Cover Page for Statistical Analysis Plan

Sponsor Name	MyoKardia, A Bristol Myers Squibb Company
NCT Number	NCT03470545
Sponsor Trial ID	MYK-461-005
Official Study Title	A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy
Document Date	21 April 2020

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. [redacted]
Protocol Version	Amendment 5
Date	October 2019
SAP Version	Version 2
Date	21 April 2020

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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

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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

[redacted]

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

[redacted]

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

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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 [redacted]

[redacted]

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.

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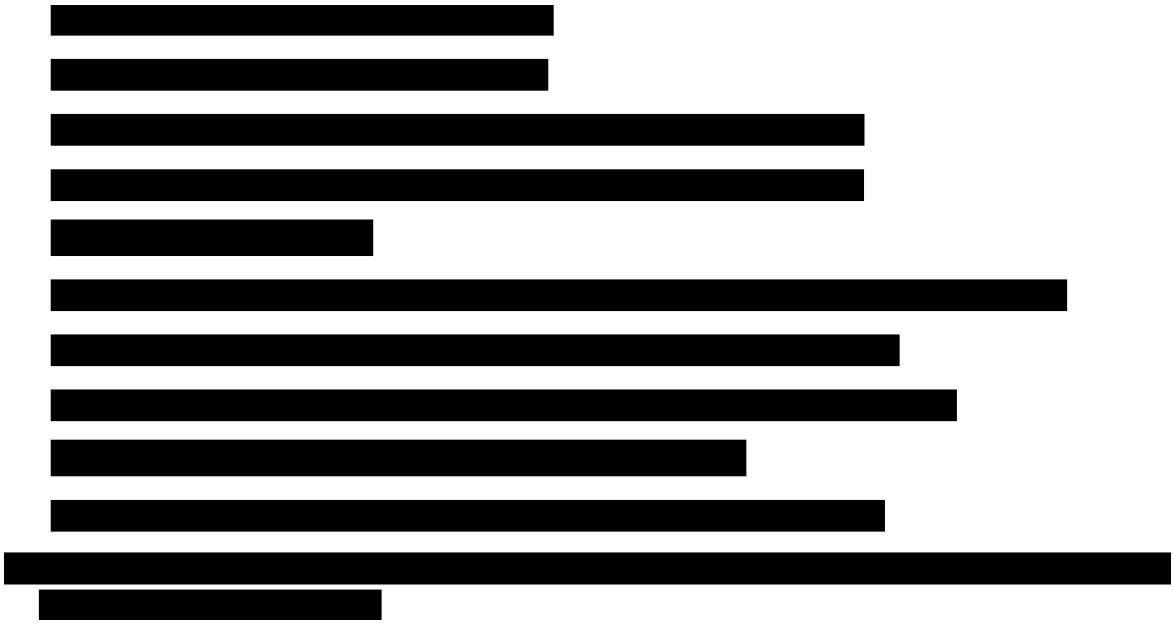

6.4. Missing Data

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.

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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.

[redacted]

[redacted]

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.

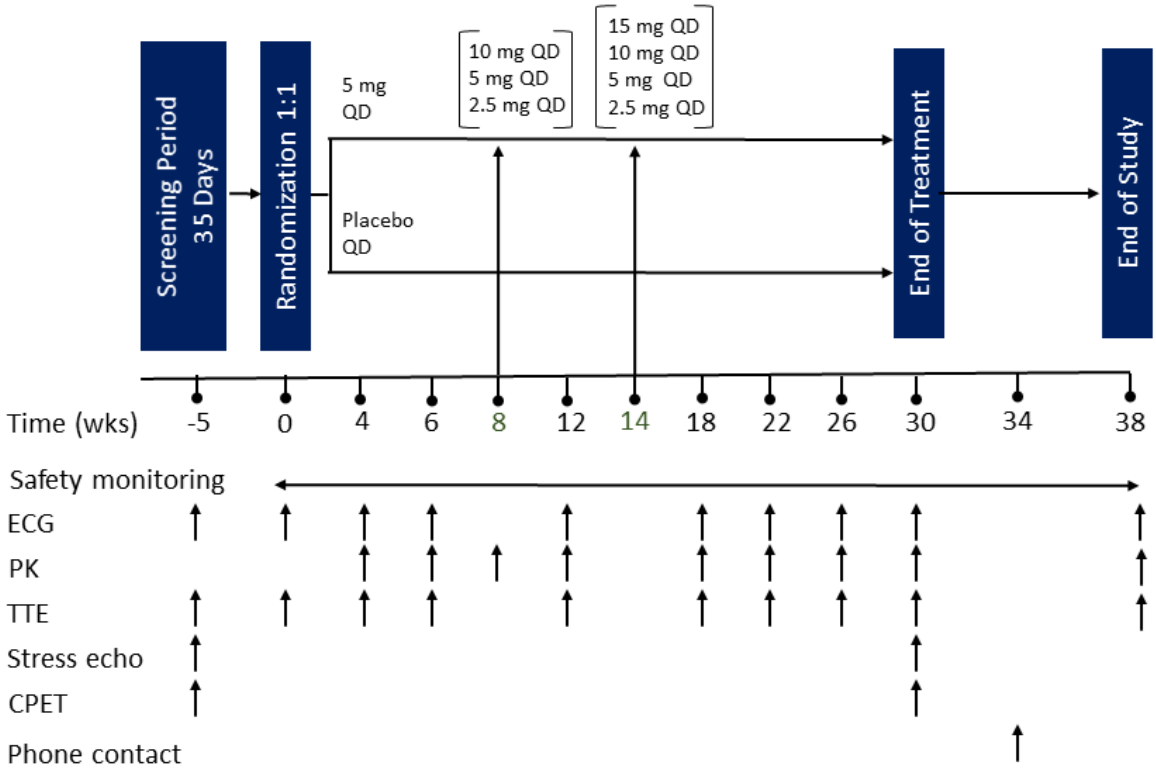
14. SUMMARY OF CHANGES IN THE PROTOCOL PLANNED ANALYSES

[redacted]

[redacted]

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													
[redacted]			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
[redacted]		X												
[redacted]	X													
[redacted]		X									X	X		
Symptom Assessment														
NYHA functional classification	X	X	X	X	X	X	X	X	X	X	X	X		X
Patient-Reported Outcomes	[redacted]s													
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														
[redacted]		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

[redacted]

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