CTC-005

A Phase 3, Multicenter, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of *Aficamten* Compared with Placebo in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

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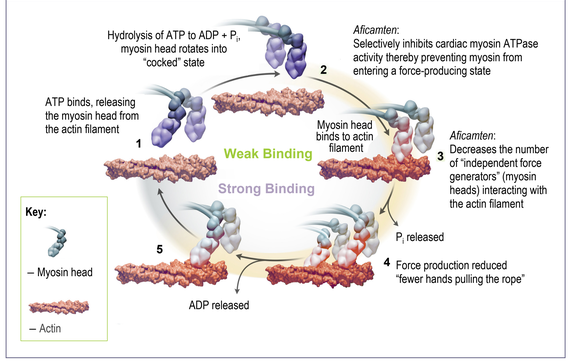
BACKGROUND

- The fundamental pathophysiologic abnormality underlying hypertropic cardiomyopathy (HCM) is myocardial hypercontractility with associated cardiac hypertrophy, impaired relaxation, and altered myocardial energetics.
- Patients with non-obstructive HCM (nHCM) have limited therapeutic options.
- *Aficamten* is a next-in-class small-molecule allosteric cardiac myosin inhibitor that decreases cardiac hypercontractility by selectively and reversibly inhibiting cardiac myosin (**Figure 1**).[1]

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 have not been established.
ADP, adenosine diphosphate; ATP, adenosine triphosphate; P_i, inorganic phosphate.

- In the Phase 2 REDWOOD-HCM trial (Cohort 4), 10 weeks of treatment with *aficamten* was well tolerated in 41 participants with symptomatic nHCM, and with a reassuring safety profile.[2]
  - Echocardiogram-based dose titration led to a 10.6-point improvement in mean KCCQ-CSS, with 55% of participants experiencing ≥1 NYHA functional class (FC) improvement.
  - Overall, LVEF decreased by 5.4% by Week 10, which reversed during a 2-week washout period, with no treatment-related serious adverse events.
  - From baseline to Week 10, there was a 22% reduction in hs-TnI and a 56% reduction in NT-proBNP.

ACACIA-HCM Study

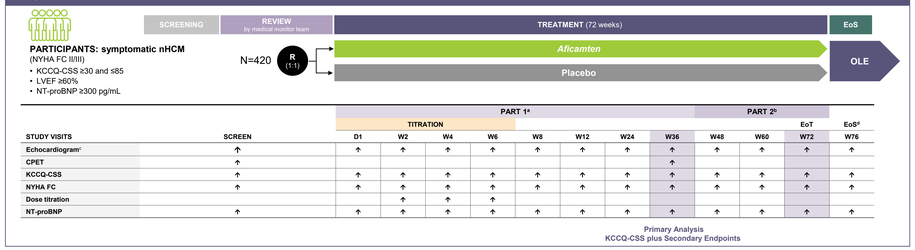
- The data from the Phase 2 study confirmed support for further evaluation of *aficamten* in participants with symptomatic nHCM in the Phase 3 trial ACACIA-HCM (**A**ssessment **C**omparing ***A**ficamten* to Placebo on **C**ardiac Endpoints **I**n **A**dults with Non-Obstructive **HCM**).
- The trial will evaluate the effect of ≥36 weeks (up to 72 weeks) of treatment with *aficamten* on health status, cardiac biomarkers, cardiac remodeling, and clinical outcomes in participants with symptomatic nHCM.

STUDY DESIGN

Study Schema

- Phase 3, randomized, placebo-controlled, double-blind, trial of *aficamten* in participants with symptomatic nHCM (**Figure 2**).
- Streamlined trial protocol to emphasize rapid titration to maximum tolerated dose and few visits post-titration.
- A cardiac MRI and a PK substudy will enroll up to 100 and 30 participants, respectively.
- At the end of study participation, participants will roll-over into an open-label extension (OLE) study.

Figure 2. ACACIA-HCM: Study schema



		PART 1[a]								PART 2[b]			
		TITRATION										EoT	EoS[c]
STUDY VISITS	SCREEN	D1	W2	W4	W6	W8	W12	W24	W36	W48	W60	W72	W76
Echocardiogram[c]	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
CPET	↑								↑				
KCCQ-CSS	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
NYHA FC	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Dose titration		↑	↑	↑	↑								
NT-proBNP	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
									Primary Analysis KCCQ-CSS plus Secondary Endpoints				

[a] Part 1: All participants followed until Week 36. [b] Part 2: Participants completing Week 36 continue until either Week 72 (followed by EoS at Week 76) *or* until the last randomized participant in Part 1 completes Week 36. [c] Site-read focused echocardiogram for titration visit (sole criterion). *Aficamten* dose range 5–20 mg. [d]4-week follow-up after last dose.
D, day; EoS, end of study; EoT, end of treatment; R, randomization; W, Week.

Study Drug

- *Aficamten* or placebo will be administered orally once per day (QD).
- All participants will start on 5 mg *aficamten* QD, with the potential to escalate through 10, 15, and 20 mg QD. Dose adjustments will be driven by blinded, site-read echocardiograms at 2-week intervals (Weeks 2, 4, and 6) (**Tables 1** and **2**).

Table 1. Titration period dose titration

	Dose 1 (Starting Dose) (Day 1)	Dose 2[a] (Week 2)	Dose 3[a] (Week 4)	Dose 4[a] (Week 6)
LVEF ≥60% on echocardiogram	5 mg	Next higher dose, 10 mg max	Next higher dose, 15 mg max	Next higher dose, 20 mg max

[a] After a dose is down-titrated, no further uptitration is permitted. If LVEF <50% on 5 mg, participants will receive placebo.

Table 2. Echocardiogram criteria for scheduled dose titration

LVEF	*Aficamten*
≥60%	Increase dose (Weeks 2, 4, and 6 only)
≥50% to <60%	Remain on the same dose
<50%	Reduce dose (any visit)
<40%	Temporary discontinuation (any visit)

Procedures

- Primary and secondary endpoints will be assessed at Week 36 (**Figure 2**).
- After Week 36 (Part 1), participants can continue in the same arm until Week 72 (Part 2) until the last randomized patient has completed follow-up at Week 36; after that, participants can roll over into a long-term OLE study.
- When participants exit the study, they will have an end of treatment visit followed by a 4-week washout period, after which they will have a repeat echocardiogram, clinical examination, and blood work (end of study).

Statistical Power

- The study will randomize ~420 participants in a 1:1 ratio, providing >90% power to detect a difference in the mean KCCQ-CSS of 5 (SD 15) between the 2 treatment arms, with a 2-sided type I error of 0.05 and an assumed 10% rate of missing data.

ENDPOINTS

Endpoints
Primary Endpoint
• Change from baseline to Week 36 in KCCQ-CSS
Secondary Endpoints
• Change from baseline to Week 36 in: – Composite of 2 Z-scores of CPET parameters: peak oxygen uptake (pVO_2) and VE/VCO_2 slope – Proportion of participants with ≥1 class improvement in NYHA FC – NT-proBNP – Left atrial volume index
• Time to first event for the composite of cardiovascular death, heart transplantation or LVAD, aborted sudden cardiac death, nonfatal stroke, heart failure hospitalization, or cardiac arrythmia (atrial fibrillation or ventricular tachyarrhythmia) requiring treatment or hospitalization
Safety Endpoints
• Incidence of adverse events • Incidence of LVEF <50% and worsening HF and/or 30% increase in NT-proBNP • Incidence of LVEF <40%

Key Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• 18–85 years of age	• Significant valvular heart disease
• LVOT-G <30 mmHg at rest and <50 mmHg with provocation	• Infiltrative, genetic, or storage disorder causing cardiac hypertrophy that mimics nHCM
• BMI ≤40 kg/m^2	• Current >70% coronary artery stenosis
• Symptomatic (NYHA FC II/III) nHCM	• History of: – LV systolic dysfunction (LVEF <45%) – Syncope, symptomatic ventricular arrhythmia, or sustained ventricular tachyarrhythmia with exercise within 3 months – Resistant hypertension
• KCCQ-CSS score ≥30 and ≤85	• Inability to exercise on a treadmill or bicycle
• LVEF ≥60%	• Oxygen saturation reading <90%
• CPET: Respiratory exchange ratio ≥1.00; peak VO_2 ≤90% of age and sex predicted maximum	• Prior treatment with *aficamten* or mavacamten
• NT-proBNP: – ≥300 pg/mL or ≥900 pg/mL if in AFF – Black participants: ≥225 pg/mL or ≥675 pg/mL if in AFF	• Septal reduction therapy within 6 months of screening
• Hemoglobin ≥10 g/dL	
• Beta-blocker use stabilized >2 weeks	

Trial Status and Locations

- The trial is currently enrolling participants.
- ~150 international sites are planned worldwide in 20+ countries.

SUMMARY

- ACACIA-HCM is a pivotal Phase 3 trial evaluating *aficamten* for nHCM.
- The trial is ongoing, with participation worldwide.

References

1. Chuang C, et al. *J Med Chem* 2021;64:14142-52.
2. Masri A, et al. ACC 72nd Annual Scientific Sessions, poster 1560-153; New Orleans, LA, USA, March 4–6, 2023.

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Abbreviations

AFF, atrial fibrillation/flutter; BMI, body mass index; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; echo, echocardiogram; HCM, hypertrophic cardiomyopathy; HF, heart failure; hs-TnI, high sensitivity troponin-I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVAD, left ventricular assist device; LVEDV, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; LVOT-G, LVOT gradient; MWT, maximal wall thickness; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; oHCM, obstructive HCM, pVO_2, peak oxygen uptake; PK, pharmacokinetics; RER, respiratory exchange ratio; SoC, standard of care; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen volume.

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