Circulation: Heart Failure

METHODS PAPERS

Efficacy and Safety of Aficamten in Children and Adolescents With Obstructive Hypertrophic Cardiomyopathy: Study Design and Rationale of CEDAR-HCM

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BACKGROUND: Hypertrophic cardiomyopathy (HCM) is an important cause of morbidity and mortality in children, but treatment options are limited. Aficamten, a next-in-class cardiac myosin inhibitor, directly targets the hypercontractility underlying HCM. Aficamten improved exercise capacity, health status, and symptoms in adults with obstructive HCM in the pivotal, phase 3 SEQUOIA-HCM trial (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; NCT05186818).

METHODS: CEDAR-HCM (Clinical Evaluation of dosing With Aficamten to Reduce Obstruction in Pediatric Population With HCM) is an international, multicenter, randomized, double-blind, placebo-controlled trial followed by an open-label extension to evaluate the efficacy, safety, and pharmacokinetics of aficamten in pediatric participants with symptomatic obstructive HCM. The trial will enroll ≈55 adolescents (12 to <18 years) and subsequently expand to include at least 10 children (6 to <12 years) with nonsyndromic obstructive HCM, left ventricular ejection fraction ≥60%, Valsalva left ventricular outflow tract gradient ≥50 mm Hg, and New York Heart Association functional class ≥II. Participants will be randomized 2:1 to aficamten or placebo in addition to standard of care therapy or as monotherapy, with echocardiogram-guided dose adjustments targeting a Valsalva left ventricular outflow tract gradient <30 mm Hg while maintaining left ventricular ejection fraction ≥50%. The primary end point is the change in Valsalva left ventricular outflow tract gradient from baseline to week 12. Secondary end points include change in resting left ventricular outflow tract gradient, cardiac biomarkers, New York Heart Association functional class, and assessment of pharmacokinetics. After completing the 12-week randomized period, eligible participants will continue into a long-term open-label extension.

RESULTS: The trial is currently enrolling.

CONCLUSIONS: Results of CEDAR-HCM will provide insight into the safety and efficacy of aficamten in adolescents and in children as young as 6 years of age.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT06412666.

Key Words: adolescents ■ cardiac myosins ■ echocardiography ■ morbidity ■ ventricular remodeling

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WHAT IS NEW?

- CEDAR-HCM (Clinical Evaluation of Dosing With Aficamten to Reduce Obstruction in Pediatric Population With HCM) is the first randomized, placebo-controlled trial to evaluate aficamten in pediatric patients with obstructive hypertrophic cardiomyopathy, addressing a critical gap in evidence and treatment opportunity for children aged 6 to <18 years.
- The study features dose titration based on site-read echocardiography, a short double-blind period, and an integrated open-label extension to assess longer-term safety, efficacy, and cardiac remodeling.
- CEDAR-HCM is the first study planning to examine the use of cardiac myosin inhibitors in patients aged 6 to <12 years.

WHAT ARE THE CLINICAL IMPLICATIONS?

- CEDAR-HCM will provide prospective evidence to evaluate aficamten as a potential therapeutic option in children with obstructive HCM, addressing a major unmet need in current clinical practice.
- Results will provide critical information to consider the expansion of treatment options beyond traditional therapies.

Nonstandard Abbreviations and Acronyms

CEDAR-HCM	Clinical Evaluation of Dosing With Aficamten to Reduce Obstruction in Pediatric Population With HCM
CMI	cardiac myosin inhibitor
HCM	hypertrophic cardiomyopathy
LSM	least squares mean
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
REDWOOD-HCM	Randomized Evaluation of Dosing With CK-3773274 in HCM
SEQUOIA-HCM	Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM

Hypertrophic cardiomyopathy (HCM) is a disease of the heart muscle that affects individuals of all ages.[1,2] Although clinically overt disease is less common in children than in adults, morbidity and mortality are substantial, with HCM being an important cause of sudden cardiac death in young individuals.[3] Although the cause of childhood-onset HCM is heterogeneous, most cases are caused by variants in genes encoding components of the cardiac sarcomere. After excluding syndromic causes, genetic testing yields a diagnosis in over 60% of children—nearly double the rate seen in adults.[4,5] Many children with HCM experience breathlessness, chest pain, and syncope or presyncope, and face lifelong risks of atrial fibrillation, stroke, and heart failure. Despite this, treatment of childhood-onset HCM has remained unchanged for decades, is extrapolated from adult practice, is largely empirical, and often ineffective.

In adults with HCM, left ventricular (LV) outflow tract (LVOT) obstruction is a major determinant of symptoms.[6] Current guidelines define LVOT obstruction as an echocardiographic peak instantaneous gradient ≥30 mm Hg.[2] It is caused by complex interactions between the mitral valve and the hyperdynamic, hypertrophied myocardium, leading to systolic anterior motion of the mitral valve and contact with the interventricular septum that obstructs the LVOT. This is frequently associated with posteriorly directed mitral valve regurgitation resulting from deformation of the mitral valve coupled with systolic intracavitary pressure overload. LVOT obstruction is present at rest in ≈20% to 25% of children with HCM, and up to 60% develop obstruction with provocation.[7]

Traditionally, guideline-directed treatment of symptomatic obstructive HCM in children and adults relied on beta-blockers or calcium channel-blockers, followed by disopyramide, with invasive septal reduction therapy reserved for those who remain symptomatic on maximal tolerated medical management.[1–3] However, the benefit has been limited by variable efficacy, unwanted side effects, access to experienced proceduralists, and associated risks from invasive therapy. Recently, treatment of adults with symptomatic obstructive HCM has been transformed by the development of cardiac myosin inhibitors (CMIs), where phase 3 clinical trials demonstrated significant improvements in symptoms, functional capacity, and LVOT gradient reductions comparable to invasive procedures.[8,9] This success led to an update in national and international HCM practice guidelines to incorporate CMIs into clinical management.[1,2] However, CMIs have not been prospectively studied in the pediatric population, highlighting an important unmet need in the treatment of symptomatic children with obstructive HCM.[3]

STUDY RATIONALE

Aficamten is a next-in-class CMI that binds to a distinct site in the catalytic domain (subfragment-1, S1) of cardiac myosin. Aficamten slows phosphate release, resulting in decreased ATPase activity and stabilizing myosin in its weak actin-binding state.[10] Consistent with a half-life of ≈80 hours, steady-state is achieved after ≈2 weeks of daily dosing, allowing for rapid reversibility and reliable dose optimization using echocardiographic findings without the need for pharmacokinetics monitoring.[11] Aficamten is metabolized by multiple cytochrome P450 enzymes (CYP2C9, CYP3A, CYP2D6, and CYP2C19),

which reduces reliance on any single degradation pathway, resulting in a low potential for clinically significant drug–drug interactions, and limiting the impact of CYP genetic polymorphisms on drug metabolism.[12] Additionally, aficamten did not impact the QT interval in healthy volunteers and demonstrated no evidence of teratogenicity in preclinical studies.[13,14] Together, these pharmacological characteristics suggest a favorable safety profile for use in pediatric patients.

SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM) was an international, multicenter, randomized, placebo-controlled, double-blind, phase 3 trial of aficamten versus placebo added onto background therapy in adults with symptomatic obstructive HCM.[8] A total of 282 eligible participants on stable background therapy underwent 1:1 randomization to aficamten (n=142) or placebo (n=140). The primary end point of the trial was the change in peak oxygen uptake from baseline to week 24. The primary end point and all 10 secondary end points showed statistically significant benefit ($P<0.0001$ for all), favoring aficamten over placebo. The least squares mean (LSM) difference in peak oxygen uptake between groups was 1.74 mL/kg per minute (95% CI, 1.04–2.44; $P<0.0001$). Most relevant to the CEDAR-HCM study (Clinical Evaluation of Dosing With Aficamten to Reduce Obstruction in Pediatric Population With HCM), aficamten resulted in a −48 mm Hg (95% CI, −55.1 to −41.6; $P<0.0001$) and -50 mm Hg (95% CI, −56.9 to −43.6; $P<0.0001$) LSM change in Valsalva LVOT gradient from baseline to week 12 and 24, respectively. Treatment efficacy was achieved with modest reductions in LV ejection fraction (LVEF; LSM change in LVEF from baseline to Week 24 for aficamten versus placebo of −4.8% [95% CI, −6.3 to −3.2]). Transient asymptomatic reduction in LVEF by core lab interpretation occurred in 5 (3.5%) patients in the aficamten group and 1 (0.7%) in the placebo group, with no treatment interruptions or clinical heart failure.

An integrated safety analysis, inclusive of data from all prior clinical trials with aficamten in adult patients with obstructive HCM, demonstrated that aficamten had a favorable safety profile that was similar to placebo.[15] Out of 283 patients receiving aficamten, 11 (3.9%) experienced a site-read LVEF <50%, resulting in an exposure-adjusted incidence rate of 5.3 events per 100 patient-years. None of these events was associated with clinical sequelae, and all were successfully managed by dose reduction. A total of 1588 echocardiograms were performed during maintenance phase treatment, indicating that <1% of echocardiograms performed yielded actionable results. New onset atrial fibrillation occurred in 4 (2.4%) participants on aficamten (exposure-adjusted incidence rate, 4.9 per 100 patient-years) and 5 (3.3%) on placebo (exposure-adjusted incidence rate, 6.5 per 100 patient-years). Additionally, 48-week safety data from FOREST-HCM (NCT04848506) demonstrated that aficamten was well tolerated with rare asymptomatic and transient instances of LVEF <50% that resolved without the need for treatment discontinuation.[16]

These favorable efficacy and safety data support the study of aficamten in children and adolescents with obstructive HCM. Here, we describe the design of CEDAR-HCM, the first randomized, placebo-controlled clinical trial of aficamten in children with symptomatic obstructive HCM.

METHODS

Data Sharing Statement

Interested researchers may submit a request containing the research objectives, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). Requests are reviewed by a committee of internal and external advisors. If approved, necessary statistical outputs will be provided to address the research question under the terms of a data-sharing agreement. Requests may be submitted to medicalaffairs@cytokinetics.com.

Overview

CEDAR-HCM is a phase 2/3, international, multicenter, randomized, double-blind, placebo-controlled trial and open-label extension study designed to evaluate the efficacy, safety, and pharmacokinetics of aficamten in pediatric participants with symptomatic obstructive HCM. Approval for the study was obtained from the ethics committees at all participating sites. The study is being conducted in adherence with the principles outlined in the Declaration of Helsinki and the International Conference of Harmonization Guidelines for Good Clinical Practice. Written informed consent will be obtained from all participants. The trial is registered at https://clinicaltrials.gov/ under the identifier NCT06412666. The list of CEDAR-HCM investigators is provided in Table S1.

CEDAR-HCM will enroll ≈55 adolescents (12 to <18 years) and at least 10 children (6 to <12 years) from 25 to 35 sites across the United States, Canada, the United Kingdom, Spain, Italy, and Japan. Enrollment will commence with adolescents to obtain safety, efficacy, and pharmacokinetics data. Results from the first ≈25 participants will inform the decision to expand to children aged 6 to <12 years. Dose selection in the younger cohort will rely on population pharmacokinetics modeling using data from the adult program and the first 25 adolescent participants in this study.

Objectives and End Points

Key objectives and end points for the study are presented in Table. The primary efficacy end point is the change in Valsalva LVOT gradient from baseline to week 12, based on the robust reduction in Valsalva LVOT gradient observed at week 12 in the SEQUOIA-HCM trial.[8] Secondary efficacy end points include changes in resting LVOT gradient, cardiac biomarkers, New York Heart Association functional classification, and pharmacokinetics of aficamten. Assessment of the safety and tolerability of aficamten is an additional secondary end point.

Table. Primary and Secondary Efficacy and Safety Objectives and End Points

Period 1	
Objectives	End points
Primary	
• To assess the effect of aficamten compared with placebo on the change from baseline in Valsalva LVOT gradient	• Change in Valsalva LVOT gradient from baseline to week 12
Secondary	
• To assess the effect of aficamten compared with placebo on the change from baseline in resting LVOT gradient	• Change in resting LVOT gradient from baseline to week 12
• To evaluate the PK of aficamten	• All participants: observed Ctrough and C2hpostdose of aficamten over the 12-week treatment period. • Intensive PK substudy: observed Cmax, tmax, AUCtau, and Ctrough for aficamten.
• To evaluate the effect of aficamten compared with placebo on cardiac biomarker levels	• Change in NT-proBNP from baseline to week 12. • Change in hs-cTnI from baseline to week 12.
• To evaluate the effect of aficamten compared with placebo on the NYHA functional class	• Change in NYHA Functional Class from baseline to week 12. • Proportion of participants with ≥1 NYHA Functional class improvement from baseline to week 12
Safety	
• To evaluate the safety and tolerability of aficamten compared with placebo	• Participant incidence of: ◦ Drug interruption or early discontinuation ◦ AEs and SAEs ◦ Clinically significant changes in vital signs, 12-lead ECGs, and safety laboratory parameters ◦ Appropriate ICD discharges and aborted sudden cardiac death ◦ LVEF <50% ◦ LVEF <50% with clinical heart failure ◦ Reported major adverse cardiac events (CV death, cardiac arrest, nonfatal stroke, nonfatal myocardial infarction, cardiogenic syncope, and heart failure hospitalization)
Periods 2 and 3	
Primary	
• To determine the safety of aficamten in pediatric participants with symptomatic obstructive HCM	• Participant incidence of AEs and SAEs
Secondary	
• Assess long-term effects of aficamten on LVOT gradient	• Change in the following measurements at 12-week intervals (period 2) and 24-week intervals (period 3) from week 14 through week 66 (period 2) and to the end of treatment (period 3): ◦ Peak LVOT gradient at rest and with Valsalva provocation ◦ Proportion of participants with resting LVOT gradient <30 mm Hg ◦ Proportion of participants with Valsalva LVOT gradient <50 mm Hg ◦ Proportion of participants with Valsalva LVOT gradient <30 mm Hg ◦ Proportion of participants with LVEF ≥50%, resting LVOT gradient <30 mm Hg, and Valsalva LVOT gradient <50 mm Hg • Time to the following event through the last follow-up: ◦ First resting LVOT gradient <30 mm Hg ◦ First Valsalva LVOT gradient <50 mm Hg ◦ First Valsalva LVOT gradient <30 mm Hg ◦ First LVEF ≥50%, resting LVOT gradient <30 mm Hg, and Valsalva LVOT gradient <50 mm Hg
• Assess the effect of aficamten on functional outcomes	• Change in NYHA functional class from week 14 to 66 (period 2) and to the end of treatment (period 3) • Proportion of participants with ≥1 NYHA functional class improvement from week 14 to 66 (period 2) and to the end of treatment (period 3)
Safety	
• To determine the safety and tolerability of aficamten in pediatric participants with symptomatic obstructive HCM	• Participant incidence of: ◦ Drug interruption or early discontinuation ◦ LVEF <40% ◦ LVEF <50% ◦ LVEF <50% with clinical heart failure ◦ Clinically significant changes in vital signs, 12-lead ECGs, and safety laboratory parameters ◦ Appropriate ICD discharges and aborted sudden cardiac death ◦ Reported major adverse cardiac events (CV death, cardiac arrest, nonfatal stroke, nonfatal myocardial infarction, cardiogenic syncope, and heart failure hospitalization)

AE indicates adverse event; AUC_{tau}, area under the concentration-time curve; $C_{2hpostdose}$, concentration 2 h postdose; C_{max}, maximum concentration; C_{trough}, trough concentration; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; hs-cTnI, high-sensitivity cardiac troponin I; ICD, Implantable Cardioverter Defibrillator; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal-pro–B-type natriuretic peptide; NYHA, New York Heart Association functional class; PK, pharmacokinetics; SAE, serious adverse event; and T_{max}, time to max concentration.

Several exploratory end points will also be assessed, including cardiac remodeling (using both echocardiography and cardiac magnetic resonance imaging) and health-related quality of life (Table S2).

Study Population

Eligibility criteria for CEDAR-HCM (Figure; Table S3) were developed to enroll adolescents (12 to <18 years) and children (6 to <12 years) with symptomatic obstructive HCM with or without background therapy (beta-blocker, calcium channel-blocker, and disopyramide).

Obstructive HCM is defined as meeting all of the following inclusion criteria: LV hypertrophy with a nondilated LV chamber in the absence of other cardiac disease; an LV end-diastolic wall thickness that meets a Z-score threshold of >2.5, in the absence of family history, or >2, in the presence of a positive family history or positive genetic test, a Valsalva LVOT gradient ≥50 mm Hg, and LVEF ≥60%. Screening echocardiograms will be analyzed by the core echocardiography laboratory (the Brigham and Women's Hospital Echocardiography Core Laboratory, Boston, MA) to determine participant eligibility. Eligible adolescent patients will have a body weight of ≥35 kg. However, since this weight cut-off is lower than that studied in the adult cohorts of REDWOOD-HCM (Randomized Evaluation of Dosing With CK-3773274 in HCM) and SEQUOIA-HCM (45 kg), initial enrollment will include only participants with a screening weight ≥45 kg. After at least 10 participants with baseline body weight ≥45 kg have undergone dose titration up to week 4 without observed safety signals, enrollment will be opened to adolescents with a baseline body weight ≥35 kg. Phenocopies of HCM (eg, Noonan syndrome, Danon disease, Fabry disease) will be excluded based on principal investigator assessment of clinical features, family history, and available diagnostic data (including genetic data, when available). Genetic testing is optional for all participants but is not mandated as part of the screening process.

Study Design

The study consists of 3 periods: (1) a 12-week, randomized, placebo-controlled, double-blind phase (period 1); (2) a 52-week, open-label extension (period 2); and (3) a 144-week long-term extension (period 3). The overall trial schema is shown in Figure S1.

Period 1—Double-Blind Period

Participants will be randomized 2:1 to receive aficamten or a placebo treatment. Doses of 5, 10, 15, or 20 mg once daily aficamten or matching placebo will be administered in an escalating manner using site-read echocardiography to guide dose titration. All staff will be blinded to the randomized treatment assignment, but not to the dose. Sham dose titrations will be performed in the placebo group to minimize the risk of unblinding. After a starting dose of 5 mg, doses will be increased at weeks 2, 4, and 6 if a participant has a Valsalva LVOT gradient ≥30 mm Hg and a biplane LVEF ≥55%. Participants will continue taking background HCM medications (beta-blocker, calcium channel-blocker, and disopyramide) and investigators will be encouraged to maintain the stable doses throughout period 1, as clinically appropriate.

Period 2—Open-Label Extension

After completing 12 weeks of blinded treatment (period 1), all participants will undergo a 2-week washout from weeks 12 to 14 to facilitate transition into the open-label extension without compromising blinding during period 1. All participants who completed period 1 and have an LVEF ≥55% following washout may elect to roll over to the open-label extension (period 2), during which they will receive 52 weeks of treatment with aficamten. Dose adjustment of open-label aficamten will follow the same titration criteria and schedule as in period 1. To determine an individually optimized dose, each participant will start at the lowest dose (5 mg) and undergo site-read echocardiography-guided dose titration by 5-mg increments up to a maximum of 20 mg once daily. Initial dose titration will occur every 2 weeks during the first 6 weeks of the open-label extension period to achieve an individually optimized dose. Thereafter, participants will undergo serial echocardiograms every 12 weeks (3 months) for maintenance monitoring and may have additional ad hoc dose titrations (if the maximum dose of 20 mg is not achieved during titration) to achieve an LVEF ≥50% and Valsalva LVOT gradient <30 mm Hg.

Period 3—Long-Term Extension

After completing the week 66 visit (12-week randomization, 2-week washout, and 52-week open-label extension), all eligible participants who complete period 2 will be offered participation in the long-term extension (period 3) during which they will continue to receive their individually optimized dose of aficamten for an additional 144 weeks without undergoing an additional washout period (total duration of aficamten is 208 weeks, inclusive of period 1, 2, and 3). Participants will have scheduled echocardiograms every 24 weeks with optional ad hoc visits for dose adjustment purposes, to maintain an LVEF ≥50% and Valsalva LVOT gradient <30 mm Hg. Period 3 will also use a clinically driven monitoring paradigm, with protocolized alternating phone calls and in-clinic follow-up visits every 12 weeks (3 months), while allowing for substitution of phone calls with in-person clinic visits based on clinical judgement. Phone visits must be transitioned to an in-clinic visit, including an echocardiogram, if the most recent preceding LVEF is between 50% and 55%.

JUSTIFICATION OF DOSE

A starting dose of 5 mg once daily and a maximum dose of 20 mg once daily of aficamten were selected based on favorable safety, tolerability, pharmacokinetics, and efficacy profiles observed in adult phase 2 and phase 3 studies.[8,11] The appropriateness of these doses for the adolescent dosing regimen was confirmed using population pharmacokinetics modeling. Briefly, the population pharmacokinetics model adequately describing aficamten pharmacokinetics in adults was modified by incorporating weight-based allometric scaling (clearance and volume of distribution), and steady-state concentration-time profiles were simulated in a large virtual adolescent population (12 to <18 years) with obstructive HCM. These simulations indicated that the

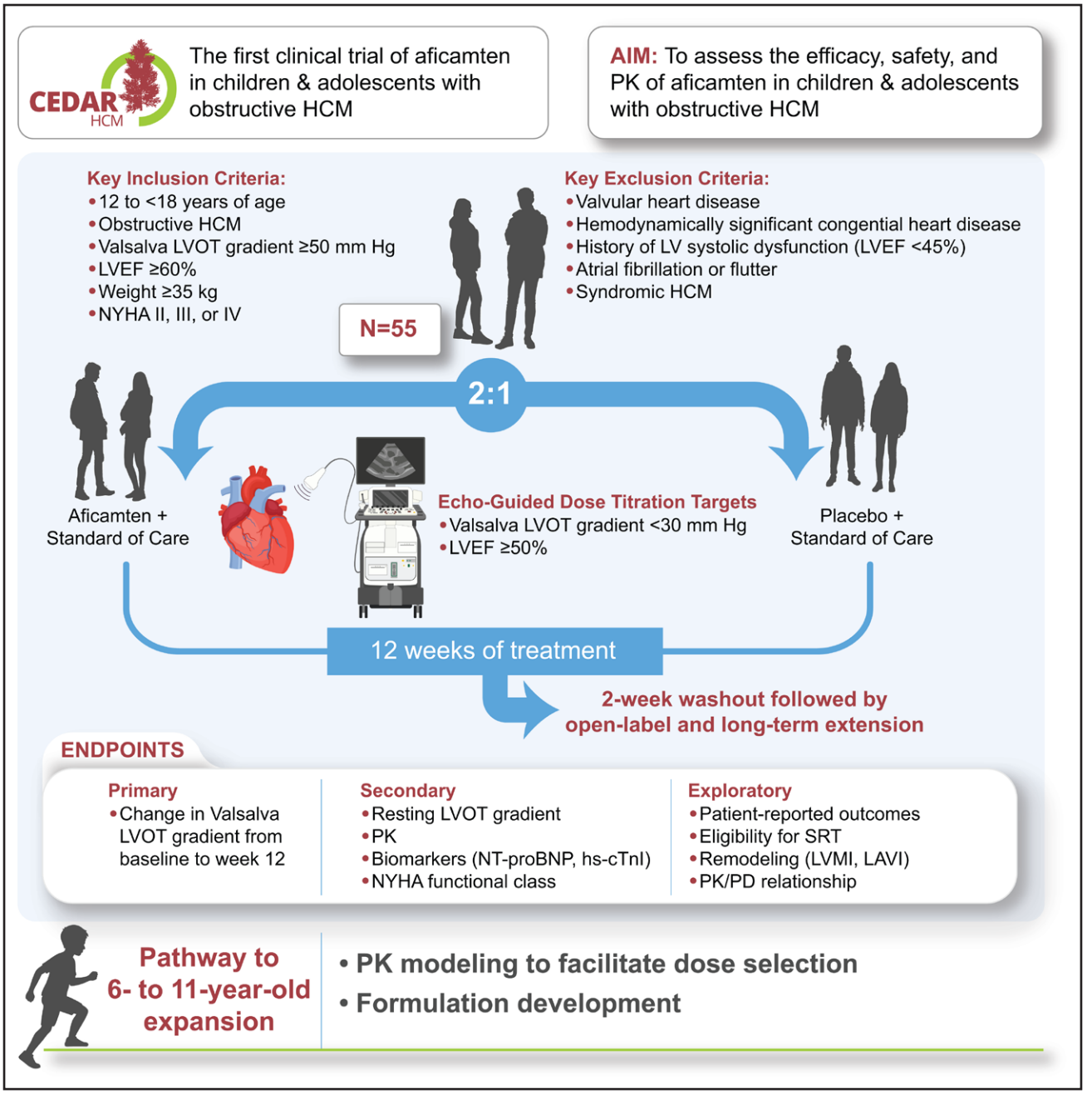

Figure. Study design of the CEDAR-HCM trial (Clinical Evaluation of dosing With Aficamten to Reduce Obstruction in Pediatric Population With HCM).

HCM indicates hypertrophic cardiomyopathy; hs-cTnI, high-sensitivity cardiac troponin I; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal-pro–B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamics; PK, pharmacokinetics; and SRT, septal reduction therapy.

adult dosing regimen would yield adolescent exposures within the adult exposure range for most participants weighing ≥45 kg, supporting its appropriateness for this weight group. Due to the potential for elevated exposures in adolescents weighing 35 kg to <45 kg, initial trial enrollment is restricted to participants weighing ≥45 kg. Inclusion of participants ≥35 kg will be allowed after safety is confirmed in the initial cohort of at least 10 participants.

Dose Titration

Echocardiograms will be interpreted by the core echocardiography laboratory for participant screening and statistical analyses. However, site-read echocardiograms will be utilized for dose adjustment throughout the study to facilitate same-day dose dispensation, reduce overall visit burden, and more effectively approximate real-world dosing and maintenance. A site-designated

echocardiologist, with no other study responsibilities, will review all participant echocardiograms and determine LVEF and LVOT gradients. Dose adjustments will be managed by an interactive web response system based on the site-reported LVEF and Valsalva LVOT gradient.

Echocardiographic criteria for dose titration are shown in Table S4. During period 1 (double-blind period), dose titrations (including sham dose titrations in the placebo group) are managed by an interactive web response system based on site-read measurements of LVOT gradient and biplane LVEF. In periods 2 and 3, all decisions to increase or decrease the aficamten dose (scheduled dose titrations or ad hoc dose titrations) will be made by the principal investigator or designee based on the same echocardiographic criteria as in period 1. During periods 2 or 3, for participants who have been on a maximum tolerated dose of aficamten for at least 4 weeks, the principal investigator or designee may consider reducing or discontinuing background therapies used for the management of HCM symptoms (eg, beta-blocker, calcium channel-blocker, or disopyramide) as clinically indicated and tolerated by participants.

Optional Intensive Pharmacokinetic Substudy and Expansion Into Patients 6 to 11 Years of Age

Robust pharmacokinetics and pharmacodynamic data are essential in understanding the concentration-effect relationships and for guiding dose selection in the pediatric population. The overall pharmacokinetics strategy in the CEDAR-HCM trial involves routine collection of pharmacokinetics data during scheduled visits in conjunction with an optional intensive pharmacokinetics substudy. Participants enrolled in the intensive pharmacokinetics substudy will have serial plasma samples (predose, 0.5, 1, 2, 3, 4, and 6 hours postdose) collected at the week 8 or 12 visit. This approach allows thorough characterization of aficamten pharmacokinetics in adolescents (12 to <18 years) and enrichment of the pharmacokinetics data set to facilitate model development and ultimately inform aficamten dosing in younger children (6 to <12 years).

A partial extrapolation approach for efficacy will be used in younger children (6 to <12 years). This strategy is supported by the clinical similarities in obstructive HCM between adolescents and younger children, including comparable cause, symptom burden, cardiac phenotype, and outcomes.[17] Given these parallels, the pharmacokinetics pharmacodynamic relationship for aficamten—specifically its effects on Valsalva LVOT gradient and LVEF—is expected to be similar across age groups. Before initiating a study in younger children, adolescent pharmacokinetics and pharmacodynamic data will be compared with adult data using linear mixed effects modeling to confirm similarity. Final dose selection will be based on population pharmacokinetics modeling and simulation analyses of adult and adolescent data to establish a weight-based regimen that achieves comparable aficamten exposure in younger children.

Optional Cardiac Magnetic Resonance Substudy

An optional cardiac magnetic resonance substudy will assess the effects of aficamten on cardiac structure, function, and myocardial fibrosis. Patients who are unable to tolerate cardiac magnetic resonance without sedation will be excluded, as will those with an Implantable Cardioverter Defibrillator or pacemaker. A cardiac magnetic resonance will be performed during the screening period, at the end of period 2, and every 48 weeks throughout period 3.

Optional Genetic Testing

Genetic variation has the potential to affect disease severity, progression, and therapeutic response. Optional genetic testing will be conducted on study day 1 for participants who consent/assent.

Statistical Considerations and Sample Size Calculation

The prespecified primary analysis will test the null hypothesis that there is no treatment difference in the change from baseline to week 12 in Valsalva LVOT gradient between aficamten and placebo groups. A sample size of 55 adolescent participants with 2:1 randomization will provide at least 80% power (at a 2-sided significance level of 0.05) to detect a 25 mm Hg reduction in Valsalva LVOT gradient from baseline to week 12 in the aficamten versus placebo group, with a common SD of 30 mm Hg. A blinded interim analysis will be conducted to assess study power.

The treatment effect on the primary end points relating to the change from baseline to week 12 in Valsalva LVOT gradient will be evaluated using mixed model repeated measures. Sensitivity analyses will be performed to account for missing data. The LSM, LSM treatment difference, and the SE from each imputed data set will be combined using Rubin rules to produce an overall LSM estimate of the treatment difference.

The sample size for the 6- to <12-year-old cohort was determined based on pharmacokinetics and in line with regulatory guidance for pediatric studies.[18] Using a 27% coefficient of variation in aficamten apparent oral clearance, a sample size of ≈7 participants receiving active treatment was deemed sufficient to support the objectives of the partial extrapolation approach.

Oversight

An independent data monitoring committee will conduct periodic unblinded safety reviews.

DISCUSSION

Pediatric clinical trials are underrepresented in scientific literature, including in pediatric cardiology. The relative rarity of specific pediatric cardiovascular diseases makes it challenging to design adequately powered randomized trials. Ethical considerations, such as obtaining truly informed consent/assent from minors and the need for age-appropriate formulations of medications, also complicate trial design and implementation. Moreover, the lack of research infrastructure in pediatrics, challenges in identifying valid clinical end points, and difficulty in recruitment further hinder pediatric-focused clinical trials.

Due to the paucity of direct trial data in children, treatment and dosage are often derived by extrapolating from adult trials and do not account for the unique differences in drug metabolism and physiology between children and adults. One study found that in over 30 000 children hospitalized with cardiovascular disease, 78% received >1 cardiovascular medication off-label, and 31% received >3 cardiovascular medications off-label.[19] This practice routinely exposes children to therapeutics of unproven safety and efficacy.[20] Given the lack of data, there is also justifiable reluctance in initiating newer therapies in children, thus preventing them from benefiting from the latest advances.

Children with obstructive HCM face a substantial unmet need that is distinct from adults. While septal myectomy is an effective option in many adults and children with HCM, concerns around a higher rate of complications and a greater likelihood of recurrent obstruction related to body size have been reported, particularly in small children, resulting from limited myectomy at initial operation, the presence of concomitant mid-ventricular obstruction, structural abnormalities of the papillary muscles and ongoing ventricular remodeling in the context of somatic growth.[21] This may lead to repeat interventions with significant longitudinal impacts. A pharmacological therapy that could delay, or potentially even eliminate, the need for myectomy would therefore represent a major advance in the care of children with HCM.

Based on the success of aficamten in safely and effectively resolving obstructive physiology, decreasing symptoms burden, and improving functional capacity in adults with symptomatic obstructive HCM,[8] CEDAR-HCM has been designed to test the hypothesis that aficamten can similarly safely and effectively reduce the LVOT gradient in children and adolescents. The selection of maximal Valsalva LVOT gradient as the primary efficacy end point was informed by the results of the SEQUOIA-HCM trial[8] and provides an objective and clinically relevant measure of efficacy that minimizes the effect of placebo. Although peak oxygen uptake was used as the primary efficacy end point in SEQUOIA-HCM,[8] it is not feasible in CEDAR-HCM given the inclusion of younger patients, aged 6 to 11 years, who may be unable to reliably perform exercise testing. Symptom assessment in pediatrics is also challenging, particularly in young children, due to reliance on parental assessment of symptom burden. Reductions of both resting and Valsalva LVOT gradients with aficamten treatment are significantly correlated with increases of peak oxygen uptake in adults with obstructive HCM,[22] suggesting that a robust gradient reduction in children will be associated with meaningful functional benefit. This objective end point will enable extrapolation of adult efficacy data to support pediatric labeling. Moreover, the large LVOT gradient reduction observed in prior aficamten studies suggests that fewer pediatric patients with obstructive HCM will be required to adequately power CEDAR-HCM, supporting study feasibility.

Secondary efficacy end points, including improvements in cardiac biomarkers and New York Heart Association functional class, allow more granular assessment of symptoms and functional improvements. Changes in biomarkers, particularly N-terminal pro-B-type natriuretic peptide, may reflect disease severity and potential beneficial cardiac remodeling, offering potential insights into long-term disease trajectory.[23]

Unique aspects of the design of CEDAR-HCM include the 2:1 randomization that maximizes the number of participants receiving aficamten in the initial double-blind, placebo-controlled phase, the short double-blind treatment period of 12 weeks facilitated by the rapid onset of action for aficamten, and the pathway to expand the trial to children aged 6 to 11 years. Data on nearly 400 children aged 6 to 12 years from the International Paediatric Hypertrophic Cardiomyopathy Consortium demonstrated a higher prevalence of symptoms, LVOT obstruction, and adverse clinical outcomes in younger children compared with adolescent patients with HCM, suggesting an important unmet need in younger pediatric patients with HCM.[17]

CEDAR-HCM incorporates a pragmatic trial design relying solely on site-read echocardiograms for dose titration. It also incorporates the investigator's clinical judgement into all dose adjustments during the open-label extension, which may help to increase provider confidence with aficamten and better approximate real-world experience.

Expansion of aficamten into children is supported by its favorable safety profile. Aficamten has a predictable, dose-proportional pharmacokinetics profile with low between- and within-subject variability in exposure.[11] Its relatively short half-life enables more rapid dose titration, faster achievement of steady-state, and more rapid washout, thereby facilitating reversibility of pharmacodynamic effects in the event of systolic dysfunction.[11] Additionally, metabolism through multiple CYP pathways reduces the potential for clinically significant drug–drug interactions,[12] further enhancing its safety in the pediatric setting.

Future research directions for aficamten in pediatrics may also include expansion into nonobstructive HCM,

a clinically relevant population given the higher prevalence of nonobstructive phenotypes in children and adolescents.[17] The feasibility of this approach will be informed by results from an ongoing study of aficamten in adults with nonobstructive HCM (ACACIA-HCM; NCT06081894).

The development of CMIs has been a major advancement in the management of symptomatic obstructive HCM. International clinical practice guidelines have been updated to incorporate their use into management algorithms in adults.[1,2] The results of CEDAR-HCM will provide critical evidence to extend the benefits of aficamten to adolescents and children as young as 6 years of age.

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Supplemental Material

Tables S1–S4
Figure S1

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