Protocol: CY 6021

Title: A Multi-Center, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, and Tolerability and Pharmacodynamics of CK3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy

NCT04219826

Approval Date: 09NOV2021

PROTOCOL CY 6021

A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CK-3773274 IN ADULTS WITH SYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY

Protocol Version and Date:	Amendment 04 dated 09 November 2021
Previous Version(s):	Amendment 03 dated 17 February 2021 Amendment 02 dated 13 July 2020 Amendment GBR-01 dated 24 January 2020 Amendment 01 dated 09 August 2019 Original Protocol dated 29 July 2019
Product:	CK-3773274
Regulatory Authority Identifier Number(s):	IND 138814 EudraCT Number 2019-002785-12
Sponsor:	Cytokinetics, Inc. 280 East Grand Avenue South San Francisco, CA 94080, USA

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	CY 6021
Protocol Title:	A Multi-Center, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy
Protocol Version and Date:	Amendment 04 dated 09 November 2021

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 Conference on 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 study in accordance with the protocol referenced herein.

Investigator Name: _____ Date: _____

Investigator Signature: _____

PROTOCOL APPROVAL PAGE

Protocol Number:	CY 6021
Protocol Title:	A Multi-Center, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy
Protocol Version and Date:	Amendment 04 dated 09 November 2021
Sponsor:	Cytokinetics, Inc. 280 East Grand Avenue South San Francisco, CA 94080

[redacted], MD, PhD
Associate Medical Director, Clinical Research, Cardiovascular

Date:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 03	17 February 2021
Amendment 02	13 July 2020
Amendment GBR-01	24 January 2020
Amendment 01	09 August 2019
Original Protocol	29 July 2019

Amendment 04 (09 November 2021)

The purpose of this amendment is to describe the design update for Cohort 4.

No updates to the Benefit/Risk Assessment (Section 2.3) were warranted [redacted]

Table 1: Protocol Amendment Summary of Changes

Section # and Name	Description of Change	Brief Rationale
Global	Update of protocol version date. Editorial (formatting, typographical, and grammatical) corrections throughout the protocol.	Administrative changes.
Global	Replaced "oHCM" with "HCM" in many places throughout	To include patients with oHCM and nHCM in this study
Study Title	Removed "Left Ventricular Outflow Tract Obstruction"	To allow inclusion of patients with nHCM in Cohort 4
Section 1.1 Synopsis	Clarified objectives and endpoints relevant to specific cohorts Added objectives and endpoints for Cohort 4	Updated to reflect changes made to the body of the protocol
Section 1.2 Schema	Added Cohort 4 Study Schema	To differentiate Cohort 4 from previous cohorts.
Section 1.3 Schedule of Activities	Added "(Cohorts 1, 2, and 3)" to the title of the section	To identify that Section 1.3 only pertains to Cohorts 1, 2, and 3
Section 1.4 Schedule of Activities	Added separate schedule of activities for patients enrolled in Cohort 4	To clarify the laboratory and PRO assessments for patients enrolled in Cohort 4.

Table 1: Protocol Amendment Summary of Changes (Continued)

Section # and Name	Description of Change	Brief Rationale
Section 1.5 Key Contacts	Updated contact information for Sponsor's Study Contact and Sponsor's Medical Monitor	Administrative changes
Section 2.1 Study Rationale	[redacted]	To specify [redacted]
Section 2.2.1 Background, Hypertrophic Cardiomyopathy	[redacted]	To justify [redacted]
Section 2.2.2.1 Overview of Nonclinical Studies [redacted]	Updated results from studies [redacted]	To provide updated information [redacted]
Section 2.3 Benefit/Risk Assessment	Added information [redacted]	To describe updated design for Cohort 4.
Section 3 Objectives and Endpoints	Clarified objectives and endpoints relevant to specific cohorts Added objectives and endpoints for Cohort 4	[redacted]
Section 4.1 Overall Study Design	Updated language to describe Cohort 4 design	To describe updated design for Cohort 4.
Section 4.2 Scientific Rationale for Study Design	Updated language to describe Cohort 4 design	To describe updated design for Cohort 4.
Section 4.3 Justification for Dose	Added justification for the dosing regimen to be used in Cohort 4	To provide the rationale for the selected dosing regimen.
Section 5.1 Inclusion Criteria	Added Criteria 114 and 115	New inclusion requirements for Cohort 4.
Section 5.2 Exclusion Criteria	Updated language in Criterion 205	To clarify that patients who have undergone SRT are eligible for Cohort 4.
	Updated language in Criterion 208	To clarify that disopyramide is only excluded for Cohorts 1, 2 and 4.
	Added Criterion 224	New exclusion requirement for Cohort 4.

Table 1: Protocol Amendment Summary of Changes (Continued)

Section # and Name	Description of Change	Brief Rationale
Section 5.4 Screen Failures	Added requirements for Cohort 4	To provide definition for patients who screen fail for Cohort 4.
Section 6.5.1 Drug-Drug Interactions	[redacted]	To provide updated information on potential drug-drug interactions.
Section 6.6 Dose Modification Table 7	Specified dosing for Cohort 4.	To define the dosing for Cohort 4.
Section 6.6.1 Scheduled Dose Modification	Reorganized paragraphs and clarified specific to cohorts. Added specific language for Cohort 4	To provide consistency on language
Section 6.6.2 Safety Considerations	Added language requiring approval from the Medical Monitor prior to restarting IP after interruption.	To provide additional oversight from the study Medical Monitor.
Section 6.6.3 Dose Level Stopping Rules	[redacted]	To specify dose level stopping rules in Cohort 4.
Section 6.7 Access to Investigational Product after the End of the Study	[redacted]	[redacted]
Section 8.1 Efficacy Assessments	Added language [redacted]	[redacted]
Section 8.1.1 Efficacy Assessments - Echocardiography	[redacted]	[redacted]

Table 1: Protocol Amendment Summary of Changes (Continued)

Section # and Name	Description of Change	Brief Rationale
Section 8.1.3 Efficacy Assessments – Health Status and Health-related Quality of Life	[redacted]	[redacted]
Section 8.3 Adverse Events and Serious Adverse Events	Added language to specify safety reporting procedures.	To clarify safety reporting.
Section 9.2 Sample Size Determination	Added language describing Cohort 4	To provide sample size information for Cohort 4.
Section 9.4.4 Statistic Analysis – Pharmcodynamic Endpoints	Added language to specify endpoints that are relevant to specific cohorts.	To clarify endpoints for Cohort 4.
Section 9.4.5 Other Exploratory Endpoints	[redacted]	[redacted]
Section 9.4.6 Patient Disposition	Added language for Cohort 4	Cohort 4 is an active IP cohort; all patients are assigned to CK-3773274.
Section 9.4.11 Echocardiography Analysis	Added Cohort 4	To include Cohort 4 as part of Echocardiography Analysis
Section 9.4.12 Health Safety and Health-related Quality of Life Analysis	To provide information on quality of life analyses specific to Cohort 4	To address the effect of CK-3773274 in patients with nHCM in Cohort 4.
Section 10.2 Appendix 2: Clinical Laboratory Tests Table 12	[redacted]	[redacted]
Section 10.5 Appendix 5: Genetics	[redacted]	The analysis is not being performed.

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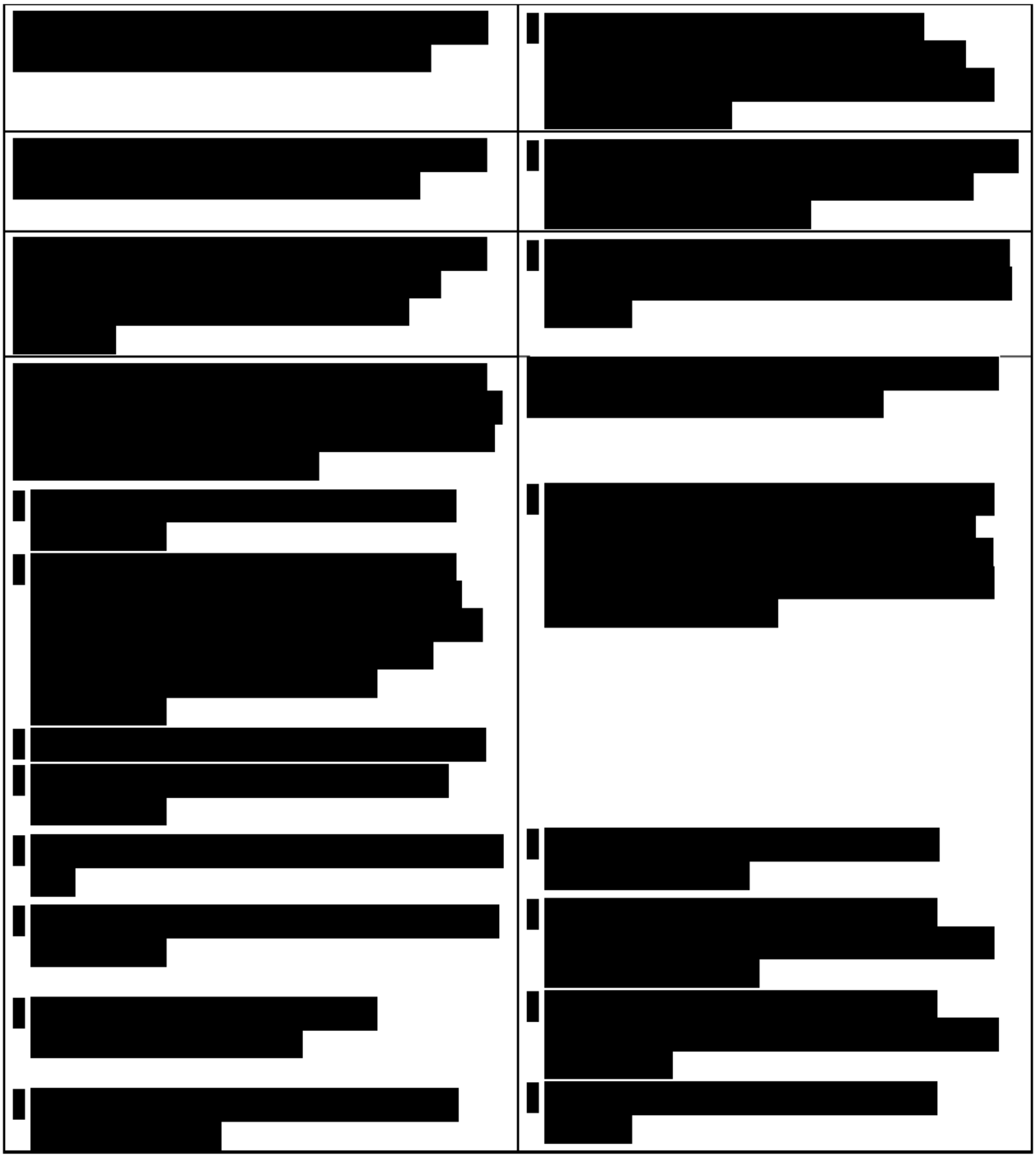
1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Investigational Product(s) (IP): CK-3773274	
Name of Active Ingredient(s): CK-3773274	
Protocol Title: A Multi-Center, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy	
Phase of Development: Phase 2	
Rationale: This is the first study of CK-3773274 in patients with hypertrophic cardiomyopathy (HCM). 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.	
Objectives and Endpoints:	
Objectives	***Endpoint(s)***
Primary	
To determine the safety and tolerability of CK-3773274 in patients with symptomatic HCM	• Patient incidence of reported adverse events (AEs) • Patient incidence of reported serious adverse events (SAEs) • Patient incidence of left ventricular ejection fraction (LVEF) <50%
Secondary	
To describe the concentration-response relationship of CK-3773274 on the resting and post-Valsalva left ventricular outflow tract gradient (LVOTG) on echocardiogram over 10 weeks of treatment in patients with oHCM (Cohorts 1, 2, 3 only)	• Slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the resting LVOTG • Slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the post-Valsalva LVOTG
To describe the dose response relationship on LVOT-G (resting and Valsalva) of CK-3773274 in patients with symptomatic oHCM (Cohorts 1, 2, 3 only)	• Change from baseline in resting and post-Valsalva LVOTG over time as a function of dose • Change from baseline in resting and post-Valsalva LVOTG to Week 10
To evaluate the concentration-response relationship of CK-3773274 on resting left ventricular ejection fraction (LVEF) over 10 weeks of treatment in patients with HCM	• Slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the resting LVEF

To evaluate the plasma concentrations of CK-3773274 in patients with HCM	• Observed maximum plasma concentration (C_{max}) and trough plasma concentration (C_{trough}) for CK-3773274 during dosing
Exploratory	
[redacted]	• [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



Overall Design:

This is a Phase 2, multi-center, randomized, placebo-controlled, double-blind, dose finding study in patients with symptomatic HCM.

Cohorts 1 and 2: Two sequential cohorts of patients with oHCM will be enrolled in a randomized, placebo-controlled, double blind fashion. Within each cohort, patients will be randomized 2:1 to active or placebo treatment and receive up to three escalating doses of CK-3773274 or placebo based on echocardiographic guidance. Patients receiving disopyramide are excluded from Cohorts 1 and 2. Overall, the treatment duration will be 10 weeks with a 4-week follow-up period after the last dose

Cohort 3: A third cohort will be enrolled consisting of patients with oHCM whose background HCM therapy must include disopyramide. Within this cohort, patients will receive up to three escalating doses of CK-3773274, titrated based on echocardiographic guidance. Overall, the treatment duration will be 10 weeks with a 4-week follow-up period after the last dose.

Cohort 4: A fourth cohort will be enrolled consisting of patients with nHCM. Background therapy can include beta-blockers and/or calcium channel blockers, either as monotherapy or in combination. Patients receiving disopyramide are excluded from Cohort 4. Within this cohort, patients will receive up to three doses of CK-3773274, titrated based on echocardiographic guidance. Overall, the treatment duration will be 10 weeks with a 4-week follow-up period after the last dose.

Study Center(s):

This study will take place at approximately 30 sites in North America and Europe.

Number of Patients:

Approximately 95 patients will be enrolled in the study.

In Cohorts 1 and 2, each cohort will comprise approximately 18 patients who will be randomized to investigational product (IP): CK-3773274 or placebo.

In Cohort 3, approximately 8-12 patients will be assigned to CK-3773274.

In Cohort 4, approximately 30-40 patients will be assigned to CK-3773274.

Key Eligibility Criteria:

A full listing of eligibility criteria can be found in Section 5.1.

Inclusion Criteria

Patients who meet all the following criteria at screening may be included in the study:

- Males and females between 18 and 85 years of age at screening.
- Body weight is ≥45 kg at screening.
- Diagnosed with HCM per the following criteria:
  - Has left ventricular (LV) hypertrophy with non-dilated LV chamber in the absence of other cardiac disease.
  - Has minimal wall thickness ≥15 mm (minimal wall thickness ≥13 mm is acceptable with a positive family history of HCM or with a known disease-causing gene mutation).
- Adequate acoustic windows for echocardiography.
- For Cohorts 1, 2, and 3, has LVOT-G during screening as follows:
  - Resting gradient ≥50 mmHg

  OR
  - Resting gradient ≥30 mmHg and <50 mmHg with post-Valsalva LVOT-G ≥50 mmHg
- LVEF ≥60% at screening.
- NYHA Class II or III at screening.
- Patients on beta-blockers, verapamil, diltiazem, or ranolazine should have been on stable doses for >4 weeks prior to randomization and anticipate remaining on the same medication regimen during the study.
- For Cohort 3: Patients must be taking disopyramide. Patients should have been on stable disopyramide doses for >4 weeks prior to screening and anticipate remaining on the same medication regimen during the study.
- For Cohort 4 has resting and post-Valsalva LVOT-G < 30 mmHg at the time of screening
- For Cohort 4 has elevated NT-proBNP > 300 pg/mL at the time of screening

Exclusion Criteria

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

- Aortic stenosis or fixed subaortic obstruction.
- Known infiltrative or storage disorder causing cardiac hypertrophy that mimics HCM (eg, Noonan syndrome, Fabry disease, amyloidosis).
- History of LV systolic dysfunction (LVEF <45%) at any time during their clinical course.
- Documented history of current obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.
- Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the study period (Cohorts 1, 2, and 3 only). Patients having undergone septal reduction therapy > 12 months prior to screening who remain symptomatic from nHCM, and who meet all other criteria for inclusion, may be enrolled in Cohort 4.
- For Cohorts 1, 2 and 4: Has been treated with disopyramide or antiarrhythmic drugs that have negative inotropic activity within 4 weeks prior to screening. (For Cohort 3, use of disopyramide is required).
- Paroxysmal atrial fibrillation or flutter documented during the screening period.
- Paroxysmal or permanent atrial fibrillation requiring rhythm restoring treatment (eg, direct-current cardioversion, ablation procedure, or antiarrhythmic therapy) ≤6 months prior to screening. (This exclusion does not apply if atrial fibrillation has been treated with anticoagulation and adequately rate-controlled for >6 months.)
- History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.
- Has received prior treatment with CK-3773274 or is currently receiving mavacamten.
- For Cohort 4: has any documented history of LVOT-G ≥ 30 mmHg at rest, with Valsalva, or with exercise (for subjects who have had prior septal reduction therapy, this exclusion criteria only applies to gradients detected following septal reduction therapy).

IP Dosing Groups and Duration:

The dose escalation scheme is shown in Table 2.

Table 2: CY 6021 Dosing Scheme

Cohort	Dose 1	Dose 2	Dose 3
Cohort 1	5 mg	10 mg	15 mg
Cohort 2	10 mg	20 mg	30 mg
Cohort 3	5 mg	10 mg	15 mg
Cohort 4	5 mg	10 mg	15 mg

For Cohorts 1, 2, 3

Each patient will receive Dose 1 for 2 weeks. At Week 2, the patient will have an echocardiogram 2 hours following administration of their dose of IP. Patients will up-titrate to Dose 2 if either of the following conditions are met on echocardiography:

- Resting LVOT-G ≥30 mmHg and the biplane LVEF ≥50%

OR

- Resting LVOT-G <30 mmHg, post-Valsalva LVOT-G ≥50 mmHg, and the biplane LVEF ≥50%

Otherwise, the patient will remain on Dose 1.

After 2 more weeks on the assigned dose (ie, Week 4), 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 either of the following conditions are met on echocardiography:

- Resting LVOT-G ≥30 mmHg and the biplane LVEF ≥50%

OR

- Resting LVOT-G <30 mmHg, post-Valsalva LVOT-G ≥50 mmHg, and the biplane LVEF ≥50%

Otherwise, the patient will remain on the same dose.

If at a scheduled echocardiogram (Week 2, Week 4 or Week 6), the LVEF is <50%, then the patient will be returned to a prior dose level or to placebo if the patient is on Dose 1. If a patient's dose is reduced to placebo or IP is discontinued (from Dose 1), then the patient will remain on placebo (Cohorts 1 and 2) or off IP (Cohort 3) for the duration of the study. If the scheduled echocardiogram shows a LVEF of < 40% at any time, then the study drug will be paused independent of the current dose.

If an unscheduled echocardiogram read by the Echo Cardiologist shows an LVEF < 50%, and the patient has symptoms of low cardiac output, the patient will be discontinued from study drug.

Eligible patients will be followed until they complete the Week 14 assessments.

For Cohort 4

Each patient will receive Dose 1 for 2 weeks. At Week 2, the patient will have an echocardiogram 2 hours following administration of their dose of IP. Patients will up-titrate to Dose 2 if LVEF ≥ 55% on echocardiogram. Otherwise, the patient will remain on the same dose.

After 2 more weeks on the assigned dose, 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 LVEF ≥ 55% on echocardiogram. Otherwise, the patient will remain on the same dose.

If at a scheduled echocardiogram (Week 2, Week 4 or Week 6), the LVEF is <50%, then the patient will be returned to a prior dose level or IP will be discontinued if the patient was on Dose 1. If discontinued, then the patient will remain off drug for the duration of the study. If the scheduled echocardiogram shows a LVEF of < 40% at any time, then the study drug will be temporarily discontinued independent of the current dose.

If an unscheduled echocardiogram read by the Echo Cardiologist shows an LVEF < 50%, and the patient has symptoms of low cardiac output, the patient will be permanently discontinued from study drug.

Eligible patients will be followed until they complete the Week 14 assessments.

Data Monitoring Committee:

Representatives of Cytokinetics and the Steering Committee (SC) will conduct interim reviews of the available blinded and unblinded safety, echocardiographic, and de-identified PK data (Cohorts 1 and 2) to recommend the dose levels of CK-3773274 to be administered in the next cohort. An unblinded Data Monitoring Committee (DMC) will review the recommendations along with the available safety, and echocardiographic data. The DMC may either endorse the recommendation or suggest a change in study conduct, including alteration of planned dosing regimen.

Statistical Methods:

Safety analyses will be performed on the safety analysis set which includes all patients who received at least one dose of IP, grouped according to the maximum actual dose received. The pharmacodynamics analysis set (PDS) will consist of all patients who received any amount of IP and have a baseline and at least one post-baseline echocardiographic assessment during the double-blind treatment period by actual treatment group, CK-3773274 or placebo. 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 tabulated by system organ class and preferred term.

Descriptive statistics by cohort, treatment, and/or dose will be provided for selected demographics, safety, PK, and PD data.

The slope of the relationship of the plasma concentrations of CK-3773274 on select echocardiographic variables measured at baseline and Weeks 2, 4, 6, and 10 (eg, LVEF, resting or post-Valsalva LVOT-G) will be evaluated using mixed-effect repeated measures model for all planned measurements of LVOT-G, with terms for the baseline value, and time-matched value of the plasma concentrations of CK-3773274, with a random intercept assumption. The models will be based on PDS and performed by cohort and/or in Cohorts 1 and 2 combined. Similar models may be fitted including time-matched CK-3773274 dose level.

The treatment effect on secondary and exploratory endpoints relating to change from baseline to Week 10 will be evaluated in PDS, Cohorts 1 and 2 only, using analysis of covariance for continuous variables (with terms for treatment, and baseline value) and logistic regression for categorical or binary data. The analyses will test the null hypothesis that there is no treatment difference in change from baseline to Week 10 between patients receiving placebo and those receiving CK-3773274 by cohort. The analyses may be repeated with data combined across Cohorts 1 and 2, in which case the cohort may be used as the stratification factor.

The effect of the PK of CK-3773274 on select echocardiographic variables will be evaluated using a concentration bin analysis of variance in PDS, Cohorts 1 and 2 only, by cohort and/or in Cohorts 1 and 2 combined. Plasma concentration bin as a categorical variable will be used in the analysis.

The effect of CK-3773274 dose on echocardiographic variables will also be evaluated including the dose as a continuous variable in the analysis.

Secondary and exploratory endpoints related to change from baseline and responder endpoints in patients receiving disopyramide (Cohorts 3 and 4) will be evaluated using descriptive summaries.

The effect of background disopyramide on PK will be assessed by analysis of variance (ANOVA) models including the data from Cohort 1 subjects randomized to CK-3773274 and from Cohort 3 subjects. The models will be fit for natural log-transformed plasma concentrations: Day 1 (1 hour post-dose), C_{trough}, and C_{max}.

The effect of background disopyramide therapy on pharmacodynamic response over time through Week 10 will be assessed by analysis of covariance (ANCOVA) models for change from baseline in LVOT-G at rest, LVOT-G post-Valsalva, and LVEF, including the data from Cohort 1 subjects randomized to CK-3773274 and from Cohort 3 subjects assigned to CK-3773274.

The slope of change from baseline to Week 10 in Health Status and Health-related Quality of Life endpoints will be evaluated using a mixed-effect repeated measures model in the US subjects randomized to Cohort 2. The treatment effect on change from baseline to Week 10 endpoints will be evaluated using analysis of covariance. Change from baseline endpoints in the patients assigned to receive CK-3773274 in Cohorts 3 or 4 will be evaluated using descriptive summaries. Individual responses to the HCM Global Impression of Status and Global Impression of Change questionnaires will be summarized categorically.

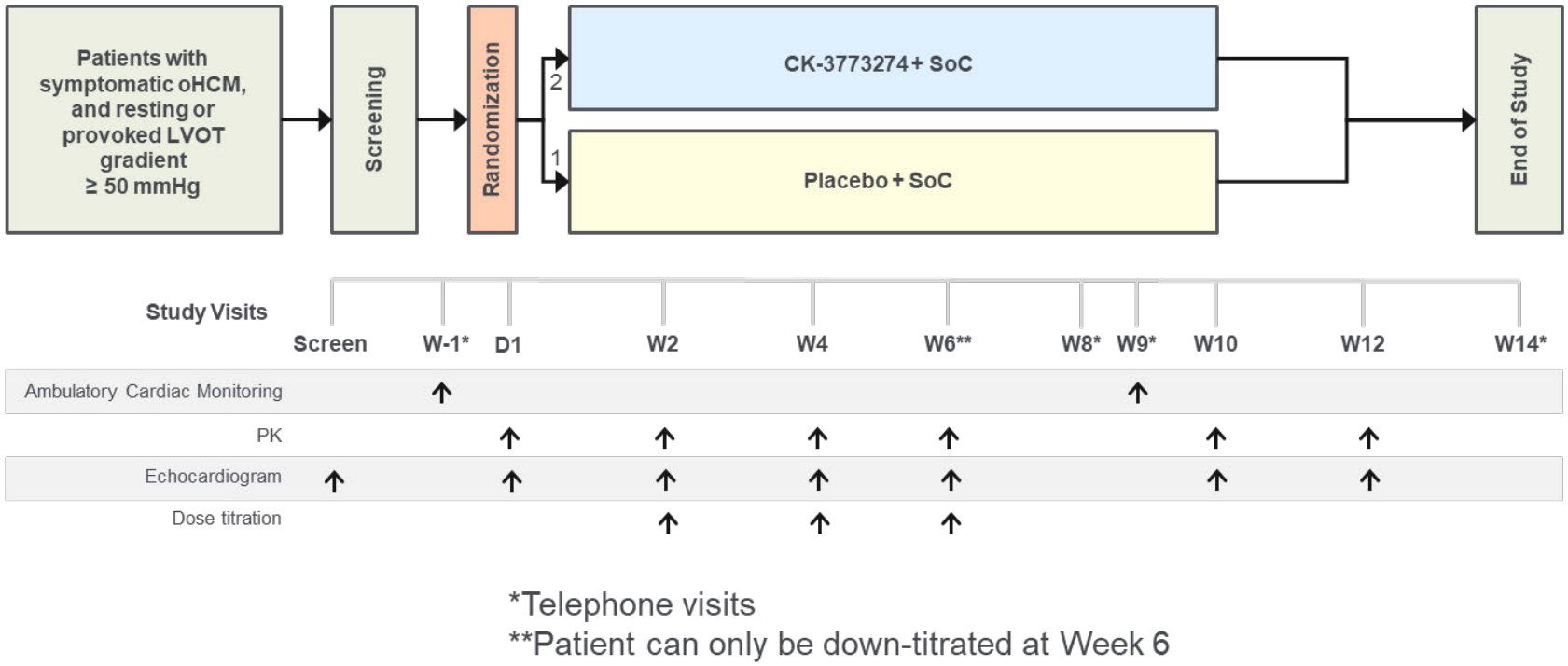
Continuous variables may be log transformed prior to the analysis. Analyses will be further detailed in the Statistical Analysis Plan.

Interim data analyses (Cohorts 1 and 2 only) will be conducted by representatives of Cytokinetics and the SC in a blinded manner and by the DMC in an unblinded manner to consider recommendations for the dose levels of CK-3773274 to be administered in the next cohort. An interim analysis of cohort data will occur after at least 10 randomized patients have completed the Week 6 visit and when the PK and echocardiography data from those visits are available.

1.2. Schema

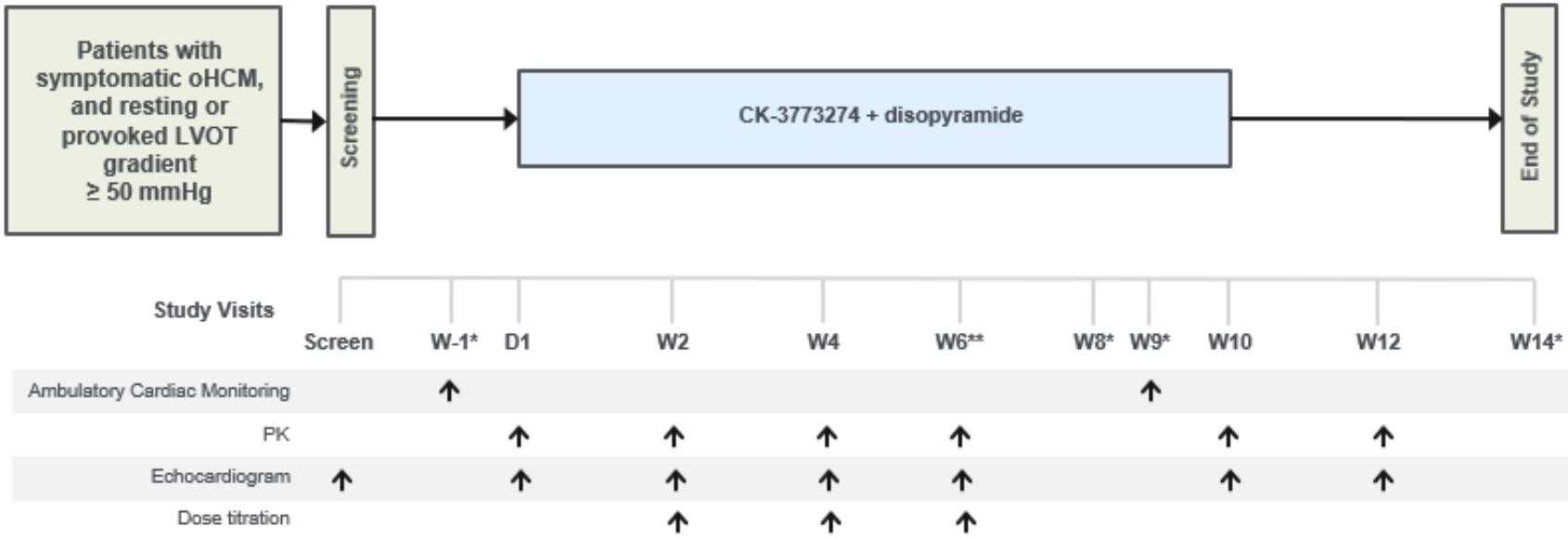
Figure 1: Study Schema

Cohort 1 & 2



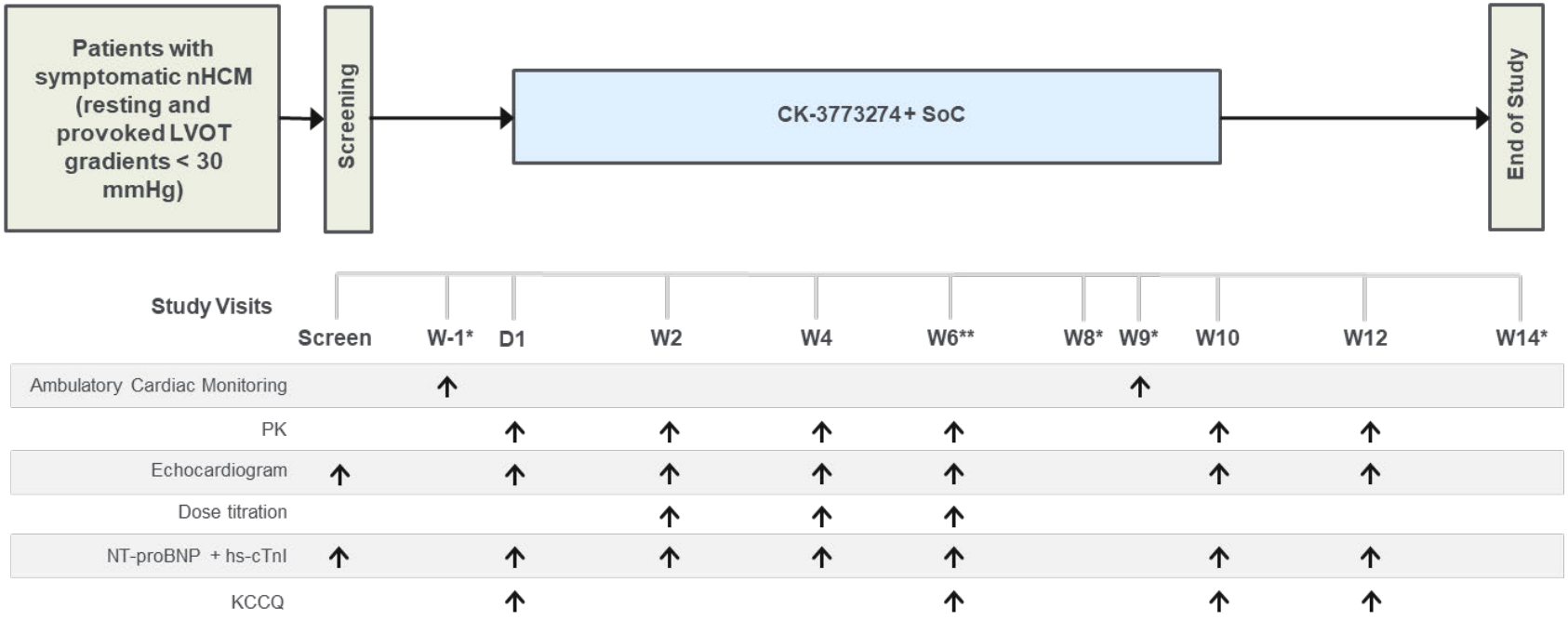
*Telephone visits
**Patient can only be down-titrated at Week 6

Cohort 3



*Telephone visits
**Patient can only be down-titrated at Week 6

Cohort 4


Patients with symptomatic nHCM (resting and provoked LVOT gradients < 30 mmHg)
Screening
CK-3773274 + SoC
End of Study
Study Visits
Screen
W-1*
D1
W2
W4
W6**
W8*
W9*
W10
W12
W14*
Ambulatory Cardiac Monitoring
PK
Echocardiogram
Dose titration
NT-proBNP + hs-cTnI
KCCQ
*Telephone visits
**Patient can only be down-titrated at Week 6

1.3. Schedule of Activities (Cohort 1, 2, and 3)

Study Procedure	Screening		Day 1	Week 2	Week 4	Week 6	Week 8 (Phone Visit)	Week 9 (Phone Visit)	Week 10	Week 12	EOS (Week 14; Phone Visit)	ED[a]
	<28 days	Week -1 (Phone Visit)										
GENERAL PROCEDURES & SAFETY ASSESSMENTS												
Informed consent	X											
Inclusion/exclusion criteria	X											
Medical history	X											
Demographics	X											
Height/weight	X											
Physical examination	X								X	X		X
Vital signs	X		X	X	X	X			X	X		X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE evaluation	X[b]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)	X		X	X	X	X			X	X		X
Echocardiography (full protocol)[c]	X		X						X	X		X
Echocardiography (truncated protocol)[c]				X	X	X						
Ambulatory cardiac monitoring[d]		X						X				
Cohorts 1 & 2: Randomization			X									
Cohort 3: Assigned to CK-3773274			X									
CENTRAL LABORATORY												
Genotype sample	X											
Laboratory assessments	X		X			X			X	X		X
NT-proBNP	X		X						X	X		X
Pregnancy test (WOCBP only)[e]	X		X			X				X		X
PK samples[f]			X	X	X	X			X	X		X

Study Procedure	Screening		Day 1	Week 2	Week 4	Week 6	Week 8 (Phone Visit)	Week 9 (Phone Visit)	Week 10	Week 12	EOS (Week 14; Phone Visit)	ED[a]
	<28 days	Week -1 (Phone Visit)										
INVESTIGATIONAL PRODUCT												
In-clinic IP dosing			X	X	X	X			X			
IP dose adjustment				X	X	X[g]						
PATIENT-REPORTED OUTCOMES AND ASSESSMENTS												
NYHA Functional Classification	X	[redacted]										
Patient reported outcomes[h]			X			X			X			

ECG = electrocardiogram; ED = early discontinuation; EOS = end of study; IP = investigational product; WOCBP = women of childbearing potential.

[a] Patients who withdraw from the study should complete an early discontinuation (ED) visit as soon as possible. A safety contact (eg, phone call) should occur 4 weeks following last dose of IP to ascertain vital status and AEs.

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

[c] Echocardiography will be done prior to dosing on Day 1 and 2-2.5 hours after dosing in the clinic at Weeks 2, 4, 6 and 10. Patients will fast at least 2 hours prior to any scheduled echocardiogram.

[d] Ambulatory Cardiac Monitoring will be done for at least 5 days prior to Day 1.

[e] Only for WOCBP. Serum pregnancy test at screening; for other visits a urine pregnancy test may be used.

[f] Please refer to Table 10 for PK timing.

[g] Patients can only be down-titrated at Week 6.

[h] Only for US patients.

1.4. Schedule of Activities (Cohort 4)

Study Procedure	Screening		Day 1	Week 2	Week 4	Week 6	Week 8 (Phone Visit)	Week 9 (Phone Visit)	Week 10	Week 12	EOS (Week 14; Phone Visit)	ED[a]
	<28 days	Week -1 (Phone Visit)										
GENERAL PROCEDURES & SAFETY ASSESSMENTS												
Informed consent	X											
Inclusion/exclusion criteria	X											
Medical history	X											
Demographics	X											
Height/weight	X											
Physical examination	X								X	X		X
Vital signs	X		X	X	X	X			X	X		X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE evaluation	X[b]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)	X		X	X	X	X			X	X		X
Echocardiography (full protocol)[c]	X		X						X	X		X
Echocardiography (truncated protocol)[c]				X	X	X						
Ambulatory cardiac monitoring[d]		X						X				
Assigned to CK-3773274			X									
CENTRAL LABORATORY												
Genotype sample	X											
Laboratory assessments	X		X			X			X	X		X
NT-proBNP and hs-cTnI	X		X	X	X	X			X	X		X
Pregnancy test (WOCBP only)[e]	X		X			X				X		X
PK samples[f]			X	X	X	X			X	X		X
INVESTIGATIONAL PRODUCT												
In-clinic IP dosing			X	X	X	X			X			

Study Procedure	Screening		Day 1	Week 2	Week 4	Week 6	Week 8 (Phone Visit)	Week 9 (Phone Visit)	Week 10	Week 12	EOS (Week 14; Phone Visit)	ED[a]
	<28 days	Week -1 (Phone Visit)										
IP dose adjustment				X	X	X[g]						
PATIENT-REPORTED OUTCOMES AND ASSESSMENTS												
NYHA Functional Classification	X	[redacted]										
[redacted]												

ECG = electrocardiogram; ED = early discontinuation; EOS = end of study; IP = investigational product; WOCBP = women of childbearing potential.

[a] Patients who withdraw from the study should complete an early discontinuation (ED) visit as soon as possible. A safety contact (eg, phone call) should occur 4 weeks following last dose of IP to ascertain vital status and AEs.

[b] Only considered related to study collected during the screening period until initiation of IP (Day 1). Any non-serious medical occurrence not related to a study procedure during this period should be collected as medical history.

[c] Echocardiography will be done prior to dosing on Day 1 and 2-2.5 hours after dosing in the clinic at Weeks 2, 4, 6 and 10. Patients will fast at least 2 hours prior to any scheduled echocardiogram.

[d] Ambulatory Cardiac Monitoring will be done for at least 5 days prior to Day 1.

[e] Only for WOCBP. Serum pregnancy test at screening; for other visits a urine pregnancy test may be used.

[f] Please refer to Table 10 for PK timing.

[g] Patients can only be down-titrated at Week 6.

1.5. Key Contacts

Sponsor's Study Contact:
[redacted]
Clinical Trials Manager, Clinical Operations
Email: [redacted]
Phone: [redacted]
Fax: [redacted]

Sponsor's Medical Monitor:
[redacted] MD, PhD
Associate Medical Director, Clinical Research, Cardiovascular
Email: [redacted]
Mobile: [redacted]
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Serious Adverse Event Reporting:
Drug Safety
Email: DrugSafety@cytokinetics.com
Fax: +1 (650) 243-4199

2. INTRODUCTION

This is the first patient study 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. Study Rationale

The development of a targeted therapeutic drug that directly reduces myocardial contractility in the sarcomere may yield potential advantages over current therapies for hypertrophic cardiomyopathy (HCM) because it potentially addresses the underlying pathophysiology of HCM. CK-3773274 is a cardiac myosin inhibitor with potential to:

- Reduce symptoms, reduce ventricular hypercontractility and improve cardiac relaxation in patients with HCM
- Reduce left ventricular outflow tract (LVOT) obstruction in patients with obstructive HCM (oHCM)

This study is intended to establish the safety and tolerability of CK-3773274, evaluate pharmacokinetics and to determine its pharmacodynamic (PD) effect in patients with HCM, and to identify an optimal dosing regimen for future development.

2.2. Background

2.2.1. Hypertrophic Cardiomyopathy

[redacted]

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 that seems to drive the disease, improving diastolic function and also reducing LVOT obstruction in those patients with oHCM.

CK-3773274 has been studied in a Phase 1 study of healthy adult participants. This Phase 2 study will be the first investigation of CK-3773274 in patients with HCM.

2.2.2.1. Overview of Nonclinical Studies of CK-3773274

Please refer to the Investigator's Brochure for detailed information on CK-3773274.

Pharmacology

CK-3773274 is an allosteric, cardiac myosin inhibitor that binds directly to the motor domain of cardiac myosin and prevents it from entering the force-producing state. CK-3773274 directly inhibits the adenosine triphosphatase activity in cardiac myofibrils and is selective for cardiac myosin compared to smooth and fast skeletal muscle myosin. In isolated cardiomyocytes, CK-3773274 reduced contractility without any changes to the intracellular Ca^{2+} transients. CK-3773274 showed acute dose- and concentration-dependent reductions in cardiac contractility in both rat and dog that were fully reversible with reductions in plasma concentration and, as shown in rat, with co-administration of the β-agonist, dobutamine. Repeat dose administration of CK-3773274 in rats induced similar levels of change in contractility (left ventricular fractional shortening [LVFS]) over 10 days, further demonstrating a dose and concentration-dependent PD effect with no exacerbation or loss of PD response. The concentration-response relationship in rat and dog was similar when corrected for free drug concentrations and indicates a similarity in response to this mechanism of action across species.

In a core battery of safety pharmacology studies, test article-related effects of acute oral CK-3773274 administration on central nervous and respiratory system function in male rats were limited to the 9 mg/kg high-dose level and included transient decreases in alertness, arena rearing counts and body temperature accompanied by slightly drooping eyelids and transient increases in respiratory rate and/or decreased tidal volume. In telemetry studies of male beagle dogs administered 0.5, 1 or 2 mg/kg/day of CK-3773274 for 7 consecutive days, transient hemodynamic effects consistent with the known PD properties of CK-3773274 (decreased contractility) were noted at all dose levels evaluated on Days 1 and/or 7. There were no test article-related effects on quantitative or qualitative electrocardiogram (ECG) parameters at any dose level evaluated on either Day 1 or Day 7. The half-maximal inhibitory concentration (IC_{50}) of CK-3773274 on human ether-à-go-go related gene potassium current was estimated to be greater than 10 μM. All central nervous, respiratory and cardiovascular system effects noted in vivo were fully resolved by 24 hours post-dose.

Drug Metabolism and Pharmacokinetics

CK-3773274 was classified as a high permeability compound in Caco-2 monolayers and exhibited moderate-to-high oral bioavailability in mice, rats, dogs and monkeys. It has a low plasma clearance and moderate-to-high volume of distribution. After repeat oral dose administration in rats and dogs for up to 28 days, systemic exposures (area under the plasma-concentration curve [AUC] and maximum plasma concentration [C_{max}]) increased with dose in a roughly dose-proportional manner. There was no sex-related difference in exposures to CK-3773274 in rats or dogs.

CK-3773274 distributed rapidly into tissues of the rat after oral administration (time to maximum observed plasma concentration, t_{max} ~1 hour). There was low penetration of

CK-3773274 into brain tissue in the rat, with exposures in the brain approximately 0.5% of those in plasma. Protein binding of CK-3773274 was moderate-to-high in plasma from all species tested. Distribution was roughly equal in red blood cells (RBCs) and plasma in human, dog and monkey whole blood, and favored the plasma compartment in rat blood. In RBC partitioning studies, equal partitioning was observed between RBC and plasma compartments in whole blood obtained from human, dog and monkey. In rat whole blood samples, CK-3773274 partitioned greater into the plasma compartment.

Six putative metabolites of CK-3773274 have been identified to date. The most prevalent metabolite in all species was M1 (CK-3834282). There were no human-specific metabolites detected. Results of cytochrome P450 (CYP) phenotyping implicate CYP2D6 as the primary isoform involved in formation of M1 from CK-3773274 with a fraction metabolized of approximately 50% from studies in plated human hepatocytes. CYPs 2C9, 2C19 and 3A4 likely contribute to the formation of M1 from CK-3773274. However, results from the Phase 1 study showed that CYP2D6 does not play a major role in CK-3773274 elimination.

CK-3773274 did not significantly inhibit CYP isozymes (7 isozyme panel) in a direct or time-dependent manner. In assays using hepatocytes from 3 human donors, CK-3773274 did not induce CYP2B6 or CYP3A4 but may have potential to induce CYP1A2 at a high concentration of 50 μM. The results suggest that drug interactions involving CYP metabolism are unlikely for CK-3773274.

CK-3773274 is not a substrate of P-gp, BCRP, OATP1B1 or OATP1B3. CK-3773274 inhibited P-gp-, OAT3-, OATP1B1-, MATE1- and MATE2-K-mediated probe substrate transport with half-maximal inhibitory concentration (IC_{50}) values of 4.86, 12.1, 71.2, 36.4 and 83.5 μM, respectively. CK-3773274 did not significantly inhibit BCRP-, OAT1-, OCT2- or OATP1B3-mediated transport at a concentration of 50 μM. The results indicate that, depending on the necessary clinical exposures required to achieve a meaningful PD effect caution may need to be exercised when administering CK-3773274 with known substrates of P-gp and OAT3 (see Section 6.5).

Toxicology

General toxicology studies conducted with CK-3773274 in dogs include non-Good Laboratory Practice (GLP) and GLP repeat-dose studies up to 13 weeks in duration.

In the GLP 13-week toxicity study conducted in rats using doses of 0, 1.5, 3, and 6 mg/kg/day, the no-observed-adverse-effect-level (NOAEL) was determined to be 3 mg/kg/day for males and 6 mg/kg/day for females. Systemic exposure (C_{max} and AUC) to CK-3773274 at the NOAEL on Day 91 was 4,700 ng/mL and 73,000 ng·h/mL, respectively, in males and 10,800 ng/mL and 99,200 ng·h/mL, respectively, in females. There were no CK-3773274-related clinical signs, changes in body weight, food consumption, ophthalmic findings or changes in any clinical pathology parameters including cardiac troponin I. Administration of CK-3773274 was associated with early deaths in two toxicology males dosed at 6 mg/kg/day. The principal microscopic findings were minimal to moderate dilatation of the atrium/ventricle of the heart in males at ≥1.5 mg/kg/day and females at 6 mg/kg/day.

In the GLP 13-week toxicity study conducted in dogs using doses of 0, 0.5, 1, and 2 mg/kg/day, the NOAEL was determined to be 1 mg/kg/day. Systemic exposure (C_{max} and AUC) to

CK-3773274 at the NOAEL on Day 91 was 387 ng/mL and 3,330 ng·h/mL, respectively, in males and 430 ng/mL and 3,670 ng·h/mL, respectively, in females. The administration of CK-3773274 at 2 mg/kg/day was associated with an early death in one male. There were no CK-3773274-related effects on food consumption, ophthalmic findings, coagulation parameters, cardiac troponin I biomarker or urinalysis parameters. Cardiac ventricular dilatation was observed at 2 mg/kg/day and increased heart weights in males at ≥1 mg/kg/day.

The adverse cardiac effects noted in these studies are consistent with the anticipated physiological response to pharmacological target engagement of CK-3773274. The adaptive response of cardiac dilatation is a consequence of an excessive chronic pharmacologic effect, namely a large, persistent decrease in cardiac function. The NOAEL values for the 13-week toxicity studies are tabulated below in Table 3 with a summary of the exposures and related safety margins based on exposures from the first in human experience at steady-state exposures for a 10 mg dose (CY 6011, summarized in Section 2.2.2.2).

Table 3: Total and Free Concentrations of CK-3773274 in CY 6011 and 13-Week Toxicity Studies

Species	NOAEL (mg/kg/day)	Mean[a] Total Concentration of CK-3773274		Mean[a] Free Concentration of CK-3773274		Margins[b]	
		C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	C_{max}	AUC_{24}
Human[c]	-	144	2,690	15.0	280	-	-
Rat	3.0 (M)	4,700	73,000	75	1,168	5.0	4.2
	6.0 (F)	10,800	99,200	173	1,587	11.5	5.7
Dog	1.0 (M)	387	3,330	96	829	6.4	3.0
	1.0 (F)	430	3,670	107	914	7.1	3.3

F = female; M = male.
[a] Reported as arithmetic mean.
[b] Margins are calculated based on free (non-plasma protein bound) concentrations of CK-3773274 in rats and dogs compared to humans at plasma protein binding values of 98.4% (rat), 75.1% (dog) and 89.6% (human) from NCD18-17. Values are not allometrically scaled.
[c] CY 6011 Cohort L (10 mg once daily × 14 days), Day 14 data.
Source: NCD18-46, NCD18-47

The results of the genotoxicity testing battery indicate that CK-3773274 is neither mutagenic nor clastogenic/aneugenic and does not pose a genotoxic risk to human.

2.2.2.2. Overview of Clinical Studies of CK-3773274

Prior to the start of CY 6021, one human clinical study, CY 6011, with CK-3773274 has been performed in healthy adult participants.

Study CY 6011 was a Phase 1, randomized, placebo-controlled, double-blind, multi-part study in healthy participants. The study evaluated single ascending doses (SAD) and multiple ascending doses (MAD), food effect, the impact of a CYP2D6-Poor Metabolizer phenotype on PK, and the PK of the tablets used in the current study in comparison with the formulation employed in the

SAD/MAD portions. There was no evident effect of food or the CYP2D6-Poor Metabolizer phenotype on the PK of CK-3773274. The PK of the tablets was similar to the PK used in the SAD/MAD portions, whose conduct is summarized below.

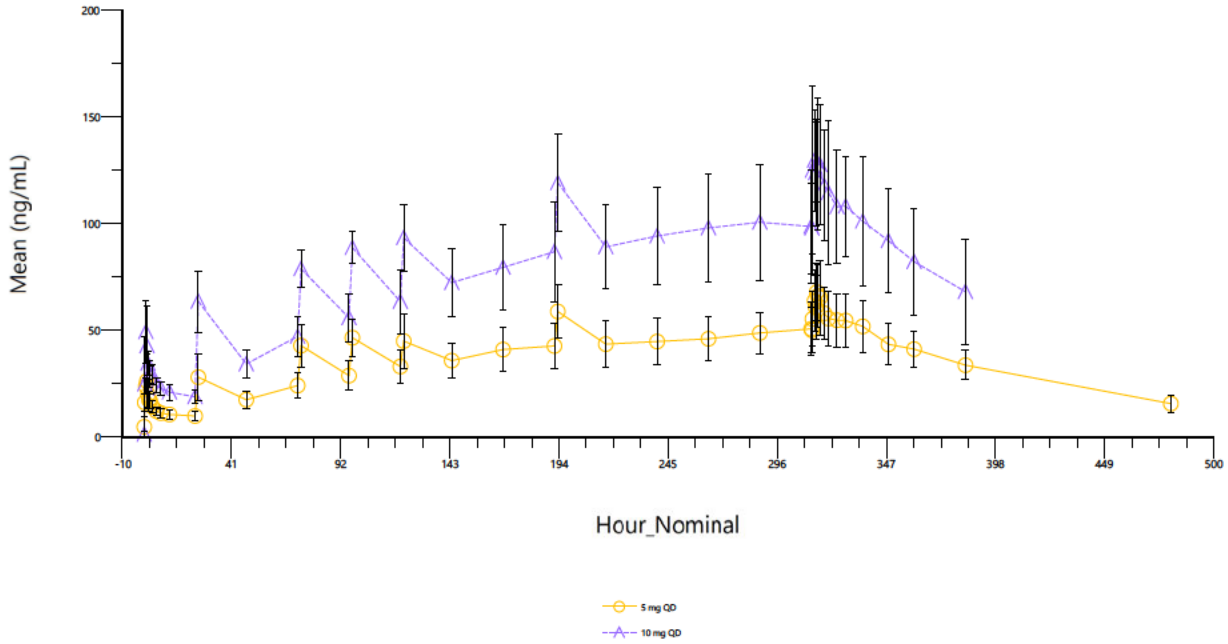
The SAD and MAD portions of the study were designed to define a pharmacologically active dose range that reduces left ventricular ejection fraction (LVEF), as measured by echocardiography, by 5 to 15 percentage points. It was not designed to identify a maximum tolerated dose.

During the SAD portion of the study, seven cohorts of healthy participants (57 total participants) received a single dose of CK-3773274 (either 1, 3, 10, 25, 40, 50, or 75 mg) or placebo administered orally. For the highest dose cohort (75 mg single dose), one participant in the sentinel pair received IP and the rest were dosed with 50 mg or placebo. Forty-seven (47) adverse events (AEs) and no serious adverse events (SAEs) occurred in the SAD cohorts; all AEs were mild to moderate. The most common AEs across all SAD cohorts were gastrointestinal symptoms (n=16, including dyspepsia, nausea, bloating and gastroesophageal reflux) and headache. There have been no clinically significant laboratory abnormalities, including no troponin elevations, nor any clinically significant ECG or vital sign changes. Dose escalation stopping criteria (LVEF<45% in one or more participant) were met in the 75 mg cohort. One participant developed an LVEF of 35% approximately 2 hours after dosing that recovered to normal range (LVEF >50%) within 4 hours after it was noted. The participant remained asymptomatic with stable vital signs. More modest (5-15%) decreases in LVEF were noted in patients at lower doses and there were no AEs associated with the decrease in LVEF.

During the MAD portion of the study, data from two cohorts of 8 participants each (16 total participants) that received single daily doses of CK-3773274 (either 5 or 10 mg once daily) or placebo administered orally over 14 days are available. Nine (9) AEs and no SAEs occurred in the MAD cohorts; all AEs were mild. The most common AEs the in the MAD cohorts have been gastrointestinal symptoms and headache. There have been no clinically significant laboratory abnormalities, including no troponin elevations, nor any clinically significant ECG or vital sign changes. Dose escalation stopping criteria (LVEF <50% in two or more patients) were met by two patients in the MAD group who received 10 mg once daily (LVEF = 46.6% [62.8% pre-dose] and 48.5% [61.9% pre-dose]); both patients completed 14 days of dosing and remained asymptomatic with stable vital signs. The LVEF returned to the normal range (LVEF >50%) within 24 hours of stopping drug.

The AUC_{24} and C_{max} of CK-3773274 were approximately dose-proportional in the SAD and MAD portions of CY 6011. The average apparent plasma terminal elimination half-life ($t_{½}$) was approximately 3.5 days; steady-state plasma concentrations of CK-3773274 were clearly obtained within 14 days of dosing (see Figure 2). The pharmacokinetic (PK) parameters obtained during the MAD portion of the study are shown in Table 4.

Figure 2: CY 6011: Plasma Concentrations of CK-3773274 over Time by Dose Level



At 5 and 10 mg, PK profiles were sampled on Day 1 and Day 14; sampling at 1.5 hours after dosing on Days 2, 4, 5, 6, and 9; sampling at trough conducted daily through Day 17 and at Day 21.

Table 4: CY 6011: Final Steady-State PK Parameters

Dose (N)	C_{max} (ng/mL)	t_{max} (h)	AUC_{tau} (ng·h/mL)	$t_{½}$ (h)	AR
5 mg (6)	69 (23.2%)	2.75 (1.5-4.0)	1320 (23.0%)	86.4 (11.9)	4.75
10 mg (6)	141 (19.7%)	2.5 (0.5-3.0)	2632 (22.8%)	79.8 (14.1)	4.82

$t_{½}$ = apparent plasma terminal elimination half-life; t_{max} = time to maximum observed plasma concentration
Data are shown as geometric mean (percent coefficient of variation) except for t_{max}, which is shown as median (minimum-maximum), and $t_{½}$, which is shown as the arithmetic mean (standard deviation). Accumulation ratio calculated as (AUC_{24} on Day 14)/(AUC_{24} on Day 1).
Source: CY 6011 Tables 14.2.1.2.2.2 and 14.2.1.2.2.4 (19MAY2020 18:06)

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

[redacted]

[redacted]

2.3.1.1. Mitigation Strategy

The main mitigation strategy is performing echocardiography-based dose titration based on each individual's PD response to CK-3773274 with clear stopping criteria for individuals and cohort dose levels. All echocardiograms will be read at the site by the same reader to facilitate rapid and consistent interpretation. In addition, a Data Monitoring Committee (DMC) will provide independent oversight of the study.

[redacted]

n unblinded DMC will review the recommendation along with the available safety, PK, and echocardiographic data. The DMC may either endorse the recommendation or suggest a change in study conduct, including alteration of planned dosing regimen.

2.3.2. 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 HCM by trying to address the underlying pathophysiology of HCM. [redacted]

Patient contributions to the performance of this study may yield a new therapeutic modality for the treatment of their disease.

3. OBJECTIVES AND ENDPOINTS

Table 5: Study Objectives and Endpoints

Objectives	Endpoint(s)
Primary	
To determine the safety and tolerability of CK-3773274 in patients with symptomatic HCM	• Patient incidence of reported AEs • Patient incidence of reported SAEs • Patient incidence of LVEF <50%
Secondary	
To describe the concentration-response relationship of CK-3773274 on the resting and post-Valsalva LVOT-G on echocardiogram over 10 weeks of treatment in patients with oHCM (Cohorts 1, 2, 3 only)	• Slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the resting LVOT-G • Slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the post-Valsalva LVOT-G
To describe the dose response relationship on LVOT-G (resting and Valsalva) of CK-3773274 in patients with symptomatic oHCM (Cohorts 1, 2, 3 only)	• Change from baseline in resting and post-Valsalva LVOT-G over time as a function of dose • Change from baseline in resting and post-Valsalva LVOT-G to Week 10
To evaluate the concentration-response relationship of CK-3773274 on resting left ventricular ejection fraction (LVEF) over 10 weeks of treatment in patients with HCM.	• Slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the resting LVEF
To evaluate the plasma concentrations of CK-3773274 in patients with HCM	• Observed maximum plasma concentration (C_{max}) and trough plasma concentration (C_{trough}) for CK-3773274 during dosing
Exploratory	
[redacted]	• [redacted]

Table 5: Study Objectives and Endpoints (Continued)

Objectives	Endpoint(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 5: Study Objectives and Endpoints (Continued)

Objectives	Endpoint(s)
[redacted]	[redacted]

NT-proBNP = N-terminal pro-B-type natriuretic peptide; [redacted].

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multi-center, dose finding study in patients with symptomatic HCM. Four sequential cohorts will be enrolled. The first two cohorts will include patients with oHCM who are not receiving disopyramide. Cohort 3 will only include patients with oHCM receiving disopyramide. Cohort 4 will only include patients with nHCM. Patients who have undergone septal reduction therapy (SRT) will not be eligible for participation in Cohorts 1, 2, or 3 but will be eligible for participation in Cohort 4. [redacted] Within each of the first two cohorts, patients will be randomized 2:1 to active or placebo treatment and receive up to three escalating doses of CK-3773274 or placebo based on echocardiographic guidance. In the third and fourth cohorts, all patients will receive up to three escalating doses of CK-3773274 based on echocardiographic guidance. Overall, the treatment duration will be 10 weeks with a 4-week follow-up period after the last dose.

Approximately 95 patients will be randomized or assigned in four sequential cohorts with approximately 18 patients randomized per cohort in the first two cohorts, approximately 8-12 patients assigned to receive CK-3773274 in the third cohort, and approximately 30-40 patients assigned to receive CK-3773274 in the fourth cohort. After a four-week screening period, eligible patients will be randomized to once daily CK-3773274 or placebo in a 2:1 ratio for the first two cohorts or given once daily CK-3773274 in the third and fourth cohorts. Representatives of Cytokinetics and the SC will conduct interim reviews of the blinded safety, echocardiographic, and de-identified PK data available from Cohort 1 to recommend the dose levels of CK-3773274 to be administered in Cohort 2. An unblinded DMC will review the recommendation along with the available safety, PK, and echocardiographic data. The DMC may either endorse the recommendation or suggest a change in study conduct, including alteration of planned dosing regimen.

Approximately 30 investigative sites in North America and Europe will participate in this study.

4.2. Scientific Rationale for Study Design

This study is designed to provide data supporting a potentially clinically effective dosing regimen for CK-3773274 in patients with symptomatic HCM, the intended population for future Phase 3 studies. In patients with oHCM, reduction of the LVOT-G is expected to correlate with improvement in patient symptoms and exercise tolerance, clinical endpoints that require much larger studies to evaluate. Thus, in this first Phase 2 study of CK-3773274, general safety and LVOT-G are being employed in Cohorts 1, 2, and 3 as endpoints to guide dose selection for a Phase 3 study in oHCM. General safety and LVEF are being used in Cohort 4 to guide dose selection for a Phase 3 study in nHCM.

Since patient characteristics vary substantially in this disease, individualized dose titration to a PD response is being employed to maximize efficacy and safety. For patients with oHCM in Cohorts 1, 2, and 3, this will include a reduction of the LVOT-G to <30 mmHg along with preservation of LVEF ≥50%. For patients with nHCM in Cohort 4, this will include preservation of LVEF ≥ 55%. The eligibility criteria were crafted to enable enrollment of a patient population

representative of the intended Phase 3 populations while ensuring the safety of the study population in this trial.

For Cohorts 1 and 2, a placebo control and double-blinded approach are being employed in this study to avoid bias in data collection, including the safety assessments and PD measures that comprise the primary and secondary endpoints. For these cohorts, participants will continue taking background medications exclusive of disopyramide.

Patients enrolled in Cohort 3 will all be assigned to receive CK-3773274 and all patients must be taking disopyramide as a background medication. When used in conjunction with other Type 1A or 1C anti-arrhythmic drugs, disopyramide may produce negative inotropic effects. Although CK-3773274 has a different mechanism of action from anti-arrhythmic drugs, it selectively inhibits cardiac contractility and can lower LVEF. This cohort will assess the safety, tolerability and PK-PD effects of CK-3773274 in patients taking disopyramide.

Cohort 4 will include patients with nHCM receiving background standard of care medical therapy. All subjects in Cohort 4 will be assigned to receive CK-3773274. This cohort will assess the safety, tolerability and PK-PD effects of CK-3773274 in patients with nHCM.

4.3. Justification for Dose

The doses of CK-3773274 are summarized in Table 7. A dose of 5 mg was chosen for the starting dose as this was found to be well-tolerated in healthy participants after achieving steady state PK. Within-patient escalation will only occur when the patient's current dose is well-tolerated, and the patient meets the escalation criteria described in Section 6.6.

The dose escalation scheme in Cohort 1 is conservative. Both the initial dose (5 mg × 14 days) and the second dose (10 mg × 14 days) were well tolerated by healthy participants in CY 6011. The final dose in Cohort 1 will represent a 50% increase in dose (15 mg × 14 days) rather than a dose doubling, to mitigate the risk of excessive PD effect.

In Cohort 3, background HCM medications must include disopyramide, a potential negative inotrope. The Cohort 3 starting dose of 5 mg of CK-3773274 was well-tolerated at steady-state PK in healthy participants in CY 6011 and in oHCM patients in CY 6021 Cohort 1. The dose escalation scheme for Cohort 3 is conservative and will follow the echocardiography-guided dose titration criteria described in Section 6.6.

Cohort 4 will employ a starting dose of 5 mg of CK-3773274. Echocardiography-based dose titration will utilize LVEF alone as the metric for dose adjustment. The objective is to escalate the dose to a maximum of 15 mg daily if clinically tolerated and the LVEF remains ≥ 55%. The dose escalation scheme for Cohort 4 is also conservative and will follow the echocardiography-guided dose titration criteria described in Section 6.6.

4.4. End of Study Definition

A patient is considered to have completed the study if he/she has completed all phases of the study including the End of Study (EOS) Visit.

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

5. STUDY POPULATION

Before patients begin any study-specific activities/procedures, Cytokinetics requires a copy of the site's written 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. All patients must personally sign and date the ICF before commencement of study-specific activities/procedures. The patient may sign and date the ICF electronically if the investigator feels that it protects the safety of the patient and prior documented approval of the process is given by the Sponsor.

A patient is considered enrolled when the patient has signed the ICF. The patient is considered randomized after meeting all eligibility criteria and is randomized in the IVRS/IWRS. Randomization should occur during the Day 1 visit. The investigator is to document the enrollment 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 exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

101. Able to comprehend and willing to sign an ICF and willing to comply with all study 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 at screening.
103. Body weight is ≥45 kg at screening.
104. Diagnosed with HCM per the following criteria:
    a. Has LV hypertrophy and non-dilated LV chamber in the absence of other cardiac disease.
    b. Has minimal wall thickness ≥15 mm (minimal wall thickness ≥13 mm is acceptable with a positive family history of HCM or with a known disease-causing gene mutation).
105. Adequate acoustic windows for echocardiography.
106. For Cohorts 1, 2, and 3 has LVOT-G during screening as follows:
    a. Resting gradient ≥50 mmHg

    OR

    b. Resting gradient ≥30 mmHg and <50 mmHg with post-Valsalva LVOT-G ≥50 mmHg
107. LVEF ≥60% at screening.
108. New York Heart Association (NYHA) Class II or III at screening.
109. Patients on beta-blockers, verapamil, diltiazem, or ranolazine should have been on stable doses for >4 weeks prior to randomization and anticipate remaining on the same medication regimen during the study.

110. Male patients are eligible to participate if they agree to the following during the study and for at least 10 weeks after the last dose of investigational product (IP):
    a. Refrain from donating sperm

    Plus either:

    b. Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

    OR

    Must agree to use a male condom and, when his female partner is a woman of childbearing potential, have his female partner use a highly effective method of contraception (as described in Appendix 4 [Section 10.4])

111. A female patient is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    a. Is not a woman of childbearing potential (WOCBP; as described in Appendix 4 [Section 10.4])

    OR

    Is a WOCBP and using a highly effective method of contraceptive (as described in Appendix 4 [Section 10.4]) during the study 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) within 3 days before the first dose of study intervention.

    Note: The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

    Contraceptive use by men or WOCBPs should be consistent with the guidance in Appendix 4 (Section 10.4) and local regulations regarding the methods of contraception for those participating in clinical studies.

112. Able to complete all screening procedures.
113. Taking stable doses of disopyramide for >4 weeks prior to screening (Cohort 3 only).
114. For Cohort 4 has resting and post-Valsalva LVOT-G < 30 mmHg at the time of screening.
115. For Cohort 4 has elevated NT-proBNP > 300 pg/mL at the time of screening.

5.2. Exclusion Criteria

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

201. Aortic stenosis or fixed subaortic obstruction.

202. Known infiltrative or storage disorder causing cardiac hypertrophy that mimics HCM (eg, Noonan syndrome, Fabry disease, amyloidosis).

203. History of LV systolic dysfunction (LVEF <45%) at any time during their clinical course.

204. Documented history of current obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.

205. Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the study period (Cohorts 1, 2, and 3 only). Patients having undergone septal reduction therapy > 12 months prior to screening who remain symptomatic from nHCM, and who meet all other criteria for inclusion, may be enrolled in Cohort 4.

206. Prior treatment with cardiotoxic agents such as doxorubicin or similar.

207. For Cohorts 1, 2, and 4: Has been treated with disopyramide or antiarrhythmic drugs that have negative inotropic activity within 4 weeks prior to screening.
For Cohort 3: Has been treated with an antiarrhythmic drug other than disopyramide that has negative inotropic activity within 4 weeks prior to screening.

208. Has any ECG abnormality considered by the investigator to pose a risk to patient safety (eg, second degree atrioventricular block type II).

209. Paroxysmal atrial fibrillation or flutter documented during the screening period.

210. Paroxysmal or permanent atrial fibrillation requiring rhythm restoring treatment (eg, direct-current cardioversion, ablation procedure, or antiarrhythmic therapy) ≤6 months prior to screening. (This exclusion does not apply if atrial fibrillation has been treated with anticoagulation and adequately rate-controlled for >6 months.)

211. History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.

212. ICD placement within 3 months prior to screening or planned ICD placement during the study.

213. History of appropriate ICD shock for life-threatening ventricular arrhythmia within six months prior to screening.

214. Recipient of a major organ transplant (eg, heart, lung, liver, bone marrow, renal) or anticipated transplantation within 12 months from randomization).

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 disease, are permitted.

216. 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 study evaluation, procedures, or completion.

217. Hemoglobin <10.0 g/dL at screening.

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.

221. Currently participating in another investigational device or drug study 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 study are not permitted.
222. Has received prior treatment with CK-3773274 or mavacamten.
223. Has a known hypersensitivity to any excipients in CK-3773274 Tablets, Film-Coated.
224. For Cohort 4: has any documented history of LVOT-G ≥ 30 mmHg at rest, with Valsalva, or with exercise (for subjects who have had prior septal reduction therapy, this exclusion criteria only applies to gradients detected following septal reduction therapy).

5.3. Lifestyle Considerations

Patients will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.4. Screen Failures

For Cohorts 1 and 2, screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized to IP. For Cohorts 3 and 4, screen failures are defined as patients who consent to participate in the clinical trial but are not assigned to CK-3773274. 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 study-related procedures.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

5.5. Retesting

Vital signs, hemoglobin, and liver function assessments may be repeated once during the screening period. The new results used to determine eligibility if all the following criteria are met:

- The first screening value is inconsistent with the patient's immediate prior medical history
- In the investigator's judgment, the results of the assessments in question are likely to be transient
- Results of retesting can be evaluated for eligibility and the patient randomized within the allowed screening period

If the patient meets LVEF and LVOT-G-based eligibility criteria per site evaluation of a screening echocardiogram, but the core laboratory deems acoustic windows inadequate, an echocardiogram may be repeated once during the screening period to ensure adequate acoustic windows can be obtained consistently.

6. INVESTIGATIONAL PRODUCT

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

6.1. Investigational Product(s) Administered

Table 6: Investigational Products

Arm Name	Active	Placebo
IP/Product Name	CK-3773274	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg	Matching placebo
Dosage Level(s)	See Table 7	See Table 7
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	[redacted]	[redacted]
Packaging and Labeling	IP will be provided in bottles. Each bottle will be labeled as required per country requirement.	IP will be provided in bottles. Each bottle will be labeled as required per country requirement.

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/assigned to CK-3773274 in the study 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, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IP 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 patients in Cohorts 1 and 2 will be centrally assigned to randomized IP using an Interactive Voice/Web Response System (IVRS/IWRS). Patients in Cohort 3 will be assigned to receive only CK-3773274 by the IVRS/IWRS. Before the study is initiated, the log in information & directions for the IWRS will be provided to each site.

An unblinded sonographer at the study site will perform the echocardiograms. An unblinded cardiologist, who is not the study investigator and is called the Echo Cardiologist, will read the echocardiograms, measure the LVOT-G and LVEF and enter the echocardiogram results in the IVRS/IWRS for dose titration adjustments. The investigator and study staff will be blinded to the echocardiograms and the results. Patients on placebo will also have dose titrations (both up and down) to maintain the blind.

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

The IVRS/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 highly 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 and Administration

6.4.1. IP 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 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.

A record of the number of CK-3773274 tablets dispensed to and taken by each patient must be maintained and reconciled with IP and compliance records. IP dosing start and stop dates, including dates for dosing delays and/or dose reductions will also be recorded in the CRF.

6.4.2. IP Administration

IP is taken orally, once daily, per the normal lifestyle of the patient (morning preferred). IP should be taken at approximately the same time each day. IP may be taken with or without food; there are no fasting requirements. If a patient forgets to take IP within 6 hours of their scheduled time, they should skip the dose and not take a double dose the next day. Patients must hold IP on clinic visit days as they will be dosed in clinic.

NOTE: depending on the dose and titration schedule, a patient's daily dose may consist of more than one tablet. If the patient's dose requires multiple tablets, all tablets are to be taken at the same time.

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 study 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 ranolazine should have been on stable doses for >4 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial.

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 study.

During the trial, medications and doses should remain stable whenever appropriate. However, 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 [redacted]

[redacted] 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 (e.g. dobutamine) is allowable at any time during the study. 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 Modification

In each cohort, a patient will receive up to three escalating doses of CK-3773274 as shown in Table 7.

Table 7: CY 6021 Dosing Scheme

Cohort	Dose 1	Dose 2	Dose 3
Cohort 1	5 mg	10 mg	15 mg
Cohort 2	10 mg	20 mg	30 mg
Cohort 3	5 mg	10 mg	15 mg
Cohort 4	5 mg	10 mg	15 mg

6.6.1. Scheduled Dose Modifications

An unblinded sonographer at the study site will perform the scheduled echocardiograms. An unblinded cardiologist, who is not the study investigator and is called the Echo Cardiologist will read the echocardiograms, measure the LVOT-G and LVEF and enter the echocardiogram results in the IVRS/IWRS for dose titration decisions. The investigator and study staff will be blinded to the echocardiograms and the results.

For Cohorts 1, 2, 3

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

- Resting LVOT-G ≥30 mmHg and the biplane LVEF ≥50%

OR

- Resting LVOT-G <30 mmHg, post-Valsalva LVOT-G ≥50 mmHg, and the biplane LVEF ≥50%

Otherwise, the patient will remain on Dose 1.

If LVEF is <50% at Week 2, the patient will be down-titrated to placebo.

After 2 more weeks on the assigned dose (ie, Week 4), each patient will have an echocardiogram 2 hours following administration of their dose of IP. Patients will escalate to the next higher dose if either of the following conditions are met on echocardiography:

- Resting LVOT-G ≥30 mmHg and the biplane LVEF ≥50%

OR

- Resting LVOT-G <30 mmHg, post-Valsalva LVOT-G ≥50 mmHg, and the biplane LVEF ≥50%

Otherwise, the patient will remain on the same dose. If LVEF is <50% at Week 4, the patient will be returned to a prior dose level or to placebo if the patient was on Dose 1.

After 2 more weeks on the assigned dose (ie, Week 6), each patient will have an echocardiogram 2 hours following administration of their dose of IP. If LVEF is <50% at Week 6, the patient will be down-titrated to a prior dose level or to placebo if the patient was on Dose 1.

If at any time, a patient's dose is down-titrated to placebo, then they will remain on placebo for the duration of the study.

For Cohort 4

Each patient will receive Dose 1 for 2 weeks. At Week 2, the patient will have an echocardiogram 2 hours following administration of their dose of IP. Patients will up-titrate to Dose 2 if LVEF ≥ 55% on the echocardiogram. If the LVEF is ≥ 50% but < 55% at Week 2, the patient will remain on Dose 1. If LVEF is <50% at Week 2, then IP will be discontinued.

At Week 4, 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 LVEF ≥ 55% or remain on the same dose if the LVEF is ≥ 50% but < 55%. If LVEF is <50% at Week 4, the patient will be down-titrated to a prior dose level or IP will be discontinued if the patient was on Dose 1.

At Week 6**,** each patient will have an echocardiogram 2 hours following administration of their dose of IP**.** Patients will remain on the same dose if the LVEF ≥ 50%. If LVEF is <50% at Week 6, the patient will be down-titrated to a prior dose level or IP will be discontinued if the patient was on Dose 1.

6.6.2. Safety Considerations

If the Echo Cardiologist notes echocardiographic findings that cross the defined safety threshold of LVEF <40% or feels the patient requires urgent medical attention, the Echo Cardiologist will discuss the results with the investigator or qualified designee. The Medical Monitor will be informed in these cases.

If a patient's LVEF is <40% at a scheduled echocardiogram visit (Week 2, Week 4, or Week 6), a repeat echocardiogram may be performed at the discretion of the investigator to confirm the initial finding (preferably within 24 hours of the original echocardiogram). If the echocardiography findings are confirmed, then the IP dose will be reduced to a prior tolerated dose level after at least a 2-day drug holiday and a local echocardiogram documenting an LVEF >50% and after approval from the Medical Monitor. Dosing may be discontinued at any time at the discretion of the investigator.

If an LVEF is < 50% per on-site assessment of an unscheduled echocardiogram and the patient has symptoms of low cardiac output, the Medical Monitor should be informed, and the patient will be discontinued from study drug.

Any dose interruption, as described above, must be documented in the CRF and include the reason for stopping, the stop date, and the restart date.

6.6.3. Dose Level Stopping Rules

If four or more patients have had an LVEF <50% (Cohorts 1, 2, 3) or LVEF < 40% (Cohort 4) at the same dose level, then escalation to that dose and higher doses will no longer be permitted until the data are reviewed by the DMC.

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

CY 6022 is an ongoing open label extension study for eligible patients with HCM who have completed a prior study of CK-3773274, such as CY 6021. Participation in the open label extension study is at the discretion of the patient and not a condition of participation in CY 6021. [redacted] The treatment duration for CY 6022 is anticipated to be multiple years, concluding when marketing authorization is achieved in the patient's country or Cytokinetics terminates the study.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Investigational Product

In rare instances, it may be necessary for a patient to permanently discontinue (definitively discontinue) IP. If IP is definitively discontinued, the patient should be encouraged to remain in the study and continue all safety assessments including AE collection, vital signs and laboratory assessments. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of IP and follow-up and for any further evaluations that need to be completed.

Reasons for removal from protocol-required IP or procedural assessments include any of the following:

- withdrawal by patient
- safety concern (eg, due to an AE, pregnancy)
- death
- lost to follow-up
- decision by Cytokinetics (other than patient request, safety concern, lost to follow-up)

If a clinically significant finding is identified after randomization, the investigator or qualified designee will determine if the patient can continue in the study and if any change in patient management is needed. Any new clinically relevant finding should be reported as an AE.

7.1.1. Temporary Discontinuation

Please see Section 6.6 for further information on temporary drug discontinuation. The investigator must consult with the Medical Monitor prior to restarting IP. If dosing is interrupted for more than 3 consecutive days in the first 6 weeks and more than 7 consecutive days thereafter, the patient may be discontinued from the study. That patient may be replaced after discussion with the Medical Monitor.

7.1.2. 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 (as described below) 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 6 (Section 10.6) for guidance on the assessment and management of abnormal hepatic laboratory values.

7.2. Patient Discontinuation/Withdrawal from the Study

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Patients can decline to continue receiving IP and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. 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 study. Whenever safe and feasible it is imperative that patients remain on-study 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).

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up (eg, medical records checks). Patients requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study.

Patients who withdraw 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 unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing. The ICF for the study should note that although a patient is free to leave the study 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 will review public records as permitted by applicable law to determine vital status of the patient at the end of the study or before.

Reasons for removal of a patient from the study include:

- decision by Cytokinetics
- withdrawal of consent from study
- death
- lost to follow-up

See Section 7.1 for additional reasons for removal of patient from the study.

7.3. 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 study site.

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

- The site must attempt to contact the patient 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 study.

- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (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 withdrawn from the study and are lost to follow-up.

Discontinuation of specific sites or of the study are handled as part of Appendix 1 (Section 10.1).

8. STUDY ASSESSMENTS AND PROCEDURES

There will be a total of 7 in-person and 4 phone study visits per patient, with windows to aid in scheduling as shown in Table 8. If a patient visit must be scheduled outside the visit window, the Medical Monitor should be contacted.

Table 8: CY 6021 Visit Windows

Visit	Visit Window
Screening	Up to 28 days prior to Day 1 visit (as per protocol)
Week -1 (phone visit)	±1 day
Day 1 (First Dosing Day)	
Week 2[a]	+3 days
Week 4[a]	+3 days
Week 6[a]	+3 days
Week 8 (phone visit)	±3 days
Week 9 (phone visit)	±3 days
Week 10	±3 days
Week 12	±3 days
Week 14 (EOS; phone visit)	Must be at least 28 days from last IP dose +3 days

[a] Visit should occur at least 14 days but no more than 17 days from the previous visit.

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct. 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.

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

8.1. Efficacy Assessments

There is no primary efficacy endpoint in this study.

Secondary efficacy endpoints include PD assessment of the effects of CK-3773274 in patients with HCM using echocardiography.

Exploratory efficacy assessments will include [redacted]

8.1.1. Echocardiography

Patients will fast for at least 2 hours prior to each scheduled echocardiogram. Echocardiography will be done prior to dosing on Day 1. Echocardiography will be performed 2-2.5 hours after dosing in the clinic on Weeks 2, 4, 6, and 10. See Table 10 for summary of the echocardiography time points.

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 parameters in Table 9.

Table 9: CY 6021 Echocardiographic Parameters to be Measured

Resting LVOT-G	LVEDV	IVST
Post-Valsalva LVOT-G	LVESD	IVCT
LVEF	LVESV	IVRT
LVFS	LVCO	E/E' ratio
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 a cardiologist at the investigational site.

All echocardiograms (including unscheduled) will be sent to the core laboratory for interpretation. On-site interpretation of LVEF (all cohorts) and LVOT-G (Cohorts 1, 2, and 3 only) will be used for dose escalation decisions. The core laboratory quantification of the echocardiograms will be used for all statistical analyses.

8.1.2. [redacted]

After interviewing the patient, the investigator (or qualified designee) will record [redacted]

8.1.3. Health Status and Health-related Quality of Life

When available, patients in the US (and EU included in Cohort 4) will complete patient-reported outcome (PRO) questionnaires prior to dosing at Day 1, at Week 6, and at Week 10 (and Week 12 in Cohort 4). The following instruments will be used at these visits:

- Cohorts 2, 3, and 4
  - SF-36 Physical Functioning subscale
- Cohorts 2 and 3, only
  - PROMIS Dyspnea Severity Short Form 10a
  - Two additional items from the PROMIS Dyspnea Severity item bank: DYSSV027 (low intensity leisure activity) and DYSSV028 (moderate-intensity leisure activity)
  - PROMIS Fatigue Short Form 7a
  - PROMIS Physical Function Short Form 8b
  - HCM Global Impression of Status and Global Impression of Change questionnaires
- Cohort 4 only
  - KCCQ
  - SAQ7
  - PGI-C (Week 10 only)
  - CGI (Week 10 only)

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, and neurological systems. Height and weight will also be measured and recorded at screening. Height and weight will be measured while patient is fully clothed with shoes removed.

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

8.2.2. Vital Signs

Temperature, 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 after the patient has rested for at least 5 minutes in a quiet setting without distractions (eg, television, cell phones).

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.

8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (see 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 required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Patients should be sitting or supine prior to the ECG for at least 5 minutes. The investigator may perform additional ECG recordings as needed for the care of the patient.

A patient will be withdrawn from the study by the PI or designee if, in their medical judgment, ECG findings are present which make continued study 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 or echocardiogram results as determined by the investigator or the Medical Monitor.

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

8.2.4. Ambulatory Cardiac Monitoring

During the week prior to the first dose and the week prior to the last dose of IP, patients will wear an ambulatory cardiac monitoring device. Patients will be provided the device at screening and will wear it for at least five but no more than 7 days prior to first dose and at least 5 days prior to the last dose. Patients will return the device at the visit after completion of wear period.

Data from the monitoring device will be read by a central reader and will be made available to Cytokinetics on a regular basis.

8.2.5. 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.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study 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).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE or AE or result in a dose modification), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

8.3.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial patient. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any AE observed by the investigator or reported by the patient are recorded in the patient's medical record.

The definition of an AE includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (i.e., more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

If the severity of an AE changes from the date of onset to the date of resolution, record as a single event with the worst severity on the AE CRF.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

In addition, the investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all SAEs to resolution or determined to be clinically stable.

8.3.2. Serious Adverse Events

An SAE is defined as an AE that meets at least one of the following regulatory criteria:

- fatal
- immediately life-threatening (places the patient at immediate risk of death)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent disability/incapacity

- congenital anomaly/birth defect
- other medically important serious event

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

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury (DILI) or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

8.3.3. Time Period and Frequency for Collecting AE and SAE Information

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the patient that occur after initiation of IP through 4 weeks following the last dose of IP. AEs must be recorded in the AE CRF. SAEs are reported to Cytokinetics from the time of signing of the ICF through 4 weeks following the last dose of IP, as noted in Section 8.3.6.

All AEs considered related to study procedures and all SAEs that occur during the screening period (after signing of the ICF until initiation of IP) are also reported in the CRF.

Medical occurrences that are not associated with study 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.

All SAEs must both be reported to Cytokinetics and recorded in the AE CRF, as indicated in Appendix 3 (Section 10.3). The investigator will submit any SAE or updated SAE information to Cytokinetics within 24 hours of awareness.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation (ie, more than 4 weeks following the last dose of IP). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify Cytokinetics.

8.3.4. Method of Detecting AEs and SAEs

The method of recording and assessing AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.5. Follow-up of AEs and SAEs

The investigator is required to proactively ensure each AE is followed to resolution, stabilization, or the EOS, whichever comes first. SAEs are followed to resolution or stabilization and reporting may continue after the EOS and database lock. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.6. Regulatory Reporting Requirements 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 signing of the ICF through 4 weeks following the last dose of IP are reported to Cytokinetics **immediately and no later than 24 hours** following the investigator's knowledge of the event.

To report an SAE:

Email: DrugSafety@cytokinetics.com

Facsimile: +1 (650) 243-4199

Cytokinetics has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. Cytokinetics will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to Health Authorities, IRBs/IECs, and investigators is the reference safety information section of the Investigator's Brochure [CK-3773274 IB].

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Cytokinetics policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Cytokinetics will review and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.7. Pregnancy

If a woman becomes pregnant while on IP, the IP must be discontinued. The Principal Investigator or designee must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

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.

If a pregnancy is reported, the investigator should inform Cytokinetics within 24 hours of learning of the pregnancy on the Pregnancy Report Form to DrugSafety@cytokinetics.com, as per the procedures outlined in Appendix 4 (Section 10.4).

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

8.3.8. Female Patients Who Breastfeed

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

The Principal Investigator or designee will collect breastfeeding information on any female patient who breastfeeds while taking the study drug 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 Principal Investigator's or designee's knowledge of event.

8.4. Treatment of Overdose

For this study, 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. The use of rescue medications to treat a low cardiac output state is recommended if necessary. 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:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for any AEs/SAEs and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis as soon as practical and note the date of the last dose of IP.
4. 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.

8.5. Pharmacokinetics

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). Samples will be used to evaluate the PK of CK-3773274 and its metabolites. Instructions for the collection and handling of biological samples will be provided in the study 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 10 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 study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Table 10: Summary of PK and Echocardiography Time Points

Visit	PK Time Point[a]	Echocardiography Time Point	Type of Echocardiogram
Screening	NA	No specific time requirement	Full protocol
Day 1	Pre-dose and 1 hour	Pre-dose	Full protocol
Week 2	Pre-dose, 0.5, 1 and 2 hours post-dose	2-2.5 hours post dose	Truncated protocol
Week 4	Pre-dose, 0.5, 1 and 2 hours post-dose	2-2.5 hours post dose	Truncated protocol
Week 6	Pre-dose, 0.5, 1 and 2 hours post-dose	2-2.5 hours post dose	Truncated protocol
Week 10	Pre-dose, 0.5, 1 and 2 hours post-dose	2-2.5 hours post dose	Full protocol
Week 12 (EOS)	Untimed PK at visit	No specific time requirement	Full protocol
Early Discontinuation	Untimed PK at visit	No specific time requirement	Full protocol

NA = not applicable
[a] When PK collection and an echocardiogram are scheduled for the same time point, PK collection should be completed prior to the echocardiogram.

8.6. Pharmacodynamics

Echocardiography is the main assessment modality of the PD of CK-3773274. Please see Section 8.1.1 for description of the echocardiographic procedures.

8.7. Genetics

As HCM is a genetic disease, a blood sample will be collected for analysis through the use of 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, drug metabolism, susceptibility to developing AEs, or to increase the knowledge and understanding of cardiovascular, muscle and disease biology.

See Appendix 5 (Section 10.5) 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. Biomarkers

No long-term banking of blood for biomarkers will be done in this study.

8.9. Immunogenicity Assessments

No immunogenicity assessments will be done for this study.

8.10. Medical Resource Utilization and Health Economics

No medical resource utilization or health economic assessments will be done for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is the first study of CK-3773274 in patients with HCM and the analyses of dose, PK, and PD, and their relationships are descriptive and hypothesis-generating in nature. The analyses evaluating treatment effect on secondary and exploratory endpoints relating to change from baseline to Week 10 will test the null hypothesis that there is no treatment difference in change from baseline between patients receiving placebo and those receiving CK-3773274. The analyses may be repeated by cohort or in data combined across cohorts. There will be no adjustments for multiplicity.

9.2. Sample Size Determination

Approximately 18 eligible patients per cohort will be randomly assigned to once daily CK-3773274 or placebo in a 2:1 ratio in Cohorts 1 and 2; approximately 8-12 patients will be assigned to receive CK-3773274 in Cohort 3. Approximately 15 evaluable patients per cohort in Cohorts 1 and 2 will yield approximately 30 evaluable patients in the CK-3773274 group and 15 evaluable patients in the placebo group. Approximately 8-12 patients assigned to CK-3773274 in Cohort 3 will yield at least 6 evaluable patients receiving CK-3773274. Approximately 30-40 patients will be assigned to CK-3773274 in Cohort 4. Evaluable patients in this study are those who received at least one dose of IP, CK-3773274 or placebo, and have at least one post-dose evaluation as further described in Section 9.3.

The sample size was not chosen based on statistical considerations. Randomizing approximately 18 patients per cohort is considered adequate for the initial evaluation of safety and tolerability of CK-3773274 in this population. Enrolling at least 8 patients in Cohort 3 is considered adequate for the initial evaluation of safety and tolerability of CK-3773274 in patients receiving disopyramide. Enrolling 30-40 in Cohort 4 is considered adequate for the initial evaluation of safety and tolerability of CK-3773274 in patients with nHCM.

9.3. Populations for Analyses

The analysis populations are defined in Table 11.

Table 11: Analysis Sets

Analysis Set	Description
Enrolled	All patients who signed the ICF.
All Randomized or Assigned CK-3773274 Set	Patients randomly assigned to once daily CK-3773274 or placebo in 2:1 ratio in Cohorts 1 and 2 and all patients assigned to receive CK-3773274 in Cohort 3
Safety Analysis Set	All patients who received at least one dose of IP, CK-3773274 or placebo. Patients will be grouped according to the maximum actual dose of IP received.
Pharmacokinetics Analysis Set (PKS)	All patients who have at least one measurable plasma concentration of CK-3773274, provided they have no major protocol violations deviations that could affect the PK of CK-3773274.

Table 11: Analysis Sets (Continued)

Analysis Set	Description
Pharmacodynamics Analysis Set (PDS)	All patients who received any amount of IP and have a baseline and at least one post-baseline echocardiography assessment during the double-blind treatment period. Patients will be grouped according to their actual treatment, CK-3773274 or placebo.

9.4. Statistical Analyses

The Statistical Analysis Plan 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

Data will be analyzed by study part separately within each cohort. Select analyses and summaries will combine the data across the cohorts. Summary statistics for continuous variables will include numbers of patients, means, medians, standard deviations, minima, and maxima. For categorical variables, frequencies and percentages will be reported.

Assumptions for statistical models will be evaluated. If assumptions are substantially violated, alternative analysis methods will be considered. Missing data will not be imputed unless specified.

Baseline will be defined as the last available measurement taken before the first dose of IP unless otherwise specified. Patients will be grouped according to the initial treatment received, CK-3773274 or placebo, and, in general, any patients who receive any amount of CK-3773274 or placebo will be included in the analyses.

Statistical hypotheses will be tested at the nominal 10% two-sided significance level. When applicable, 90% confidence intervals will be presented, unless otherwise specified.

9.4.2. Safety Endpoints

9.4.2.1. Primary Safety Endpoints

The primary endpoints of the study are:

- Patient incidence of reported AEs from first dose of IP up to safety follow-up
- Patient incidence of reported SAEs from first dose of IP up to safety follow-up
- Patient incidence of LVEF <50% from first dose of IP up to safety follow-up.

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

9.4.2.2. Exploratory Safety Endpoints

Exploratory safety endpoints [redacted] will include:

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

9.4.3. Pharmacokinetic Endpoints

The secondary PK endpoints are observed C_{max} and C_{trough} for CK-3773274 during dosing, at timepoints listed in Table 10.

PK will also be assessed through the development of population PK model. Details of the model development and assessment will be specified in the Modelling Analysis Plan and will be documented in a separate report.

9.4.4. Pharmacodynamic Endpoints

The secondary PD endpoints of the study are:

- The slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the resting LVOT-G (Cohorts 1, 2 and 3)
- The slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the post-Valsalva LVOT-G (Cohorts 1, 2 and 3)
- The change from baseline in resting and post-Valsalva LVOT-G over time as a function of dose (Cohorts 1, 2 and 3)
- The change from baseline in resting and post-Valsalva LVOT-G to Week 10 (Cohorts 1, 2 and 3)
- Slope of the relationship of the plasma concentration of CK-3773274 to the change from baseline in the resting LVEF

Echocardiography parameters are evaluated by the core laboratory at baseline and during treatment at the Weeks 2, 4, 6, and 10 and after a 2-week washout at Week 12 (follow-up visit).

9.4.4.1. Exploratory Pharmacodynamic Endpoints

The exploratory PD endpoints include but are not limited to:

[redacted]

9.4.5. Other Exploratory Endpoints

Other exploratory endpoints include:

[redacted]

9.4.6. Patient Disposition

The number of patients who are randomized (Cohorts 1 and 2) or assigned to CK-3773274 (Cohorts 3 and 4), 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 within each cohort. Reasons for premature discontinuation as recorded on the termination page of the CRF will be summarized.

9.4.7. Demographics and Other Baseline Characteristics

Patient demographics and other baseline characteristics will be summarized descriptively by cohort, treatment and/or dose.

9.4.8. Investigational Product Exposure

IP exposure will be summarized, including the number of doses administered at each dose level, 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.

9.4.9. Safety Analysis

Safety analyses will be performed on safety analysis set. Patients will be grouped according to the maximum actual dose of IP received. Select safety summaries may be produced by the titration sequence within the subset of patients randomized or assigned to CK-3773274.

9.4.9.1. 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 preferred terms and grouped by 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 the follow up visit will be summarized. All AEs will be included in patient listings.

9.4.9.2. Serious Adverse Events

Summaries of SAEs (by preferred term and system organ class) and SAE severity will be presented.

9.4.9.3. 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.

9.4.9.4. Clinical Laboratory Parameters

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

9.4.9.5. Vital Signs

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

9.4.9.6. 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.

9.4.10. Pharmacokinetic Analysis

Descriptive statistics including mean, standard deviation, geometric mean, coefficient of variation, median, and range will be provided for the plasma concentrations. Individual or geometric mean concentrations over time will be graphically displayed.

The effect of background disopyramide on PK plasma concentrations will be assessed by ANOVA models including the data from Cohorts 1and 2 subjects randomized to CK-3773274 and from Cohort 3 subjects assigned to CK-3773274. The models will be fit for natural log transformed plasma concentrations: Day 1 (1 hour post-dose), C_{trough}, and C_{max}.

9.4.11. Echocardiography Analysis

The slope of the relationship of the plasma concentrations of CK-3773274 on select echocardiographic variables, including resting or post-Valsalva LVOT-G, will be evaluated using a mixed-effect repeated measures model for all planned measurements. The model will include terms for the baseline value and time-matched value of the plasma concentration of CK-3773274. A random intercept will be assumed in the model. The plasma concentrations may be logarithmically transformed prior to the analysis. The analyses may be performed by Cohort and/or in Cohorts 1 and 2 combined.

The effect of CK-3773274 dose on echocardiographic variables will be similarly evaluated including the dose as a continuous variable rather than plasma concentration in the analysis. This analysis will include all PDS patients treated with CK-3773274.

The treatment effect on secondary and exploratory endpoints relating to change from baseline to Week 10 will be evaluated in PDS, Cohorts 1 and 2 only, using analysis of covariance for continuous variables (with terms for treatment and baseline value) and logistic regression for categorical or binary data by cohort. The analyses will test the null hypothesis that there is no treatment difference in change from baseline to Week 10 between patients receiving placebo and those receiving CK-3773274 by cohort. The analyses may be repeated with data combined across Cohorts 1 and 2, in which case the cohort may be used as the stratification factor.

The effect of the PK of CK-3773274 on select echocardiographic variables will be evaluated using a concentration bin analysis of variance in PDS, Cohorts 1 and 2 only. Plasma concentration bin as a categorical variable will be used in the analysis. The analyses may be performed by Cohort and/or in Cohorts 1 and 2 combined.

The effect of CK-3773274 dose on echocardiographic variables will also be evaluated including the dose as a continuous variable in the analysis.

Secondary and exploratory endpoints related to change from baseline in patients receiving disopyramide (Cohort 3) and patients in Cohort 4 will be evaluated using descriptive summaries.

The effect of background disopyramide therapy on pharmacodynamic response over time through Week 10 will be assessed by ANCOVA models for change from baseline in LVOT-G at rest, LVOT-G post-Valsalva, and LVEF, including the data from Cohort 1 subjects randomized to CK-3773274 and from Cohort 3 subjects assigned to CK-3773274. The models will include terms for baseline and Cohort.

For the PD parameters with statistical distributions likely to depart from normal, the values may be log transformed prior to the analysis. The analysis results will be back-transformed and reported in terms of proportional change from baseline.

Both exploratory graphical and model-based PK-PD analyses may be conducted with select PD endpoints. A detailed description of these analyses will be presented in the Statistical Analysis Plan.

9.4.12. Health Status and Health-related Quality of Life Analysis

The slope of change from baseline to Week 10 in Health Status and Health-related Quality of Life endpoints will be evaluated using a mixed-effect repeated measures model in the US subjects randomized to Cohort 2. The treatment effect on change from baseline to Week 10 will be evaluated using analysis of covariance.

Change from baseline in patients assigned to CK-3773274 in Cohort 3 and Cohort 4 will be evaluated using descriptive summaries.

Individual responses to the HCM Global Impression of Status and Global Impression of Change questionnaires will be summarized categorically.

Further details of the analyses will be provided in the Statistical Analysis Plan.

9.5. Interim Analyses

Both blinded and unblinded interim analyses of the available safety, echocardiography, and PK data will be performed at the discretion of the Sponsor, with the PK data de-identified for the blinded analysis. Due to the exploratory nature of the study, there are no formal efficacy or futility stopping rules and the analyses will be descriptive in nature. The analyses will be described in the Interim Analysis Plan.

Representatives of Cytokinetics and the SC will review the blinded analysis results and recommend the dose levels of CK-3773274 to be administered in the next cohort. The DMC will review the unblinded analysis results, as described in Section 9.6. The timing of the interim review or the criteria for dose selection are not driven by statistical considerations. An interim analysis of Cohort 1 data will occur after at least 10 randomized patients have completed Week 6 visit and when the PK and echocardiography data from those visits are available. Including 10 randomized patients ensures that at least 6 patients randomized to CK-3773274 have been up-titrated to their maximum individual dose level and provided safety, PK, and PD data after two weeks a that dose level (ie, once steady-state PK has been reached).

Additional interim data analyses may also be conducted to facilitate planning future development.

9.6. Data Monitoring Committee

An unblinded DMC will review the dose level recommendations along with the unblinded analysis results, prior to initiating Cohort 2. The DMC may either endorse the recommendation or suggest a change in study conduct, including alteration of planned dosing regimen.

For details on the DMC, refer to Appendix 1 (Section 10.1).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study 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 study is initiated.

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study 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 study 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 study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

Patients must be informed that their participation is voluntary. Patients will be required 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 study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written 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 study.

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

Patients who are rescreened are required to sign a new ICF.

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 study-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 study organization will include an SC and DMC.

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

The DMC will be established in order to review the SC recommendations regarding the cohort dose levels. The DMC will also be responsible for periodic review of study data to ensure the safety of study patients, and for review of SAEs on an ongoing basis. 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) study team involved in study 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 study 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 study-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 study including quality checking of the data.

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

Study 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The study site should plan on retaining such documents for approximately 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Cytokinetics. No records may be transferred to another location or party without written 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 study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open.

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

The investigator may initiate study-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 study 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 study is prematurely terminated or suspended, Cytokinetics shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study 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 12 will be performed by the central laboratory.

Local laboratory results are not required for dosing decisions and/or response evaluation; they are only expected for urgent evaluation where same-day results are required for patient management. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Information regarding use of local laboratories (date/time of draw and results) should be kept with the patient source documentation.

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 study as determined necessary by the investigator or required by local regulations.

Table 12: Protocol-Required Safety Laboratory Assessments

Chemistry		Urinalysis	Hematology	Other Assessments
Sodium	Total bilirubin	Specific gravity	Hemoglobin	CK-3773274 plasma concentration (PK)
Potassium	Direct bilirubin	pH	Hematocrit	
Chloride	CK	Blood	RBC	Pregnancy test[a]
Calcium	ALP	Protein	RDW	FSH[a]
Magnesium	LDH	Glucose	MCV	NT-proBNP
Phosphorus	AST (SGOT)	Bilirubin	MCH	hs-cTnI
Urea	ALT (SGPT)		MCHC	
Creatinine			WBC	
			Platelets	
			INR	

ALP = alkaline phosphatase; CK = creatine kinase; FSH = follicle-stimulating hormone; hs-cTnI = high sensitivity cardiac troponin I; INR = international normalized ratio; 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; RBC = red blood cell; RDW = red cell distributions width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell

[a] A pregnancy test is required for WOCBP; FSH only at screening if needed.

Investigators must document their review of each laboratory report.

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

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Event

AE Definition

An AE is defined as any untoward medical occurrence in a clinical study patient. The event does not necessarily have a causal relationship with IP.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- 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 study.
- 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.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.
- SAEs occurring before initiation of IP and assessed as related to study procedures must be recorded on the AE CRF.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Serious Adverse Event

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

1. **Results in death**
2. **Is life-threatening**
   - The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at immediate 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.
3. **Requires inpatient hospitalization or prolongation of existing hospitalization**
   - In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
   - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. **Results in persistent disability/incapacity**
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. **Is a congenital anomaly/birth defect**
6. **Other situations:**
   - Medical or scientific judgment should be exercised in deciding whether SAE 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should 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.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording/Reporting

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF and report SAEs within 24 hours of awareness to Cytokinetics.
- It is not acceptable for the investigator to send photocopies of the patient's medical records to Cytokinetics in lieu of completion of the AE/SAE CRF.
- There may be instances when copies of medical records for certain cases are requested by Cytokinetics. In this case, all patient identifiers, except the patient number, will be redacted on the copies of the medical records before submission to Cytokinetics.

The investigator will 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.

Assessment of Intensity

- The investigator will assess the intensity for each AE and SAE reported during the study and assign it to one of the following categories:
  - Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
  - An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between IP and each occurrence of each AE/SAE.
- 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.

- The investigator will use clinical judgment to determine the relationship.
- 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.

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 study or during a recognized follow-up period, the investigator will provide Cytokinetics with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Cytokinetics within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Cytokinetics via Paper Form

- Facsimile or email transmission of the SAE paper CRF is the preferred method to transmit this information to Cytokinetics.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

To report an SAE:

Email: **DrugSafety@cytokinetics.com**

Facsimile: +1 (650) 243-4199

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

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 study 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 study. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before study 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 study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study 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 hormonal contraception is used as a highly effective method of birth control, 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 study patient.

Collection of Pregnancy Information:

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

Email: **DrugSafety@cytokinetics.com**

Facsimile: +1 (650) 243-4199

Note: Sites are not required to provide any information on the Pregnancy Report Form that violates the country or region's local privacy laws.

While pregnancy itself is not considered to be an AE or SAE, it is reportable within 24 hours of investigator awareness. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to Cytokinetics as described in Section 8.3.6. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Pregnancies will be followed until their conclusion.

Male Patients with Partners Who Become Pregnant

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 study. This applies only to male patients who receive IP.

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. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial information will be recorded on the Pregnancy Report Form and submitted to Cytokinetics as per Section 8.3.6 within 24 hours of learning of a patient's pregnancy.

The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and forward to Cytokinetics on a Pregnancy Report Form. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. The follow-up of an infant (if applicable) will be conducted up to 12 months after the birth of the child.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Any female patient who becomes pregnant while participating in the study will discontinue IP or be withdrawn from the study.

10.5. Appendix 5: 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 be part of this study.

DNA samples will be used for research related to this study 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 study summary.

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Drug-induced Liver Injury Reporting & Additional Assessments

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin (TBL) and/or international normalized ratio (INR) elevation according to the criteria specified in Section 7.1.2 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 Appendix 3 (Section 10.3).

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 Withholding 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 withholding 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 return to normal or 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 is to 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.

10.7. Appendix 7: Abbreviations

Table 13: List of Abbreviations

Abbreviation/Term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
C_{max}	Maximum plasma concentration observed
C_{trough}	Trough plasma concentration observed
CRF	Case report form
CRO	Contract research organization
CYP	Cytochrome P450
DILI	Drug induced liver injury
DMC	Data monitoring committee
ECG	Electrocardiogra(m/phy)
EOS	End of study
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter defibrillators
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IVRS/IWRS	Interactive voice/web response system
LV	Left ventricle(ular)
LVEF	Left ventricular ejection fraction
LVFS	Left ventricular fractional shortening
LVOT	Left ventricular outflow tract
LVOT-G	Left ventricular outflow tract gradient

Abbreviation/Term	Explanation
HCM	Hypertrophic cardiomyopathy
MAD	Multiple ascending dose
nHCM	Non-obstructive hypertrophic cardiomyopathy
NOAEL	No-observed-adverse-effect-level
NYHA	New York Heart Association
oHCM	Obstructive hypertrophic cardiomyopathy
PD	Pharmacodynamics
PDS	Pharmacodynamics analysis set
PK	Pharmacokinetics
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SC	Steering Committee
SoA	Schedule of activities
TBL	Total bilirubin
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

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

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 Association. (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., Hellawell, J. L., Lucove, J. C., Farzaneh-Far, R. and Olivotto, I. (2016). "Occurrence of clinically diagnosed hypertrophic cardiomyopathy in the united states." The American Journal of Cardiology 117(10): 1651-1654.

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.

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.