STATISTICAL ANALYSIS PLAN

Protocol Number:	MYK-461-005 (EXPLORER-HCM)
Protocol Title:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL STUDY TO EVALUATE MAVACAMTEN (MYK-461) IN ADULTS WITH SYMPTOMATIC OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY**
Indication:	Hypertrophic Cardiomyopathy
Phase:	3
Investigational Medicinal Product:	Mavacamten (MYK-461) or matching placebo
Sponsor:	MyoKardia, Inc. 1000 Sierra Point Parkway Brisbane, CA 94005
Protocol Version	Amendment 5
Date	October 2019
SAP Version	Version 2
Date	21 April 2020

SIGNATURE PAGE

Protocol Number:	MYK-461-005 (EXPLORER-HCM)
Protocol Title:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL STUDY TO EVALUATE MAVACAMTEN (MYK-461) IN ADULTS WITH SYMPTOMATIC OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY**
SAP Version:	Version 2.0
Date:	21 April 2020

Authored by: Wanying Li, Ph.D.

Signature: *[See Attached E-Signature]* Date: _____

Approved by:

Biometrics: Liang Fang, Ph.D.

Signature: *[See Attached E-Signature]* Date: _____

Clinical Research: Amy Sehnert, M.D.

Signature: *[See Attached E-Signature]* Date: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

A	peak velocity of late transmitral flow
ADAU	Average Daily Accelerometry Unit
AE	adverse event
AESI	adverse event of special interest
AF	atrial fibrillation
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
BSA	body surface area
CEAC	Clinical Event Adjudication Committee
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMR	cardiac magnetic resonance
CPET	cardiopulmonary exercise testing
CV	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
E	peak velocity of early diastolic transmitral flow
e'	peak velocity of early diastolic septal and lateral mitral annular motion
ECG	electrocardiogram
ECHO	echocardiography
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5-dimensions 5-levels questionnaire
EOS	end of study
EOT	end of treatment
ESC	European Society of Cardiology
ET	early termination
FDA	The United States Food and Drug Administration
HCM	hypertrophic cardiomyopathy
HCMSQ	Hypertrophic Cardiomyopathy Symptom Questionnaire
HF	Heart failure
HR	heart rate

ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	investigational medicinal product
IPD	important protocol deviations
ITT	intention-to-treat
IXRS	interactive response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	Left atrial volume index
LLOQ	lower limit of quantitation
LV	left ventricular
LVEDVI	LV end-diastolic volume index
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MedDRA	Medical Dictionary for Regulatory Activities
nHCM	nonobstructive hypertrophic cardiomyopathy
NT-proBNP	N-terminal pro b-type natriuretic peptide
NSVT	nonsustained ventricular tachycardia
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PAP	Psychometric Analysis Plan
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
PT	preferred term
pVO_2	peak oxygen consumption
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee

SD	standard deviation
SOC	system organ class
SRT	septal reduction therapy
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States
VCO_2	carbon dioxide production
VE	volume expired
VT	ventricular tachycardia
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire-Specific Health Problem

1. INTRODUCTION

Hypertrophic cardiomyopathy (HCM), an autosomal dominant genetic disease, is defined clinically by the presence of increased left ventricular (LV) wall thickness associated with nondilated ventricular chambers that is not solely explained by abnormal loading conditions, such as another cardiac or systemic disease (Gersh et al, 2011; Elliott 2014). The phenotypic hallmark of HCM is myocardial hypercontractility accompanied by reduced LV compliance, reflected clinically as reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. Mutations in cardiac myosin and other sarcomere proteins in individuals with HCM appear to increase net power generation by the sarcomere (Chuan et al, 2012; Sommese et al, 2013; Sung et al, 2012), consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically. HCM may be associated with obstruction of the left ventricular outflow tract (LVOT) in ~70% of cases, referred to as obstructive HCM (oHCM), or in ~30% of cases be non-obstructive (nHCM). Current medical treatment consists of the use of beta blockers, verapamil, diltiazem, or disopyramide (when available), as described in the 2014 European Society of Cardiology (ESC) (Elliott 2014) and in the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for the diagnosis and management of hypertrophic cardiomyopathy (Gersh 2011). However, despite these treatments, symptoms may persist. For patients with advanced symptomatic obstructive disease, treatment may include septal reduction therapies (SRTs) (eg, surgical myectomy or percutaneous alcohol septal ablation), which can be effective in reducing obstruction of the left ventricular outflow tract (LVOT) but are invasive procedures. No United States (US) Food and Drug Administration (FDA)-approved medical therapies exist for patients with symptomatic nonobstructive hypertrophic cardiomyopathy (nHCM), and no interventional options are available, short of cardiac transplant.

Mavacamten is a novel small molecule allosteric modulator of striated muscle myosin that selectively targets cardiac myosin and reversibly inhibits its binding to actin. Mavacamten's profile of myosin modulation is predicted to reduce dynamic LVOT obstruction in individuals with obstructive HCM (oHCM) by reducing systolic hypercontractility and dynamic obstruction in the near term and reducing ventricular hypertrophy with chronic treatment. MyoKardia is developing mavacamten for the treatment of adults with symptomatic oHCM to relieve obstruction, improve symptoms, and increase exercise capacity.

MYK-461-005, EXPLORER-HCM, is a Phase 3 study designed to evaluate the safety and efficacy of a 30-week course of mavacamten compared with placebo in participants with symptomatic oHCM. At selected study sites, participants could also have been enrolled in a cardiac magnetic resonance (CMR) imaging substudy. This statistical analysis plan (SAP) describes all planned analyses for the main study and CMR substudy in protocol MYK-461-005 and provides justifications of these analyses.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to compare the effect of a 30-week course of mavacamten with placebo on clinical response comprising exercise capacity and clinical symptoms in participants with symptomatic oHCM.

2.2. Secondary Objectives

The secondary efficacy objectives of this study are:

- To compare the effect of a 30-week course of mavacamten with placebo on symptoms and LVOT obstruction as determined by Doppler echocardiography
- To compare the effect of a 30-week course of mavacamten with placebo on exercise capacity, clinical symptoms, and patient-reported outcomes (PRO) individually
- To assess the safety and tolerability of mavacamten
- To assess the pharmacokinetic (PK) characteristics of mavacamten

2.3. Exploratory Objectives

To assess the effect of a 30-week course of mavacamten on LVOT obstruction; disease biomarkers; symptoms, health-related quality of life, and work activity as assessed by patient-reported outcomes (PRO); cardiac rhythm patterns as assessed by continuous cardiac rhythm monitoring; functional capacity as assessed by accelerometer.

2.4. CMR Imaging Substudy Objective

The objective of the substudy is to assess the effect of mavacamten on cardiac mass and structure as evaluated by CMR.

3. OVERALL STUDY DESIGN AND PLAN

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo (1:1) in participants with symptomatic oHCM. Approximately 220 participants will be enrolled. This includes ~80 participants (~40 per treatment group) who consent to participate in a CMR substudy at selected sites. Randomization will be stratified according to New York Heart Association (NYHA) functional classification (II or III) (i.e. NYHA class II or III), current treatment with β-blocker (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no).

The expected study duration is approximately 43 weeks: up to 5 weeks for screening, a 30-week treatment period, and an 8-week post-treatment follow-up period (±7 days).

4. RANDOMIZATION AND BLINDING PROCEDURES

4.1. Randomization

Participants who meet the inclusion/exclusion criteria will be randomized via an interactive response system (IXRS) in a 1:1 ratio to receive double-blind treatment with either mavacamten 5 mg or matching placebo QD. Randomization will be stratified according to NYHA class (II or III), current treatment with β-blocker (yes or no), type of ergometer (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no).

4.2. Study Blinding

Participants will be randomized to receive mavacamten or matching placebo in a double-blind manner such that the principal investigator; site staff, including the pharmacist; and the participant will not know which study drug is being administered. In addition, the sponsor, the central and core laboratories, and clinical site monitors will be blinded to assigned treatment. Mavacamten and matching placebo will be identical in appearance to preserve the blind. Study drug (mavacamten or matching placebo) will be labeled with a unique identifying number that will be assigned to a participant through the IXRS.

Blinded results (ie, echocardiography results, and PK data) will be transferred to the IXRS by the respective core laboratories in order to perform dose adjustments and dose discontinuations in a blinded manner. In addition, sham dose discontinuation and unscheduled visits, if necessary, will be performed in the placebo arm to preserve the blind. However, site personnel who perform specific tasks, such as reviewing echocardiograms for safety, may be unblinded (see Study Reference Manual). In the case of LVEF ≤ 30% the investigator will be notified as described in Section 7.3.3 of the protocol. The pharmacovigilance team will be unblinded for suspected unexpected serious adverse reaction (SUSAR) reporting. The IDMC may also be unblinded to treatment allocation and all safety and efficacy data.

4.3. Methods for Unblinding

All efforts should be made to keep participants blinded to treatment assignment. However, participants may be unblinded to treatment assignment upon request from the Investigator and agreement by the sponsor if knowledge of treatment assignment will impact future treatments or clinical care of the participant. Unblinding by the investigator independently of the sponsor also may occur if an adverse event (AE) or toxicity necessitates identification of the study drug for the welfare of the participant. Please refer to the Suvoda Interactive Web Response System Manual for the unblinding process and contact information.

5. DETERMINATION OF SAMPLE SIZE

Approximately 220 participants will be randomized, with 110 participants in each of the 2 groups. Randomization will be stratified for NYHA class (II or III), current treatment with β-blocker (yes/no), type of ergometer (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no). The sample size should provide adequate power to determine the superiority of mavacamten in improving peak oxygen consumption (pVO_2) and NYHA class relative to placebo (see Section 12.2.1 of the protocol). The power calculation is derived

assuming a true clinically meaningful difference of 25% between mavacamten and placebo participants in achieving the clinical response. Based on the MYK-461-004 PIONEER-HCM Phase 2 study, 50% of the participants receiving mavacamten met the clinical responder definition by the end of 12-week treatment period. Assuming the same percentage of participants in the active treatment arm and 25% in placebo arm will achieve the clinical response at the end of the 30-week dosing period in the current study, the proposed sample size of 110 participants per arm will provide 96% power at the 2-sided 5% statistical significance level. Participants who terminate early or cannot be assessed for the clinical response at the end of the 30-week dosing period will be considered nonresponders.

6. GENERAL STATISTICAL CONSIDERATIONS

The primary analysis will be conducted through the 30-week treatment period. Data collected through this time point will be cleaned and locked prior to conducting the primary analysis.

Once all participants have completed their Week 38/end of study (EOS) visit, all data will be cleaned and locked, and analyses using this data will be used to inform study objectives relating to follow-up safety and reversibility of drug effect.

SAS® version 9.4 or higher will be used for statistical analyses, tabulations, and graphical presentations.

In general, descriptive summaries will be presented by treatment group (placebo and mavacamten) for values at each visit. The descriptive summary for continuous variables will also be provided for the change from baseline and, if appropriate, for the change from week 30 to week 38. Summaries of continuous variables will include the number of subjects (N), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. For variables with highly skewed distribution (e.g. log-normal distribution), geometric mean and %CV will also be reported in descriptive summaries. Inferential analysis for those variables may be performed after log-transformation as deemed appropriate. Descriptive summaries for categorical variables will include the number and percentage of subjects. Unless otherwise stated, denominators for percentages will be the number of subjects in the analysis population.

Between-group comparisons will focus on the comparative performance of mavacamten versus placebo. All statistical tests will be conducted at a 2-sided significance level of 0.05.

In general, baseline is defined as the last nonmissing value on or before the first dose date and time (as applicable). For certain data types (eg, accelerometer, PROs, cardiac rhythm monitoring, etc.), special considerations may be required. Refer to the specific data section for details.

Unless otherwise noted, nonsafety (ie. efficacy, pharmacodynamics [PD]) information displayed "by visit" will utilize analysis visits as defined by the analysis visit window as opposed to the visits at which the information was collected (ie, nominal visit). Data collected at unscheduled or early termination (ET) visits will also be mapped to analysis visits. The analysis day for the purposes of deriving the analysis visit windows are derived as follows (reference date is the study drug initiation date, or the randomization date if the study drug initiation date is missing):

- If date of information (year, month, and day) is completely missing, analysis day cannot be calculated and will be treated as missing. If the date is partially missing, date will be imputed according to the rules outlined in Section 6.4.
- If date is < reference date, analysis day = date of information – reference date. If date ≥ reference date, analysis day = (date of information – reference date) + 1.

The visit windows for efficacy and PD assessments will be defined according to their respective collection schedules. The rule for defining the analysis window is +/-14 days from the target visit date for all post-baseline visits, except for Week 30 and Week 38, which have +/- 28 day windows. If 2 adjacent visit windows overlap, the limits of the windows will be adjusted to the midpoint between the 2 visits. The specific window definitions for each endpoint are available in Appendix 2 Table 3 to Table 9.

For efficacy and PD analyses, if a value does not fall within an analysis window, it will not be included in the summary analysis. However, these values will be included in data listings and SAS data sets. For post-baseline data, when more than 1 value is available within the same analysis visit, the value collected closest to the target visit day will be used for analysis. If 2 values are the same distance to the closest to target visit day (for example, 1 value is before and the other value is after the target day), then the latest value will be selected as the analysis value. For a specific analysis window, if the latest collected time point has 2 or more values collected, then for continuous data, the average among these results will be derived, and for categorical data (eg, yes or no) the clinically 'worse' value will be selected.

Safety data and PK data will be summarized by the nominal visit (per protocol), and unscheduled visits will be presented in listings only. If a participant had treatment early terminated (ET) and had additional visits after the ET visit, those visits will be relabeled as FU (ie, follow-up)-1, FU-2, and FU-3, etc. at 4-week intervals following the ET visit.

6.1. Study Endpoints

Primary Efficacy Endpoints:

The primary efficacy endpoint was a clinical response at Week 30 defined as achieving:

1. An improvement of at least 1.5 mL/kg/min in pVO_2 as determined by cardiopulmonary exercise testing (CPET) and a reduction of one or more class in NYHA class

   OR

2. An improvement of 3.0 mL/kg/min or more in pVO_2 with no worsening in NYHA class.

Secondary Efficacy Endpoints:

- Change from baseline to Week 30 in post-exercise LVOT peak gradient
- Change from baseline to Week 30 in pVO_2 as determined by CPET
- Proportion of subjects who had at least 1 class of NYHA improvement from baseline to Week 30

- Change from baseline to Week 30 in patient-reported health-related QoL as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS)
- Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) shortness-of-breath (SoB) subscore

Exploratory Efficacy Endpoints:

- Proportion of subjects achieving a post-exercise LVOT peak gradient < 50 mmHg at Week 30
- Proportion of subjects achieving a post-exercise LVOT peak gradient < 30 mmHg at Week 30
- Proportion of subjects with any decrease in post-exercise LVOT peak gradient from baseline to Week 30
- Proportion of subjects achieving complete response (NYHA Class I and LVOT peak gradient < 30 mmHg for all 3 types of gradients: resting, Valsalva, and post-exercise) at Week 30
- Changes from baseline to Week 30 in cardiopulmonary function as assessed by CPET
- Changes from baseline to Week 30 in echocardiographic indices of cardiac structure (eg, LV ventricular wall thickness, atrial and ventricular chamber size and volumes), as well as systolic and diastolic function
- Change from baseline to Week 30 in N-terminal pro b-type natriuretic peptide (NT-proBNP) concentration over time
- Changes from baseline to Week 30 in the following patient-reported endpoints:
  - Perceived health status/health-related QoL as assessed by the EuroQol 5-dimensions 5-levels questionnaire (EQ-5D-5L) scores
  - Work productivity and activity impairment as assessed by the Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP) scores
  - Perceived severity of symptoms as assessed by Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) scores
  - Health-related QoL as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score and overall summary score
  - Severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) total score and the 2 domain subscores tiredness and cardiovascular [CV] symptoms
- Proportion of subjects who had clinically meaningful changes in KCCQ-23 scores
- Proportion of subjects who had clinically meaningful changes in HCMSQ scores

- Changes from baseline to Week 30 in daily step count and other accelerometer parameters
- Change from baseline to Week 30 in hs-cardiac troponin-I

PK Endpoints:

- Mavacamten plasma concentration over time
- PK parameters using a population PK approach (to be summarized in a separate population PK report)

Safety Endpoints:

- Incidence of major adverse cardiac events (death, stroke, acute myocardial infarction)
- Incidence of hospitalizations (both CV and non-CV)
- Incidence of heart failure (HF) events, (includes HF hospitalizations and urgent emergency room/outpatient visits for HF)
- Incidence of atrial fibrillation/flutter (new from screening)
- Incidence of implantable cardioverter defibrillator (ICD) therapy and resuscitated cardiac arrest
- Incidence of ventricular tachyarrhythmia (including ventricular tachycardia (VT), ventricular fibrillation, and Torsades de Pointe)
- Incidence of syncope and seizures
- Frequency and severity of treatment-emergent adverse events (TEAEs), treatment-emergent SAEs, and laboratory abnormalities (including trends in NT-proBNP)
- Change from baseline to Week 30 in cardiac rhythm patterns

CMR Substudy Primary Endpoint:

- Change from baseline to Week 30 in LV mass index

CMR Substudy Exploratory Endpoints:

- Change from baseline to Week 30 in myocardial fibrosis as measured by late gadolinium enhancement
- Changes from baseline to Week 30 in cellular hypertrophy, left atrial volume and function, LV wall thickness and LV function

6.2. Analysis Populations

Four analysis populations are defined in this study:

- Intention-to-treat (ITT) Population: All randomized subjects, regardless of whether they receive study drug, with analyses conducted according to randomized treatment assignment

- Safety Analysis Population: All randomized subjects who receive at least 1 dose of study drug with analyses conducted by actual treatment received.
- PK Analysis Population: All randomized subjects who receive at least 1 dose of mavacamten and have at least 1 detectable mavacamten plasma drug concentration
- CMR Substudy Population: All subjects who consent to participate in the CMR substudy and have CMR scans available to evaluate at both Day 1 at Week 30, with analyses conducted according to the randomized treatment assignment

6.3. Stratification Factors and Subgroups

The baseline values for the following stratification factors will be summarized using descriptive statistics:

- NYHA class (II or III)
- Current treatment with β-blocker (yes or no)
- Type of ergometer (treadmill or exercise bicycle)
- Consent for the CMR substudy (yes or no).

The assigned (IXRS) and actual (CRF) stratification factors will be summarized and listed for mis-stratified participants.

Selected efficacy endpoints (refer to Section 8) will be analyzed by the following subgroups at baseline:

- Beta-blocker use (yes vs no; actual value)
- Type of exercise testing (treadmill vs bicycle; actual value)
- NYHA class (II vs III; actual value)
- Consent for the CMR substudy (yes vs no; actual value)
- Sex (male vs female)
- Age (<= 49, 50-64, >=65)
- BMI (< 30 vs >= 30)
- Race (white vs not white)
- Region (US vs ex-US)
- Presence of HCM pathogenic mutation (pathogenic or likely pathogenic vs variant of uncertain significance (VUS) vs not pathogenic)
- Time from diagnosis of oHCM (<= 5 years vs > 5 years)
- Calcium channel blocker use (yes vs no)
- SRT history (yes vs no)
- ICD implanted (yes vs no)

- History of hypertension (yes vs no)
- Resting LVEF (< 75% vs >= 75%)
- LVOT resting peak gradient (<= 50 mmHg vs > 50 mmHg)
- LVOT resting peak gradient (<= 30 mmHg vs > 30 mmHg)
- E/e'* (<= 14 vs > 14)
- Left atrial volume index (<= median vs > median based on ITT population)
- NT-proBNP (<=median vs >median based on ITT population)
- hs-Cardiac troponin-I (<= upper limit of normal (ULN) vs > ULN)
- E/e'* >14 or hs-Cardiac Troponin >ULN vs others
- Creatinine clearance (CrCl) (< 60 mL/min vs >= 60 mL/min)

* The subgroup analysis that are related to E/e' will be repeated for all three types of E/e': lateral, septal and average.

6.4. Missing Data

In general, missing data will not be imputed unless specifically stated in this SAP. For mixed-model repeated-measure analyses, missing data are handled implicitly by the model. For the responder analysis of primary and secondary endpoints, refer Section 8.1 and 8.2 for the specific handling rules.

Handling of Missing Data:

- For values below the lower limit of quantitation (LLOQ), 1/2 LLOQ will be imputed unless otherwise specified.
- For values above the upper limit of quantitation (ULOQ), ULOQ + 1 unit of significant digit will be imputed unless otherwise specified.
- In general, for missing or partial dates the following is noted:
  - Start Dates:
    - If day is missing, then impute it to be the start of the month (eg, 01MMMYYYY); except if the month and year is equal to the first dose date month and year then impute the day to be the same day as the first dose date.
    - If month is missing, then impute it to be the start of the year (eg, 01JANYYYY), except if the year is equal to the first dose date year then impute the day and month to be the same as the first dose date.
    - If year is missing, then do not impute.
  - End Dates:
    - If day is missing, then impute it to be the end of the month (eg, 31MMMYYYY), except if the month and year is equal to the last

assessment date month and year then the day should be imputed to the last assessment date day.

- If month is missing, then impute it to be the end of the year (eg, 31DECYYYY), except if the year is equal to the last assessment date year then the day and month should be imputed to the last assessment date day and month.
- If year is missing then do not impute.

- For all other type of dates:
  - If only day is missing, then impute it to be the start of the month (eg, 01MMMYYYY).
  - If month and day are missing, then impute it to be the start of the year (eg, 01JANYYYY).
  - If year is missing, then do not impute.

6.5. Multiplicity Control

A sequential testing procedure will be used for multiplicity control. If the primary endpoint is not statistically significantly different between treatment groups, none of the tests for secondary endpoints will be considered statistically significant despite the nominal p-values. Contingent upon significance in the primary endpoint, each of the secondary efficacy endpoints will be tested sequentially in the following order, at a 2-sided alpha level of 0.05:

1. Change from baseline to Week 30 in post-exercise LVOT peak gradient
2. Change from baseline to Week 30 in pVO_2 as determined by CPET
3. Proportion of subjects who had at least 1 class of NYHA improvement from baseline at Week 30
4. Change from baseline to Week 30 in patient-reported health-related QoL as assessed by the KCCQ-23 CSS
5. Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCMSQ SoB subscore

If any of the endpoints are not statistically significantly different between treatment groups, the tests for all subsequent endpoints will not be considered statistically significant despite the nominal p-values.

7. SUBJECT DISPOSITION

The number and percentage of subjects who complete and who prematurely discontinue study drug or study, as well as the reasons for premature discontinuation, will be summarized by randomized treatment assignment for the ITT Population. The reason for screen failure will be summarized for all screened subjects.

7.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by randomized treatment assignment for the ITT Population.

Body surface area (BSA) will be derived using the Du Bois method.

Cytochrome P450 (CYP) 2C19 genotypes and phenotypes will also be summarized.

7.2. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received for the Safety Analysis Population.

The duration of study drug exposure is defined as last dose date – first dose date + 1 day, regardless of intermittent interruptions. Adjusted duration will also be derived by taking protocol-defined interruptions into account.

Compliance will be calculated based on the total cumulative dose received divided by the total expected cumulative dose. Compliance of taking pills will be calculated based on the total number of pills taken divided by the adjusted duration.

Treatment exposure and compliance will be summarized using descriptive statistics. The compliance of participants with compliance < 80% and those with compliance > 100% will be summarized.

Actual dose adjustments that occurred during the study and expected dose adjustments based on protocol-specified criteria will be listed by subject and time point. Any inconsistencies will be flagged.

7.3. Protocol Deviations

Prior to Week 38 database lock, all protocol deviations will be reviewed and confirmed by the sponsor. All important protocol deviations will be presented in a by-subject data listing. Important protocol deviations (IPDs) will be identified by the sponsor and summarized. International Council for Harmonisation (ICH) E3 guidance defines IPD as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

7.4. Medical History and Concomitant Medications

Medical history, HCM history, concomitant and prior medications will be summarized and listed by treatment group for Safety Analysis Population.

8. EFFICACY ANALYSES

All efficacy analysis will be based on the ITT Population unless otherwise noted. Descriptive statistics for efficacy parameters by time point and change from baseline will be provided, including the estimates of treatment group differences and the 95% confidence intervals (CIs) based on normal approximation, as appropriate. Descriptive statistics for change from week 30 to week 38 may also be provided, as appropriate. Stratified statistical tests will be performed for

between-group comparisons. Unstratified tests may be performed as sensitivity analyses for binary response endpoints. The 3 stratification factors are:

- NYHA class (II or III)
- Current treatment with β-blocker (yes or no)
- Type of ergometer (treadmill or exercise bicycle)

Consent for the CMR substudy will not be included as a stratification factor to avoid creating small sample size problems for certain stratum. Assigned stratification by IXRS will be used in the main analyses. Actual stratification as recorded on CRF will be used in sensitivity analyses.

8.1. Primary Efficacy Endpoints

The primary efficacy endpoint is clinical response at Week 30, defined as achieving: 1) an improvement of ≥ 1.5 mL/kg/min in pVO_2 as determined by CPET and a reduction ≥ 1 NYHA class, or 2) an improvement of ≥ 3.0 mL/kg/min in pVO_2 with no worsening in NYHA class. If Week 30 pVO2 is missing, no imputation will be performed, and the participant will be considered as a non-responder. If pVO2 is available but NYHA class is missing at Week 30, the NYHA class at Week 30 will be imputed with the NYHA class at Week 26, if available. If there are multiple records of NYHA class within Week 26 analysis window, the latest one will be used. The clinical response status at Week 30 will be assessed after the imputations for applicable cases. Participants whose response status at Week 30 is missing will be classified as nonresponders.

The clinical response rate will be summarized for each treatment group with descriptive statistics. The estimates of treatment group differences and the 95% CIs based on normal approximation will be provided. The Cochran-Mantel-Haenszel (CMH) test for stratified categorical data will be used to test the statistical significance of the association between clinical response status (responder vs nonresponder) and treatment group (mavacamten vs placebo). Unstratified analysis using a Chi-square test will be performed as a sensitivity analysis.

A forest plot summarizing the 95% CI of the difference in clinical response rates at Week 30 between mavacamten and placebo treatment groups will be generated for the subgroups listed in Section 6.3 to evaluate the consistency of treatment effects in the subgroups.

8.2. Secondary Efficacy Endpoints

Five secondary endpoints are defined and will be tested sequentially in the following order:

1. Change from baseline to Week 30 in post-exercise LVOT peak gradient
2. Change from baseline to Week 30 in pVO_2 as determined by CPET
3. Proportion of subjects who had at least 1 class of improvement from baseline in NYHA class at Week 30*
4. Change from baseline to Week 30 in patient-reported health-related QoL as assessed by the KCCQ-23 CSS
5. Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCMSQ SoB subscore

*If the NYHA class is missing at Week 30, it will be imputed with the NYHA class at Week 26, if available. If there are multiple records of NYHA class within Week 26 analysis window, the

latest one will be used. The response status at Week 30 will be assessed after the imputations for applicable cases. Participants whose NYHA response status at Week 30 is missing will be classified as nonresponders.

These endpoints will be summarized for each treatment group at each visit with descriptive statistics. The estimates of treatment group differences and the 95% CIs based on normal approximation will be provided.

The CMH test will be used to assess the categorical secondary endpoint (proportion of subjects with at least 1 class of improvement in NYHA) between the mavacamten and placebo groups. Between-group comparisons of the continuous secondary efficacy endpoints will be based on analysis of covariance (ANCOVA) for LVOT gradient and pVO_2, and based on a mixed model for repeated measurements (MMRM) for KCCQ-23 CSS and HCMSQ SoB because these PROs were collected at multiple post-baseline visits. For ANCOVA, treatment group (mavacamten vs placebo), baseline value of the corresponding endpoint of interest, and the 3 stratification factors (beta blocker use, NYHA class, ergometer type) will be treated as fixed effects. In MMRM, in addition to the fixed effects described above, time point (as a categorical variable) and the interaction between treatment and time point will be included. Subject will be treated as a random effect, and compound symmetric variance covariance component will be used. All post-baseline data up to Week 30 will be included in the model.

An unstratified analysis will also be conducted as a sensitivity analysis using the Chi-square test for categorical endpoint.

A forest plot summarizing the 95% CI of the between-group difference for these 5 secondary endpoints at Week 30 will be generated for the subgroups listed in Section 6.3 to evaluate the consistency of treatment effects in the subgroups.

The KCCQ-23 is a self-administered 23-item questionnaire that quantifies physical limitations, symptoms, QoL, social interference, and self-efficacy (Green et al, 2000). The total symptom score is derived from the symptom frequency and symptom burden scores. The CSS is derived from the physical limitation and total symptom scores. The overall summary score is derived from the physical limitation, symptom, QoL, and social interference domains. Scores range from 0 to 100, with higher scores reflecting better health status. KCCQ-23 will be collected on Day 1 and at Week 6, Week 12, Week 18, Week 30/end of treatment (EOT), and Week 38/EOS and summarized by analysis visit as defined by the analysis window specified in Appendix 2 Table 10. Baseline value is defined as the last non-missing KCCQ-23 value prior to or on the first dose date.

The CSS will be analyzed as a secondary efficacy endpoint as specified above, and the total symptom score and overall summary score will be analyzed as exploratory efficacy endpoints using the method described in Section 8.3.1.

The HCMSQ is a self-administered, 11-item questionnaire that assesses the core symptoms of HCM (tiredness/fatigue, heart palpitations, chest pain, dizziness, and shortness of breath). During the screening period, participants will complete the HCMSQ for a minimum of 7 consecutive days. From Day 1 through Week 6, participants will complete the HCMSQ daily. For the remainder of the treatment period, participants will complete the HCMSQ for at least 7 consecutive days prior to study visits at Weeks 10, 14, 18, 22, 26, 30 (EOT) and 38 (EOS). The weekly average HMCSQ scores will be derived using the scoring algorithm detailed in

Appendix 3, and summarized by analysis visit as defined by the analysis window in Appendix 2 Table 11.

Because the weekly average HCMSQ scores only include data up to 7 days for calculation, the data collected outside the 7-day period will be excluded from analysis. At each visit, the 7-day period will be determined so that the last day of the period is the last day with non-missing HCMSQ score prior to or on the actual clinic visit (or first dose date if for baseline). If the participant completes the questionnaire fewer than 4 days over the 7-day period, the weekly average HCMSQ scores for that visit will be treated as missing.

Shortness of breath subscore will be analyzed as secondary efficacy endpoint as specified above, and the other subscores (tiredness and cardiovascular symptoms) in addition to the total score will be analyzed as exploratory efficacy endpoints using the method described in Section 8.3.1.

8.3. Exploratory Efficacy Analysis

8.3.1. General Analysis Methods

All the exploratory endpoints described in this section will be summarized for each treatment group at each visit with descriptive statistics. The estimates of treatment group mean differences and the 95% CIs based on normal approximation will be provided.

The comparison of the exploratory efficacy endpoints between the mavacamten and placebo groups will be based on change from baseline at Week 30. For continuous endpoints, stratified analyses using the ANCOVA or MMRM may be used for these comparisons for continuous endpoints. In ANCOVA, treatment group (mavacamten vs placebo), baseline value of the corresponding endpoint of interest, and the 3 stratification factors (beta blocker use, NYHA class, ergometer type) will be treated as fixed effects. In MMRM, in addition to the fixed effects described above, time point (as categorical variable) and the interaction between treatment and timepoint will be included. Subject will be treated as a random effect, and a compound symmetric variance covariance component will be used. All post-baseline data up to Week 30 will be included in the model. For categorical endpoints, stratified analyses using the CMH test will be used. The p-values generated from these analyses will not be adjusted for multiplicity and will be considered descriptive.

In the subsequent subsections, for each of the exploratory endpoints, details are provided on: 1) specific parameters to be analyzed, 2) figures to be generated to visually explore the relationships between the selected endpoints, 3) figures to be generated to assess the treatment effects in subgroups, and 4) additional endpoint-specific exploratory analyses.

8.3.2. CPET

Exploratory efficacy endpoints for CPET parameters to be summarized will include, but are not limited to, the following:

- Volume expired (VE)/ carbon dioxide production (VCO_2)
- VE/VCO_2 slope (ventilatory efficiency)
- Circulatory power
- Ventilatory Power

- Peak workload
- Respiratory exchange ratio (RER)
- % Predicted peak VO_2

The distribution of the changes in selected CPET parameters by treatment group will be visualized to give a more comprehensive description of the data.

8.3.3. Transthoracic Echocardiography (TTE; ECHO)

The proportion of subjects achieving a post-exercise LVOT peak gradient < 50 mmHg at Week 30 and the proportion of subjects achieving a post-exercise LVOT peak gradient < 30 mmHg at Week 30 will be summarized using descriptive statistics and compared between the mavacamten and placebo groups using the CMH test. Participants whose baseline post-exercise LVOT peak gradient were < 50 mmHg or < 30 mmHg will be excluded from the analyses. The proportion of subjects with LVEF < 50% at Week 30 will be summarized by treatment group using descriptive statistics.

In addition, the following ECHO parameters (including, but not limited to) will also be analyzed as exploratory efficacy endpoints. Indices parameters (eg, LV end-diastolic volume index [LVEDVI]) will be derived by dividing each respective parameter by BSA calculated using the height at baseline and weight at each respective visit.

- Systolic function:
  - Left ventricular ejection fraction (LVEF)
  - Left ventricular fractional shortening (LVFS)
  - Left ventricular stroke volume (LVSV)
  - Left ventricular Cardiac Output (LVCO)
- Diastolic function
  - e' (lateral, septal, average)
  - E/e' (lateral, septal, average)
  - E/A ratio
- Structural parameters
  - Interventricular septal thickness (IVS)
  - Posterior wall thickness
  - Maximal LV wall thickness (at baseline)
  - LVOT gradient (resting, Valsalva, and post exercise)
  - LV end-diastolic volume
  - LV end-diastolic volume index
  - LV end-systolic volume
  - LV end-systolic volume index

- Left atrial (LA) volume
- LA volume index (LAVI)
- LV mass index

- Other
  - Presence of systolic anterior motion (SAM) of the mitral valve
  - Presence of mitral regurgitation (MR)

The following figures will be presented for ECHO data:

- Mean (+/-SD) over time line plots for selected ECHO parameters, including LVOT gradient (resting, Valsalva, and post exercise), LVEF, LAVI, E/e' (septal, lateral, average)
- Forest plots of the 95% CI of the mean difference in change from baseline at Week 30 between the mavacamten and placebo groups for all ECHO parameters listed above
- Forest plots of the 95% CI of the mean difference in change from baseline at Week 30 in key ECHO parameters (eg, LVEF, E/e', LAVI) between the mavacamten and placebo groups for the subgroups listed in Section 6.3.

8.3.4. NT-proBNP

Median (+/- Q1, Q3) over time line plots will be generated for NT-proBNP concentration.

8.3.5. PRO Analyses

The EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire is a validated instrument of general QoL and is critical for acceptance by many health technology assessment bodies for coverage decisions. The tool is translated in multiple languages, is validated on various electronic platforms, and takes only a few minutes to administer. EQ-5D-5L will be collected on Day 1 and at Weeks 6, 12, 18, 30/EOT, and 38/EOS and summarized based on the analysis windows defined in Appendix 2 Table 10. Baseline value is defined as the last non-missing EQ-5D-5L value on or prior to the first dose date.

The PGIS questionnaire is a single-item questionnaire that asks participants to rate their overall symptom severity in the past week on a 5-point categorical rating scale (none, mild, moderate, severe, very severe). PGIS will be collected at screening, Weeks 6, 10, 14, 18, 22, 26, 30/EOT, and 38/EOS, and summarized based on the analysis windows defined in Appendix 2 Table 10. Baseline value is defined as the last non-missing PGIS value on or prior to the first dose date.

The PGIC questionnaire is a single-item questionnaire that asks participants to rate their overall change in symptom severity over time (since the participant started taking the study drug) on a 7-point categorical rating scale (very much better to very much worse). PGIC will be collected on Weeks 6, 10, 14, 18, 22, 26, 30/EOT, and 38/EOS, and summarized based on the analysis windows defined in Appendix 2 Table 10.

The WPAI-SHP questionnaire was created as a patient-reported quantitative assessment of ability to work and perform regular activities. Specifically, the WPAI-SHP asks about the impact of a specific health problem (in this case HCM) on absenteeism, presenteeism, and daily activity

impairment. Baseline value is defined as the last non-missing WPAI-SHP value on or prior to the first dose date.

Compliance for each PRO assessment will be summarized by visit and treatment group for the number of subjects that met the compliance criteria of the respective assessment, and for the average number of days a subject completed a questionnaire (if collected over a period of days).

8.3.5.1. PRO responder analysis

Responder analysis will be performed for each of the following PRO scores:

- HCMSQ: Shortness of breath, Tiredness, Cardiovascular symptoms, Total
- KCCQ-23: TSS, CSS and OSS

Responders are defined as the participants who achieved clinically meaningful changes from baseline. The thresholds for clinically meaningful changes were derived following the psychometric analysis plan (PAP) using data from Study MYK-461-006 (MAVERICK-HCM), a phase 2 proof-of-concept study in non-obstructive HCM. Another set of thresholds will also be derived as described in the PAP using the data from this study (MYK-461-005; EXPLORER-HCM) without actual treatment information. For KCCQ-23, thresholds reported in the literature for heart failure will be included, as well.

Table 1: Responder Thresholds for HCMSQ

	MAVERICK-HCM	EXPLORER-HCM
Total Score	≤ -2	TBD
Shortness of Breath	≤ -2	TBD
Tiredness	≤ -1	TBD
Cardiovascular Symptoms	≤ -1	TBD

Table 2: Responder Thresholds for KCCQ-23

	MAVERICK-HCM	Literature*	EXPLORER-HCM
Overall summary score (OSS)	≥ 10	≥ 5	TBD
Clinical summary score (CSS)	≥ 10	≥ 5	TBD
Total summary score (TSS)	≥ 10	≥ 5	TBD

* Spertus J, Peterson E, Conard MW, et al., "Monitoring clinical changes in patients with heart failure: a comparison of methods," Am Heart J, 150:707-15 (2005).

The responder rate (based on each set of responder thresholds) will be summarized by visit and treatment arm. Participants who cannot be qualified as responders in the study due to their baseline scores will be excluded. For the HCMSQ instrument, these are participants who have missing value at baseline or have a baseline score < 0 - clinically meaningful threshold. For the KCCQ-23 instrument, these are participants who have missing value at baseline or have a baseline score > 100 – clinically meaningful threshold. Participants who have missing data at the post-baseline visit will be considered non-responders for that visit.

Responder rate at Weeks 30 will also be compared between treatment groups using CMH test with stratification factors: NYHA class (II or III), and current treatment with β-blocker (yes or no), and type of ergometer used during the study (treadmill or exercise bicycle). The forest plots will be used to illustrate the response rate differences between treatment groups and the associated 95% CIs.

A more detailed analysis of PRO data will be specified in the PAP and the results will be summarized in a separate report.

8.3.6. Accelerometer

Participants will be provided with an accelerometer to be worn on the wrist from screening to Day 1, and from Week 26 to Week 30 to collect data on physical activity. The following parameters and the change from baseline will be summarized by treatment group using descriptive statistics and will include estimates of treatment group differences and 95% CIs based on normal approximation for the ITT population.

- Average daily accelerometry unit (ADAU) is the average of daily square-root of (Wear-Filtered Axis X count^2+ Wear-Filtered Axis Y count^2 + Wear-Filtered Axis Z count^2)
- Average daily step counts (wear-filtered)
- Average daily active hours: the average of the wear-filtered daily hours in activity level higher than sedentary
- Average daily hours in moderate or higher activity (wear-filtered)

Accelerometer compliance is defined as device wear time ≥ 1200 minutes/day. All compliant days within the following visit windows will be included in the analysis:

Table 3: Accelerometry Data Analysis Windows

Analysis Visit	Analysis Visit Window
Baseline	Screening ≤ analysis day ≤ 1
Week 26	169 < analysis day ≤ 239

Compliance will be summarized by visit and treatment for the number of subjects that met compliance criteria (ie, ≥ 1200 minutes/day) for at least 1 day, and will be summarized in those compliant subjects for their average number of wear minutes per day and their average number of compliant days using descriptive statistics.

8.3.7. hs-Cardiac Troponin I

Median (+/- Q1, Q3) over time line plots will be generated for hs-Cardiac Troponin I concentration.

A shift table of hs-cardiac troponin-I (<=ULN and >ULN) by treatment group and visit will be provided. A boxplot of change from baseline in cardiac troponin-I by treatment group and visit will also be presented.

8.3.8. NYHA Class

A shift table of NYHA class from baseline will be summarized by visit. The change from baseline to Week 30 in NYHA class expressed as numerical numbers will also be analyzed using the methods as described in Section 8.3.1.

8.3.9. Additional Exploratory Analysis

Correlation analyses and associated visualization may be performed among the efficacy, PK and safety data to provide insights on disease nature and drug mechanism, which include but not limited to:

- Changes in echocardiographic features (eg, LAVI, LVEF, LVOT peak gradient) vs EKG patterns enabled by AI algorithms
- Change in NT-proBNP vs Change in pVO2
- Change in NT-proBNP vs Change in hs-Cardiac troponin I
- Change in NT-proBNP vs Change in LVEF or occurrence of LVEF<50%
- Change in NT-proBNP vs Incidence of atrial fibrillation
- Change in pVO2 vs Change in NYHA class
- Change in HR (from ECHO) vs Change in LVEF

9. PHARMACOKINETIC ANALYSES AND PHARMACODYNAMIC

The PK and PK/PD analyses described in this section will be based on the PK Populations. PK data from this study may be included as part of a population PK analysis and summarized in a separate report. Mavacamten plasma concentration values < LLOQ will be imputed following the imputation methods described in Section 6.4.

Mavacamten plasma concentrations at each visit will be summarized for overall and by CYP2C19 phenotype status using descriptive statistics. The distribution of mavacamten plasma concentrations at each visit will also be summarized by category of <350, 350 to 700, >700 to <1000, and >=1000.

The following PK/PD relationships will be presented in scatterplots:

- Mavacamten concentration versus post-exercise LVOT gradient change from baseline through Week 30
- Mavacamten concentration versus LVEF change from baseline through Week 30
- Mavacamten concentration versus LVEF from baseline through Week 30
- Mavacamten concentration versus pVO_2 (determined by CPET) change from baseline through Week 30
- Mavacamten concentration versus NT-proBNP change from baseline through Week 30

Selected efficacy endpoints (e.g. primary endpoint, change in pVO2, NYHA improvement and change in post-exercise LVOT peak gradient) will be summarized descriptively by the Week 30 mavacamten concentration categories (<350, 350 to 700, >700 to <1000, and >=1000).

10. SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Population using the following common rules:

- The baseline value is defined generally as the last available value before the first administration of study drug.
- The analysis of the safety variables will be descriptive and no hypothesis testing is planned.

The safety analyses will focus on the treatment emergent period, which is defined as the time from the first administration of study drug to the last administration of study drug plus 56 days.

A by-subject listing of all AEs will be provided.

10.1. Adverse Events

AEs will be mapped to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. AEs will be monitored during the study, and AE data will be analyzed with respect to overall incidence, as well as severity and relationship of AEs to study drug. AEs with onset during the treatment emergent period or with onset before the first dose of study drug that increase in severity or become serious during the treatment-emergent period will be considered TEAEs.

AE summary tables will present the number and percentage of subjects experiencing at least one TEAE by SOC and PT by treatment group for the Safety Analysis Population. Multiple occurrences of the same event in the same participant will be counted only once in the tables. In addition, the AE summary tables will also be presented by SOC, PT, and severity grade.

AE summary tables will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent serious AEs, study drug related AEs (per investigator assessment), study drug related SAEs, all TEAEs leading to permanent treatment discontinuation, and all TEAEs leading to death. Similarly, AE incidence during the pre-treatment period (ICF signed date up to the first administration of study drug) will be summarized by SOC and PT. Adverse events of special interest (AESI; per protocol) will be summarized for frequency of occurrence and symptomatic responses.

TEAEs may also be summarized by Standardised MedDRA Queries (SMQs) or other groupings deemed relevant based on AESIs and SAEs observed in the study. Selected TEAEs (e.g. atrial fibrillation, atrial flutter, heart failure, syncope, presyncope and dizziness) will be summarized and listed by historical medical conditions and treatment group. By-subject listings of all AEs, SAEs, TEAEs leading to treatment interruption or discontinuation or study discontinuation will also be provided.

10.1.1. Deaths

The following death summaries will be generated in a summary table or listed in a by-subject data listing:

- Number and percentage of subjects who died by treatment group for the Safety Analysis Population
- Death in non-randomized subjects or randomized but not treated subjects
- TEAEs leading to death (death as an outcome on the AE eCRF page as reported by the investigator) by primary SOC and PT showing number and percentage of subjects

10.1.2. Pregnancy

The following pregnancy summaries will be generated:

- Number of participants who became pregnant summarized by treatment group
- Outcomes of the pregnancies and analysis of the outcomes
- TEAE experienced during the pregnancy by primary SOC and PT showing the number and percent of participants

10.1.3. Overdose

Overdose is defined per protocol as taking more capsules of study drug than directed. The following overdose information will be provided:

- Number of subjects who experienced overdose summarized by treatment group
- Listing of the cause and occurrence of the overdose
- Summary of TEAEs as symptomatic response to overdose by primary SOC and PT showing the number and percent of subjects

10.2. 12-lead Electrocardiogram

12-lead electrocardiogram (ECG) data will be summarized for all subjects in the Safety Analysis Population, for subjects without pacing, and for subjects with baseline QRS <120 ms versus ≥120 ms in the analyses described in this section.

The RR, PR, QRS, and QT intervals will be measured and read by a central laboratory. HR will be calculated as 60/(RR × 1000) (with RR expressed in msec) and rounded to the nearest integer.

10.2.1. Correction for Heart Rate

Corrected QT interval (QTc) will be calculated using the manually over-read QT values. Each individual ECG QT value will be corrected for HR. The measured QT data will be corrected for HR using Fridericia-corrected QT interval (QTcF) as per the following formulae/method (with QT, RR, and QTc expressed in msec):

Fridericia's correction:

$$QTcF = \frac{QT}{(RR/1000)^{(1/3)}}$$

10.2.2. ECG Numeric Variables

HR, PR, QRS, and QTcF and changes from baseline will be summarized by treatment group using descriptive statistics. The change from baseline of these ECG parameters at each time point will be listed for each subject.

10.2.3. Categorical Analysis

The number and percentage of subjects with maximun post-dose QTcF values > 450 msec, > 480 msec, >500 msec, > 520 msec, and >550 msec will be summarized by treatment group. Participants with QTcF values > 500 msec will be listed along with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The number and percentage of subjects with QTcF increase from baseline > 30 msec and > 60 msec will be summarized by treatment group.

10.2.4. Morphology Findings

ECG morphologies for each subject will be listed.

10.2.5. Concentration-QTcF Analyses

The relationship between mavacamten concentration and ΔQTcF will first be evaluated by a scatterplot of time-matched concentration and ΔQTcF data. A linear mixed model will be used to estimate the slope and 95% CI of the concentration-QTcF relationship. For the linear mixed-effects model, the fixed effects can include but not limited to concentration and sex, and subject will be included as a random effect. Compound symmetry will be implemented for the variance-covariance structure.

10.3. Safety Laboratory Data

Safety laboratory data will be summarized by treatment group and visit using descriptive statistics.

Shift tables reflecting changes from baseline (ie, normal to low, high, etc.) will be presented in lieu of descriptive statistics of changes from baseline. Listings of laboratory values will be generated and the results that are out of the reference range will be flagged.

10.3.1. Potential Drug-induced Liver Injury

The liver function tests, namely alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL) are used to assess possible drug -induced liver injury (DILI).

A graph of distribution of peak values of ALT versus peak values of TBL will be presented. ALT and TBL values will be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 × the upper limit of normal (ULN) for ALT and a horizontal line corresponding to 2 × ULN for TBL.

The number and percentage of subjects with elevated liver function tests (based on safety laboratory data) during the TEAE period will be summarized by categories of elevation (>3 × ULN, >5 × ULN, >10 × ULN, >20 × ULN for ALT and AST, >1.5 × ULN for ALP, and >1.5 × ULN and >2 × ULN for TBL), along with the following categories of normalization (i.e. return to ≤1 × ULN, or return to baseline if baseline > ULN): never normalized, normalized after permanent discontinuation of study drug, normalized during treatment period and elevated after permanent discontinuation of study drug. Potential Hy's law cases will be investigated by summarizing the number of subjects with elevated ALT or AST (>3 x ULN) and with elevated total bilirubin (>2 x ULN) where transaminase elevation coincides with or precedes BILI elevation.

10.4. Vital Signs Data

Vital signs, including heart rate (HR), systolic blood pressure, and diastolic blood pressure, values and changes from baseline will be summarized by treatment group and visit using descriptive statistics.

10.5. Cardiac Rhythm Monitoring (Including Holter Monitor)

The summary statistics of maximum HR, atrial fibrillation (Afib) percentage time, and VT (sustained or non-sustained) frequency will be calculated for each cumulative 48-hour Holter monitoring period and summarized by treatment group and visit. For each of the cardiac event type (Afib and VT), the number of subjects with ≥ 1 occurrence will be summarized. The percentage of time in Afib and number of VT episodes per subject will also be summarized. Additional parameters (eg, supraventricular tachycardia, premature ventricular contractions, pauses) may be summarized and analyzed as appropriate.

10.6. Other Safety Analysis

Listing of patients with ICD therapy (shock) and appropriateness of therapy as per event adjudication will be provided.

Abnormal physical examination results will be listed by subject and clinical significance.

The number of subjects who met treatment discontinuation criteria per protocol, as well as who met each temporary study drug interruption, will be summarized by treatment and criteria met.

11. PHARMACOGENOMIC/HCM GENOTYPE

HCM genotype, including HCM genes with identified variants (pathogenic or not pathogenic) based on current and previous testing will be summarized by treatment group and overall. Participants with no past or current HCM genotype test results will be categorized as Unknown. If a participant has both past and current HCM genotype test result, the current result will be used for data analysis. A by-subject listings of the results from current and previous HCM genotype testing will be provided.

12. CARDIAC MAGNETIC RESONANCE IMAGING SUBSTUDY

Results from the CMR imaging substudy will be summarized by treatment group using descriptive statistics for the CMR Substudy Population. Changes in LV mass index, myocardial fibrosis, cellular hypertrophy, LA structure and function, and ventricular structure and function will be summarized. Within-group 30-week changes from baseline will be assessed against a null of zero change using Wilcoxon Signed Ranks tests. Between-group differences in the magnitude and direction of those changes will be evaluated using Wilcoxon-Mann-Whitney tests.

13. INTERIM ANALYSIS

No interim analysis is planned for this study. Week 30 analysis is the primary analysis to evaluate the efficacy, and week 38 analysis is the safety follow up analysis.

14. SUMMARY OF CHANGES IN THE PROTOCOL PLANNED ANALYSES

Additional analyses may be performed to address the COVID-19 impact on efficacy, safety and other study conduct as appropriate.

Other changes are listed below:

1. Specify KCCQ-23 Clinical Summary Score and HCMSQ Shortness-of-Breath are to be secondary endpoints based on the recommendations from FDA.
2. Added KCCQ-23 responder (proportion of subjects with clinically meaningful changes) and HCMSQ responder to exploratory endpoints based on the recommendation from FDA.
3. Added two exploratory endpoints: 1) Proportion of subjects with any decrease in post-exercise LVOT peak gradient from baseline to Week 30; 2) Proportion of subjects achieving complete response at Week 30.
4. Removed HCM risk prediction score from exploratory objectives and exploratory endpoints because the scoring algorithm is heavily dependent on LVOT peak gradient which compromises the score interpretation under mavacamten treatment.
5. Moved cardiac rhythm patterns from exploratory efficacy endpoint to safety endpoint.
6. Removed per-protocol population and PK/PD analysis population as no analyses are planned for these two populations.
7. Modified the PK analysis population and CMR substudy population definition to better align with the analysis intention.
8. TEAE are to be summarized by SOC and PT instead of by SOC, HLGT, HLT, and PT.
9. Summary of pregnancy will not include the pregnancy test results from the partners of participants because they were not collected in the study.
10. Updated language in the DILI section.

15. REFERENCES

Chuan P, Sivaramakrishnan S, Ashley EA, Spudich JA. Cell-Intrinsic Functional Effects of the α-Cardiac Myosin Arg-403-Gln Mutation in Familial Hypertrophic Cardiomyopathy. Biophysical Journal. 2012;102(12):2782–90.

Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J*. 2014;35(39):2733-2779. doi:10.1093/eurheartj/ehu284.

Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. Journal of the American College of Cardiology. 2011;58(25).

Green C, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. Journal of the American College of Cardiology. 2000;35(5):1245–55.

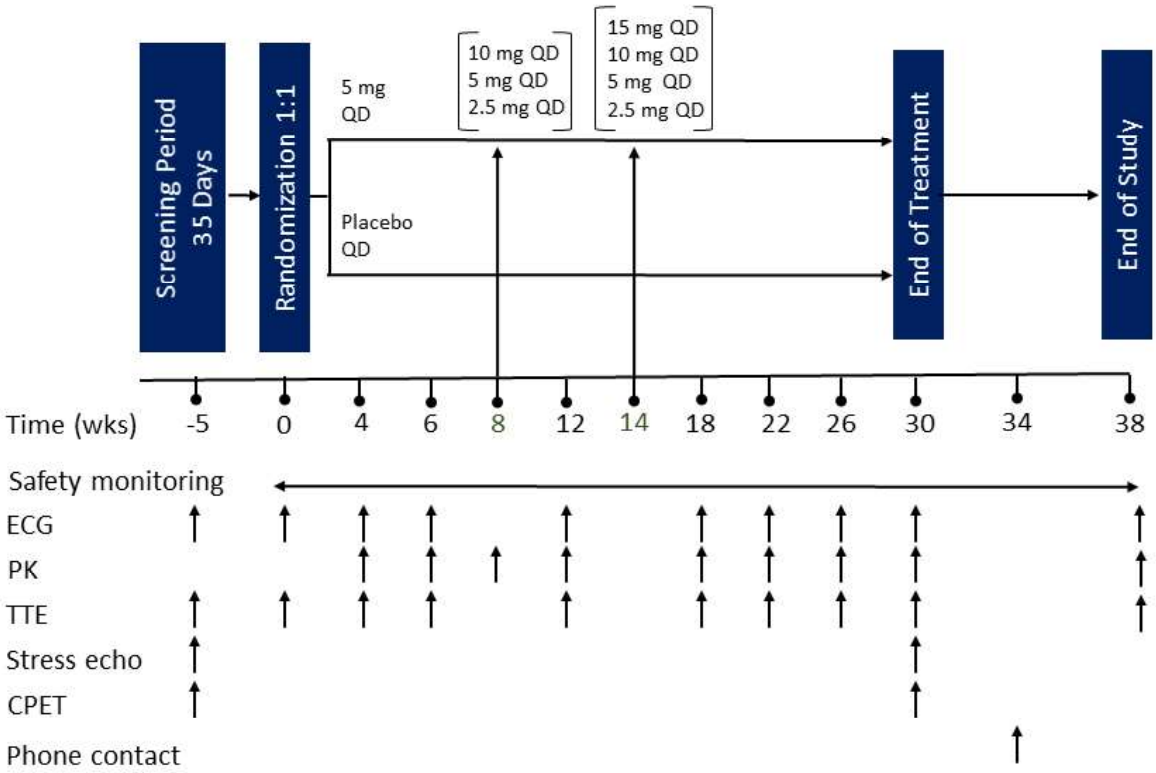
Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2016;29(4):277–314.

Sommese RF, Sung J, Nag S, Sutton S, Deacon JC, Choe E, et al. Molecular consequences of the R453C hypertrophic cardiomyopathy mutation on human -cardiac myosin motor function. Proceedings of the National Academy of Sciences. 2013;110(31):12607–12.

Sung J, Choe E, Elting M, Nag S, Sutton S, Deacon J, et al. Single Molecule Studies of Recombinant Human α- and β-Cardiac Myosin to Elucidate Molecular Mechanism of Familial Hypertrophic and Dilated Cardiomyopathies. Biophysical Journal. 2012;102(3).

APPENDIX 1.

Figure 1: Study Schema



Abbreviations: CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; PK, pharmacokinetics; QD, once daily; stress echo, post-exercise stress echocardiography; TTE, transthoracic echocardiogram; wks, weeks.

Table 4: Schedule of Study Procedures

Assessment[a]	Screening[b] Day -35 to Day -1	Day 1	Week 4 (±7 d)	Week 6 (±7 d)	Week 8 (±7 d)	Week 12 (±7 d)	Week 14 (±7 d)	Week 18 (±7 d)	Week 22 (±7 d)	Week 26 (±7 d)	ET[c]	Week 30 (±7 d)/ EOT	Week 34 (±7 d) (call)	Week 38 (±7 d)/ EOS
General Procedures														
Informed consent	X													
Medical history	X													
Randomization		X												
Physical examination[d]	X	X	X	X		X		X	X	X	X	X		X
Body height	X													
Body weight (in clinic)	X										X	X		
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD information downloaded[f]	X					X					X	X		
ECG[g]	X	X	X	X		X		X	X	X	X	X		X
Vital signs[h]	X	X	X	X		X		X	X	X	X	X		X
Cardiopulmonary Assessments														
Resting TTE[i]	X	X	X	X		X		X	X	X	X	X		X
Post-exercise stress echocardiography[j]	X										X	X[j]		
CPET[k]	X										X	X		
Cardiac monitoring device[l]	X					X				X				
Accelerometer attached[m]	X									X				
Laboratory Assessments														
Hepatitis panel and HIV test	X													
PK sample[n]			X	X	X	X		X	X	X	X	X		X
Coagulation panel	X	X		X				X			X	X		
Chemistry	X	X		X				X			X	X		X
Hematology	X										X	X		X
Urinalysis	X										X	X		
hs-cardiac troponin I	X	X		X				X			X	X		X
NT-proBNP[o]		X	X	X	X	X	X	X	X	X	X	X		X

Table 4: Schedule of Study Procedures (Continued)

Assessment[a]	Screening[b] Day -35 to Day -1	Day 1	Week 4 (±7 d)	Week 6 (±7 d)	Week 8 (±7 d)	Week 12 (±7 d)	Week 14 (±7 d)	Week 18 (±7 d)	Week 22 (±7 d)	Week 26 (±7 d)	ET[c]	Week 30 (±7 d)/ EOT	Week 34 (±7 d) (call)	Week 38 (±7 d)/ EOS
FSH[p]	X													
Serum pregnancy test (women)[q]	X													
Urine pregnancy test (women)[q]		X	X		X	X		X	X	X	X	X	X	X
HCM genotyping[r]		X												
Pharmacogenetics[s]	X													
Exploratory biomarkers (blood)		X									X	X		
Symptom Assessment														
NYHA functional classification	X	X	X	X	X	X	X	X	X	X	X	X		X
Patient-Reported Outcomes	See Table 2 in the Protocol for schedule of PRO assessments													
Investigational Medical Product														
IMP QD		←	—	—	—	—	—	—	—	—		→		
IMP administered at site[t]		X	X	X	X	X	X	X	X	X		X		
IMP compliance[u]			X	X	X	X	X	X	X	X	X	X		
Substudy														
CMR substudy[v]		X										X		

Abbreviations: AE, adverse event; BP, blood pressure; call, telephone contact; CMR, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; CYP, cytochrome P450; d, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment, ET, early termination; FSH, follicle-stimulating hormone; HCM, hypertrophic cardiomyopathy; HIV, human immunodeficiency virus; HR, heart rate; hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; ICF, informed consent form; IMP, investigational medicinal product; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetic; PRO, patient-reported outcomes; QD, once daily; QTcF, Fridericia correction; SAE, serious adverse event; TTE, transthoracic echocardiography.

[a] Preferred order of assessments is ECG, vital signs, PK, and TTE, all prior to study drug dosing unless otherwise described below.

[b] Screening will require more than 1 visit to accommodate all of the study procedures.

[c] The ET visit will be scheduled as soon as possible after the participant permanently discontinues study drug. The participant will be encouraged to participate in the remaining scheduled study visits, particularly the Week 30 visit and the Week 38/EOS visit. If a participant permanently discontinues treatment at or before Week 22, the final visit will be at Week 30.

[d] At Screening, ET, Week 30/EOT, and Week 38, a complete physical examination will be conducted, including a neurological examination. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.

Table 4: Schedule of Study Procedures (Continued)

[e] Changes in baseline conditions from once the ICF is signed will be recorded as an AE. All changes unless otherwise specified that occur after the administration of study drug will be considered treatment-emergent AEs. This assessment will occur either by phone call or an in-person visit.

[f] For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at baseline, at Week 12, and at Week 30, or as clinically indicated after any ICD discharge interrogation occurring during the double-blind treatment period.

[g] Twelve (12)-lead ECGs will be performed after 10 minutes of rest at Screening and prior to dosing at all onsite study visits (except Weeks 8 and 14). Each time an ECG is completed, a 10-second paper ECG will be obtained and maintained in the study participant's source documentation. QTcF value from Day 1 ECG will not be used for eligibility or for temporary discontinuation. The Day 1 QTcF value will be used as the baseline to determine percent change at future visits when criteria for temporary discontinuation are applied. (Note: If for any reason a D1 QTcF is not determined, then QTcF from screening ECG will be used in percent change calculation.)

[h] At Screening, ET, Week 30/EOT, and Week 38, complete vital signs including temperature, HR, respiratory rate, and BP will be obtained. At all other visits, only HR and BP are required. If PK sampling is conducted at a visit, vital signs should be collected before PK sampling. Vital signs should be taken with the study participant in the same position at all visits. BP should be taken via an automated recorder after resting for at least 5 minutes.

[i] Resting TTE should be performed prior to post-exercise stress echocardiography or CPET. Resting TTE images and views will be acquired at each onsite visit prior to dosing as detailed in the echo site instruction manual. Instantaneous LVOT peak gradient (resting) and provoked LVOT peak gradient (Valsalva maneuver) will be assessed by the core laboratory. Left ventricular ejection fraction (LVEF) will be measured at the clinical site by the certified site sonographer and subsequently by the core laboratory. The LVEF site read will be kept blinded from the investigator and other study site personnel, except in case of locally measured LVEF≤30%.

[j] For post-exercise stress echocardiography, participants will undergo a standard symptom-limited exercise test after a 4-hour fast by standardized treadmill or bicycle ergometer during Screening and Week 30/EOT prior to dosing. Instantaneous LVOT peak gradient will be assessed immediately post-exercise by TTE. Post-exercise stress echocardiography may be performed on a different day than CPET. If the 2 procedures are performed on the same day, participants must exercise only once, and participants will undergo CPET and then post-exercise TTE. Post-exercise stress echocardiography should be acquired the same day or within 72 hours of the Resting TTE and should also be performed as close as possible to ET if it occurs. If post-exercise stress echocardiography and CPET are performed on different days, the same sequence of visits must be performed for both screening and EOT.

[k] CPET by standardized treadmill or bicycle ergometer will be performed during Screening and at Week 30/EOT prior to dosing. CPET is done after a 4-hour fast. Record the fasting status and the date and time of the last dose taken prior to CPET. Any concomitant medication may be administered prior to all exercise testing. CPET should also be performed as close as possible to ET if it occurs.

[l] A cardiac monitoring device will be applied during Screening, Week 12, and at the Week 26 visits and retrieved at the Day 1, Week 14, and Week 30 visits, respectively.

[m] An accelerometer will be fastened to the participant's wrist at Screening (at least 11 days before Day 1) and at the Week 26 visit to collect data on activity. Participants will return the accelerometer at the next study visit for data upload and analysis.

[n] Participants should not take study drug on day of visit prior to blood draw for PK. PK sample will be collected ≤2 hours before dosing. Additionally, on Week 30 (last dose), another PK sample will be collected within 1 to 2 hours postdose.

[o] NT-proBNP should be drawn before exercise testing if exercise testing is being performed that day.

[p] FSH testing at Screening for postmenopausal women to confirm postmenopausal status.

[q] Pregnancy testing for all females of childbearing potential: serum pregnancy test at Screening; urine pregnancy test at all other visits shown (every 4-6 weeks), and conduct serum test if any urine test is positive. The Week 34 pregnancy testing will be conducted at home.

Table 4: Schedule of Study Procedures (Continued)

[r] Separate consent is required for HCM genotyping. Note that if a participant with a prior HCM clinical genotype test that was positive for genetic mutation consents to provide their results, then no further genotype assessment will be performed; however, participants who have not been tested, participants who have tested negative for HCM mutations on clinical panels, and participants who have a positive HCM genotype result but cannot provide the results or will not consent to provide the results may consent to have blood drawn on Day 1 for assessment of HCM genotype.

[s] The pharmacogenetic panel will include CYP 2C19 genotyping and potentially additional DNA sequencing. Pharmacogenetic Screening for CYP 2C19 genotyping will occur at Screening; samples from screen failures must be destroyed.

[t] At all onsite visits, study drug will be administered at the investigational site to facilitate collection of PK samples ≤ 2 hours prior to dosing. Note: There is no PK sample at Day 1 or Week 14. With the exception of Week 30 when a PK sample is also drawn within 1 to 2 hours postdose, Study drug will be administered at the end of the visit when all other assessments have been done, including any drawing of blood.

[u] All participants will return their study drug dosing containers to the site pharmacy for capsule counts. Refer to the Pharmacy Manual for details.

[v] The CMR substudy assessment can be completed up to 5 days before the Day 1 visit and up to 5 days before the EOT visit.

APPENDIX 2.

Table 5: Analysis Window Definition for NYHA class and NT-proBNP

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	Screening <= analysis day <=1	1
Week 4	15 < analysis day <= 36	29
Week 6	36 < analysis day <= 50	43
Week 8	50 < analysis day <= 71	57
Week 12	71 < analysis day <= 92	85
Week 14	92 < analysis day <=113	99
Week 18	113< analysis day <=141	127
Week 22	141< analysis day <=169	155
Week 26	169<analysis day <=197	183
Week 30	197<analysis day <=239	211
Week 38	239<analysis day <=295	267

Table 6: Analysis Window Definition for CPET, Stress Echo and CMR Measurements

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	Screening <= analysis day <=1	1
Week 30	183 < analysis day <= 239	211

Table 7: Analysis Window Definition for Resting TTE

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	Screening <= analysis day <=1	1
Week 4	15 < analysis day <= 36	29
Week 6	36 < analysis day <= 57	43
Week 12	71 < analysis day <= 99	85
Week 18	113< analysis day <=141	127
Week 22	141< analysis day <=169	155
Week 26	169<analysis day <=197	183
Week 30	197<analysis day <=239	211
Week 38	239<analysis day <=295	267

Table 8: Analysis Window Definition for hs-Cardiac Troponin I

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	Screening <= analysis day <=1	1
Week 6	29< analysis day <=57	43
Week 18	113<analysis day <=141	127
Week 30	197 < analysis day<=239	211
Week 38	239<analysis day<=295	267

Table 9: Analysis Window Definition for PGIS and PGIC

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	Screening <= analysis day <=1	1
Week 6	29 < analysis day <= 57	43
Week 10	57 < analysis day <= 85	71
Week 14	85 < analysis day <=113	99
Week 18	113< analysis day <=141	127
Week 22	141< analysis day <=169	155
Week 26	169<analysis day <=197	183
Week 30	197<analysis day <=239	211
Week 38	239<analysis day <=295	267

Table 10: Analysis Window Definition for WPAI-SHP, EQ-5D-5L, and KCCQ-23

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	Screening <= analysis day <=1	1
Week 6	29 < analysis day <= 57	43
Week 12	71 < analysis day <= 99	85
Week 18	113< analysis day <=155	127
Week 30	197<analysis day <=239	211
Week 38	239<analysis day <=295	267

Table 11: Analysis Window Definition for HCMSQ

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	Screening <= analysis day <= 1	1
Week 4	15 <= analysis day < 36	29
Week 6	36 <= analysis day < 57	43
Week 10	57 <= analysis day < 85	71
Week 14	85 <= analysis day < 113	99
Week 18	113 <= analysis day < 141	127
Week 22	141 <= analysis day < 169	155
Week 26	169 <= analysis day < 197	183
Week 30	197 <= analysis day < 239	211
Week 38	239 <= analysis day < 295	267

APPENDIX 3. HCMSQ SCORING ALGORITHM

The HCMSQ is completed each day for 7 days, and each of the items is scored computing a score for each day the diary is completed and then averaging score over the 7-day period. This is referred to as the item weekly score. A weekly score is calculated if there are at least 4 days of data (i.e., no more than 3 days missing); otherwise the weekly score is set to missing. Each item should have the same number of daily entries as the electronic diary did not allow for items to be skipped. Three domain scores and one total score is calculated from 8 items of the HCMSQ:

- **Shortness of Breath domain**: this is the sum of the item scores for items 1-3 and item 6. For item 2, if "I did not attempt…" response choice is endorsed, set subscale score to missing for that day. For item 3, if "I did not attempt…" response choice is endorsed, impute score as the mean of items 1, 2, and 6 for that day. The potential score range is 0 to 18, where lower scores indicate less shortness of breath.
- **Tiredness domain**: only one item contributes to this domain; the domain score is the item score for item 7. The potential score range is 0 to 4, where lower scores indicate less tiredness.
- **Cardiovascular Symptoms domain**: this is the sum of the item scores for items 8-10. The potential score range is 0 to 12, where lower scores indicate less cardiovascular symptoms.
- **Total Score**: the total score is an equally weighted sum of the three domains. It is calculated as the sum of the Shortness of Breath domain divided by 4 (as there are 4 items in the domain), the Tiredness domain (1 item), and the Cardiovascular Symptoms Domain divided by 3 (as there are 3 items in the domain); if "I did not attempt" response choice for item 2 is endorsed, then Total score is treated as missing for that day.The potential score range is 0 to 12.5, where lower scores indicate less symptoms.

Signature Page for VV-CLIN-000034

Approval	Liang Fang Clinical 22-Apr-2020 23:28:58 GMT+0000

Approval	Joel Selcher Regulatory 23-Apr-2020 00:36:57 GMT+0000

Approval	Amy Sehnert Clinical 23-Apr-2020 03:39:15 GMT+0000