CTC-001

Safety, Efficacy, and Quantitative Understanding of Obstruction, Impact of *Aficamten* in Hypertrophic Cardiomyopathy (SEQUOIA-HCM) Study Design: A Phase 3 Study

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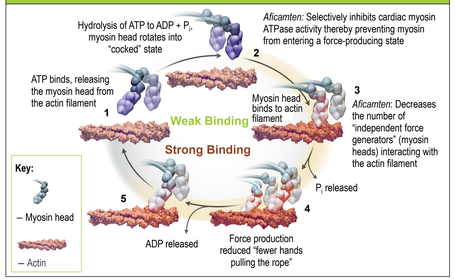
BACKGROUND

- HCM is a disease of the cardiac sarcomere, and the fundamental pathophysiologic abnormality is myocardial hypercontractility with associated cardiac hypertrophy. In patients with obstructive disease (oHCM), dynamic left ventricular outflow tract (LVOT) obstruction creates a high-pressure LVOT gradient (LVOT-G) during systole. Patients with oHCM often develop signs and symptoms of heart failure, such as dyspnea and fatigue.
- *Aficamten* is a next-in-class small molecule cardiac myosin inhibitor that decreases cardiac hypercontractility by selectively and reversibly inhibiting cardiac myosin (**Figure 1**).[1]
- *Aficamten* stabilizes the lever arm of myosin in the relaxed position, decreasing the number of myosin molecules available to bind actin and generate force during systole.

Figure 1. *Aficamten* mechanism of action



ADP, adenosine diphosphate; ATP, adenosine triphosphate; P_i, inorganic phosphate

- In the Phase 1 study, *aficamten* had a favorable safety profile and pharmacokinetic properties allowing for 2-week titration intervals.[2]
- In the Phase 2 REDWOOD-HCM trial, 10 weeks of *aficamten* was well tolerated, with an adverse event profile similar to placebo.[3]
  - The echocardiographic-based dose-adjustment approach led to marked reduction in LVOT-G and improvement in symptoms compared with placebo in patients with oHCM on standard of care therapy with or without disopyramide, in the absence of clinically significant LVEF reductions or treatment interruptions.[3,4]
  - Secondary objectives showed decreases in LAVI[5] and improvements in echocardiographic diastolic indices, biomarkers, and quality of life.[3,4]

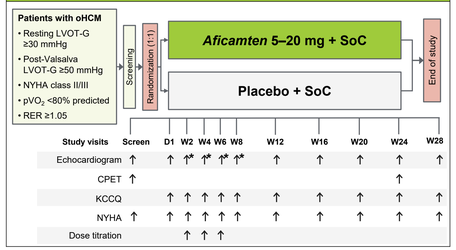
SEQUOIA-HCM

- The data from the Phase 2 study defined the doses for further assessment and supported the evaluation of *aficamten* in symptomatic oHCM in a Phase 3 trial, SEQUOIA-HCM (NCT05186818).
- The trial will be undertaken to evaluate the effect of *aficamten* treatment for 24 weeks on exercise capacity in patients with symptomatic oHCM.

DESIGN

- SEQUOIA-HCM is a Phase 3, randomized, placebo-controlled, double-blind, parallel-group, multicenter trial of *aficamten* in patients with oHCM (**Figure 2**).

Figure 2. SEQUOIA-HCM trial overview



* Site-read focused echocardiogram for titration visit (sole criteria).

Study Drug

- *Aficamten* (or placebo) will be administered orally once per day, with or without food.
- All patients will start on 5 mg once daily of *aficamten*, with the potential to escalate through 10, 15, and 20 mg once daily. Dose adjustments will be driven solely by blinded, site-read echocardiograms at 2-week intervals (Weeks 2, 4, and 6), as shown below.

Echocardiogram Criteria for Scheduled Dose Titrations at Weeks 2, 4, & 6

Biplane LVEF		Post-Valsalva LVOT-G	Action
<50%			Reduce Dose[a]
≥50% – 55%			No Dose Change
≥55%	and	<30 mmHg	No Dose Change
≥55%	and	≥30 mmHg	Increase Dose

[a] Once a dose is down-titrated, no further escalation is permitted. If the patient has LVEF <50% while receiving 5 mg, they will receive placebo.

- Patients will continue background oHCM therapy throughout.

Procedures

- CPET and other assessments will take place as shown in **Figure 2**, with the final efficacy assessment at Week 24.
- After Week 24, there will be a 4-week washout period followed by repeat echocardiogram, clinical examination, and blood work at Week 28 (end of study).
- Patients will be immediately eligible for roll-over into an open-label extension study (REDWOOD-HCM OLE; NCT04848506) for long-term access to *aficamten*.

Statistical Power

- The study will randomize ~270 patients in a 1:1 ratio, providing more than 90% power to detect a difference of change in pVO_2 of 1.5 (standard deviation 3.5) between the two treatment arms with a 2-sided type I error of 0.05.

ENDPOINTS

Endpoints

Primary Endpoint

- Change from baseline to Week 24 in peak oxygen uptake (pVO_2) on CPET

Secondary Endpoints

- Change from baseline to Week 12 and Week 24 in:
  - KCCQ-CSS
  - Proportion of patients with ≥1 class improvement in NYHA functional class
  - Post-Valsalva LVOT-G
  - Proportion of patients with post-Valsalva LVOT-G <30 mmHg
- Change from baseline to Week 24 in:
  - Exercise capacity, as measured by the change in total workload during CPET

Exploratory Endpoints

- Change from baseline to Week 24 in:
  - Oxygen uptake efficiency slope (VO_2/logVE slope), circulatory power (VO_2 × systolic BP), and ventilatory anaerobic threshold
  - Echocardiographic measurements (LVEF, LVESV, LVEDV, and LAVI)
  - NT-pro-BNP, cTnI, and other biomarkers
  - CMR measurements (LVMI, LVEF, MWT, LAVI, LVESV, and LVEDV)

Safety Endpoints

- Incidence of major adverse cardiac events; incidence of LVEF <50%

PATIENTS

Key Inclusion Criteria

- Male or female, ≥18 to ≤85 years; body mass index <35 kg/m^2
- Diagnosed with HCM by standard criteria[6]
- NYHA class II or III at screening
- Resting LVOT-G ≥30 mmHg **and** post-Valsalva LVOT-G ≥50 mmHg during screening*
- LVEF ≥60% at screening*
- RER ≥1.05 and pVO_2 <80% predicted on screening CPET*
- Hemoglobin ≥10 g/dL at screening
- Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on stable doses for >6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial

*per core laboratory

Key Exclusion Criteria

- Known or suspected infiltrative, genetic, or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis)
- Significant valvular heart disease (per investigator judgment).
  - Moderate–severe valvular aortic stenosis
  - Moderate–severe mitral regurgitation not due to systolic anterior motion of the mitral valve
- History of LV systolic dysfunction (LVEF <45%) or stress cardiomyopathy at any time during the patient's clinical course
- Treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the trial period
- Documented paroxysmal atrial fibrillation during the screening period
- History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening
- Received prior treatment with *aficamten* or mavacamten

CMR Substudy Exclusion Criteria

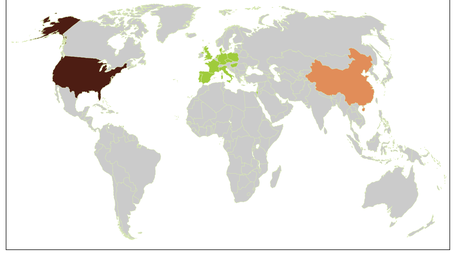
A CMR substudy will evaluate the impact of *aficamten* on additional metrics of cardiac structure and function.

- Patients will be excluded if they:
  - Are unable to tolerate CMR
  - Have an implantable cardioverter defibrillator
  - Have a cardiac pacemaker

Trial Status and Locations

- The trial is currently enrolling patients and is anticipated to complete in 2023.
- **Figure 3** shows locations of currently active sites.
  - Approximately 100 international sites are planned, at centers in North America, Europe, and Asia.

Figure 3. SEQUOIA-HCM trial locations



Activation of sites is ongoing; for currently active locations, please see https://www.clinicaltrials.gov/ct2/show/NCT05186818

SUMMARY

- SEQUOIA-HCM is a pivotal Phase 3 trial evaluating *aficamten* in addition to standard of care for oHCM.
  - It will be the largest trial ever conducted for oHCM.
  - The trial is ongoing with participation worldwide and expected completion in 2023.

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Disclosures

AO, CC, TPA, MSM, IO, MA, NC, CM, LC, H-DD, PG, AH, MM, AO, ATO, JT-H, JV, HW, and AM are members of the steering committee or investigators for the SEQUOIA-HCM trial, and report research funding from Cytokinetics, Inc. CC reports speaker fees from Alnylam and advisory fees from Cytokinetics. MSM reports consultant/advisor fees from Imbria and Takeda, and steering committee fees for REDWOOD-HCM from Cytokinetics. IO reports speakers' bureau fees from Boston Scientific, Amicus, and Novartis, consultant/advisor fees from Bristol Myers Squibb (BMS), Cytokinetics, Sanofi Genzyme, Amicus, Bayer, Tenaya, and Rocket Pharma, and research grant funding from BMS, Cytokinetics, Sanofi Genzyme, Amicus, Bayer, Menarini International, and Boston Scientific. MA reports consultant and lecture fees from BMS. PG-P reports speakers' bureau fees from Pfizer and Alnylam, consultant/advisor fees from Pfizer, Alnylam, MyoKardia/BMS, Cytokinetics, Neuroimmune, BridgeBio, Attralus, and AstraZeneca, research/educational grants to his institution from Pfizer, BridgeBio, and Alnylam. ATO reports consultant/advisor fees from Cytokinetics, BMS/MyoKardia, and Pfizer. HW reports consultant/advisor fees from Cytokinetics, BioMarin, and BridgeBio. AM reports consultant/advisor fees from Tenaya, Attralus, Cytokinetics, BMS, and Ionis, and Research Grants from Ionis, Akcea, Pfizer, Ultromics, and Wheeler Foundation. NC is on the advisory boards for mavacamten at BMS and for *aficamten* at Cytokinetics. H-DD reports grants from Novartis, CSL Behring, Cytokinetics. AH reports consultant/advisor fees from Cytokinetics, BMS, Sanofi Genzyme, Amicus, Pfizer. MM reports consultant/advisor fees from Cytokinetics and BMS/Myokardia and speakers' bureau fees from BMS and Pfizer. AO reports investigator fees from MyoKardia (BMS), consultant/advisor fees from Biotronik Polska, Abbott Polska, and traveling fees from Hammermed. JT-H is a consultant for Leo Pharma. CM, TPA, LC and JV report no additional disclosures. SBH, DJ, SK, FIM, LM, and AW are employees of Cytokinetics, Inc., and hold stock in the company. SLP was an employee of Cytokinetics at the time of this study.

Abbreviations

CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; cTnI, high-sensitivity cardiac-troponin I; HCM, hypertrophic cardiomyopathy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI, left atrial volume index; 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, New York Heart Association; oHCM, obstructive HCM, pVO_2, peak oxygen uptake; RER, respiratory exchange ratio; SoC, standard of care; VO_2, oxygen volume.

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