Statistical Analysis Plan: 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

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STATISTICAL ANALYSIS PLAN

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STUDY DRUG: CK-3773274

PROTOCOL NUMBER: CY 6021

STUDY TITLE:

A Multi-Center, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, and Tolerability and Pharmacodynamics of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy

SPONSOR:

Cytokinetics, Inc.
280 East Grand Avenue
South San Francisco, CA 94080

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and approved by:

[redacted], ME
[redacted]
Cytokinetics, Inc.

See appended signature page
Signature

Date

This document has been reviewed and approved by:

[redacted], PhD
[redacted]
Cytokinetics, Inc.

See appended signature page
Signature

Date

[redacted], MD, FACC, FASE
[redacted]
Cytokinetics, Inc.

See appended signature page
Signature

Date

[redacted], MD, PhD
[redacted]
Cytokinetics, Inc.

See appended signature page
Signature

Date

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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BSA	body surface area
CI	confidence interval
C_{max}	maximum plasma concentration observed
C_{trough}	trough plasma concentration observed
CSR	clinical study report
CV	coefficient of variation
DMC	data monitoring committee
ECG	electrocardiogra(m/phy)
[redacted]	[redacted]
eCRF	electronic case report form
[redacted]	[redacted]
GLSM	geometric least squares mean
HCM	hypertrophic cardiomyopathy
HR	heart rate
HRQoL	health related quality of life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IWRS	interactive web-based randomization system
LAV	left atrial volume
LAV-I	left atrial volume index

Abbreviation	Term
ln	natural logarithm function
LOQ	limit of quantification
LSM	least squares mean
LV	left ventricular
LVCO	left ventricular cardiac output
LVCO-I	left ventricular cardiac output index
[redacted]	[redacted]
LVEDV	left ventricular end-diastolic volume
LVEDV-I	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction
[redacted]	[redacted]
LVESV	left ventricular end-systolic volume
LVESV-I	left ventricular end-systolic volume index
[redacted]	[redacted]
LVOT-G	left ventricular outflow tract gradient
[redacted]	[redacted]
[redacted]	[redacted]
LVSV	left ventricular stroke volume
LVSV-I	left ventricular stroke volume index
MedDRA	Medical Dictionary for Regulatory Activities Terminology
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PD	pharmacodynamics
PDS	pharmacodynamics analysis set
PK	pharmacokinetics
PKS	pharmacokinetics analysis set
PRO	patient reported outcomes
PT	preferred term
Q_1	first quartile
Q_3	third quartile
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SEM	standard error of mean
SOC	system organ class
SVT	supraventricular tachycardia
TFLs	tables, figures, and listings
ULN	upper limit of normal
VT	ventricular tachycardia
[redacted]	[redacted]
WHO	World Health Organization

SAP VERSION HISTORY

Version and Date	Revision	Rationale
Final 1.0, 30 October 2020	Not applicable: original version	Not applicable
Amendment 1.0, 11 January 2022	[redacted]	[redacted]
	[redacted]	The new objectives were added in Study Protocol Amendment 3 and 4
	[redacted]	[redacted]
	Section 3: added description of Cohort 3 and 4	Cohort 3 description added in Study Protocol Amendment 3; Cohort 4 added in Protocol Amendment 4
	[redacted]	[redacted]
	[redacted]	Inadvertent prior omission
	[redacted]	[redacted]
	[redacted]	[redacted]

Version and Date	Revision	Rationale
	[redacted]	[redacted]
	[redacted]	[redacted] 2.
	[redacted]	[redacted]
	[redacted]	Inadvertent prior omission
	[redacted]	[redacted]
	Minor revisions throughout the document	Clarity and consistency

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol CY 6021.

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to database lock and unblinding of the study data. Further study information can be found in the protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to determine the safety and tolerability of CK-3773274 in patients with symptomatic hypertrophic cardiomyopathy (HCM).

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- To describe the concentration-response relationship of CK-3773274 on the resting and post-Valsalva left ventricular outflow tract gradient (LVOT-G) on echocardiogram over 10 weeks of treatment (Cohorts 1, 2, 3 only) and on resting LVEF for all cohorts.
- To describe the dose response relationship on LVOT (resting and Valsalva) of CK-3773274 in patients with symptomatic HCM (Cohorts 1, 2, 3 only).
- To evaluate the plasma concentrations of CK-3773274 in patients with HCM.

2.1.3. Exploratory Objectives

The following exploratory objectives of this study as specified in the study protocol are:

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- Patient incidence of reported adverse events (AEs),
- Patient incidence of reported serious adverse events (SAEs),
- Patient incidence of left ventricular ejection fraction (LVEF) <50%.

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- 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,
- 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,
- Observed C_{max} and trough plasma concentration (C_{trough}) for CK-3773274 during dosing.

2.2.3. Exploratory Endpoints

The following exploratory endpoints are listed in the study protocol:

[redacted]

[redacted]

2.2.3.1. Additional Exploratory Endpoints

[redacted]

Table 2: [redacted]

Study Protocol Variable Name[a]	Endpoint Name for the TFLs	Abbreviated Endpoint Name(s) for the SAP and TFLs/Derivation
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 2: Echocardiographic Variable Names and Derivations for Presentation of Results (Continued)

Study Protocol Variable Name[a]	Endpoint Name for the TFLs	Abbreviated Endpoint Name(s) for the SAP and TFLs/Derivation
[redacted]	[redacted]	[redacted]
n/a	[redacted]	[redacted]
[redacted]		
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
n/a	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]

Table 2: Echocardiographic Variable Names and Derivations for Presentation of Results (Continued)

Study Protocol Variable Name[a]	Endpoint Name for the TFLs	Abbreviated Endpoint Name(s) for the SAP and TFLs/Derivation
n/a	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
[redacted]		
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]
n/a	[redacted]	[redacted]

[a] [redacted]

[redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 2, multi-center, randomized, placebo-controlled, double-blind, dose finding study in patients with symptomatic oHCM. Three sequential cohorts will be enrolled. The first two cohorts will exclude patients receiving disopyramide. Cohort 3 will only include patients receiving disopyramide. 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 cohort, all patients will receive up to three escalating doses of CK-3773274 based on echocardiographic guidance. There is no placebo control group in Cohort 3. Cohort 4 will only include patients with nHCM. 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 per cohort in the first two cohorts and approximately 8-12 patients assigned to receive CK3773274 in the third 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 cohort and fourth cohort.

Representatives of Cytokinetics and the Steering Committee (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 data monitoring committee (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.

3.2. Definition of Study Drugs

Study drugs used in the study are listed in Table 3. All study drugs listed are investigational products (IP).

Table 3: Study Drugs

	Study Arm	
	Active	**Placebo**
IP 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)	Echocardiography-guided dose titration with cohort-specific dose levels. See Table 4	Random dose titration using placebo tablets
Route of Administration	Oral	Oral

Table 3: Study Drugs (Continued)

	Study Arm	
	Active	**Placebo**
Use	Experimental	Placebo
Packaging	IP will be provided in bottles containing 40 tablets each	IP will be provided in bottles containing 40 tablets each

3.2.1. Cohort Dose Levels

In each cohort, a patient assigned to CK-3773274 will receive up to three escalating doses of the study drug as shown in Table 4.

Table 4: CY 6021 Dosing Scheme for the Patients Randomized to CK-3773274

Cohort	Dose 1	Dose 2	Dose 3
Cohort 1	5 mg = 1×5 mg tablet	10 mg = 2×5 mg tablets	15 mg = 3×5 mg tablets
Cohort 2	10 mg = 1×10 mg tablet	20 mg = 2×10 mg tablets	30 mg = 3×10 mg tablets
Cohort 3	5 mg = 1×5 mg tablet	10 mg = 2×5 mg tablets	15 mg = 3×5 mg tablets
Cohort 4	5 mg = 1×5 mg tablet	10 mg = 2×5 mg tablets	15 mg = 3×5 mg tablets

Tablets of the same strength and, for Cohorts 1 and 2, matching placebo will be used to implement dose titration within each cohort as described in Section 3.2.2.

3.2.2. Dose Titration

Each patient will receive Dose 1 or, for Cohorts 1 and 2, matching placebo once daily for 2 weeks. At Week 2, the patients will have an echocardiogram at 2 hours following administration of study drug.

For Cohorts 1, 2 and 3:

Patients receiving CK-3773274 will up-titrate to Dose 2 if either of the following conditions are met, based on the local echocardiography assessment:

- LVOT-G at rest ≥ 30 mmHg and LVEF ≥ 50%

OR

- LVOT-G at rest < 30 mmHg, LVOT-G during Valsalva maneuver ≥ 50 mmHg, and 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 study drug. Patients receiving CK-3773274 will up-titrate to the next higher dose if either of the following conditions are met, based on the local echocardiography assessment:

- LVOT-G at rest ≥ 30 mmHg and LVEF ≥ 50%

OR

- LVOT-G at rest < 30 mmHg, LVOT-G during Valsalva maneuver ≥ 50 mmHg, and 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 study drug. If LVEF is <50% at Week 6, the patients receiving CK-3773274 will be returned to a prior dose level or to placebo if the patient was on Dose 1.

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

If four or more of the 18 patients in each cohort have had an LVEF < 50% 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.

Patients randomized to placebo in Cohorts 1 and 2 will undergo a random titration for the number of placebo tablets administered to mimic one of the possible PD-driven dose titration scenarios in the patients randomized to CK-3773274.

For Cohort 4:

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

3.3. Sample Size Considerations

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 CK3773274 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. Evaluable patients in this study are those who received at least one dose of study drug, CK-3773274 or placebo, and have at least one post-dose evaluation as further described in Section 5.4.

The sample size was not chosen based on statistical considerations. Randomizing approximately 18 patients per cohort in Cohorts 1 and 2 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.

3.4. Randomization

Approximately 36 patients will be randomized in Cohorts 1 and 2 with approximately 18 patients per cohort. After a four-week screening period, eligible patients will be randomized to once daily CK-3773274 or placebo in a 2:1 ratio.

Subjects in Cohort 3 and 4 will be assigned to CK-3773274.

All patients will be centrally assigned to randomized IP in Cohorts 1 and 2 or to CK-3773274 in Cohort 3 and 4 using an Interactive Web Response System (IWRS).

The patient is considered randomized or assigned to CK-3773274 when he or she is randomized or assigned IP in the IWRS after meeting all eligibility criteria. Randomization or assignment to CK-3773274 should occur during the Day 1 visit.

During the Week 2 visit, each patient randomized to placebo in Cohorts 1 and 2 will be re-randomized in the IWRS to a placebo journey, a random dose-titration scenario to mimic one of the possible echocardiography-guided dose titration scenarios in the patients randomized to CK-3773274 (Section 3.2.2)

3.5. Clinical Assessments

Schedule of activities and assessments defined in Study Protocol Section 1.3. is provided in Table 5. A summary of PK and echocardiography time points is provided in Table 6.

Table 5: Protocol Schedule of Activities

For Cohorts 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	[redacted]										
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]		[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 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 in the protocol for PK timing.

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

h Only for US patients.

For 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											

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)										
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			
IP dose adjustment				X	X	X[g]						
PATIENT-REPORTED OUTCOMES AND ASSESSMENTS												
NYHA Functional Classification	X	[redacted]										
[redacted]												

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)										
[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 in the protocol for PK timing.

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

Table 6: Summary of PK and Echocardiography Time Points

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

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

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.

4. PLANNED ANALYSES

4.1. Interim Analyses

4.1.1. Interim Cohort Review

Representatives of Cytokinetics and the SC will conduct interim review of the blinded safety, echocardiographic, and de-identified PK data available from a cohort to recommend the dose levels of CK-3773274 to be administered in the next cohort or to facilitate planning future development of CK-3773274. An unblinded DMC will review the recommendation for the dose level in the next cohort 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.

The timing of the interim review or the criteria for dose selection are not driven by statistical considerations. An interim analysis of cohort 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. The data cut off point will be approximately 4 weeks after the last required Week 6 visit, based on the anticipated availability of the required data.

Meanwhile, cohort enrollment will continue until either approximately 18 patients are randomized or until the DMC reviewed cohort data and recommended opening the next cohort, whichever is the earlier.

The interim analysis will follow an interim analysis plan. The clinical data for the interim review will undergo routine cleaning and vendor data timepoint reconciliation, but the data will not be finalized prior to the analysis.

The unblinded analysis will be conducted by an external statistical group. The study team will remain blinded to individual treatment assignments and to the analysis results that may reveal individual treatment assignments.

4.1.2. Complete Cohort Interim Analysis

A complete cohort interim analysis may occur after each cohort enrollment is complete, all patients enrolled in the cohort have completed the study including the 4 week safety follow up, and all data has been entered into the clinical data base, verified and frozen. Unblinding of each cohort patient treatment assignments may occur after the database lock for all Cohort data.

4.2. Final Analyses

The final analysis will occur after all patients enrolled in the study have completed the study including the 4 week safety follow up, all data has been entered into the clinical data base, verified, and locked. Unblinding for the final analysis will occur after the database lock.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table, Figure, and Individual Patient Data Listing Considerations

Summary tables and listings (eg post text tables and individual patient data listings) will be prepared according to ICH Guideline E3 and include a "footer" providing explanatory notes that indicate, as a minimum:

1. Date of data extraction,
2. Date of output generation,
3. SAS program name, including the path that generates the output,
4. Any other specific details that require further elaboration.

The appropriate listings supporting the tables will be included and not specified in the individual sections throughout the document. Post-text tables will include reference(s) to the patient data listing(s) that support the summary data.

Summary tables and listings and derived datasets will be generated using SAS ® software version 9.4 or above.

In general, the tables and figures summarizing the data will be produced separately for each cohort and organized by treatment group. The order of drug presentation for Cohorts 1 and 2 will be placebo followed by CK-3773274, followed by an overall total column, combining placebo and CK-3773274 data. Cohort 3 and 4 data presentations will only include CK-3773274 treatment group.

In the tables summarizing data for the study overall, treatment group will be further organized by the highest dose level administered throughout the study. The order will be from the lowest dose level to the highest dose level, followed up by all doses of CK-3773274 combined. Examples of tables summarizing data for the study overall include demographics, baseline characteristics, extent of exposure, concomitant medications, and adverse event summaries.

The tables summarizing data by visit over time, eg summaries of pharmacodynamic parameters, safety laboratory parameters, vital signs, and electrocardiogram data, will show change from baseline by dose level at visit. For Cohorts 1 and 2, baseline data will be additionally summarized in an overall total column pooling the data across treatment arms.

The figures summarizing the data over time will include displays of baseline and post-baseline data by baseline/visit and by treatment (placebo or CK-3773274) and displays of post-baseline on-treatment data by dose level at visit.

Medications and medical conditions are coded using standard dictionaries. World Health Organization (WHO) Drug standard dictionary version September 2019 b3 is used for coding of concomitant medications; anatomical therapeutic chemical (ATC) level 3 classification and preferred name will be used in data listings and summaries. MedDRA dictionary version 22.1 is used for coding of medical history and adverse events; system organ class (SOC) and preferred term (PT) will be used in data summaries.

Patient data listings will be sorted by patient ID and, within each patient, chronologically by assessment, start, or onset date and time.

5.2. Data Management

Data will be entered into a clinical data base with programmed edit checks to ensure data coherence and integrity. The data will be reviewed and cleaned according to a data management plan. The data transfers from external vendors will follow pre-approved data transfer agreements and reconciled with the clinical data base entries. Medication and medical conditions coding will be reviewed by qualified personnel.

5.3. Data Presentation Conventions

Continuous variables will be summarized using descriptive statistics: the number of patients with available data (n), mean, standard deviation (SD), median, first quartile (Q_1), third quartile (Q_3), minimum, and maximum.

For select variables, summaries based on the lognormal distribution assumptions may be appropriate, therefore the geometric mean and geometric coefficient of variation (CV) (%) will also be displayed. Geometric CV (%) will be derived as $100\% \times \text{sqrt}(\exp(s^2)-1)$, where s is the standard deviation of the natural logarithm (ln) transformed data.

Presentations of the results of statistical analyses of continuous variables using the normal distribution assumption will include least squares mean (LSM) estimates of the parameters of interest, standard errors of mean (SEM), and the associated 90% confidence intervals (CIs). Presentations of the results of statistical analyses of continuous variables using the lognormal distribution assumption will include geometric LSM (GLSM) estimates and the associated 90% CIs. Presentations of the results of statistical analyses of categorical variables will include odds ratios and the associated 90% CIs. Nominal two-sided p-values will accompany statistical analysis results.

The mean, median, Q_1, Q_3, and geometric mean will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value. Geometric CV (%) will be presented with one decimal place.

For the statistical analyses results that are on the same scale as a measured value (e.g. change from baseline or treatment difference estimates), the LSM estimates and LSM estimate 90% CI boundary values will be formatted to one more decimal place than the measured value; SEM estimates will be formatted to two more decimal places than the measured values. The format for the LSM estimates of slope will be formatted to at least three significant digits for LSM estimates and LSM estimate 90% boundaries and to at least four significant figures for the SEM.

GLSM estimates for the proportional change from baseline, proportional change treatment ratios, odds ratios, and the corresponding 90% CIs will be presented with two decimal places.

Categorical variables will be summarized using counts and percentages. Percentages will be calculated using the total number of patients per treatment group and presented with one decimal place.

Date variables will be formatted as YYYY-MMM-DD for the presentation. Time will be formatted in military (24 hour) time format as HH:MM.

P-values, if applicable, will be presented to 3 decimal places. If the p-value is less than 0.001, then it will be presented as <0.001. If the rounded p-value equals 1.000, it will be displayed as >0.999.

Figures displaying continuous data over time may include box plots, plots showing means and standard deviation bars, plots showing geometric means, and line plots of individual data. Box plots will include overlays showing individual data points, formatted by dose level at visit. Figures displaying statistical analysis results will show LSM estimates or GLSM estimates and the corresponding 90% confidence intervals. Figures displaying means or LSM estimates will be presented on linear scale. Figures displaying geometric means or GLSM estimates may be presented on linear or semilogarithmic scale.

Scatter plots showing date-matched individual data points will be formatted by dose level at visit.

Categorical data may be presented as bar charts. The bars showing counts of patients across multiple categories will be stacked.

The table, figures, and listings (TFL) shells and the TFL table of contents (TOC) provide the expected layout of the TFLs. Any changes to the actual TFL formats or other minor revisions to the TFL shells will not necessitate a revision to the SAP nor will they constitute a deviation from the planned analyses. Only substantial differences to the analyses require a SAP revision or a documentation in the CSR.

5.4. Analysis Populations

5.4.1. All Screened Patients

All patients who signed the informed consent form are included in the All Screened Patients population.

Patients who gave informed consent but are not randomized are considered screen failures. The following reasons for screen failures are collected: inclusion/exclusion criteria (including specific criteria not met), principal investigator decision, subject decision, lost to follow up, other. For the patients who failed two screening periods (screening and re-screening), the reasons for failing either period will be included.

5.4.2. Randomized Patients

All patients randomized (Cohorts 1 and 2) or assigned to CK-3773274 (Cohort 3 and 4) in the IWRS will be included in the randomized patients analysis set. Patients will be grouped according to the randomized or assigned treatment. This analysis set will be primarily used for the summaries of patient disposition described in Section 6.1.

5.4.3. Safety Analysis Set

Safety analysis set will include 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.

A reason for exclusion from safety analysis set will be:

- Patient not dosed.

5.4.4. Pharmacokinetics Analysis Set (PKS)

Pharmacokinetics Analysis Set (PKS) will include all dosed patients who have at least one evaluable plasma concentration sample, provided they have no major protocol violations deviations that could affect the PK of CK-3773274.

Reasons from exclusion from the PKS will be:

- Patient not dosed,
- No evaluable plasma concentrations,
- Major deviation affecting PK.

5.4.5. Pharmacodynamics Analysis Set (PDS)

Pharmacodynamics Analysis Set (PDS) will include all patients who received at least one dose of IP and have a baseline and at least one post-baseline core laboratory echocardiography assessment including non-missing LVEF measurements and non-missing LVOT-G at rest. Patients will be grouped according to their actual treatment, CK-3773274 or placebo.

Reasons from exclusion from the PDS will be:

- Patient not dosed,
- No baseline LVEF or LVOT-G at rest assessments,
- No post-baseline LVEF or LVOT-G at rest assessments.

5.5. Baseline Definition

In general, baseline will be defined as the last non-missing measurement/assessment prior to the first dose of the IP.

The records collected on the same date as the first dose of the IP that do not have assessment time are considered to have occurred prior to the first dose.

For the echocardiographic variables based on the core laboratory assessments, local assessments will not be included in the derivation of baseline.

For the 12-lead electrocardiography (ECG) variables, averages of triplicate measurements will be computed as described in Section 5.6.9 prior to the derivation of baseline.

The baseline cardiac rhythm characterization assessment values will be those from the most recent acceptable ambulatory cardiac monitoring assessment with recording end prior to the first dose of the IP.

5.6. Derived and Transformed Data

5.6.1. Baseline Characteristics Variables

In general, baseline characteristics will be derived using the information collected during screening. For the rescreened patients, the information from the most recent screening visit will be used.

5.6.1.1. Demographics Variable Derivation

The age will be calculated using the following formula:

Age (years) = FLOOR ((screening date– date of birth)/365.25),

Where FLOOR() is the function rounding the result down to the nearest integer. Only year of birth is collected in this study. For the calculation of the patient's age, the date of birth will be imputed with 01 January.

Patient age will be categorized as < 65 years or ≥ 65 years.

5.6.1.2. Body Measurements Variable Derivation

Baseline body surface area (BSA) will be calculated using the weight and height at screening using the DuBois and DuBois formula and rounded to two decimal points for the presentation of results:

BSA (m^2) = 0.007184 * (weight $^{0.425}$ * height $^{0.725}$).

5.6.1.3. Medical History Variable Derivation

Medical history is collected on separate electronic case report forms (eCRFs) as:

- HCM history, including whether any of the following oHCM criteria were met
  - LV hypertrophy and non-dilated LV chamber in the absence of other cardiac disease,
  - Positive family history of HCM,
  - Known HCM-causing gene mutation;
- Select cardiovascular medical history capturing any history of
  - Myocardial infarction,
  - Obstructive coronary artery disease,
  - Paroxysmal atrial fibrillation,
  - Syncope,
  - Sustained ventricular tachycardia,
  - Ventricular fibrillation,
  - Torsades de Pointes;
- General or other medical history.

Time since initial HCM diagnosis will be calculated using the following formula and rounded to one decimal place for the presentation of the results:

Time since diagnosis (years) = (screening date – date of diagnosis)/365.25.

Imputation of the missing date of diagnosis is described in Section 5.7.4.

5.6.2. Study Day

If the date of interest occurs on or after the first dose date, then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose, then study day will be calculated as (date of interest – date of first dose). There is no study day 0.

5.6.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

Proportional change from baseline is calculated as (post-baseline result/baseline result).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

5.6.4. Visit Windows

Analysis visit windows for 12-lead ECG, vital signs, echocardiography, safety laboratory, and cardiac biomarker data, NYHA class, and PROs are summarized in Table 7. Measurements collected after the first dose of the IP through Day 8 will be excluded from the summary tables. After Day 8, the windows will be contiguous for the assessments done at every scheduled visit. For less frequent assessments, the measurements outside the analysis windows specified in Table 7 will be excluded. Day 1 records that do not have assessment time are considered pre-dose.

Table 7: Analysis Visit Windows

Analysis Visit	Target Study Day	Analysis Visit Windows (Study Day)		
		12-Lead ECG, Vital Signs, Echo-cardiography, PK, and NYHA Class	Safety Laboratory and Troponin-I, Patient Reported Outcomes	NT-proBNP
Baseline[a]	1	-28 to 1 (pre-dose[b])		
Week 2	15	9[c] to 22	n/a[d]	n/a[d]
Week 4	29	23 to 36	n/a[d]	n/a[d]
Week 6	43	37 to 57	37[c] to 57	n/a[d]
Week 10	71	58 to the maximum of (77, last dose day + 6)	58 to the maximum of (77, last dose day + 6)	58[c] to the maximum of (77, last dose day + 6)
Week 12	85	≥ maximum of (78, last dose day +7)	≥ maximum of (78, last dose day + 7)	≥ maximum of (78, last dose day + 7)

[a] Baseline is defined as the last assessment within the window

[b] Day 1 records that do not have assessment time are considered pre-dose

[c] Assessments after the first dose of study drug and prior to the first post-dose analysis window will not be included in the summary tables
[d] Not a protocol scheduled visit

Ambulatory cardiac monitoring is to occur for at least 5 days and no more than 7 days prior to the first dose of study drug and for at least 5 days prior to the last dose. For the purposes of the inclusion in the analysis of cardiac rhythm pattern characterization, a minimum of 24-hour collection based on the start of recording date/time and total analyzed time is required.

5.6.5. Multiple Assessments

For multiple assessments within a post-baseline analysis visit window, the assessment closest to the target study day will be chosen. For the equidistant dates, the later of the two will be chosen.

Note that for the 12-lead ECG variables, the average of triplicate values will be derived as described in Section 5.6.9 prior to the application of this rule.

5.6.6. Pharmacokinetics Plasma Concentration Bins

To enable PK/PD analysis of the relationship of echocardiographic variables to plasma concentration ranges, all Week 2, Week 4, Week 6, and Week 10 maximum post-dose plasma concentration values across all PKS patients who had received at least one dose of CK-3773274 will be assigned to one of the four bins: Bin 1, Bin 2, Bin 3, and Bin 4 using the following algorithm.

First, minimum, maximum, median, Q_1, and Q_3 of all maximum post-dose PK plasma concentration values above the limit of quantification (LOQ) from Week 2, Week 4, Week 6, and Week 10 visits will be derived. Second, the Week 2, 4, 6, and 10 maximum post-dose plasma concentration values from the patients who had received at least one dose of CK-3773274 prior to the PK sample collection will be assigned to Bin 1, Bin 2, Bin 3, or Bin 4:

- Bin 1 will contain the values that are less than or equal to Q_1; this would include any values below LOQ from the patients who had received CK-3773274;
- Bin 2 will contain the values greater than Q_1 and less than or equal to the median;
- Bin 3 will contain the values greater than the median and less than or equal to Q_3;
- Bin 4 will contain the values greater than Q_3 up to the maximum value.

Week 2, 4, 6 and 10 visits from placebo patients will be assigned to the Placebo Bin. These values are expected to be below LOQ; this bin will be used as a reference in the statistical analysis. Bins are derived for each Cohort 1 and 2 separately for by Cohort analyses. For analyses combining Cohort 1 and 2, bins are derived based on data from both cohorts.

5.6.7. Values Below the Limit of Quantification

5.6.7.1. Safety Laboratory and Cardiac Biomarkers Values Below the Limit of Quantification

For the purposes of the analysis, safety laboratory and cardiac biomarker results below the LOQ will be imputed by $LOQ - 0.1^d$, where d is the number of decimal places with which the parameter is reported.

For instance, if a parameter is reported to 2 decimal places and the LOQ is 0.30, then the values below LOQ will be imputed with 0.29; if a parameter is reported to 1 decimal place and the LOQ is 5.9, then the values below LOQ will be imputed with 5.8.

5.6.7.2. Pharmacokinetics Plasma Concentration Values Below the Limit of Quantification

For the calculation of summary statistics with the exception of geometric mean and geometric CV(%), plasma concentration values below LOQ of 1.00 ng/mL will treated as 0 before the first quantifiable concentration and as missing elsewhere. Geometric mean and CV(%) will be derived using quantifiable data.

For the purposes of the PK concentration-response analyses, plasma concentration values below LOQ will be replaced by zero, with the exception of the analyses requiring logarithmic transformation of plasma concentrations, for which the values below LOQ will be replaced by the LOQ (1 ng/dL).

5.6.8. Echocardiographic Data

Unless otherwise specified, echocardiographic variables will be based on the core echocardiography laboratory assessments.

5.6.8.1. Continuous Echocardiographic Variables

The echocardiographic parameters listed in Table 2 and changes from baseline at Week 2, 4, 6, 10, and 12 will be analyzed. For LVOT-G at rest and LVOT-G during Valsalva maneuver, the proportional change from baseline will be also analyzed.

[redacted]

For the presentation of results, the BSA-indexed variables will be rounded to the same number of decimal places as the corresponding non-indexed variables provided by the echocardiography core laboratory.

[redacted]

[redacted]

5.6.9. Vital Signs

Vital sign variables in the following categories will be considered potentially clinically significant:

- Systolic blood pressure ≤ 80 or ≥ 160 mmHg,
- Diastolic blood pressure ≤ 50 or ≥ 100 mmHg,
- Heart rate ≤ 50 or ≥ 120 beats/min,
- Respiration rate > 22 breaths/min.

5.6.10. 12-Lead ECG

Triplicate 12-lead ECGs will be obtained at each protocol specified time point. The measurements of the following variables in each set of triplicates will be averaged prior to the analysis: HR, RR interval, PR interval, QRS duration, QT interval, QT interval corrected using Bazett's formula (QTcB), QT interval corrected using Fridericia's formula (QTcF).

Changes from baseline will be derived for these parameters.

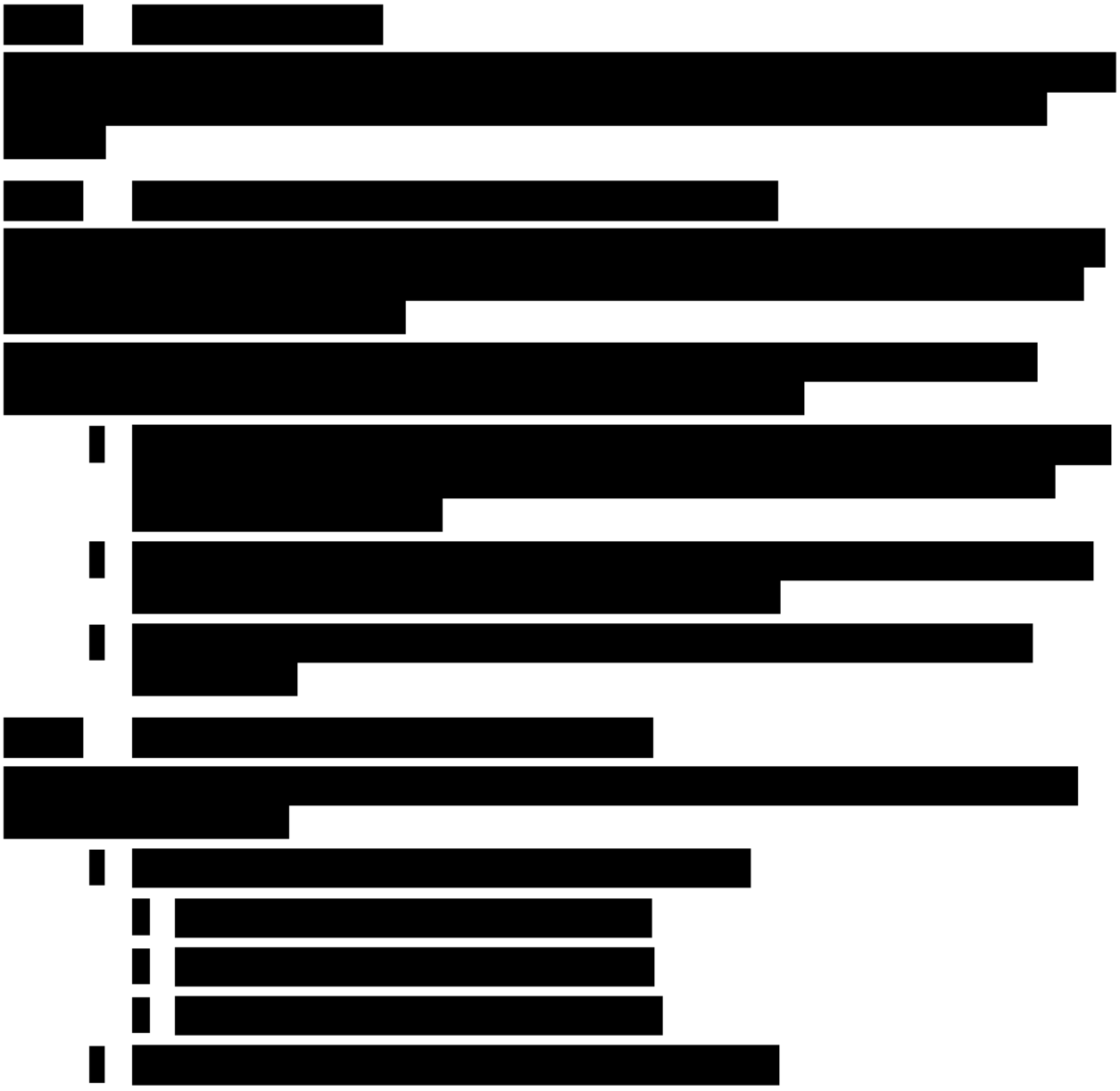
Additionally, the 12-lead ECG variables will be assigned to the following categories at each visit:

- QTcB and QTcF values: ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec
- QTcB and QTcF changes from baseline: ≤ 30, > 30 to ≤ 60, and > 60 msec
- PR values: < 200, ≥ 200 to < 220, and ≥ 220 msec
- QRS values: < 120 and ≥ 120 msec.

The QTcB and QTcF values and changes from baseline will also be assigned to the above categories based on the maximum post-baseline value, including scheduled and unscheduled visits.

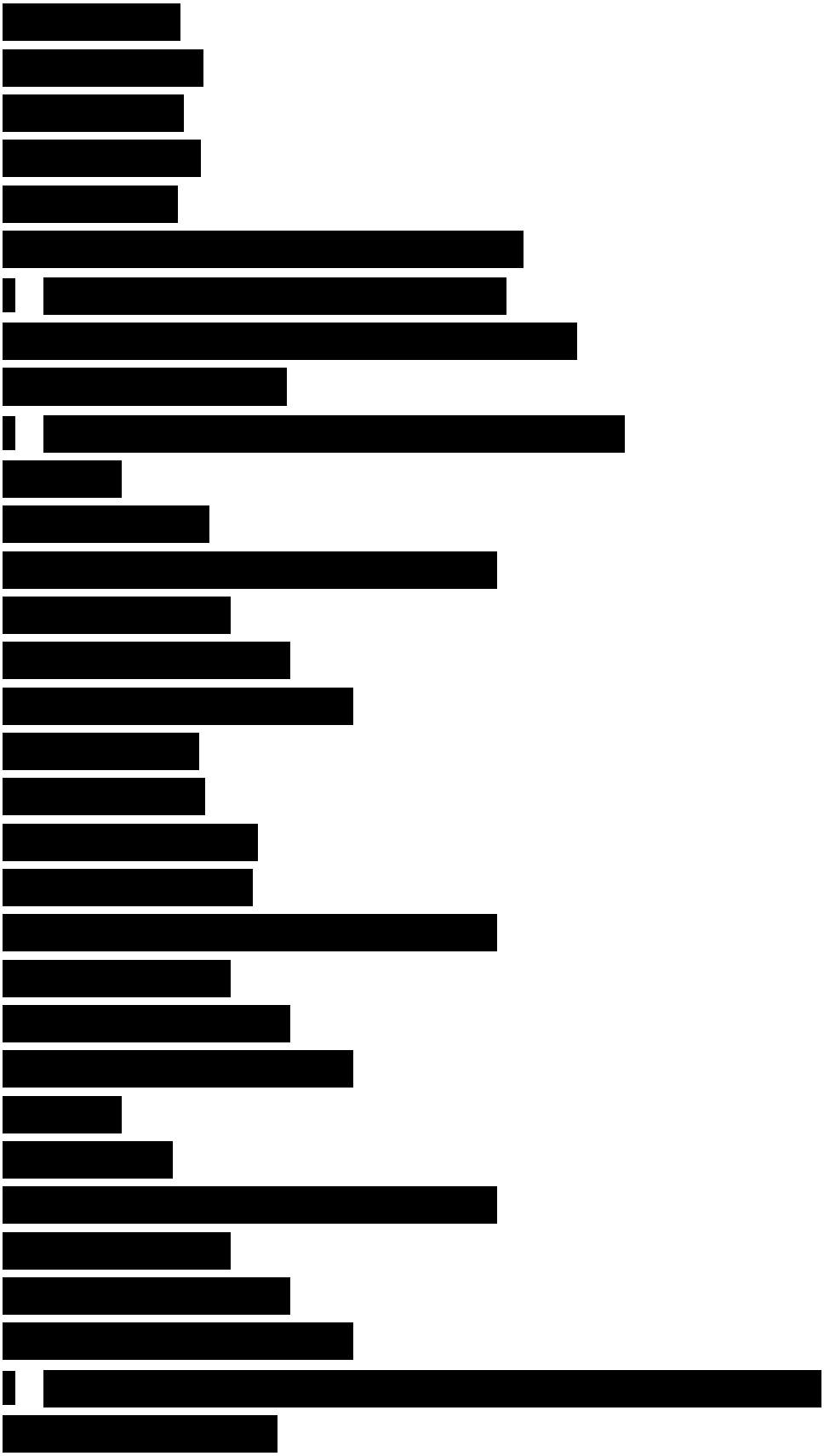
5.6.11. Abnormal Liver Function Tests

The ratio of the observed value to the upper limit of normal range (ULN) ratio will be derived for alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. The timepoints with ALT ULN ratio >3.0, AST ULN ratio > 3.0, or total bilirubin ULN ratio >2.0 will be listed, indicating the patients who experienced total bilirubin ULN ratio >2.0 and either ALT ULN ratio >3.0 or AST ULN ratio > 3.0 at any time. Additionally, patients with total bilirubin ULN ratio >2.0 and either ALT ULN ratio >3.0 or AST ULN ratio > 3.0 at any time will be noted.



[redacted]

[redacted]



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[redacted]

[redacted]

[redacted]

[redacted]

5.6.16. IP Exposure and Compliance

IP dosing periods will be derived based on the dosing information collected on the IP administration eCRFs during study visits, IP dose interruption and adjustment eCRF, and end of treatment eCRF, assuming the patient received IP every day from Day 1 through the end of treatment, unless a dose interruption is recorded.

Study drug dose during each treatment period will be derived using the information provided on study drug accountability eCRF. For Day 1 visit, the eCRF indicates the number of tablets to be administered daily starting the same day; for Week 2, 4, and 6 visits, the eCRF indicates the number of tablets to be administered daily starting the following day. The number of daily tablets will be adjusted according to the IP dose interruption and adjustment eCRF. The tablet dose strength will be derived from the IWRS IP bottle type information, and the daily dose for each dosing period will be derived as the number of tablets times the tablet dose strength. If the study drug accountability information is missing, the patient will be assumed to continue to be dosed from a previously dispensed kit.

Total exposure to the IP (mg) will be defined as daily dose times the number of days in a dosing period, summed over all dosing periods.

IP compliance will be derived at each scheduled dispensation visit: Week 2, Week 4, Week 6, and Week 10, and overall:

> IP compliance =100% * (number of tablets dispensed – number of tablets returned)/expected number of tablets administered.

Number of tablets dispensed and returned will be collected on the study drug accountability eCRF. For the IP bottles not returned, the number of tablets returned will be set to 40 in this derivation, assuming no tablets were taken. Expected number of tablets administered will be derived as the number of daily tablets times the days in an IP dosing period, summed over all dosing periods.

5.6.17. Treatment Emergent Adverse Event and Prior Dose Definitions

Treatment-Emergent Adverse Events (TEAEs) are defined as the AEs which are not present prior to the first dose of study drug and start thereafter, or present prior to the first dose of study drug and increase in severity, frequency, or outcome thereafter. For the analysis purposes, TEAE classification will be derived based on the onset date.

For each TEAE:

- Highest prior dose will be defined as the highest dose level prior to TEAE onset.
- Dose level at onset will be defined as the most recent dose level prior to TEAE onset.

Prior doses are those with dose date-time ≤ AE onset date-time. If only AE onset date is available, prior doses are those with dose date ≤ AE onset date.

The last study day when the IP was administered at the highest prior dose level and the last study day when the IP was administered at the dose level at onset will be noted.

Handling of partially missing AE dates used in these definitions is described in Section 5.7.3.

5.7. Handling of Missing Data

5.7.1. Missing Efficacy Endpoints

Handling of cardiac biomarker values and pharmacokinetics plasma concentration values below LOQ is described in Section 5.6.6.

Missing response data for health status and health related quality of life questionnaires will be handled as described in Section 5.6.15.

No other efficacy value imputations are planned.

5.7.2. Missing Start and Stop Dates for Prior and Concomitant Medication

To classify medications as prior, present at entry, or concomitant, missing start and stop dates of medications will be imputed as follows:

- If the medication start date day is missing, it will be imputed with the first of the month,
- If the medication start date day and month are missing, they will be imputed with 01 January,
- If the medication start year is missing, the date will be imputed with 01-January of the patient's birth year,
- If the medication stop date day is missing, it will be imputed with the last day of the month or the date of the last contact with the patient, whichever is the earlier,
- If the medication stop date day and month are missing, they will be imputed with 31 December or the date of the last contact with the patient, whichever is the earlier,
- For the ongoing medications, the stop date will be imputed with the date of the last contact with the patient.

5.7.3. Missing Start and Stop Dates for Adverse Events

To classify AEs as treatment-emergent, to determine the AE dose at onset and the highest prior dose level, and to derive AE duration, missing AE start and stop dates will be imputed as follows:

- If the AE start date day is missing, it will be imputed with the first day of the month or the date of the first dose of study drug, whichever is the later,
- If the AE start date day and month are missing, they will be imputed with 01-January or the date of the first dose of study drug, whichever is the later,
- If the AE stop date day is missing, it will be imputed with the last day of the month or the date of the last contact with the patient, whichever is the earlier,
- If the AE stop date day and month are missing, they will be imputed with 31-December or the date of the last contact with the patient, whichever is the earlier,
- For the ongoing AEs, the stop date will be imputed with the date of the last contact with the patient.

5.7.4. Missing Start Dates for Medical History

To derive time since initial diagnosis of HCM, missing medical history dates will be imputed as follows:

- If the medical history start date day is missing, it will be imputed with the first of the month,
- If the medical history date day and month are missing, they will be imputed with 01-January,
- If the medical history date is completely missing, it will be imputed with 01-January of the patient's birth year.

6. STUDY POPULATION

6.1. Patient Disposition

Patient disposition will be summarized based on all randomized patients (Section 5.4.2). The following will be summarized:

- The number and percentage of patients who completed the study and the number of patients who discontinued from the study early,
- For the patients who discontinued from the study early, reasons for early discontinuation,
- The number and percentage of patients who received at least one dose of the IP,
- For the patients who received at least one dose of the IP, the number and percentage of patients who completed study treatment and the number of patients who discontinued the study treatment early,
- For the patients who discontinued the study treatment early, reasons for early discontinuation.

The number and percentage of randomized patients included in each analysis set defined in Section 5.4.3, Section 5.4.4, and Section 5.4.5 will be summarized. Analysis set membership and any reasons for exclusion from analysis sets will be listed.

6.2. Screen Failures

A summary of screen failure reasons will be based on all screened patients (Section 5.4.1) and will display the number and percentage of screen failures and a summary of reasons for screen failures. No other summaries of screen failures will be produced.

6.3. Protocol Deviations

Protocol deviations will be collected by the study management contract research organization.

A summary of all protocol deviations and of important protocol deviations by category of deviation will be provided.

6.4. Demographic and Baseline Characteristics

The following demographics and baseline characteristics will be summarized:

- Age, including categories
- Sex
- Race, ethnicity,
- Height, weight, body mass index, BSA
- Site-reported values of LVEF, LVOT-G at rest, and LVOT-G during Valsalva maneuver at screening

The variables requiring derivations are described in Section 5.6.1.

Baseline values of echocardiographic data (core laboratory assessment), 12-lead ECG, cardiac biomarkers, vital signs, safety laboratory parameters, cardiac rhythm characterization variables, NYHA classification, health status and HRQoL variables will be summarized as part of the descriptive summaries for those parameters, by treatment arm and overall.

6.5. Listing of Inclusion and Exclusion Criteria

A listing of patients who were randomized but did not satisfy all eligibility criteria will be provided.

6.6. Medical History and Medical Conditions Present at Entry

HCM-related medical history will be summarized, including time since initial diagnosis (Section 5.6.1) and number and percentage of patients meeting the oHCM criteria.

Select cardiovascular medical history and other medical history will be summarized by the MedDRA SOC and preferred term.

6.7. Prior Medication History

Medications will be classified as prior, if the end date is strictly before the first dose of the IP.

The handling of missing start and stop dates is described in Section 5.7.2.

The number and percentage of patients receiving prior medications will be summarized by ATC class 3 and preferred name.

7. EFFICACY

7.1. General Considerations

The primary objective of this study is to determine the safety and tolerability of CK-3773274 in patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). While the analyses of PK and PD may provide initial indication of the relevant activity of CK-3773274 in this population, they are secondary and hypothesis-generating in nature.

The analyses may be conducted by cohort or in data combined across Cohorts 1 and 2 or all three cohorts.

7.2. Statement of the Null and Alternative Hypotheses

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 vs. the alternative hypothesis that the treatment difference exists.

The analyses evaluating the slope of relationship of changes from baseline in specified parameters to dose or date-matched maximum post-dose plasma-concentrations will test the null hypothesis that the slope is zero vs. the alternative hypothesis that the slope is not zero.

The analyses evaluating the relationship of specified parameters to plasma concentration ranges will test the null hypotheses that there is no difference between each CK-3773274 plasma concentration bin and placebo bin.

The analyses evaluating the effect of background disopyramide therapy on pharmacokinetics and pharmacodynamics parameters will test the null hypothesis that there is no difference between patients not receiving background disopyramide therapy and the patients receiving disopyramide.

Statistical hypotheses will be tested at the nominal 10% two-sided significance level.

7.3. Subgroup Analyses

Due to the small sample size, there will be no pre-defined subgroup analyses.

7.4. Multiple Comparisons and Multiplicity

Due to the secondary and hypothesis generating nature of the efficacy analyses in this study, there will be no adjustments for multiplicity. This increases a chance of nominally statistically significant results due to random fluctuations in data. Any statistical comparisons need to be interpreted with caution and considered in the context of other results.

7.5. Analysis of the Primary Efficacy Endpoint

Not applicable.

7.6. Analysis of the Secondary Efficacy Endpoints

7.6.1. Secondary Echocardiographic Endpoint Analysis

The secondary echocardiographic endpoint analysis will be based on the PDS.

LVOT-G at rest and LVOT-G during Valsalva maneuver at baseline, Week 2, Week 4, Week 6, and Week 10 and changes from baseline at Week 2, Week 4, Week 6, and Week 10 will be summarized as described in Section 5.3, including geometric mean and CV (%) for the values and proportional changes from baseline.

The treatment effect on change from baseline in echocardiographic variables will be evaluated using analysis of covariance (ANCOVA) model by cohort in Cohorts 1 and 2 and combining data across the two cohorts.

7.6.1.1. Analysis of Proportional Change from Baseline at Week 10 in LVOT-G at Rest

Proportional change from baseline at Week 10 will be evaluated using a mixed-effect repeated measures model for the ln(LVOT-G at rest measurements) at Week 2, 4, 6, and 10.

The ANCOVA model will include ln(proportional change from baseline) as the dependent variable, and ln(baseline value) as a covariate. The terms for treatment (CK-3773274 or placebo), visit, and treatment-by-visit interaction will be included as fixed effects. The unstructured variance-covariance structure will be used, unless the model does not converge, in which case a first order autoregressive variance-covariance structure model will be used instead.

The treatment effect estimates will be back-transformed (ie exponentiated) for the presentation in the TFLs. GLSM estimates for proportional change from baseline at Week 10 will be produced for each treatment arm along with the corresponding 90% CIs. The difference between treatments will be described by the GLSM estimate of proportional change from baseline ratio and the corresponding 90% CIs.

The example prototype code for this analysis:

An additional analysis comparing Week 12 proportional change from baseline between the treatment arms may be conducted.

7.6.1.2. Analysis of Change from Baseline at Week 10 LVOT-G at Rest

Change from baseline at Week 10 will be evaluated using mixed-effect repeated measures model for the LVOT-G at rest measurements at Week 2, 4, 6, and 10.

The ANCOVA model will include change from baseline as the dependent variable, and baseline value as a covariate. The terms for treatment (CK-3773274 or placebo), visit, and treatment-by-visit interaction will be included as fixed effects. The unstructured variance-covariance structure will be used, unless the model does not converge, in which case a first order autoregressive variance-covariance structure model will be used instead.

LSM estimates for change from baseline will be produced for each treatment arm along with the corresponding 90% CIs. The difference between treatments will be described by the LSM estimate of change from baseline difference and the corresponding 90% CIs.

The example prototype code for this analysis:

[redacted]

An additional analysis comparing Week 12 change from baseline between the treatment arms may be conducted.

7.6.1.3. Analysis of Change from Baseline in LVOT-G at Rest as a Function of Dose

The relationship of the dose of CK-3773274 to the change from baseline in LVOT-G at rest will be evaluated using a mixed-effect repeated measures model for the LVOT-G at rest measurements at Week 2, 4, 6, and 10.

The ANCOVA model will include change from baseline as the dependent variable, and baseline value of LVOT-G at rest and the dose of CK-3773274 immediately prior to the LVOT-G at rest evaluation as covariates, with a random intercept assumption. The unstructured variance-covariance structure will be used, unless the model does not converge, in which case a first order

autoregressive variance-covariance structure model will be used instead. For the patients receiving placebo dose, the dose will be set to zero.

The example prototype code for this analysis:

The analysis results will be described in terms of the slope of the relationship and the corresponding 90% CI.

Additional sensitivity analyses including prior dose level in the model and/or treating dose as a categorical variable may be conducted.

7.6.1.4. Analysis of Proportional Change from Baseline in LVOT-G During Valsalva Maneuver at Week 10

The analyses described in Section 7.6.1.1 will be repeated for LVOT-G during Valsalva maneuver.

7.6.1.5. Analysis of Change from Baseline in LVOT-G During Valsalva Maneuver at Week 10

The analyses described in Section 7.6.1.2 will be repeated for LVOT-G during Valsalva maneuver.

7.6.1.6. Analysis of Change from Baseline in LVOT-G During Valsalva Maneuver as a Function of Dose

The analyses described in Section 7.6.1.3 will be repeated for LVOT-G during Valsalva maneuver.

7.6.2. Secondary Pharmacokinetics Endpoint Analysis

The observed plasma concentration values of CK-3773274 and metabolites will be summarized based on the PKS (Section 5.4.4) as described in Section 5.3, including geometric mean and CV (%), by visit, dose level at visit, and nominal sample collection time. The number of values below LOQ will be shown.

The observed C_{max} and C_{trough} of CK-3773274 at Week 2, 4, 6, and 10 visit will be summarized based on the PKS (Section 5.4.4) as described in Section 5.3, including geometric mean and CV (%), by visit and dose level at visit. The number of values below LOQ will be shown.

Mean (SD) of plasma concentrations of CK-3773274 will be plotted vs nominal time by visit, nominal sample collection time, and, within each visit, by dose at visit. Separate panels will be

prepared for each visit, using the same vertical axis scale. Geometric mean plasma concentrations will be plotted likewise; semi-logarithmic scale will be used for these plots.

7.6.3. Secondary Pharmacokinetics/Pharmacodynamics Endpoint Analysis

The secondary PK/PD analyses will be based on the PDS (Section 5.4.5), by cohort (Cohort 1 or 2 only) and combining the data across the two cohorts. Concentration-response analysis in LVOT-G (resting and Valsalva) may be explored including Cohorts 1, 2 and 3 and concentration-response analysis in LVEF may be explored including all cohorts.

7.6.3.1. Concentration-response Analysis of Change from Baseline in LVOT-G at Rest

The ANCOVA model for the concentration-response analysis of change from baseline in LVOT-G at rest will include change from baseline at Week 2, 4, 6, and 10 as the dependent variable, maximum date-matched value of the plasma concentration of CK-3773274 and baseline value of LVOT-G at rest as covariates, and a random intercept to account for repeated measures. The unstructured variance-covariance structure will be used. The analysis results will be described in terms of the slope of the relationship and the corresponding 90% CI.

The example prototype code for this analysis:

[redacted]

The analysis results will be presented graphically showing a scatter plot of change from baseline against plasma concentration values, with a line and 90% CI boundaries drawn using the LSM estimates of slope and the intercept.

7.6.3.2. Concentration-response Analysis of Change from Baseline in LVOT-G During Valsalva Maneuver

Concentration-response analysis of change from baseline in LVOT-G during Valsalva maneuver will be conducted in the same manner as for LVOT-G at rest (Section 7.6.3.1).

7.6.3.3. Concentration-response Analysis of Proportional Change from Baseline in LVOT-G at Rest

For the concentration-response analysis of proportional change from baseline in LVOT-G at rest, natural logarithm of LVOT-G at rest baseline values, proportional changes from baseline to post-dose at Weeks 2, 4, 6, and 10, and of date-matched maximum plasma concentrations of CK-3773274 will be derived.

The ANCOVA model will include ln(proportional change from baseline) as the dependent variable, and ln(baseline value) and ln(date-matched maximum value of the plasma concentration of CK-3773274) as covariates, with a random intercept assumption. The

unstructured variance-covariance structure will be used. The analysis results will be described in terms of the slope of the relationship and the corresponding 90% CI.

The example prototype code for this analysis:

[redacted]

The analysis results will be presented graphically showing a scatter plot of ln(prop change from baseline) against ln(plasma concentration values), with a line and 90% CI boundaries drawn using the slope estimate and the LSM intercept estimate.

7.6.3.4. Concentration-response Analysis of Proportional Change from Baseline in LVOT-G During Valsalva Maneuver

Concentration-response analysis of proportional change from baseline in LVOT-G during Valsalva maneuver will be conducted in the same manner as for LVOT-G at rest (Section 7.6.3.3).

7.7. Analysis of the Exploratory Efficacy Endpoints

7.7.1. [redacted]

7.7.1.1. [redacted]

[redacted]

7.7.1.2. Analysis of [redacted]

[redacted]

7.7.1.3. Analysis of [redacted]

[redacted]

7.7.1.3.1. Analysis of [redacted]

[redacted]

The example prototype code for this analysis:

[redacted]

7.7.1.3.2. Analysis of the [redacted]

[redacted]

[redacted]

The example prototype code for this analysis:

[redacted]

7.7.1.3.3. Analysis of [redacted]

The analyses [redacted]

7.7.1.3.4. Analysis of [redacted]

The analyses [redacted]

7.7.1.3.5. Analysis of [redacted]

The analyses [redacted]

7.7.2. [redacted]

The effect of background disopyramide therapy on PK plasma concentrations will be assessed by [redacted]

[redacted]

The example prototype code for this analysis, [redacted]

[redacted]

7.7.3. [redacted]

[redacted]

7.7.3.1. Analysis of [redacted]

[redacted]

The example code for this analysis is:

[redacted]

[redacted]

The analysis [redacted]

7.7.3.2. Analysis of [redacted]

[redacted]

The example code for this analysis:

[redacted]

The analysis [redacted]

7.7.3.3. [redacted]

[redacted]

7.7.4. Exploratory [redacted]

[redacted]

The example prototype code for this analysis:

[redacted]

7.7.5. Exploratory [redacted]

[redacted]

The example code for this analysis:

[redacted]

[redacted]

[redacted]

7.7.6. Exploratory [redacted]

[redacted]

8. SAFETY AND TOLERABILITY

The summaries of safety and tolerability will be based on the Safety Analysis Set (Section 5.4.3).

8.1. IP Dosing and Exposure Summaries

8.1.1. Summaries of IP Exposure

The summary of exposure to the IP will display descriptive statistics for the number of days on treatment and for total exposure to the IP defined in Section 5.6.16.

Early termination of the study treatment will be summarized showing number and percentage of patients who discontinued the study treatment on or prior Day 15, Day 29, Day 43, Day 57, or Day 71.

8.1.2. Summary of Dose Titration

IWRS-guided dose titration (Section 3.2.2) will be summarized showing the number and percentage of patients in the following categories, grouped by the highest assigned dose, based on the dose sequence:

Table 9: Dose Titration Categories

Doses Assigned at				Dose Sequence Category	Highest Assigned Dose Category
Randomization	Week 2	Week 4	Week 6		
Dose 1	Dose 2	Dose 3	Dose 3	D1-D2-D3-D3	D3
Dose 1	Dose 2	Dose 3	Dose 2	D1-D2-D3-D2	
Dose 1	Dose 2	Dose 3	(none)	D1-D2-D3	
Dose 1	Dose 2	Dose 2	Dose 2	D1-D2-D2-D2	D2
Dose 1	Dose 2	Dose 2	Dose 1	D1-D2-D2-D1	
Dose 1	Dose 2	Dose 2	(none)	D1-D2-D2	
Dose 1	Dose 2	Dose 1	Dose 1	D1-D2-D1-D1	
Dose 1	Dose 2	Dose 1	Placebo	D1-D2-D1-D0 or D1-D2-D1	
Dose 1	Dose 2	Dose 1	(none)		
Dose 1	Dose 2	(none)	(none)	D1-D2	
Dose 1	Dose 1	Dose 2	Dose 2	D1-D1-D2-D2	
Dose 1	Dose 1	Dose 2	Dose 1	D1-D1-D2-D1 or D1-D1-D2	
Dose 1	Dose 1	Dose 2	(none)		
Dose 1	Dose 1	Dose 1	Dose 1	D1-D1-D1-D1	D1
Dose 1	Dose 1	Dose 1	Placebo	D1-D1-D1-D0 or D1-D1-D1	
Dose 1	Dose 1	Dose 1	(none)		

Table 9: Dose Titration Categories (Continued)

Doses Assigned at				Dose Sequence Category	Highest Assigned Dose Category
Randomization	**Week 2**	**Week 4**	**Week 6**		
Dose 1	Dose 1	Placebo	Placebo	D1-D1-D0-D0, D1-D1-D0, or D1-D1	
Dose 1	Dose 1	Placebo	(none)		
Dose 1	Dose 1	(none)	(none)		
Dose 1	Placebo	Placebo	Placebo	D1-D0-D0-D0, D1-D0-D0, D1-D0 or D1	
Dose 1	Placebo	Placebo	(none)		
Dose 1	Placebo	(none)	(none)		
Dose 1	(none)	(none)	(none)		

8.1.3. Dose Modifications and Discontinuation

Dose modifications and interruptions will be summarized by treatment (placebo or CK-3773274) and by dose level prior to the dose modification or discontinuation. The number and percentage of patients in each of the following modification or discontinuation category will be displayed, along with the reasons for the modification or discontinuation:

- Dose discontinuations as reported on the IP termination eCRF,
- Dose interruptions defined as zero tablets entered on the IP interruption or adjustment eCRF
- Dose decrease defined as reduced non-zero number of tablets entered on the IP interruption or adjustment eCRF
- Dose decrease defined as increased number of tablets entered on the IP interruption or adjustment eCRF

Dose level prior to dose modification or discontinuation is defined as the dose level on the day before dose modification started or before the IP was permanently discontinued.

8.1.4. IP Compliance

IP compliance will be summarized by visit and overall using descriptive statistics.

8.2. Adverse Event Summaries

Only TEAEs will be summarized.

To allow description of AEs profile as it relates to dose titration, adverse event summaries will be prepared in three ways:

- Summary of number and percentage of patients by treatment group, and, for CK-3773274 group, highest dose level administered
- Summary of number of events by treatment and dose level at AE onset (as defined in Section 5.6.17)

- Summary of number and percentage of patients by treatment group and highest dose level administered, with each AE category split by dose level at the AE onset

AE listings will include highest dose prior to AE onset and the last day when that dose level was administered, dose level at AE onset and the last day when that dose was administered.

The summaries by SOC and PT will be sorted by the decreasing order of incidence or frequency in the CK-3773274 column: if applicable, SOC will be sorted first, with PTs sorted within their SOC.

8.2.1. Overview of Adverse Events

Overview of TEAEs will display the number and percentage of:

- Patients with at least one TEAE,
- Patients with at least one TESAE,
- Patients with at least one TEAE leading to early termination,
- Patients with at least one TEAE related to the study drug,
- Patients with at least one moderate or severe TEAE,
- Patients with at least one severe TEAE,
- Patients with fatal TEAE.

Corresponding summaries of the number of events by treatment and dose level at AE onset and of number and percentage of patients with each AE category split by dose level at the AE onset will also be produced.

8.2.2. Summaries of Adverse Events by System Organ Class and Preferred Term

The following subsets of TEAEs will be summarized by SOC and PT:

- All TEAEs
- TEAEs related to study drug
- TEAEs leading to early discontinuation of study drug
- TESAEs

A summary of all TEAEs by PT will be produced.

Corresponding summaries of the number of events by treatment and dose level at AE onset and of number and percentage of patients with each AE category split by dose level at the AE onset will also be produced.

8.2.3. Summary of Adverse Events by Maximum Severity

Summary of TEAEs by maximum severity will display number and percentage of AEs with maximum severity being mild, moderate, or severe within each SOC and PT.

8.2.4. Serious Adverse Events and Adverse Events Leading to Early Discontinuation of Study Drug

TESAEs and TEAEs leading to discontinuation of study drug will be listed. The listing of TESAEs will include seriousness criteria and, if applicable, hospital admission and discharge dates.

8.3. Summary of Post-baseline Incidence of LVEF < 50%

Categories of post-baseline LVEF < 50% described in Section 5.6.8.2 will be summarized showing the number and percentage of patients as described in Section 5.3.

8.4. Cardiac Rhythm Pattern Characterization Summaries

Ambulatory cardiac monitoring total recorded time and total analyzed time pre-dose and at the end of treatment will be summarized descriptively as described in Section 5.3.

The following variables will be summarized descriptively, including changes from pre-dose to end of treatment:

- Average HR
- Minimum HR
- Maximum HR
- Supraventricular tachycardia (number of runs) per 24 hour
- Supraventricular ectopy average beats per 24 hour
- Average number of SVT events per 24 hour
- Average number of sustained SVT events per 24 hour
- Longest SVT event (beats)
- Ventricular ectopy average beats per 24 hour
- Ventricular tachycardia (number of runs) per 24 hour
- Longest VT event (beats)
- Bradycardia average beats per 24 hour
- Average number of bradycardia events per 24 hour
- Longest bradycardia event (beats)
- Average number of pauses > 2.0 seconds per 24 hour
- Maximum pause length

The following variables will be summarized using the number and percentage of patients prior to dosing and during the last week of dosing with:

- Basic rhythm
- Presence of AF

a. Presence of Atrial Fibrillation

- b. Presence of Atrial FlutterAverage of number of Pauses (> 2.0 seconds).per 24 hour

Listings of cardiac rhythm pattern characterization will include additional information, such as the number of SVT, sustained SVT, VT, and bradycardia events and the number of pauses.

8.5. Concomitant Medications

Medications will be classified as concomitant, if the start date is strictly before the last dose of the IP. And the end date is the same as or after the first dose of study drug. The handling of missing start and stop dates is described in Section 5.7.2.

Medications will be classified as present at entry, if the medication start date is the same as or prior to the first dose of the IP and the medication end date is the same as or after the first dose of the IP.

The number and percentage of patients receiving concomitant medications and concomitant medications present at entry will be summarized by ATC class 3 and preferred name.

A listing of prior and concomitant medications will include the medication dose, route, frequency, and indication.

8.6. Safety Laboratory Data

Safety laboratory values and changes from baseline will be summarized by treatment group (CK-3773274 or placebo) over time. Change from baseline at each post-baseline on-treatment visit will be additionally summarized by dose level at visit.

Summary of post-baseline abnormal laboratory data by treatment and, for post-baseline on-treatment visits, by dose level at visit will be produced, showing number and percentage of patients with values above upper limit of normal and below lower limit of normal.

ALP, ALT, AST, and total bilirubin values and the corresponding ULN ratios will be listed for the patient visits with ALT ULN ratio >3.0, AST ULN ratio > 3.0, or total bilirubin ULN ratio >2.0. Data from the patients with total bilirubin ULN ratio > 2.0 and either ALT ULN ratio >3.0, AST ULN ratio > 3.0 will be flagged.

Box plots of select laboratory values and changes from baseline by treatment or, for changes from baseline, by dose level at visit may be produced.

8.7. 12-Lead ECG

Continuous 12-lead ECG variables and changes from baseline described in Section 5.6.9 will be summarized descriptively and categorical variables will be summarized using number and percentage of patients by treatment group (CK-3773274 or placebo) over time. The changes from baseline at each post-baseline on-treatment visit and categories at those visits will be additionally summarized by dose level at visit.

Box plots of select laboratory values and changes from baseline by treatment or, for changes from baseline, by dose level at visit may be produced.

ECG findings and interpretation will be listed.

Relationship of changes from baseline in QTcF, QTcB, PR interval, and QRS duration to dose of CK-3773274 will be evaluated as described for change from baseline in LVOT-G at rest in Section 7.6.1.3

8.8. Vital Signs

Vital signs and changes from baseline will be summarized descriptively by treatment group (CK-3773274 or placebo) over time. The changes from baseline at each post-baseline on-treatment visit will be additionally summarized by dose level at visit.

Box plots of select vital signs and changes from baseline by treatment or, for changes from baseline, by dose level at visit may be produced.

9. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There were no changes from the protocol-specified analyses.

10. REFERENCES

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