Protocol: CY 6032

Title: A Phase 3, Multi-center, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

NCT05767346

Approval Date: 14-Mar-2024

PROTOCOL CY 6032

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF AFICAMTEN COMPARED TO METOPROLOL IN ADULTS WITH SYMPTOMATIC OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

Protocol Version and Date:	Amendment 03 dated 14 March 2024
Previous Version(s):	Original Protocol dated 23 August 2022 Amendment 01 dated 14 October 2022 Amendment 02 dated 07 February 2023 Amendment 02 Administrative Update 13 September 2023 Amendment 02 EU 05 December 2023
Product:	Aficamten (CK-3773274)
Regulatory Authority Identifier Number(s):	IND 138814 EU CTR 2023-504809-37-00
Sponsor:	Cytokinetics, Inc. 350 Oyster Point Blvd. South San Francisco, CA 94080, USA

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	CY 6032
Protocol Title:	A Phase 3, Multi-center, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy
Protocol Version and Date:	Amendment 03 dated 14 March 2024

Principal Investigator Commitment

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice (GCP) guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct this trial in accordance with the protocol referenced herein.

Investigator Name: _____ Date: _____

Investigator Signature: _____

PROTOCOL APPROVAL PAGE

Protocol Number:	CY 6032
Protocol Title:	A Phase 3, Multi-center, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy
Protocol Version and Date:	Amendment 03 dated 14 March 2024
Sponsor:	Cytokinetics, Inc. 350 Oyster Point Blvd. South San Francisco, CA 94080

[redacted]

Mar-14-2024 | 12:33:10 PDT

[redacted]

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 03	14 March 2024
Amendment 02 EU	05 December 2023
Amendment 02 Administrative Update	13 September 2023
Amendment 02	07 February 2023
Amendment 01	14 October 2022
Original Protocol	23 August 2022

Amendment 03 (14 March 2024)

The purpose of this amendment is to modify the KCCQ-CSS eligibility criteria to increase the eligible patient population and to incorporate requests made by the European Medicines Agency (EMA) which were addressed in Amendment 02 EU dated 05 December 2023. In addition, the sponsor is updating the HCM Participant Experience Sub-study to clarify the procedures for those participants who discontinue investigational product (IP) early and will continue in the sub-study. Global edits were made throughout the protocol to clarify Titration Vital Signs and Titration Vitals Medical Monitor and to remove references to case report forms (CRFs).

Table 1: Protocol Amendment 03 Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated the number of sites and key eligibility criteria	To align the synopsis with the main protocol
1.3 Schedule of Activities	Clarified procedural instructions	To provide clarification
1.4 Key Contacts	Updated the sponsor's trial contact	To replace with current sponsor's trial contact[a]
4.1.1 Number of Sites	Updated the number of sites	To reflect the number of sites that were selected
5.1 Inclusion Criteria	Updated inclusion criteria #103 to specify qualification of BMI for study eligibility is only required at Screening Visit and #106 to update the KCCQ-CSS eligibility score	To enroll a more inclusive patient population
	Added specific timepoint for echocardiographic eligibility for inclusion criterion #107	To provide clarification

Table 1: Protocol Amendment 03 Summary of Changes (Continued)

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added new exclusion criterion #225 to exclude patients with any known clinically significant or severe lactose intolerance or hypersensitivity to aficamten, metoprolol succinate, or any of the excipients in the study drug tablets (including placebo)	To address request made by EMA[a]
	Added new exclusion criterion #226 to documented history of current obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or myocardial infarction	To exclude participants with current obstructive coronary artery disease
6.1 Investigational Products Administered	Added excipients in the study drug tablets (including placebo) to Table 3	To address request made by EMA[a]
6.5.1 Prior Therapy	Added mavacamten to list of medical therapies	Added for clarification
6.5.2 Concomitant Therapy	Updated to provide guidance on the re-introduction of standard-of-care medications	To address request made by EMA[a]
6.5.3 Drug-Drug Interactions	Amended to include updated drug-drug interaction study data	To include updated drug-drug interaction study data
6.6.5 Scheduled Down-titration of Metoprolol at Week 24	Amended down-titration schedule for participants on 200 mg metoprolol or placebo for metoprolol	To provide clarification
7.2.1 Management of Participants after Permanent Discontinuation of IP	Updated to provide guidance on the re-introduction of standard-of-care medications	To address request made by EMA[a]
7.4 Participant Consent Withdrawal	Amended information regarding reasons for participant consent withdrawal	To address request made by EMA[a]
8.1.1 Screening Visits	Updated the timeframe of cardiopulmonary exercise testing (CPET) used for eligibility	To allow for flexibility of CPET completion prior to randomization
8.1.1.1 Screening SOC Washout Period	Amended to describe how safety will be ensured during screening washout	To address request made by EMA[a]
8.2.2 Echocardiography	Added when the unmasked echocardiologist or unmasked designee will enter Titration Vital Signs and echocardiogram data	To provide clarification

Table 1: Protocol Amendment 03 Summary of Changes (Continued)

Section # and Name	Description of Change	Brief Rationale
8.3.3 Vital Signs	Delineated Titration Vital Signs and Titration Vitals Medical Monitor for use throughout the protocol	To define vital signs entered in interactive web response system (IWRS) for titration and mitigate risk of unmasking for masked/blinded Sponsor or contract research organization (CRO) staff
8.4.1.7 Reporting Procedures for SAEs	Added SAEs assessed as related to trial procedures occurring during the screening period are reported as an SAE	For consistency
8.4.1.9 Regulatory Reporting	Added reference to metoprolol succinate	For consistency
8.8 Optional Sample Collection for Future Analyses	Clarified that optional sample collection for future research will not be implemented in countries where restrictions may apply	To provide clarification
8.10 HCM Participant Experience Optional Sub-study	Added procedures for participants who discontinue IP treatment early and will continue in the sub-study	To provide information on participants who discontinue IP treatment early
10.1.4 Data Protection	Updated to include more information on data privacy and protection	To address request made by EMA[a]
10.2 Appendix 2: Clinical Laboratory Tests	Added pregnancy testing procedures	For consistency
11 References	Added a new reference from the update in Section 6.5.3	To include updated drug-drug interaction study data
Global change	Removed references to case report form throughout the protocol	As Section 10.1.6 dictates that data should be entered into the CRF, other references to CRF were removed for consistency throughout the protocol
Global Change	Updated protocol version and date. Made minor edits and clarifications throughout the protocol.	Administrative change

[a] This change was previously incorporated in Amendment 02 EU dated 05 December 2023.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Investigational Product (IP): Aficamten

Name of Active Ingredient: CK-3773274

Protocol Title:

A Phase 3, Multi-center, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Phase of Development: Phase 3

Rationale:

Aficamten is a next-generation small molecule cardiac myosin inhibitor being developed as a chronic, oral treatment for participants with hypertrophic cardiomyopathy (HCM). Aficamten is designed to reduce the hypercontractility that underlies the pathophysiology of HCM. Selective inhibition of cardiac myosin with aficamten may yield potential advantages over current therapies for obstructive hypertrophic cardiomyopathy (oHCM) by directly reducing myocardial hypercontractility and addressing the fundamental cause of this sarcomeric disease.

This is the second Phase 3 trial of aficamten in participants with symptomatic oHCM. CY 6032 is a Phase 3 trial designed to evaluate the effect of aficamten compared with beta-blocker (metoprolol succinate [metoprolol]) on exercise capacity, heart failure symptoms, cardiac structure and function, and safety and tolerability in participants with symptomatic oHCM. The overall objective of this active comparator trial is to evaluate the safety and efficacy of aficamten as: 1) first-line therapy for participants who are recently diagnosed and/or treatment naïve; or as 2) monotherapy for participants previously receiving standard of care (SOC) medical therapy for symptomatic oHCM.

Objectives and Endpoints:

Objectives	***Endpoint(s)***
Primary	
To evaluate the effect of aficamten compared with metoprolol on exercise capacity in participants with symptomatic oHCM	• Change in peak oxygen uptake (pVO_2) by cardiopulmonary exercise testing (CPET) from baseline to Week 24
Secondary	
To evaluate the effect of aficamten compared with metoprolol on New York Heart Association (NYHA) Functional Classification	• Proportion of participants with ≥ 1 class improvement in NYHA Functional Class from baseline to Week 24

To evaluate the effect of aficamten compared with metoprolol on participant health status	• Change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on structural remodeling	• Change in left ventricular mass index (LVMI) from baseline to Week 24 • Change in left atrial volume index (LAVI) from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels	• Change from baseline values in NT-proBNP from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on post -Valsalva left ventricular outflow tract gradients (LVOT-G)	• Change in post-Valsalva LVOT-G from baseline to Week 24
Safety	
To evaluate the safety and tolerability profile of aficamten compared with metoprolol in participants with oHCM	• Participant incidence of reported major adverse cardiac events (cardiovascular [CV] death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization) • Participant incidence of adverse events (AE) • Participant incidence of left ventricular ejection fraction (LVEF) < 50%
Exploratory	
To evaluate the effect of aficamten compared with metoprolol on exercise capacity and functional class in symptomatic oHCM participants	• Number of participants on aficamten at Week 24 achieving either: – Change from baseline of ≥ 1.5 mL/kg/min in pVO_2 AND – ≥ 1 class improvement in NYHA Functional Class **OR** – Change of ≥ 3.0 mL/kg/min from baseline in pVO_2 AND – No worsening of NYHA Functional Class

To evaluate the effect of aficamten compared with metoprolol on participant response over time	• Proportion of participants with categorical improvement in KCCQ-CSS at Weeks 12 and 24 • Proportion of participants with resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G < 50 mmHg, and NYHA Class I at Weeks 12 and 24 • Proportion of participants with resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G < 50 mmHg, and ≥ 1 class improvement in NYHA Functional Class from baseline to Weeks 12 and 24
To evaluate the effect of aficamten compared with metoprolol on cardiac troponin levels	• Change in high sensitivity cardiac troponin I (hs-cTnI) from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on a measure of diastolic function	• Change in ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e' [lateral wall]) from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on interventricular septal thickness (IVST) remodeling	• Change in IVST from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on other CPET parameters	• Change from baseline to Week 24 in: – Ventilatory efficiency/carbon dioxide production (VE/VCO_2 slope) – Circulatory power (VO_2 × systolic blood pressure [SBP]) – Ventilatory anaerobic threshold (VAT) – Total workload (watts) – Heart rate response
To evaluate the effect of aficamten compared with metoprolol on health status and health-related quality of life as measured by patient-reported outcome (PRO) questionnaires	• Change from baseline to Week 24 in individual responses to the EuroQol 5 dimension 5-level instrument (EQ-5D-5L), Clinical Global Impression (CGI), Patient Global Impression of Change (PGI-C), and Seattle Angina Questionnaire-7 (SAQ-7)
To assess the pharmacokinetics of aficamten and its metabolites	• Pharmacokinetic parameters through Week 24

Overall Design:

This is a Phase 3, multi-center, randomized, double-blind, active-comparator trial in participants with symptomatic oHCM and elevated LVOT-G. Eligible participants will be randomized in a 1:1 ratio to aficamten or metoprolol. Randomization will be stratified by CPET exercise modality (treadmill/bicycle), and recently diagnosed vs chronic oHCM. The number of participants using the bicycle CPET exercise modality will be capped at approximately 50%.

Trial Centers:

This multinational trial will take place at approximately 80 investigational sites.

Number of Participants:

Approximately 170 participants will be randomized.

Key Eligibility Criteria:

Inclusion Criteria

Participants who meet all the following criteria may be included in the trial:

- Males and females between 18 to 85 years of age, inclusive, at the signing of informed consent
- Body mass index < 35 kg/m^2. Qualification of BMI for study eligibility is only required at the participant's first screening visit.
- Diagnosed with oHCM per the following criteria by cardiac magnetic resonance imaging (CMR) or echocardiography:
  - Has left ventricular (LV) hypertrophy with non-dilated LV chamber in the absence of other cardiac disease and
  - Has an end-diastolic LV wall thickness as measured by the echocardiography core laboratory:
    - ≥ 15 mm in one or more myocardial segments
      OR
    - ≥ 13 mm in one or more wall segments *and* a known disease-causing gene mutation or positive family history of HCM
- NYHA class II or III
- Has a KCCQ-CSS score of ≤ 90 at screening
- Has a screening echocardiogram with the following determined by the echocardiography core laboratory:
  - Resting LVOT-G ≥ 30 mm Hg and/or post-Valsalva LVOT-G ≥ 50 mmHg
    AND
  - LVEF ≥ 60%
- Respiratory exchange ratio (RER) ≥ 1.05 and pVO2 < 100% predicted on the screening CPET per the core laboratory
- Hemoglobin ≥ 10 g/dL
- Patients previously exposed to mavacamten are allowed to participate but must be off mavacamten for at least 8 weeks prior to signing of informed consent and must be approved by the Medical Monitor prior to enrollment. Approximately 10% of oHCM patients who were previously treated with mavacamten can participate in the study with Medical Monitor approval

Exclusion Criteria

Any of the following criteria will exclude potential participants from the trial:

- Medical indication for either beta blocker or calcium-channel blockers prohibiting drug discontinuation other than oHCM
- History of intolerance or medical contraindication to beta blocker therapy
- Resting SBP of > 160 mmHg
- Resting heart rate of > 100 bpm
- Significant valvular heart disease
  - Moderate-severe valvular aortic stenosis or fixed subaortic obstruction
  - Mitral regurgitation not due to systolic anterior motion of the mitral valve (per Investigator judgment)
- Known or suspected infiltrative, genetic or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis)
- History of LV systolic dysfunction (LVEF < 45%) or stress cardiomyopathy at any time during their clinical course
- Inability to exercise on a treadmill or bicycle (eg, orthopedic limitations)
- Documented room air oxygen saturation reading < 90% at screening
- Planned septal reduction treatment that cannot be deferred during the trial period
- History of septal reduction therapy (surgical myectomy or alcohol septal ablation) within 6 months of screening. Patients who had septal reduction therapy greater than 6 months before screening are allowed, up to approximately 10% of total.
- History of paroxysmal or persistent atrial fibrillation or atrial flutter. Atrial flutter treated with radio frequency ablation without recurrence within the last 6 months prior to screening is allowed.
- Current or recent (< 4 weeks prior to signing of informed consent) therapy with disopyramide
- History of syncope, symptomatic ventricular arrhythmia, or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening
- Has received prior treatment with aficamten or previously intolerant (reduced LVEF requiring permanent drug discontinuation) to mavacamten

Summary of Study Procedures:

All participants on SOC therapy will undergo a washout period consisting of up to 14 days of weaning from SOC therapy, followed by an additional 7 days completely off SOC therapy prior to undergoing Screening Visit 2 assessments.

The Screening period will begin at the time of informed consent and will include both the Screening pre-SOC washout (Screening Visit 1) and post-SOC washout (Screening Visit 2) period clinical assessments. Those not currently on medical therapy for oHCM do not require a washout period and will only participate in Screening Visit 2.

After meeting eligibility criteria, participants will be randomized to receive either aficamten and placebo for metoprolol, or metoprolol and placebo for aficamten.

Randomization will be stratified by CPET exercise modality (treadmill/bicycle), and recently diagnosed vs chronic oHCM as follows:

1. Recently Diagnosed: Participants who are treatment naïve or currently untreated (no SOC medical therapy within the past 12 months), or recently diagnosed participants (history of oHCM ≤ 12 months with or without use of SOC therapy); and
2. Chronic oHCM: Participants with chronic oHCM (> 12 months) currently treated or having received SOC therapy within the past 12 months

All randomized participants may receive up to 4 escalating doses of IP over the initial 6 weeks of the trial as outlined in the Table below.

Participants will have IP dispensed in a double-blinded fashion at each trial visit. All site staff, including the unmasked echocardiologist and the unmasked designee, will be blinded to randomized treatment assignments. During the initial 6 weeks of the treatment period, IP doses will be individually up titrated or adjusted according to echocardiographic and vital sign criteria (see Table below). To prevent the investigator and site staff from viewing the echocardiogram or results, the unmasked echocardiologist, who is not involved in other aspects of the study, will review the echocardiographic (LVEF, resting LVOT- G, and post-Valsalva LVOT- G) and vital signs (SBP and resting heart rate) data and enter the data into the interactive web response system (IWRS). An unmasked designee, who is also not involved in other aspects of the study, may be delegated to enter the data into IWRS on the unmasked echocardiologist's behalf. Dose adjustment will be carried out according to the prespecified algorithm in a blinded fashion. Neither the unmasked echocardiologist nor the unmasked data entry designee will reveal echocardiogram results to the rest of the study team, unless in the event of a critical safety issue (e.g., LVEF < 40%). Additionally, participant vital signs after randomization will not be accessible to the sponsor and clinical research organization study teams (aside from the individuals who perform source documentation verification), but to ensure oversight from a patient safety and data quality perspective, a medical monitor from the sponsor who is not directly involved in the study will review vital signs data. This person will be referred to as the "Titration Vitals Medical Monitor." Vital signs noted during other study procedures are not used for IP titration; therefore, they are not considered masked and can be viewed by the study team (site, CRO, and Sponsor).

Participants receiving aficamten will start at a dose of 5 mg once daily (Dose 1) and may escalate to doses of 10, 15, and 20 mg once daily if they continue to meet the echocardiographic escalation

criteria. Otherwise, the participants will remain at their current dose when escalation criteria were not met.

Participants receiving metoprolol will start at a dose of 50 mg once daily (Dose 1) and may escalate to doses of 100, 150, and 200 mg once daily if they continue to meet the 2 echocardiographic and 2 vital sign escalation criteria or will remain at their current dose when escalation criteria are not met.

If at any time during the trial a participant experiences an intolerable adverse event (AE), which in the investigator's judgment is drug-related and compels the participant to request IP discontinuation, the dose of IP may be reduced to the previous dose level. For participants receiving Dose 1, IP will be discontinued.

The treatment duration will be 24 weeks with a 4-week follow-up period after the last dose (Weeks 24 through 28).

At the Week 24 visit, metoprolol and metoprolol placebo will be down-titrated for safety purposes. Aficamten and aficamten placebo will not be down-titrated. The primary endpoint measures of pVO_2 will be obtained by CPET at randomization and at Week 24.

Vital Sign and Echocardiography Criteria for IP Dose Adjustment

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.**		
SBP	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

bpm = beats per minute; IP = investigational product; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradients; NA = not applicable; SBP = systolic blood pressure

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will be established for this trial to formally review the accumulating unblinded data periodically in order to assess risk to participants during the conduct of the trial. Details regarding the scope of responsibilities, meetings, and communication procedures, as well as information requirements will be outlined in the DMC Charter. The DMC will have access to actual treatment assignments and participant-level data from the clinical trial database.

Statistical Methods:

Sample Size:

Assuming a difference in change from baseline in pVO_2 of 2 mL/kg/min for aficamten compared to metoprolol, a standard deviation (SD) of 3 mL/kg/min, and 10% of participants missing change from baseline data of the primary endpoint, a sample size of 170 participants (randomized at 1:1 ratio to aficamten and to metoprolol) provides more than 90% power to detect the difference in pVO_2 change from baseline to Week 24 with a 2-sided type I error of 0.05.

Statistical Analyses:

Unless specified otherwise, efficacy analyses will be performed on the Full Analysis Set (FAS), which includes all randomized participants who receive at least one dose of IP and at least one post-baseline efficacy assessment. The primary analysis will test the null hypothesis that there is no treatment difference in the primary endpoint between participants randomized to metoprolol and those randomized to aficamten in the FAS. Change from baseline in pVO_2 will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment group, randomization stratification factors (CPET exercise modality and recently diagnosed vs chronic oHCM), baseline pVO_2 and baseline CPET weight as covariates. The proportion of responders will be analyzed using Cochran–Mantel–Haenszel (CMH) test stratified by randomization factors. The p-value and 95% confidence interval (CI) will be obtained using exact method. Other change from baseline endpoints will be analyzed using mixed model repeated measures (MMRM) with treatment, visit, randomization stratification factors, visit-by-baseline and treatment-by-visit interactions as fixed effect and baseline assessment as covariate.

To preserve the overall type I error rate at 0.05 for the primary and secondary endpoints, a multiple testing procedure will be used and detailed in the Statistical Analysis Plan (SAP).

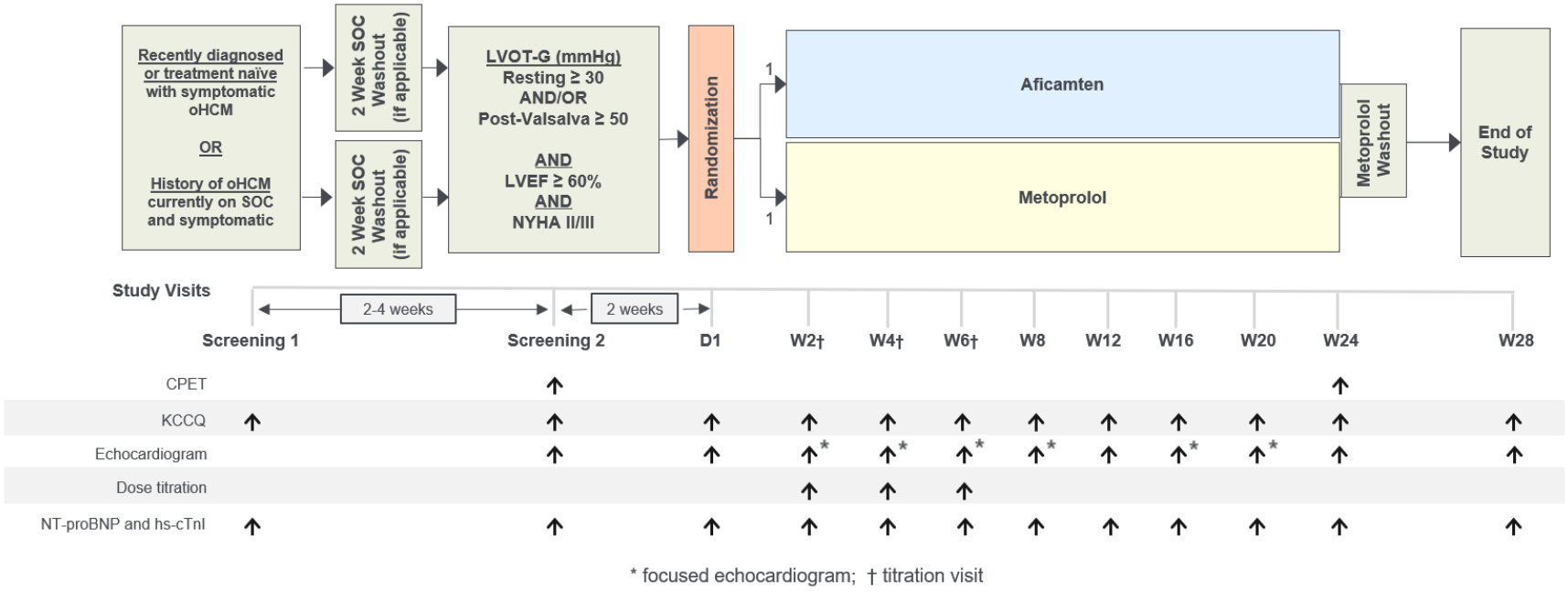
Safety analyses will be performed on the safety analysis set which includes all participants who received at least one dose of IP. The pharmacokinetics analysis set will consist of participants who have at least one plasma concentration of aficamten.

The number and percentage of participants reporting any treatment-emergent AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) dictional coded System Organ Class and preferred term.

Analyses will be further detailed in the SAP.

1.2. Schema

Figure 1: Trial Schema



CPET = cardiopulmonary exercise test; hs-cTnI = high sensitivity cardiac troponin I; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; NYHA = New York Heart Association; NT-proBNP = N-terminal prohormone brain natriuretic peptide; oHCM = obstructive hypertrophic cardiomyopathy; SOC = standard of care

1.3. Schedule of Activities

Trial Procedure	SV1[a]	SV2[a]	Day 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	EOT (Week 24)[a]	EOS[c] (Week 28)	ED[d]
Visit Window	**≤ 42 Days Prior to Day 1**		**N/A**	**+ 3 Days**	**+ 3 Days**	**+ 3 Days**	**+ 3 Days**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**+ 7 Days**	**ASAP After Withdrawal (+ 7 Days)**
GENERAL PROCEDURES & SAFETY ASSESSMENTS													
Informed consent	X	X[e]											
Enrollment in IWRS	X	X[e]											
Wean and washout of SOC therapy	X												
Inclusion/exclusion criteria	X	X[e]											
Medical/Surgical history	X	X[e]											
Demographics	X	X[e]											
Height/clinic weight[f]	X	X									X		
Physical examination	X	X									X		X
Titration Vital signs and O_2 Saturation[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE evaluation[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X
CPET/CPET weight[i]		X									X		
Echocardiogram[j]		X[k]	X[k]	X[l]	X[l]	X[l]	X[l]	X[k]	X[l]	X[l]	X[k]	X[k]	X[k]
Randomization			X										
CENTRAL LABORATORY													
Laboratory assessments	X	X	X					X			X	X	X
NT-proBNP	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP only)[m]	X	X	X	X	X	X	X	X	X	X	X	X	X
hs-cTnI	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Procedure	SV1[a]	SV2[a]	Day 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	EOT (Week 24)[a]	EOS[c] (Week 28)	ED[d]
Visit Window	**≤ 42 Days Prior to Day 1**		**N/A**	**+ 3 Days**	**+ 3 Days**	**+ 3 Days**	**+ 3 Days**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**+ 7 Days**	**ASAP After Withdrawal (+ 7 Days)**
Aficamten PK samples[n]			X	X	X	X	X		X		X		X
Serum and Plasma Collection for Future Analyses[o]	X	X	X					X			X	X	X
Genotype sample[p]			X										
PATIENT-REPORTED OUTCOMES AND FUNCTIONAL ASSESSMENTS													
NYHA Functional Class	X	X	X	X	X	X	X	X	X	X	X	X	X
KCCQ[q]	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[q]	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI							X				X	X	X
PGI-C[q]							X				X	X	X
SAQ-7[q]	X	X	X		X		X	X	X	X	X	X	X
HCM PARTICIPANT EXPERIENCE OPTIONAL SUB-STUDY													
HCM Participant Experience Interviews[r]		X								X			X
HCM Participant Experience Surveys[r]			X	X	X	X	X	X	X	X	X		
INVESTIGATIONAL PRODUCT													
IP dose administration at site[s]			X	X	X	X	X	X	X	X	X		
IP dispensation for daily dosing at home[t]			X	X	X	X	X	X	X	X	X[u]		
IP dose titration[v]				X	X	X							
IP dose adjustment[w]							X	X	X	X			

AE = adverse event; ASAP = as soon as possible; CGI = Clinical Global Impression scale; CPET = cardiopulmonary exercise testing; d = day; ECG = electrocardiogram; Echo = echocardiogram; ED = early discontinuation; EDC = electronic data capture; EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQol 5-dimension 5-level instrument; HCM = hypertrophic cardiomyopathy; hs-cTnI = high sensitivity cardiac troponin I; IP = investigational product; IWRS = interactive web response system; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradients; NT-proBNP = N-terminal

prohormone brain natriuretic peptide; NYHA = New York Heart Association; PGI-C = Patient Global Impression of Change scale; PK = pharmacokinetic; PRO = patient-reported outcome; SAE = serious adverse events; SAQ-7 = Seattle Angina Questionnaire-7; SOC = standard of care; SV = Screening Visit; WOCBP = women of childbearing potential

[a] The screening period will begin at the time of informed consent and will include both the pre-SOC washout (Screening Visit 1) and post-SOC washout (Screening Visit 2) period clinical assessments. Those not currently on medical therapy for oHCM do not require a washout period and will only participate in Screening Visit 2.

[b] If a participant is temporarily unable to exercise on the treadmill or bicycle (whichever modality was used at baseline) due to an adverse event (eg, ankle sprain, upper respiratory infection, migraine), but not due to HCM symptoms, or if the site is unable to perform CPET (eg, equipment malfunction), then the Week 24 visit may be postponed by up to 4 weeks. The participant should continue to receive IP via unscheduled visit(s) until the Week 24 visit. Sites should contact participants shortly before the Week 24 visit and confirm their ability to perform CPET. If necessary, the Week 24 visit may be split across two consecutive days within the visit window. If the visit is split, all assessments, except the CPET, should occur on the first day of the split visit. The CPET should occur on the second day of the split visit. Dosing will occur on-site on both split visit days. Down-titration of metoprolol or placebo for metoprolol will begin the day following a split visit at the Week 24 visit.

[c] The EOS visit will occur at Week 28 or 4 weeks after a postponed Week 24 visit. For participants who early-terminate IP more than 4 weeks before Week 24 and continue to stay on-trial for all follow-up assessments, the Week 24 visit can be considered the EOS visit (and the EOS visit does not need to be performed).

[d] Participants who discontinue IP permanently should consult with the investigator regarding the several options described in Section 7.2.1 before making the final decision to complete an ED visit. Participants who withdraw from IP should complete an ED visit as soon as possible, ideally within 7 days of the last dose of IP. For early-terminated participants, they will need to down-titrate metoprolol or placebo for metoprolol at home after the ED visit. Please see Section 6.6.5 for details around down-titration of metoprolol or placebo for metoprolol. In addition, a safety contact (eg, phone call) should occur 4 weeks (± 7 days) following the last dose of IP to assess adverse events and vital status.

[e] Only if first screening visit is SV2 (ie, Participants not currently on medical therapy for oHCM who do not require a washout period).

[f] Height is measured at the Screening visit only. For participants requiring SOC washout, BMI should be collected at SV1 for eligibility. BMI used for inclusion purposes will be calculated by EDC.

[g] Vital signs include heart rate, respiratory rate, and blood pressure. Titration vital signs should be collected prior to laboratory testing and will consist of one heart rate reading and three consecutive blood pressure readings recorded at one-minute intervals. Each blood pressure reading will be recorded. Blood pressures must be collected using an automated oscillometer and follow instructions as described in Appendix 6 (Section 10.6). Oxygen Saturation is only done at screening.

[h] Only SAEs and AEs considered related to trial procedures are collected during the screening period until initiation of IP (Day 1) and should not be reported as medical history. AE resulting from SOC washout during screening period should be considered related to study procedure. Any medical condition not related to a trial procedure during this period should be collected as medical history.

[i] The CPET used for eligibility should be completed during the screening period, with a minimum of approximately one week prior to randomization. Participants requiring washout must complete washout prior to completing the screening CPET. The CPET should be performed after other visit activities including IP administration. CPET weight should be collected immediately prior to CPET exercise. CPET weight should be collected with participant shoes removed and their pockets emptied. It is not permissible to rely on a participant's stated weight or height.

[j] Screening echocardiogram read by echocardiography core laboratory. Echocardiograms will be done prior to dosing on Day 1 and 2 hours (± 60 mins) after dosing in the clinic at Weeks 2, 4, 6, 8, 12, 16, 20, and 24. The unmasked echocardiologist or unmasked designee will enter Titration Vital Signs and echocardiogram data at SV2, Day 1 prior to dosing, and at Weeks 2, 4, 6, 8, 12, 16, 20, 24 and unscheduled visits. Contrast for echocardiogram is not allowed at any study visit.

[k] Full echocardiogram to be performed.

[l] Focused echocardiogram (LVOT-G + LVEF) to be performed.

[m] Only for WOCBP. Serum pregnancy test at Screening visit. A WOCBP must have a negative pregnancy test (urine or serum as required by local regulations) at Day 1, prior to the first dose of IP. For WOCBP requiring a washout, a serum pregnancy should be done at SV1; a urine pregnancy test may be completed for these patients at SV2. FSH only at screening, if needed. Where permitted by local regulations, a urine pregnancy test may be performed at all other required timepoints. If a urine pregnancy test is positive, a serum pregnancy test must be performed.

[n] When PK collection and an echocardiogram are scheduled for the same time point, pre-dose PK collection should be completed prior to the echocardiogram. Pre-dose PK sampling can be done any time before the IP dose during required clinic visit days. The post-dose PK may be collected after the echocardiogram. Post-dose PK sampling has 2 hour ± 10 minute window after IP dosing.

[o] Optional for participants who provide consent.

[p] A blood sample for genotyping will be collected on Day 1 from participants who provide consent.

[q] All PROs, KCCQ, EQ-5D-5L, PGI-C, and SAQ-7, should be done prior to other assessments. The entire 23 question KCCQ should be completed at every visit. For study eligibility purposes, the KCCQ-CSS score will be calculated by EDC from the overall questionnaire.

[r] At participating centers in the US, English language-speaking participants who have consented to the HCM Participant Experience Optional Sub-study will have two semi-structured, qualitative (entry and exit) interviews conducted remotely by trained personnel from an independent vendor. The entry interview will be completed during the screening period. The exit interview will be completed after the Week 20 visit but before the last on-site dose of IP at Week 24. The interviews will be performed remotely. Additionally, participants will complete surveys remotely prior to Day 1, and at visits corresponding to Weeks 2, 4, 6, 8, 12, 16, 20 and 24. Willing participants who discontinue from the main study early should complete the exit interview ideally within 3 days but up to 10 business days from their last dose of IP. If the participant stops IP, but continues to complete main study follow-up visits/assessments, they should continue to complete e-surveys and the exit interview per the schedule of activities above.

[s] On clinic visit days after Day 1, participants should take IP after the blood draw. At the Week 24 visit, participants should take their final full dose of IP onsite before the CPET.

[t] After Day 1, participants will take their daily dosing of IP at home around the same time each day, except when they are taking their IP on-site during clinic visit days.

[u] End of Treatment Metoprolol Washout see Section 6.6.5. All study participants will down-titrate metoprolol or placebo for metoprolol at home starting the day after the Week 24 visit for up to approximately 14 days, as needed. If the Week 24 visit is split into two consecutive days, metoprolol washout will begin after all Week 24 assessments are completed (i.e., on the day following the last day of the Week 24 split visit). Site staff will contact participants to follow up that they are following the down-titration instructions appropriately.

[v] See Section 6.6.1.

[w] See Sections 7.1 and 7.2 for IP interruptions and permanent IP discontinuation.

1.4. Key Contacts

Sponsor's Trial Contact:	[redacted] Email: CY6032ClinicalOperations@cytokinetics.com [redacted]
Sponsor's Medical Monitor:	[redacted] Email: CY6032MedicalMonitor@cytokinetics.com [redacted]
Serious Adverse Event Reporting:	Drug Safety Email: CY6032DrugSafety@cytokinetics.com [redacted]

2. INTRODUCTION

This is a Phase 3 trial of aficamten (CK-3773274), a next-generation small molecule cardiac myosin inhibitor being developed as a chronic, oral treatment for participants with hypertrophic cardiomyopathy (HCM).

2.1. Trial Rationale

Aficamten is designed to reduce the hypercontractility that underlies the pathophysiology of HCM. Selective inhibition of cardiac myosin with aficamten may yield potential advantages over current therapies for obstructive hypertrophic cardiomyopathy (oHCM) by directly reducing myocardial hypercontractility and addressing the fundamental cause of this sarcomeric disease. Study CY 6032 is the second Phase 3 trial of aficamten in participants with symptomatic oHCM.

This Phase 3 trial is designed to evaluate the effect of aficamten compared with beta-blocker (metoprolol succinate [metoprolol]) on exercise capacity, heart failure symptoms, cardiac structure and function, and safety and tolerability in participants with symptomatic oHCM. The overall objective of this active comparator trial is to evaluate the safety and efficacy of aficamten as: 1) first-line therapy for participants who are recently diagnosed and/or treatment naïve; or as 2) monotherapy for participants previously receiving standard of care (SOC) medical therapy for symptomatic oHCM.

2.2. Background

2.2.1. Hypertrophic Cardiomyopathy

HCM results from disease-causing genetic variants, often affecting the genes encoding the proteins of the cardiac sarcomere, such as myosin (Maron, B. J. 2018). Histologic features include myofibrillar disarray, myocyte hypertrophy and interstitial fibrosis. Clinically, HCM is characterized by left ventricular (LV) hypertrophy unexplained by loading conditions and a nondilated LV with preserved or increased ejection fraction (Gersh 2011). Imaging studies of participants with HCM show hypertrophied LV walls, enhanced ventricular contractility, normal end-diastolic LV volume, reduced end-systolic volume, impaired diastolic compliance and often left atrial enlargement (Marian 2017). From population-based insurance claims and national health system data, the prevalence of clinically identified individuals with HCM in the US and EU (including the United Kingdom) is approximately 1:2000 and 1:3195 (Husser 2018; Magnusson 2017; Maron, M. S. 2016; Pujades-Rodriguez 2018).

Approximately 70% of patients with phenotypic HCM will demonstrate an element of left ventricular outflow tract (LVOT) obstruction (Maron, M. S. 2006). The mechanisms for developing obstruction are well defined and involve a complex interplay between alterations in ventricular flow between asymmetric septal hypertrophy and the mitral valve leaflets. The result is abnormal systolic contact with the mitral valve leaflets (most commonly the anterior leaflet) and the development of an LVOT gradient (LVOT-G). By nature, oHCM is a dynamic condition with variable systolic gradients. In the setting of reduced afterload or reduced preload, symptoms change depending on the gradient and often worsen during exertion. Additional clinical manifestations of HCM include an elevated risk for ventricular fibrillation and sudden cardiac death; heart failure syndrome due to diastolic dysfunction; chest pain due to microvascular ischemia; palpitations and stroke due to atrial fibrillation; syncope and presyncope due to either

ventricular arrhythmias or an abnormal blood pressure response to exercise; and, in a minority of patients, progression to systolic heart failure.

Contemporary management strategies for oHCM have resulted in the majority of patients achieving normal or near-normal longevity and improved morbidity; however, there has been little progress with the development of novel pharmacotherapies. Recent approval by the US FDA of mavacamten (April 2022), a first-in-class cardiac myosin inhibitor, provides support for the value of a disease-targeted approach to medical therapy (Olivotto 2020). Current medical treatment consists of beta-blockers, verapamil, or diltiazem as recommended in the 2014 European Society of Cardiology and in the 2020 American College of Cardiology Foundation / American Heart Association guidelines for the diagnosis and management of HCM. For patients with advanced symptomatic disease unresponsive to medications, septal reduction therapies (surgical myectomy or percutaneous alcohol ablation of the septum) can provide effective LVOT-G reduction (Elliott 2014; Gersh 2011; Ponikowski 2016; Ommen 2020). A subgroup of patients, who have been resuscitated from sudden cardiac death or who are at risk of sudden cardiac death, may undergo placement of an implantable cardioverter defibrillator (ICD) (Kristensen 2014). For those patients with HCM with end-stage disease who have both significant systolic impairment and diastolic dysfunction, cardiac transplantation may be the only treatment option (Gersh 2011). Disease-related mortality is most often attributable to sudden cardiac death, heart failure, and embolic stroke.

Pathogenic sequence variants in over a dozen genes encoding sarcomere-associated proteins cause HCM. MYH7 and MYBPC3, encoding β-myosin heavy chain and myosin-binding protein C, respectively, are the two most common genes involved, together accounting for approximately 50% of the HCM families (Elliott 2014). Mechanistically, disease-causing genetic variants in HCM appear to increase the net power generation in the sarcomere in vitro (Chuan 2012; Sommese 2013; Spudich 2016; Toepfer 2019). The findings in these studies are consistent with the underlying myocardial pathophysiology of the LV in patients with HCM being hypercontractile with diminished compliance (Wilson 1967).

These nonclinical investigations have enhanced our understanding of the molecular pathogenesis of HCM and have stimulated efforts to identify cardiac myosin modulators that can target the underlying mechanism of hypercontractility in oHCM.

2.2.2. Aficamten

Aficamten, a small molecule allosteric inhibitor of cardiac myosin, is being developed as an oral treatment for patients with chronic HCM. Aficamten is designed to reduce the hypercontractility that underlies the pathophysiology of HCM in the cardiac sarcomere. The intended pharmacologic effect is reduction in force produced by the cardiac sarcomere resulting in less LVOT obstruction and improved diastolic function in patients with oHCM.

Aficamten has been studied in a Phase 1 trial in healthy adult participants (CY 6011). Ongoing trials with aficamten include a multi-cohort Phase 2 trial (CY 6021 [REDWOOD-HCM]) in participants with oHCM and non-obstructive HCM, an open-label extension trial (CY 6022) for participants who have completed a prior aficamten study, and a Phase 3 trial (CY 6031 [SEQUOIA-HCM]) placebo-controlled trial in participants with oHCM receiving SOC therapy.

This second Phase 3 trial will assess the efficacy and safety of aficamten, compared with metoprolol, in participants with oHCM.

Refer to the Investigator's Brochure (IB) for detailed information on the nonclinical and clinical studies of aficamten.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Excessive exposures to aficamten may result in an exaggerated pharmacodynamic (PD) effect, namely a decrease in LV systolic function, resulting in decreases in stroke volume and cardiac output with compensatory increases in heart rate. In nonclinical toxicology studies, sustained depression of cardiac function led to increases in heart weight and dilatation of the cardiac chambers. These adverse cardiac effects are consistent with the anticipated physiological response to an excessive PD effect of aficamten.

In the first-in-human CY 6011 study, short-term decreases in cardiac function produced no changes in vital signs or electrocardiogram (ECG) parameters. The effect of aficamten of decreased left ventricular ejection fraction (LVEF) reversed within 24 to 48 hours of discontinuation of dosing (single ascending dose and multiple ascending dose cohorts). The participants who had decreases in LVEF to < 50% remained asymptomatic.

In the first 3 cohorts of CY 6021, a decline in LVEF < 50% per core laboratory evaluation was reported for 2 of 41 participants in the aficamten group (Cohort 2, one each at Weeks 2 and 10), and no participants in the placebo group. The LVEF returned to above 50% at the next observed time point 2 weeks later and there were no associated adverse events (AEs). There were no reports of post-baseline LVEF < 40%.

Together, these findings indicate that the treatment effect of aficamten on LVEF is well tolerated and readily reversible with either a reduction of dose or discontinuation of treatment.

2.3.1.1. Mitigation Strategy

The main mitigation strategy will consist of an individualized dose titration scheme based on each participant's PD response to aficamten with application of prespecified echocardiographic criteria, including LVEF thresholds for dose escalation, down-titration, and investigational product (IP) discontinuation.

Participants enrolled in this trial will be required to have an LVEF ≥ 60% prior to randomization, as confirmed by the central echocardiography laboratory. A low starting dose of 5 mg (once daily) and a maximum dose of 20 mg (once daily) were chosen as these were found to be well tolerated in CY 6021 in participants with oHCM and effective at reducing the LVOT-G without adversely impacting overall LVEF. Dose escalation for each participant will occur based on the criteria described in Section 6.6). Importantly, in contrast to CY 6021, the lower limit of LVEF for dose escalations will be increased from 50% to 55% to provide a safety margin from the threshold of LVEF (< 50%) that will trigger dose reduction. If the LVEF is < 50% at any time, the dose of aficamten will be down-titrated, and if the LVEF is < 40% at any time, aficamten will be temporarily interrupted.

An independent Data Monitoring Committee (DMC) will be established for this trial to formally review the accumulating unblinded data periodically to assess the risk to participants during the conduct of the trial. DMC members will include echocardiologists and HCM experts and will have access to treatment assignments and participant-level data in support of safety oversight.

2.3.2. Aficamten Benefit Assessment

The development of a targeted therapeutic drug that directly reduces myocardial contractility in the sarcomere may yield potential clinical benefit for patients with oHCM by trying to address the underlying pathophysiology of HCM. Aficamten is a cardiac myosin inhibitor with the potential to reduce LVOT obstruction and thereby reduce symptoms in patients with hyperdynamic ventricular contractility in oHCM.

In the Phase 2 trial, CY 6021, participants with oHCM received up to 3 doses of aficamten or placebo (randomized 2:1) in a dose escalating manner with echocardiography used to guide dose titration. Two cohorts of approximately 20 participants each were enrolled and treated for 10 weeks. Doses were 5, 10, and 15 mg once daily in the first cohort; and 10, 20, and 30 mg once daily in the second cohort. In both cohorts, aficamten significantly and substantially reduced the LVOT-G in a dose- and exposure-dependent manner. The majority of participants treated with aficamten (78.6% in Cohort 1 and 92.9% in Cohort 2) achieved the hemodynamic response criteria, defined as resting gradient < 30 mmHg and post-Valsalva gradient < 50 mmHg at Week 10 compared to placebo (7.7%). A third cohort, in which all participants were assigned aficamten, was enrolled to assess the effect of aficamten in addition to SOC therapy that includes disopyramide. Doses of aficamten were 5, 10, and 15 mg once daily. Aficamten significantly reduced LVOT-G (46% achieved complete hemodynamic response). Importantly, there were no LVEF < 50% per core laboratory or prolonged QTc events observed.

Given that the LVOT-G is the primary cause of symptoms in patients with oHCM, participation in this trial may afford those randomized to aficamten symptom reduction and increased exercise capacity. Participant contributions to the performance of this trial may yield a new therapeutic modality for the treatment of their disease.

3. OBJECTIVES AND ENDPOINTS

Table 2: Trial Objectives and Endpoints

Objectives	***Endpoints***
Primary	
To evaluate the effect of aficamten compared with metoprolol on exercise capacity in participants with symptomatic oHCM	• Change in peak oxygen uptake (pVO_2) by cardiopulmonary exercise testing (CPET) from baseline to Week 24
Secondary	
To evaluate the effect of aficamten compared with metoprolol on NYHA Functional Classification	• Proportion of participants with ≥ 1 class improvement in NYHA Functional Class from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on participant health status	• Change in KCCQ-CSS from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on structural remodeling	• Change in LVMI from baseline to Week 24 • Change in LAVI from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on NT-proBNP levels	• Change from baseline values in NT-proBNP from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on post-Valsalva LVOT-G	• Change in post-Valsalva LVOT-G from baseline to Week 24
Safety	
To evaluate the safety and tolerability profile of aficamten compared with metoprolol in participants with oHCM	• Participant incidence of reported major adverse cardiac events (CV death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization) • Participant incidence of AEs • Participant incidence of LVEF < 50%

Table 2: Trial Objectives and Endpoints (Continued)

Objectives	*Endpoints*
Exploratory	
To evaluate the effect of aficamten compared with metoprolol on exercise capacity and functional class in symptomatic oHCM participants	• Number of participants on aficamten at Week 24 achieving either: – Change from baseline of ≥ 1.5 mL/kg/min in pVO_2 AND – ≥ 1 class improvement in NYHA Functional Class **OR** – Change of ≥ 3.0 mL/kg/min from baseline in pVO_2 AND – No worsening of NYHA Functional Class
To evaluate the effect of aficamten compared with metoprolol on participant response over time	• Proportion of participants with categorical improvement in KCCQ-CSS at Weeks 12 and 24 • Proportion of participants with resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G < 50 mmHg, and NYHA Class I at Weeks 12 and 24 • Proportion of participants with resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G < 50 mmHg, and ≥ 1 class improvement in NYHA Functional Class from baseline to Weeks 12 and 24
To evaluate the effect of aficamten compared with metoprolol on cardiac troponin levels	• Change in hs-cTnI from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on a measure of diastolic function	• Change in E/e' (lateral wall) from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on IVST remodeling	• Change in IVST from baseline to Week 24
To evaluate the effect of aficamten compared with metoprolol on other CPET parameters	• Change from baseline to Week 24 in: – Ventilatory efficiency/carbon dioxide production (VE/VCO_2 slope) – Circulatory power (VO_2 × SBP) – VAT – Total workload (watts) – Heart rate response

Table 2: Trial Objectives and Endpoints (Continued)

Objectives	*Endpoints*
To evaluate the effect of aficamten compared with metoprolol on health status and health-related quality of life as measured by questionnaires	• Change from baseline to Week 24 in individual responses to the EQ-5D-5L, CGI, PGI-C, and SAQ-7
To assess the PK of aficamten and its metabolites	• PK parameters through Week 24

AE = adverse events; CGI = Clinical Global Impression scale; CPET = cardiopulmonary exercise testing; CV = cardiovascular; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; EQ-5D-5L = EuroQol 5-dimension 5-level instrument; HCM = hypertrophic cardiomyopathy; hs-cTnI = high sensitivity cardiac troponin I; IVST = interventricular septal thickness; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVOT-G = Left ventricular outflow tract gradient; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; PGI-C = Patient Global Impression of Change scale; PK = pharmacokinetic; PRO = patient-reported outcomes; pVO_2 = peak oxygen uptake; SAQ-7 = Seattle Angina Questionnaire-7; SBP = systolic blood pressure; VAT = ventilatory anaerobic threshold; VO_2 = oxygen uptake

4. TRIAL DESIGN

4.1. Overall Design

This is a Phase 3, multi-center, randomized, double-blind, active-comparator trial in participants with symptomatic oHCM and elevated LVOT-G. Approximately 170 eligible participants will be randomized in a 1:1 ratio to aficamten or metoprolol. Central randomization will be stratified by cardiopulmonary exercise testing (CPET) exercise modality (treadmill/bicycle), and recently diagnosed vs chronic oHCM. The number of participants using the bicycle CPET exercise modality will be capped at approximately 50%.

This study consists of four periods: Screening SOC Washout Period, Screening Period, Treatment Period, and EOT Metoprolol Washout Period.

Screening SOC Washout Period:

Study participants who signed the informed consent form will enter the two screening period visits as follow:

- Screening Visit 1 (Pre-SOC Washout) – All participants on SOC therapy will undergo a washout period consisting of approximately 14 days of weaning from SOC therapy, followed by an additional 7 days completely off SOC therapy prior to Screening Visit 2.

Screening Period:

- Screening Visit 2 (Screening | Post-SOC Washout) – All participants who completed Screening Visit 1 will also complete Screening Visit 2. Participants who are not currently on medical SOC therapy for oHCM at the time of informed consent will only complete the Screening Visit 2.
    - Assessments that are repeated at Screening Visit 2 and impact eligibility (i.e., laboratory results, ECG, NYHA) will be used to determine eligibility.

Treatment Period:

Participants who meet eligibility criteria at the conclusion of Screening Visit 2 will be randomized to receive either aficamten and placebo for metoprolol, or metoprolol and placebo for aficamten.

Randomization will be stratified by CPET exercise modality (treadmill/bicycle), and recently diagnosed vs chronic oHCM as follows:

1. Recently Diagnosed: Participants who are treatment naïve or currently untreated (no SOC medical therapy within the past 12 months), or recently diagnosed participants (history of oHCM ≤ 12 months with or without use of SOC therapy).
2. Chronic oHCM: Participants with chronic oHCM (> 12 months) currently treated or having received SOC therapy within the past 12 months.

All randomized participants may receive up to 4 escalating doses of IP over the initial 6 weeks of the trial.

Participants receiving aficamten will start at a dose of 5 mg once daily (Dose 1) and may escalate to doses of 10, 15, and 20 mg once daily if they continue to meet the escalation criteria as

described in Section 6.6.1. The dose of aficamten will not be up-titrated if escalation criteria are not met, and aficamten will be down-titrated or temporarily discontinued if low LVEF thresholds are met.

Participants receiving metoprolol will start at a dose of 50 mg once daily (Dose 1) and may escalate to doses of 100, 150, and 200 mg once daily if they continue to meet the escalation criteria as described in Section 6.6.1. The dose of metoprolol will not be up-titrated if escalation criteria are not met, and metoprolol will be down-titrated or temporarily discontinued if low LVEF or low vital sign thresholds are met.

Participants will have IP dispensed in a double-blind fashion at each trial visit. All site staff, including the unmasked echocardiologist and the unmasked designee, will be blinded to randomized treatment assignments. During the initial 6 weeks of the treatment period, IP doses will be individually adjusted according to echocardiographic and vital sign criteria. The unmasked echocardiologist, who is not involved in other aspects of the study, will review the echocardiographic (LVEF, resting LVOT-G, and post-Valsalva LVOT-G) and vital sign (systolic blood pressure [SBP] and resting heart rate) data and enter the data into the interactive web response system (IWRS). An unmasked designee, who is also not involved in other aspects of the study visits, may be delegated to enter data into IWRS on the unmasked echocardiologist's behalf. Dose adjustment will be carried out according to the prespecified algorithm in a blinded fashion. Neither the unmasked echocardiologist nor the unmasked data entry designee will reveal echocardiogram results to the rest of the study team, unless in the event of a critical safety issue (e.g., LVEF < 40%). Additionally, participant vital signs after randomization will not be accessible to the sponsor and clinical research organization study teams (aside from the individuals who perform source documentation verification), but to ensure oversight from a patient safety and data quality perspective, a medical monitor from the sponsor who is not directly involved in the study will review vital signs data. This person will be referred to as the "Titration Vitals Medical Monitor" and is not considered masked. Vital signs noted during other study procedures are not used for IP titration and can be viewed by the study team (site, CRO, and Sponsor).

If at any time during the trial a participant experiences an intolerable AE, which in the investigator's judgment is drug-related and compels the participant to request IP discontinuation, the dose of IP may be reduced to the previous dose level. For participants receiving Dose 1, IP will be discontinued.

End of Treatment (EOT) Metoprolol Washout Period:

At Week 24 EOT visit, all study participants will take their final IP dose on-site. The next day at home, participants will down-titrate metoprolol or placebo for metoprolol for up to approximately 14 days as needed. Participants will confirm they completed the metoprolol or placebo for metoprolol washout as a safety follow-up during the end of study (EOS) visit.

The overall trial design is described by a trial schema in Figure 1. The trial endpoints and objectives are defined in Table 2.

4.1.1. Number of Sites

Approximately 80 investigational sites worldwide will participate in this trial.

4.1.2. Number of Participants

Approximately 170 participants will be randomized.

4.1.3. Replacement of Participants

Participants who are withdrawn or removed from treatment or the trial will not be replaced.

4.1.4. Trial Duration

The trial is comprised of four study periods: Screening SOC Washout, Screening, Treatment, and End of Treatment (EOT) Metoprolol Washout. After signing the informed consent form, participants will complete assessments to determine trial eligibility during a 6-week Screening period starting at Screening Visit 1 (SV1) for participants who need to wash out their SOC therapy (if applicable) followed by Screening Visit 2 (SV2) to complete remaining Screening assessments. The double-blind Treatment period will last 24 weeks after randomization at Day 1. Following the final on-site dose of IP taken at the Week 24 EOT visit, participants will begin the next day at home to complete their up to 2-week EOT Metoprolol Washout with a safety follow-up performed at the Week 28 EOS visit. The total study duration is approximately 34-38 weeks.

4.2. Scientific Rationale for Trial Design

Aficamten is a next-generation small molecule cardiac myosin inhibitor being developed as an oral treatment for patients with chronic HCM. Trial rationale is provided in Section 2.1.

Cardiac myosin inhibitors (CMIs) have demonstrated a favorable benefit-risk profile with respect to hemodynamic, functional, and symptomatic improvements, but have only been studied in patients already receiving SOC therapy to date (Maron, M. 2021; Olivotto 2020). CMIs have been developed specifically for oHCM whereas the treatments currently used (beta-blockers, calcium channel blockers, and disopyramide) were developed for other medical conditions and subsequently applied to oHCM due to their underlying negative inotropic characteristics. While beta-blockers have been shown to reduce symptom burden and improve hemodynamics, they do not improve exercise capacity (Dybro 2021) and can be associated with poor tolerability. Additionally, CMIs have not been tested specifically in recently diagnosed or treatment naïve patients. This trial is designed to evaluate whether monotherapy with aficamten shows improvement in exercise capacity, compared with a beta-blocker, in both recently diagnosed and chronic symptomatic oHCM patients.

Patient characteristics vary substantially in this disease, therefore, individualized dose titration based on PD response is being used in this trial to maximize efficacy and safety. The criteria for evaluation of PD response include effects known to result from administration of aficamten (decrease in LVEF and LVOT-G) or metoprolol (decrease in LVEF, LVOT-G, blood pressure, and heart rate). The eligibility criteria are designed to enable enrollment of a population representative of the oHCM population of interest while maintaining the safety of participants in the trial.

A double-blind, placebo-matched approach will be used in this trial to avoid bias in the data collection, including safety assessments and PD measures that comprise the trial endpoints.

4.3. Justification for Dose

The doses of aficamten are summarized in Section 6.6.1. A starting dose of 5 mg and a maximum dose of 20 mg were chosen as these were found to be well tolerated in the Phase 2 trial of participants with oHCM and effective at reducing the LVOT-G without adversely impacting overall LVEF (see Section 2.3.2). Doses for metoprolol were selected based on current regional guideline documents (Elliott 2014; Ommen 2020) and titrated based on PD effects described in Section 6.6.1.

Dose titration will be individualized for each participant based on the criteria described in Section 6.6.

4.4. End of Study Definition

The study completion date is defined as the date of the last visit of the last participant in the trial.

5. TRIAL POPULATION

Before participants begin any trial-specific activities/procedures, Cytokinetics requires a copy of the site's institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other participant information and/or recruitment material, if applicable. A signed ICF must be obtained from each participant before commencement of any trial-specific activities/procedures.

A participant's participation in the trial begins after signing the informed consent. After confirming the participant has met all eligibility criteria, randomization should then occur before the first dose on Day 1 is administered. The site is to document the informed consent signature, eligibility criteria have been met, and randomization dates in the participant's medical record.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exceptions, is not permitted.

5.1. Inclusion Criteria

Unless otherwise stated below, for screening assessments that are repeated from Screening Visit 1 to Screening Visit 2, the results from the assessments performed at Screening Visit 2 should be used to determine initial eligibility.

Participants are eligible to be included in the trial only if all the following criteria apply:

101. Able to comprehend and willing to sign an ICF and willing to comply with all trial procedures and restrictions for the duration specified in the Schedule of Activities (SoA; Section 1.3)
102. Males and females between 18 to 85 years of age, inclusive, at the signing of informed consent
103. Body mass index < 35 kg/m^2. Qualification of BMI for study eligibility is only required at the participant's first screening visit.
104. Diagnosed with oHCM per the following criteria by cardiac magnetic resonance imaging (CMR) or echocardiography:
    a. Has LV hypertrophy with non-dilated LV chamber in the absence of other cardiac disease and
    b. Has an end-diastolic LV wall thickness as measured by the echocardiography core laboratory:
        - ≥ 15 mm in one or more myocardial segments

          OR
        - ≥ 13 mm in one or more wall segments *and* a known-disease-causing gene mutation or positive family history of HCM
105. New York Heart Association (NYHA) class II or III at Screening Visit 2
106. KCCQ-CSS score ≤ 90 at Screening Visit 2
107. Adequate acoustic windows for echocardiography at Screening Visit 2

108. Has a screening echocardiogram with the following as determined by the echocardiography core laboratory:
    a. Resting LVOT-G ≥ 30 mm Hg and/or post-Valsalva LVOT-G ≥ 50 mmHg at screening

       AND

    b. LVEF ≥ 60% at screening
109. Respiratory exchange ratio (RER) ≥ 1.05 and peak oxygen uptake (pVO_2) < 100% predicted on the screening CPET per the core laboratory
110. Hemoglobin ≥ 10 g/dL at screening
111. Male participants are eligible to participate if they agree to the following:
    a. Refrain from donating sperm during the trial and for at least 10 weeks after the last dose of IP

       And

    b. During the trial and for 4 weeks after the last dose of IP either:
        - Abstain from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent in writing

          OR

        - If his female partner is a woman of childbearing potential, must agree to use a male condom and have his female partner use a highly effective method of contraception (as described in Appendix 3 [Section 10.3])
112. A female participant is eligible to participate if she is not pregnant, breastfeeding, or planning to donate eggs, and at least one of the following conditions applies:
    a. Is not a woman of childbearing potential (WOCBP; as described in Appendix 3 [Section 10.3])

       OR

    b. Is a WOCBP and refraining from donating egg/ova, during the trial and for at least 10 weeks after the last dose of IP and using a highly effective method of contraceptive (as described in Appendix 3 [Section 10.3]) during the trial and for at least 4 weeks after the last dose of IP

       A WOCBP must have a negative pregnancy test (urine or serum as required by local regulations) at Day 1, prior to the first dose of trial intervention

       Note: The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
113. Contraceptive use by men or WOCBPs should be consistent with the guidance in Appendix 3 (Section 10.3) and local regulations regarding the methods of contraception for those participating in clinical trial
114. Is willing and able to complete all screening procedures
115. Patients previously exposed to mavacamten are allowed to participate but must be off mavacamten for at least 8 weeks prior to signing of informed consent and must be

approved by the Medical Monitor prior to enrollment. Approximately 10% of oHCM patients who were previously treated with mavacamten can participate in the study with Medical Monitor approval

5.2. Exclusion Criteria

Unless otherwise stated below, for Screening assessments that are repeated from Screening Visit 1 to Screening Visit 2, the results from the assessments performed at Screening Visit 2 should be used to determine initial eligibility.

Participants will be excluded from the trial if any of the following criteria apply

201. Medical indication for either beta blocker or calcium-channel blockers prohibiting drug discontinuation other than oHCM
202. History of intolerance or medical contraindication to beta blocker therapy
203. Resting SBP of > 160 mmHg at the time of screening
204. Resting heart rate of > 100 beats per minute (bpm) at the time of screening
205. Significant valvular heart disease
    a. Moderate-severe valvular aortic stenosis or fixed subaortic obstruction
    b. Mitral regurgitation not due to systolic anterior motion of the mitral valve (per Investigator judgment)
206. Known or suspected infiltrative, genetic or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis)
207. Prior treatment with cardiotoxic agents such as doxorubicin or similar within 10 years prior to screening
208. History of LV systolic dysfunction (LVEF < 45%) or stress cardiomyopathy at any time during their clinical course
209. Has any ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second degree atrioventricular block type II)
210. Inability to exercise on a treadmill or bicycle (eg, orthopedic limitations)
211. Documented room air oxygen saturation reading < 90% at screening
212. Planned septal reduction treatment that cannot be deferred during the trial period
213. History of septal reduction therapy (surgical myectomy or alcohol septal ablation) within 6 months of screening. Patients who have had septal reduction therapy greater than 6 months before screening are allowed, up to approximately 10% of total.
214. History of paroxysmal or persistent atrial fibrillation or atrial flutter. Atrial flutter treated with radio frequency ablation without recurrence within the last 6 months prior to screening is allowed.
215. Current or recent (< 4 weeks prior to signing of informed consent) therapy with disopyramide
216. History of syncope, symptomatic ventricular arrhythmia, or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening
217. Recent (< 3 months prior to signing of informed consent) ICD implantation or planned ICD implantation during the trial period

218. History of appropriate ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to signing of informed consent
219. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 by the modified Modification of Diet in Renal Disease equation at screening
220. Hepatic impairment defined by a total bilirubin (TBL) ≥ 1.5 × the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × ULN at screening. Participants with documented Gilbert syndrome and TBL ≥ 1.5 × ULN due to unconjugated hyperbilirubinemia, without other hepatic impairment, are permitted
221. Recipient of a major organ transplant (eg, heart, lung, liver, bone marrow, renal) or anticipated transplantation within 12 months from randomization
222. Any history or evidence of other clinically significant disorder, malignancy, active infection, other condition, or disease that, in the opinion of the Investigator or the Medical Monitor, would pose a risk to participant safety or interfere with the trial evaluation, procedures, or completion
223. Currently participating in another investigational device or drug trial or received an investigational device or drug < 1 month (or 5 half-lives for drugs, whichever is longer) prior to signing of informed consent. Other investigational procedures while participating in this trial are not permitted. Assessments for entry into the CY 6022 open-label extension study are permitted at the EOS visit
224. Has received prior treatment with aficamten or previously intolerant (reduced LVEF requiring permanent drug discontinuation) to mavacamten
225. Any known clinically significant or severe lactose intolerance or hypersensitivity to aficamten, metoprolol succinate, or any of the excipients in the study drug tablets (including placebo).
226. Documented history of current obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.

5.3. Lifestyle Considerations

Participants must abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests and before CPET. Participants must not exercise at all for 12 hours prior to CPET. Participants must also fast for at least 4 hours prior to CPET. Alcohol or any medications that may cause drowsiness should be avoided for 8 hours prior to CPET.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to IP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, reason for screen failure, eligibility criteria, and any serious adverse events (SAEs) related to trial-related procedures.

The screening eligibility period is up to 42 days as defined in Section 4.1. An individual who does not meet the criteria for participation in this trial is referred to as a screen failure. Participants may be rescreened one time after initial screening when the reason for screen failure is resolved or expected to be resolved.

Participants must re-sign an informed consent before they are rescreened. At rescreening, they must meet all inclusion/exclusion criteria at the time of rescreening and have all elements of the screening visit performed again to be eligible.

If an element of the screening visit could not be adequately performed for logistical or technical reasons (eg, trained evaluator was out sick, equipment malfunction), the participant can return within the screening eligibility period to adequately complete the assessment.

Retesting for abnormal laboratory results within the original screening period may also be performed if there is reason to believe the repeat laboratory results may improve and not be clinically significant and the participant is otherwise eligible to participate. Participants who are retested during the original screening eligibility period do not need to re-sign an informed consent. The screening window is established by the date the ICF was initially signed and not by the date lab retesting takes place. Repeat echocardiogram within the original screening period may be performed at the discretion of the site principal investigator if the echocardiology core lab judges the image quality to be inadequate.

No waivers will be granted regarding inclusion/exclusion criteria.

6. INVESTIGATIONAL PRODUCT

This section describes any IP, marketed products, or placebo intended to be administered to a trial participant according to the trial protocol.

6.1. Investigational Products Administered

Descriptions of aficamten and matching placebo are found in Table 3. Metoprolol (50 mg [47.5 mg metoprolol succinate (trade name, metoprololsuccinat STADA® 47.5 mg)] tablet) will be commercially sourced and labeled for use in an investigational trial. Placebo for metoprolol succinate will have the same appearance, including labeling, and excipients, however, lack the active ingredient.

Regardless of treatment arm, participants will receive both bottles and blister packages to maintain the blind.

Table 3: Investigational Products

Arm Name	Active (Aficamten)	Placebo (Aficamten)	Active (Metoprolol succinate)	Placebo (Metoprolol succinate)
IP/Product Name	Aficamten (CK-3773274)	Placebo	Metoprolol succinate Metoprololsuccinat STADA®	Placebo
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Excipients	[redacted]	[redacted]	[redacted]	[redacted]
Unit Dose Strength(s)	5 mg	Matching placebo	47.5 mg metoprolol succinate tablet	Matching placebo
Dosage Level(s)	5, 10, 15, 20 mg	NA	50, 100, 150, 200 mg	NA
Route of Administration	Oral	Oral	Oral	Oral

Table 3: Investigational Products (Continued)

Arm Name	Active (Aficamten)	Placebo (Aficamten)	Active (Metoprolol succinate)	Placebo (Metoprolol succinate)
Use	Experimental	Placebo	Comparator	Placebo
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	[redacted]	[redacted]	[redacted]	[redacted]
Packaging and Labeling	IP will be provided in bottles. Each bottle will be labeled as required per country requirement.	IP will be provided in bottles. Each bottle will be labeled as required per country requirement.	IP will be provided in blister packages. Each blister package will be labeled as required per country requirement.	IP will be provided in blister packages. Each blister package will be labeled as required per country requirement.

HPMC = hydroxypropyl methylcellulose; IMP = investigational medicinal product; IP = investigational product; NIMP = non-investigational medicinal product; PEG = polyethylene glycol

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

Only participants randomized in the trial may receive IP and only authorized site staff may supply or administer IP. All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, chain of custody, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information regarding IP storage condition, dispensation, packaging, labeling, and accounting procedures are provided in the Pharmacy Manual. IP should be stored at or below 25°C.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized IP using an IWRS.

Participants will have IP dispensed in a double-blinded fashion at each trial visit summarized in the SoA (Section 1.3).

All site staff, including the unmasked echocardiologist and the unmasked designee, will be blinded to randomized treatment assignments.

During the initial 6 weeks of the treatment period, IP doses will be individually titrated or adjusted according to echocardiographic and vital sign criteria. To prevent the investigator and site staff from viewing the echocardiogram or results, the unmasked echocardiologist, who is not involved in other aspects of the study visits, will review the echocardiographic (LVEF, resting LVOT-G, and post-Valsalva LVOT-G) and vital signs (SBP and resting heart rate) data and enter the data into IWRS. An unmasked designee, who is also not involved in other aspects of the study visits, may be delegated to enter data into IWRS on the unmasked echocardiologist's behalf. Dose adjustment will be carried out according to the prespecified algorithm in a blinded fashion. Neither the unmasked echocardiologist nor the unmasked data entry designee will reveal echocardiogram results to the rest of the study team, unless in the event of a critical safety issue (e.g., LVEF < 40%). Additionally, participant vital signs after randomization will not be accessible to the sponsor and clinical research organization study teams (aside from the individuals who perform source documentation verification), but to ensure oversight from a patient safety and data quality perspective, a medical monitor from the sponsor who is not directly involved in the study will review vital signs data. This person will be referred to as the "Titration Vitals Medical Monitor." Vital signs noted during other study procedures are not used for IP titration; therefore, they are not considered masked and can be viewed by the study team (site, CRO, and Sponsor).

Before the trial is initiated, the log-in information and directions for the IWRS will be provided to each site. The IWRS will be programmed with blind-breaking instructions and the unblinding procedure is documented in the trial manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator is highly encouraged to contact Cytokinetics prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, Cytokinetics must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation, as applicable.

6.4. Investigational Product Compliance

When participants are dosed at the site, the date and time of the dose administered in the clinic will be recorded in the source documents.

When participants self-administer IP at home, compliance with IP will be assessed at each site visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source document.

Returned IP may not be re-dispensed to the participants. Deviation(s) from the prescribed dosage regimen should be recorded.

For IP accountability, a record of the following should be documented at every visit and reconciled with IP and compliance records:

- The date and kits dispensed
- Date and number of tablets returned

IP dosing first and last dates, including dates for dosing interruptions will also be recorded. All temporary IP interruptions of greater than 3 consecutive days should be recorded (stop and start dates and reason for interruption) and the Medical Monitor should be notified.

6.5. Prior and Concomitant Therapy

6.5.1. Prior Therapy

During Screening, participants will be asked about their SOC medical therapy for oHCM (beta-blocker, calcium-channel blocker, and mavacamten medication) history over the past 12 months.

6.5.2. Concomitant Therapy

Any medication, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the participant is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants may continue to take prescription medications, which in the opinion of the investigator and the Medical Monitor, will not interfere with the trial.

While medications and doses should remain stable whenever appropriate during the trial, investigators may prescribe or adjust any concomitant medication or treatment deemed necessary to provide adequate supportive care.

The re-introduction of SOC medications (beta-blockers, non-dihydropyridine calcium channel blockers, or disopyramide) after randomization is not prohibited, nor is septal reduction therapy. While these interventions are discouraged because they may independently impact the study endpoints, they are permitted per medical necessity according to the opinion of the investigator. If the investigator decides that re-introduction of SOC medications is warranted, the investigator is highly encouraged to contact the Cytokinetics Medical Monitor prior to re-introducing the SOC medications.

6.5.3. Drug-Drug Interactions

In vitro studies demonstrated that aficamten is likely metabolized by multiple cytochrome P450 (CYP) enzymes including CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Furthermore, in vitro studies demonstrated that aficamten may be an inhibitor of P-glycoprotein (P-gp) in vivo. These potential interactions were explored further in human studies.

Collectively, preliminary data from clinical drug interaction studies (CY 601-10 and CY 6014) indicated that CYP2C9 accounts for approximately 53% of aficamten metabolism with smaller contributions from CYP2D6, CYP3A (21% each) and CYP2C19 (4%). Based on the Phase 1

work, CYP2C8 is not expected to play a major role. As a perpetrator of drug-drug interactions, aficamten was identified as a weak inhibitor of P-gp (CY 6014).

Strong inducers of multiple pathways or strong and moderate CYP2C9 inhibitors (see example of drugs in Table 4; not a complete list) have the potential to decrease or increase aficamten exposure, respectively and should be used with caution, particularly if these drugs are being initiated or discontinued during aficamten treatment.

The Medical Monitor should be contacted for any questions regarding potential drug-drug interactions.

In vitro, aficamten modestly inhibited the OAT3 transporter (IC_{50} = 12.1 µM). Given the observed maximum aficamten plasma concentration was 516 ng/mL at 20 mg QD in HCM patients in the Phase 2 study, CY 6021 and the fraction unbound in plasma of aficamten is 0.056 (CY 6017), the estimated potential for meaningful inhibition of OAT3 by aficamten is low (R- value = 0.007; FDA cut-off ≥ 0.1, FDA guidance 2020). The same assessments were conducted for the two major circulating metabolites CK-3834282 and CK-3834283, which also predict low potential for meaningful inhibition of OAT3. Consequently, aficamten may be administered with OAT3 substrates.

Table 4: List of Strong CYP Inducers, strong and moderate CYP2C9 inhibitors

Strong Cytochrome P450 Inducers:	apalutamide avasimibe carbamazepine enzalutamide ivosidenib lumacaftor mitotane phenytoin rifampin St. John's Wort
Strong CYP2C9 inhibitors	sulfaphenazole
Moderate CYP2C9 inhibitors	adagrasib amiodarone asciminib cannabidiol fluconazole miconazole mifepristone nitisinone

CYP = cytochrome P450
Please note, this is not a comprehensive list.

6.5.4. Rescue Medicine

The use of rescue medications in the event of a low cardiac output state (eg, dobutamine) is allowed at any time during the trial (Section 8.5). The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6. Dose Modifications

All criteria must be met for dose escalation, but only one criterion must be met for down-titration or IP discontinuation. If down titration occurs, no further up titration will be allowed. IP cannot be -up titrated after Week 6 but may be -down titrated to the next lowest dose as described in Section 6.6.2.

If the LVEF is < 40% at any time on either arm, IP will be temporarily discontinued and restarted at the next lower dose as instructed in Section 6.6.3.

The treatment duration will be 24 weeks with a 4-week follow-up period after the last dose (Weeks 24 through 28). The primary endpoint of pVO_2 will be measured by CPET at randomization and at Week 24.

Any dose interruption lasting longer than three days, as described above, must be documented to include the reason for interruption, the date of the last dose, and the restart date.

6.6.1. Scheduled Dose Titrations

All randomized participants may receive up to 4 escalating doses of IP over the initial 6 weeks of the trial as outlined below in Table 5.

Participants receiving aficamten will start at a dose of 5 mg once daily (Dose 1) and may escalate to doses of 10, 15, and 20 mg once daily if they continue to meet the 2 echocardiographic escalation criteria or will remain at their current dose when escalation criteria are not met.

Participants receiving metoprolol will start at a dose of 50 mg once daily (Dose 1) and may escalate to doses of 100, 150, and 200 mg once daily if they continue to meet the 2 echocardiographic and 2 vital sign escalation criteria or will remain at their current dose when escalation criteria are not met.

Table 5: Criteria for Scheduled Dose Titrations

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.		
SBP	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

bpm = beats per minute; IP = investigational product; LVEF = left ventricular ejection fraction; LVOT-G = Left ventricular outflow tract gradient; NA = not applicable; SBP = systolic blood pressure

6.6.2. Dose Reductions

All criteria must be met for dose escalation, but only one criterion must be met for down-titration or discontinuation. IP cannot be up-titrated after Week 6, but will be down-titrated to the next lowest dose at any visit throughout trial participation if any of the following criteria are met:

1. LVEF < 50% (all participants)
2. Heart rate < 50 bpm (participants assigned to metoprolol only)
3. SBP < 90 mmHg (participants assigned to metoprolol only)

If at any time during the trial a participant experiences an intolerable AE, which in the investigator's judgment is drug-related and compels the participant to request IP discontinuation, the dose of IP may be reduced to the previous dose level. For participants receiving Dose 1, IP will be discontinued.

If the LVEF is < 40% at any time on either arm, IP will be temporarily discontinued; IP can be restarted at the next lower dose, as instructed in Section 6.6.3.

6.6.3. LVEF Safety Threshold

If the unmasked echocardiologist, who is not involved in other aspects of the study visits, observes that the LVEF has crossed the defined safety threshold of < 40% or deems that the participant requires urgent medical attention, the unmasked echocardiologist or the unmasked designee, who is also not involved in other aspects of the study visits, will enter the LVEF value

in the IWRS and discuss the results with the investigator or qualified designee. The Medical Monitor will be informed in these cases.

If a participant's LVEF is < 40% at any time, the following steps should occur after consultation with the Medical Monitor:

- IP should be stopped and held for at least 7 days.
- Repeat echocardiograms should be performed per investigator judgment until a normal LVEF (≥ 55%) has been documented at which point the participant can be re-started on IP after being down-titrated.
- Document dose interruption and include the reason for interruption in the source, the date of the last dose, and the restart date (Section 7.1).

6.6.4. Hepatotoxicity Stopping and Rechallenge Rules

Participants with abnormal hepatic laboratory values (i.e., alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis may meet the criteria for withholding or permanent discontinuation of IP or other protocol-required therapies as specified in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. See Appendix 5 (Section 10.5) for guidance on the assessment and management of abnormal hepatic laboratory values.

In the event of a hepatotoxicity event requiring immediate lab assessment, the investigator will be permitted to process the blood sample for expedited analysis by submitting a sample to the local lab and sending a sample to the central laboratory. This process will allow the investigator to treat the study participant in an expedited manner. Only laboratory samples analyzed by the central laboratory will be used for study analysis.

6.6.5. Scheduled Down-titration of Metoprolol at Week 24

The last dose of aficamten and placebo for aficamten will occur on-site at Week 24 (or at a delayed Week 24 visit). No additional bottles of aficamten will be dispensed at this visit, and the dosing of aficamten and placebo for aficamten will be stopped.

To maintain the blind, all participants will down-titrate metoprolol or placebo for metoprolol the next day at home after the Week 24 visit. Site staff will contact the participants to follow up that they are following the down-titration steps at home appropriately.

For early-terminated participants, they will also need to down-titrate metoprolol or placebo for metoprolol at home after the ED visit.

Table 6: Down-titration Schedule for Participants on 200 mg Metoprolol or Placebo for Metoprolol

Titration Day	Titration Duration	Maximum Dose	No. of Tablets
Participant's dose from Week 20 to on-site dosing at Week 24.		200 mg metoprolol or placebo for metoprolol	4 tablets per day from blister card
Starting the day after the Week 24 visit, participants should complete the following down-titration steps at home.			
Day 1 – Day 4	4 days	150 mg metoprolol or placebo for metoprolol	3 tablets per day from blister card
Day 5 – Day 8	4 days	100 mg metoprolol or placebo for metoprolol	2 tablets per day from blister card
Day 9 – Day 12	4 days	50 mg metoprolol or placebo for metoprolol	1 tablet per day from blister card
Day 13	**Down-titration completed**		0 tablet per day

Table 7: Down-titration Schedule for Participants on 150 mg Metoprolol or Placebo for Metoprolol

Titration Day	Titration Duration	Maximum Dose	No. of Tablets
Participant's dose from Week 20 to on-site dosing at Week 24.		150 mg metoprolol or placebo for metoprolol	3 tablets per day from blister card
Starting the day after the Week 24 visit, participants should complete the following down-titration steps at home.			
Day 1 – Day 4	4 days	100 mg metoprolol or placebo for metoprolol	2 tablets per day from blister card
Day 5 – Day 8	4 days	50 mg metoprolol or placebo for metoprolol	1 tablet per day from blister card
Day 9	**Down-titration completed**		0 tablet per day

Table 8: Down-titration Schedule for Participants on 100 mg Metoprolol or Placebo for Metoprolol

Titration Day	Titration Duration	Maximum Dose	No. of Tablets
Participant's dose from Week 20 to on-site dosing at Week 24.		100 mg metoprolol or placebo for metoprolol	2 tablets per day from blister card
Starting the day after the Week 24 visit, participant should complete the following down-titration steps at home.			
Day 1 – Day 4	4 days	50 mg metoprolol or placebo for metoprolol	1 tablet per day from blister card
Day 5	**Down-titration completed**		0 tablet per day

Table 9: Down-titration Schedule for Participants on 50 mg Metoprolol or Placebo for Metoprolol

Participants assigned to this dose level at Week 24 will not require further down-titration.

Titration Day	Titration Duration	Maximum Dose	No. of Tablets
Participant's dose from Week 20 to on-site dosing at Week 24.		50 mg metoprolol or placebo for metoprolol	1 tablet per day from blister card
Starting the day after the Week 24 visit, participants should complete the following down-titration steps at home.			
Day 1	**Down-titration completed**		0 tablet per day

6.7. Access to Investigational Product after the End of the Trial

Participants who complete CY 6032 and meet eligibility criteria will be offered participation in an open-label extension trial. Participation in the open-label extension trial is at the discretion of the participant and not a condition of participation in CY 6032. The commitment to the conduct of an open-label extension trial will be at Cytokinetics's discretion.

7. TEMPORARY INTERRUPTION OF INVESTIGATIONAL PRODUCT, DISCONTINUATION OF INVESTIGATIONAL PRODUCT, AND PARTICIPANT CONSENT WITHDRAWAL

Emergent safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue, interrupt or permanently discontinue IP.

Unless a safety concern arises, the investigator should make every effort to keep a participant on the IP for as long as possible during the trial. The degree to which a participant withdraws from the trial varies. There are three types of IP discontinuation: temporary IP interruption, permanent IP discontinuation and participant withdrawal of consent.

7.1. Temporary IP Interruption

Initially, any IP interruption should be considered temporary unless permanent IP discontinuation is mandated by the protocol.

A temporary IP interruption:

- Will be implemented when a predefined safety threshold has been met (Section 6.6)
- May be considered by the investigator in the case of an AE/SAE or for another reason

If a temporary IP interruption occurred because a safety threshold was met, blinded treatment will be resumed at least 7 days later, either at a lower dose or with a permanent switch to placebo if the participant was at 5 mg aficamten or 50 mg metoprolol, as determined by the IWRS (Section 6.6.3).

If the IP was temporarily interrupted because of an AE/SAE, the investigator should make the best effort to resume IP as soon as practically possible, assuming there are no remaining safety concerns.

If dosing is interrupted for more than 3 consecutive days in the first 6 weeks and more than 7 consecutive days thereafter, the investigator should contact the Medical Monitor to discuss the participant.

All temporary IP interruptions of greater than 3 consecutive days should be documented (start and stop dates and reason for interruption) and the Medical Monitor should be notified.

7.2. Permanent Discontinuation of IP

In all cases, participants should be encouraged to discuss stopping IP with the investigator or the investigator's designee. Best efforts should be made to address the participant's questions, adjust concomitant medical therapies if needed and arrange follow-up safety assessments. For early-terminated participants, they will need to down-titrate metoprolol or placebo for metoprolol at home after the ED visit. Refer to Section 6.6.5 and Section 7.2.1 for management of participants who permanently discontinue IP.

Any permanent discontinuation of IP should be recorded including the reason for permanent discontinuation.

Reasons for permanent IP discontinuation may include any of the following:

- Participant request
- Pregnancy
- All criteria for possible drug-induced liver injury (DILI) are met (Appendix 5 [Section 10.5])
- The investigator judges that continued administration of IP would be detrimental to the participant's safety or well-being.
- Protocol violation
- Lost to follow-up
- Any breaking of the trial blind requested by the investigator
- Death
- The Sponsor requests that the participant permanently discontinue IP.

7.2.1. Management of Participants after Permanent Discontinuation of IP

If IP is permanently discontinued, the participant should be encouraged to remain in the trial to continue to obtain outcome measures and safety data (see Section 7.2).

For those participants who remain in the trial after IP has been permanently discontinued, the re-introduction of SOC may be considered when medically necessary. If the investigator decides that re-introduction of SOC medications is warranted, the investigator is highly encouraged to contact the Cytokinetics Medical Monitor prior to re-introducing the SOC medications.

There are several options for a participant after permanently discontinuing IP:

- Participant agrees to complete the early discontinuation (ED) visit as soon as possible after the decision is made and continue to return to clinic for all remaining trial visits
- Participant agrees to complete the early discontinuation (ED) visit as soon as possible after the decision is made, the follow-up visit 4 weeks after the last dose taken, and EOS visit
- Participant only agrees to complete the ED visit
- Participant agrees to be contacted by phone to obtain participant trial data
- Participant withdraws consent (see Section 7.4) and does not agree to any further trial procedures or visits
- For those participants who have not withdrawn consent and have difficulty returning for all remaining trial visits, they can be contacted by phone to obtain participant trial data.

7.3. Discontinuation from Trial Procedures

Participants can decline to continue receiving IP and/or other protocol-required therapies or procedures at any time during the trial but continue participation in the trial. If this occurs, the investigator is to discuss with the participant the appropriate processes for discontinuation from

IP or other protocol-required therapies and must discuss with the participant the options for continuation of the SoA (Section 1.3) including different options of follow-up (e.g., in person, by phone/mail, through family/friends, in correspondence/communication with other treatment physicians, from the review of medical records) and collection of data, including endpoints and AEs. Participants who have discontinued IP and/or protocol required therapies or procedures should not be automatically removed from the trial. Whenever safe and feasible it is imperative that participants remain on-trial to ensure safety surveillance and/or collection of outcome data. The investigator must document the change to the SoA (Section 1.3) and the level of follow-up that is agreed to by the participant (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

7.4. Participant Consent Withdrawal

Participants have the right to withdraw consent and no longer participate in the trial at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Consent withdrawal means the participant no longer wishes to undergo any follow-up visits, trial procedures, investigator contact, and non-participant contact follow-up (eg, medical records check).

- Discontinuing IP should be distinguished from consent withdrawal for follow-up since the participant may agree to undergo trial procedures or still be contacted even though they have stopped taking IP (see Section 7.3).
- Consent withdrawal should be accompanied by documentation of the reason for withdrawal.
- Participants who withdraw consent should be asked explicitly about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Preferably, the participant should withdraw consent in writing and, if the participant or the participant's representative refuses or is physically unable, the site should document and sign the reason for the participant's failure to withdraw consent in writing. The ICF for the trial should note that although a participant is completely free to leave the trial and stop taking IP, the investigators hope the participant will remain for follow-up status evaluations.

For participants who have withdrawn consent for further follow-up, investigators may review public records as permitted by applicable law to determine vital status of the participant before or at the end of the trial.

7.5. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site must attempt to contact the participant or the participant's family and reschedule the missed visit as soon as possible and counsel the participant on the

importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the trial.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant or the participant's family (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have discontinued from the trial and are lost to follow-up.

Closing of specific sites or discontinuation of the trial are handled as part of Appendix 1 (Section 10.1.8).

8. TRIAL ASSESSMENTS AND PROCEDURES

Trial assessments and procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exceptions are not allowed. Adherence to the trial design requirements, including those specified in the SoA (Section 1.3), is essential and required for trial conduct.

There will be at least 11 in-person trial visits per participant, with windows to aid in scheduling as shown in Table 10.

Table 10: CY 6032 Visit Windows

Visit	Visit Window
Screening Visit 1 or 2	Up to 42 days prior to Day 1 visit
Day 1 (First Dosing Day)	N/A
Week 2	+3 days
Week 4	+3 days
Week 6	+3 days
Week 8	+3 days
Week 12	±3 days
Week 16	±7 days
Week 20	±7 days
Week 24 (EOT)	±7 days
Week 28 (EOS)	+7 days
Early Discontinuation (ED)	+7 days

EOS = end of study; EOT = end of treatment; N/A = not applicable
All visits should be scheduled based on Day 1.

Emergent safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue, interrupt or permanently discontinue IP.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The ED visit should be completed as soon as possible after the patient discontinues IP, ideally within 7 days after the last dose of IP.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Visit Schedule

Activities will be completed during clinic visits as described in this section. General guidance for the preferred order of assessments and procedures are outlined below:

- On visit days, participants should wait to take their daily IP dose at the clinic.
- Patient-reported outcomes should be completed by participants prior to any other activities (i.e., Kansas City Cardiomyopathy Questionnaire [KCCQ, administered first], EuroQol 5-dimension 5-level instrument [EQ-5D-5L], Seattle Angina Questionnaire-7 [SAQ-7], and Patient Global Impression of Change [PGI-C]).
- Vital signs and ECGs must be performed prior to blood draws or other invasive procedures.
- Echocardiograms should be done prior to IP dosing on Day 1 and 2 hours (± 60 mins) after IP dosing in the clinic at other time points.
- IP should be administered after completion of vital signs, ECG, and blood draws.
- CPET should be performed after other visit activities including IP administration.

Please refer to the Study Reference Manual for additional details.

8.1.1. Screening Visits

The informed consent will be administered prior to performing any study related activities. Participants who sign the informed consent form will complete Screening assessments as defined in the SoA (Section 1.3). The Screening period can last up to approximately 6 weeks in duration to allow greater flexibility for visit scheduling and the potential for retesting and repeated assessments as needed and consists of two visits (Screening Visit 1 and Screening Visit 2) as described in Section 8.1.1.1 below.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet eligibility for the study. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Laboratory values obtained at Screening and reported through the central laboratory will be used to determine participant eligibility. See Section 8.1 for preferred order of assessments.

For participants requiring SOC washout, BMI should be collected at SV1 for eligibility. BMI used for inclusion purposes will be calculated by EDC.

The CPET should not be completed until the participant is otherwise deemed eligible. The CPET used for eligibility should be completed during the screening period, with a minimum of approximately one week prior to randomization. Participants requiring washout must complete washout prior to completing the screening CPET. The CPET should be performed after other visit activities including IP administration. CPET weight should be collected immediately prior to CPET exercise. CPET weight should be collected with participant shoes removed and their pockets emptied. It is not permissible to rely on a participant's stated weight or height.

8.1.1.1. Screening SOC Washout Period

Participants will begin their washout of SOC therapy (i.e., beta-blocker and/or calcium channel blocker) starting at Screening Visit 1. At the discretion of the principal investigator, participants will be instructed to reduce their SOC therapy dose by 25% to 50% every 48 hours until they are completely off SOC therapy. Participants must be monitored during the washout period for signs and symptoms of worsening heart failure, chest pain, and other potential adverse events, which will be periodically reviewed by the Medical Monitor and Data Monitoring Committee. Participants will then proceed to Screening Visit 2, which will occur no sooner than 2 weeks and no later than 4 weeks after Screening Visit 1. Participants will be required to be completely off SOC therapy for at least 7 days prior to Screening Visit 2. Participants who cannot tolerate washout of SOC therapy for any reason will screen fail and will not proceed to Screening Visit 2.

Participants who are not on any SOC therapy will proceed to Screening Visit 2 and can skip the SOC therapy washout at Screening Visit 1.

8.1.2. Day 1

Participants who meet all eligibility criteria including confirmation from the CPET core laboratory at the end of the screening period will return to the site for randomization and Day 1 activities as defined in the SoA (Section 1.3).

8.1.3. Weeks 2 through 20

Refer to the SoA (Section 1.3) for Weeks 2 through 20.

8.1.4. Week 24: End of Treatment Visit

Week 24 is defined as the End of Treatment (EOT) visit and includes assessments and procedures critical for analysis of the trial's endpoints. These assessments are outlined in the SoA (Section 1.3). Additionally, the following should be considered in advance of Week 24:

- Contact participants shortly before the Week 24 EOT visit to confirm their ability to perform the CPET and schedule the procedure to ensure it is completed within the protocol-defined window.
- For participants temporarily unable to exercise on the treadmill or bicycle (whichever modality was used at baseline) due to an AE (eg, ankle sprain, upper respiratory infection, migraine), but not due to HCM symptoms, or if the site is unable to perform the CPET (eg, equipment malfunction), then the Week 24 visit may be postponed by up to 4 weeks and those participants should continue to receive IP until the visit.
- If necessary, the Week 24 visit may be split across two consecutive days within the visit window. If the visit is split, all assessments, except the CPET, should occur on the first day of the split visit. The CPET should occur on the second day of the split visit. Dosing will occur on site on both split visit days.
- Participants will begin the down-titration of metoprolol or placebo for metoprolol the next day at home after the Week 24 EOT visit. Note that if the Week 24 EOT visit is a split visit, down-titration will occur at the delayed Week 24 EOT visit. Please refer to Section 6.6.5 for additional details.

8.1.5. Week 28: End of Study Visit

Participants should complete an EOS visit:

- For participants who complete all trial visits, the EOS visit will occur at Week 28 (or 4 weeks after a delayed Week 24 visit).
- For participants who early-terminate IP more than 4 weeks before Week 24 and continue to stay on-trial for all follow-up assessments, the Week 24 visit will be the last study visit (and the EOS visit does not need to be performed).
- For participants who withdraw consent and do not wish to continue the participation in follow-up assessments, an EOS visit should be performed 4 weeks after their final IP dose, if possible.

To ensure a 4-week safety follow-up (to assess any AEs), the EOS Exit Date must correspond to either 4 weeks after last dose, or at their last study visit (ie, Week 24), whichever is later.

8.1.6. Early Discontinuation Visit

For participants who discontinue the trial prematurely, the activities outlined in the SoA (Section 1.3) will be completed during an ED visit as soon as possible. In addition, a safety contact (eg, phone call) should occur 4 weeks following ED visit to assess AEs and vital status.

8.1.7. Unscheduled Visit

Assessments may be completed at the investigator's discretion during an Unscheduled visit. In addition, assessments performed at a scheduled visit that are not defined in the SOA (Section 1.3) will be considered unscheduled assessments.

8.2. Efficacy Assessments

8.2.1. Cardiopulmonary Exercise Testing

All participants will undergo CPET with gas-exchange analysis and the methodology will be standardized across all participating sites, as described in the CPET manual. Testing will include continuous ECG monitoring by trained personnel and be performed in an area that is equipped for cardiopulmonary resuscitation. Treadmill is the preferred modality for exercise testing. For CPET laboratories that do not perform treadmill testing, cycle ergometry is an acceptable alternative. Exercise protocols for both modalities will be provided in the CPET manual. Participants must use the same testing modality for all exercise tests during the trial. Whenever possible, CPET should be administered by the same trial personnel using the same equipment and performed after the other trial procedures on that visit day (including, KCCQ, EQ-5D-5L, SAQ-7, PGI-C, NYHA class, CGI, vital signs, ECG, blood sampling, echocardiogram, IP administration). Participants naïve to exercise protocols will be familiarized with the technique during screening.

All CPET testing will be symptom-limited, and participants will be strongly encouraged to achieve maximal exertion and an RER ≥ 1.05. The reason(s) for termination of sub-maximal exercise tests will be documented. A test will be identified as being maximal effort if the RER is ≥ 1.05.

Participants should not engage in strenuous exercise for 24 hours prior to the CPET, and participants should not exercise at all within 12 hours prior to the test. Participants should fast for at least 4 hours prior to CPET. All regularly scheduled medications should be taken as normal. Participants should avoid taking alcohol or medications that cause drowsiness within 8 hours prior to the test.

The Week 24 CPET should be performed at approximately the same time of day (eg, morning, mid-day, afternoon) as the baseline CPET at screening, at a consistent time after the last dose of metoprolol and IP.

If a life-threatening arrhythmia, early ischemia, severe hypotension or other serious finding is identified by the investigator during CPET, the participant will be asked to stop the exercise test, and his/her physicians will be notified of the results. If the participant is performing the screening test, s/he will not be randomized to the trial. Enrolled participants who have a non-life-threatening event or finding that stops the test can resume testing when it is safe to do so and after appropriate treatment, per the investigator.

All sites must be qualified by the CPET core laboratory prior to the initiation of screening. To qualify, sites will perform an exercise test on two healthy adults and submit them for core laboratory review. Sites may be required to submit additional normal exercise tests during the conduct of the trial for review by the CPET core laboratory in order to confirm proper function of testing equipment. Sites may be qualified based on exercise tests recently reviewed by the CPET core laboratory during the conduct of other trials.

8.2.2. Echocardiography

Full echocardiography will be done during screening and prior to dosing on Day 1. Full or focused echocardiography will be performed 2 hours (± 60 min) after dosing in the clinic on Weeks 2, 4, 6, 8, 12, 16, 20, and 24 according to SoA (Section 1.3). Full echocardiography will also be performed at Week 28. The unmasked echocardiologist or unmasked designee will enter Titration Vital Signs and echocardiogram data at Screening Visit 2, Day 1 prior to dosing, and at Weeks 2, 4, 6, 8, 12, 16, 20, 24 and unscheduled visits. Contrast for echocardiogram is not allowed at any study visit.

Certified sonographers will perform echocardiography using standard high-quality, high-fidelity machines approved by Cytokinetics. Whenever possible, the same sonographer will perform all studies for a single participant. Echocardiograms will be performed after the participant has been resting in a supine position for at least 10 minutes and in accordance with the echocardiography manual. Instructions for the performance of the Valsalva maneuver and imaging the LVOT-G will also be included in the echocardiography manual.

When echocardiograms are scheduled at the same time as blood draws, vital signs, and/or ECGs, the order of evaluation will be vital signs, ECGs, blood draw and echocardiogram. The post-dose PK may be collected after the echocardiogram.

Echocardiographic parameters to be measured will at least include the LV parameters in Table 11 in addition to right heart function metrics detailed in the echocardiography protocol.

Table 11: CY 6032 Echocardiographic LV Parameters to be Measured

Resting LVOT-G	LVEDV	IVST
Post-Valsalva LVOT-G	LVESD	IVCT
LVEF	LVESV	IVRT
LVFS	LVCO	E/e' ratio (septal and lateral)
GLS	LV Stroke Volume	LAV
LVEDD	LVOT VTI	Maximal LVWT

E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; GLS = global longitudinal strain; IVCT = isovolumic contraction time; IVRT = isovolumic relaxation time; IVST = interventricular septum thickness; LAV = left atrial volume; LV = left ventricular; LVCO = left ventricular cardiac output; LVEDD = left ventricular end diastolic diameter; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; LVESV = left ventricular end systolic volume; LVFS = left ventricular fractional shortening; LVOT-G = left ventricular outflow tract; LVOT VTI = left ventricular outflow tract velocity time integral; LVWT = left ventricular wall thickness

Unscheduled echocardiograms may be obtained when clinically indicated, for example to assess an AE or follow-up a clinically significant change in a prior echocardiogram, as determined by the investigator. Results will be interpreted by the unmasked echocardiologist at the investigational site.

All echocardiograms (including unscheduled) will be sent to the core laboratory for interpretation. On-site interpretation of LVEF and LVOT-G will be used for dose escalation and reduction decisions via IWRS. The core laboratory quantification of the echocardiograms will be used for all statistical analyses.

8.2.3. New York Heart Association Functional Classification

After interviewing the participant, the investigator (or qualified designee) will record the NYHA Functional Classification (Criteria Committee of the New York Heart 1994). The NYHA classification is as follows:

- Class I - No symptoms and no limitation in ordinary physical activity (eg, shortness of breath when walking, climbing stairs)
- Class II - Mild symptoms (e.g., mild shortness of breath and/or angina) and slight limitation during ordinary activity
- Class III - Marked limitation in activity due to symptoms, even during less than ordinary activity (e.g., walking short distances [20-100 m]). Comfortable only at rest
- Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound participants

8.2.4. Clinical Global Impression Scale

The investigator (or qualified designee) will record the CGI scale assessment of the patient's global functioning at the time points outlined in the SoA (Section 1.3).

8.2.5. Patient-Reported Outcomes

The following questionnaires will be completed at trial visits specified in the SoA (Section 1.3):

- KCCQ
- EQ-5D-5L
- PGI-C
- SAQ-7

Participants will be asked to complete the KCCQ, EQ-5D-5L, PGI-C, and SAQ-7 questionnaires in a quiet place prior to the medical consultation and prior to undergoing any tests and procedures to avoid biasing their responses.

Site staff will verify the questionnaires for completeness before the participants leave the clinic or hospital.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular (CV), respiratory, and neurological systems. Breast, genital, and rectal examinations are not required unless specific evaluation is warranted.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examinations may be conducted at any time during the treatment period if clinically indicated.

8.3.2. Height and Weight

Height and clinic weight will be measured while the participant is fully clothed with shoes removed. A CPET weight will also be obtained prior to a participant completing their CPET. Height will be measured at screening only.

8.3.3. Vital Signs

At the Screening visit, a room air oxygen saturation will be assessed.

At all visits, heart rate, respiratory rate, and blood pressure will be assessed.

“Titration vital signs” or “IWRS vitals” are vital signs (blood pressure and heart rate) collected for the purpose of titration and entry into IWRS. Titration vital signs may be accessible to any site staff for safety monitoring. However, titration vital signs should not be shared with or made accessible to the Sponsor or CRO, with the following exceptions:

- The CRO’s CRA performing source data verification
- The unmasked data manager

- The Sponsor's vitals medical monitor specifically referred to as the "Titration Vitals Medical Monitor"

Note: Blood pressure and/or heart rate collected during other study procedures (e.g., ECG) are not used for IP titration. For this reason, they are not masked and may be made available to the study team, PI, site staff, CRO, and Sponsor for the safety monitoring of study participants.

Titration vital signs must be performed prior to blood draws or other invasive procedures.

Blood pressure and heart rate measurements will be assessed with the participant in a sitting position. Blood pressure and heart rate measurements should be performed with an automated oscillometer after the participant has rested for at least 5 minutes in a quiet setting without distractions (e.g., television, cell phones, talking). Whenever possible the same oscillometer should be used throughout the trial. Detailed guidance for proper blood pressure measurements is provided in Appendix 6 (Section 10.6).

Titration vital signs (to be taken before blood collection for laboratory tests) will consist of 1 heart rate reading and 3 consecutive blood pressure readings recorded at intervals of at least 1 minute. The 3 blood pressure readings will be recorded; the average will be used for eligibility and dose titration. The same titration vital signs will also be entered into IWRS by the unmasked echocardiologist or unmasked designee, who are not involved in other aspects of the study visits.

8.3.4. Electrocardiograms

Single 12-lead ECGs will be obtained at the timepoints outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECGs must be performed prior to blood draws or other invasive procedures.

Participants should be sitting or supine in a rested and calm state for at least 5 minutes prior to the ECG. The investigator may perform additional ECG recordings as needed for the care of the participant.

A participant will be withdrawn from the trial by the investigator or designee if, in their medical judgment, ECG findings are present which make continued trial participation not in the participant's best interest.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings.

Unscheduled ECGs may be collected at additional time points, for example in case of an AE or based on vital signs as determined by the investigator or the Medical Monitor.

All ECG tracings will be kept as part of the participant's permanent trial file at the site. Digital recordings will be analyzed and stored at a central ECG laboratory.

8.3.5. Laboratory Assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and see the SoA (Section 1.3) for the timing and frequency.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the trial as an AE. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.4. Adverse Events and Serious Adverse Events

8.4.1. Adverse Events

8.4.1.1. Definition of Adverse Event

An **AE** is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IP, whether or not related to the IP.

AEs include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after IP administration even though it may have been present before the start of the trial
- Abnormal assessments, eg, change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at trial start or worsened during the course of the trial
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at trial start or worsened during the course of the trial, require treatment or led to dose reduction, interruption or permanent discontinuation of IP. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

8.4.1.2. Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death

- Is life threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Important medical event

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An AE would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (eg, overnight stay).

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons
- Hospitalization for pre-planned (ie, planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, eg, hospitalization for coronary angiography in a participant with stable angina pectoris

However, complications that occur during an exempted hospitalization are AEs or SAEs (for example if a complication prolongs a pre-planned hospitalization).

8.4.1.3. Intensity of Adverse Events

The investigator must assess the intensity for each AE and SAE reported during the trial according to a three-point scale: mild, moderate, severe.

If the intensity of an AE worsens during IP administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

The three categories of intensity are defined as follows:

Mild	The event is noticeable to the participant. It does not influence daily activities and does not require intervention.
Moderate	The event makes the participant uncomfortable. Performance of daily activities are influenced, and intervention is needed.

Severe	The event causes noticeable discomfort and interferes with daily activities. The participant may not be able to continue in the trial, and treatment or intervention is needed.

A mild, moderate, or severe AE may or may not be serious. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

8.4.1.4. Relationship to Investigational Product

Each AE must be assessed by the investigator, based on clinical judgment, as to whether or not there is a reasonable possibility of causal relationship to the IP (aficamten or metoprolol) and reported as either related or unrelated.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Cytokinetics. However, it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to Cytokinetics.
- The investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.

8.4.1.5. Relationship to Trial Procedures

An AE is defined as related to trial procedures if it appears to have a reasonable possibility of a causal relationship to protocol-required procedures.

8.4.1.6. Reporting of AEs

The investigator is responsible for ensuring that all SAEs and AEs observed by the investigator or reported by the participant that occur after starting the IP through trial exit are recorded.

Only SAEs and AEs considered related to trial procedures are reported after signing of the informed consent until IP administration.

Medical conditions that are not associated with trial procedures and that begin before the start of IP but after signing of the ICF will be recorded as Medical History/Current Medical Conditions not as an AE.

8.4.1.7. Reporting Procedures for SAEs

Prompt notification by the investigator to Cytokinetics of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP under clinical investigation are met.

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the participant that occur after starting the IP through EOS, or 4 weeks after the last administration of IP, whichever is later, as well as SAEs assessed as related to trial procedures occurring during the screening period are reported to Cytokinetics on an SAE Report Form within 24 hours following the investigator's knowledge of the event and recorded as an SAE. These events must be reported regardless of the investigator-attributed causal relationship with IP.

The SAE Report forms must be emailed or faxed to Cytokinetics Drug Safety (contact details are provided on the SAE Report form):

Email: **CY6032DrugSafety@cytokinetics.com**

[redacted]

The investigator must attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The investigator must complete the SAE Report form in English and must assess the causal relationship of the event to IP.

If the participant is hospitalized in a hospital other than the trial site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

New information relating to a previously reported SAE must be reported to Cytokinetics within 24 hours following knowledge of the new information. Cytokinetics Drug Safety may contact the investigator to obtain further information.

8.4.1.8. Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Cytokinetics to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the trial or during a protocol-defined follow-up period, the investigator will provide Cytokinetics with a copy of any post-mortem findings including histopathology if it has been performed.

AEs must be followed until they resolve or until the participant completes the trial, whichever comes first.

SAEs still ongoing at the EOS must be followed until resolution or stabilization, or until the event outcome is provided, eg, death. Reporting may continue after EOS and database lock.

New SAEs occurring after the 4-week follow-up period must be reported to the Cytokinetics drug safety department within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the IP.

8.4.1.9. Regulatory Reporting

The reference safety document to assess expectedness of a suspected serious adverse reaction and reported by Cytokinetics to Health Authorities, IRBs/IECs, and investigators is the reference safety information section of the IB [Aficamten IB] and reference safety information section of the metoprolol succinate labels.

Cytokinetics will report SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

The investigator is to notify the appropriate IRB/IEC of SAEs occurring at the site and other AE reports received from Cytokinetics, in accordance with local procedures and statutes.

8.4.1.10. Pregnancy and Breastfeeding

Female Participants who Become Pregnant

If a woman becomes pregnant while on IP, IP must be discontinued. The investigator must counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Please refer to Appendix 3 (Section 10.3) regarding contraceptive guidance.

Irrespective of the treatment received by the participant, any pregnancy occurring in a female participant, or female partner of a male participant, after starting the IP up to 4 weeks following IP discontinuation must be reported to Cytokinetics within 24 hours of the investigator's knowledge of the event.

Pregnancies must be recorded and reported on the Cytokinetics Pregnancy form, which is emailed or faxed to Cytokinetics Drug Safety (contact details are provided on the Pregnancy Report form):

Email: **CY6032DrugSafety@cytokinetics.com**

[redacted]

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of IP and until the conclusion of the pregnancy. The follow-up of an infant (if applicable) will be conducted up to 12 months after the birth of the child.

Any pregnancy complication or elective termination of a pregnancy for medical reasons must be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Any post-trial pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to Cytokinetics as described in Section 8. While the investigator is not obligated

to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.

Male Participants with Partners Who Become Pregnant

If the partner of a male participant becomes pregnant while on IP, he may continue receiving treatment; however, he must use barrier method (ie, condom) during sexual intercourse to avoid further fetal exposure.

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this trial.

After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator must complete the Pregnancy Report Form and submit it to Cytokinetics within 24 hours of receipt of the partner's consent. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Cytokinetics.

Female Participants Who Breastfeed

If a female participant breastfeeds while on IP, IP will be discontinued.

The investigator will collect breastfeeding information on any female participant who breastfeeds while taking the IP through one month after the end of IP treatment. The mother and infant health information will be recorded on the Pregnancy Report Form and submitted to Cytokinetics immediately and no later than 24 hours following the investigator's knowledge of the event.

8.5. Treatment of Overdose

For this trial, any dose of IP that exceeds the protocol-specified dose or dosing frequency will be considered an overdose.

There is no established treatment for an overdose. In the event of overdose, monitor for signs and symptoms including but not limited to hypotension, cardiac dysrhythmia, tachycardia, tachypnea, peripheral and pulmonary edema, decrease renal function, dizziness, dyspnea, palpitation, fatigue. The use of rescue medications (eg, dobutamine) to treat a low cardiac output state is recommended if necessary.

If a participant experiences low cardiac output due to systolic dysfunction, the investigator should follow appropriate regional heart failure treatment guidelines.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately who may recommend:
  - Close monitoring of the participant for any AEs/SAEs and laboratory abnormalities.
  - Obtaining a plasma sample for PK analysis as soon as practical and note the date of the last dose of IP.

- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

Blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of aficamten as specified in the SoA (Section 1.3). Samples will be used to evaluate the PK of aficamten and potentially its metabolites. Instructions for the collection and handling of biological samples will be provided in the laboratory manual.

The actual date and time (24-hour clock time) of each pre- and post-dose sample will be recorded. The time of administration of IP will be recorded. It is important to provide instructions to participants that they should not take their dose on the day of their clinic visit until in the clinic.

See Table 12 for a summary of PK sampling time points. All 2-hour post-dose samples should be drawn within ± 10 minutes of the scheduled time point. The post-dose PK may be collected after the echocardiogram. Drug concentration information that would unblind the trial will not be reported to investigative sites or blinded personnel until the trial has been unblinded.

Table 12: Summary of PK Time Points

Visit	PK Time Point
Day 1	Pre-dose and 2 hours post-dose
Week 2	Pre-dose and 2 hours post-dose
Week 4	Pre-dose and 2 hours post-dose
Week 6	Pre-dose and 2 hours post-dose
Week 8	Pre-dose and 2 hours post-dose
Week 16	Pre-dose and 2 hours post-dose
Week 24 (EOT)	Pre-dose and 2 hours post-dose
Early Discontinuation	Untimed

EOT = end of treatment; PK = pharmacokinetic

8.7. Optional Genetics Sample

As HCM is a genetic disease, blood and/or DNA from participants who consent, may be analyzed through the use of both clinically reportable testing (Clinical Laboratory Improvement Amendments (CLIA) certified laboratory), and non-clinically reportable (non-CLIA certified laboratory) whole genome sequencing, whole exome sequencing, next-generation sequencing, and/or other method to identify genetic variants and pathogenic sequence variants that are predictive of participant phenotype, response to IP, resistance to IP, metabolism of IP, susceptibility to developing AEs, or to increase the knowledge and understanding of CV, muscle and disease biology.

If a participant consents, and where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from participants consenting to provide the sample. In the event of

DNA extraction failure, a replacement genetic blood sample may be requested from the participant. CLIA certified genetic test results may be made available to sites.

See Appendix 4 (Section 10.4) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.8. Optional Sample Collection for Future Analyses

For participants who provide consent, serum, plasma, and DNA samples (as described in Section 8.7) will be collected and banked in this trial for future research on biomarkers and genetics. Serum, plasma, and DNA samples will be stored in a long-term storage facility designated by Cytokinetics for up to 20 years.

Optional sample collection for future research will not be implemented in countries where restrictions may apply.

8.9. Immunogenicity Assessments

No immunogenicity assessments will be done for this trial.

8.10. HCM Participant Experience Optional Sub-study

At participating centers in the US, English language-speaking participants who have consented to the HCM Participant Experience Optional Sub-study will have two semi-structured, qualitative (entry and exit) interviews conducted remotely by trained personnel from an independent vendor. The entry interview may occur any time after signing informed consent and before Day 1. The exit interview may occur at any time after the Week 20 visit but before the last dose of IP at Week 24. The interviews will be performed remotely. The entry interview will collect information in the participants' words about their own perceptions of baseline functionality, symptom burden, activities of daily living and expectations going into the study. The exit interview will collect information in the participant's words about their experience with any change in functionality and impact of oHCM, symptom burden, activities of daily living and overall treatment experience. Additionally, all participants will complete surveys remotely at baseline (prior to Day 1) and corresponding to the planned visits at Weeks 2, 4, 6, 8, 12, 16, 20 and just prior to Week 24. These surveys will track self-selected personal goals to capture aspects of oHCM that are most meaningful or troublesome to them throughout the course of the trial. These goals will use the Specific, Measurable, Achievable, Relevant, Time-bound (SMART) framework.

Willing participants who discontinue from the main study early should complete the exit interview ideally within 3 days but up to 10 business days from their last dose of IP. If the participant stops IP but continues to complete main study follow up visits/assessments, they should continue to complete e-surveys and exit interview per the schedule of activities above.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The analyses evaluating treatment effect on the primary and secondary efficacy endpoints will test the null hypothesis that there is no treatment difference between participants receiving aficamten and those receiving metoprolol in the Full Analysis Set (FAS). Adjustments for multiplicity will be specified in Section 9.4.1.1.

9.2. Sample Size Determination

Assuming a difference in change from baseline in pVO_2 of 2 mL/kg/min for aficamten compared to metoprolol, a standard deviation (SD) of 3 mL/kg/min, and 10% of participants missing change from baseline data of the primary endpoint, a sample size of 170 participants (randomized at 1:1 ratio to aficamten and to metoprolol) provides more than 90% power to detect the difference in pVO_2 change from baseline to Week 24 with a 2-sided type I error of 0.05.

9.3. Populations for Analyses

The analysis populations are defined in Table 13.

Table 13: Analysis Sets

Analysis Set	Description
All Randomized Set	All randomized participants.
Full Analysis Set (FAS)	All randomized participants who receive at least one dose of randomized investigational product (IP) and have at least one post-baseline efficacy measurement. Participants will be analyzed according to their randomized treatment group assignment. Efficacy endpoints will be analyzed based on the FAS.
Safety Analysis Set	All randomized participants who received at least one dose of IP, aficamten or metoprolol. Participants will be analyzed by their randomized treatment group assignment. If a participant receives treatment throughout the trial that is different than the randomized treatment group assignment, then this participant will be grouped by the actual treatment group.
Pharmacokinetics (PK) Analysis Set	All randomized participants who have at least one evaluable plasma concentration of aficamten.

9.4. Statistical Analyses

The Statistical Analysis Plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Summary tables will present descriptive statistics such as number of participants, mean, median, SD, minimum and maximum for continuous variables, and number of participants and the percentage for categorical variables, overall and by treatment in the planned analysis sets. For model-based analysis, least squares means (LSMs), difference of LSMs between treatments, their standard errors and 95% confidence intervals (CI), and two-sided p-values for the relative statistical inferences will be presented. Baseline is defined as the last available measurement taken before the first dose of randomized IP unless otherwise specified. Statistical analysis methods will be detailed in the SAP.

9.4.1.1. Multiplicity Adjustment

The null hypothesis for the primary and secondary efficacy variables in the FAS will be tested in the pre-specified order using a closed testing procedure in order to preserve the overall type I error rate at 0.05. The testing sequence of secondary endpoints for Week 24 will be detailed in the SAP.

9.4.2. Primary Endpoint

The primary endpoint of the trial is the change in pVO_2 by CPET from baseline to Week 24.

The primary estimand is the difference in means of the change from baseline to Week 24 in pVO_2 between aficamten and metoprolol for the target population of potentially treatable aficamten participants despite intercurrent events after the first randomized dose of IP. Participants without a dose of IP will be excluded from the FAS as they are anticipated to not represent participants from a treatable population defined as participants who would meet the eligibility requirements of this trial and are capable and willing to be dosed. Missing data will be imputed using multiple imputation method based on the extent of missing data and the pattern of missing reasons. Details will be specified in the SAP. The distribution of missing CPET data at Week 24 and the reasons for the missing data will be tabulated in the FAS. The primary analysis of the primary endpoint will use an Analysis of Covariance (ANCOVA) model with treatment group, randomization stratification factors (CPET exercise modality and recently diagnosed vs chronic oHCM), baseline pVO_2, and baseline weight as covariates in the FAS. Sensitivity analyses will be performed by repeating the primary analysis examining assumptions that data are not missing at random: control-based imputation and tipping point analysis will be performed. In control-based imputation, missing pVO_2 from participants who discontinued aficamten treatment or missing pVO_2 from participants from the metoprolol arm will be imputed based on the model that is constructed using observed pVO_2 data from the metoprolol arm. Missing pVO_2 from participants who remained on aficamten treatment will be imputed based on the model that is constructed using observed pVO_2 data from the aficamten arm. Tipping point analysis will be performed by applying a range of negative shift to adjust the imputed value of missing pVO2 in aficamten group. The tipping point can be identified while the result is no longer statistically significant. The LSMs, LSM treatment difference, and the standard error from each imputed dataset will be combined using Rubin's rules to produce an overall LSM estimate of the treatment difference, its 95% CI, and p-value.

Other sensitivity analyses and the details will be included in the SAP.

9.4.3. Secondary Endpoints

The secondary endpoints of the trial are:

- Proportion of participants with ≥ 1 class improvement in NYHA Functional Class from baseline to Week 24
- Change in KCCQ-CSS from baseline to Week 24
- Change in left ventricular mass index (LVMI) from baseline to Week 24
- Change in left atrial volume index (LAVI) from baseline to Week 24
- Change from baseline values in N-terminal prohormone brain natriuretic peptide (NT-proBNP) from baseline to Week 24
- Change in post-Valsalva LVOT-G from baseline to Week 24

Change in KCCQ-CSS and change in post-Valsalva LVOT-G, change in LAVI and change in LVMI from baseline to Week 24 will be analyzed using a mixed model repeated measures (MMRM) model with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix will be specified. For NT-proBNP, the log transformed proportional change (defined as ratio of post randomization NT-proBNP value over baseline) will be analyzed using a MMRM model with log baseline as covariate, treatment group, randomization stratification factors, visit, log baseline by visit and treatment by visit interaction as fixed effects. Median and median difference of NT-proBNP between treatment groups and 95% confidence of the median difference will also be presented.

Proportion of participants with ≥ 1 class improvement in NYHA Functional Class from baseline to Week 24 will be analyzed using Cochran–Mantel–Haenszel (CMH) test stratified by randomization factors. Participant's Week 20 NYHA Functional Class will be used when Week 24 NYHA Functional Class is not available. Participants who do not have Week 24 NYHA Functional Class will be treated as non-responders. The p-value and 95% CI will be obtained using the exact method. Adjustment of multiplicity of the primary and secondary endpoints is specified in Section 9.4.1.1.

9.4.4. Exploratory Endpoints

The exploratory endpoints of the trial are:

- Compared with baseline, number of participants at Week 24 achieving either:
  - Change from baseline of ≥ 1.5 mL/kg/min in pVO_2
    AND
  - ≥ 1 class improvement in NYHA Functional Class
    OR
  - Change of ≥ 3.0 mL/kg/min from baseline in pVO_2
    AND
  - No worsening of NYHA Functional Class
- Proportion of participants with categorical improvement in KCCQ-CSS at Weeks 12 and 24

- Proportion of participants with resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G < 50 mmHg, and NYHA Class I at Weeks 12 and 24
- Proportion of participants with resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G < 50 mmHg, and ≥ 1 class improvement in NYHA Functional Class from baseline to Weeks 12 and 24
- Change in hs-cTnI from baseline to Week 24
- Change in ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e' [lateral wall]) from baseline to Week 24
- Change in interventricular septum thickness (IVST) from baseline to Week 24
- Change from baseline to Week 24 in:
  - Ventilatory efficiency/carbon dioxide production (VE/VCO_2 slope)
  - Circulatory power ($VO_2 \times SBP$)
  - Ventilatory anaerobic threshold (VAT)
  - Total workload (watts)
  - Heart rate response
- Change from baseline to Week 24 in individual responses to the EQ-5D-5L, CGI, PGI-C, and SAQ-7
- PK parameters through Week 24

Proportion of responders will be analyzed using CMH test stratified by randomization factors. Change from baseline in continuous echocardiography parameters will be analyzed using MMRM model with baseline as covariate, randomization stratification factors, visit, treatment group, and baseline by visit and treatment group by visit as interaction. An unstructured covariance matrix will be specified. Change from baseline in other CPET parameters will be analyzed using the same primary model for the primary endpoint. Median and median difference in NT-proBNP between treatment group and 95% confidence of the median difference will be presented. Log transformed NT-proBNP may be performed and analyzed using MMRM model with log baseline as covariate, visit, randomization stratification factors, treatment group as fixed effects and treatment group by visit interaction. The same model for KCCQ-CSS will be used to analyze the change from baseline in SAQ-7 and EQ-5D-5L.

9.4.5. Safety Analysis

Safety analyses will be performed on safety analysis set.

9.4.5.1. Adverse Events

A treatment-emergent AE is an AE with an onset after initiation of IP, or an AE present at initiation of IP dosing that worsens in severity during the treatment. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized by preferred terms and System Organ Class. The version of the MedDRA dictionary will be

specified in the clinical study report. AEs will be classified according to severity. The number and percentage of participants reporting AEs will be tabulated.

Only treatment-emergent AEs with an onset from the first dose until 4 weeks after last dose of IP will be summarized. All AEs will be included in participant listings.

Participant incidence of reported major adverse cardiac events (CV death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization) will be summarized by treatment group and event type. Participant incidence of LVEF < 50% will be summarized by treatment group.

9.4.5.2. Serious Adverse Events

Summaries of SAEs (by preferred term and System Organ Class) and SAE severity will be presented.

The safety follow-up is defined as 4 weeks following the last dose of IP.

9.4.6. Pharmacokinetic Endpoints

Plasma concentrations of aficamten and PK parameter maximum plasma concentration observed (C_{max}) and trough plasma concentration observed (C_{trough}) will be summarized using descriptive statistics including mean, SD, geometric mean, geometric coefficient of variation, median, and range. Geometric mean concentrations over time will be graphically displayed.

9.4.7. Participant Disposition

The number of participants who are randomized, who complete the planned treatment, and who prematurely discontinue from the planned treatment and/or the trial will be presented by treatment group and overall. Reasons for premature discontinuation will be summarized.

9.4.8. Demographics and Other Baseline Characteristics

Participant demographics and other baseline characteristics will be summarized descriptively by treatment group.

9.4.9. Investigational Product Exposure

IP exposure will be summarized, including the total number of doses administered, total amount of drug administered, and the total duration of IP administration, defined as the date of the last dose minus the date of first dose + 1.

9.4.10. Concomitant Medications

Concomitant medications will be summarized and classified by drug class and preferred term using the World Health Organization (WHO) Drug Dictionary. The version of the WHO Drug Dictionary will be specified in the clinical study report.

9.4.11. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from baseline at each protocol specified assessment time point will be presented.

9.4.12. Vital Signs

Descriptive statistics for vital signs and changes from baseline at each protocol specified assessment time point will be presented.

9.4.13. Electrocardiogram

Descriptive statistics for ECG parameters (eg, heart rate, PR interval, QRS interval, QT interval, and QTc interval [both Bazett's and Fridericia's corrections]) and changes from baseline at each protocol specified assessment time point will be presented. Select ECG parameters will be analyzed using a repeated measures analyses with dose and time points as factors and baseline ECG parameter as a covariate. Dose-response trend will be estimated.

9.5. Interim Analyses

There are no interim analyses planned for this study.

9.6. Data Monitoring Committee

An independent DMC will be established for this trial to formally review the accumulating unblinded data periodically in order to assess risk to participants during the conduct of the trial. Details regarding the scope of responsibilities, meetings and communication procedures, as well as information requirements will be outlined in the DMC Charter. The DMC will have access to actual treatment assignments and participant-level data from the clinical trial database.

For details on the DMC, refer to Appendix 1 (Section 10.1.5).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.

The investigator will be responsible for the following:

- Providing summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical trials (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide Cytokinetics with sufficient, accurate financial information as requested to allow Cytokinetics to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the participant or his/her legally authorized representative and answer all questions regarding the trial.

Participants must be informed that their participation is voluntary. Participants must be able to comprehend and be willing to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial center.

The medical record must include a statement that informed consent was obtained before any trial-specific activities/procedures were performed and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants are not required to sign a new ICF if they are retested during the initial screening window.

10.1.4. Data Protection

Physical, administrative, and technical safeguards as per industry and local or national standards will be incorporated into this study. Detailed requirements, standards, and data protection elements will be itemized in each executed EU study site agreement and will include at minimum all required elements contained in the General Data Protection Regulation (GDPR), Standard Contractual Clauses, and applicable Annexes as may be deemed applicable for the parties' relationships (controller or processor).

Participants

Participants will be assigned a unique identifier by Cytokinetics. Any participant records or datasets that are transferred to Cytokinetics will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal trial-related data will be used by Cytokinetics in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Cytokinetics, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study participants will be informed that they may withdraw from the study at any time, including withdrawing their participation for study-related use of any clinical trial data, and exercising any applicable data subject rights that may be pertinent given local laws or governing data privacy regulations or standards (such as deletion, amendment, or accounting of data).

Physical, Technical, and Administrative Safeguards for Data

Physical safeguarding of study data shall include, but is not limited to, restricted access to the hardware, data storage, and systems/files used in this study. Applicable study hardware will be individually coded, tracked, and linked to each study site to ensure physical safeguarding and

accountability. Physical storage of data will be at the data vendor's on-premise or cloud-based location with applicable industry requirements and standards for controlled and limited access.

Technical safeguards for study data shall include, but is not limited to, data being stored only in permitted or authorized means at study sites, authorized data vendors, or authorized study data management parties (e.g., those per applicable Data Sharing or Data Transfer Agreements). No data will be stored or transferred via portable physical file storage, such as USB flash drives. Study data will be routinely and systematically backed up and managed in accordance with standard data retention, governance, and handling procedures. Data recovery and disaster management procedures for study data are also part of standard data governance requirements.

Administrative safeguards for study data shall include, but is not limited to, a security program, security event monitoring, and standard industry-level encryption (at rest and in-transit), and file-transfer protocols. Additional technical, administrative, and organizational measures are designed to protect Personal Data, including use of pseudonymization and/or key coding to import the data. Sponsor will not be granted access to any mechanisms for re-identification of participant study data (e.g., key coding legend will not be provided or shared). Study data will also be subject to standard data privacy requirements such as user validation and identity management (for example, using Two-Factor Authentication), consent management, data vaulting and segregation for role-based access, auditing and tracking of users and registered account access holders, and standard data retention policies and procedures.

Cybersecurity Breach

The Sponsor, and Sites, will maintain applicable protocols and standards for handling cybersecurity breach in accordance with applicable local law or governing regulations, including security event monitoring, incident response, issue identification and triage, immediate actions, notice requirements, remediation, analytical review, and systemic or organizational mitigation as may deemed applicable in any such breach or cybersecurity scenario, depending on the facts and circumstances at hand.

10.1.5. Committees Structure

The trial organization will include an Executive Committee (EC), Steering Committee (SC) and independent Data Monitoring Committee (DMC).

The EC will contribute to trial design, implementation, data analysis, and communication of trial results and will consist of experts external to Cytokinetics who are qualified by their medical and scientific expertise and experience, one of the trial investigators, and a Cytokinetics representative. The responsibilities of the EC will be described in an EC charter.

The SC will contribute to implementation of the trial, data analysis, and communication of trial results. They will be HCM experts external to Cytokinetics and represent the different geographies the trial will be conducted in. The responsibilities of the SC will be described in a SC charter.

An independent DMC will be established for this trial to formally review the accumulating data periodically in order to assess risk to participants during the conduct of the trial. The DMC will include an external cardiologist with relevant expertise and other designated members with relevant expertise, e.g., representing clinical science, clinical pharmacology, and biostatistics.

The independent DMC membership will exclude the individuals from Cytokinetics or the contract research organization (CRO) trial team involved in trial conduct. The DMC members will have access to treatment assignments and participant level data from the clinical trial database. DMC membership, responsibilities, relationship with Cytokinetics and the CRO, and the purpose and timing of the meetings will be further described in the DMC charter.

10.1.6. Data Quality Assurance

All participant data relating to the trial will be recorded on printed or electronic CRF unless transmitted to Cytokinetics or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Cytokinetics or designee is responsible for the data management of this trial including quality checking of the data.

Cytokinetics assumes accountability for actions delegated to other individuals (e.g., CROs).

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial, must be retained by the investigator in accordance with the strictest regulation applicable to this trial and as obligated by the clinical trial agreement. No records may be destroyed during the retention period without the approval of Cytokinetics. No records may be transferred to another location or party without notification to Cytokinetics.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported in the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

10.1.8. Trial and Site Start and Closure

The trial start date is the date on which the clinical trial will be open for recruitment of participants. The first act of recruitment is the first site activated.

Cytokinetics or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of Cytokinetics. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by Cytokinetics or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local regulatory authorities, Cytokinetics's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further IP development

If the trial is prematurely terminated or suspended, Cytokinetics shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 14 will be performed by the central laboratory. Pregnancy testing for WOCBP at time points after screening may be performed locally.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Table 14: Protocol-Required Safety Laboratory Assessments

Chemistry		Urinalysis	Hematology	Other Assessments
Sodium	Total bilirubin	Specific gravity	Hemoglobin	Aficamten plasma concentration
Potassium	Direct bilirubin	pH	Hematocrit	
Chloride	CK	Blood	RBC	Pregnancy test[a]
Calcium	ALP	Protein	RDW	FSH[a]
Magnesium	LDH	Glucose	MCV	NT-proBNP[b]
Phosphorus	AST	Bilirubin	MCH	hs-cTnI
Urea	ALT		MCHC	PT-INR[c]
Creatinine	GGT		WBC	
Iron	TIBC		Platelets	
Glucose	Ferritin			
Total protein	Bicarbonate			

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; hs-cTnI = high sensitivity cardiac troponin I; LDH = lactic acid dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PT-INR = Prothrombin-International Normalized Ratio; RBC = red blood cell; RDW = red cell distributions width; SV1 = Screening Visit 1; SV2 = Screening Visit 2; TIBC = total iron binding protein; WBC = white blood cell; WOCBP = women of childbearing potential

[a] Only for WOCBP. Serum pregnancy test at Screening visit. A WOCBP must have a negative pregnancy test (urine or serum as required by local regulations) at Day 1, prior to the first dose of IP. For WOCBP requiring a washout, a serum pregnancy should be done at SV1; a urine pregnancy test may be completed for these patients at SV2. FSH only at screening, if needed. Where permitted by local regulations, a urine pregnancy test may be performed at all other required timepoints. If a urine pregnancy test is positive, a serum pregnancy test must be performed.

b NT-proBNP results will be masked throughout the trial.

c PT-INR should be drawn at screening.

Investigators must document their review of each laboratory report.

Laboratory results that could unblind the trial will not be reported to investigative sites or other blinded personnel until the trial has been unblinded.

10.3. Appendix 3: Contraceptive Guidance

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining trial entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating- hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L or mIU/mL) is required.
   - Females on hormone replacement therapy and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their hormone replacement therapy during the trial. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before trial enrollment.

Highly Effective Method of Contraception

A highly effective method of contraception is one that has a failure rate of <1% per year when used consistently and correctly.

Examples of highly effective contraception that have low user dependency are:

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner, only when the absence of sperm has been confirmed and vasectomized partner is the sole sexual partner of the female participant

Examples of highly effective contraception that are user-dependent are:

- Combined hormonal methods of birth control include oral, intravaginal, transdermal, injectable, or implantable
- Oral or injectable progestogen-only hormone contraception associated with the inhibition of ovulation
- Sexual abstinence

  Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

  The participant must agree to remain abstinent and confirm so in writing.

Contraception Guidance:

Women of Childbearing Potential

WOCBP must use at least one highly effective method of birth control. If any of the above highly effective method of birth control is used, a male condom must also be used. Male condom and female condom should not be used together (due to risk of failure with friction).

If additional medications are given during treatment, the investigator is to review the prescribing information/summary of product characteristics for all concomitant therapy, as they may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these changes with the trial participant.

10.4. Appendix 4: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to IP, susceptibility to, and severity and progression of disease. Variable response to IP may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, if a participant consents, and where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from participants consenting to provide the sample.

DNA samples will be used for research related to this trial may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

The results of genetic analyses may be reported in the clinical study report or in a separate trial summary.

Cytokinetics will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

10.5. Appendix 5: Liver Safety: Actions and Follow-up Assessments

Drug-induced Liver Injury Reporting & Additional Assessments

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin (TBL) and/or international normalized ratio (INR) elevation require the following:

- The event is to be reported to Cytokinetics as a serious adverse event (SAE) within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded).
- The AE documentation that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Cytokinetics.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 8.4.1.2.

Criteria for Permanent Discontinuation of Investigational Product and Other Protocol -required Therapies due to Potential Hepatotoxicity

IP **must** be discontinued permanently, and the participant should be followed according to the following recommendations for possible DILI, if ALL of the criteria below are met:

- TBL > 2 × upper limit of normal (ULN) or INR > 1.5

AND

- Increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT Value	AST or ALT Elevation
< ULN	> 3 × ULN

AND

- No other cause for the combination of the above laboratory abnormalities is apparent; important alternative causes for elevated AST/ALT and TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (e.g., Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms

- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Nonhepatic causes (e.g., rhabdomyolysis, hemolysis)

Criteria for Conditional Interruption of Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

For participants who do not meet the criteria for permanent discontinuation of IP outlined above and have no underlying liver disease, the following rules are recommended for interruption of IP and other protocol required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT Value	**AST or ALT Elevation**
Any	> 8 × ULN at any time
Any	> 5 × ULN but < 8 × ULN for ≥ 2 weeks
Any	> 5 × ULN but < 8 × ULN and unable to adhere to enhanced monitoring schedule
Any	> 3 × ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice)

OR

- TBL > 3 × ULN at any time

IP and other protocol-required therapies, as appropriate must be withheld pending investigation into alternative causes of DILI. If IP is withheld, the participant is to be followed according to recommendations in this section for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline.

Rechallenge of Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the participant must be discussed and agreed upon unanimously by the participant, investigator, and Medical Monitor. Participants reinitiating IP after withholding

for potential hepatotoxicity will restart IP, according to initial randomized allocation, on the same IP dose as established before the event and will not further titrate the dose.

If signs or symptoms recur with rechallenge, then IP must be permanently discontinued. Participants who clearly meet the criteria for permanent discontinuation must never be rechallenged.

Additional Clinical Assessments and Observation

All participants in whom IP(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI or who experience AST or ALT elevations > 3 × ULN are to undergo a repeat test and a period of "close observation" until abnormalities have stabilized, returned to normal, or returned to the participant's baseline levels. Recommended assessments and testing frequency that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 48 hours of receiving results with repeat testing until stabilized.
- In cases of TBL > 2 × ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR should be performed within 48 hours of receiving results with repeat testing 2-3 times per week until stabilized.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP(s) or protocol-required therapies has/have been discontinued AND the participant is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia.
  - Obtain serum total immunoglobulin (IgG), Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis.
  - Obtain serum acetaminophen (paracetamol) levels.
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies.

  - Obtain creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear.
  - Perform appropriate liver imaging if clinically indicated.
- Obtain appropriate blood sampling for PK analysis if this has not already been collected.
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist).

Follow the participant and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all IP(s) and protocol required therapies.

The potential DILI event and additional information such as medical history, concomitant medications, and laboratory results must be captured in source documentation.

10.6. Appendix 6: Blood Pressure Measurement

Table 15: Overview of Proper Seated BP Measurement in the Office

Key Steps for Proper BP Measurements	Specific Instructions
Step 1: Properly prepare the participant	1. Have the participant relax, sitting in a chair with feet flat on floor and back supported. The participant should be seated for 5 min without talking or moving around before recording the first BP reading.
	2. The participant should avoid caffeine, exercise, and smoking for at least 30 min before measurement.
	3. Ensure that the participant has emptied his/her bladder.
	4. Neither the participant nor the observer should talk during the rest period or during the measurement.
	5. Remove clothing covering the location of cuff placement.
	6. Measurements made while the participant is sitting on an examining table do not fulfill these criteria.
Step 2: Use proper technique for BP measurements	Use an upper-arm cuff BP measurement device that has been validated and ensure that the device is calibrated periodically.
	Support the participant's arm (e.g., resting on a desk). The participant should not be holding his/her arm because isometric exercise will affect the BP levels.
	Position the middle of the cuff on the participant's upper arm at the level of the right atrium (midpoint of the sternum).
	Use the correct cuff size such that the bladder encircles 75% –100% of the arm.
Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings.[a]
	Separate repeated measurements by 1–2 min.
Step 4: Properly document accurate BP readings	Record SBP and DBP to the nearest even number.
Step 5: Enter the BP readings in IWRS and EDC	Each set of BPs will be entered into IWRS and EDC.
Step 6: Provide BP readings to participant	Provide participants with their SBP/DBP readings both verbally and in writing. Someone should help the participant interpret the results.

BP = blood pressure; DBP = diastolic blood pressure; EDC = electronic data capture; IWRS = interactive web response system; SBP = systolic blood pressure

[a] When a BP measurement is obtained in 1 arm followed by the other arm and the BP is substantially lower in the second arm, it is possible that the difference could be caused by acclimation. In this circumstance, BP should be remeasured in the first arm.
Source: Muntner 2019

10.7. Appendix 7: Abbreviations

Table 16: List of Abbreviations

Abbreviation/Term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of Covariance
ASAP	As soon as possible
AST	Aspartate aminotransferase
bpm	Beats per minute
CBC	Complete blood count
CFR	Code of Federal Regulations
CGI	Clinical Global Impression scale
CI	Confidence interval
CIOMS	Council of International Organizations of Medical Sciences
CK	Creatinine kinase
CLIA	Clinical Laboratory Improvement Amendments
CMH	Cochran–Mantel–Haenszel
CMI	Cardiac myosin inhibitor
CMR	Cardiac magnetic resonance
CPET	Cardiopulmonary exercise testing
CRF	Case report form
CRO	Contract research organization
CV	Cardiovascular
CYP	Cytochrome P450
d	day
DBP	Diastolic blood pressure
DILI	Drug induced liver injury
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
EC	Executive Committee
ECG	Electrocardiogram(m/phy)

Abbreviation/Term	Explanation
ECHO	Echocardiogram
ED	Early discontinuation
EDC	Electronic data capture
E/e’	Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
EQ-5D-5L	Euro Qol 5 dimension 5-level instrument
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyl transferase
GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPMC	Hydroxypropyl methylcellulose
hs-cTnI	high sensitivity cardiac troponin I
IB	Investigator’s Brochure
ICD	Implantable cardiac defibrillator
ICF	Informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVCT	Isovolumic contraction time

Abbreviation/Term	Explanation
IVST	Interventricular septal thickness
IWRS	Interactive web response system
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score
LAM	Lactational amenorrhoea method
LAV	Left atrial volume
LAVI	Left atrial volume index
LDH	Lactic acid dehydrogenase
LKM1	Liver Kidney Microsomal antibody 1
LSM	Least squares means
LV	Left ventricle(ular)
LVCO	Left ventricular cardiac output
LVEDD	Left ventricular end diastolic diameter
LVEDV	Left ventricular end diastolic volume
LVESD	Left ventricular end systolic diameter
LVESV	Left ventricular end systolic volume
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
LVOT	Left ventricular outflow tract
LVOT-G	Left ventricular outflow tract gradient(s)
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NA	Not applicable
NIMP	Non-investigational medicinal product
NT-proBNP	N-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association
oHCM	Obstructive hypertrophic cardiomyopathy
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PGI-C	Patient Global Impression of Change scale
P-gp	P-glycoprotein

Abbreviation/Term	Explanation
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PT-INR	Prothrombin Time and International Normalized Ratio
pVO_2	Peak oxygen uptake
RBC	Red blood cell
RDW	Red cell distributions width
RER	Respiratory exchange ratio
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAQ	Seattle Angina Questionnaire
SBP	Systolic blood pressure
SC	Steering Committee
SD	Standard deviation
SoA	Schedule of activities
SOC	Standard of care
SV	Screening Visit
TBD	To be determined
TBL	Total bilirubin
TIBC	Total iron binding protein
TRO	Toronto Regional Operations
ULN	Upper limit of normal
VAT	Ventilatory anaerobic threshold
VCO_2	Carbon dioxide production
VE	Ventilatory efficiency
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes (Table 1) for the current amendment is located directly before the Table of Contents (TOC).

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