CTC-006

A Phase 3 Randomized Controlled Trial Comparing *Aficamten* vs Metoprolol in Patients With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

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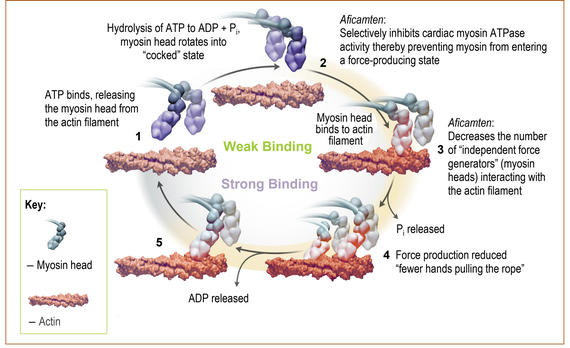
BACKGROUND

- Hypertrophic cardiomyopathy (HCM) is a disease affecting the cardiac sarcomere, resulting in myocardial hypercontractility and cardiac hypertrophy.
- People with obstructive HCM (oHCM) have left ventricular outflow tract (LVOT) obstruction that creates an LVOT gradient (LVOT-G) during systole and is the primary driver for the development of heart failure symptoms.
- Beta-blockers are currently the first-line agent for the treatment of symptomatic oHCM based on guidance provided by ESC and ACC/AHA.[1,2]
- Although beta-blockers have been shown to reduce symptom burden and improve hemodynamics, they do not improve exercise capacity and can be associated with poor tolerability.[3,4] Moreover, there are no controlled data on the long-term effects of beta-blockers on cardiac structure and function.
- *Aficamten* is a next-in-class cardiac myosin inhibitor (CMI) that selectively and reversibly stabilizes the lever arm of cardiac myosin in the relaxed position, decreasing the number of myosin molecules bound to actin, resulting in decreased contractility (**Figure 1**).[5]
- *Aficamten* was safe and well tolerated in healthy participants in a Phase 1 study.[6] In addition, the pharmacokinetic properties of *aficamten* allowed for titration as early as 2 weeks.[6]
- The Phase 2 REDWOOD-HCM study demonstrates that treatment with *aficamten* for 10 weeks was generally well tolerated in participants with symptomatic oHCM.[7,8]
  - There were also marked improvements in LVOT-G (resting and Valsalva), NYHA functional class (FC), and cardiac biomarkers (NT-proBNP and hs-cTnI).

Figure 1. *Aficamten* mechanism of action



Note: *Aficamten* is an investigational agent that is not approved by any regulatory agency, including the US FDA. Its safety and efficacy has not been established.
ADP, adenosine diphosphate; ATP, adenosine triphosphate; P_i, inorganic phosphate.

OBJECTIVES

- The **overall objective** of this head-to-head comparison trial is to evaluate the safety and efficacy of *aficamten* as:
  - **First-in-line therapy** for participants recently diagnosed with symptomatic oHCM and/or treatment-naïve; or
  - **Monotherapy** for participants previously receiving standard of care (SOC) medical therapy for symptomatic oHCM.
- **Primary objective:** To evaluate the effect of *aficamten* compared with metoprolol on exercise capacity in participants with symptomatic oHCM.
- **Secondary objectives:** To evaluate the effect of *aficamten* compared with metoprolol from baseline to Week 24 on NYHA FC, health status, structural remodeling (according to echocardiographic parameters), cardiac biomarkers, and post-Valsalva LVOT-G.
- A unique patient experience substudy for participants in the USA will provide understanding of the patient experience with oHCM.

STUDY DESIGN

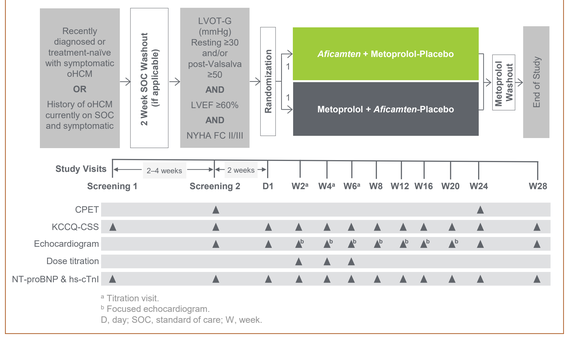
- MAPLE-HCM (**M**etoprolol vs ***A***fficamten in **P**atients with **L**VOT Obstruction on **E**xercise Capacity in **HCM**) is a Phase 3 head-to-head trial (NCT05767346) designed to compare the efficacy of *aficamten* vs metoprolol on exercise capacity, heart failure symptoms, cardiac structure and function, and safety and tolerability in participants with symptomatic oHCM.

Study Schema

- Trial to enroll ~170 participants.

Randomization will be double-blind and double-dummy:
Aficamten + Metoprolol-Placebo
vs
Metoprolol + ***Aficamten***-Placebo

Figure 2. Study schema



[a] Titration visit.
[b] Focused echocardiogram.
D, day; SOC, standard of care; W, week.

ENDPOINTS

Endpoints
Primary Endpoint
• Change in pVO_2 from baseline to Week 24, assessed by CPET.
Secondary Endpoints (Week 24)
• Change from baseline in: – Proportion of participants with ≥1 class improvement in NYHA FC. – KCCQ-CSS. – Left ventricular mass index (LVMI) and left atrial volume index (LAVI). – NT-proBNP. – Post-Valsalva LVOT-G.
Safety Endpoints
• Incidence of reported major adverse cardiac events (CV death, cardiac arrest, nonfatal stroke, nonfatal myocardial infarction, CV hospitalization). • Incidence of AEs. • Incidence of LVEF <50%.

Design

- Randomization will be stratified according to CPET exercise modality (treadmill vs bicycle) and recently diagnosed vs chronic oHCM.
- All participants may receive up to 4 escalating doses of investigational product over the initial 6 weeks:
  - *Aficamten* 5, 10, 15, 20 mg.
  - Metoprolol 50, 100, 150, 200 mg.
- The titration schema for dose adjustments will be based on echocardiographic metrics in the *aficamten* arm, and both echocardiographic metrics and vital signs in the metoprolol arm.

Titration algorithm

Dose Adjustment Metric	*Aficamten*	Metoprolol
For dose escalation, all criteria must be met. For down-titration or IP discontinuation, only one criterion must be met.		
Systolic BP	NA	≥90 mmHg – can increase dose <90 mmHg – reduce dose (any visit)
Heart rate	NA	≥55 bpm – can increase dose 50–54 bpm – no dose change <50 bpm – reduce dose (any visit)
LVEF	≥55% – can increase dose 50–54% – no dose change <50% – reduce dose (any visit) <40% – temporary discontinuation (any visit)	≥55% – can increase dose 50–54% – no dose change <50% – reduce dose (any visit) <40% – temporary discontinuation (any visit)
Post-Valsalva LVOT-G	≥30 mmHg – can increase dose <30 mmHg – no dose change	≥30 mmHg – can increase dose <30 mmHg – no dose change

BP, blood pressure; IP, investigational product; NA, not applicable.

Sample Size Assumptions

- Assuming:
  - Change in pVO_2 of 2 mL/kg/min for *aficamten* compared with metoprolol.
  - Standard deviation of 3 mL/kg/min for the primary endpoint.
  - 10% missingness for the primary endpoint.
- A sample size of 170 participants will provide >90% power to detect a significant difference at Week 24.

Key Entry Criteria

Key Inclusion Criteria

- NYHA FC II or III at screening
- Screening echocardiogram with:
  - Resting LVOT-G ≥30 mmHg **AND/OR**
  - Valsalva LVOT-G ≥50 mmHg **AND**
  - LVEF ≥60%
- Respiratory exchange ratio (RER) ≥1.05 and pVO_2 <100% predicted
- KCCQ-CSS ≥35 and ≤90
- Participants previously exposed to mavacamten are allowed to participate but must be off mavacamten for ≥8 weeks prior to signing of informed consent; Medical Monitor approval needed

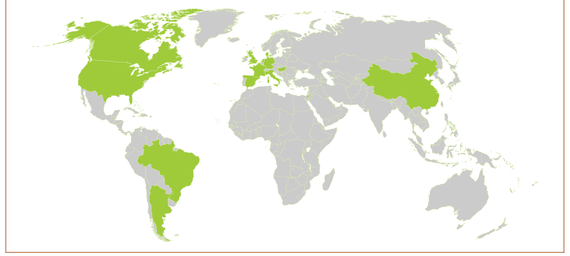
Key Exclusion Criteria

- Medical indication for either beta-blocker or calcium channel blockers prohibiting drug discontinuation
- Contraindication to beta-blocker therapy
- Resting systolic BP >160 mmHg
- Resting heart rate >100 bpm
- History of paroxysmal or persistent atrial fibrillation or atrial flutter. Atrial flutter treated with radiofrequency ablation without recurrence within the last 6 months prior to screening is allowed
- History of septal reduction therapy within 6 months of screening

Trial Status

- The study is currently open to enrollment in the USA with other regions to follow.

Figure 3. World Map



SUMMARY

- MAPLE-HCM is the first Phase 3 multicenter, randomized, double-blind, head-to-head comparison of *aficamten* to current standard of care (metoprolol) in adults with symptomatic oHCM.
- Despite beta-blocker treatment representing foundational treatment for >60 years in oHCM, MAPLE-HCM will generate the first assessment of chronic treatment with metoprolol in participants with oHCM.
- Data from this important trial are aimed at producing the necessary evidence to inform the use of aficamten as a potential first-line monotherapy, and its placement among the pharmacologic options for oHCM.
- Enrollment is currently ongoing with anticipated study completion in 2025.

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Abbreviations

ACC, American College of Cardiology; AE, adverse event; AHA, American Heart Association; CPET, cardiopulmonary exercise testing; CV, cardiovascular; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; hs-cTnI, high sensitivity cardiac troponin-I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOT-G, left ventricular outflow tract-gradient; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2 peak oxygen uptake.

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