# Incidence and impact of atrial fibrillation in patients with obstructive HCM treated with *aficamten*: An analysis from the REDWOOD-HCM, SEQUOIA-HCM, and FOREST-HCM trials

Ethan J. Rowin, MD[1]; Martin S. Maron, MD[1]; Iacopo Olivotto, MD[2]; Caroline J. Coats, MD, PhD[3]; Theodore P. Abraham, MD[4]; Michael E. Nassif, MD[5]; Roberto Barriales-Villa, MD[6]; Sara Saberi, MD, MS[7]; Tyrell J. Simkins, DO, PhD[8]; Jenny Wei, PhD[8]; **Ahmad Masri, MD, MS**[9]; on behalf of the REDWOOD-HCM, SEQUOIA-HCM, and FOREST-HCM Investigators

[1]Lahey Hospital and Medical Center, Burlington, MA, USA; [2]Meyer Children's Hospital, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Florence, Italy; [3]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, Scotland; [4]University of California San Francisco, San Francisco, CA, USA; [5]University of Missouri Kansas City Healthcare Institute for Innovations in Quality and Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; [6]Complexo Hospitalario Universitario A Coruña, INIBIC, CIBERCV-ISCIII, A Coruña, Spain; [7]University of Michigan, Ann Arbor, Michigan, USA; [8]Cytokinetics, Incorporated, South San Francisco, CA, USA; [9]Oregon Health & Science University, Portland, OR, USA

AUGUST 31, 2025

ESC Congress 2025 Madrid TOGETHER WITH World Congress of Cardiology

# Disclosures & Acknowledgements

Ahmad Masri reports research grants from Pfizer, Ionis, Attralus, Cytokinetics, and Janssen and consulting fees from BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Cytokinetics, Bristol Myers Squibb, Alnylam, Haya, Edgewise, Alexion, Akros, Prothena, BioMarin, Lexeo, AstraZeneca, Rocket and Tenaya.

The REDWOOD-HCM, SEQUOIA-HCM, and FOREST-HCM Trials were funded by Cytokinetics, Incorporated

We thank the following individuals for their contributions to this clinical trial:

- Participants and their families
- Investigators and study site staff
- Steering Committee members
- Editorial support for the preparation of this presentation was provided by Elyse Smith, PhD, CMPP, on behalf of Engage Scientific Solutions, and was funded by Cytokinetics, Incorporated.

# Background

## Atrial Fibrillation (AF):

- **Common in obstructive hypertrophic cardiomyopathy** (oHCM)[1]
- **Pre-CMI Era:** ~2% per year and associated with morbidity[1]
- **SEQUOIA-HCM**[2]: AF incidence – 2.9% placebo vs 2.8% aficamten
- **Mavacamten:** rates of 2–4.55%
  - EXPLORER-HCM[3] ,VALOR-HCM[4] ,MAVA-LTE[5]

## Cardiac Myosin Inhibitors (CMIs):

- Target the hypercontractility underlying HCM
- Relieve outflow obstruction and improve symptoms in oHCM
- Higher than anticipated rates of new-onset AF over extended periods of mavacamten drug exposure[4-7]

## *Aficamten*:

- **A next-in-class oral, selective CMI**
- **Improvements in[8]:**
  - Exercise capacity
  - LVOT gradients
  - Symptoms and quality of life
- **Modest decrease of LVEF**
- **Stable, predictable PK/PD relationship**
- **Multiple CYP pathway metabolism → minimal DDI**
- **Half-life of ~3.5 days**
  - Dose adjustment without interruption
  - Rapid titration to clinical response[2]
  - Rapid reversibility



LVEF, left ventricular ejection fraction; LVOT, Left ventricular outflow tract obstruction.

1. Rowin EJ, et al. *Circulation.* 2023;148(22):1797-1811; 2. Coats CJ, et al. *J Am Heart Assoc.* 2024;13(15):e035993. 3. Olivotto I, et al. *Lancet.* 2020;396(10253):759-769. 4. Desai MY, et al. *Circulation.* 2025;151(19):1378-1390. 5. Garcia-Pavia P, et al. *Eur Heart J.* 2024;45(47):5071-5083; 6. Owens AT, at al. Heart Failure & World Congress on Acute Heart Failure 2025; Belgrade, Serbia; 7. Davis BJ, et al. *J Am Heart Assoc.* 2025;14(6):e038758; 8. Maron MS, et al. *N Engl J Med.* 2024;390(20):1849-1861;

# Background

- **CMIs have distinct characteristics, binding sites, pharmacology, metabolism, and PK/PD relationship**
- **Efficacy and safety should be studied at the individual CMI level**

## OBJECTIVE

**To analyze rates of new-onset AF and the impact of AF on the efficacy and safety of *aficamten*** over an extended period in patients with oHCM receiving ≥48 weeks *aficamten* treatment in FOREST-HCM (following participation in the parent trial)

# Methods

N=173

**STUDY DESIGN**

**Patients with oHCM were treated with *aficamten* (5–20 mg) for ≥48 weeks in FOREST-HCM (global multicenter open-label extension study)**

following participation in REDWOOD-HCM or SEQUOIA-HCM

## OBSERVATION

### No AF History:

- **Followed for new-onset AF**

  Rate of new-onset AF was compared with the individual predicted risk of AF from[1,2]:

  **1 HCM-AF score:**
  HCM-specific validated prediction model to quantify risk for new-onset AF over a 2-year period and also quantifying risk as low (<1%/year), intermediate (1-2%/year) or high (>2%/year)

  **2 CHARGE-AF score:**
  Validated predictive model to quantify risk for AF in the general population based on comorbidities and gives a risk for AF development over a 5-year period

### History of AF at the time of *aficamten* initiation:

- **Followed for recurrence**

## ANALYSIS

**The following outcomes for patients with AF events were compared with those without AF events throughout the follow-up period:**

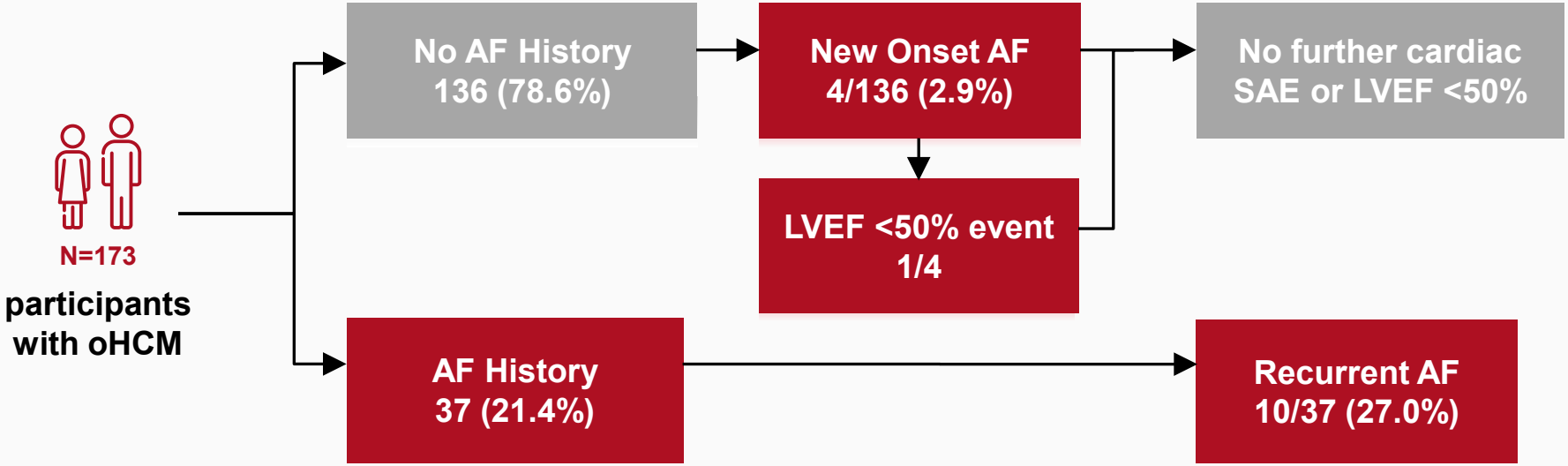
- **Mortality**
- **Systolic dysfunction** (LVEF <50%)
- **Acute heart failure**
- **Efficacy at the latest follow up ≥48 weeks** (reduction in outflow gradients, improvement in NYHA class and KCCQ–CSS)



1. Carrick RT, et al. *Circ Arrhythm Electrophysiol.* 2021;14(6):e009796.; 2. Alonso A, et al. *J Am Heart Assoc.* 2013;2(2):e000102.

AF, atrial fibrillation; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

# Results




**During 269 participant-years of follow-up with *aficamten* (median 1.7 years):**

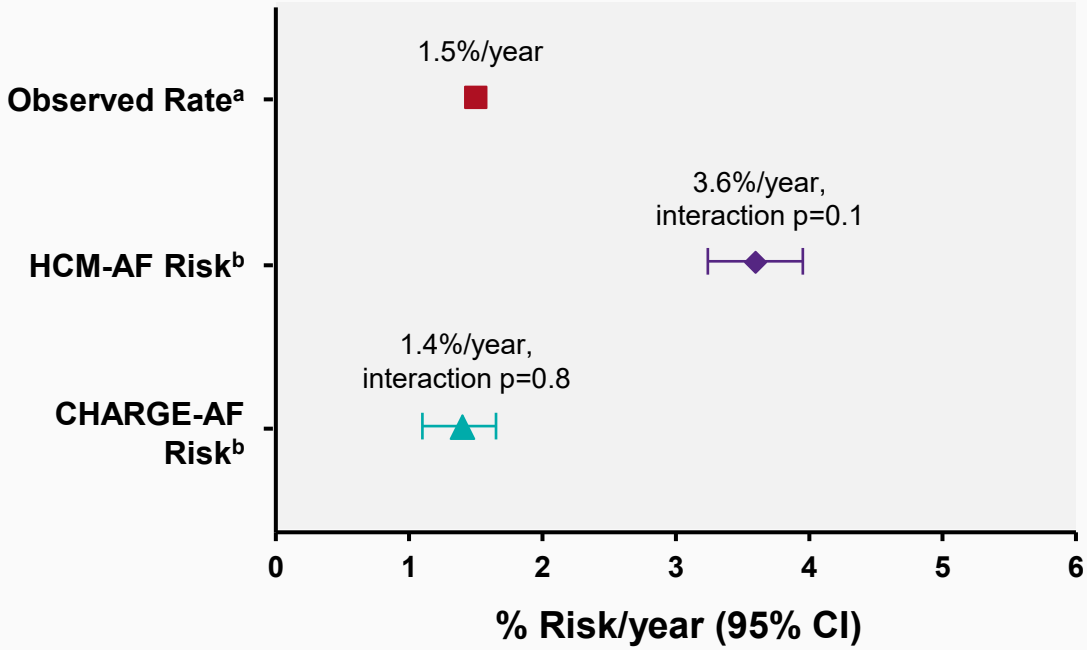
- 4/136 (2.9%) participants developed new-onset AF at a median of 32 weeks with no new onset after 64 weeks (Range: 0.1-63 weeks; **Incidence rate: 1.5%/yr**)



AF, atrial fibrillation; LVEF, left ventricular ejection fraction

# Results: Observed vs Predicted New-Onset AF Rates

The observed rate of new-onset AF in *aficamten* studies was **similar or lower than that predicted** by HCM-AF or CHARGE-AF risk calculators for the same study population




[a] Calculated based on the number of new onset AF cases occurring over 48 weeks of follow up
[b] Calculated risk is the mean per year risk for each score ±95% CI of patients without a history of AF at the time of study entry into FOREST-HCM

AF, atrial fibrillation

# Results: Clinical outcomes and AEs by on-treatment occurrences of AF from baseline to Week 48

| | New-onset or recurrent AF episodes on *aficamten* (n=14) | No AF history or new-onset AF during treatment (n=132) | New-onset or recurrent AF episodes vs no AF on *aficamten* | |
|---|---|---|---|---|
| **Efficacy (change from baseline)** | | | **Between Group Diff** | **p-value** |
| KCCQ-CSS, mean (SE) | 11.1 (3.3) | 15.5 (1.1) | −4.3 (3.5) | 0.2 |
| Improvement in ≥1 NYHA functional class, n (%) | 11 (78.6) | 96 (72.7) | 5.8[a] | 0.6 |
| LVOT at rest, mmHg, mean (SE) | −47.6 (4.0) | −42.2 (1.3) | −5.5 (4.2) | 0.19 |
| LVOT gradient with Valsalva, mmHg, mean (SE) | −76.0 (7.2) | −58.4 (2.3) | −17.5 (7.5) | 0.02 |
| LV ejection fraction (%) | −4.4 (1.5) | −4.0 (0.5) | −0.3 (1.6) | 0.8 |
| NT-proBNP, geometric mean (95% CI) of prop. change | 0.4 (0.2–0.5) | 0.2 (0.2–0.3) | 1.5[b] | 0.07 |
| Troponin I, geometric mean (95% CI) of prop. change | 0.4 (0.3–0.5) | 0.6 (0.5–0.6) | 0.7[b] | 0.04 |
| **Events of Interest, per 100 patient-years (EAIR)** | | | | |
| Mortality | 0 | 0 | – | |
| LVEF <50% | 3.8 | 3.2 | – | |
| LVEF ≤30% | 0 | 0 | – | |
| Acute HF hospitalization | 0 | 0.4[c] | – | |
| Ventricular arrhythmia requiring treatment | 0 | 0.4 | – | |
| Embolic stroke | 3.8[d] | 0.4 | – | |

- **Patients with any AF episode experienced similar degrees of symptom and outflow gradient improvement**
- **There was no difference in rates of serious adverse cardiac events through latest follow up** compared with the 132 patients without AF history who did not experience an AF event

[a]Rate difference. [b]Ratio of geometric least squares means. 1 patient with acute HFH, no systolic dysfunction. [d]Embolic stroke occurred in 1 of the 14 patients with new-onset or recurrent AF on direct oral anticoagulant and was considered secondary to previously undiagnosed atrial septal defect.
AE, adverse event; AF, atrial fibrillation; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; EAIR, Event Adjusted Incidence Rate.

# Conclusions

- The annualized risk for new-onset AF during *aficamten* treatment was low (1.5%/year), occurring in just 4 participants
- The observed incidence of new-onset AF was numerically lower than predicted rates based on the HCM-AF risk score, and similar to the rate by CHARGE-AF
- There was no evidence AF (new onset or recurrent) impacted safety or efficacy of *aficamten* in oHCM patients

**Prolonged treatment with *aficamten* for ≥48 weeks did not lead to increased AF risk**

***Aficamten* is effective in oHCM patients studied regardless of AF history**



AF, atrial fibrillation

# Simultaneous publication in *Heart Rhythm*

**Low Incidence of Atrial Fibrillation in Patients with Obstructive HCM Treated with Aficamten: An Analysis from the REDWOOD-HCM, SEQUOIA-HCM and FOREST-HCM Trials**

**Running title: Incidence of Atrial Fibrillation on Aficamten**

Ethan J. Rowin, MD[1]; Martin S. Maron, MD[1]; Iacopo Olivotto, MD[2]; Caroline J. Coats, MD, PhD[3]; Theodore P. Abraham, MD[4]; Michael E. Nassif, MD[5]; Roberto Barriales-Villa, MD[6]; Sara Saberi, MD, MS[7]; Stephen B. Heitner, MD[8]; Daniel L. Jacoby, MD[8]; Stuart Kupfer, MD[8]; Fady I. Malik, MD, PhD[8]; Tyrell Simkins, DO, PhD[8]; Jenny Wei, PhD[8]; Ahmad Masri, MD, MS[9]; on behalf of the REDWOOD-HCM, SEQUOIA-HCM, and FOREST-HCM Investigators

[1]Lahey Hospital and Medical Center, Burlington, MA, USA; [2]Meyer Children's Hospital, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Florence, Italy; [3]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, Scotland; [4]University of California San Francisco, San Francisco, CA, USA; [5]University of Missouri Kansas City Healthcare Institute for Innovations in Quality and Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; [6]Complexo Hospitalario Universitario A Coruña, INIBIC, CIBERCV-ISCIII, A Coruña, Spain; [7]University of Michigan, Ann Arbor, Michigan, USA; [8]Cytokinetics, Incorporated, South San Francisco, CA, USA; Oregon Health & Science University, Portland, OR, USA[9]