Development Program** | **Fady Malik, M.D., Ph.D.,** EVP, Research & Development<br>**Steve Heitner, M.D.,** VP, Head of Clinical Research<br>**Daniel Jacoby, M.D.,** Executive Medical Director, Clinical Research Cardiovascular<br>**Mariko Harper, M.D., M.S., FACC**<br>**Shepard D. Weiner, M.D.** |
| **Aficamten: Global Commercial Launch Preparations** | **Daniel Kates. M.D., M.B.A.** SVP, Medical Affairs<br>**Andrew Callos**, EVP, Chief Commercial Officer<br>**John Jacoppi**, VP, US Marketing for *Aficamten*<br>**Jeff Lotz**, VP, US Sales & Operations<br>**Genie Dubuk**, VP, Customer Experience and Insights<br>**Sunil Karnawat, Ph.D.**, VP, Global Value, Access & Distribution<br>**Joseph Dagher**, SVP, Head of Europe |
| **Break** | |
| ***Omecamtiv Mecarbil*: Phase 3 Confirmatory Trial & Beyond** | **Fady Malik, M.D., Ph.D.**, EVP, Research & Development<br>**Punag Divanji, M.D.**, Medical Director, Clinical Research, Cytokinetics<br>**Andrew Callos**, EVP, Chief Commercial Officer<br>**G. Michael Felker, M.D., MHS, FACC, FAHA, FHFSA** |
| **CK-586: Development Program & HFpEF Market Opportunity** | **Stuart Kupfer, M.D.**, SVP, Chief Medical Officer<br>**Steve Heitner, M.D.**, VP, Head of Clinical Research<br>**Andrew Callos**, EVP, Chief Commercial Officer |
| **Q&A** | **Diane Weiser**, SVP, Corporate Affairs |
| **Closing Remarks** | **Robert Blum**, President & CEO |

# Introduction

**Robert Blum**
President and Chief Executive Officer

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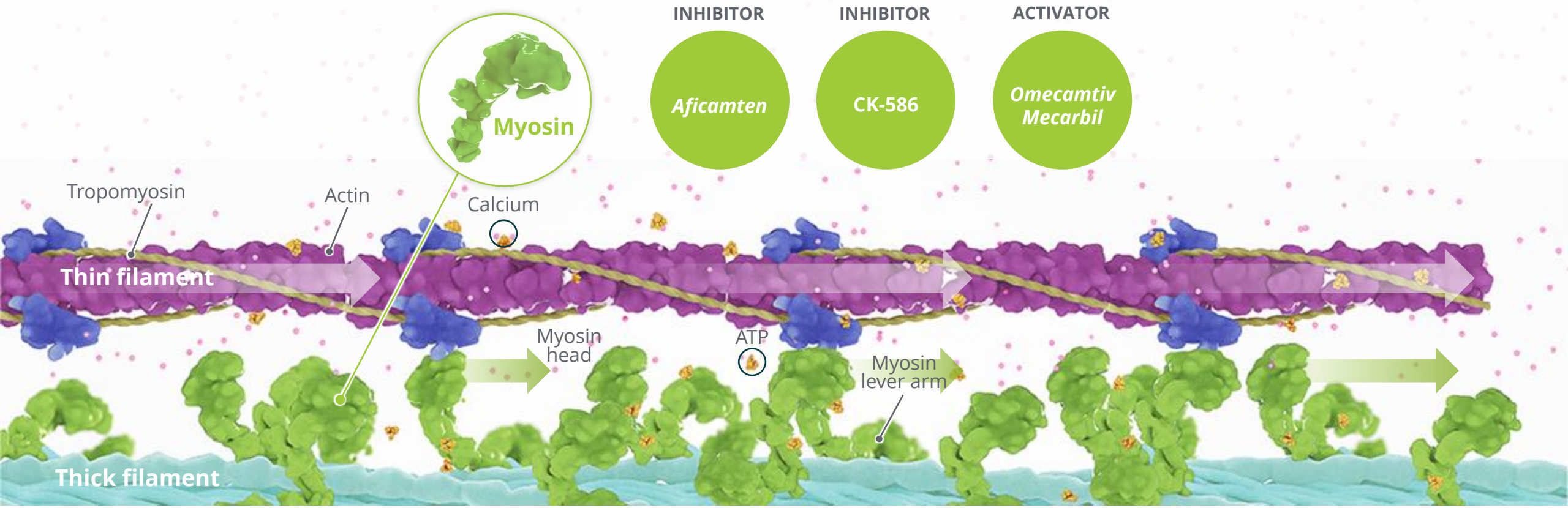
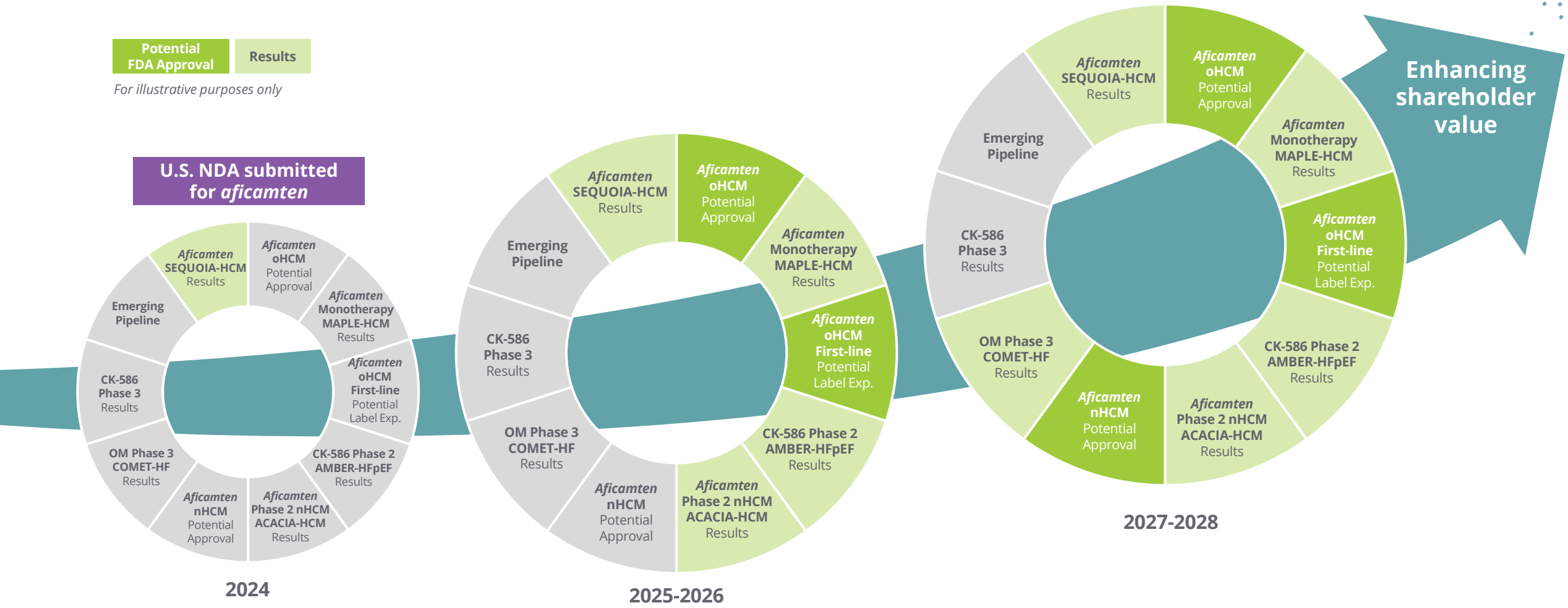
# Pioneers in Cardiac Myosin Modulation

## Pipeline of cardiac myosin modulators arising from one biology



# Myosin Platform Fuels Multiple Milestones and Increased Value




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

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# Addressing Difficult to Treat Populations Within Heart Failure

## Specialty cardiology franchise strategy applies to markets with similar characteristics

**HCM**

**Opportunity for *aficamten* as the anchor**

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

**HFrEF**
Severely reduced EF

**Expanding into adjacent population**

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

**HFpEF**
Supranormal EF

**Addressing underserved segment of HF market**

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


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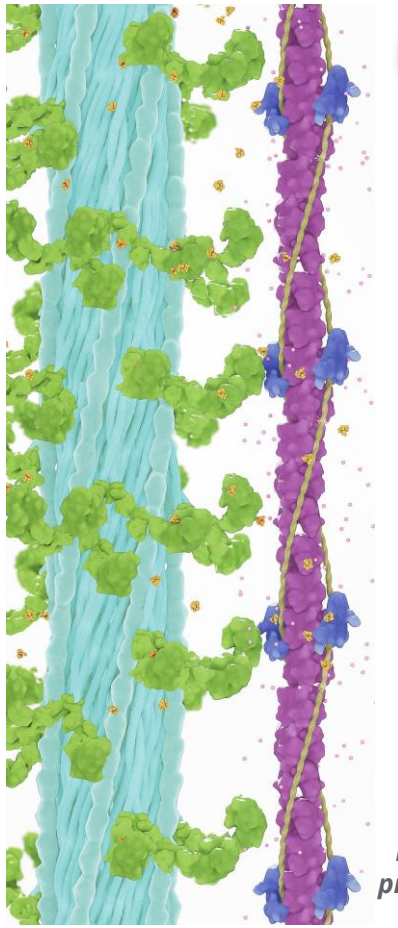
# Building a Specialty Cardiology Franchise Anchored by *Aficamten*

## Potential patient market for specialty cardiology franchise strategy



***Estimated prevalence in US only***

**Myosin-Targeted Therapies**

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

*Aficamten*

**oHCM**
***SEQUOIA-HCM***
First potential indication

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

*Aficamten*

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

*Aficamten*

**nHCM**
***ACACIA-HCM***
Potential to expand into nHCM

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

*Omecamtiv Mecarbil*

**HFrEF**
Potential in HFrEF

**800K[4]**
**HFpEF + EF ≥ 65% in 2030**

CK-586

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

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


*1. Cardiovascular Research Group: CVrg Market Strategies: Heart Failure, p 48, Q4 2022; Maron BJ: et al: Prevalence of Hypertrophic Cardiomyopathy In A General Population of Young Adults, Circulation 1995;92;785-789; Semsarian C. et al: New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy, J. Am, Coll. Cardiol. 2015; 65: 1249-1254;*
*2. Lu DY et al: Clinical Outcomes in Patients With Nonobstructive, Labile, and Obstructive Hypertrophic Cardiomyopathy. J. Am. Heart Assoc. 2018;7:1-11*
*3. Greene et al JACC 2023; 81:413-424*
*4. Dunlay et al (2012) Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30.*

# Financial Outlook

**Sung Lee**
Executive Vice President, CFO

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# Well-Positioned for Growing Value Over Time

### Strong Balance Sheet

- **$1.4B** cash & investments as of June 30, 2024
- Secured further access to financing, up to **$500M,** subject to satisfaction of conditions

### Pipeline Breadth and Depth

- U.S. commercial readiness for *aficamten*
- Label expansion studies for *aficamten*
- Ph 3 trial of *omecamtiv mecarbil*
- Ph 2 trial of CK-586

### Research Platform

- Platform capable of generating future drug candidates

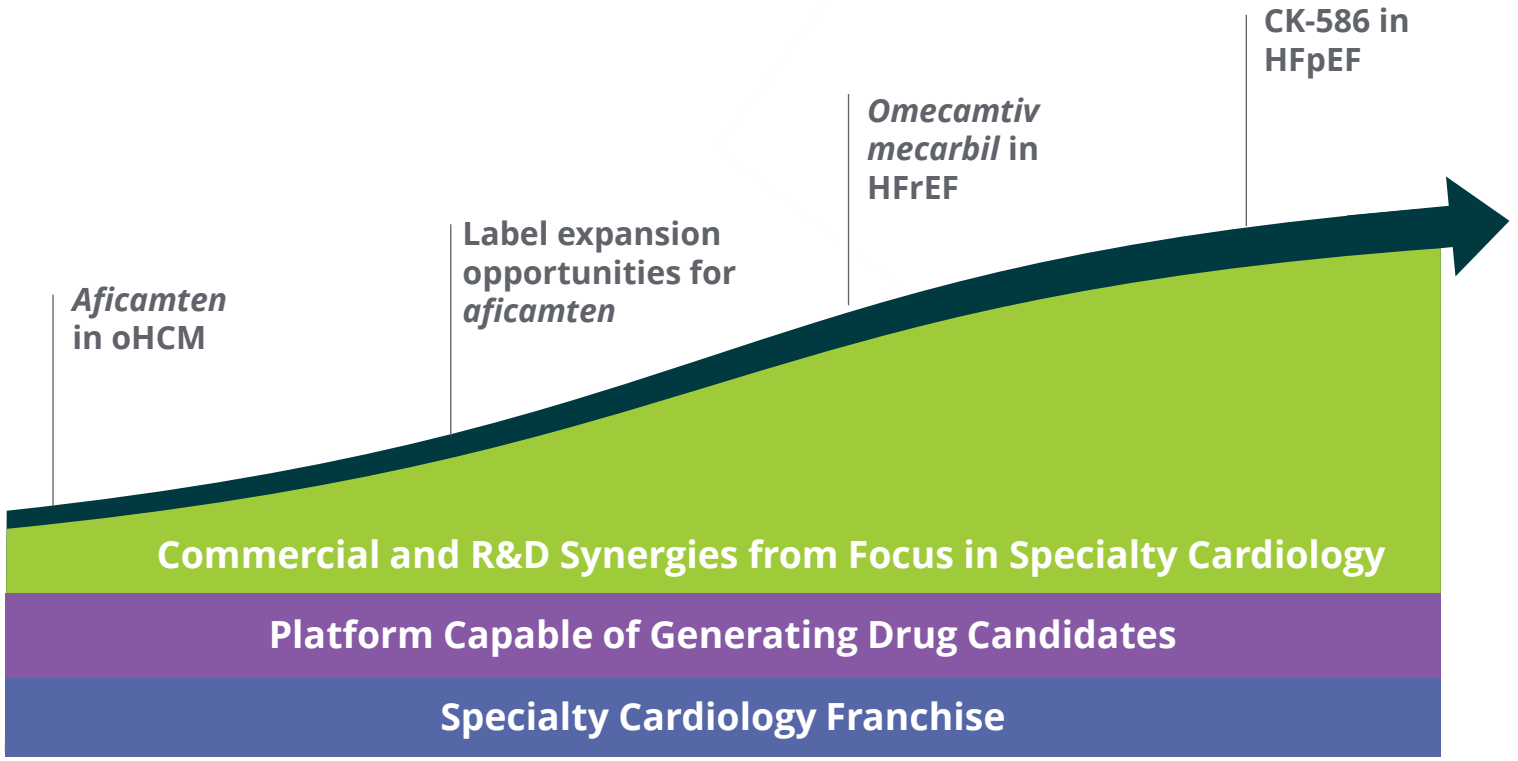
### Sustainable Growth

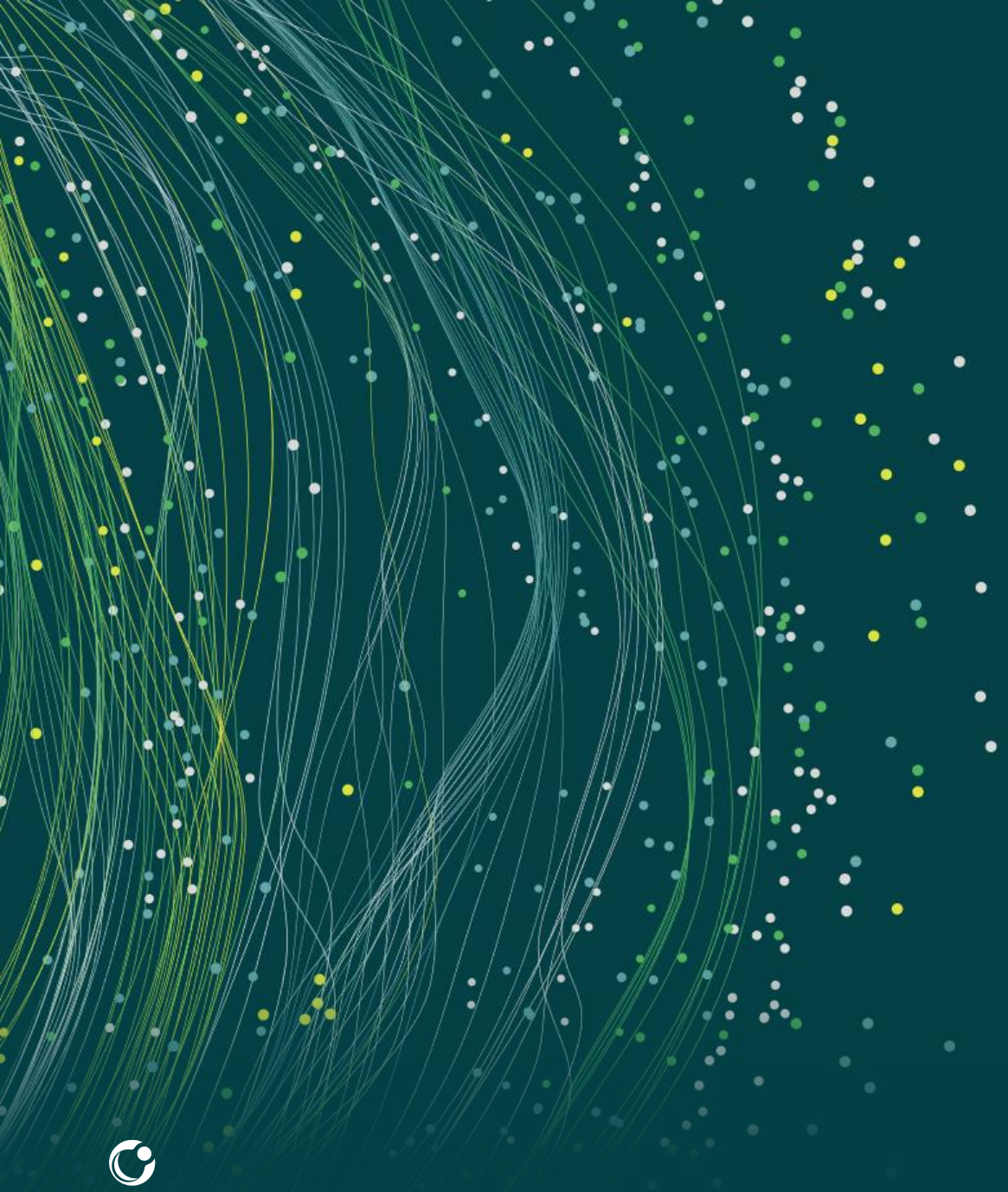
Ambition to become a multi-medicine integrated biopharma built on a specialty cardiology franchise

# Business Model Built on a Specialty Cardiology Franchise

**Specialty cardiology franchise model designed to:**

- Drive revenue growth with multiple potential medicines
- Enhanced margins
- Fuel waves of R&D innovation





# Myosin Modulation Platform

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

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# Addressing Unmet Need with Myosin Modulation

## Extensive clinical development programs

### *Aficamten*

| REDWOOD HCM | SEQUOIA HCM | MAPLE HCM | ACACIA HCM | CEDAR HCM | FOREST HCM |
|---|---|---|---|---|---|
| Phase 2 clinical trial in HCM | Pivotal Phase 3 clinical trial in oHCM | Pivotal Phase 3 clinical trial of *aficamten* as monotherapy vs. metoprolol in oHCM | Pivotal Phase 3 clinical trial in nHCM | Clinical trial in a pediatric population with oHCM | Open-label extension clinical study in HCM |
| Complete | Complete | Enrollment Complete | Enrolling | Enrolling | Enrolling by Invitation |

### *Omecamtiv Mecarbil*

| COSMIC-HF | METEORIC-HF | GALACTIC-HF | COMET-HF |
|---|---|---|---|
| Phase 2 clinical trial in HFrEF | Phase 3 clinical trial of exercise capacity in HFrEF | Pivotal Phase 3 CV outcomes clinical trial in HFrEF | Confirmatory Phase 3 clinical trial in HFrEF |
| Complete | Complete | Complete | Expected to Start Q4 2024 |

### *CK-586*

| AMBER HFpEF |
|---|
| Phase 2 clinical trial in HFpEF |
| Expected to Start Q4 2024 |

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

# *Aficamten*: Development Program & Discussion

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

*AFICAMTEN*: DEVELOPMENT PROGRAM

**TOPIC 1**

# Dosing, Efficacy and Ease of Use

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

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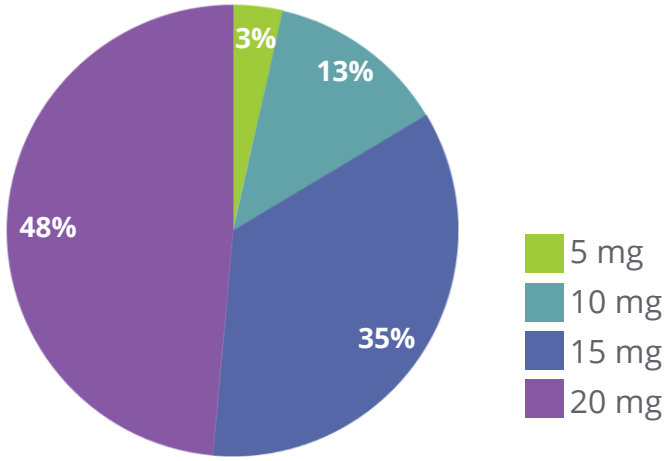
# Dosing and Titration

## No heart failure events observed, large treatment effect

### *Aficamten* dose at Week 8
**(end of titration)**




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

### SEQUOIA-HCM Echocardiogram Criteria for Dose Titration

| Biplane LVEF | Post-Valsalva LVOT-G | Action |
|---|---|---|
| **≥ 55%** | < 30 mm Hg | No change |
| | ≥30 mm Hg | Increase dose by 5 mg |
| **≥ 50% to 55%** | N/A | No change |
| **≥ 40% to < 50%** | N/A | Reduce dose by 5 mg* |
| **< 40%** | N/A | Temporary discontinuation |

* If LVEF < 50% on 5 mg, the patient was assigned to placebo (which did not occur during trial)

*hs-cTnI, high-sensitive cardiac troponin; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary score; MWT, maximal wall thickness; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association.*

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

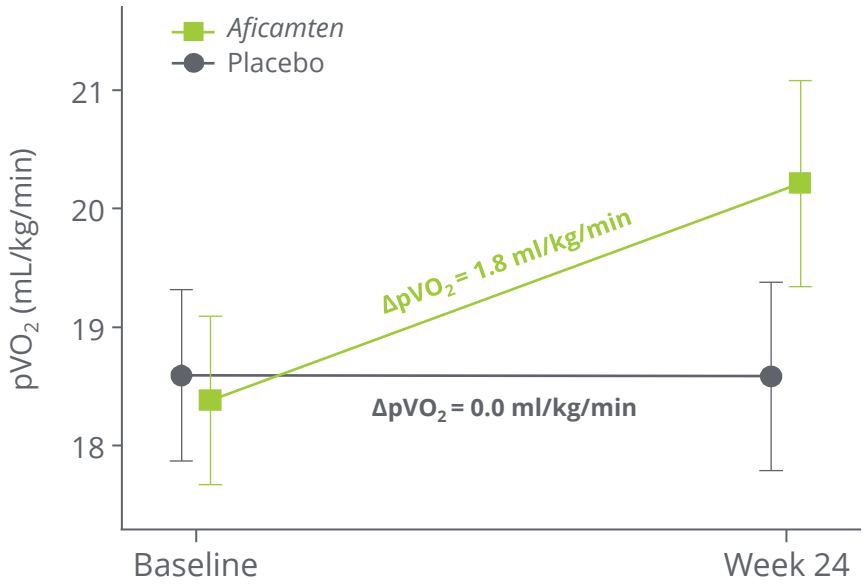
***Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.***

# Primary Endpoint

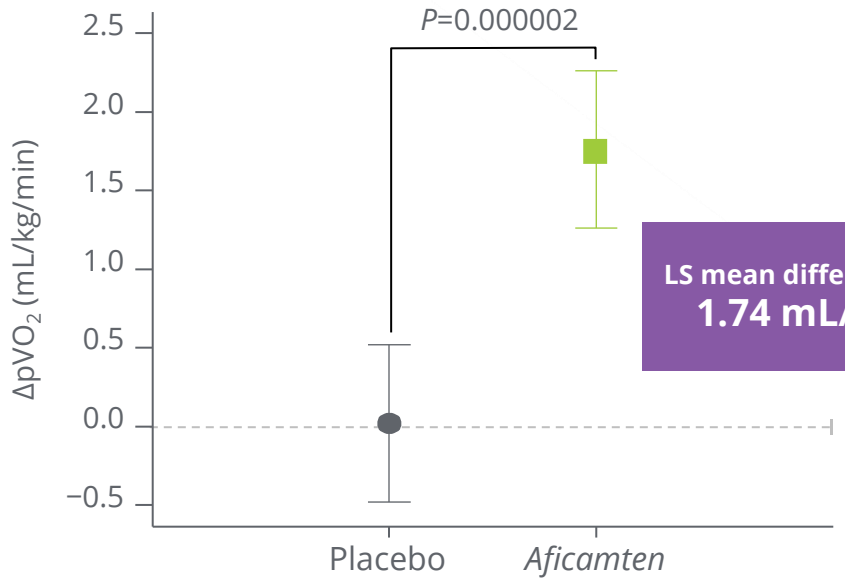
## Significant improvement in exercise capacity compared to placebo

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

### Absolute Change from Baseline to Week 24




### LS mean Change from Baseline to Week 24




Data are mean and 95% CI

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

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

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# Subgroup Analysis

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

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

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

Favors Placebo — Favors Treatment

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

Favors Placebo — Favors Treatment

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

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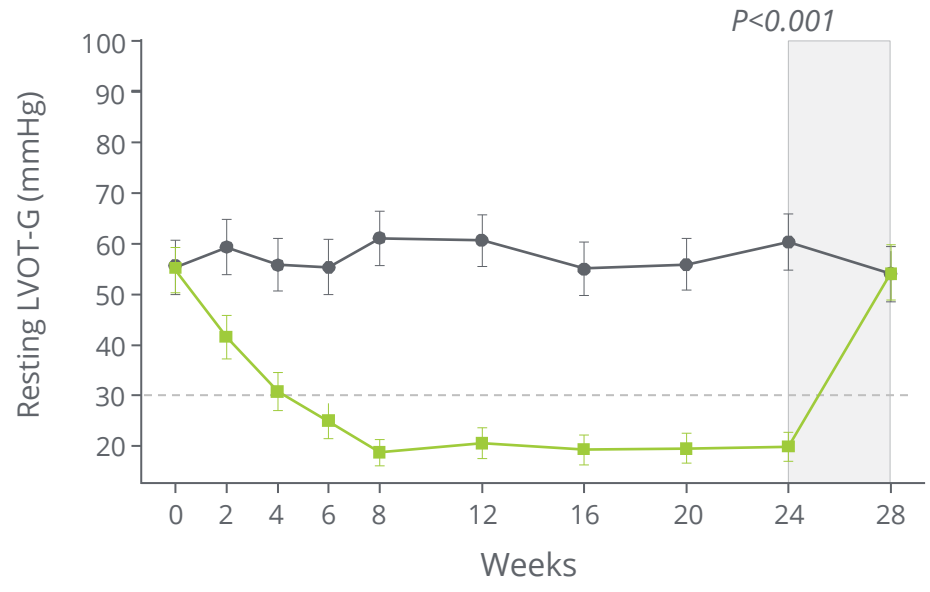
# Secondary & Exploratory Endpoints

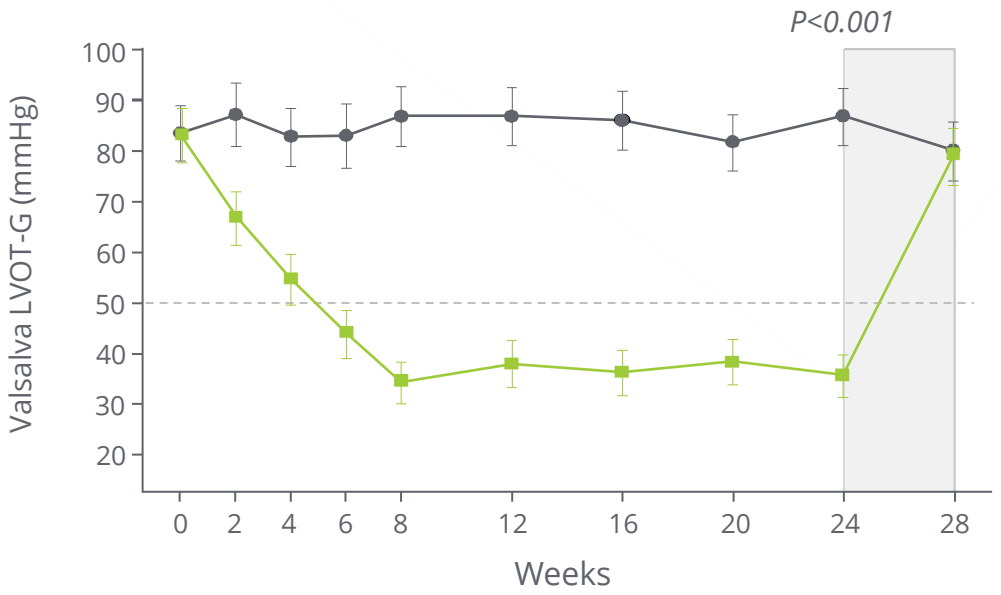
## Significant improvement in gradients by ~60% with no significant adverse change in LVEF

**LS mean difference: - 50 mmHg**

### Resting LVOT-G




### Valsalva LVOT-G




*Aficamten*
Placebo
Washout

*Error bars are 95% CI*

*Hegde S, et al. Impact of Aficamten on Echocardiographic Cardiac Structure and Function in Symptomatic Obstructive Hypertrophic Cardiomyopathy. JACC. 2024.*

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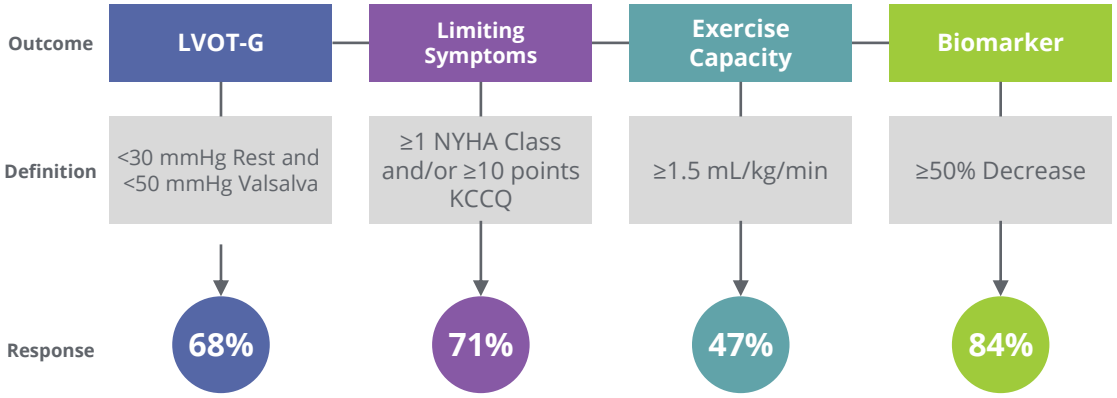
# Clinically Relevant Improvements

## 2/3 patients achieved complete hemodynamic response in prespecified analyses

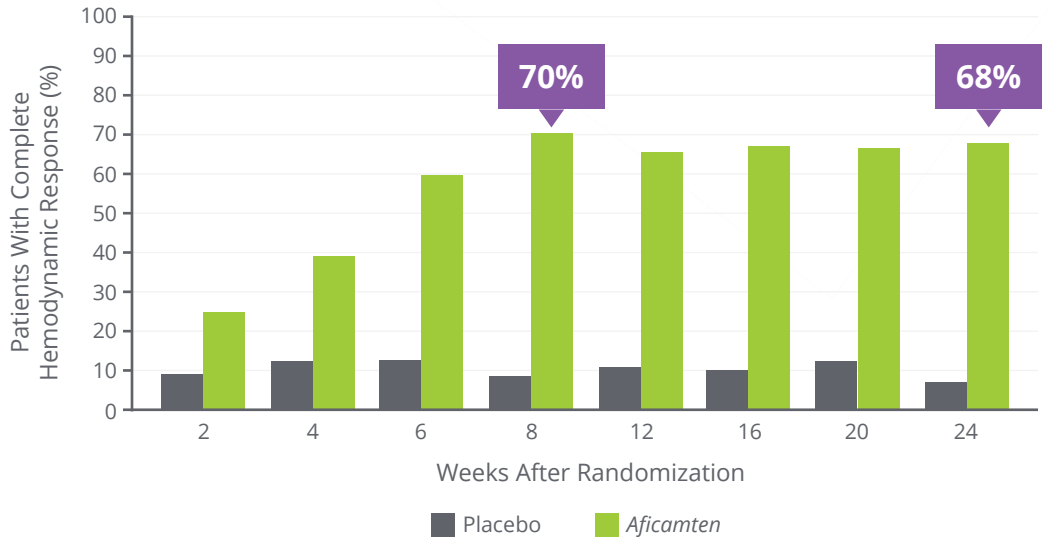
### Responder Analysis: Achievement of 4 Clinically Relevant Assessments




*P*<0.002
vs. placebo

### Complete Hemodynamic Response

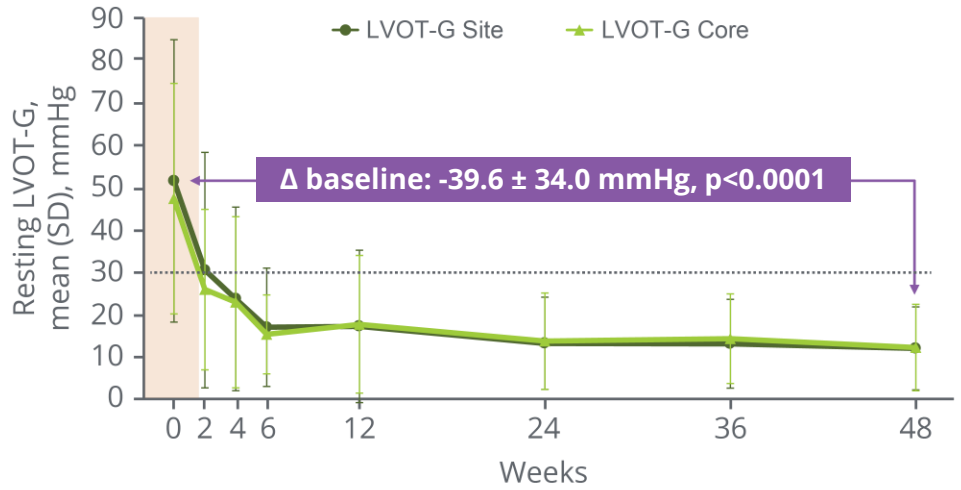
Resting LVOT-G <30 mmHg & Valsalva LVOT-G <50 mmHg




*Maron MS, et al. "Impact of Aficamten on Disease and Symptom Burden in Obstructive Hypertrophic Cardiomyopathy: Results from SEQUOIA-HCM ." HFSA 2024.*
***Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.***

# LVOT Gradients

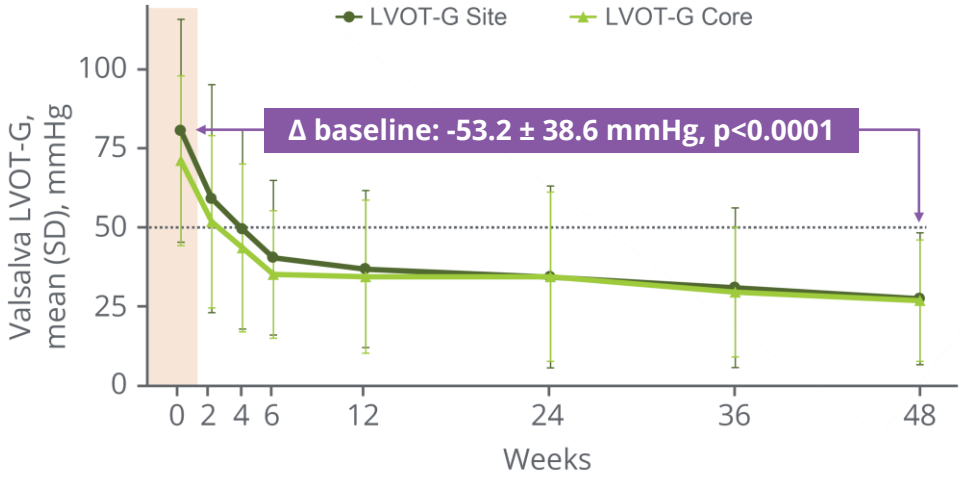
## Resting LVOT-G




**No. of Patients and *P*-value compared with baseline**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Core** | 45 | 45† | 45† | 45† | 44† | 44† |
| **Site** | 45 | 45† | 45† | 44† | 43† | 45† |

## Valsalva LVOT-G




**No. of Patients and *P*-value compared with baseline**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Core** | 45 | 45† | 45† | 45† | 44† | 44† |
| **Site** | 45 | 45* | 45† | 44† | 43† | 45† |

**P<0.001; †P<0001*
*interim safety and efficacy of aficamten in 46 patients with oHCM over 48 weeks from FOREST-HCM*
*Saberi S, et al. "Efficacy and Safety of Aficamten in the First Cohort of Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy Completing 48-Week Follow-up: Findings From FOREST-HCM". ACC.24.*
***Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.***

*AFICAMTEN*: DEVELOPMENT PROGRAM

**TOPIC 1**

# Dosing, Efficacy and Ease of Use

## Discussion

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

*AFICAMTEN*: DEVELOPMENT PROGRAM

**TOPIC 2**

# Emerging Safety Profile

**Steve Heitner, M.D.**
VP, Head of Clinical Research

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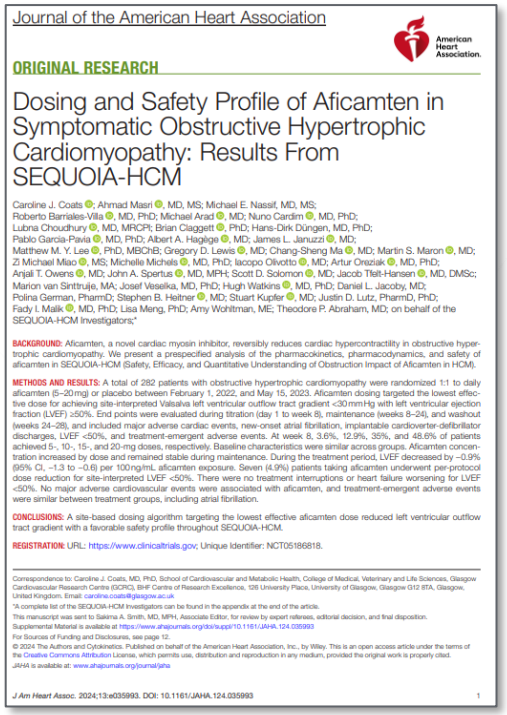
# Safety Data

**AEs with ≥5% incidence**

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

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

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



Journal of the American Heart Association

ORIGINAL RESEARCH

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

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

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

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

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

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

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

*A complete list of the SEQUOIA-HCM Investigators can be found in the appendix at the end of the article.
This manuscript was sent to Sakima A. Smith, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.035993
For Sources of Funding and Disclosures, see page 12.



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

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



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

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


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

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

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

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

Integrated Safety Analysis to reflect real world clinical application.

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

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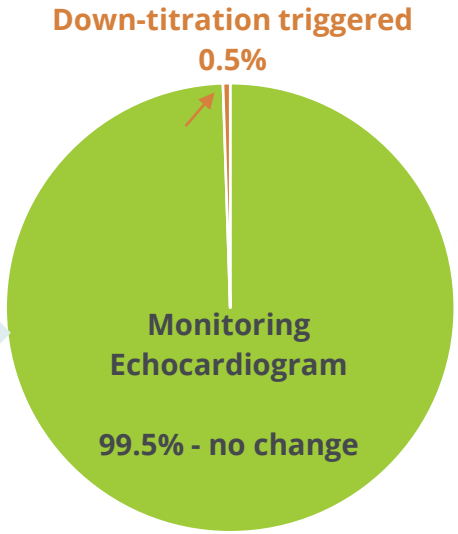
# Few Dose Reductions During Maintenance

## Dose Titration Phase

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

## Maintenance Phase

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




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

** As of Sept 15, 2023.*

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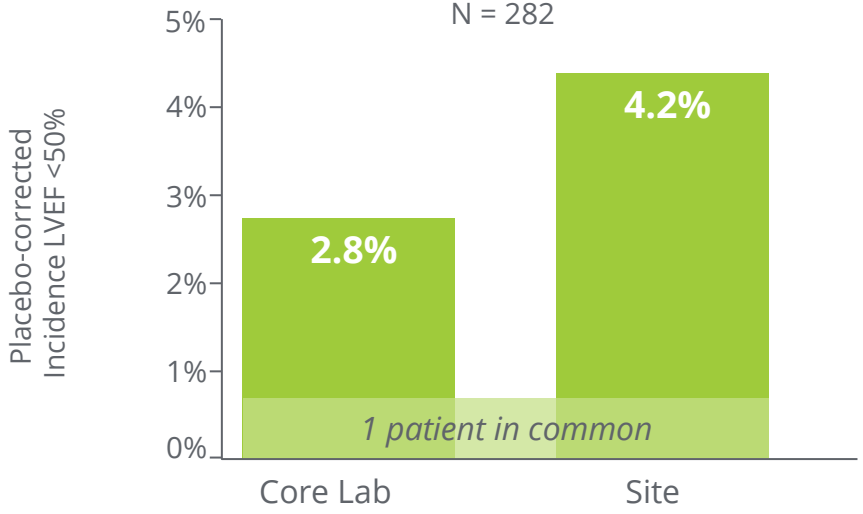
# Implementation of Dosing in Real-World Setting (FOREST-HCM)

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

SEQUOIA HCM

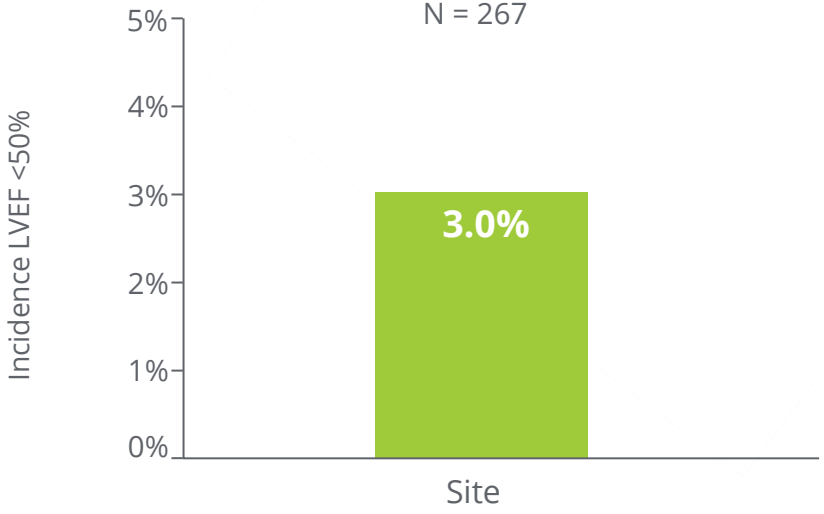
N = 282




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

FOREST HCM

N = 267




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

*SEQUOIA-HCM Source: Coats CJ. Dosing and Safety Profile of Aficamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy. ESC Heart Failure 2024.*
*FOREST-HCM Source: Data on file – data cut 15 Apr 24*

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*AFICAMTEN*: DEVELOPMENT PROGRAM

**TOPIC 2**

# Emerging Safety Profile

**Discussion**

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*AFICAMTEN*: DEVELOPMENT PROGRAM

**TOPIC 3**

# Symptom Improvement & Biomarkers

**Daniel Jacoby, M.D.**
Executive Medical Director, Clinical Research Cardiovascular

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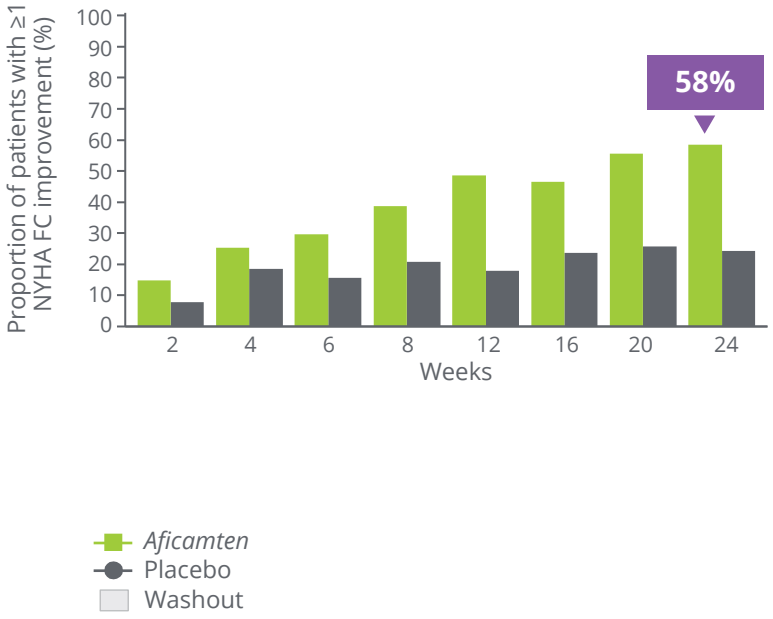
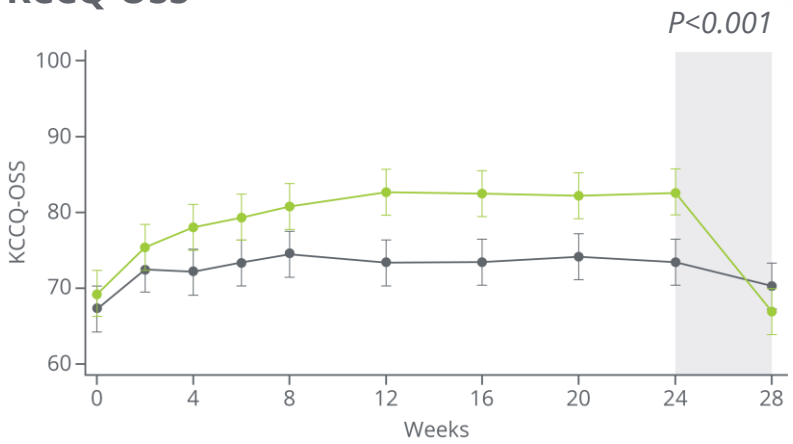
# Secondary & Exploratory Endpoints

## Significant improvement in patient symptom burden and quality of life

### ≥1 NYHA FC Improvement[1]



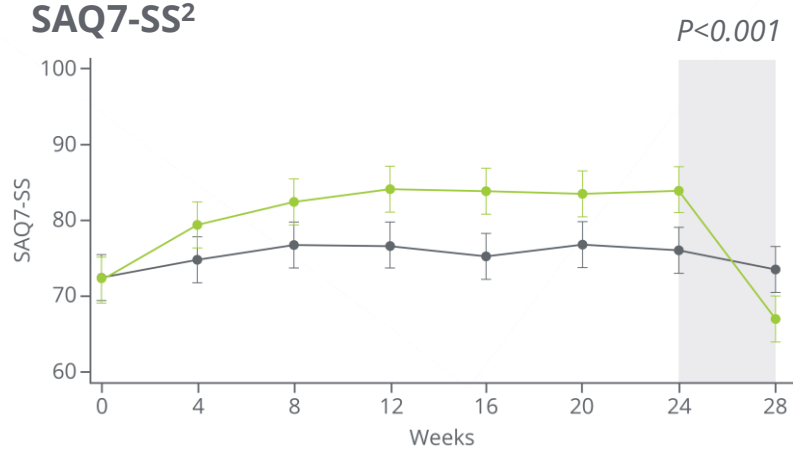

### KCCQ-OSS[2]




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

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

### SAQ7-SS[2]




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

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


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

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# Responder Analysis

## Significant improvement in exercise capacity and symptoms in composite responder endpoint

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

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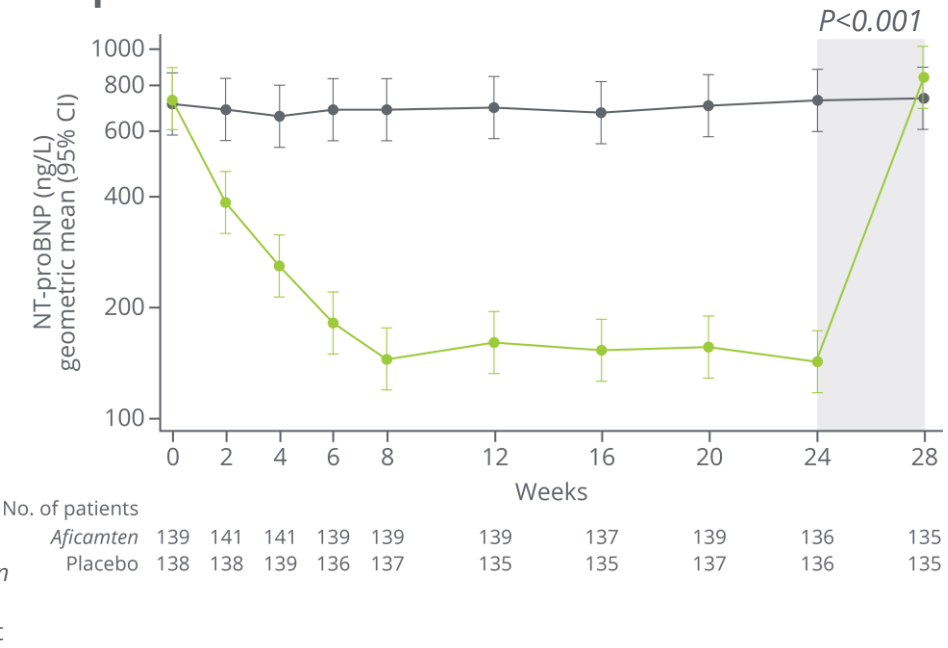
# Improvement in Biomarkers

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

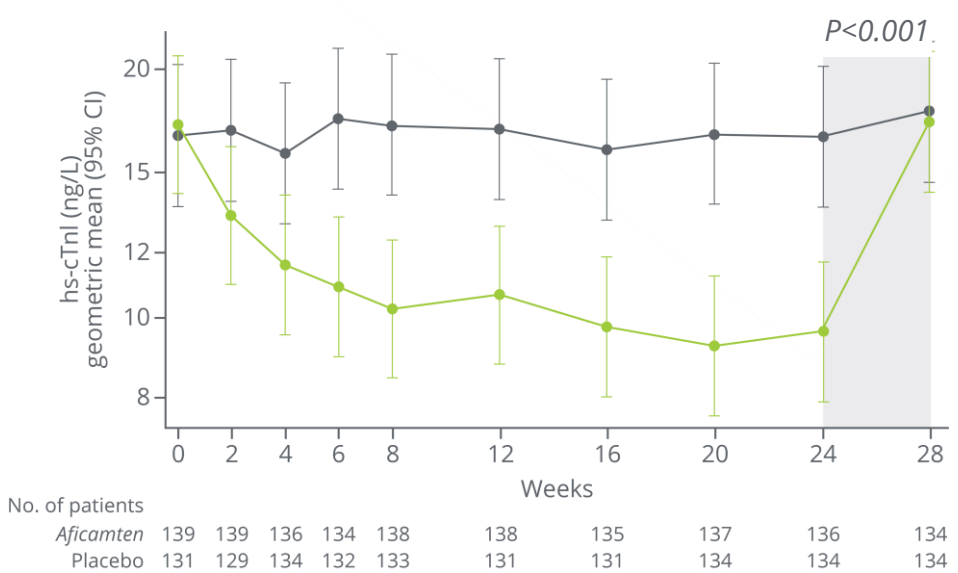
Treatment with *aficamten* led to **80% reduction from baseline to week 24**

### NT-proBNP




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

### hs-CTnI




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

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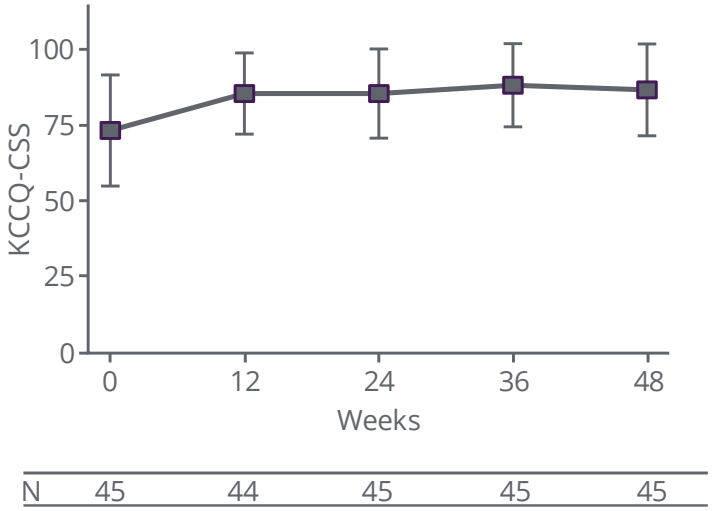
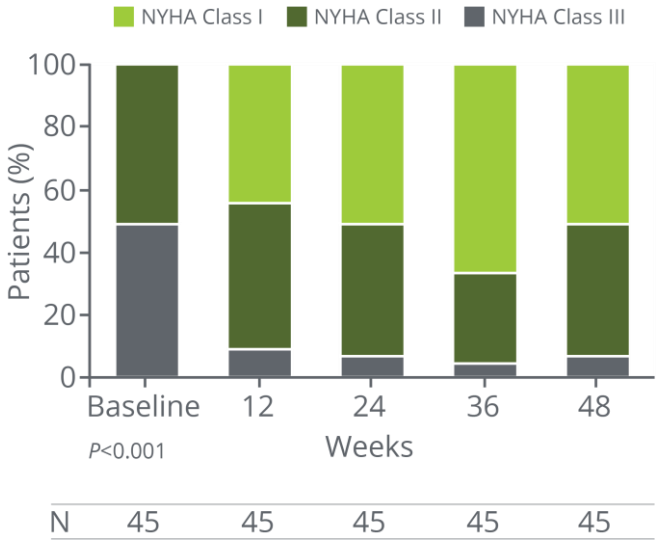
# Open-Label: Potential Improvement in Symptoms, Biomarkers

## KCCQ-CSS[1]



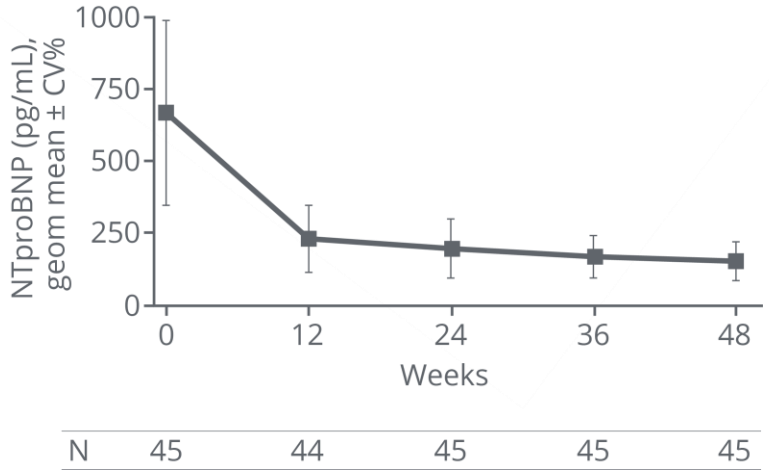

**71% of patients had ≥ 5-point increase**
**30% of patients had ≥ 10-point increase**

## NYHA Class[2]




**82% of patients** experienced
≥1 NYHA class improvement

## NT-proBNP[2]




**NT-proBNP decreased by 63%**
from baseline to Week 48

***FOREST-HCM is an ongoing open-label extension clinical trial. Data represent the most recent publicly available interim data.***


*1. Masri A, et al. Aficamten in Patients with Obstructive Hypertrophic Cardiomyopathy: An Integrated Safety Analysis . ESC 2024.*
*2. Saberi S, et al. "Efficacy and Safety of Aficamten in the First Cohort of Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy Completing 48-Week Follow-up: Findings From FOREST-HCM". ACC.24.*

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*AFICAMTEN*: DEVELOPMENT PROGRAM

**TOPIC 3**

# Symptom Improvement & Biomarkers

## Discussion

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# *Aficamten*: Global Launch Preparations

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*AFICAMTEN*: GLOBAL LAUNCH PREPARATIONS

# *Aficamten*: Medical Affairs

**Daniel Kates, M.D., M.B.A.**
SVP, Medical Affairs

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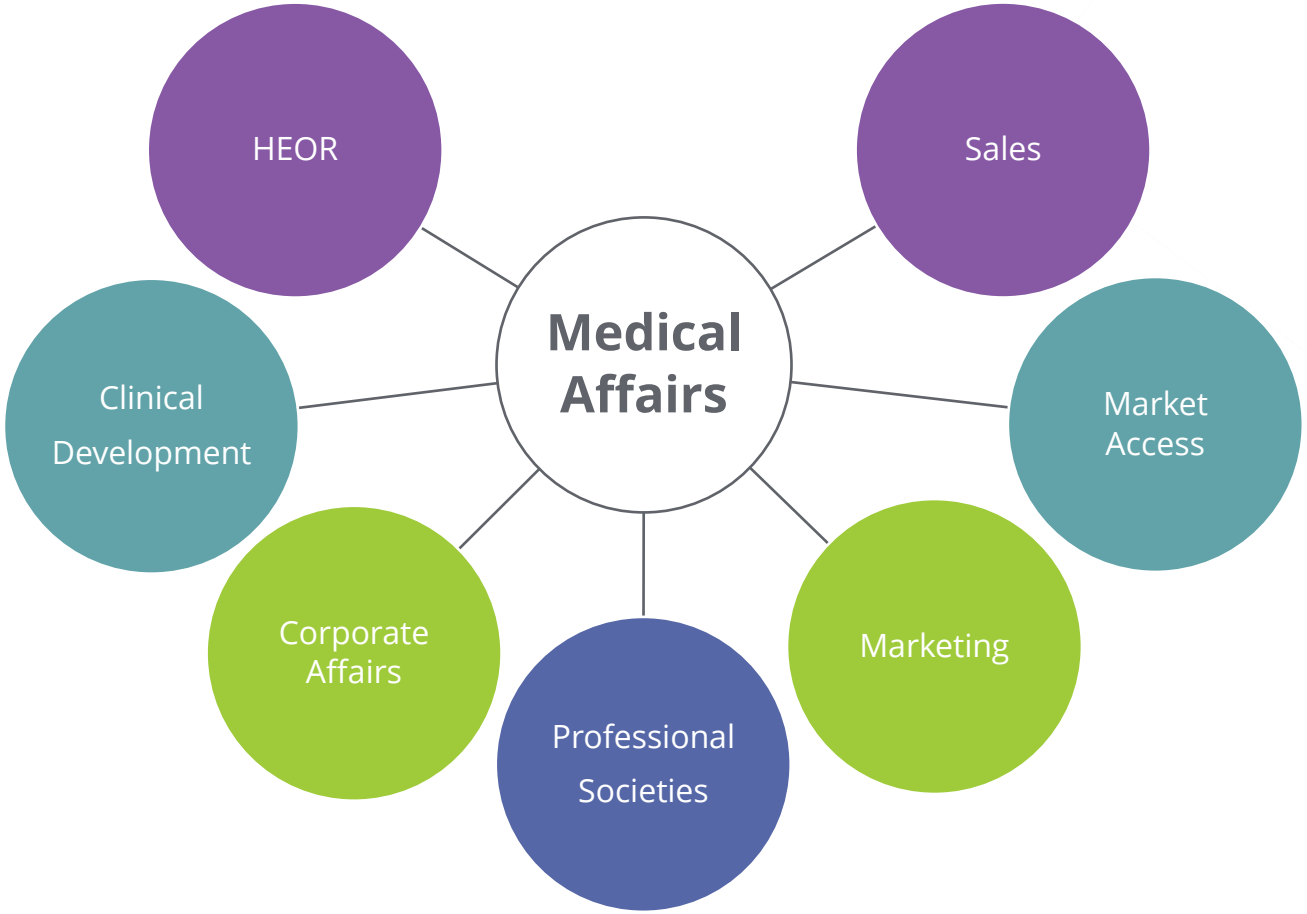
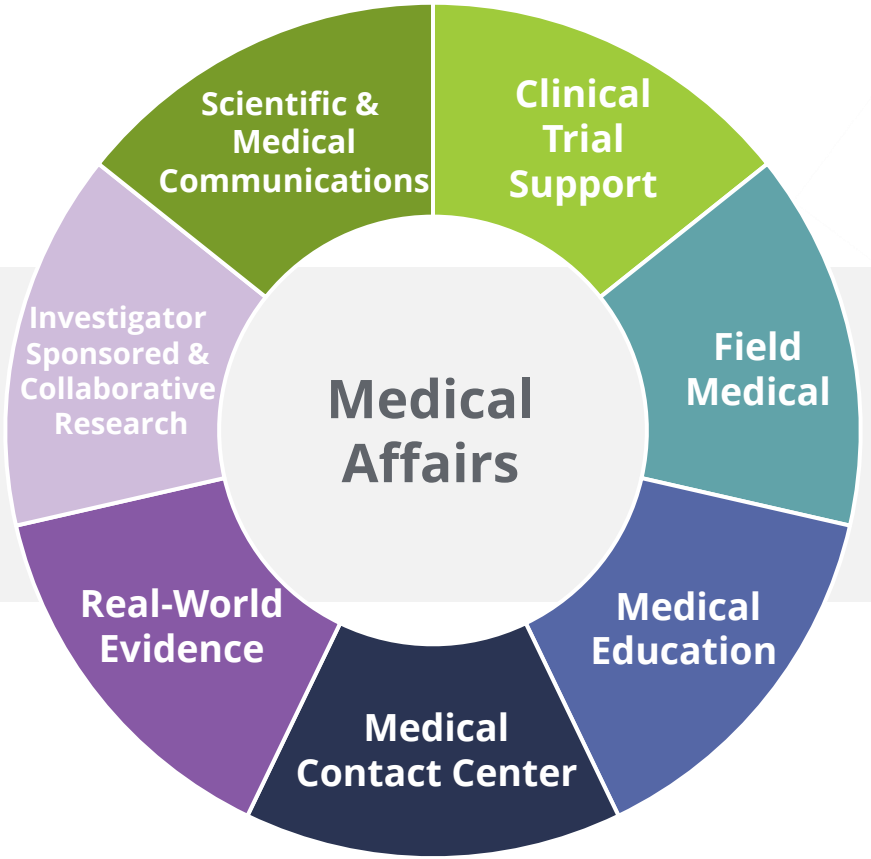
# Medical Affairs: Bridging Gaps



# Medical Affairs: A Key Connection with the Scientific & HCP Community



# Medical Affairs with Global Presence

## Team members covering North America & Europe

### Our US Therapeutic Medical Science Liaisons are Highly Specialized in CV and Deeply Experienced

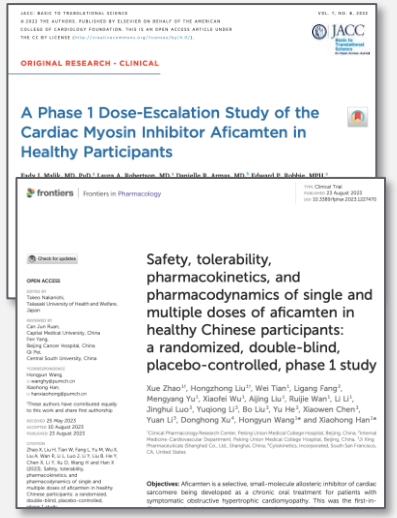
Dedicated CV MSL team focused on physicians, scientists and medical providers

### Our US Managed Healthcare Medical Science Liaisons Have Collectively Supported 58 Drug Launches

Dedicated US Managed Healthcare MSL team focused on educating payer clinical decision-makers

# Substantial and Growing Publication Output

## Phase 1



A Phase 1 Dose-Escalation Study of the Cardiac Myosin Inhibitor Aficamten in Healthy Participants

Safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of aficamten in healthy Chinese participants: a randomized, double-blind, placebo-controlled, phase 1 study

## Phase 2

REDWOOD HCM

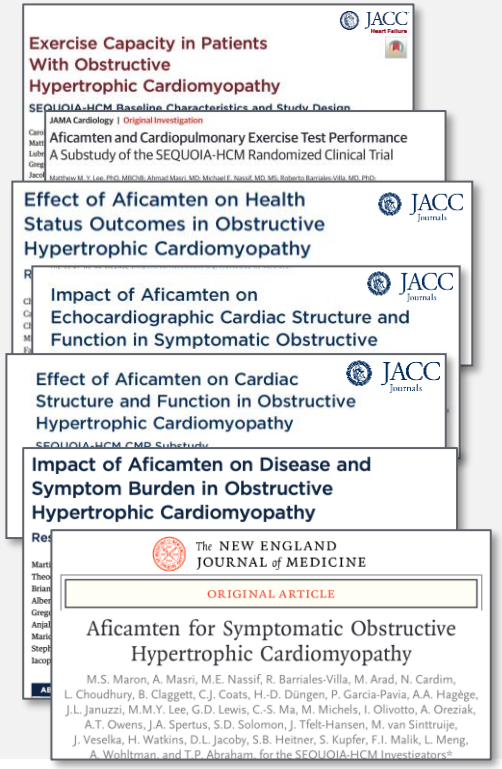
Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy

Aficamten for Drug-Refractory Severe Obstructive Hypertrophic Cardiomyopathy in Patients Receiving Disopyramide: REDWOOD-HCM Cohort 3

Efficacy and Safety of Aficamten in Symptomatic Nonobstructive Hypertrophic Cardiomyopathy: Results From the REDWOOD-HCM Trial, Cohort 4

## Phase 3

SEQUOIA HCM



Exercise Capacity in Patients With Obstructive Hypertrophic Cardiomyopathy

Aficamten and Cardiopulmonary Exercise Test Performance
A Substudy of the SEQUOIA-HCM Randomized Clinical Trial

Effect of Aficamten on Health Status Outcomes in Obstructive Hypertrophic Cardiomyopathy

Impact of Aficamten on Echocardiographic Cardiac Structure and Function in Symptomatic Obstructive

Effect of Aficamten on Cardiac Structure and Function in Obstructive Hypertrophic Cardiomyopathy

Impact of Aficamten on Disease and Symptom Burden in Obstructive Hypertrophic Cardiomyopathy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

FOREST HCM

Safety and efficacy of aficamten in patients with non-obstructive hypertrophic cardiomyopathy: A 36-week analysis from FOREST-HCM

MAPLE HCM

*Anticipated 2025*

*Not an exhaustive list of publications*

# Medical Affairs Plays a Key Role in Supporting Independent CME


*CME = Continuing Medical Education*

# Leading the Way to Elevate HCM

## Supported creation of first HCM dedicated medical society


***HCM Society Mission Statement:*** *HCMS exists to bring together an innovative and productive community of physicians, scientists and medical providers dedicated to improving the diagnosis and treatment of people with hypertrophic cardiomyopathy through clinical excellence, research and education.*

*Source: https://hcmsociety.org/*

# Driving Continued Evidence Generation

*AFICAMTEN*: GLOBAL LAUNCH PREPARATIONS

# Building a Specialty Cardiology Company Anchored on *Aficamten*

**Andrew Callos**
EVP, Chief Commercial Officer

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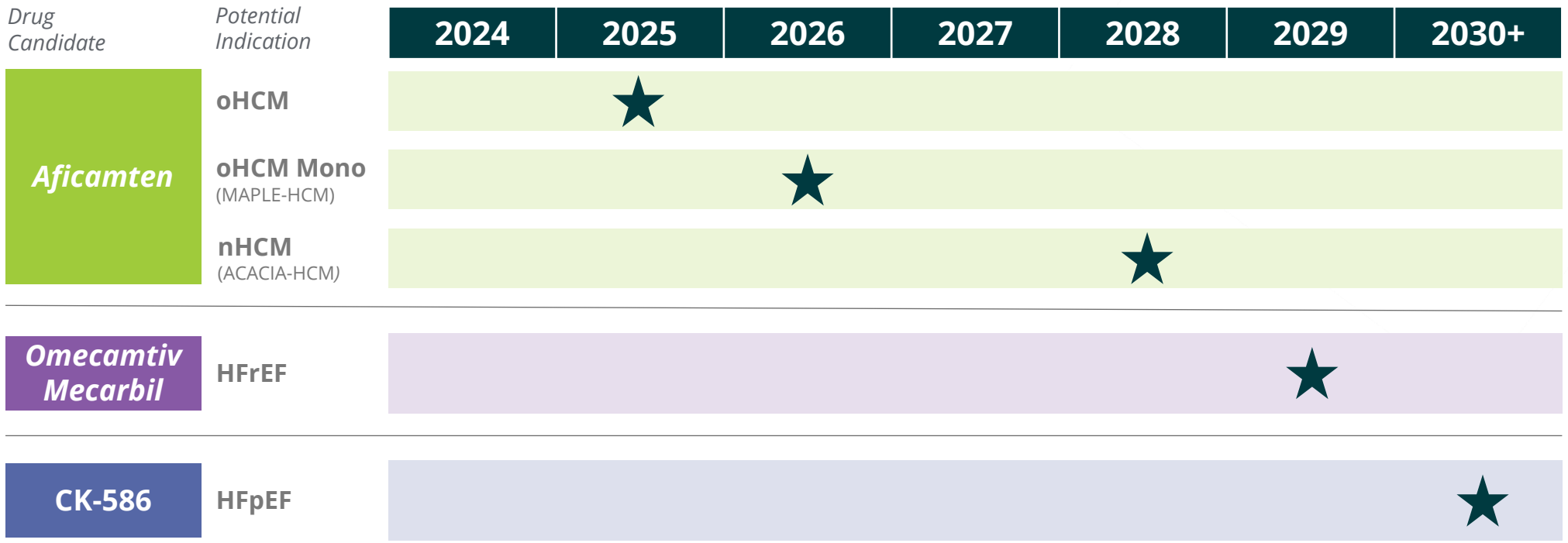
# Potential for Multiple Specialty Cardiology Launches




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

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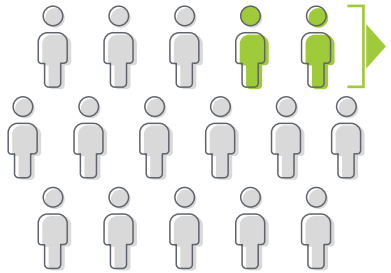
# Specialty Cardiology Business Has Potential for High ROI

## Concentrated Prescribers

~80K cardiologist/PCPs treat CV diseases

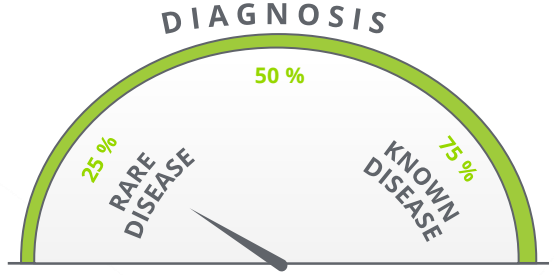


**~10K**

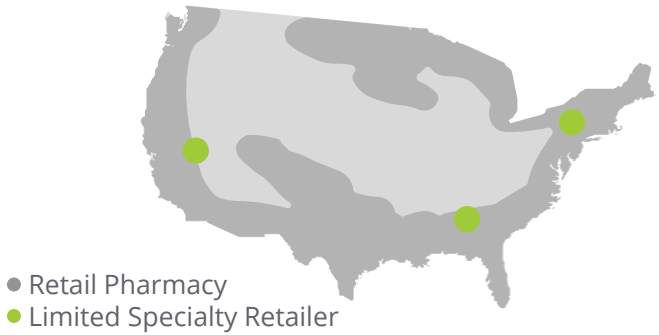
**cardiologists treat ~80% HCM**

## Higher Revenue Per Prescriber

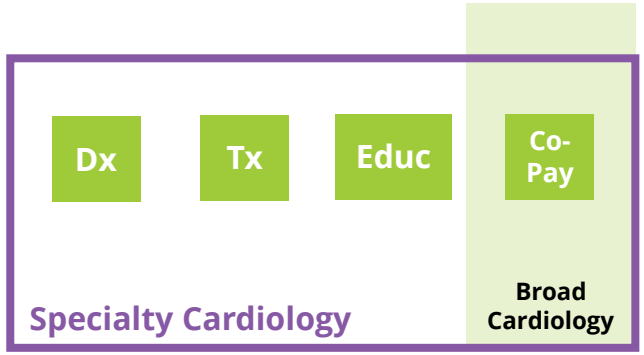

## Opportunity To Grow Market Through Diagnosis




## Distribution Limited to Specialty Retailers




## Differentiated Patient Experience




## Path to Reimbursement


**Broad Cardiology**

**High Rebates**

**Winners/loser**

**Specialty Cardiology**

Access to Label

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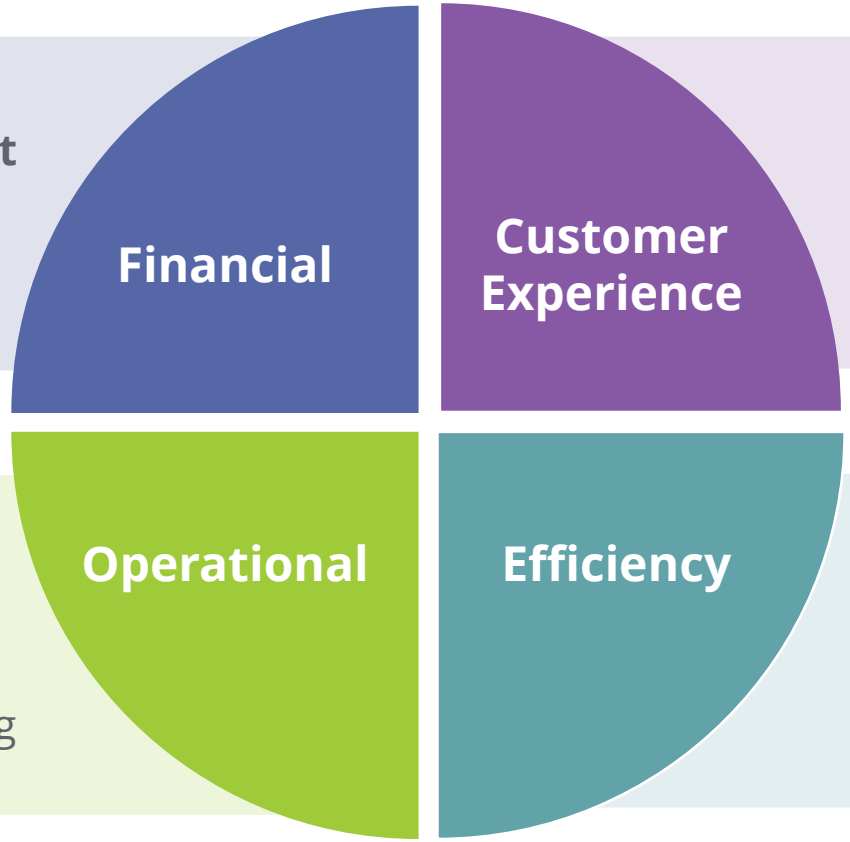
# Potential Benefits of a Specialty Cardiology Franchise

- Significant **FTE cost savings**
- **Reduced operational support** teams, IT systems & analytics
- **Efficiency** in sales training, meetings




- **1:1** customer – rep relationship
- **Single point of contact** for HCP & office staff enables **improved access & focus**

- **Flexibility** in team structure based on local market needs
- **No** multiple representative coordination concerns
- **Simplified IC**, CRM & reporting
- Single point of **accountability**

- **Multiple products** can be discussed on every call
- "Low value" targets for one product can be replaced with "high value" targets from other products

# Commercial Leadership Team Experience

## Our Collective Experience

- Average of **28+ Years** of experience
- Mix of Big Pharma and Biotech experiences
- **~50** product launches across the US and EU









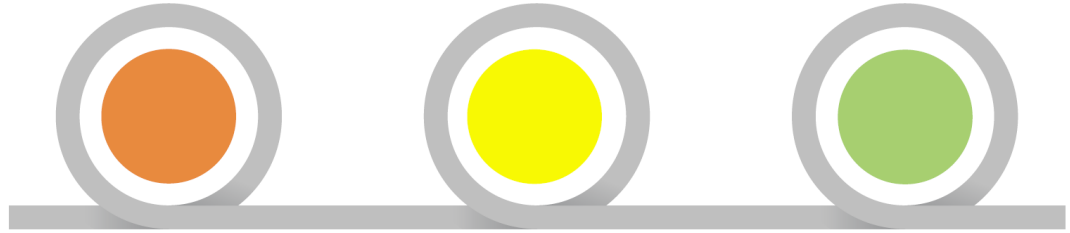

# Comprehensive Program Management Launch Readiness

## Tracking launch workstreams, risk mitigation and overall launch readiness across functions

*Definition of Risk / Issue Ranking*

**The Launch Scorecard Highlights Issues / Risks According to Three Levels**

*Scoring our status provides transparency on areas that need attention, help enable prioritization of resources, proactive management and ensures issues/risks are addressed promptly while minimizing potential impacts*



| High | Medium | Low |
|---|---|---|
| *Issues / risks identified, with mitigating actions identified but not activated or no mitigating actions identified* | *Issues / risks identified, with active implementation of mitigation steps* | *No issues / risks identified* |

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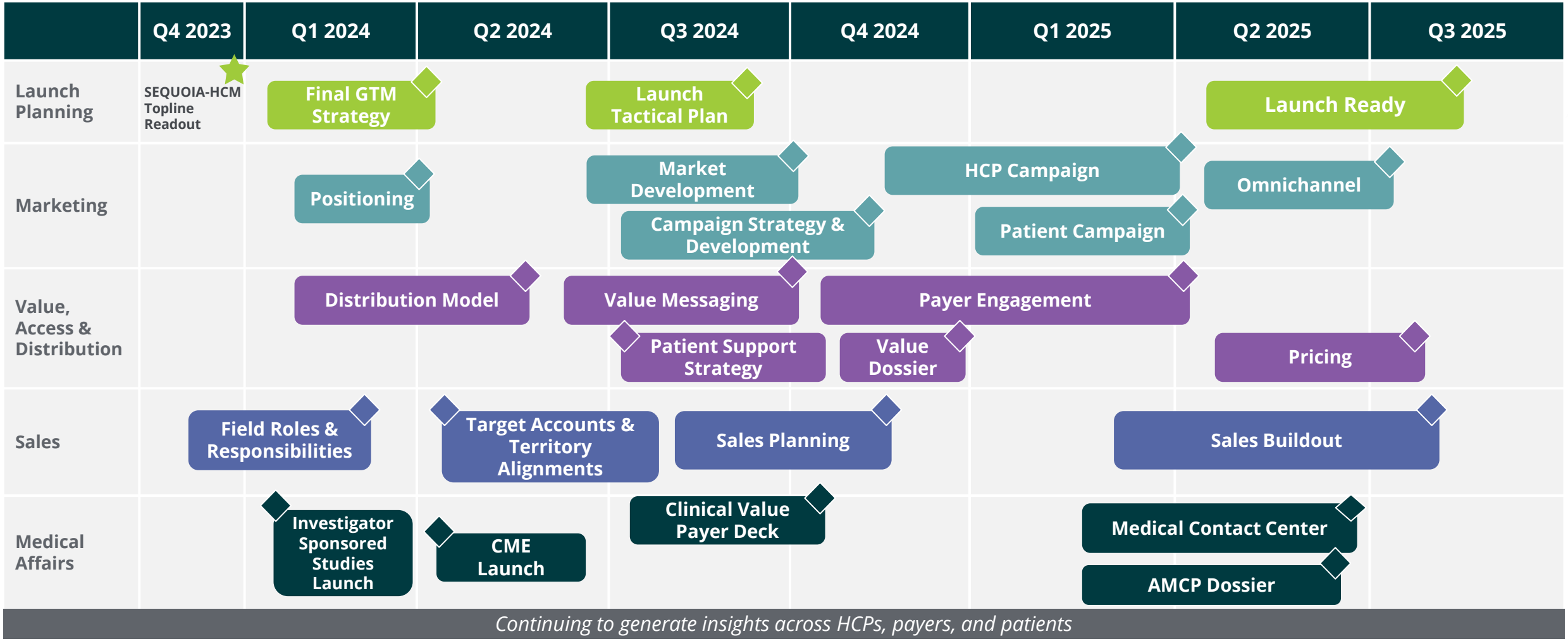
# US Launch Milestones – *Aficamten* (2024-2025)

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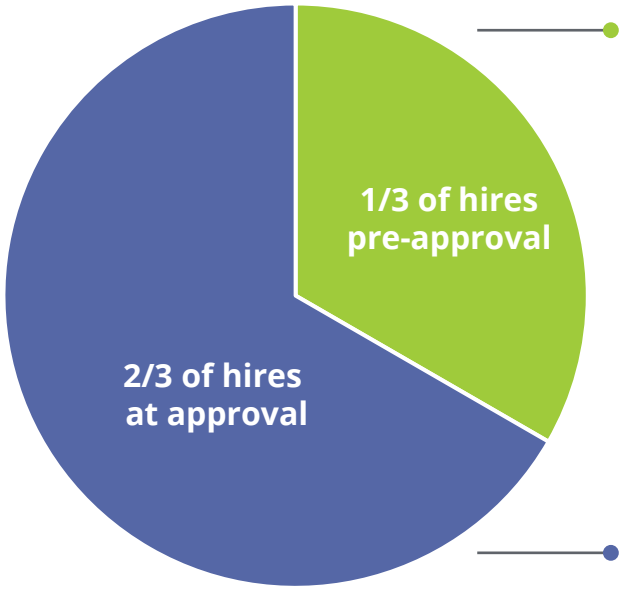
# Gated Build of Commercial Infrastructure

## Sales representative hiring to occur in proximity to approval

### 2/3 of hiring to occur at-approval




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

Sales representatives

### Activities initiated upon key de-risking events

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

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

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

# Highly Experienced Customer Facing Teams

**Payer account teams & sales leadership have extensive customer relationships & CV experience**

## Our Payer Account Leaders

- Average of **30+ Years** of experience per Account Director
- Collective **~300 years** of payer/PBM relationship experience
- **~250** product launches supported including **~100** CV products
- **100%** of top tier National and Regional payers and PBMs engaged in 2024

McKESSON
Anthem Blue Cross
OPTUM
UnitedHealthcare
CVS Health
Cigna
KAISER PERMANENTE
EXPRESS SCRIPTS
Humana
Walgreens
Medimpact Healthcare Systems

## Our Sales Leaders

- Average of ***22 years*** in industry
- Average of ***13 years*** in leadership
- Average of ***14 years*** in cardiovascular therapeutics
- ***100%*** have launch experience

# oHCM: Market Opportunity

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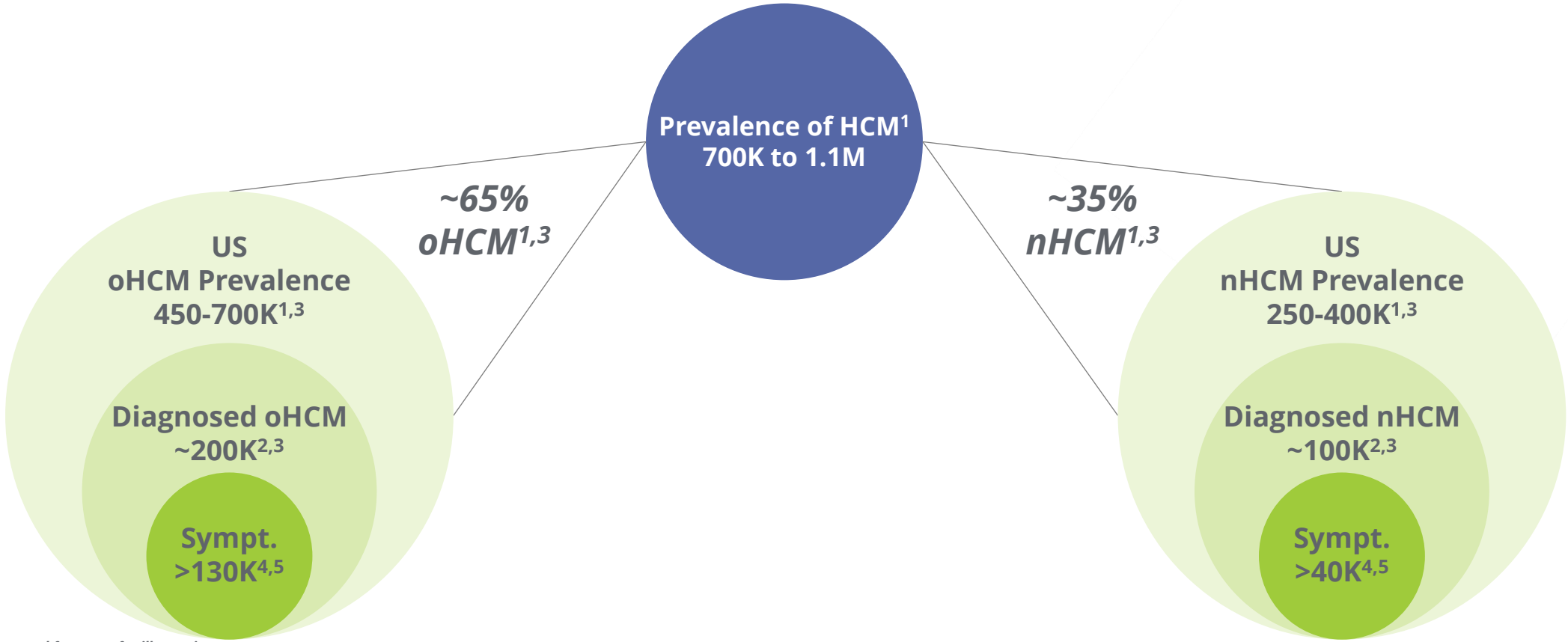
# Opportunity for CMIs in Diagnosed, Symptomatic HCM Patients




***Projections and forecasts for illustration.***

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

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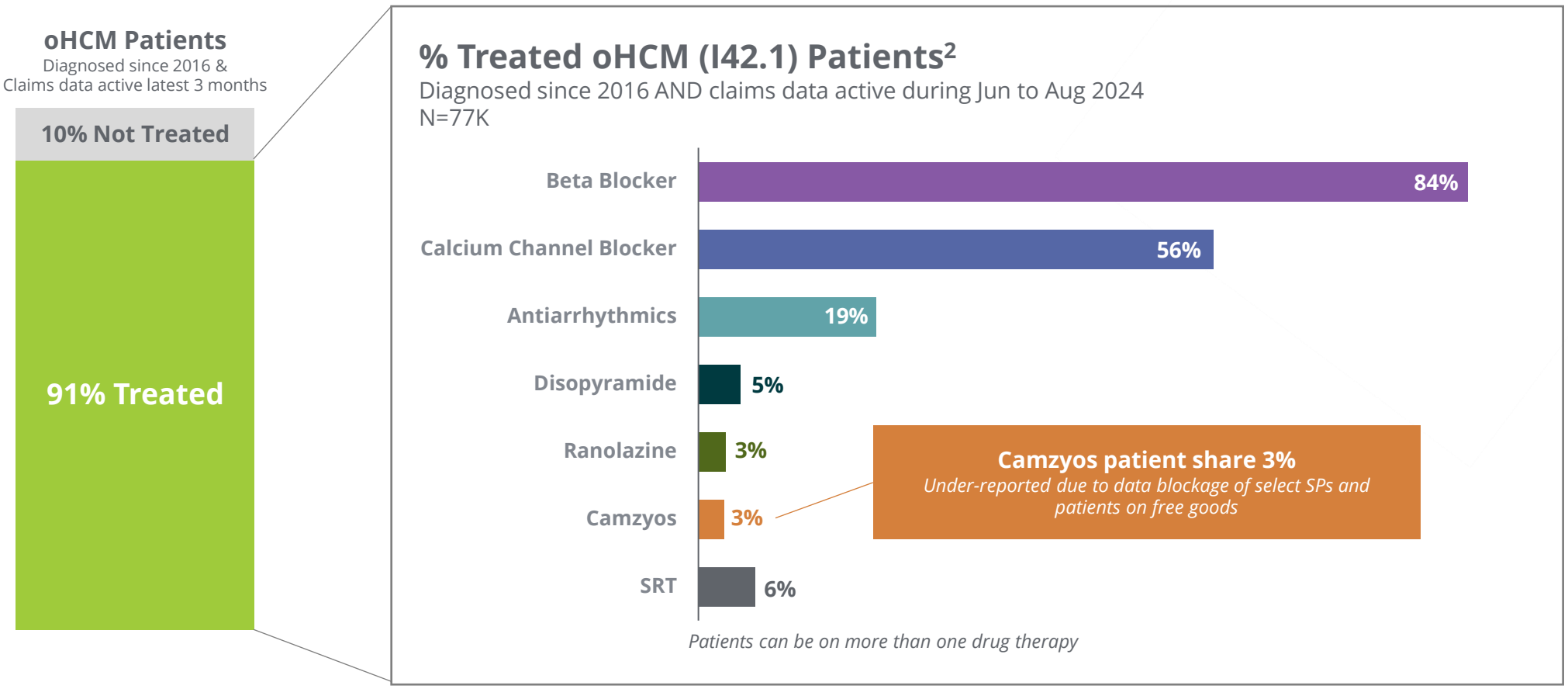
# oHCM: 91% of Diagnosed Patients are Treated, Many Not Well-Controlled[1]




*Source: Symphony PTD (Patient Transaction Data) to August 2024*
*ICD-10 code for oHCM is I42.1 (patients diagnosed since 2016 and active in claims data universe during the most recent 3 months)*

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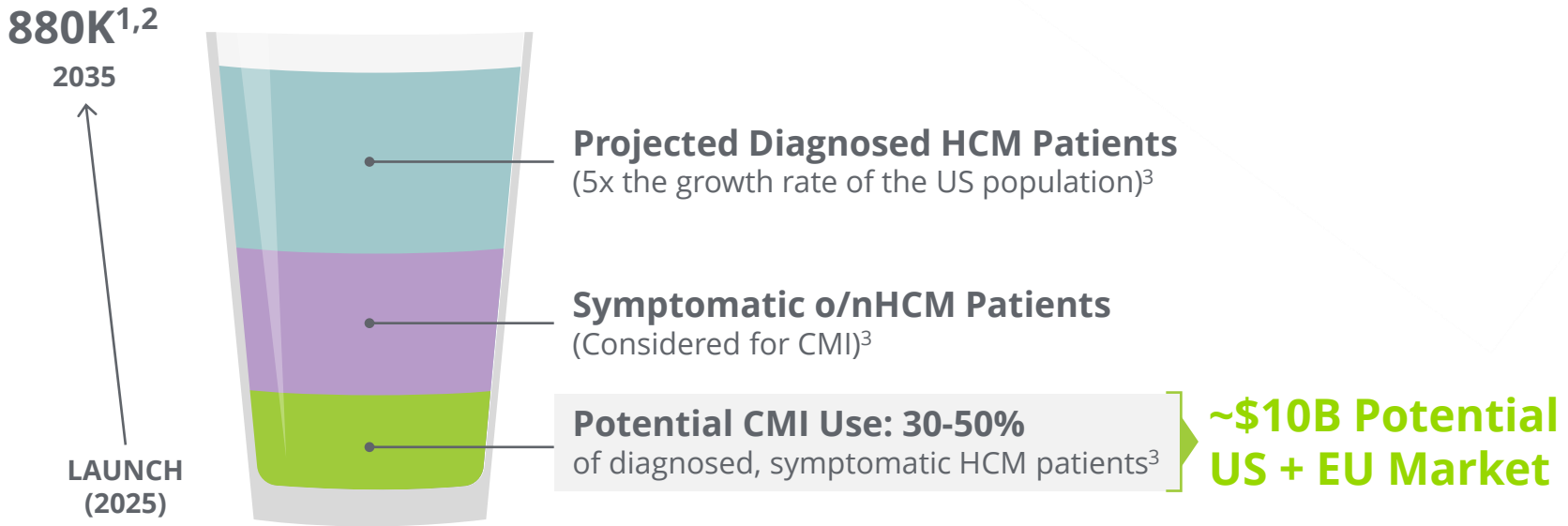
# $10B Potential Market of CMI-Eligible Patients, Majority Expected to be Available at Launch, if *Aficamten* is Approved

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

### US and EU HCM Patients in 2035

*Illustrative*




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

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*AFICAMTEN*: GLOBAL LAUNCH PREPARATIONS

# Elevating the *Aficamten* Brand Experience

**John Jacoppi**
VP, US Marketing for *Aficamten*

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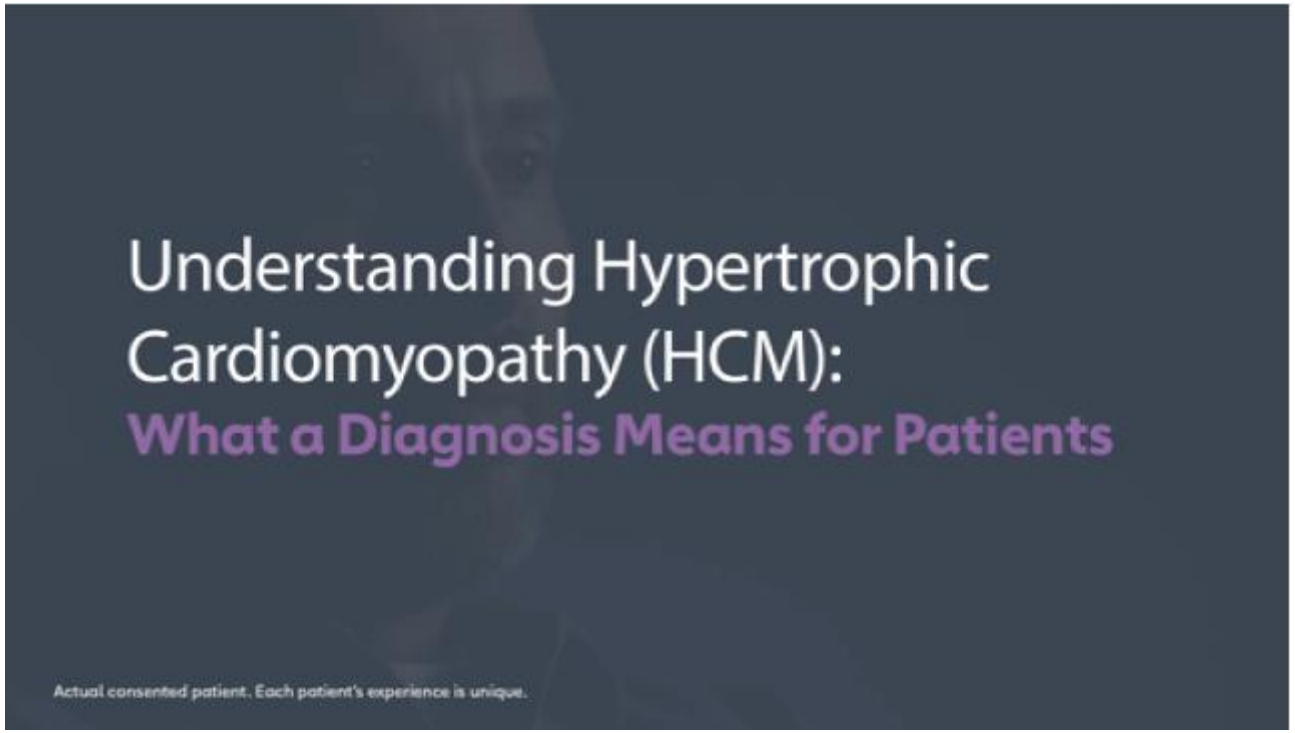
# Grounding Ourselves in the Patient Perspective




*Video unavailable*

# Our Brand Vision for *Aficamten*

## *Aficamten* exists to…

**elevate the standard of care** in HCM

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

# Our Commercial Path

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

**Our 2023 Focus** → **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)
- An optimal profile of *aficamten* is confirmed through SEQUOIA-HCM allowing us to **finalize go-to-market approach**, including designing an optimal customer experience across stakeholders

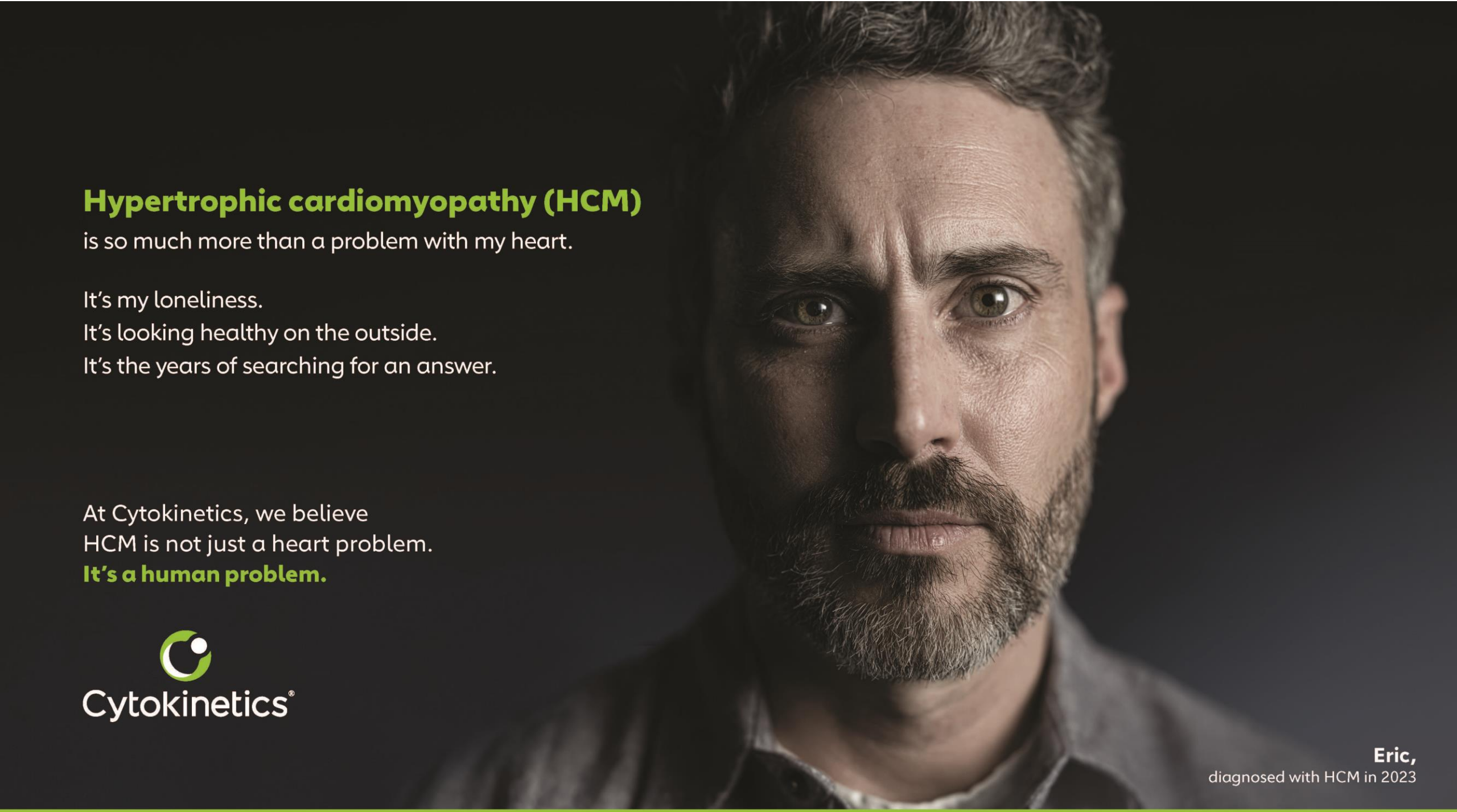
# Customer & Marketplace Insights Inform Strategy

| CMI Market & Share Growth | Significant Unmet Needs for HCPs | Patient Unmet Needs | Timing is Opportune |
|---|---|---|---|
| Demand study **confirmed market potential of *aficamten*** and showed the introduction of *aficamten* **grows the CMI market** | Multiple studies showed **burden associated with existing treatments** can force HCPs to make choices about which patients are selected for treatment | Patient research shows there is **still a significant unmet need**; SOC leaves many patients unable to fully live their lives as oHCM impacts them physically, socially, emotionally, and financially | **Positive impressions CMI class** and growing familiarity<br><br>Benefit from **increasing awareness of oHCM** |

# Unveiling Market Development Campaign

## HCP Campaign Objective

To **increase understanding of the personal burden of HCM** for patients, clinicians, and healthcare systems, and encourage HCPs to discover both the science and humanistic approach of Cytokinetics, and **how that translates to a whole-person care experience**


Hypertrophic cardiomyopathy (HCM)
is so much more than a problem with my heart.
It's my loneliness.
It's looking healthy on the outside.
It's the years of searching for an answer.
At Cytokinetics, we believe
HCM is not just a heart problem.
It's a human problem.
Cytokinetics®
Eric,
diagnosed with HCM in 2023

# Campaign Roll-Out via Seamless Digital Ecosystem

**HCP Portal**
(Medscape)

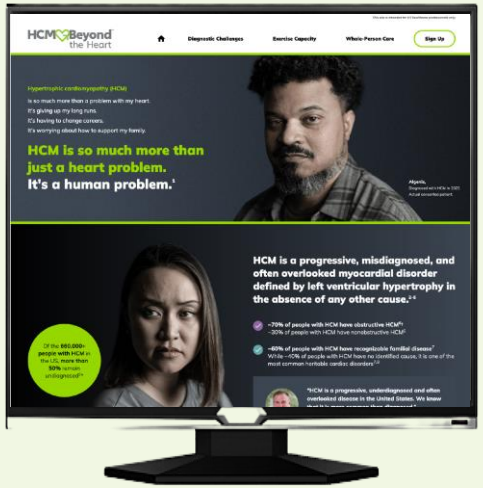
**Paid Social**
(Facebook)

**Paid Search**


**Programmatic/Digital Journals**
(Cleveland Clinic Journal of Medicine, CathLab Digest, Journal of Invasive Cardiology)


**Congress**
(HFSA, HCM Society, HCM8)

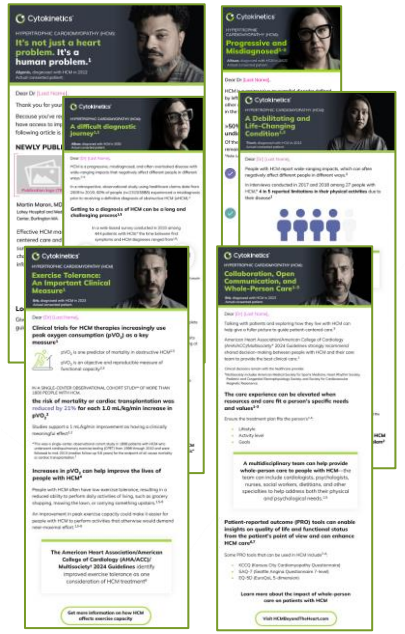
**HCP Market Development Website**
HCMBeyondTheHeart.com/hcp




Fresh on-site content & continued engagement opportunities will help to fill the funnel

**CRM Registration**

**Video Content**



*AFICAMTEN*: GLOBAL LAUNCH PREPARATIONS

# Planned Sales Strategy

**Jeff Lotz**
VP, US Sales & Operations

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# Initial HCM Customer Universe Includes ~10K HCPs

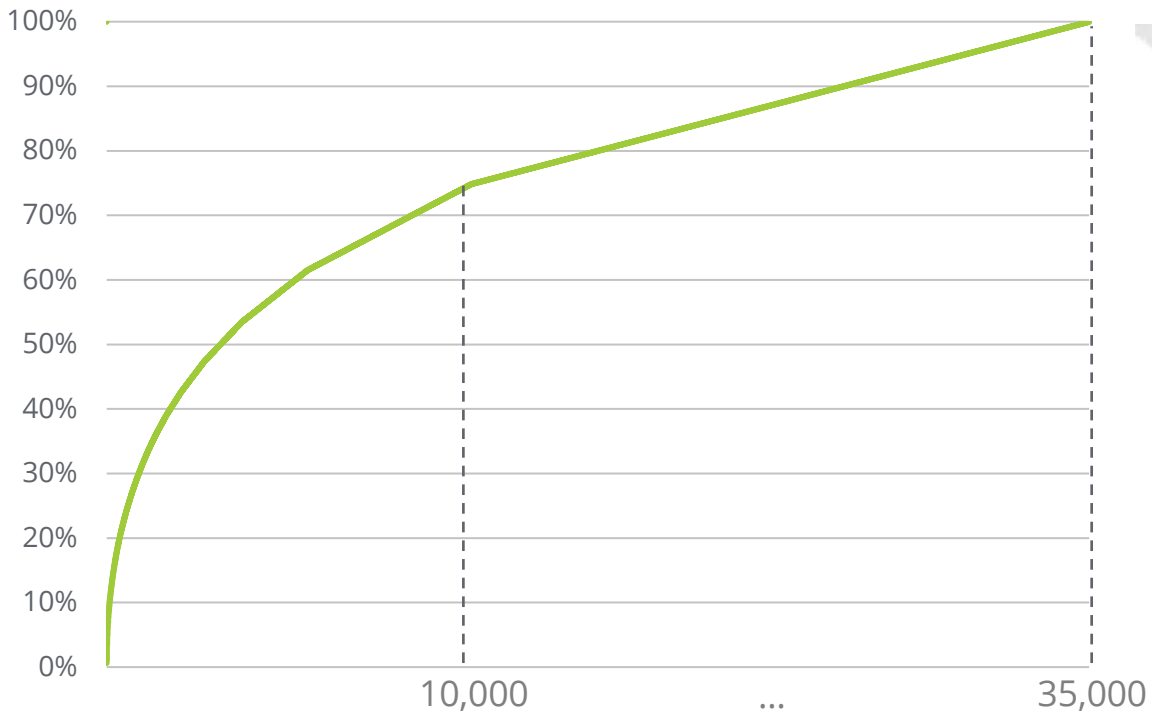
| | |
|---|---|
| **Current Understanding of Customer Universe** | **Initial lists of HCPs were defined based on:**<br>• Diagnosers<br>• Treaters<br>• HCM trial investigators/sites<br>• HCM CoEs/programs |
| **Initial Insights** | **~10K HCPs**<br>***represent ~75% of HCM patient volume*** |
| **Reps at Launch** | **~125-150 Cardiovascular Account Specialists** |

*Source: Sales Ops team analysis as of 2H 2022*

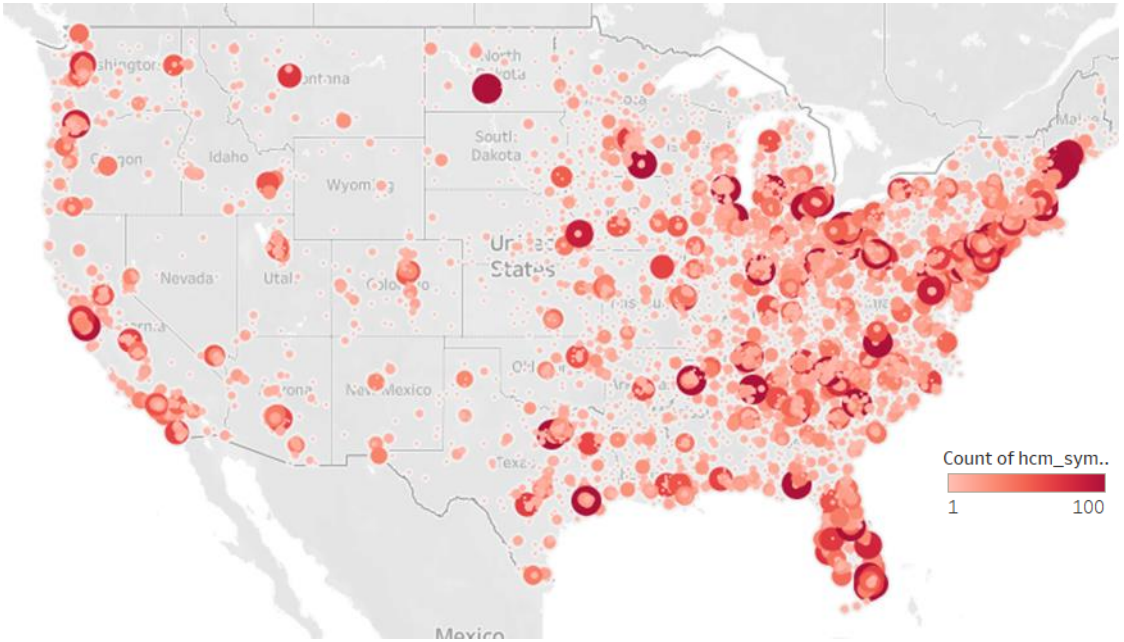
# Cardiologists Located in Concentrated Geographic Clusters Across the US

## 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
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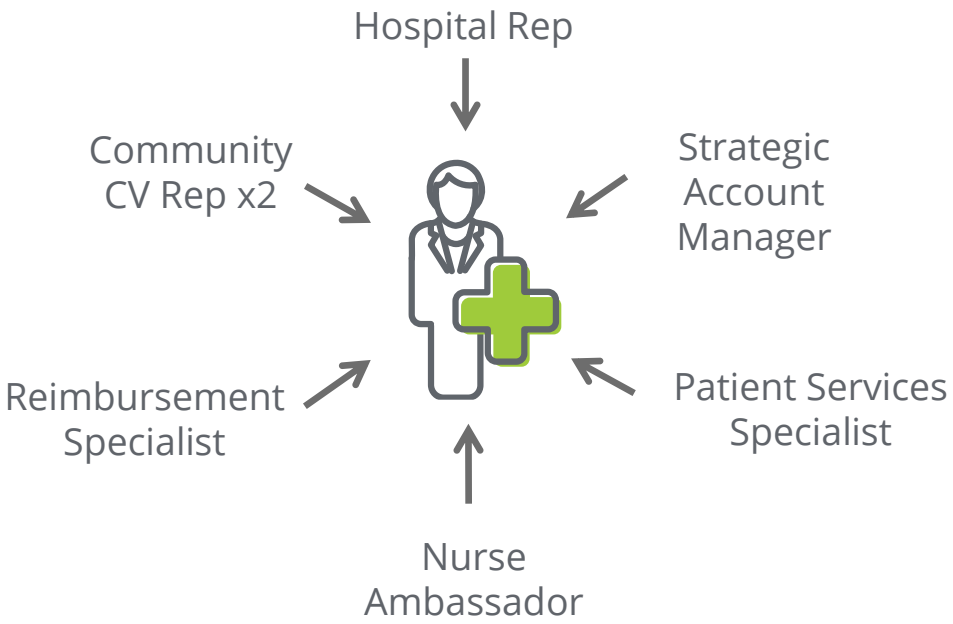
# U.S. Sales Team Designed Based on Efficiency & Customer Feedback

## Traditional Models

**Several functions with very focused roles**

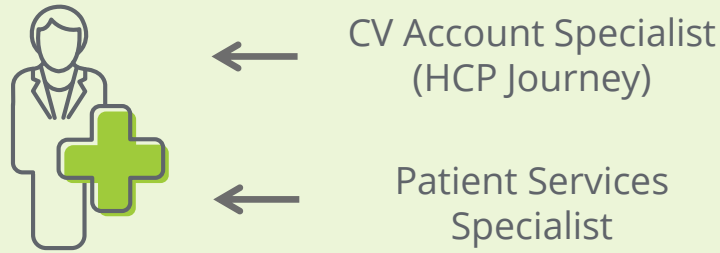
**Overwhelmed customers, "It's too much"**




## Our Design Principles

**Simple model creating quality experience**

**Hire team with deep experience in specialty**

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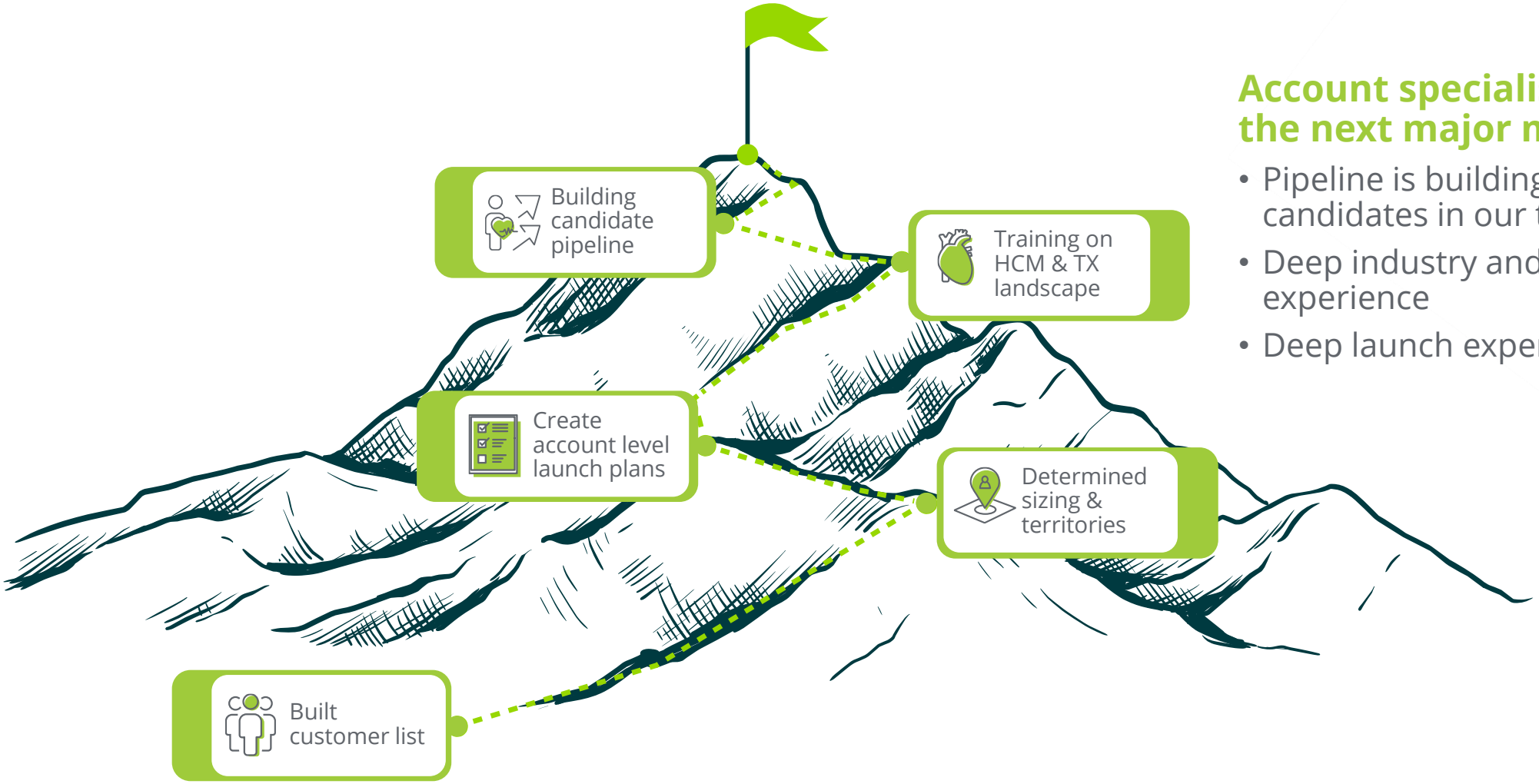
# U.S. Sales Leadership Team Preparing For Launch




## Account specialist recruiting is the next major milestone

- Pipeline is building, over 700 candidates in our talent database
- Deep industry and cardiovascular experience
- Deep launch experience

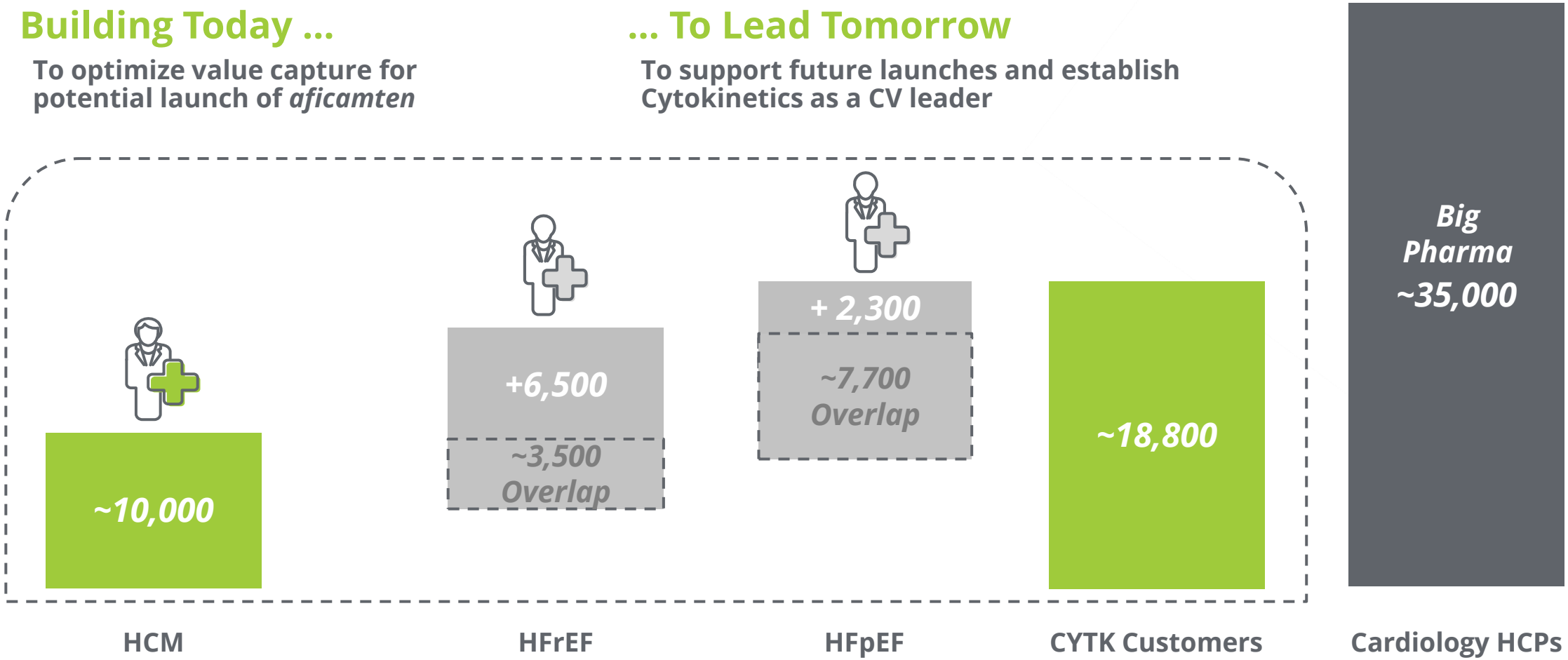
# Customer Coverage Evolves With Specialty Cardiology Franchise

## 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**



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# Creating a Differentiated Patient Experience

**Genie Dubuk**
VP, Customer Experience & Insights

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# Feedback from Nurse Advisors: CMI Treatment Journey Is Challenging

**REMS burden** is creating capacity issues and coordination challenges

"Coordinating REMS requirements in tight timelines is **challenging with so many variables**."

Holistic care of patient is **disjointed**

"Patients receive an **overwhelming number of calls** […]. It becomes overbearing and stressful, cutting into the patients' QoL and time."

**Pathway to access is confusing** and frustrating to patients and offices

"I'm **not an insurance expert** and I don't know where the patient is."

**Specialty Pharmacies are key** to timely dispensing of drug

"**Ability to coordinate better with SPs** would reduce the burden."

# Four Pillar Approach to Treatment Experience

| Patient-first | Brand Strategy Alignment | Differentiate with Purpose | Partnership |
|---|---|---|---|
| **Supporting patients** to ensure they are knowledgeable, confident and motivated to manage with oHCM treatment | **Be inclusive and approachable** in how we create a customer-centric experience | **Prioritize where we invest our resources** to differentiate from competition and innovate with purpose | **Build solutions and resources cross-functionally** and in partnership with our champions and advocates |

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# Building a Bespoke Treatment Experience

Landscape assessment to identify current trends coupled with primary and secondary insights to understand current challenges and barriers to treatment initiation

Detailed integrated CMI specific treatment experience build underway in collaboration with clinicians and patients

**Understand Challenges & Needs**

**Define Differentiators**

**Detailed Design Build**

**Test and Refine**

**Launch**

Workshops held with external stakeholders and clinicians to define critical needs and opportunities to address the specific needs of oHCM patients, caregivers and clinicians

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# Critical Success Factors

**Healthcare Provider Needs**

Minimize administrative burden of CMIs by **connecting all treatment and dispensing requirements**

**Patient Needs**

Disease and treatment education along with **integrated humanistic** experience **connecting all treatment and dispensing requirements**

**Business Objective**

Treatment experience **designed to provide differentiated elevated experience** that will increase fill rates by overcoming access, coverage and CMI specific logistical hurdles enabling **accelerated launch success**

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# Market Access

**Sunil Karnawat, Ph.D.**
VP, Global Value, Access & Distribution

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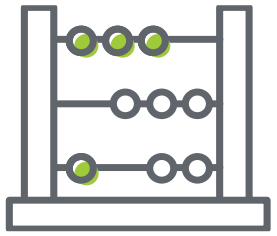
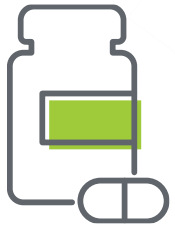
# Strategy in Place to Support Market Access at Launch



Payer value proposition strengthened with clinical & HEOR evidence

PIE engagements with key payer accounts



Channel & dispensing strategy designed to enhance patient experience

Patient support services will provide robust prior-authorization & medical exception support

*PIE: Pre-Approval Information Exchange*
*HEOR: Health Economics & Outcomes Research*

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# Payers Likely to Maintain Current CMI Management Approach for *Aficamten*

| | |
|---|---|
| **Awareness of oHCM Remains Low** | • Limited payer-directed messaging to date on current CMIs<br>• Low prevalence-driven budget impact suggests low payer management priority |
| **SEQUOIA-HCM Data Received Positively** | • pVO2 well-received as an objective clinical endpoint and predictor of clinical outcomes<br>• Clinical data for *aficamten* strengthens confidence in CMI for the potential treatment of oHCM |
| **Continued Interest in Engaging with Cytokinetics** | • Anticipate increased payer engagement with account teams after PDUFA date identified<br>• Interest in indirect treatment comparisons and evidence of disease modification |

*Sources: Competitive intelligence research conducted by LifeScience Dynamics, August 2024. Direct engagement of payers from the CYTK account teams*
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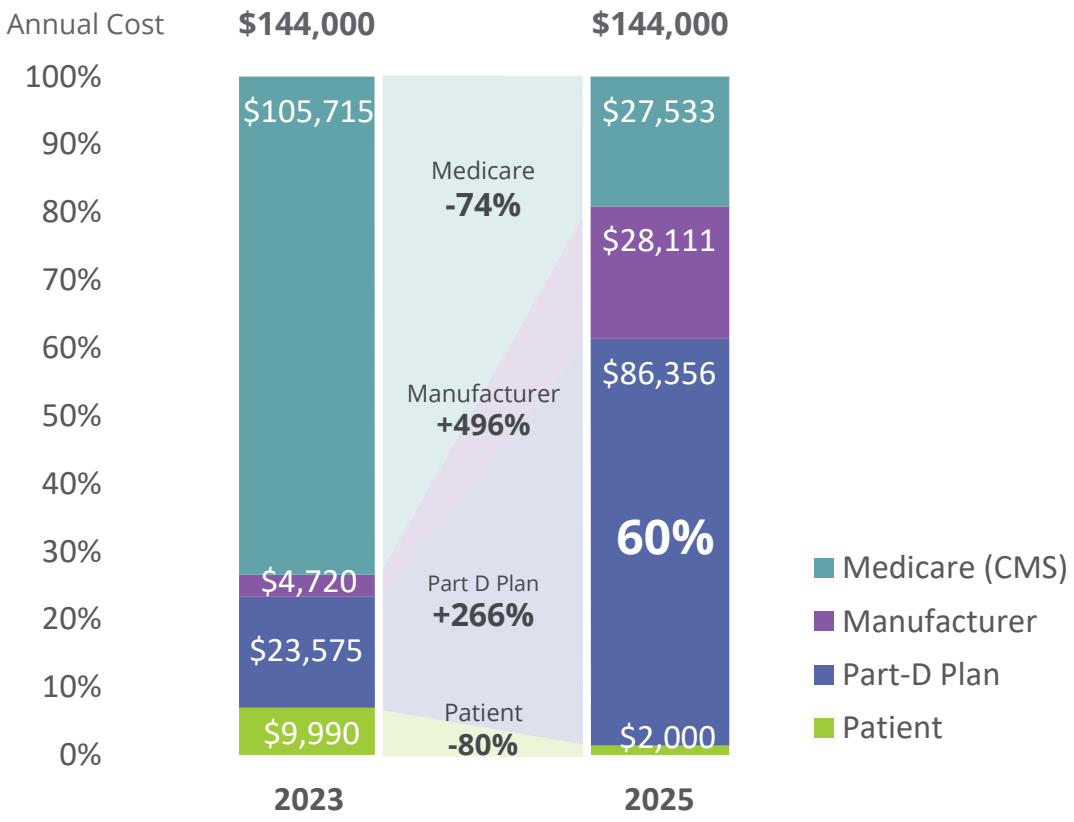
# IRA Part D Redesign Impacts Payers' Obligations in Medicare

## Cost Shifting for Specialty Drugs[1]




## Payer Survey: Impact of IRA[2]

### *Question*

*The IRA Part D benefit re-design has significantly shifted costs from CMS to Plan sponsors for 2025. What impact will this have on your design of specialty drug formularies?*

### *Answer*

*Respondents indicated **approaches to specialty drug coverage will change –** specialty drugs more likely to be available by **Medical Exception (ME)** process*

*1 AmeriSource Bergen presentation: "Inflation Reduction Act: So What's Next?" 05/02/23; calculations based on Xcenda analysis using 2022 Part D parameters in 2022 Medicare Trustees Report; analysis assumes $12,000/mo drug, 12 fills.*
*2 Rapid Payer Response (RPRTM) Survey Exploring Current US Payer Trends, Priorities and Environmental Changes (Fielded June 2024; N=18 payers)*

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# CMI Coverage Criteria Consistent with Label

## Anticipated prior authorization criteria not expected to impact prescribing

**Potential Prior Authorization Criteria**

- ☑ Diagnosis of oHCM
- ☑ NYHA II – III
- ☑ LVEF ≥ 55%
- ☑ Peak LVOT-G ≥ 50 mmHg[1]
- ☑ LVWT ≥ 15 mm or ≥ 13 mm[2]
- ☑ At least 18 years of age
- ☑ Prior use of other therapies[3]
- ☑ Cardiologist prescriber

**Key:** ☑ Very Frequent ☑ Less Frequent

Coverage criteria **based on potential label**

Prior authorization **likely has limited impact** on treating eligible CMI patients

Anticipated prior authorization & medical exception **approval rates are high**

*1 At rest or with provocation.*
*2 Individual with left ventricular hypertrophy has maximal LVWT ≥ 15 mm OR has familial HCM with a maximal LVWT ≥ 13 mm.*
*3 Non-vasodilating beta blocker (e.g., atenolol, metoprolol, bisoprolol); Non-dihydropyridine calcium channel blocker (e.g., verapamil, diltiazem); Disopyramide; 4 N=9 Medicare payers include N=2 PBM, N=1 National MCO, N=3 Regional MCO, N=3 IDN. BB: Beta Blocker; CCB: Calcium Channel Blocker; HF: Heart failure; LVEF: Left Ventricular Ejection Fraction; LVOTG: Left Ventricular Outflow Tract Gradient; LVWT: Left Ventricular Wall Thickness; ME: Medical Exception Only; NC: Not Covered; NYHA: New York Heart Association; PA: Prior Authorization. Source: Primary Research Interviews; ClearView Analysis, Internal Validation*

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# Support Payer/HTA Assessments Through Evidence Generation/Publications

**Prognostic Models**

Utilizing pVO2 and LVOT as key predictors of outcomes

**NYHA Outcomes & Economic Value**

Publishing updates on outcomes, costs, and mortality for payer engagement

**Indirect Comparisons**

Educating payers/HTA agencies on treatment differentiation

**HTA Scientific Engagement**

Collaborating with HTA researchers for early scientific advice

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# Substantial and Growing Evidence of Value

## Produced 24 publications in total in 2024


| Recently Accepted HEOR Publications | Type | Congress |
|---|---|---|
| **Differences in Healthcare Resource Use and Cost by Treatment Choice Among Patients with oHCM** | Manuscript | Amer Jour of CV Drugs |
| **The prognostic value of peak oxygen uptake in obstructive hypertrophic cardiomyopathy: a literature review to inform economic model development** | Manuscript | Journal of Medical Economics |
| **An evidence review and gap analysis for obstructive hypertrophic cardiomyopathy** | Manuscript | BMC CV Disorders |
| **Sociodemographic on economic burden in HCM** | Abstract | AHA 2024 |
| **Payer differences on costs of care in HCM** | Abstract | AMCP Nexus 2024 |
| **Beta-blocker use and incidence of new AF/AFF requiring therapy in post-SM HCM patients** | Abstract | HCMS 2024 |

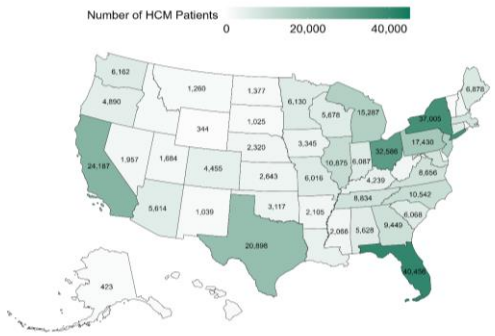
Higher pVO2 predicts fewer adverse events and mortality in cardiovascular patients, supporting its use as a **surrogate endpoint in oHCM and economic models**

# Leading the Way to Elevate HCM

## EARTH-HCM launching in Q4 2024

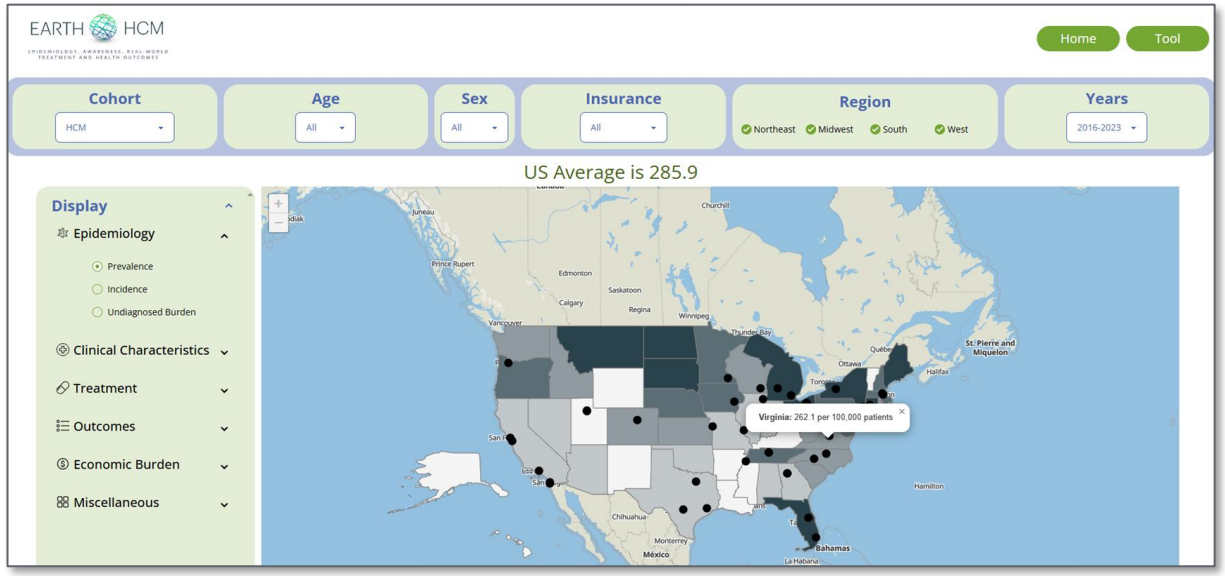
### EARTH-HCM: An open access, online tool using real-world data to visualize epidemiology, outcomes, and disparities in HCM

Creating urgency to treat oHCM patients, highlighting unmet needs and disease burden across different segments




EARTH HCM

**Prevalence of HCM patients in the US, 285.9 per 100,000 persons**



*AFICAMTEN*: GLOBAL LAUNCH PREPARATIONS

# European GTM Strategy

**Joseph Dagher**
SVP, Head of Europe

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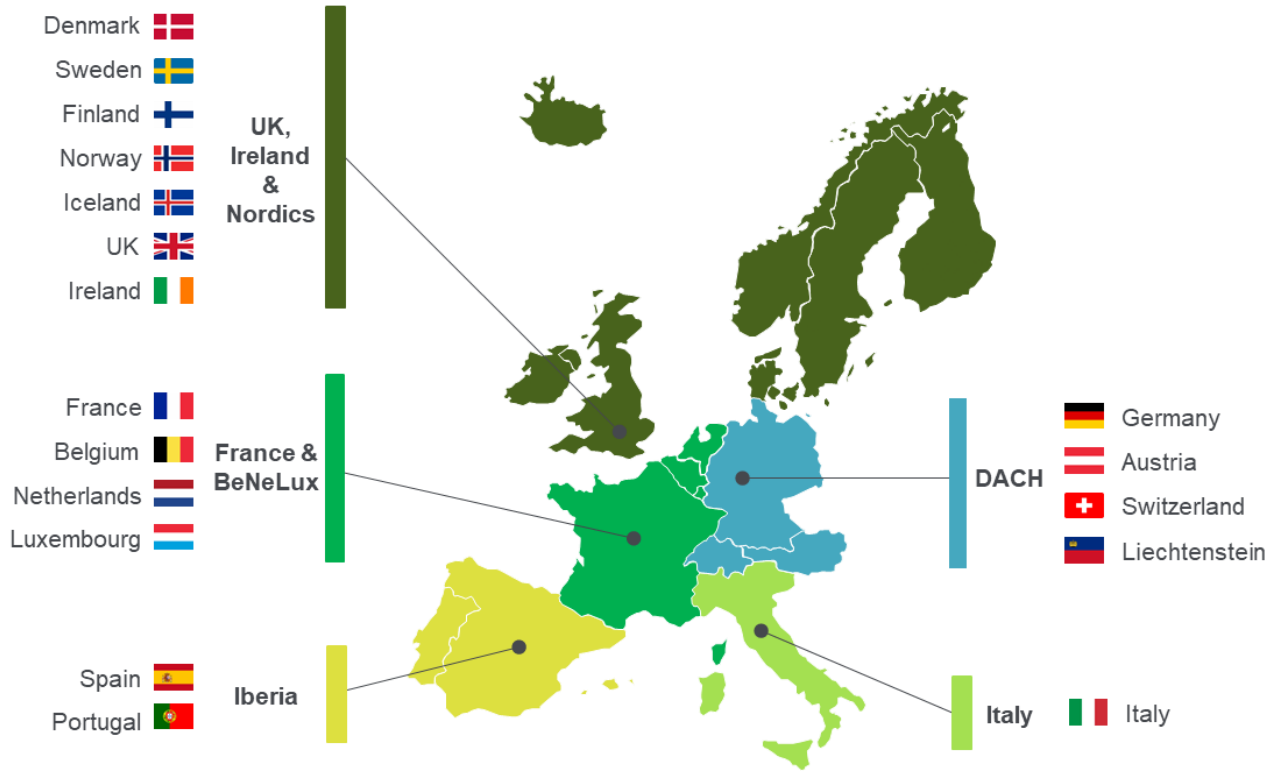
# EU GTM Structure

## Gated investment spending initially targeting EU5




**Initial focus to EU5**

- Supporting functions consolidated at EU HQ in Zug, Switzerland
- German entity is set up in Munich
- German General Manager and Medical director in place
- Ongoing recruitment for France and UK General Managers

**Expand beyond EU5 to EU18, (organized in 5 clusters) over 3 years**

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# Advancing EU Launch Readiness Activities

## Key Hires in Zug & Munich

- Highly experienced hires in Zug, Switzerland in Regulatory, Medical Affairs, Commercial, Market Access
- Highly experienced hires in Munich, Germany including General Manager, Medical Director
- Multiple product launches in cardiology & oncology both orphan & non-orphan indications
- Proven track record of successfully navigating pricing, reimbursement & market access in Europe

## Key Activities to Support Launch

- Design the EU distribution model & select EU 3PL
- Support the MIA (Manufacturing & Importation Authorization)
- Develop regulatory & labeling strategy
- Start implementing all needed processes to support German launch:
  - Market understanding (prescribers concentration curves, patient journey…)
  - HTA Dossier writing for P&R process

# EU Market Access, Pricing & HEOR Activities Ongoing

## EU Pricing Workstream

- Access & Pricing landscape in HCM, value & needs; comparators & competition, HTA strategy
- Validation of pricing assumptions (KOL/Payer)

## EU Payer & Clinician Advice

- Advice value (clinical, economic & humanistic) and willingness to pay
- Validate current evidence base for HTA submission (Burden, Tx patterns, target population and economic & humanistic differentiation)

## Indirect Treatment Comparisons

- Define the appropriate methodologies in line with country needs
- Define the publications approach and external partnerships required

## HTA Agency Engagement/Advice

**Support the EU P&MA strategy development by:**

- Evaluation of endpoints
- Changes in the Standard of Care
- ITC methodologies

## Evidence Generation Plan

**Develop EU strategic evidence generation plan to complement evidence needs required for the value proposition:**

- Peak VO2
- EU Epidemiology and Disease Burden
- Evolution in treatment patterns

## Country mobilization

- Data gap analysis and individual country requirements
- Modelling needs

**EU launch sequence and pricing strategy**

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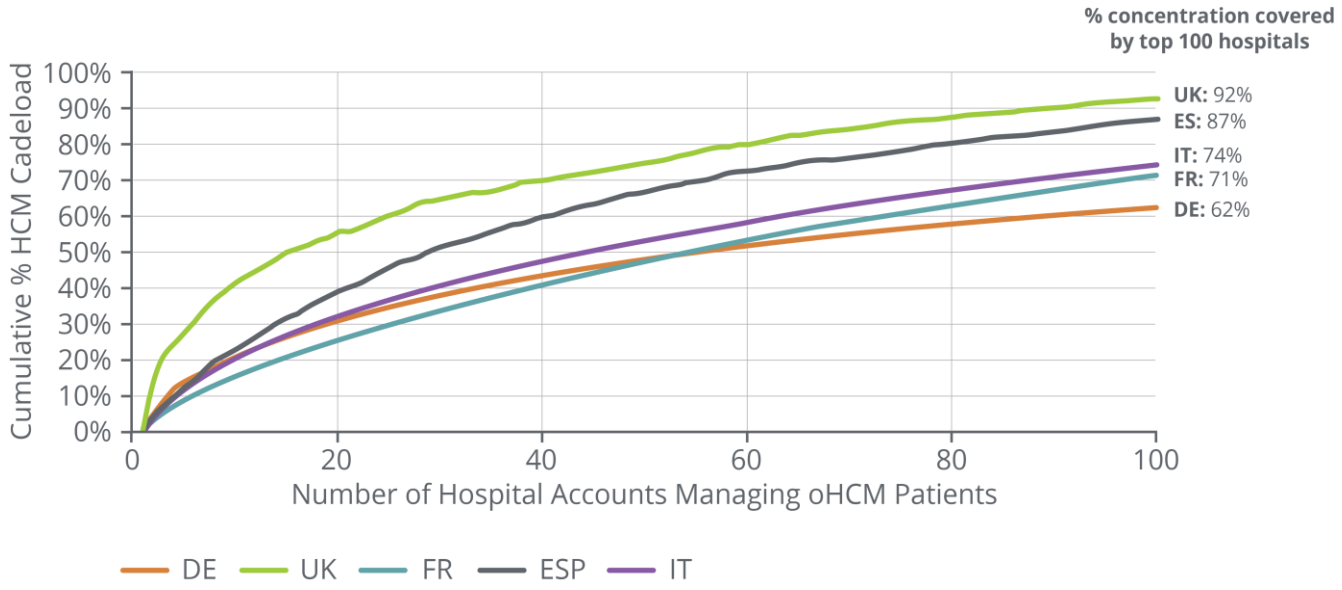
# Concentrated oHCM Market in EU5

## oHCM Care Concentration in EU5 Top 100 Hospitals*




oHCM care is most concentrated in the UK & FR, followed by Spain and IT with **<100 accounts managing 80% oHCM patients**

Genotyping testing, echo frequency, overall resource utilization are main challenges to current CMI management

**Top 100 hospitals by ICD-10 caseload (I42.1)*
*PurplExtra data, ZS market research July 2024*

## CMI prescription challenges

1. Time to present to care is variable depending on the patient's lifestyle; sedentary patients may take ~1 year to present to an HCP
2. Cardiologists emphasized that genotyping requirement is a key burden to prescription
3. Cardiologists highlight that their practices are often backlogged due to echo availability
4. Average wait time for a non-urgent echo is 6.5 weeks and urgent echo is 1.5 weeks
5. Cost of therapy to the healthcare system or cost to practice

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# Competitive Insights: CMI Pricing and Reimbursement Status

| Country | oHCM target population | Annual public list price ($)* | HTA status | Reimbursement status |
|---|---|---|---|---|
| **France** | **18,500** | **$17,671.45** | HAS TC - ASMR III, SMR important | Reimbursed |
| **Germany** | **18,900 – 19,500** | **$23,836.83** | GBA- Hint of Considerable Added Benefit | Reimbursed<br>Post-AMNOG price expected Oct 2024 |
| **Italy** | Data unavailable | Data unavailable | AIFA – Submitted, in progress | Not yet reimbursed |
| **Spain** | Data unavailable | Data unavailable | AEMPS – Positive recommendation | Reimbursed (price not published) |
| **United Kingdom** | **6,300** (England) | **$17,676.68** | England: Recommended w/ restrictions<br>Scotland: Recommended | Reimbursed with PAS |

***Prices representative of currently approved CMI. Aficamten price may be different than reported prices.***
*Abbreviations: AMNOG: Pharmaceutical Market Restructuring Act; ASMR: Amélioration du Service Médical Rendu; EAS: early access scheme; HAS: Haute Autorité de santé; HTA: health technology assessment; PAS: patient access scheme; SMR: Service Médical Rendu; TC: Transparency Committee.*

# EU: Next Steps and Priorities

- MAA submission in Q4 2024
- Finalizing EU launch sequence
- Finalize pricing strategy and pricing governance
- Finalizing distribution set-up in Europe
- Continue to develop oHCM market understanding through market research

- Early payer advice meetings with GBA & NICE
- Setting up entities and recruiting senior management roles in France, UK, Italy & Spain
- Engagement with KOLs, HTA bodies and patients' associations
- Prepare cost-effectiveness assessments
- Develop pricing and reimbursement dossiers

# 5-Minute Break

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# *Omecamtiv Mecarbil:* Phase 3 Confirmatory Trial & Beyond

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*OMECAMTIV MECARBIL*: PHASE 3 CONFIRMATORY TRIAL AND BEYOND

# Rationale for Confirmatory Phase 3 Trial

**Punag Divanji, M.D.**
Medical Director, Clinical Research, Cytokinetics

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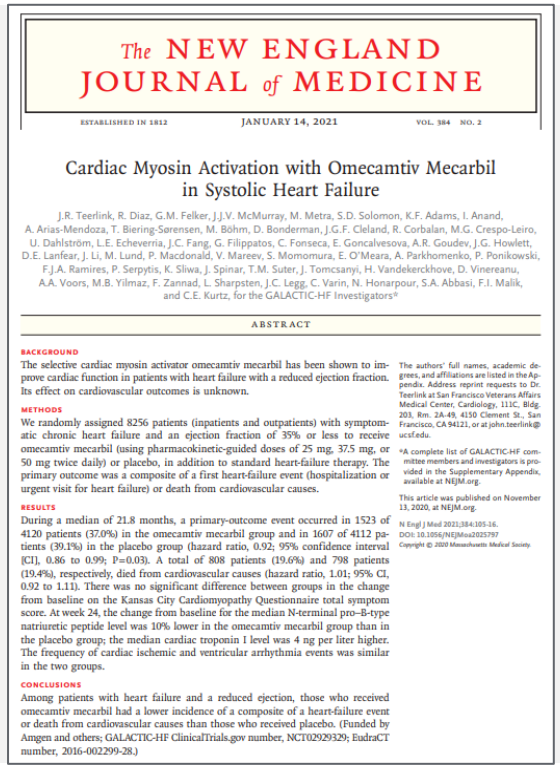
# *Omecamtiv Mecarbil*: Potential for High-Risk Severe HF Patients Despite GDMT

## Advancing efficient, pragmatic Phase 3 clinical trial

### High Unmet Need

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



The NEW ENGLAND JOURNAL of MEDICINE

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

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

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ABSTRACT

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

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

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

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

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

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

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

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DOI: 10.1056/NEJMoa2025797
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### Ph 3 clinical trial results in 8,000 patients point to important treatment benefit

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

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

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

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

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

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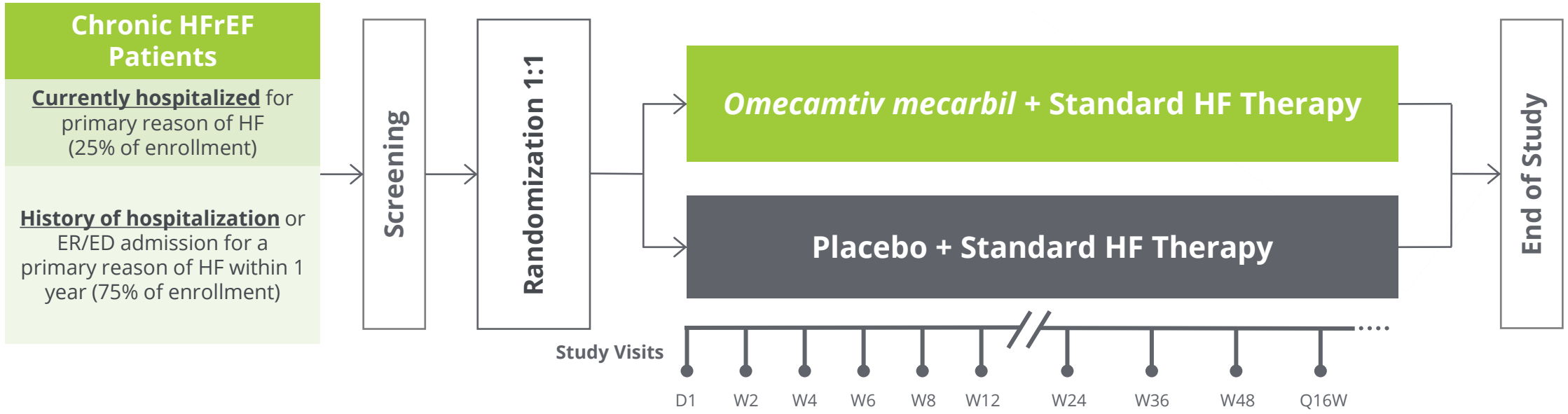
# Clinical Trial Overview

## Phase 3 clinical trial

GALACTIC-HF

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

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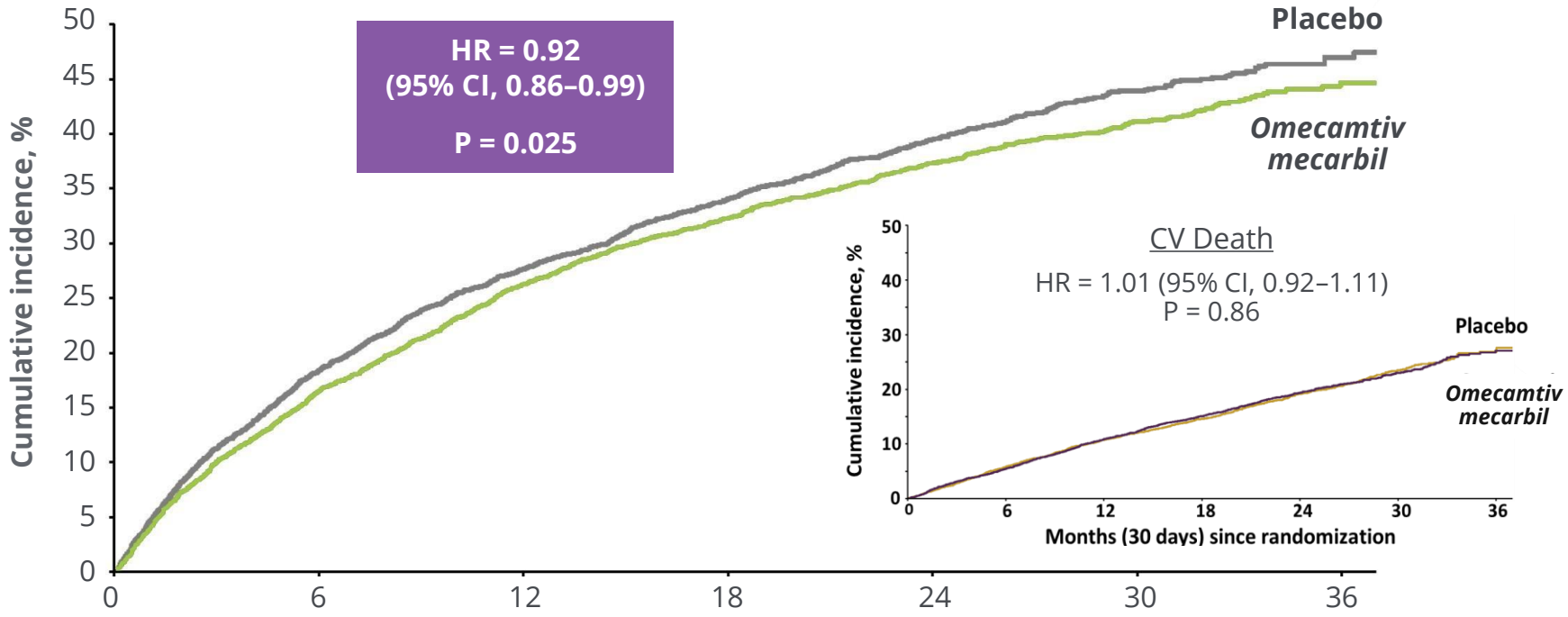
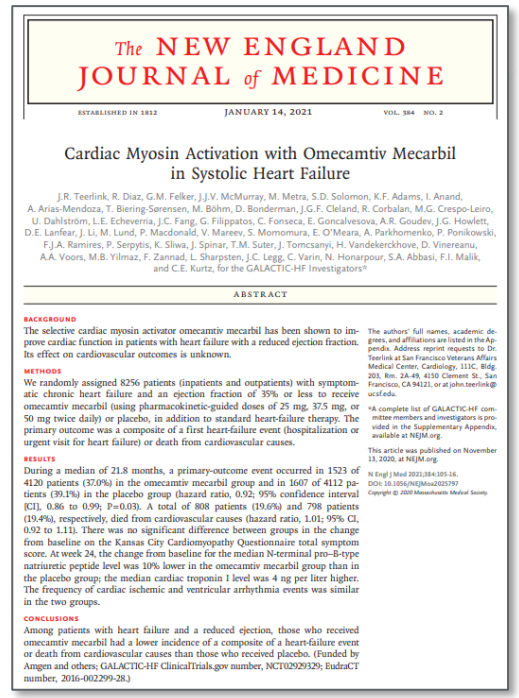
# Primary Composite Endpoint









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

*Time to first HF event or CV death*

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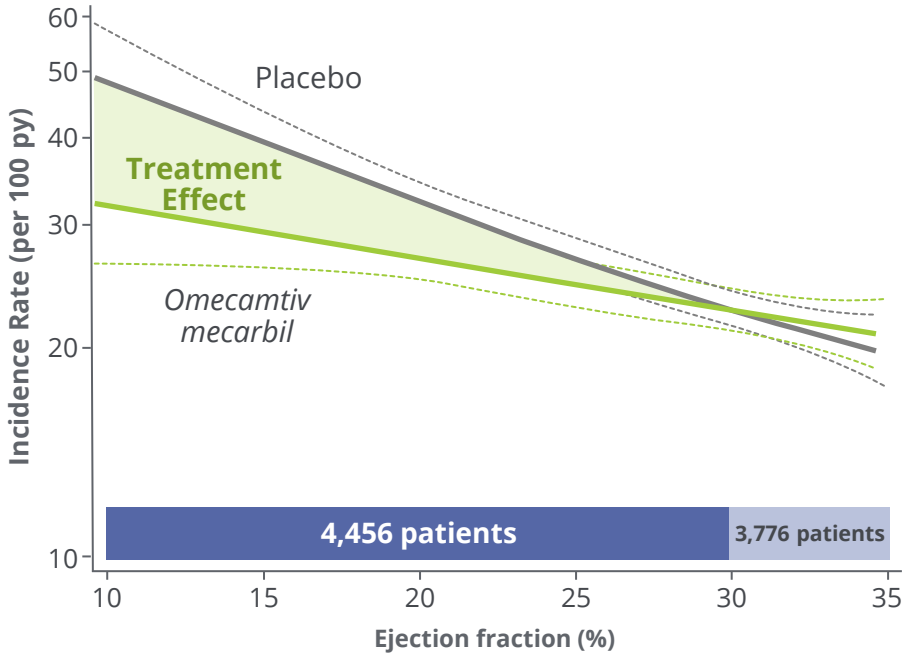
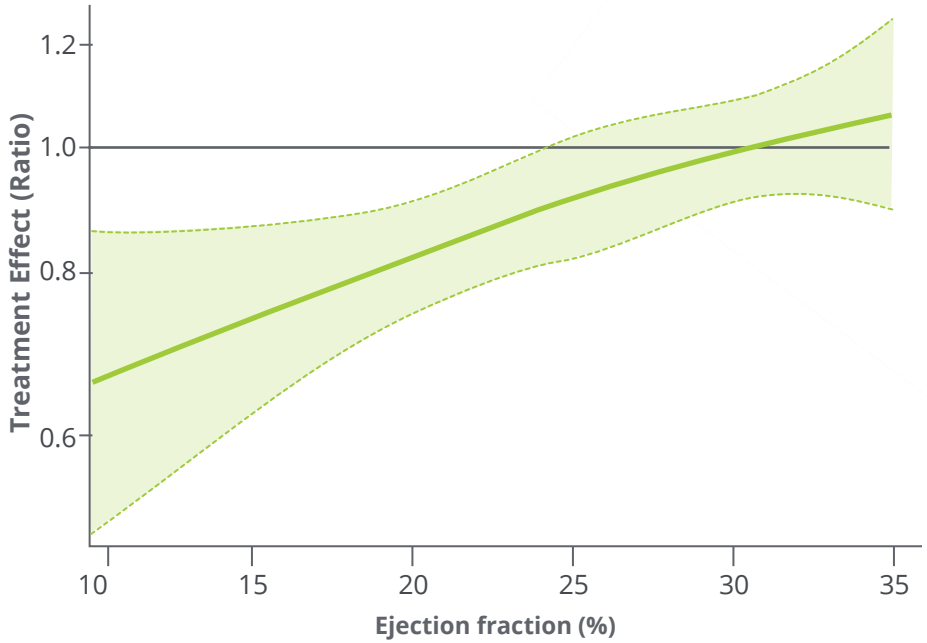
# Benefit Observed to Increase as Baseline LVEF Decreased

## Incidence of Primary Composite Endpoint




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

## Relative Treatment Effect on Primary Endpoint




JACC

ORIGINAL INVESTIGATIONS

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

ABSTRACT

*ARR = Absolute Risk Reduction. RRR = Relative Risk Reduction.*
*Teerlink JR., Diaz R., Felker GM., et al. Effect of Ejection Fraction on Clinical Outcomes in Patients treated with Omecamtiv Mecarbil in GALACTIC-HF. JACC. 2021*
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# Safety Profile in the LVEF <30% Subgroup

## Incidence of AEs of stroke lower with *omecamtiv mecarbil* compared with placebo

| | *Omecamtiv Mecarbil* (N=2335) | Placebo (N=2355) | Relative Risk or Difference (95% CI) |
|---|---|---|---|
| **Serious AE, n (%)** | 1374 (58.8) | 1457 (61.9) | 0.95 (0.91 to 1.00) |
| **AE of interest, n (%)** | | | |
| **Ventricular tachyarrhythmia (narrow SMQ)** | 187 (8.0) | 188 (8.0) | 1.00 (0.83 to 1.22) |
| **Torsade de pointes/QT prolongation (narrow SMQ)** | 118 (5.1) | 133 (5.6) | 0.89 (0.70 to 1.14) |
| **Serious adverse of ventricular arrhythmia requiring treatment** | 78 (3.3) | 82 (3.5) | 0.96 (0.71 to 1.30) |
| **Adjudicated major cardiac ischemic event, n (%)** | 104 (4.5) | 98 (4.2) | 1.07 (0.82 to 1.40) |
| **Myocardial infarction** | 67 (2.9) | 65 (2.8) | |
| **Hospitalized for unstable angina** | 8 (0.3) | 4 (0.2) | |
| **Coronary revascularization** | 60 (2.6) | 60 (2.5) | |
| **Adjudicated Strokes, n (%)** | **38 (1.6)** | **68 (2.9)** | **0.56 (0.38 to 0.83)** |

*GALACTIC-HF CSR Table 14.3.4.5.27*

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# Potential Benefit in Severe HF Patients

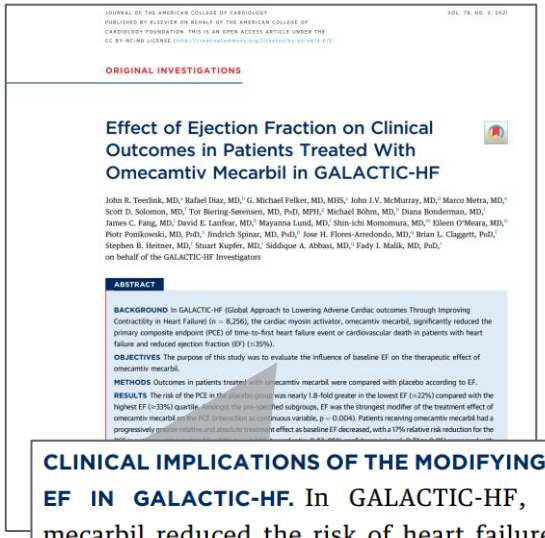

JAMA Cardiology | Original Investigation

Assessment of Omecamtiv Mecarbil for the Treatment of Patients With Severe Heart Failure
A Post Hoc Analysis of Data From the GALACTIC-HF Randomized Clinical Trial

JAMA Cardiology

## Conclusions

Among patients with severe HF defined by NYHA symptom class, LVEF, and recent HF hospitalization, omecamtiv mecarbil therapy may have provided a clinically meaningful reduction in the composite end point of time to first HF event or CV death. These data may support the possible role of omecamtiv mecarbil therapy in patients for whom current treatment options are limited.


ORIGINAL INVESTIGATIONS

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

ABSTRACT

**CLINICAL IMPLICATIONS OF THE MODIFYING EFFECT OF EF IN GALACTIC-HF.** In GALACTIC-HF, omecamtiv mecarbil reduced the risk of heart failure events in patients with EFs no >35%. The current analysis demonstrates that this treatment effect increases with decreasing EF and suggests that patients with EFs approximately ≤30% are most likely to benefit from this therapy. Additional analyses will need to be performed to identify the patients with EFs >30% who may also derive benefit.

"This trial represented one of the largest clinical trials ever done in heart failure, with a large number of severe heart failure patients. Therefore, I believe that a path was constructed in which one could go forward safely and with enhanced efficacy by stating that the patient population for the use of this drug would be those with an ejection fraction, for example, less than 25 in sinus rhythm and with pharmacokinetic-guided dosing. **Therefore, it may be a narrow path, but I think it's a path that would afford a lot of benefit to this high-risk patient population."**

**- Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA,**

Cardiovascular and Renal Drugs
Advisory Committee Meeting
to review the NDA for *omecamtiv mecarbil*

*Felker GM., Solomon SD., Claggett B., et al. Assessment of Omecamtiv Mecarbil for the Treatment of Patients With Severe Heart Failure A Post Hoc Analysis of Data From the GALACTIC-HF Randomized Clinical Trial. JAMA Cardiology. 2021*
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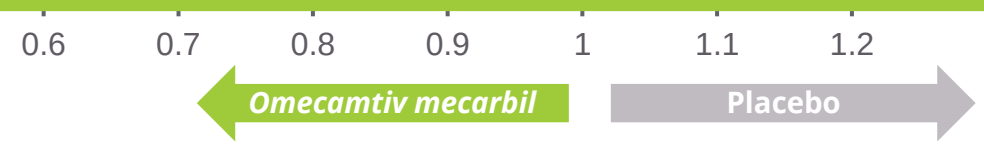
# Large Treatment Effect in Easily Defined HF Population

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

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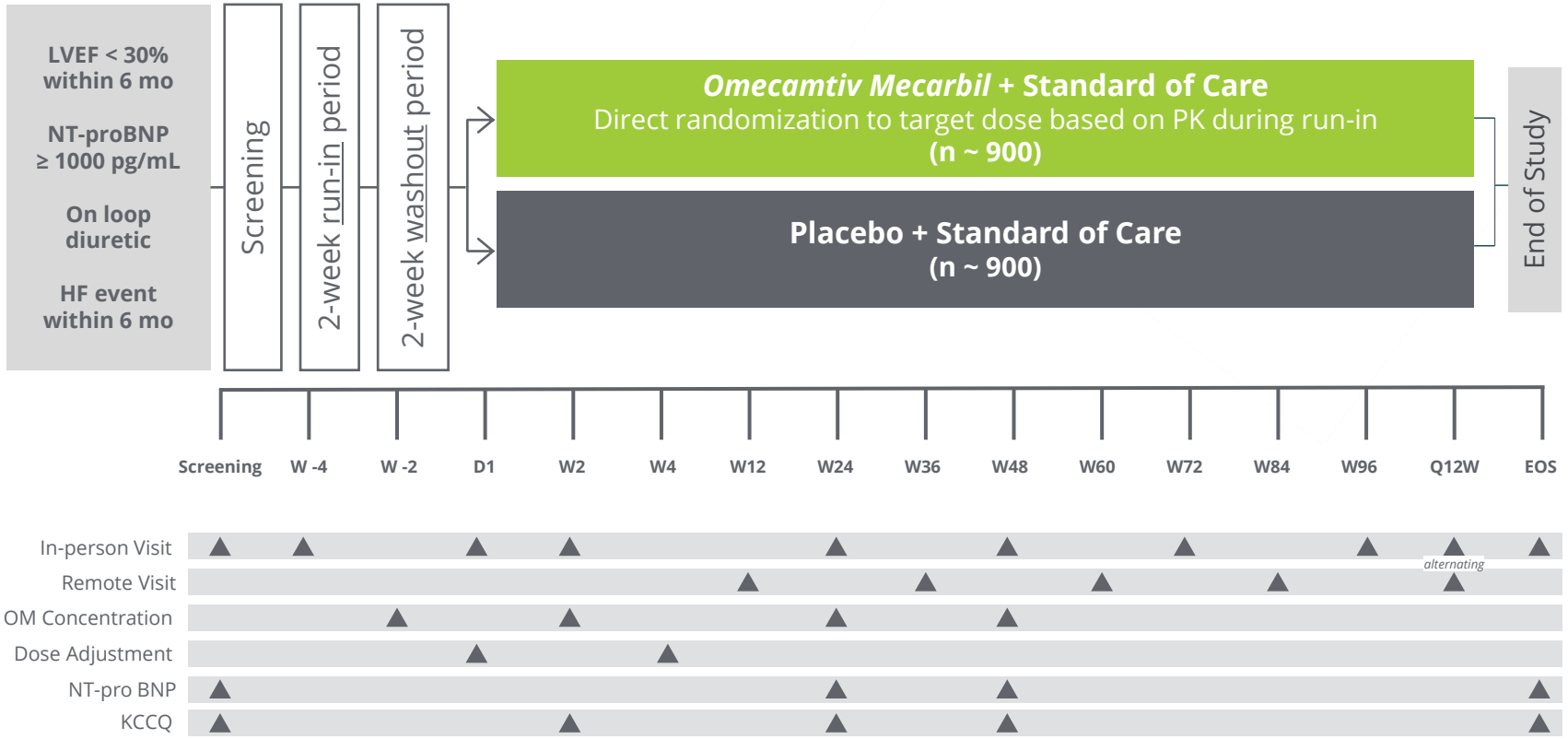
# Phase 3 Confirmatory Clinical Trial Design

## COMET-HF expected to start in Q4 2024

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

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

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*OMECAMTIV MECARBIL*: PHASE 3 CONFIRMATORY TRIAL AND BEYOND

# Commercial Opportunity

**Andrew Callos**
EVP, Chief Commercial Officer

Cytokinetics®

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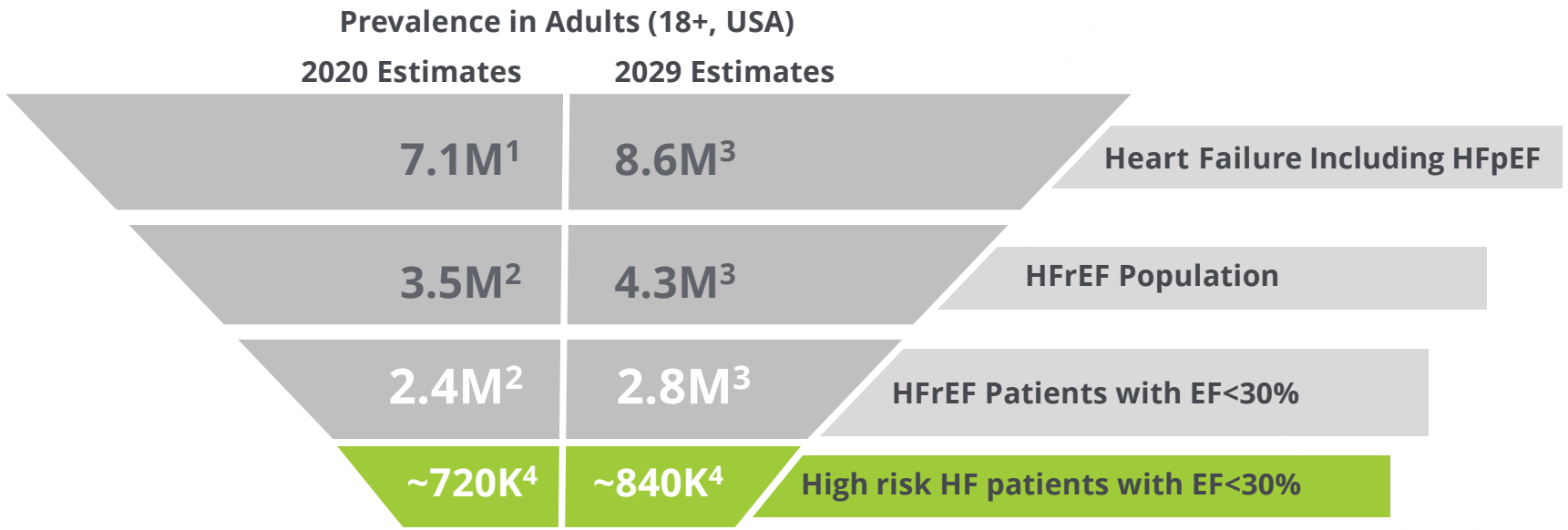
# Large and Growing Target Patient Population in US




**Proposed**
***Omecamtiv Mecarbil***
**Target Patient**

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

**Cardiac Function**

**LVEF < 30%**

+

**Markers of High-Risk HFrEF**

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


*1. Tsao 2023, AHA. Racine 2022 CVrg. Bionest 2021.*
*2. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30. PMID: 22936826; PMCID: PMC3661289.*
*3. 2.1% annual growth rate:1.9% annual growth rate of patient population 65+ (UN World Populations Prospects Nov 2019) and a 0.2% mortality impact of HF treatment (doi: 10.1136/bmj.l223 | BMJ 2019;364:l223)*
*4. Greene et al JACC 2023; 81:413-424*

** HF Event: Urgent, unscheduled outpatient visit or hospitalization*
***Omecamtiv mecarbil is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.***

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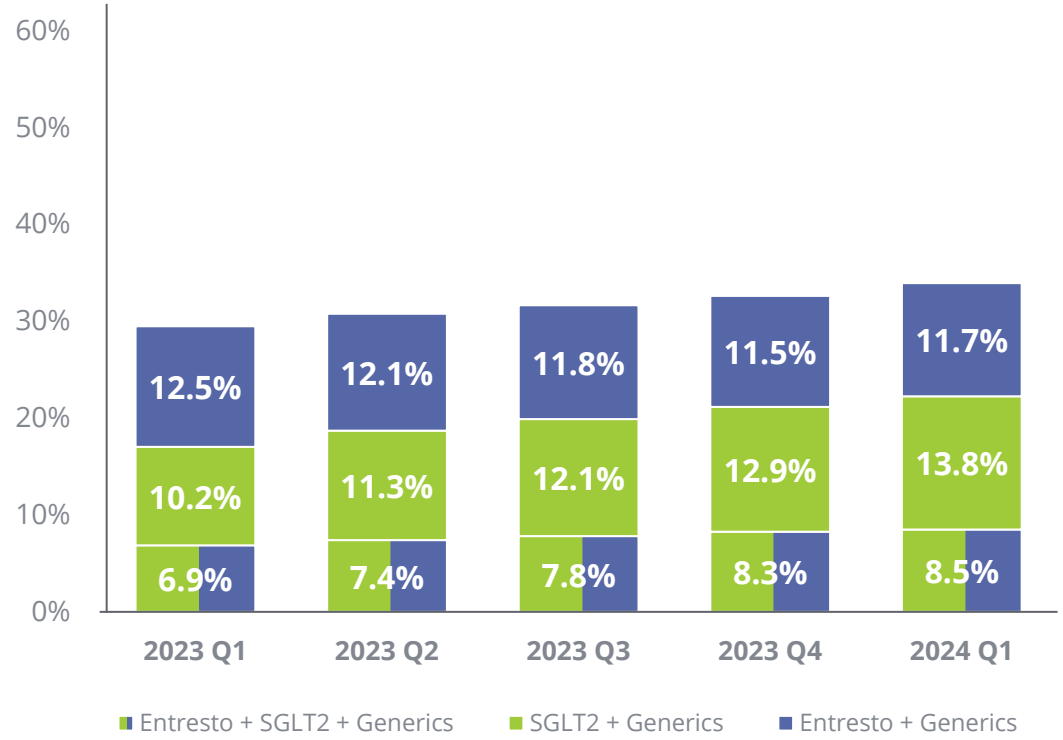
# Despite Increasing Use of SGLT2's, Risk of CV Events Remains

## Brand Containing Regimens
(Share of GDMT Treated HFrEF* Patients)

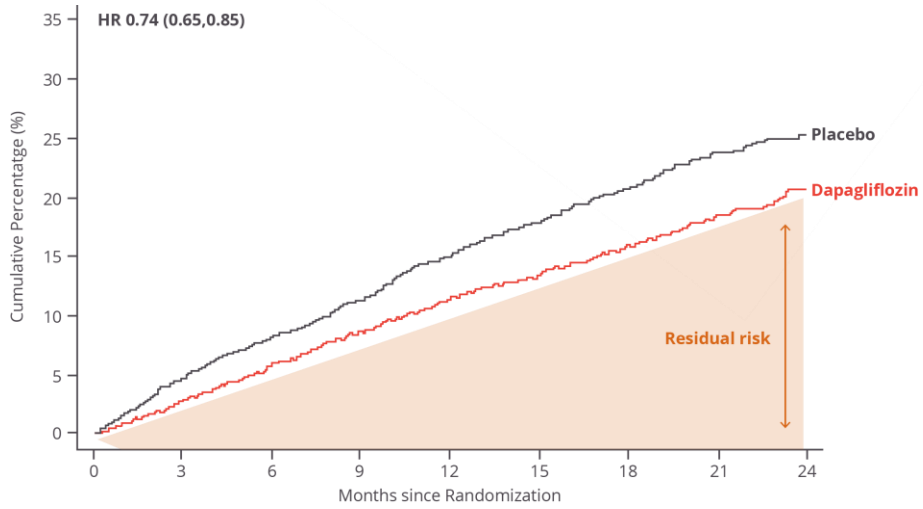



*Source: Symphony Patient Level Claims*
** Diagnosed with a HFrEF systolic specific ICD10 code I50.20/1/2/3 with a look back to 2016*
*SGTL2 includes Jardiance or Farxiga or Inpefa*

## Residual Risk of CV Events Remains Despite *dapagliflozin* Treatment

**DAPA-HF – Primary endpoint: CV Death/HF hospitalization/urgent HF visit**

**4744 patients,** Renin-angiotensin system blocker **94%,** Beta-clocker **96%,** Mineralocorticoid receptor (aldosterone) antagonist **71%**




Number at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin | 2373 | 2305 | 2221 | 2147 | 2002 | 1560 | 1146 | 612 | 210 |
| Placebo | 2371 | 2258 | 2163 | 2075 | 1917 | 1478 | 1096 | 593 | 210 |

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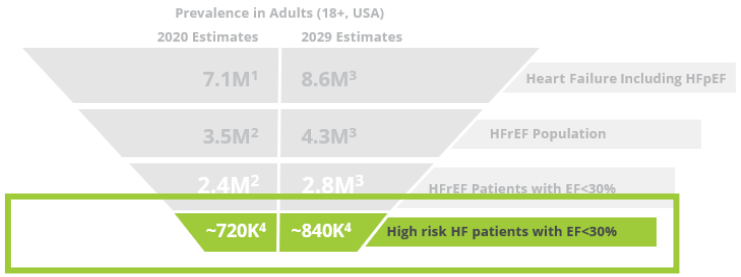
# Higher Event Rate & Costs in Patients with Severely Reduced EF




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

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

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

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


*1. Tsao 2023, AHA. Racine 2022 CVrg. Bionest 2021.*
** HF Event: Urgent, unscheduled outpatient visit or hospitalization **in terms of 2024 dollars*
*2. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30. PMID: 22936826; PMCID: PMC3661289.*
*3. 2.1% annual growth rate:1.9% annual growth rate of patient population 65+ (UN World Populations Prospects Nov 2019) and a 0.2% mortality impact of HF treatment (doi: 10.1136/bmj.l223 | BMJ 2019;364:l223)*
*4. Greene et al JACC 2023; 81:413-424*
*5. Extrapolated from Desai NR, Butler J, Binder G, Greene SJ. Prevalence and Excess Risk of Hospitalization in Heart Failure with Reduced Ejection Fraction. Poster presented at: Heart Failure Society of America (HFSA) Annual Scientific Meeting; 2022 Sep 30-Oct 3; Washington, DC.*
*6. Carnicelli AP, Clare RM, Hofmann P, Chiswell K, DeVore AD, Vemulapalli S, Felker GM, Kelsey AM, DeWald TA, Sarocco P, Mentz RJ. Clinical trajectory of patients with a worsening heart failure event and reduced ventricular ejection fraction. Am Heart J. 2022 Mar;245:110-116. doi: 10.1016/j.ahj.2021.12.003. Epub 2021 Dec 18. PMID: 34932997.*
*7. Urbich M, Globe G, Pantiri K, Heisen M, Bennison C, Wirtz HS, Di Tanna GL. A Systematic Review of Medical Costs Associated with Heart Failure in the USA (2014-2020). Pharmacoeconomics. 2020 Nov;38(11):1219-1236. doi: 10.1007/s40273-020-00952-0. PMID: 32812149; PMCID: PMC7546989.*

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

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# The Business Case for *Omecamtiv Mecarbil*

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

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

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

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# Expert Perspective: HF with Severely Reduced EF

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

**G. Michael Felker, M.D., MHS, FACC, FAHA, FHFSA**
Professor of Medicine, Division of Cardiology, Duke Clinical Research Institute

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# CK-586: Development Program

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

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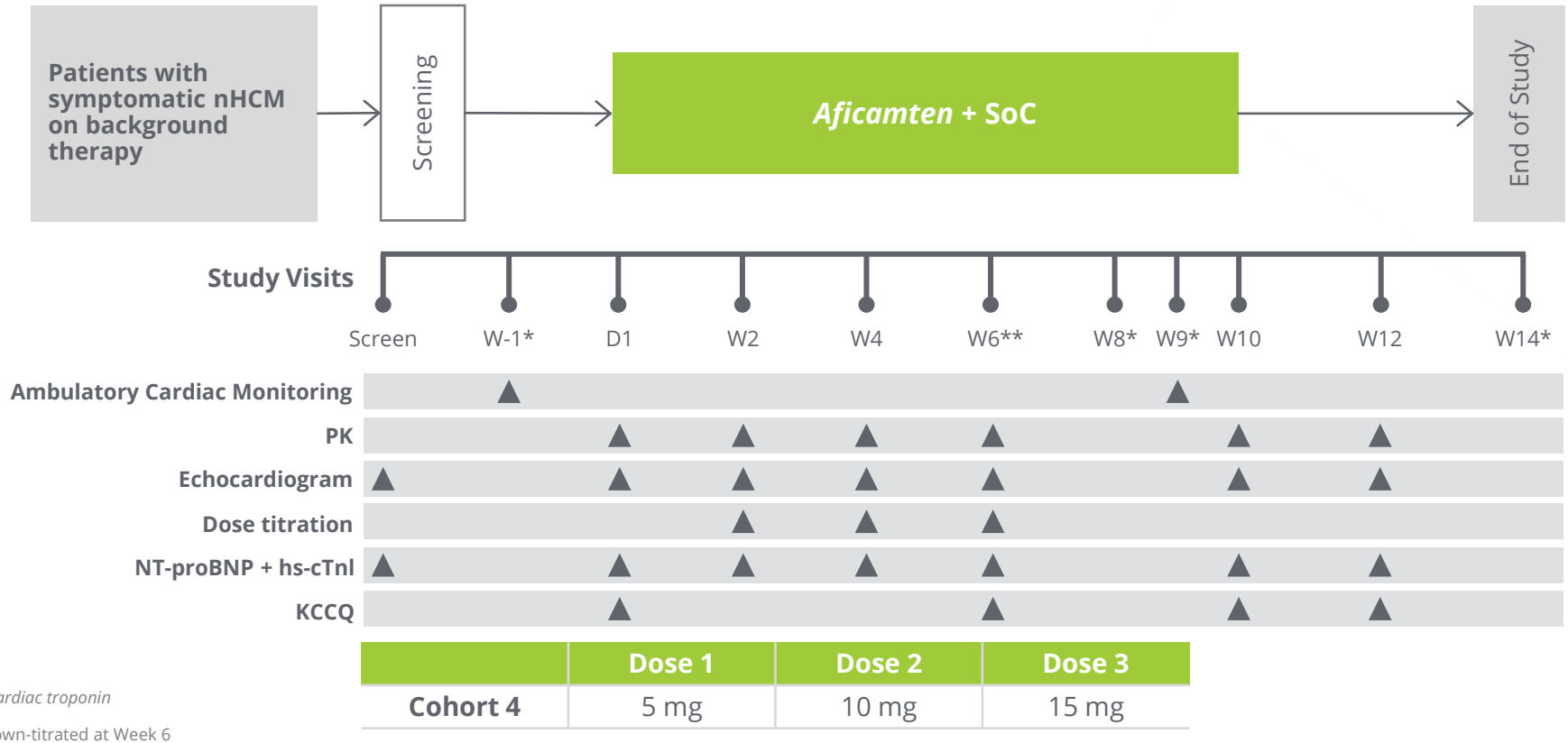
*CK-586 is an investigational agent and has not been approved for use by the U.S. Food & Drug Administration (FDA) or any regulatory agency. The safety and effectiveness of this product has not been established.*

# 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 |

*hs-cTnI: high- sensitivity cardiac troponin*
*Telephone visits
**Patient can only be down-titrated at Week 6
***Aficamten is an investigational agent and is not approved by any regulatory agency. Its safety and efficacy have not been established.***

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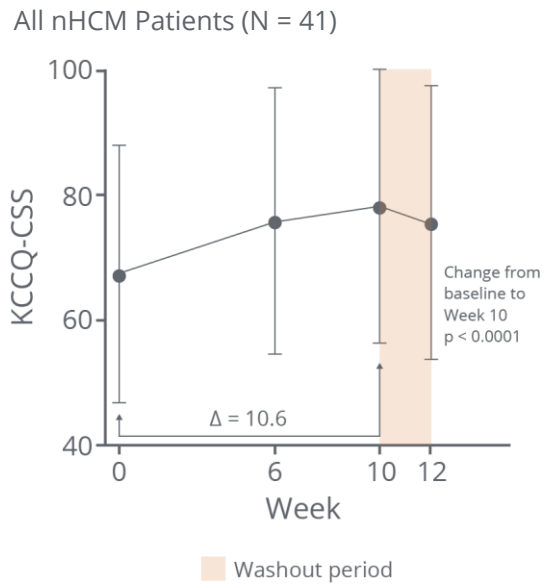
# Significant Improvements in KCCQ & NYHA Class

## Cohort 4

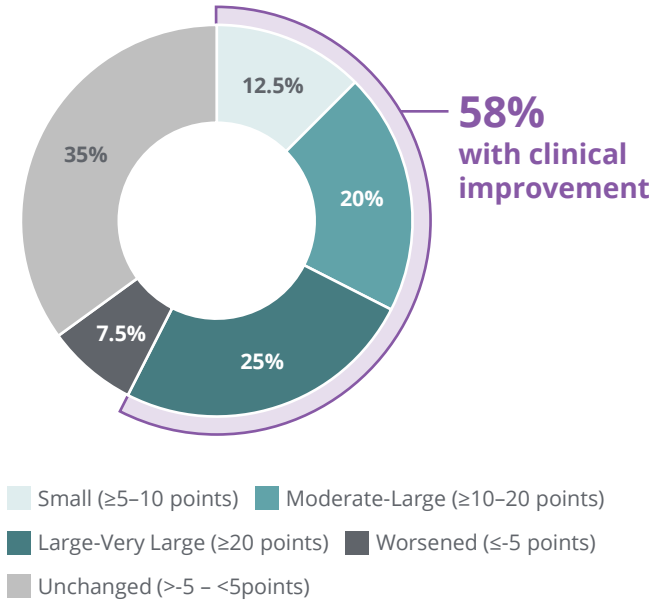
**85% of patients achieved 15 mg dose; no discontinuations due to adverse events**

### Kansas City Cardiomyopathy Questionnaire

Mean improvement in KCCQ of 10.6 points

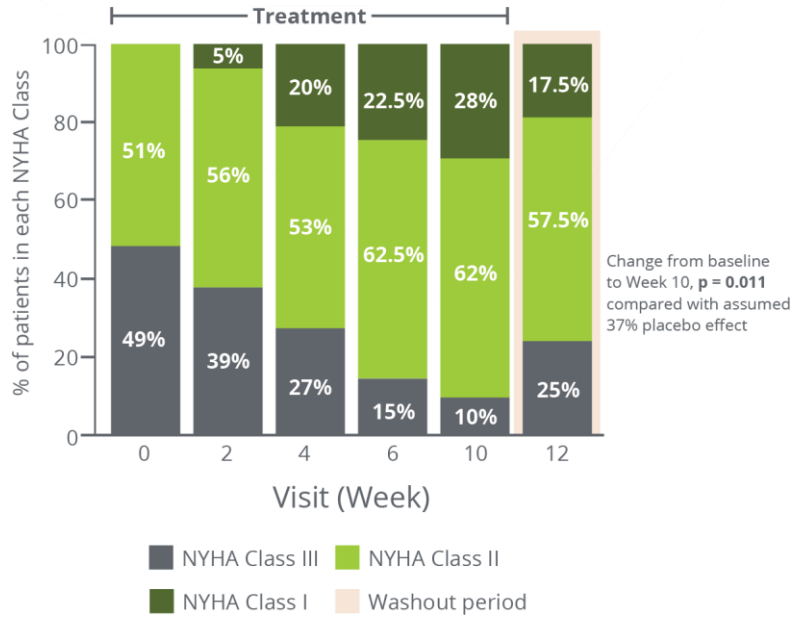



### Categorical Changes at Week 10 in KCCQ-CSS




### NYHA Functional Class

56% of patients improved by ≥1 NYHA class




Data presented as mean and standard deviation

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

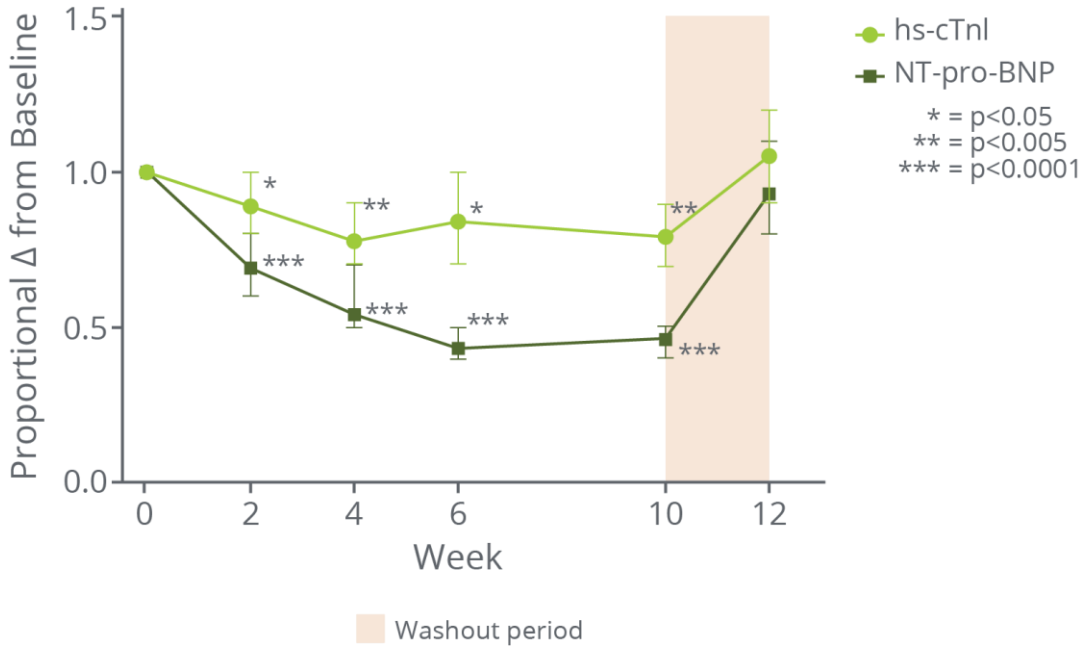
***Aficamten is an investigational agent and is not approved by any regulatory agency. Its safety and efficacy have not been established.***

# 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 mean and standard deviation

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

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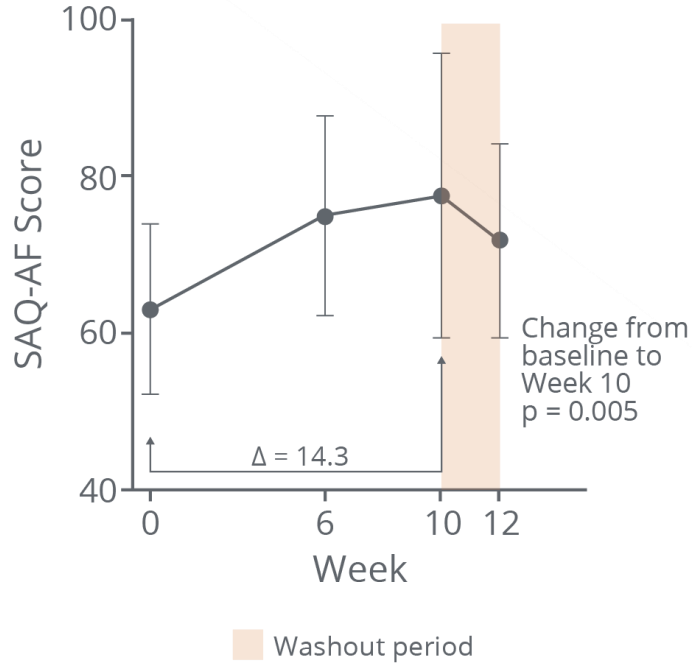
### Seattle Angina Questionnaire Angina Frequency (SAQ-AF)

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




Data presented as mean and standard deviation

# 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 |

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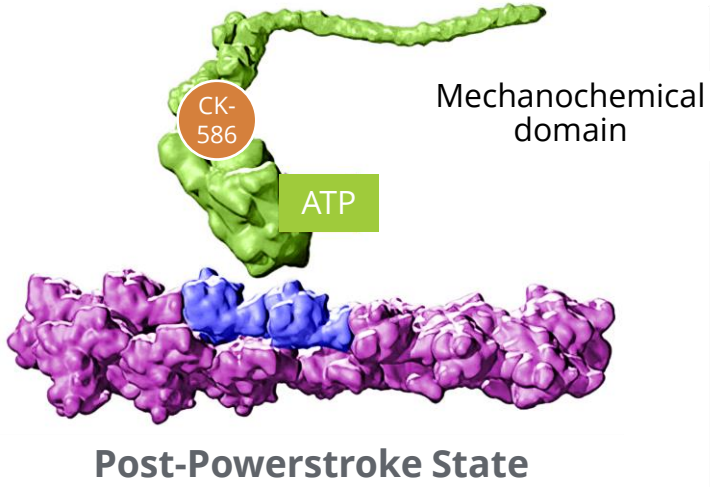
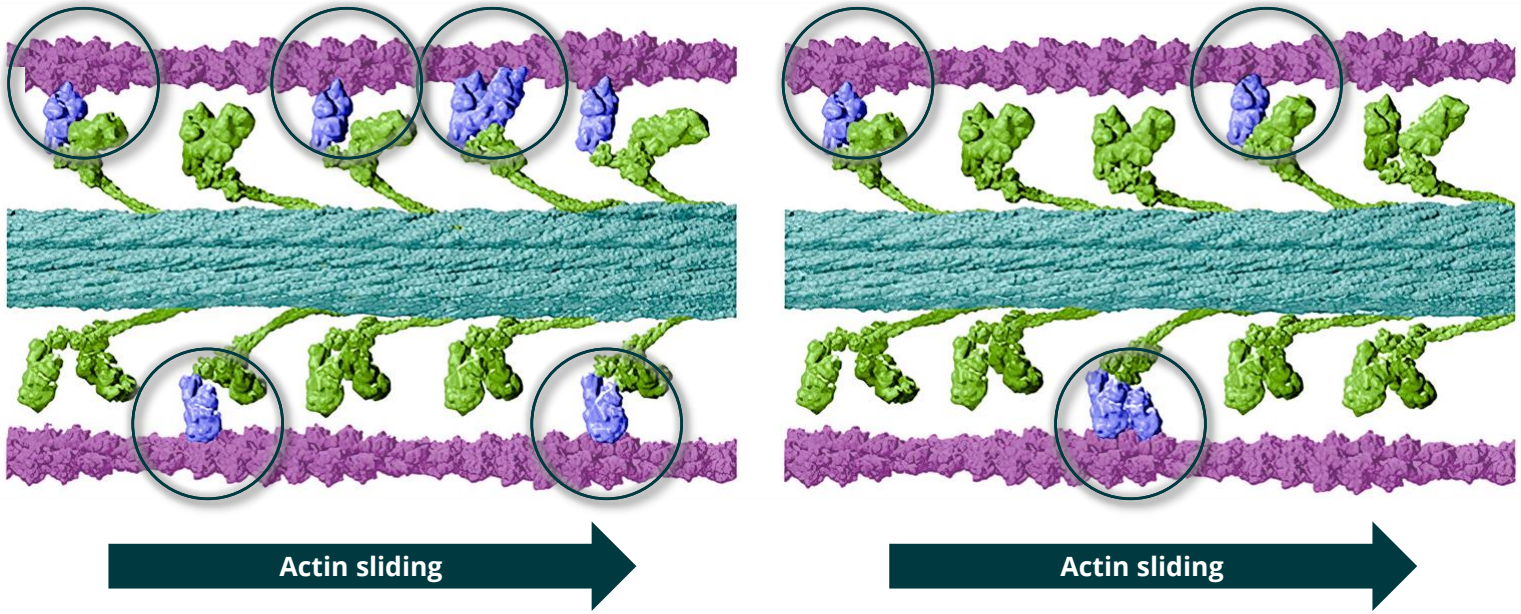
# CK-586: Distinct Mechanism of Action from *Aficamten*




**"Fewer hands pulling on the rope"**




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

# Phase 1 Data Support Advancement to Phase 2 Clinical Trial

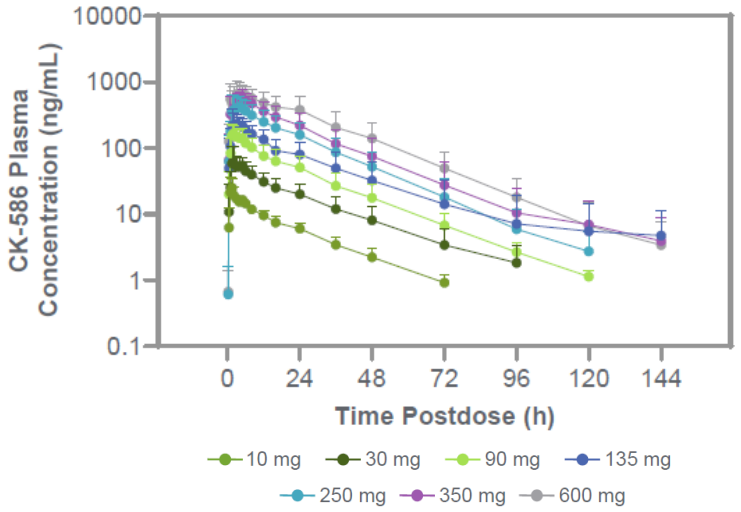
## Phase 2 dose-finding trial in HFpEF expected to start in Q4 2024

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

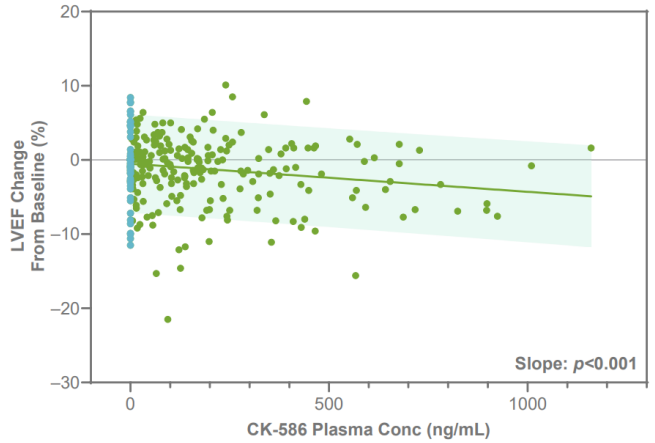
- **Less than 24-hour** half-life
- **Shallow and predictable** PK/PD relationship based on LVEF and LVFS
- **Well-tolerated** across all cohorts
- **No serious adverse events** were observed
- **Stopping criteria were not met**

### Plasma Concentration

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




### Change in LVEF vs. CK-586 Plasma Concentration




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

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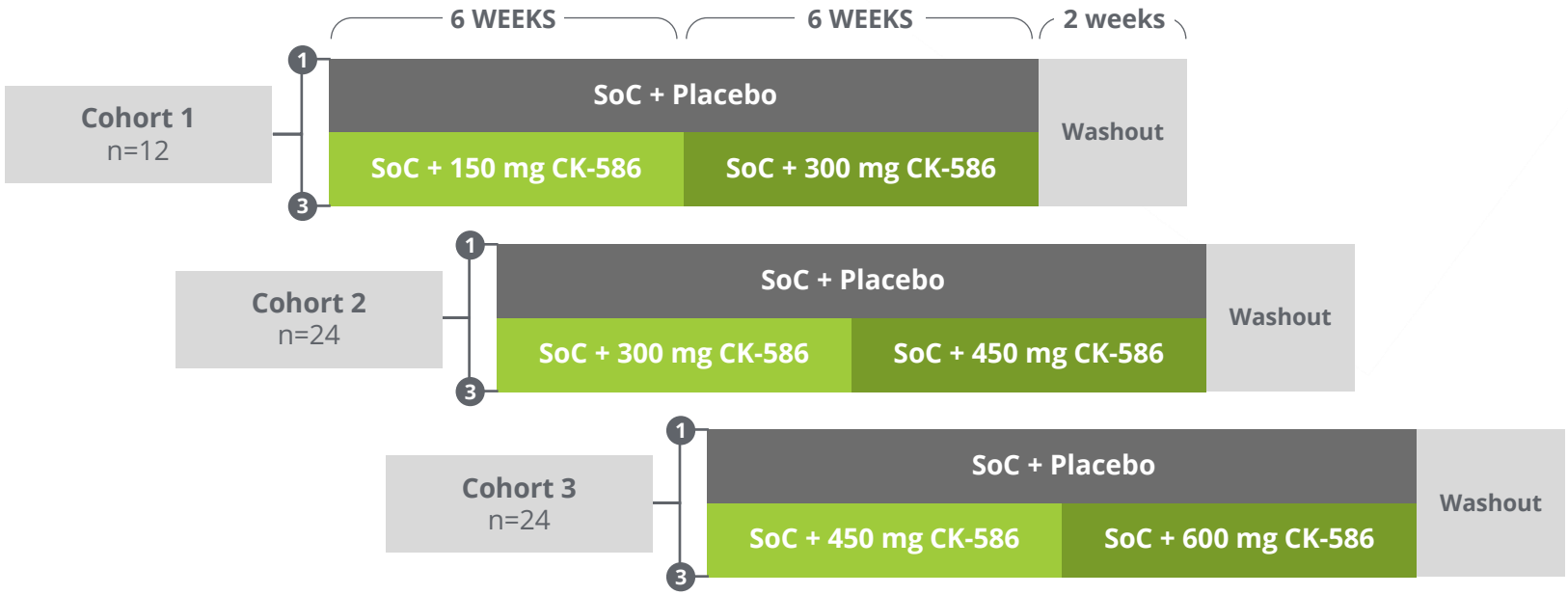
# Phase 2 Study Schema

## AMBER-HFpEF expected to start in Q4 2024

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

**Enrolling HFpEF patients with:**

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

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*CK-586: DEVELOPMENT PROGRAM & HFPEF MARKET OPPORTUNITY*

# Market Opportunity

**Andrew Callos**
EVP, Chief Commercial Officer

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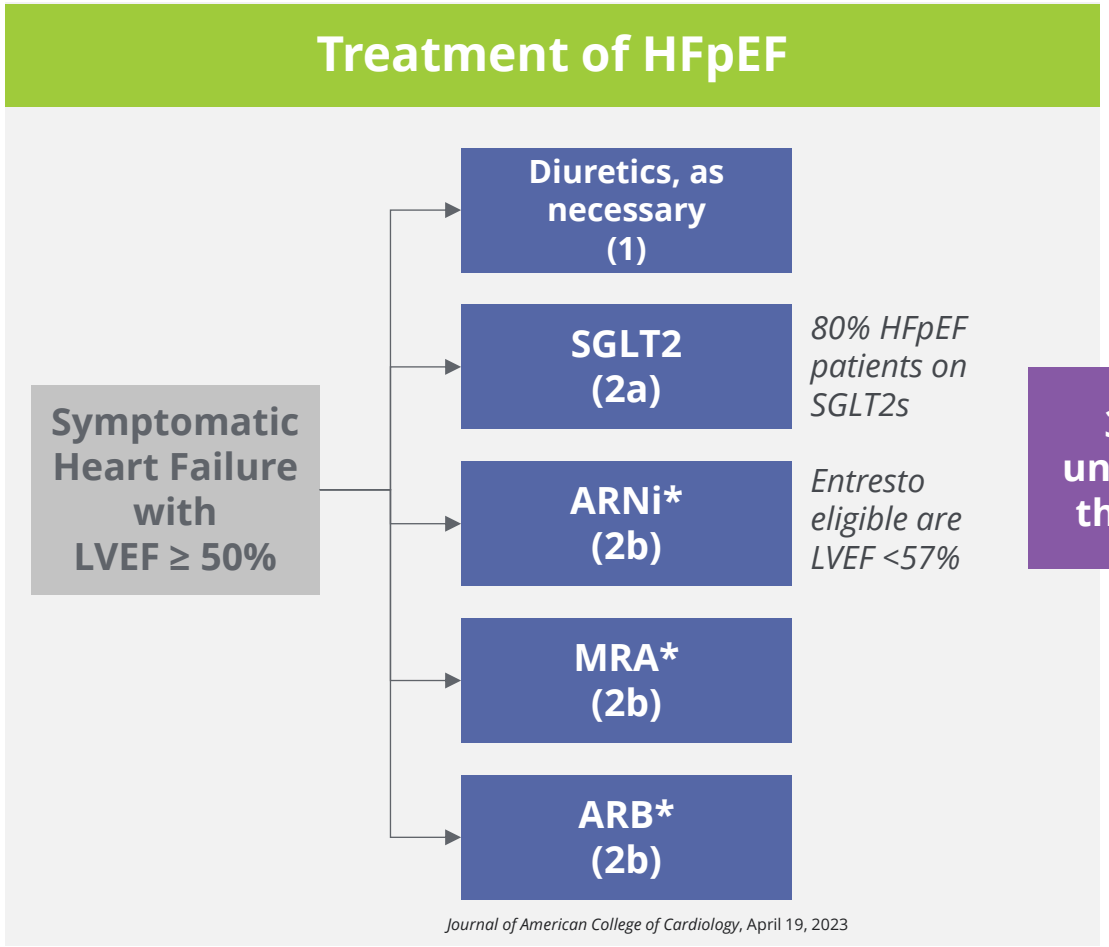
# Cardiologists Generally Treat HFpEF with HF GDMT; Large Unmet Need Remains




## Market Research Demonstrates:

- **Large unmet need** for therapies that treat HFpEF
- Cardiologists **excited about CMIs** as a novel treatment for HFpEF that may help treat the etiology of the disease

# Heart Failure with Preserved Ejection Fraction (HFpEF)

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

**~75%**

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

**~84%**

**HFpEF patients will be rehospitalized[2]**

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

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

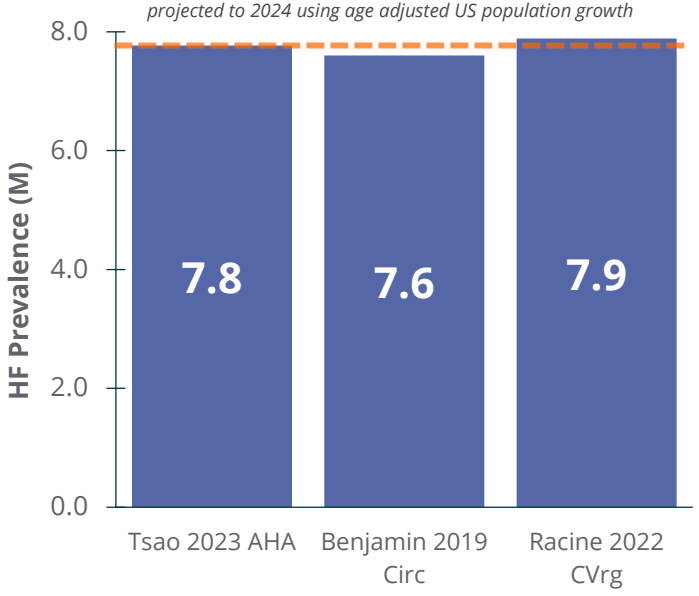
**Lifetime healthcare costs for HFpEF are ~ $126,819 per patient[5],** per-patient monthly cost for healthcare is $7,482, primarily, driven by **high rates of inpatient & outpatient visits**


*1. Jhund PS, MacIntyre K, Simpson CR, et al. Long-Term Trends in First Hospitalization for Heart Failure and Subsequent Survival Between 1986 and 2003. Circulation. 2009;119:515-523.*
*2. Bozkurt B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, Fonarow GC, Heidenreich P, Ho JE, Hsich E, Ibrahim NE, Jones LM, Khan SS, Khazanie P, Koelling T, Krumholz HM, Khush KK, Lee C, Morris AA, Page RL 2nd, Pandey A, Piano MR, Stehlik J, Stevenson LW, Teerlink JR, Vaduganathan M, Ziaeian B; Writing Committee Members. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. J Card Fail. 2023 Oct;29(10):1412-1451. doi: 10.1016/j.cardfail.2023.07.006. Epub 2023 Sep 26. PMID: 37797885; PMCID: PMC10864030.*
*3. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30. PMID: 22936826; PMCID: PMC3661289.*
*4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-e327.*
*5. Kapelios, Cardiac Failure Review 2023*
*6. Clark KAA, Reinhardt SW, Chouairi F et al (2022) Trends in heart failure hospitalizations in the US from 2008 to 2018. J Card Fail 28(2):171–180.*
*7. Lam CSP, Wood R, Vaduganathan M et al (2021) Contemporary economic burden in a real-world heart failure population with Commercial and Medicare supplemental plans. Clin Cardiol 44(5):646–655.*

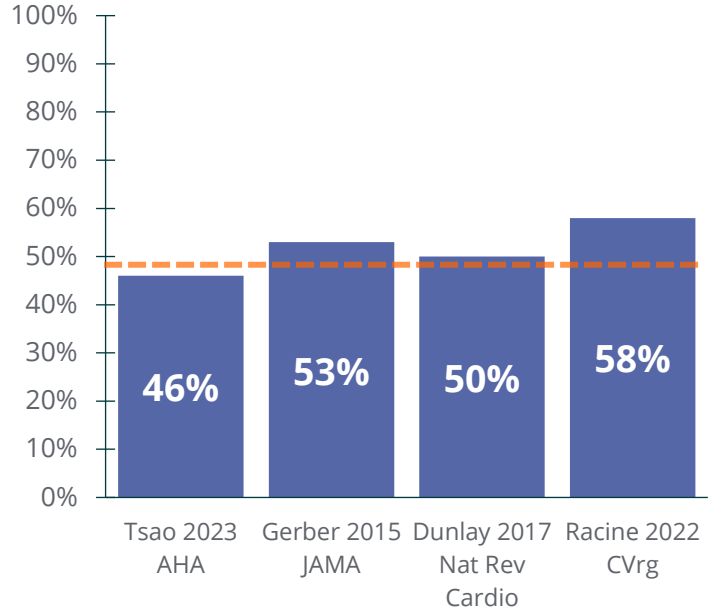
# CK-586: Focusing on Patients with HFpEF and EF ≥ 60

**7.9M**
**Heart Failure Prevalence in 2024, US**

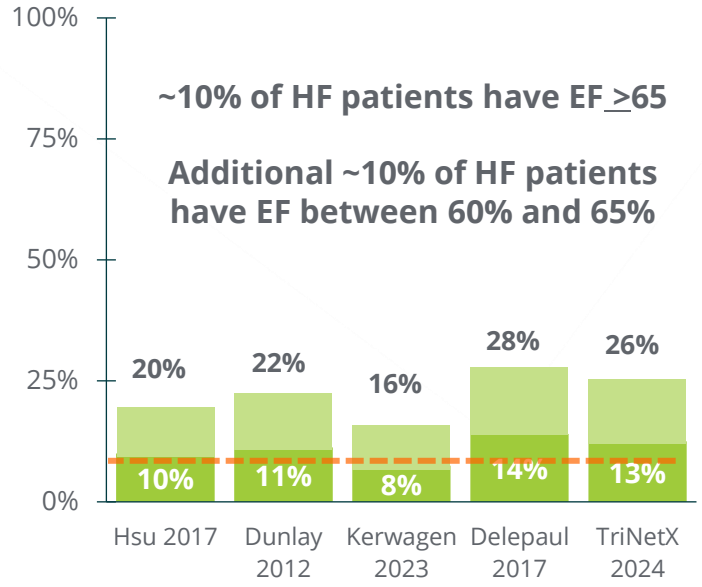
*2024 prevalence calculated using published, historic estimate and projected to 2024 using age adjusted US population growth*




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




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




*Source: Racine et al Heart Failure 2020-2029, CVrg March 2020 p 26; includes patients in long term care settings, which NHANES epi does not incorporate; Benjamin, E. et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the AHA Circulation Vol 139, Issue 10, 5 March 2019; Pages e56-e528 historic growth rate of HF 2009-2012 vs. 2013-2016: 2.1%; the population of 65+ year old is expected to grow at 1.9% according to the UN – mortality improvement of 0.2% per year.; Heidenreich P. at al: Forecasting the Impact of Heart Failure in the United States Circulation: Heart Failure Volume 6, Issue 3 May 2013; Tsao C., et al Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association, Circulation Volume 139, Issue 10 Mar 2019; UN Population Report Nov 2020; Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012 Nov;5(6):720-6. doi: 10.1161/CIRCHEARTFAILURE.111.966366. Epub 2012 Aug 30. PMID: 22936826; PMCID: PMC3661289, Gerber 2015 JAMA, Hsu JJ, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: Clinical Implications and Future Directions. JACC Heart Fail. 2017 Nov;5(11):763-771. doi: 10.1016/j.jchf.2017.06.013. Epub 2017 Oct 11. PMID: 29032140; PMCID: PMC6668914. Kerwagen F, Koehler K, Vettorazzi E, Stangl V, Koehler M, Halle M, Koehler F, Störk S. Remote patient management of heart failure across the ejection fraction spectrum: A pre-specified analysis of the TIM-HF2 trial. Eur J Heart Fail. 2023 Sep;25(9):1671-1681. doi: 10.1002/ejhf.2948. Epub 2023 Jul 31. PMID: 37368507. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, Roger-Rollé A, Domain G, Delon C, Uzan C, Boudjellil R, Carrié D, Roncalli J, Galinier M, Lairez O. Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines? ESC Heart Fail. 2017 May;4(2):99-104. doi: 10.1002/ehf2.12131. Epub 2017 Jan 31. PMID: 28451445; PMCID: PMC5396039.*

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

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# CK-586 May Address Unmet Needs of HFpEF Patients

## Proposed Mechanistic Benefits

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

## Target Product Profile

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

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

# Q&A

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# Closing Remarks

**Robert Blum**
President and Chief Executive Officer

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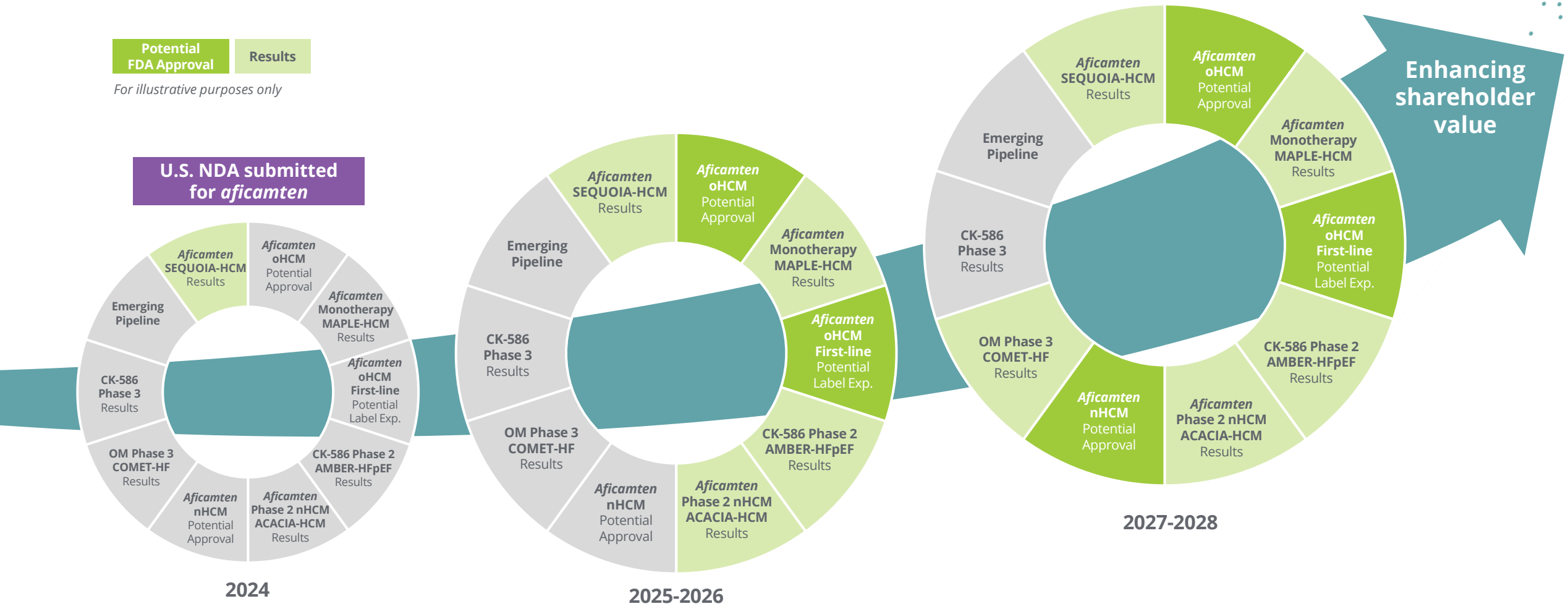
# Myosin Platform Fuels Multiple Milestones and Increased Value




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

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# Addressing Difficult to Treat Populations Within Heart Failure

## Specialty cardiology franchise strategy applies to markets with similar characteristics

**HCM**

**Opportunity for *aficamten* as the anchor**

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

**HFrEF**
Severely reduced EF

**Expanding into adjacent population**

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

**HFpEF**
Supranormal EF

**Addressing underserved segment of HF market**

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


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# Robust Pipeline, Upcoming Commercial Launch & Solid Financial Position

## Commercial

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

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

## Pipeline

***Aficamten***

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

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

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

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

## Foundation

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

**Pioneers** in muscle biology

**$1.4B cash & investments***
with further access to long-term capital, up to $500M**

** As of June 30, 2024*
** $500M comprised of $350 M in term loan facilities with Royalty Pharma, and $150M Royalty Pharma can, at its option, invest in a Phase 3 clinical trial of CK-586 in exchange for an additional 3.5% revenue participation interest in worldwide net sales of CK-586.
***Aficamten, omecamtiv mecarbil and CK-586 are investigational drugs and are not approved by any regulatory agency. Their safety and efficacy have not been established.***

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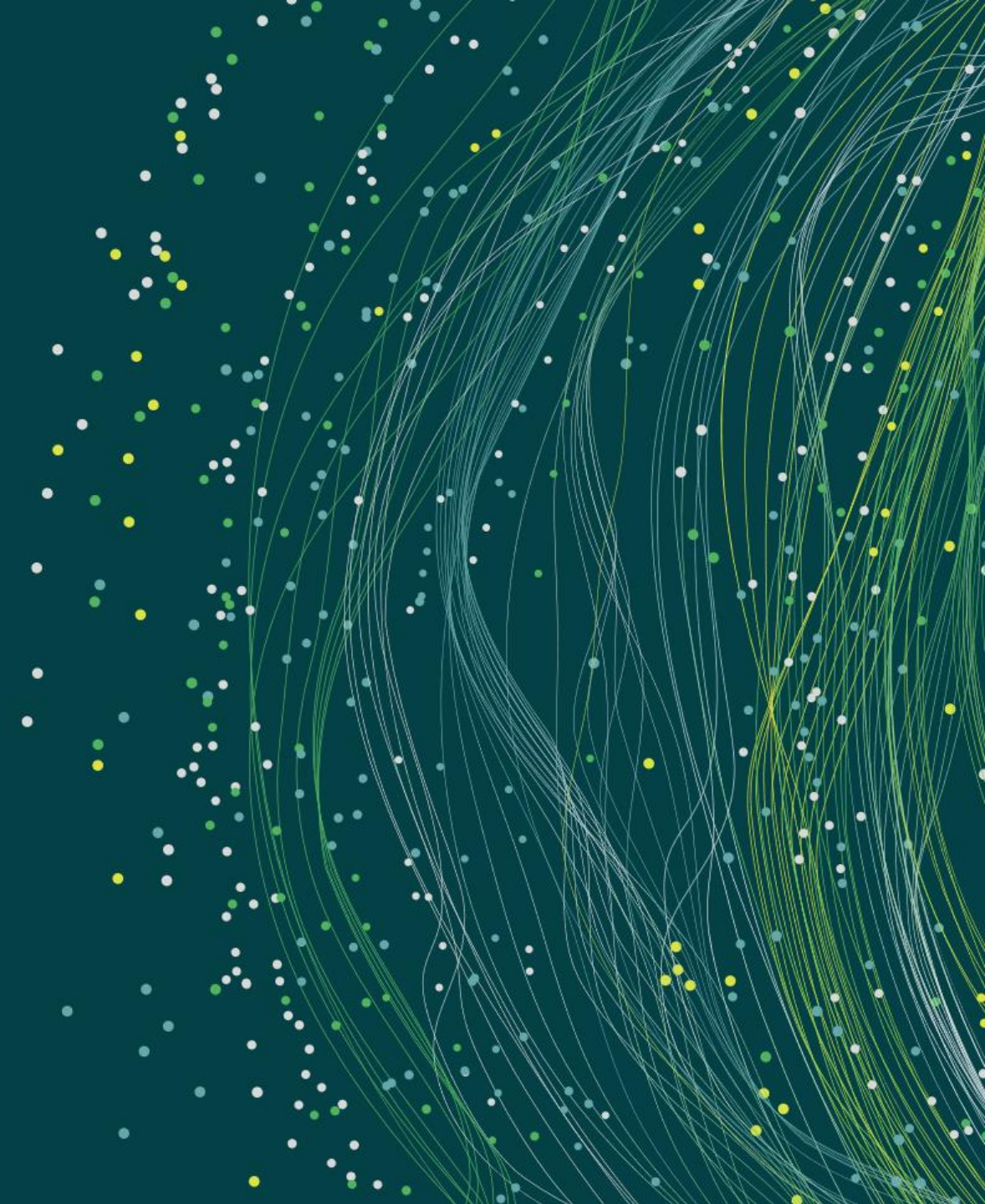
HEART***FORWARD***

Advancing Cardiac Myosin Modulation

# Thank you



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