Protocol: CY 6031

Title: A Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

NCT05186818

Approval Date: 08 December 2023

PROTOCOL CY 6031

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF CK-3773274 IN ADULTS WITH SYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY AND LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Protocol Version and Date:	Amendment 04 dated 08 December 2023
Previous Version(s):	Amendment 03 dated 03 January 2023 Amendment 02 dated 10 December 2021 Amendment 01 dated 17 August 2021 Original Protocol 26 July 2021
Product:	CK-3773274 (aficamten)
Regulatory Authority Identifier Number(s):	IND 138814 EudraCT Number 2021-003536-92
Sponsor:	Cytokinetics, Inc. 350 Oyster Point Blvd. South San Francisco, CA 94080, USA

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	CY 6031
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Protocol Version and Date:	Amendment 04 dated 08 December 2023

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 International Council for Harmonisation (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 6031
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Dec-11-2023 | 15:31:18 PST

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Date:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 04	08 December 2023
Amendment 03	03 January 2023
Amendment 02	10 December 2021
Amendment 01	17 August 2021
Original Protocol	26 July 2021

Amendment 04 (08 December 2023)

The main purpose of this amendment is as follows:

- To add a safety endpoint that contextualizes observations of LVEF <50% with clinically relevant associated findings.
- To update the definition of full analysis set.
- To update the testing hierarchy to use a closed testing procedure with pre-specified testing order to test the secondary endpoints once the primary endpoint achieves statistical significance.

Table 1: Protocol Amendment 04 Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3. Objectives and Endpoints	Added the safety endpoint of incidence of LVEF <50% with signs and symptoms of heart failure (concomitant adverse event of heart failure or dyspnea) and/or increase in NT-proBNP from baseline	This additional safety endpoint contextualizes an observation of LVEF <50% with clinically relevant associated findings
1.1 Synopsis 9.3 Populations For Analyses	Updated full analysis set definition to include all randomized patients	Per FDA's recommendation

Table 1: Protocol Amendment 04 Summary of Changes (Continued)

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 9.4.1.1 Multiplicity Adjustment	Revised testing hierarchy; and made editorial updates	The testing hierarchy was simplified from a parallel gatekeeping method to a closed testing procedure. This adjustment allows for the examination of secondary endpoints at two-sided alpha level of 0.05 once the primary endpoint achieves statistical significance at the prespecified sequential testing order

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Investigational Product(s) (IP): CK-3773274

Name of Active Ingredient(s): CK-3773274

Protocol Title:

A Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

Phase of Development: Phase 3

Rationale:

Hypertrophic cardiomyopathy (HCM) is a disease of the cardiac sarcomere for which the fundamental pathophysiologic abnormality is myocardial hypercontractility leading to cardiac hypertrophy. In patients with obstructive HCM (oHCM), dynamic left ventricular outflow tract (LVOT) obstruction creates a high-pressure outflow tract gradient during systole. Patients with oHCM often develop signs and symptoms of heart failure.

CK-3773274 is a small molecule cardiac myosin inhibitor being developed as a chronic, oral treatment for patients with HCM. CK-3773274 is designed to reduce the hypercontractility that underlies the pathophysiology of HCM. Selective inhibition of cardiac myosin with CK-3773274 may yield potential advantages over current therapies for oHCM by directly reducing myocardial hypercontractility and addressing the fundamental cause of this sarcomeric disease.

In the Phase 2 trial, CY 6021 (REDWOOD-HCM), patients with oHCM received up to three doses of CK-3773274 or placebo (randomized 2:1) in a dose escalating manner using echocardiography to guide dose titration. Two cohorts of approximately 20 patients each were enrolled and treated for 10 weeks. Doses in the first cohort were 5, 10, 15 mg once daily; the second cohort studied 10, 20, and 30 mg once daily. In both cohorts, CK-3773274 significantly and substantially reduced the LVOT gradient (LVOT-G) in a dose and exposure dependent manner. A third cohort of 13 patients with symptomatic oHCM taking standard of care therapy plus disopyramide were enrolled and treated for 10 weeks. Doses were 5, 10, 15mg once daily. CK3773274 again significantly substantially reduced LVOT-G in a dose and exposure dependent manner. There were no treatment interruptions or discontinuations, nor any treatment related serious adverse events. The results from this trial support progression of CK-3773274 to Phase 3 given the association between reductions in LVOT-G and improvements in patient symptoms and function.

This trial will evaluate the effects of treatment with CK-3773274 over a 24-week period on cardiopulmonary exercise capacity and health status in patients with symptomatic oHCM.

Objectives and Endpoints:

Objectives	***Endpoint(s)***
Primary	
To evaluate the effect of CK-3773274 on exercise capacity in patients 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 CK-3773274 on patient health status	• Change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) from baseline to Week 12 and Week 24
To evaluate the effect of CK-3773274 on New York Heart Association (NYHA) Functional Classification	• Proportion of patients with ≥1 class improvement in NYHA Functional Class from baseline to Week 12 and Week 24
To evaluate the effect of CK-3773274 on post-Valsalva left ventricular outflow tract gradients (LVOT-G)	• Change in post-Valsalva LVOT-G from baseline to Week 12 and Week 24 • Proportion of patients with post-Valsalva LVOT-G <30 mmHg at Week 12 and Week 24
To evaluate the effect of CK-3773274 on duration of eligibility for septal reduction therapy	• Duration of eligibility for septal reduction therapy (SRT) during the 24-week treatment period in patients who were eligible for SRT at baseline.
To evaluate the effect of CK-3773274 on exercise capacity	• Change in total workload during CPET from baseline to Week 24
Safety	
To evaluate the safety and tolerability profile of CK-3773274 in patients with symptomatic oHCM	• Incidence of reported major adverse cardiac events (cardiovascular [CV] death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization) • Incidence of new onset persistent atrial fibrillation • Incidence of appropriate implantable cardiac defibrillator (ICD) discharges and aborted sudden cardiac death • Incidence of left ventricular ejection fraction (LVEF) <50% • Incidence of LVEF <50% with at least one of the following: o Signs and symptoms of heart failure (concomitant adverse event of heart failure or dyspnea), AND/OR o Increase in NT-proBNP (≥30% increase), relative to results from the most recent previous visit and above the upper limit of normal, at the time of LVEF assessment <50% • Incidence of treatment emergent adverse events

Exploratory	
To evaluate the effect of CK-3773274 on exercise capacity and functional class	• Compared with baseline, proportion of patients 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 from baseline of ≥3.0 mL/kg/min in pVO_2 AND no worsening of NYHA Functional Class
To evaluate the effect of CK-3773274 on patient response over time	• Proportion of patients with improvement in KCCQ-CSS ≥5 points at Weeks 12 and 24 • Proportion of patients with resting LVOT-G <30 mmHg, post-Valsalva LVOT-G <50 mmHg, and NYHA Functional Class I at Weeks 12 and 24 • Proportion of patients with resting LVOT-G <30 mmHg, post-Valsalva LVOT-G <50 mmHg, and ≥1 class improvement in NYHA Functional Class at Weeks 12 and 24
To evaluate the effect of CK-3773274 on septal reduction therapy eligibility	• Proportion of patients who are eligible for septal reduction therapy at Week 24 among patients who were eligible for septal reduction therapy at baseline
To evaluate the effect of CK-3773274 on other CPET parameters	Change from baseline to Week 24 in: • Ventilatory efficiency (VE/VCO_2 slope) • Circulatory power (VO_2 × systolic BP) • Ventilatory anaerobic threshold (VAT)
To evaluate the effect of CK-3773274 on health status and health-related quality of life as measured by PRO questionnaire	• Change from baseline to Week 24 in individual responses to the EuroQol 5-dimension 5-level instrument (EQ-5D-5L)
To evaluate the effect of CK-3773274 on health status and quality of life related to chest pain-like angina	• Change from baseline to Week 24 in summary and domain scores for the Seattle Angina Questionnaire-7 (SAQ-7)
To evaluate the effect of CK-3773274 on cardiac function and structure	• Change from baseline to Week 24 in echocardiographic measurements of cardiac structure and of systolic function including: – LVEF – Left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV, respectively) – Left atrial volume
To evaluate the effect of CK-3773274 on biomarker levels	• Change from baseline values in NT-pro-BNP, hs-cardiac-TnI and other biomarkers through Week 24
To evaluate the effect of CK-3773274 on left ventricular mass, function, and	• Change from baseline to Week 24 in CMR measurements of:

structure by cardiac magnetic resonance (CMR) imaging	– Left ventricular (LV) mass index – LVEF – Septal, free wall, and maximal wall thickness – Left atrial volume index – LVESV – LVEDV
To assess the pharmacokinetics of CK-3773274 and its metabolites	• Pharmacokinetic parameters through Week 24

Overall Design:

This is a Phase 3 randomized, placebo-controlled, double-blind, multi-center trial in patients with symptomatic oHCM. Approximately 270 eligible patients will be randomized in a 1:1 ratio to receive CK-3773274 or placebo. Doses of 5, 10, 15, or 20 mg or matching placebo will be administered in an escalating manner using echocardiography to guide dose titration. Randomization will be stratified by use of beta-blockers and CPET exercise modality.

The trial will comprise three periods. The screening period will be up to 6 weeks in duration. The double-blind placebo-controlled treatment period will last 24 weeks. Following the final dose of investigational product (IP), there will be a 4-week safety follow-up period. IP will be administered orally once daily. During the initial six weeks of the treatment period, IP doses will be individually titrated at Weeks 2, 4, and 6 using echocardiography. Dose escalation at the Weeks 2, 4, and 6 visits will occur only if a patient has a post-Valsalva LVOT-G ≥30 mmHg and a biplane LVEF ≥55%. An echocardiogram will be performed at each subsequent visit during the trial and the dose down-titrated if necessary. The primary endpoint of pVO_2 will be measured by CPET at screening and at end of treatment (Week 24). Patients background oHCM therapy will be individually optimized according to local practice.

A CMR imaging sub-study will be open to approximately 100 patients who consent to participate.

Trial Center(s):

This trial will take place at approximately 120 sites worldwide.

Number of Patients:

Approximately 270 patients will be randomized to CK-3773274 or placebo.

Key Eligibility Criteria:

The key eligibility criteria are below. A full listing of eligibility criteria can be found in Section 5.

Inclusion Criteria

- Males and females between 18 and 85 years of age, inclusive, at screening.
- Body mass index <35 kg/m^2.
- Diagnosed with HCM per the following criteria:
  - Has LV hypertrophy and 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 of:
    a. ≥15 mm in one or more myocardial segments OR
    b. ≥13 mm in one or more wall segments *and* a known-disease-causing gene mutation or positive family history of HCM
- Has resting LVOT-G ≥30 mmHg and post-Valsalva LVOT G ≥50 mmHg during screening as determined by the echocardiography core laboratory.
- LVEF ≥60% at screening as determined by the echocardiography core laboratory.
- NYHA Functional Class II or III at screening.
- Hemoglobin ≥10g/dL at screening.
- Respiratory exchange ratio (RER) ≥1.05 and pVO2 ≤90% predicted on the screening CPET per the core laboratory.

- Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on stable doses for >6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial. Patients treated with disopyramide must also be concomitantly treated with a beta blocker and/or calcium channel blocker.

Exclusion Criteria

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

- Known or suspected infiltrative, genetic or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis).
- Significant valvular heart disease (per investigator judgment).
  - Moderate-severe valvular aortic stenosis.
  - Moderate-severe mitral regurgitation not due to systolic anterior motion of the mitral valve.
- History of LV systolic dysfunction (LVEF <45%) or stress cardiomyopathy at any time during their clinical course.
- Inability to exercise on a treadmill or bicycle (eg, orthopedic limitations).
- Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the trial period.
- Documented paroxysmal atrial fibrillation during the screening period.
- Paroxysmal or permanent atrial fibrillation is only excluded **IF**:
  - rhythm restoring treatment (eg, direct-current cardioversion, atrial fibrillation ablation procedure, or antiarrhythmic therapy) has been required ≤6 months prior to screening
  - rate control and anticoagulation have not been achieved for at least 6 months prior to screening.
- History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.
- Has received prior treatment with CK-3773274 or mavacamten.

Exclusion Criteria for CMR sub-study

- Inability to tolerate CMR.
- Has an implantable cardioverter-defibrillator (ICD).
- Has a cardiac pacemaker.

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will be established for this trial to formally review the accumulating data periodically in order to assess risk to patients 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 patient-level data from the clinical trial database.

Statistical Methods:

Sample Size Calculation: assuming a difference in change from baseline in pVO_2 of 1.5 mL/kg/min for CK-3773274 compared to placebo, a standard deviation (SD) of 3.5 mL/kg/min, and 10% of patients missing change from baseline data of the primary endpoint, a sample size of 270 patients (approximately 135 randomized to CK-3773274 and 135 randomized to placebo) 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.

During the study, the aggregate pooled missing data rate and overall pooled SD for the change from baseline in pVO_2 at Week 24 will be monitored periodically in a blinded fashion. If the pooled SD is larger than expected, Cytokinetics may consider increasing the sample size once in order to maintain the intended power.

Unless specified otherwise, efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized patients. The primary analysis will test the null hypothesis that there is no treatment difference in the primary endpoint between patients randomized to placebo and those randomized to CK-3773274 in the FAS. Change from baseline in pVO_2 will be analyzed using an ANCOVA model with treatment group, randomization stratification factors, baseline pVO_2 and baseline weight as covariates.

For preservation of the overall type I error rate at two-sided 0.05 for the primary and secondary endpoints will be tested in the following specified order using a closed testing procedure. First, the primary endpoint is tested first at two-sided 0.05. If the primary endpoint achieves statistical significance at two-sided $p \leq 0.05$, then the secondary endpoints will be tested at two-sided 0.05, with their testing being in the sequential order of KCCQ-CSS change from baseline, proportion of patients with ≥1 NYHA functional class improvement, post-Valsalva LVOT-G change from baseline, proportion of patients with post-Valsalva LVOT-G < 30 mm Hg, and duration of SRT eligibility for participants who are SRT eligible at baseline, for each after 24 weeks of treatment; then KCCQ-CSS change from baseline, proportion of patients with ≥1 NYHA functional class improvement, post-Valsalva LVOT-G change from baseline, and proportion of patients with post-Valsalva LVOT-G < 30 mmHg, for each after 12 weeks of treatment; and lastly change from baseline to Week 24 in total workload. SRT eligibility is defined as resting or post-Valsalva LVOT-G ≥ 50 mmHg AND NYHA Functional Class ≥ 3. See Figure 1 for illustration of the testing order. The detailed description of testing sequence will be provided in the Statistical Analysis Plan.

Figure 1: Statistical Testing Hierarchy for Trial Endpoints

Primary Endpoint		Significance Level
Step 1	pVO_2	0.05
Secondary Endpoints		⇩
Step 2	KCCQ-CSS (24 wk)	0.05
		⇩
Step 3	NYHA Class (24 wk)	0.05
		⇩
Step 4	Valsalva Gradient (24 wk)	0.05
		⇩
Step 5	%Valsalva Gradient (24 wk)	0.05
		⇩
Step 6	Duration SRT Eligible (24 wk)	0.05
		⇩
Step 7	KCCQ-CSS (12 wk)	0.05
		⇩
Step 8	NYHA Class (12 wk)	0.05
		⇩
Step 9	Valsalva Gradient (12 wk)	0.05
		⇩
Step 10	%Valsalva Gradient (12 wk)	0.05
		⇩
Step 11	Total workload (24 wk)	0.05

The proportion of responders in various exploratory endpoints will be analyzed using Cochran–Mantel–Haenszel (CMH) test stratified by randomization factors in FAS. The p-value and 95% confidence interval (CI) will be obtained using exact method. For the subgroup of patients who are SRT-eligible at baseline, total duration SRT eligible during the 24-week treatment period will be analyzed using an ANCOVA model with treatment group and randomization stratification factor beta blocker use/no use as fixed effects adjusting for significant baseline characteristics. Other change from baseline endpoints will be analyzed using mixed measures repeated model with treatment, visit, randomization stratification factors, treatment by visit, baseline by visit interaction as fixed effect and baseline assessment as covariate.

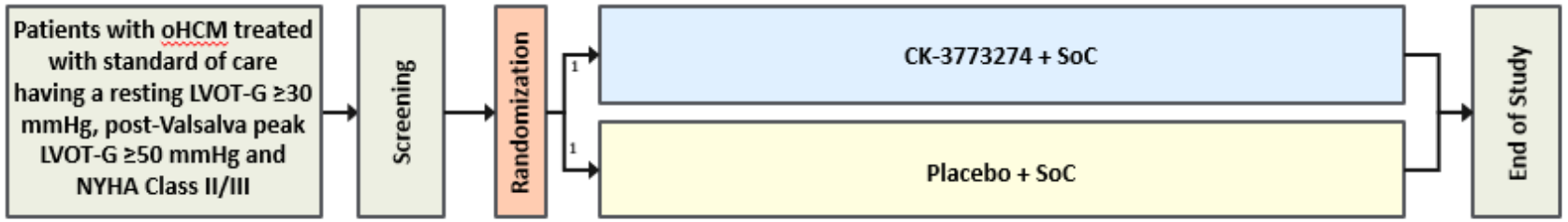
Safety analyses will be performed on the safety analysis set (SAS) which includes all patients who received at least one dose of IP. The pharmacokinetics analysis set (PKS) will consist of patients who have at least one measurable plasma concentration of CK-3773274.

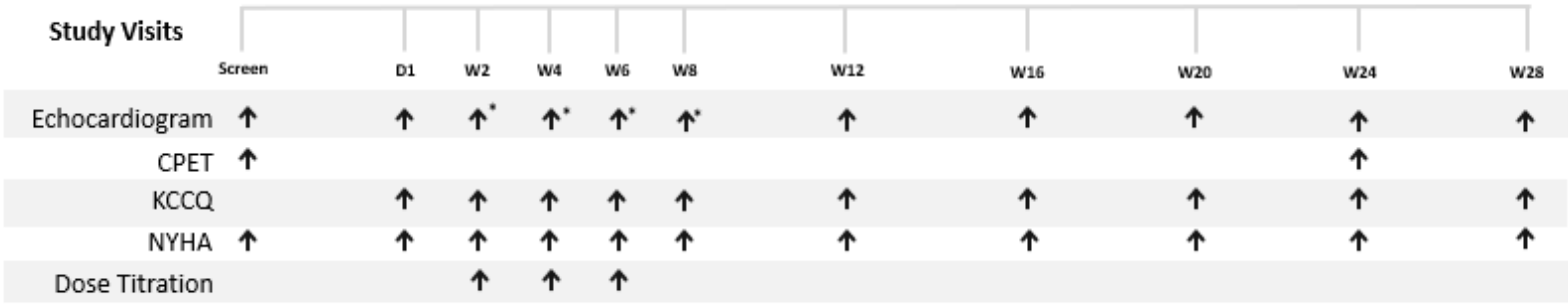
The number and percentage of patients reporting any treatment-emergent AEs will be coded using the MedDRA dictionary and be tabulated by system organ class and preferred term.

Analyses will be further detailed in the Statistical Analysis Plan.

1.2. Schema

Figure 2: Trial Schema





1.3. Schedule of Activities

Trial Procedure	Screening[a] (≤ 42 days)	Day 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	EOT[b] (Week 24)	EOS[c] (Week 28)	ED[d]
Visit Window	**Up to 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**	**As soon as possible after withdrawal**
GENERAL PROCEDURES AND SAFETY ASSESSMENTS												
Informed consent	X											
Enrollment in IWRS	X											
Inclusion/Exclusion criteria	X											
Medical/Surgical history	X											
Demographics	X											
Height/weight[e]	X									X		
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X									X		X
Adverse events/serious adverse events[g]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)	X	X	X	X	X	X	X	X	X	X	X	X
CPET	X									X		
CMR imaging sub-study[h]	X									X		
Focused Echo (LVOT-G + LVEF)[i]			X	X	X	X						
Full Echocardiogram[i]	X	X					X	X	X	X	X	X
Randomization		X										
CENTRAL LABORATORY ASSESSMENTS												
Laboratory assessments	X	X					X			X	X	X
CMR substudy Hematocrit[j]	X									X		
Pregnancy test (WOCBP only)[k]	X	X	X	X	X	X	X	X	X	X	X	X
NT-pro-BNP		X	X	X	X	X	X	X	X	X	X	X

Trial Procedure	Screening[a] (≤ 42 days)	Day 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	EOT[b] (Week 24)	EOS[c] (Week 28)	ED[d]
Visit Window	**Up to 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**	**As soon as possible after withdrawal**
hs-cTnI		X	X	X	X	X	X	X	X	X	X	X
PK samples[l]		X	X	X	X	X	X	X	X	X		X
Other biomarker samples[m]		X					X			X		
Serum and Plasma Collection for Future Analyses		X					X			X		
Genotype sample[n]		X										
PT-INR[o]	X											
PATIENT-REPORTED OUTCOMES AND FUNCTIONING ASSESSMENTS												
NYHA Functional Classification	X	X	X	X	X	X	X	X	X	X	X	X
KCCQ[p]		X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[p]		X	X	X	X	X	X	X	X	X	X	X
CGI										X	X	X
PGI-C[p]										X		X
SAQ-7[p]		X		X		X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT												
IP dose administration at site[q]		X	X	X	X	X	X	X	X	X		
IP dispensation		X	X	X	X	X	X	X	X			
IP dose titration[r]			X	X	X							
IP dose adjustment[s]						X	X	X	X			

CGI = Clinical Global Impression scale; CMR = cardiac magnetic resonance imaging; CPET = cardiopulmonary exercise testing; ECG = electrocardiogram; Echo = echocardiogram; ED = early discontinuation; EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQol 5-dimension 5-level instrument; hs-cTnI = high sensitivity cardiac troponin I; IP = investigational product; IWRS = interactive web response system; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = n-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; SAQ-7 = Seattle Angina Questionnaire-7, PGI-C = Patient Global Impression of Change scale; PK = pharmacokinetic; WOCBP = women of childbearing potential; PT-INR = prothrombin time/international normalized ratio; UNS DILI = unscheduled drug-induced liver injury

[a] The CPET must be completed within four weeks but not less than one week prior to randomization.

[b] If a patient 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 patient should continue to receive IP until the visit. Sites should contact patients 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.

[c] The EOS visit (Week 28) will occur 4 weeks after last dose. It is not required for patients who discontinue IP >4 weeks prior to the Week 24.

[d] Patients who withdraw from the trial IP should complete an early discontinuation visit as soon as possible if they no longer wish to be part of the study. An EOS visit should be performed 4 weeks after their final IP dose if possible.

[e] Height is measured at the Screening visit only.

[f] Vital signs include heart rate, respiratory rate, and blood pressure. Oxygen Saturation only done at Screening.

[g] Only SAEs and non- serious AEs considered related to trial procedures are collected during the screening period until initiation of IP (Day 1). Any medical occurrence not related to a trial procedure during this period should be collected as medical history.

[h] A CMR imaging sub-study will be open to approximately 100 patients who consent to participate. The baseline CMR imaging should be done prior to randomization. The EOT CMR should be performed after the Week 20 visit, but prior to the last dose of IP at Week 24.CMR should occur after CPET if the assessments are performed on the same day.

i Echocardiograms will be done prior to dosing on Day 1 and 2 hours after dosing in the clinic at other time points.

[j] Must be done within 24 hours of CMR.

[k] Only for WOCBP. Serum pregnancy test at Screening visit. A urine pregnancy test may be performed locally at all other required timepoints. If a urine pregnancy test is positive, a serum pregnancy test should be performed.

[l] When PK collection and an echocardiogram are scheduled for the same time point, PK collection should be completed prior to the echocardiogram.

[m] Other biomarkers are referenced in Table 9.

[n] A genotype sample will be collected on Day 1 from patients who provide consent.

[o] PT-INR should also be taken at UNS DILI visits in addition to the screening visit.

[p] All PROs, KCCQ, ED-5D-5L, SAQ-7, and PGI-C, should be done prior to other assessments.

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

[r] See Section 6.6.

[s] See Section 7.1.

1.4. Key Contacts

Sponsor's Trial Contact:	Edward Robbie Manager, Clinical Operations Email: CY6031ClinicalOperations@cytokinetics.com Phone: +1 (650) 624-3046 Fax: +1 (650) 624-3225
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Serious Adverse Event Reporting:	Cytokinetics Drug Safety Email: CY6031DrugSafety@cytokinetics.com Fax: +1 (650) 243-4199

2. INTRODUCTION

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

2.1. Trial Rationale

The development of a targeted therapeutic drug that directly reduces myocardial contractility in the sarcomere may yield potential advantages over current therapies for obstructive hypertrophic cardiomyopathy (oHCM) because it potentially addresses the underlying pathophysiology of HCM. CK-3773274 is a cardiac myosin inhibitor with potential to reduce left ventricular outflow tract (LVOT) obstruction and improve symptoms in patients with hyperdynamic ventricular contractility in oHCM.

This trial is intended to establish the efficacy and safety of CK-3773274 with respect to improvements in exercise capacity and patient symptoms, as well as reduction in left ventricular outflow tract gradient (LVOT-G) in patients with oHCM.

2.2. Background

2.2.1. Hypertrophic Cardiomyopathy

HCM results from pathogenic genetic mutations, 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 patients 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 is approximately 1:2000 and 1:3195 (Maron, M. S. 2016; Husser 2018; Magnusson 2017; Pujades-Rodriguez 2018).

Approximately 70% of patients with phenotypic HCM will demonstrate an element of 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. Current medical treatment consists of beta-blockers, verapamil, diltiazem and disopyramide 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.

Mutations 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, mutations 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 designed to identify cardiac myosin modulators that can target the underlying mechanism of hypercontractility in oHCM.

2.2.2. CK-3773274

CK-3773274, a small molecule allosteric inhibitor of cardiac myosin, is being developed as a chronic oral treatment for patients with HCM. CK-3773274 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.

CK-3773274 has been studied in a Phase 1 study of healthy adult participants and a Phase 2 study of patients with oHCM. This Phase 3 trial will assess the efficacy and safety of CK-3773274 in patients with oHCM.

Please refer to the Investigator's Brochure for detailed information on the nonclinical and clinical studies of CK-3773274.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Excessive exposures to CK-3773274 may result in an excess of the intended 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 (Section 2.2.2). These adverse cardiac effects are consistent with the anticipated physiological response to an excessive PD effect of CK-3773274.

In the first-in-human CY 6011 study, short-term decreases in cardiac function produced no changes in the vital signs or electrocardiograms (ECGs) of the participants. The effect of CK-3773274 on left ventricular ejection fraction (LVEF) reversed within 24-48 hours (single ascending dose and multiple ascending dose cohorts) of discontinuation of dosing. The participants who had decreases in LVEF to <50% remained asymptomatic until their cardiac function returned to the normal LVEF range.

In the first three cohorts of the Phase 2 trial, CY 6021 (REDWOOD-HCM), there were no adverse events of decreased LVEF reported, however, a decline in LVEF < 50% per core laboratory evaluation was reported for 2 of 41 participants in the aficamten group, and no participants in the placebo group. The decline in LVEF was asymptomatic in both patients and returned to above 50% at the next observed time point 2 weeks later. One of these participants underwent per-protocol dose reduction from 20 mg to 10 mg daily and completed the treatment period without dose interruption. The second participant who completed study treatment was noted to have an LVEF of 49.3% at Week 10 (end of treatment visit). There were no reports of post-baseline LVEF < 40%.

Together these findings indicate that the treatment effect of CK-3773274 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 be facilitated by an individualized dose titration scheme based on each patient's PD response to CK-3773274 with application of prespecified echocardiographic criteria, including LVEF thresholds for dose escalation, down-titration, and drug discontinuation.

Patients 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 and a maximum dose of 20 mg were chosen as these were found to be well-tolerated in the Phase 2 study (CY 6021) of patients with oHCM and effective at reducing the LVOT-G without adversely impacting overall LVEF. Dose escalation will be performed on an individualized basis only if the following criteria are met: both post-Valsalva LVOT-G ≥30 mmHg and biplane LVEF ≥55%. 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 CK-3773274 will be down-titrated, and if the LVEF is <40% at any time, CK-3773274 will be temporarily interrupted.

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

2.3.2. CK-3773274 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. CK-3773274 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 (REDWOOD-HCM), patients with oHCM received up to three doses of CK-3773274 or placebo (randomized 2:1) in a dose escalating manner using echocardiography to guide dose titration. Two cohorts of 21 (14 CK-3773274 and 7 placebo) and 20 patients (14 CK-3773274 and 6 placebo) each were enrolled and treated for 10 weeks. Doses in the first cohort were 5, 10, 15 mg once daily; the second cohort studied 10, 20, and 30 mg once daily. In both cohorts, CK-3773274 significantly and substantially reduced the LVOT gradient (LVOT-G) in a dose and exposure dependent manner. The majority of patients treated with CK-3773274 (78.6% in Cohort 1 and 92.9% in Cohort 2) achieved the target goal of treatment, defined as resting gradient <30 mmHg and post-Valsalva gradient <50 mmHg at Week 10 compared to placebo (7.7%). A third cohort of 13 patients taking disopyramide plus either a calcium-channel blocker or beta-blocker were enrolled and treated for 10 weeks. Doses were 5, 10, 15 mg once daily. CK-3773274 significantly and substantially reduced LVOT-G in dose and exposure dependent manner. Ten patients (77%) achieved complete or partial LVOT-G response at Week 10. Complete response was defined as rest and post-Valsalva LVOT-G <30 mmHg and <50 mmHG respectively. Partial response was defined as either rest LVOT-G ≥30mmHg with Valsalva LVOT-G <50 mmHG, or rest LVOT-G <30 mmHg with post-Valsalva LVOT-G ≥50 mmHg . Eleven of 13 (85%) achieved improvement in NYHA class by ≥1 class.

Given that the LVOT-G is the primary cause of symptoms in patients with oHCM, participation in this trial may afford those randomized to CK-3773274 symptom reduction and increased exercise capacity. Patient 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	Endpoint(s)
Primary	
To evaluate the effect of CK-3773274 on exercise capacity in patients 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 CK-3773274 on patient health status	• Change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) from baseline to Week 12 and Week 24
To evaluate the effect of CK-3773274 on New York Heart Association (NYHA) Functional Classification	• Proportion of patients with ≥1 class improvement in NYHA Functional Class from baseline to Week 12 and Week 24
To evaluate the effect of CK-3773274 on post-Valsalva left ventricular outflow tract gradients (LVOT-G)	• Change in post-Valsalva LVOT-G from baseline to Week 12 and Week 24 • Proportion of patients with post-Valsalva LVOT-G <30 mmHg at Week 12 and Week 24
To evaluate the effect of CK-3773274 on duration of eligibility for septal reduction therapy	• Duration of eligibility for septal reduction therapy (SRT) during the 24-week treatment period in patients who were eligible for SRT at baseline.
To evaluate the effect of CK-3773274 on exercise capacity	• Change in total workload during CPET from baseline to Week 24
Safety	
To evaluate the safety and tolerability profile of CK-3773274 in patients with symptomatic oHCM	• Incidence of reported major adverse cardiac events (cardiovascular [CV] death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization) • Incidence of new onset persistent atrial fibrillation • Incidence of appropriate implantable cardiac defibrillator (ICD) discharges and aborted sudden cardiac death • Incidence of left ventricular ejection fraction (LVEF) <50% • Incidence of LVEF <50% with at least one of the following: o Signs and symptoms of heart failure (concomitant adverse event of heart failure or dyspnea), AND/OR o Increase in NT-proBNP (≥30% increase), relative to results from the most recent previous visit and above the upper limit of normal, at the time of LVEF assessment <50% • Incidence of treatment emergent adverse events

Table 2: Trial Objectives and Endpoints (Continued)

Objectives	Endpoint(s)
Exploratory	
To evaluate the effect of CK-3773274 on exercise capacity and functional class	• Compared with baseline, proportion of patients 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 from baseline of ≥3.0 mL/kg/min in pVO_2 AND no worsening of NYHA Functional Class
To evaluate the effect of CK-3773274 on patient response over time	• Proportion of patients with improvement in KCCQ-CSS ≥5 points at Weeks 12 and 24 • Proportion of patients with resting LVOT-G <30 mmHg, post-Valsalva LVOT-G <50 mmHg, and NYHA Functional Class I at Weeks 12 and 24 • Proportion of patients with resting LVOT-G <30 mmHg, post-Valsalva LVOT-G <50 mmHg, and ≥1 class improvement in NYHA Functional Class at Weeks 12 and 24
To evaluate the effect of CK-3773274 on septal reduction therapy eligibility	• Proportion of patients who are eligible for septal reduction therapy at Week 24 among patients who were eligible for septal reduction therapy at baseline
To evaluate the effect of CK-3773274 on other CPET parameters	Change from baseline to Week 24 in: • Ventilatory efficiency (VE/VCO_2 slope) • Circulatory power (VO_2 × systolic BP) • Ventilatory anaerobic threshold (VAT)
To evaluate the effect of CK-3773274 on health status and health-related quality of life as measured by PRO questionnaire	• Change from baseline to Week 24 in individual responses to the EuroQol 5-dimension 5-level instrument (EQ-5D-5L)
To evaluate the effect of CK-3773274 on health status and quality of life related to chest pain-like angina	Change from baseline to Week 24 in summary and domain scores for the Seattle Angina Questionnaire-7 (SAQ-7)
To evaluate the effect of CK-3773274 on cardiac function and structure	• Change from baseline to Week 24 in echocardiographic measurements of cardiac structure and of systolic function including: – LVEF – Left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV, respectively) – Left atrial volume

Table 2: Trial Objectives and Endpoints (Continued)

Objectives	Endpoint(s)
To evaluate the effect of CK-3773274 on biomarker levels	• Change from baseline values in NT-pro-BNP, hs-cardiac-TnI and other biomarkers through Week 24
To evaluate the effect of CK-3773274 on left ventricular mass, function, and structure by cardiac magnetic resonance (CMR) imaging	• Change from baseline to Week 24 in CMR measurements of: – Left ventricular (LV) mass index – LVEF – Septal, free wall, and maximal wall thickness – Left atrial volume index – LVESV – LVEDV
To assess the pharmacokinetics of CK-3773274 and its metabolites	• Pharmacokinetic parameters through Week 24

4. TRIAL DESIGN

4.1. Overall Design

This is a Phase 3, randomized, placebo-controlled, double-blind, multi-center trial in patients with symptomatic oHCM. Approximately 270 eligible patients will be randomized in a 1:1 ratio to receive CK-3773274 or placebo. Randomization will be stratified by use of beta-blockers (yes or no) and CPET exercise modality (treadmill or bicycle) and implemented in the Interactive Web Response System (IWRS). A cap on the number of patients taking beta-blockers and will not exceed approximately 70% of total enrollment. The number of patients taking disopyramide will be capped at approximately 10% of total enrollment. The number of patients with persistent atrial fibrillation at screening will also be capped at approximately 15%, and the number of patients using the bicycle CPET exercise modality will be capped at approximately 50% as well.

IP will be administered orally once daily with or without food. During the initial six weeks of the treatment period, IP doses will be individually titrated at Weeks 2, 4, and 6 using echocardiography. Dose escalation at Weeks 2, 4, and 6 will occur only if a patient has a post-Valsalva LVOT-G ≥30 mmHg and a biplane LVEF ≥55%. Echocardiograms will be performed at each subsequent visit during the trial and the dose down titrated if necessary. The primary endpoint of pVO_2 will be measured by CPET at screening and at end of treatment (Week 24). Patients' background HCM therapy should be individually optimized according to the local practice.

All patients will be followed according to the Schedule of Activities (SoA) from randomization through the date of their final visit irrespective of whether the patient is continuing to receive IP, unless the patient has discontinued prematurely from the trial or withdrawn consent. An early discontinuation visit will be performed for patients who discontinue prematurely from the trial.

The overall study design is described by a trial schema in Figure 2.

The trial endpoints and objectives are defined in Table 2.

4.1.1. Number of Sites

Approximately 120 investigative sites worldwide will participate in this trial.

4.1.2. Number of Patients

Approximately 270 patients will be randomized in the trial.

4.1.3. Replacement of Patients

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

4.1.4. Trial Duration

The trial will comprise three periods. After signing the informed consent form, patients will complete assessments to determine trial eligibility during a screening period of up to 6 weeks in duration. The double-blind placebo-controlled treatment period will last 24 weeks. Following the final dose of IP, there will be a 4-week safety follow-up period.

4.1.5. CMR Imaging Sub-Study

A CMR imaging sub-study will be open to approximately 100 patients who consent to participate.

4.2. Scientific Rationale for Trial Design

This trial is designed to provide data supporting the clinical efficacy and safety of CK-3773274 in patients with symptomatic oHCM and an LVOT-G >50 mmHg post-Valsalva. Reduction of the LVOT-G is expected to correlate with improvement in the patients' symptoms, health status and exercise capacity.

Since patient characteristics vary substantially in this disease, individualized dose titration to a PD response (reduction of the post-Valsalva LVOT-G to <30 mmHg with preservation of LVEF ≥55%) is being employed to maximize efficacy and safety. The eligibility criteria are designed to enable enrollment of a patient population representative of the general population of patients with oHCM while ensuring the safety of the patients in this trial.

A placebo control and double-blinded approach are being employed in this trial to avoid bias in data collection, including the safety assessments and PD measures that comprise the primary and secondary endpoints.

4.3. Justification for Dose

The doses of CK-3773274 are summarized in Table 3. 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 study of patients with oHCM and effective at reducing the LVOT-G without adversely impacting overall LVEF. Within-patient dose escalation will only occur when the patient's current dose is well-tolerated, and the patient meets the criteria described in Section 6.6.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the trial.

5. STUDY POPULATION

Before patients 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 patient information and/or recruitment material, if applicable. A signed ICF must be obtained from each patient before commencement of any trial-specific activities/procedures.

A patient's participation in the trial begins after signing the informed consent. After confirming the patient 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 and randomization dates in the patient's medical record and in/on the case report form (CRF).

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

5.1. Inclusion Criteria

Patients 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 and 85 years of age, inclusive, at screening.
103. Body mass index <35 kg/m^2.
104. Diagnosed with HCM per the following criteria:
    a. Has LV hypertrophy and 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 of:
        - ≥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. Has resting LVOT-G ≥30 mmHg and post-Valsalva LVOT-G ≥50 mmHg during screening as determined by the echocardiography core laboratory
106. LVEF ≥60% at screening as determined by the echocardiography core laboratory.
107. New York Heart Association (NYHA) Functional Class II or III at screening
108. Hemoglobin ≥10 g/dL at screening.
109. Respiratory exchange ratio (RER) ≥1.05 and pVO_2 ≤90% predicted on the screening CPET per the core laboratory.
110. Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on a stable regimen for >6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial. Patients treated with disopyramide must also be concomitantly treated with a beta blocker and/or calcium channel blocker.

111. Male patients are eligible to participate if they agree to the following:

a) Refrain from donating sperm during the trial plus at least 10 weeks after the last dose of IP

AND

b) During the trial plus 4 weeks after the last dose of IP either:

1. Be abstinent 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

2. Must agree to use a male condom when his female partner is a woman of childbearing potential, and have his female partner use a highly effective method of contraception (as described in Appendix 3 [Section 10.3])

112. A female patient 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

Is a WOCBP and using a highly effective method of contraception (as described in Appendix 3 [Section 10.3]) and male partner agrees to use a condom, during the trial and for at least 4 weeks after the last dose of IP.

b. 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 study IP.

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.

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 studies.

113. Willing and able to complete all screening procedures.

5.2. Exclusion Criteria

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

201. Significant valvular heart disease (per investigator judgment).

a. Moderate-severe valvular aortic stenosis and/or regurgitation.
b. Moderate-severe mitral regurgitation not due to systolic anterior motion of the mitral valve

202. Documented history of current obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.
203. Known or suspected infiltrative, genetic or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis).
204. Prior treatment with cardiotoxic agents such as doxorubicin or similar.
205. History of LV systolic dysfunction (LVEF <45%) or stress cardiomyopathy at any time during their clinical course.
206. Has any ECG abnormality considered by the investigator to pose a risk to patient safety (eg, second degree atrioventricular block type II).
207. Documented paroxysmal atrial fibrillation during the screening period.
208. Paroxysmal or permanent atrial fibrillation is only excluded IF:
    - rhythm restoring treatment (eg, direct-current cardioversion, atrial fibrillation ablation procedure, or antiarrhythmic therapy) has been required ≤6 months prior to screening
    - rate control and anticoagulation have not been achieved for at least 6 months prior to screening
209. History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.
210. ICD placement within 3 months prior to screening or planned ICD placement during the trial.
211. History of appropriate ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to screening.
212. Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or cannot postpone plans for septal reduction therapy until after the trial period.
213. Inability to exercise on a treadmill or bicycle (eg, orthopedic limitations).
214. Documented room air oxygen saturation reading <90% at screening.
215. 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. Patients with documented Gilbert syndrome and TBL ≥1.5 × ULN due to unconjugated hyperbilirubinemia, without other hepatic impairment, are permitted.
216. Recipient of a major organ transplant (eg, heart, lung, liver, bone marrow, renal) or anticipated transplantation within 12 months from randomization.
217. History or evidence of any 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 patient safety or interfere with the trial evaluation, procedures, or completion.

218. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by the modified Modification of Diet in Renal Disease equation) at screening.
219. 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 screening. Other investigational procedures while participating in this trial are not permitted.

    Note: At the EOS visit for CY 6031, screening assessments for entry into an open-label extension study of aficamten are permitted.
220. Has received prior treatment with CK-3773274 or mavacamten.
221. Any known hypersensitivity to excipients in study drug tablets

Exclusion Criteria for CMR sub-study

222. Inability to tolerate CMR.
223. Has an ICD.
224. Has a cardiac pacemaker.
225. Does not consent to participate in CMR sub-study

5.3. Lifestyle Considerations

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

5.4. Screen Failures

Screen failures are defined as patients 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 patients 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 SAEs related to trial-related procedures.

The screening eligibility period is 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. Patients may be rescreened one time after initial screening when the reason for screen failure is resolved or expected to be resolved.

Patients 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. Patients who screen fail and rescreen do not need a repeat CMR.

If an element of the screening visit could not be performed for logistical or technical reasons (eg, trained evaluator was out sick, equipment malfunction) the patient can return within the

screening eligibility period to complete the visit. Echocardiograms and CPETs failed due to technical insufficiencies can be repeated.

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 patient is otherwise eligible to participate. Patients cannot be retested for abnormal bilirubin laboratory results. Patients 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 of the original screening visit and not by the date that laboratory retesting takes place. Patients who repeat echocardiograms and CPETs due to technical insufficiencies do not need to re-sign an informed consent.

No waivers will be granted regarding inclusion/exclusion criteria.

6. INVESTIGATIONAL PRODUCT

This section describes any IP, marketed product(s), or placebo intended to be administered to a trial patient according to the study protocol.

6.1. Investigational Product(s) Administered

Table 3: Investigational Products

Arm Name	Active	Placebo
IP/Product Name	CK-3773274	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	5mg	Matching placebo
Dosage Level(s)	5mg, 10mg, 15mg, 20mg	
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Patheon Inc. Toronto Regional Operations (TRO) 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada	Patheon Inc. Toronto Regional Operations (TRO) 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada
Excipients	Microcrystalline Cellulose Mannitol Croscarmellose Sodium Hydroxypropyl Cellulose Sodium Lauryl Sulfate Magnesium Stearate Opadry QX White	Microcrystalline Cellulose Lactose Monohydrate Croscarmellose Sodium Magnesium Stearate Opadry QX White
Packaging and Labeling	IP will be provided in blister packs which will be labeled as required per country requirement	IP will be provided in blister packs which will be labeled as required per country requirement

IMP = investigational medicinal product; NIMP = non-investigational medicinal product

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 patients 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).

Patients should be instructed to take four tablets each day from one row on the blister pack. 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 eligible patients will be centrally assigned to randomized IP using the IWRS. Before the trial is initiated, the login information & directions for the IWRS will be provided to each site.

Because viewing echocardiogram results could potentially compromise the blinded investigator and blinded study coordinator, specified unmasked study staff will perform and read the echocardiograms.

An unmasked sonographer at the site will perform the echocardiograms. An unmasked cardiologist, who is not the investigator and is called the unmasked echocardiologist, will read the echocardiograms, measure the LVOT-G and LVEF and enter the echocardiogram results in the IWRS for dose titrations and adjustments. 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. All site staff, including the unmasked echocardiologist and the unmasked designee, will be blinded to randomized treatment assignments. Neither the unmasked echocardiologist nor the unmasked data entry designee will reveal echocardiogram results to the rest of the study team, except in the event of a critical safety issue (eg, LVEF < 40%). Therefore, the investigator and site staff will remain blinded to the echocardiogram images and results.

IP will be dispensed at the trial visits summarized in the SoA (Section 1.3). Returned IP should not be re-dispensed to the patients.

Patients randomized to placebo will receive placebo throughout the study and will perform all protocol procedures in order to maintain the blind for the treatment group allocation and IP dose. Patients should continue to take IP through the morning of the Week 24 Visit.

The IWRS will be programmed with blind-breaking instructions and the unblinding procedure is documented in the study manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator is encouraged to contact Cytokinetics prior to unblinding a patient's intervention assignment unless this could delay emergency treatment of the patient. If a patient'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 and CRF, as applicable.

6.4. Investigational Product Compliance

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

When patients 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 documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

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

- the date and kits dispensed
- date and tablets returned

IP dosing first and last dates, including dates for dosing interruptions will also be recorded in the CRF.

6.5. Concomitant Therapy

Any medication, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the patient 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

Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on stable doses for >6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial. Patients treated with disopyramide must also be concomitantly treated with a beta blocker and/or calcium channel blocker. Patients' background HCM therapy should be individually optimized according to the local practice.

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

Patients 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.

6.5.1. Drug-Drug Interactions

In vitro studies showed that CK-3773274 was metabolized by CYP2D6 and CYP3A with potential contributions from CYPs 2C9 and 2C19. Since CYP2D6 was identified in vitro as a metabolizing enzyme of CK-3773274, the degree of dependence of its metabolism on CYP2D6 was explored in the first-in-human study, CY 6011, in participants with a poor metabolizing

CYP2D6 genotype. Compared to participants with an extensive metabolizing CYP2D6 genotype, the pharmacokinetics of CK-3773274 in participants with a poor metabolizing genotype were not different, suggesting that CYP2D6-mediated interactions are unlikely. In the absence of clinical data, the use of strong CYP3A inhibitors or inducers should be used with caution and careful monitoring.

Caution may be needed when administering CK-3773274 with known substrates of P-gp until drug-drug interaction studies are completed. Contact the Medical Monitor to determine if a potentially meaningful drug-drug interaction may exist.

6.5.2. Rescue Medicine

The use of rescue medications in the event of a low cardiac output state (eg, dobutamine) is allowable 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

6.6.1. Scheduled Dose Titrations

Patients randomized to CK-3773274 may receive up to four escalating doses of IP over the initial 6 weeks of the trial as outlined below in Table 4. Patients receiving CK-3773274 start at a dose of 5 mg once daily (Dose 1) and may escalate through doses of 10, 15, and 20 mg once daily if they continue to meet the escalation criteria or will stop at their current dose when escalation criteria are not met.

6.6.1.1. Week 2 Visit

After randomization each patient will receive Dose 1 once daily for two weeks. At the Week 2 visit, the patient will have an echocardiogram 2 hours following administration of their dose of IP. Patients will up-titrate to Dose 2 if the following conditions are met on echocardiography:

- Post-Valsalva LVOT-G ≥30 mmHg, and the biplane LVEF ≥55%

Otherwise, the patient will remain on Dose 1.

If LVEF is <50% at Week 2, the IWRS will assign the patient to placebo.

6.6.1.2. Week 4 Visit

After two more weeks on the assigned dose, at the Week 4 visit each patient will have an echocardiogram 2 hours following administration of their dose of IP. Patients will up-titrate to the next higher dose if the following conditions are met on echocardiography:

- Post-Valsalva LVOT-G ≥30 mmHg, and the biplane LVEF ≥55%

Otherwise, the patient will remain on the same dose.

If LVEF is <50% at Week 4, the IWRS will assign the patient to the prior dose level or to placebo if the patient was on Dose 1.

6.6.1.3. Week 6 Visit

After 2 more weeks on the assigned dose, at the Week 6 visit each patient will have an echocardiogram 2 hours following administration of their dose of IP. Patients will up-titrate to the next higher dose if the following conditions are met on echocardiography:

- Post-Valsalva LVOT-G ≥30 mmHg, and the biplane LVEF ≥55%

Otherwise, the patient will remain on the same dose.

If LVEF is <50% at Week 6, the IWRS will assign the patient to the prior dose level or to placebo if the patient was on Dose 1.

Table 4: Echocardiogram Criteria for Scheduled Dose Titrations

Echocardiogram Criteria for Scheduled Dose Titrations in Weeks 2, 4, and 6

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

[a] Once a patient's IP dose is down titrated, no further escalation is permitted. If LVEF <50% on 5 mg, the patient will receive placebo.

6.6.1.4. Week 8 Visit

After two additional weeks on the assigned dose, at the Week 8 visit each patient will have an echocardiogram 2 hours following administration of their dose of IP to ensure the LVEF is ≥50%.

If the LVEF is <50% at Week 8, the IWRS will assign the patient to the next lower dose or to placebo if the patient was on Dose 1.

6.6.2. Dose Reductions

After Week 6, no further dose escalations may occur. During the course of the study, for safety reasons, dose reductions may occur at scheduled or unscheduled visits. Dose reductions will be determined by the IWRS system based on echocardiography results. After Week 8, dose reductions will be based on echocardiogram results from the initial scheduled or unscheduled visits. If the LVEF is <50%, then the IWRS will assign the patient to the next lower dose or to placebo if the patient was on Dose 1. The IWRS will not further reduce the dose for at least seven days after the previous reduction.

6.6.3. LVEF Safety Threshold

If the unmasked echocardiologist observes that the LVEF has crossed the defined safety threshold of <40% or feels the patient requires urgent medical attention, the unmasked

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

If a patient'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 patient can be re-started on IP after being down-titrated.
- Document dose interruption in the eCRF and include the reason for interruption, the date of the last dose, and the restart date (Section 7.1).

6.6.4. Hepatotoxicity Stopping and Rechallenge Rules

Patients with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, 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.

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

Patients who complete CY 6031 and meet eligibility criteria will be offered participation in an open-label extension study of aficamten. Participation in the open-label extension study is at the discretion of the patient and not a condition of participation in CY 6031. 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 PATIENT CONSENT WITHDRAWAL

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

Unless a safety concern arises, the investigator should make every effort to keep a patient on the IP for as long as possible during the trial. The degree to which a patient withdraws from the trial varies. There are three types of discontinuation: temporary IP interruption, permanent IP discontinuation and patient 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 patient was at 5mg, 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 patient.

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

7.2. Permanent Discontinuation of IP

In all cases, patients should be encouraged to discuss stopping IP with the investigator or the investigator's designee. Best efforts should be made to address the patient's questions, adjust concomitant medical therapies if needed and arrange follow-up safety assessments. Refer to Section 7.2.1. for management of patients who permanently discontinue IP.

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

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

- Patient 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 patient'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 patient permanently discontinue IP

7.2.1. Management of Patients after Permanent Discontinuation of IP

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

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

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

7.3. Discontinuation from Trial Procedures

Patients 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 patient the appropriate processes for discontinuation from IP or other protocol-required therapies and must discuss with the patient the options for continuation of the SoA (Section 1.3) including different options of follow-up (eg, 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. Patients 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 patients 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 patient (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

7.4. Patient Consent Withdrawal

Patients 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 patient no longer wishes to undergo any follow-up visits, trial procedures, investigator contact, and non-patient contact follow-up (eg, medical records check).

- Discontinuing IP should be distinguished from consent withdrawal for follow-up since the patient 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. Patients requesting consent withdrawal for any follow-up should be informed that it may limit the public health value of the trial.

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

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

7.5. Lost to Follow up

A patient 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 site.

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

- The site must attempt to contact the patient or the patient's family and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient or the patient's family (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have discontinued from the trial and is 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, is essential and required for trial conduct.

There will be a total of 11 in-person trial visits per patient, with windows to aid in scheduling as shown in Table 5. If a patient visit must be scheduled outside the visit window, the Medical Monitor should be contacted.

Table 5: CY 6031 Visit Windows

Visit	Visit Window
Screening	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

All visits should be scheduled based on Day 1

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, patients should wait to take their daily IP dose at the clinic.
- Patient-reported outcomes questionnaires should be completed by patients prior to any other activities. (ie, KCCQ (administered first), EQ-5D-5L, SAQ-7, Patient Global Impression of Change [PGI-C])
- IP should be administered after completion of vital signs, ECG, and blood draws.
- ECGs and vital signs 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 after IP dosing in the clinic at other time points.
- CPET should be performed after other visit activities including IP administration. CMR should occur after CPET if the assessments are performed on the same day.

Please refer to the study manuals for additional details.

8.1.1. Screening Visit

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients 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 patient eligibility.

The screening period will be up to 6 weeks in duration to allow greater flexibility for visit scheduling and the potential for retesting.

The CPET should not be completed until the patient is otherwise deemed eligible. The CPET used for eligibility should be completed within four weeks but not less than one week prior to randomization.

8.1.2. Day 1

Patients 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.

8.1.3. Weeks 2 through 20

Please refer to the SoA (Section 1.3) for Weeks 2-20.

8.1.4. Week 24: End of Treatment Visit

Week 24 is defined as the EOT visit and includes assessments and procedures critical for analysis of the trial's endpoints. These assessments are outlined in the Schedule of Activities. Additionally, the following should be considered in advance of Week 24:

- Contact patients 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 patients 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 the CPET (eg, equipment malfunction), then the Week 24 visit may be postponed by up to 4 weeks and those patients should continue to receive IP until the visit
- Schedule CMR imaging for sub-study (if applicable)
  - For patients who provided consent and completed baseline imaging at screening, schedule the CMR imaging to ensure it is completed within the protocol-defined window. The baseline CMR should be performed within the 6-week screening period prior to randomization.

  - The EOT CMR should be performed after the Week 20 visit, but prior to the last dose of IP at Week 24.

- 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.

8.1.5. Week 28: End of Study Visit

All patients should complete an end of study (EOS) visit:

- For subjects who complete all study visits, the EOS visit will occur at Week 28 (or 4 weeks after a delayed Week 24 visit).
- For subjects who early-terminate IP more than 4 weeks before Week 24 and continue to stay on-study 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).
- For subjects 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 Adverse Events), 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.

Screening assessments for entry into an open-label extension study of aficamten are permitted at the EOS visit. CY 6031 EOS visit assessments must occur before the open-label screening assessments. Assessments for each visit must be done in the order defined by the protocol.

8.1.6. Early Discontinuation Visit

For patients who discontinue the trial prematurely, the activities outlined in the SoA will be completed during an Early Discontinuation visit as soon as possible.

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 will be considered unscheduled assessments.

8.2. Efficacy Assessments

8.2.1. Cardiopulmonary Exercise Testing

All patients 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. Patients

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 echocardiogram, KCCQ, EQ-5D-5L, CGI, PGI-C, NYHA class, SAQ-7, vital signs, ECG, blood sampling, IP administration). Patients naïve to exercise protocols will be familiarized with the technique during screening.

All CPET testing will be symptom-limited and patients 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.

Patients should not engage in strenuous exercise for 24 hours prior to the CPET, and patients should not exercise at all within 12 hours prior to the test. Patients should fast for at least 4 hours prior to CPET. All regularly scheduled medications should be taken as normal. Patients should avoid taking medications that cause drowsiness within 8 hours prior to the test. Weight should be collected immediately prior to each CPET.

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 beta-blocker and IP. Whenever possible, patients should perform exercise testing between three and ten hours after taking beta blocking agents.

If a life-threatening arrhythmia, early ischemia, severe hypotension or other serious finding is identified by the investigator during CPET, the patient will be asked to stop the exercise test, and his/her physicians will be notified of the results. If the patient is performing the screening test, s/he will not be randomized to the trial. Enrolled patients 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

Echocardiography will be done during screening and prior to dosing on Day 1. Echocardiography will be performed 2 hours (±30 min) after dosing in the clinic on Weeks 2, 4, 6, 8, 12, 16, 20, and 24. Echocardiography will also be performed at Week 28.

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 patient. Echocardiograms will be performed after the patient 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 blood draw should be obtained at the scheduled time point and the echocardiograms will follow.

Echocardiographic parameters to be measured will at least include the left ventricular parameters in Table 6 in addition to right heart function metrics detailed in the echocardiography protocol.

Table 6: CY 6031 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	

GLS = global longitudinal strain; IVCT = isovolumic contraction time; IVRT = isovolumic relaxation time; IVST = interventricular septum thickness; LAV = left atrial volume; 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; VTI = velocity time integral.

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. Cardiac Magnetic Resonance

A CMR imaging sub-study will assess the effects of administration of CK-3773274 dosing on cardiac morphology, function, and fibrosis in approximately 100 oHCM patients who are eligible and consent to participate. CMR will be performed during screening period and Week 24. CMR should occur after CPET if the assessments are performed on the same day.

Patients with eGFR <30 mL/min/1.73 m^2 or an allergy to gadolinium may have a non-contrast CMR.

Patients who screen fail and rescreen do not need a repeat CMR.

8.2.4. New York Heart Association Functional Classification

After interviewing the patient, the investigator (or qualified designee) will record the NYHA Functional Classification in the CRF (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 (eg, 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 (eg, walking short distances [20-100 m]). Comfortable only at rest.
- Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

8.2.5. Clinical Global Impression Scale

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

8.2.6. 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

Patients will be asked to complete the KCCQ, EQ-5D-5L, SAQ-7 and PGI-C 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 patients 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, 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 weight will be measured while patient is fully clothed with shoes removed. 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.

Blood pressure and heart rate measurements will be assessed with the patient in a supine or sitting position. Blood pressure and heart rate measurements should be performed with an automated oscillometer after the patient has rested for at least 5 minutes in a quiet setting without distractions (eg, television, cell phones). The position selected for a patient should be the same that is used throughout the trial.

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 average of the 3 blood pressure readings will be recorded in the CRF.

8.3.4. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as 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.

At each time point at which triplicate ECGs are performed, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

Patients 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 patient.

A patient 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 patient'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, PK results or PD results, as determined by the investigator or the Medical Monitor.

All ECG tracings will be kept as part of the patient'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 in the AE section of the CRF. 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 patient'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 **adverse event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation patient 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.

Adverse events 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 adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.
- 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

A **serious adverse event** (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 patient 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 patient 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 adverse event 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 patient 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 patient. It does not influence daily activities and does not require intervention.
Moderate	The event makes the patient uncomfortable. Performance of daily activities are influenced, and intervention is needed.

Severe	The event causes noticeable discomfort and interferes with daily activities. The patient 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 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 non-serious AEs observed by the investigator or reported by the patient that occur after starting the IP through study exit are recorded in the AE eCRF.

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

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

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 patients 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 patient that occur after starting the IP through end of study, or 4 weeks after the last administration of IP, whichever is later, are reported to Cytokinetics on an SAE Report Form within 24 hours following the investigator's knowledge of the event and recorded in the AE eCRF. 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: **CY6031DrugSafety@cytokinetics.com**

Facsimile: **+1 (650) 243-4199**

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 patient 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 patient 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.

Non-serious AEs must be followed until they resolve or until the patient completes the trial, whichever comes first.

Serious AEs still ongoing at the end of study must be followed up until resolution or stabilization, or until the event outcome is provided, eg, death. Reporting after study exit to Drug Safety may continue after the EOS visit.

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 used for the assessment of expectedness of a suspected serious adverse reaction for the purpose of expedited reporting to Health Authorities, IRBs/IECs, and investigators is the reference safety information section of the Investigator's Brochure [CK-3773274 IB].

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.

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

If a woman becomes pregnant while on IP, IP must be discontinued. The investigator must counsel the patient 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 patient, any pregnancy occurring in a female patient, or female partner of a male patient, 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 in the eCRF 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: **CY6031DrugSafety@cytokinetics.com**

Facsimile: **+1 (650) 243-4199**

Details of all pregnancies in female patients and female partners of male patients 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 patients, he or she may learn of an SAE through spontaneous reporting.

Male Patients with Partners Who Become Pregnant

If the partner of a male subject becomes pregnant while on study drug, 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 patient's female partner who becomes pregnant while the male patient 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 Patients Who Breastfeed

If a female patient breastfeeds while on study drug, study drug will be discontinued.

The investigator will collect breastfeeding information on any female patient who breastfeeds while taking the IP through one month after the end of study drug 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 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 patient 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:
  a. Close monitoring of the patient for any AEs/SAEs and laboratory abnormalities.
  b. 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 in the CRF.

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 patient.

8.6. Pharmacokinetics

Eighteen blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of CK-3773274 as specified in the SoA (Section 1.3) and Table 7 below. Samples will be used to evaluate the PK of CK-3773274 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 sample will be recorded. The time of administration of IP on the day of PK sampling will be recorded in the CRF. It is important to provide instructions to patients that they should not take their dose on the day of their clinic visit until in the clinic.

See Table 7 for a summary of PK sampling time points. All samples should be drawn within ±10 minutes of the scheduled time point. 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 7: 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 12	Pre-dose and 2 hours post-dose
Week 16	Pre-dose and 2 hours post-dose
Week 20	Pre-dose and 2 hours post-dose
Week 24 (EOT)	Pre-dose and 2 hours post-dose
Early Discontinuation	untimed

8.7. Genetics

As HCM is a genetic disease, blood and/or DNA from patients 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 mutations that are predictive of patient phenotype, response to IP, resistance to IP, metabolism of IP, susceptibility to developing AEs, or to increase the knowledge and understanding of cardiovascular, 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 patient. CLIA certified genetic test results may be made available to the investigator.

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. Serum for Biomarker Analysis

Blood will be collected for analysis of serum biomarkers. See Section 10.2 for list of biomarkers.

8.9. Serum and Plasma 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.

8.10. Immunogenicity Assessments

No immunogenicity assessments will be done for this trial.

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 patients receiving placebo and those receiving CK-3773274 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 1.5 mL/kg/min for CK-3773274 compared to placebo, a standard deviation (SD) of 3.5 mL/kg/min, accounting for limiting beta-blocker use (less than ~70%), limiting exercise modality of bicycle (less than ~50%) and 10% of patients missing change from baseline data of the primary endpoint, a sample size of 270 patients at randomization ratio of 1:1 (approximately 135 randomized to CK-3773274 and 135 randomized to placebo) 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.

During the study, the aggregate pooled missing data rate and overall pooled SD for the change from baseline in pVO_2 at Week 24 will be monitored periodically in a blinded fashion. If the pooled SD is larger than expected, Cytokinetics may consider increasing the sample size once in order to maintain the intended power.

9.3. Populations for Analyses

The analysis populations are defined in Table 8.

Table 8: Analysis Sets

Analysis Set	Description
All Randomized Set	All randomized patients.
Full Analysis Set	All randomized patients. Patients will be analyzed according to their randomized treatment group assignment. Efficacy endpoints will be analyzed based on the FAS.
Safety Analysis Set	All randomized patients who received at least one dose of IP, CK-3773274 or placebo. Patients will be analyzed by their randomized treatment group assignment. If a patient receives treatment throughout the study that is different than the randomized treatment group assignment, then this patient will be grouped by the actual treatment group
Pharmacokinetics Analysis Set (PKS)	All randomized patients who have at least one evaluable plasma concentration of CK-3773274, provided they have no major protocol violations deviations that could affect the PK of CK-3773274.

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 patients, mean, median, standard deviation, minimum and maximum for continuous variables, and number of patients 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. Listings will include patient ID, demographics, treatment assigned and other relevant items, and sorted by treatment assignment, patient ID and date of assessment. Unless specified otherwise, efficacy, safety and pharmacokinetics analyses will be performed on the full analysis set, safety analysis set and pharmacokinetics analysis set, respectively. 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.

For preservation of the overall type I error rate at two-sided 0.05 for the primary and secondary endpoints will be tested in the following specified order using a closed testing procedure . If the primary endpoint achieves statistical significance at two-sided $p \leq 0.05$, then secondary endpoints will be tested with two-sided 0.05, with their testing being in the sequential order of KCCQ-CSS change from baseline, proportion of patients with $\geq$1 NYHA functional class improvement, post-Valsalva LVOT-G change from baseline, proportion of patients with post-Valsalva LVOT-G < 30 mm Hg, and duration of SRT eligibility for participants who are SRT eligible at baseline, for each after 24 weeks of treatment; then KCCQ-CSS change from baseline, proportion of patients with ≥1 NYHA functional class improvement, post-Valsalva LVOT-G change from baseline, and proportion of patients with post-Valsalva LVOT-G < 30 mmHg, for each after 12 weeks of treatment; and lastly change from baseline to Week 24 in total workload. SRT eligibility is defined as resting or post-Valsalva LVOT-G ≥ 50 mmHg AND NYHA Functional Class ≥ 3. The multiple testing procedure is illustrated in Figure 1. The description of testing sequence will be detailed in the SAP.

9.4.2. Primary Endpoint(s)

The primary endpoint of the study is 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 CK-3773274 and placebo for the target population of potentially treatable CK-3773274 patients despite intercurrent events after a first dose. Missing data will be imputed using multiple imputation method under the missing at random (MAR) assumption. 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 ANCOVA model with treatment group, randomization stratification factors, 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: missing pVO_2 from patients who discontinued CK-3773274 treatment or missing pVO_2 from patients from the placebo arm will be imputed based on the model that is constructed using observed pVO_2 data from the placebo arm. Missing pVO_2 from patients who remained on CK-3773274 treatment will be imputed based on the model that is constructed using observed pVO_2 data from the CK-3773274 arm. 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% confidence interval, and p-value.

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

9.4.3. Secondary Endpoint(s)

The secondary endpoint(s) of the study are:

- Change in KCCQ-CSS from baseline to Week 12 and Week 24
- Proportion of patients with ≥1 class improvement in NYHA Functional Class from baseline to Week 12 and Week 24
- Change in post-Valsalva LVOT-G from baseline to Week 12 and Week 24
- Proportion of patients with post-Valsalva LVOT-G <30 mmHg at Week 12 and Week 24
- Duration of eligibility for septal reduction therapy (SRT) during the 24-week treatment period in patients who were eligible for SRT at baseline. Participants are classified as being SRT eligible if they have NYHA Class ≥3 AND resting or Valsalva LVOT-G ≥50 mmHg.
- Change in total workload during CPET from baseline to Week 24

Change in KCCQ-CSS and change in post-Valsalva LVOT-G from baseline to Week 12 and 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.

Proportion of patients with ≥1 class improvement in NYHA Functional Class from baseline to Week 12 and Week 24 or proportion of patients with post-Valsalva LVOT-G <30 mmHg at Week 12 and Week 24 will be analyzed using Cochran– Mantel–Haenszel (CMH) test stratified by randomization factors. Patient's Week 20 NYHA Functional Class will be used when Week 24 NYHA Functional Class is not available. Total duration of SRT eligibility (NYHA Class ≥3 AND resting or Valsalva LVOT-G ≥50 mmHg) during the 24-week treatment period will be analyzed using an ANCOVA model with treatment group and randomization stratification factor beta blocker use/no use as fixed effects adjusting for significant baseline characteristics. The p-value and 95% CI will be obtained using exact method. Adjustment of multiplicity of the primary and secondary endpoints is specified in Section 9.4.1.1.

9.4.4. Exploratory Endpoint(s)

The exploratory endpoints of the study are:

- Compared with baseline, proportion of patients 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 patients with improvement in KCCQ-CSS ≥5 points at Week 12 and Week 24
- Proportion of patients with resting LVOTG <30 mmHg, post-Valsalva LVOTG <50 mmHg, and NYHA Functional Class I at Week 12 and Week 24
- Proportion of patients with resting LVOTG <30 mmHg, post-Valsalva LVOTG <50 mmHg, and ≥1 class improvement in NYHA Functional Class at Week 12 and Week 24
- Proportion of patients who are eligible for SRT at Week 24 among patients who were eligible for SRT at baseline
- Change from baseline to Week 24 in:
  - VE/VCO_2 slope
  - $VO_2 \times$ systolic BP
  - VAT
- Change from baseline to Week 24 in individual responses to the EQ-5D-5L
- Change from baseline to Week 24 in summary and individual domain scores for the SAQ-7
- Change from baseline to Week 24 in echocardiographic measurements of cardiac structure and of systolic function including:
  - LVEF
  - LVESV and LVEDV
  - Left atrial volume
- Change from baseline values in NT-pro-BNP, hs-cardiac-TnI and other biomarkers through Week 24
- Change from baseline to Week 24 in CMR measurements of:
  - LV mass index
  - LVEF

  - Septal and free wall thickness
  - Left atrial volume index
  - LVESV
  - LVEDV
- Pharmacokinetic 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 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. Change from baseline in parameters of CMR measurements and 5Q-5D-5L will be analyzed using an ANCOVA model with baseline as covariate, randomization stratification factors and treatment group as fixed effects. Median and median difference of NT-pro-BNP between treatment group and 95% confidence of the median difference will be presented. Log transformed NT-pro-BNP 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.

9.4.5. Safety Analysis

Safety analyses will be performed on the 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 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 patients 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 patient listings.

Patient 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. Patient incidence of new onset persistent atrial fibrillation, patient incidence of appropriate ICD discharges and aborted sudden cardiac death, patient 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 CK-3773274 and PK parameter C_{max} and C_{trough} will be summarized using descriptive statistics including mean, standard deviation, geometric mean, coefficient of variation, median, and range. Geometric mean concentrations over time will be graphically displayed.

9.4.7. Patient Disposition

The number of patients who are randomized, who complete the planned treatment, and who prematurely discontinue from the planned treatment and/or the study will be presented by treatment group and overall. Reasons for premature discontinuation as recorded on the End of Study page of the CRF will also be summarized.

9.4.8. Demographics and Other Baseline Characteristics

Patient 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. Data Monitoring Committee

An unblinded DMC will regularly review the emerging data for safety monitoring purpose. The DMC or Cytokinetics can require an ad hoc DMC meeting at any time. No study activities will be suspended during the safety review. 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 ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, 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 patients.

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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (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 patient or his/her legally authorized representative and answer all questions regarding the trial.

Patients must be informed that their participation is voluntary. Patients 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.

Patients 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 patient or the patient's legally authorized representative.

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

10.1.4. Data Protection

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

The patient 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 patient who will be required to give consent for their data to be used as described in the ICF.

The patient 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.

10.1.5. Committees Structure

The trial organization will include an Executive Committee (EC), Steering Committee (SC) and 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 patients during the conduct of the trial. The DMC will include an external cardiologist with relevant expertise and other designated members with relevant expertise, eg, 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 patient 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 patient 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 (eg, 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 patients 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 study 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 patient 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 patients.

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 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 patients 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 patient and should assure appropriate patient therapy and/or follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 9 will be performed by the central laboratory. If an issue arises with the central laboratory, a local laboratory can be used for eligibility after approval from the sponsor. If the results used for eligibility cannot be obtained from the central laboratory, a local laboratory may be used with the approval of the sponsor. If a local laboratory is used, duplicate samples must be drawn at the same time and sent to the central laboratory. Pregnancy testing for WOCBP at time points after screening may be performed locally.

Protocol-specific requirements for inclusion or exclusion of patients 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 9: Protocol-Required Safety Laboratory Assessments

Chemistry		Urinalysis	Hematology	Other Assessments
Sodium	Total bilirubin	Specific gravity	Hemoglobin	CK-3773274 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 (SGOT)	Bilirubin	MCH	hs-cTnI
Urea	ALT (SGPT)		MCHC	Other biomarkers including: Galectin-3, PINP, TIMP-1, CITP and Soluble ST2
Creatinine	GGT		WBC	
Iron	TIBC		Platelets	
Glucose	Ferritin			PT-INR
Total protein	Bicarbonate			

ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); CITP = collagen type 1; 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; PINP = procollagen type 1 N-terminal propeptide; PT-INR = prothrombin time/international normalized ratio; RBC = red blood cell; RDW = red cell distributions width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; Soluble ST2 = soluble suppression of tumorigenicity 2; TIBC= total iron binding protein; TIMP-1 = tissue inhibitor matrix metalloproteinase 1; WBC = white blood cell

[a] A pregnancy test is required for WOCBP; FSH only at screening if needed. If a urine pregnancy test is positive, a serum pregnancy test should be performed.

[b] NT-proBNP results will be masked throughout the study.

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 (eg, 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 (eg, 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 patient'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 patient

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 patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

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 methods of birth control are 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 patient.

10.4. Appendix 4: Genetics

Use/Analysis of DNA

Genetic variation may impact a patient'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, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from patients 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 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 an SAE within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The AE CRF 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

CK-3773274 **must** be discontinued permanently and the patient should be followed according to the following recommendations for possible DILI, if ALL of the criteria below are met:

- TBL >2 × 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 (eg, 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 (eg, rhabdomyolysis, hemolysis)

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

For patients 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 patient 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 patient must be discussed and agreed upon unanimously by the patient, investigator, and Medical Monitor. Patients 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. Patients who clearly meet the criteria for permanent discontinuation must never be rechallenged.

Additional Clinical Assessments and Observation

All patients 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 patient'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 patient 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 patient 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 corresponding CRFs.

10.6. Appendix 6: Abbreviations

Table 10: List of Abbreviations

Abbreviation/Term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
CBC	Complete blood count
CGI	Clinical Global Impression scale
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum plasma concentration observed
C_{trough}	Trough plasma concentration observed
CMH	Cochran–Mantel–Haenszel
CMR	Cardiac magnetic resonance
CPET	Cardiopulmonary exercise testing
CRF	Case report form
CRO	Contract research organization
CV	Cardiovascular
CYP	Cytochrome P450
DILI	Drug induced liver injury
DMC	Data monitoring committee
EC	Executive Committee
ECG	Electrocardiogra(m/phy)
ED	Early discontinuation
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQol 5-dimension 5-level instrument
FAS	Full analysis set
FSH	Follicle-stimulating hormone
FU	Follow up
GCP	Good Clinical Practice

Abbreviation/Term	Explanation
GLP	Good Laboratory Practice
HCM	Hypertrophic cardiomyopathy
HIPAA	Health Insurance Portability and Accountability Act
hs-cTnI	High sensitivity cardiac troponin I
IB	Investigator's Brochure
ICD	Implantable cardioverter defibrillators
ICF	Informed consent form
ICH	International Council for Harmonisation
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
IWRS	Interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAM	Lactational amenorrhoea method
LKM1	Liver Kidney Microsomal antibody 1
LSM	Least squares mean
LV	Left ventricle(ular)
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
LVFS	Left ventricular fractional shortening
LVOT	Left ventricular outflow tract
LVOT-G	Left ventricular outflow tract gradient
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-investigational medicinal product
NT-proBNP	n-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association

Abbreviation/Term	Explanation
oHCM	Obstructive hypertrophic cardiomyopathy
PD	Pharmacodynamics
PDS	Pharmacodynamics analysis set
PGI-C	Patient Global Impression of Change scale
PK	Pharmacokinetics
PKS	Pharmacokinetics analysis set
PRO	Patient-reported outcomes
pVO_2	Peak oxygen uptake
RBC	Red blood cell
RER	Respiratory exchange ratio
SAE	Serious adverse event
SAS	Safety analysis set
SAQ-7	Seattle Angina Questionnaire -7
SC	Steering Committee
SD	Standard deviation
SoA	Schedule of activities
SoC	Standard of care
TBL	Total bilirubin
ULN	Upper limit of normal
VAT	Ventilatory anaerobic threshold
WOCBP	Women of childbearing potential

10.7. Appendix 7: Protocol Amendment History

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

11. REFERENCES

Chuan, P., Sivaramakrishnan, S., Ashley, E. A. and Spudich, J. A. (2012). "Cell-intrinsic functional effects of the α-cardiac myosin arg-403-gln mutation in familial hypertrophic cardiomyopathy." Biophysical journal 102(12): 2782-2790.

Criteria Committee of the New York Heart, A. (1994). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston: Little, Brown & Co.

Elliott, P. M., Anastasakis, A., Borger, M. A., Borggrefe, M., Cecchi, F., Charron, P., et al. (2014). "2014 esc guidelines on diagnosis and management of hypertrophic cardiomyopathy: The task force for the diagnosis and management of hypertrophic cardiomyopathy of the european society of cardiology (esc)." European Heart Journal 35(39): 2733-2779.

Gersh, B. J., Maron, B. J., Bonow, R. O., Dearani, J. A., Fifer, M. A., Link, M. S., et al. (2011). "2011 accf/aha guideline for the diagnosis and treatment of hypertrophic cardiomyopathy." Journal of the American College of Cardiology 58(25): e212-e260.

Husser, D., Ueberham, L., Jacob, J., Heuer, D., Riedel-Heller, S., Walker, J., et al. (2018). "Prevalence of clinically apparent hypertrophic cardiomyopathy in germany-an analysis of over 5 million patients." PLOS ONE 13(5): e0196612-e0196612.

Kristensen, S. D., Knuuti, J., Saraste, A., Anker, S., BÃ¸tker, H. E., Hert, S. D., et al. (2014). "2014 esc/esa guidelines on non-cardiac surgery: Cardiovascular assessment and management: The joint task force on non-cardiac surgery: Cardiovascular assessment and management of the european society of cardiology (esc) and the european society of anaesthesiology (esa)." European Heart Journal 35(35): 2383-2431.

Magnusson, P., Palm, A., Branden, E. and Morner, S. (2017). "Misclassification of hypertrophic cardiomyopathy: Validation of diagnostic codes." Clinical epidemiology 9: 403-410.

Marian, A. J. and Braunwald, E. (2017). "Hypertrophic cardiomyopathy: Genetics, pathogenesis, clinical manifestations, diagnosis, and therapy." Circulation research 121(7): 749-770.

Maron, B. J. (2018). "Clinical course and management of hypertrophic cardiomyopathy." New England Journal of Medicine 379(20): 655-668.

Maron, M. S., Iacopo, O., Andrey, G. Z., Mark, S. L., Natesa, G. P., Jeffery, T. K., et al. (2006). "Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction." Circulation 114(21): 2232-2239.

Maron, M. S., Rowin, E. J., Olivotto, I., Casey, S. A., Arretini, A., Tomberli, B., et al. (2016). "Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy." Journal of the American College of Cardiology 67(12): 1399-1409.

Ommen, S. R., Mital, S., Burke, M. A., Day, S. M., Deswal, A., Elliott, P., et al. (2020). "2020 aha/acc guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy." Circulation 142(25): e558-e631.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., et al. (2016). "2016 esc guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (esc)developed with the special contribution of the heart failure association (hfa) of the esc." European Heart Journal 37(27): 2129-2200.

Pujades-Rodriguez, M., Guttmann, O. P., Gonzalez-Izquierdo, A., Duyx, B., O'Mahony, C., Elliott, P., et al. (2018). "Identifying unmet clinical need in hypertrophic cardiomyopathy using national electronic health records." PLOS ONE 13(1): e0191214-e0191214.

Sommese, R. F., Sung, J., Nag, S., Sutton, S., Deacon, J. C., Choe, E., et al. (2013). "Molecular consequences of the r453c hypertrophic cardiomyopathy mutation on human β-cardiac myosin motor function." Proceedings of the National Academy of Sciences 110(31): 12607-12612.

Spudich, J. A., Aksel, T., Bartholomew, S. R., Nag, S., Kawana, M., Yu, E. C., et al. (2016). "Effects of hypertrophic and dilated cardiomyopathy mutations on power output by human β-cardiac myosin." The Journal of Experimental Biology 219(2): 161-167.

Toepfer, C. N., Wakimoto, H., Garfinkel, A. C., McDonough, B., Liao, D., Jiang, J., et al. (2019). "Hypertrophic cardiomyopathy mutations in mybpc3 dysregulate myosin." Science Translational Medicine 11(476): eaat1199.

Wilson, W. S., Criley, J. M. and Ross, R. S. (1967). "Dynamics of left ventricular emptying in hypertrophic subaortic stenosis: A cineangiographic and hemodynamic study." American Heart Journal 73(1): 4-16.