STATISTICAL ANALYSIS PLAN

WEEK 56

Protocol Number:	MYK-461-017 (VALOR-HCM)
Protocol Title:	**A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten In Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible For Septal Reduction Therapy**
Indication:	Hypertrophic Cardiomyopathy
Study Phase:	Phase 3
Investigational Medicinal Product:	Mavacamten (MYK-461)
Sponsor:	MyoKardia, Inc. 1000 Sierra Point Parkway Brisbane, CA 94005
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APPROVAL PAGE

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LIST OF ABBREVIATIONS

A	peak velocity of late transmitral flow
ACCF	American College of Cardiology Foundation
AE	adverse event
AESI	adverse event of special interest
AFib	atrial fibrillation
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	Alcohol septal ablation
AST	aspartate aminotransferase
BP	blood pressure
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMR	cardiac magnetic resonance
CPET	cardiopulmonary exercise testing
CYP	cytochrome P450
E/e’	peak velocity of early diastolic transmitral flow / 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
HCM	hypertrophic cardiomyopathy
HF	Heart failure
HR	heart rate
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IPD	important protocol deviations
IXRS	interactive response system

KCCQ	Kansas City Cardiomyopathy Questionnaire
LLOQ	lower limit of quantitation
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
LVSVI	left ventricular systolic volume index
LAVI	left atrial volume index
LVESVI	left ventricular end systolic volume index
LVEDVI	left ventricular end diastolic volume index
LVMASSI	left ventricular mass index
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal pro b-type natriuretic peptide
NSVT	nonsustained ventricular tachycardia
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
PT	preferred term
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
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
VE	volume expired
VT	ventricular tachycardia

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease. HCM is a chronic, progressive disease of the cardiomyocyte, largely of the cardiac sarcomere, with a diverse clinical presentation and course. A defining feature of HCM is myocardial hypercontractility accompanied by reduced LV compliance, which is reflected clinically as reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. HCM can be familial and is the most common genetic disease of the myocardium. Point mutations in one of the structural genes of the sarcomere can be documented in approximately 40% of affected individuals overall and in about 60% of those with a family history of clinical disease Hershberger et al. (2009); (Gersh et al. 2011; Maron, Maron, and Semsarian 2012; Alfares et al. 2015). Mutations in cardiac myosin and other sarcomere proteins appear to increase net power generation by the sarcomere (Chuan et al. 2012; Sommese et al. 2013; Sung J 2012), consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in HCM. HCM is categorized as obstructive (ie, oHCM [also known as HOCM]) or nonobstructive (nHCM) based on the presence or absence of LV outflow tract (LVOT) obstruction. The presence of LVOT obstruction is associated with more severe symptoms and greater risk of heart failure and cardiovascular death (Maron et al. 2003). The most prevalent burden of morbidity for patients with HCM is exertional dyspnea, which limits daily activities and can be debilitating. Current treatment guidelines for HCM include the use of beta blockers, calcium channel blockers, and disopyramide (Gersh et al. 2011; Elliott et al. 2014). However, despite treatment, symptoms and disease burden persist for many patients, and therapeutic options are limited.

Patients with oHCM with severe drug-refractory symptoms may be referred for septal reduction therapy (SRT; ie, myectomy or alcohol septal ablation [ASA]). While these procedures can be effective in reducing or eliminating LVOT obstruction, thereby alleviating symptoms, they are invasive, associated with risk, and should be performed only by experienced operators in centers of excellence with high-volume SRT performance as defined in the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines (Gersh et al. 2011).

Mavacamten is a small-molecule allosteric inhibitor of cardiac myosin that reversibly inhibits its binding to actin, thereby relieving systolic hypercontractility and improving ventricular compliance. Mavacamten's profile of myosin inhibition is predicted to reduce dynamic LVOT obstruction in individuals with oHCM by reducing systolic hypercontractility and dynamic obstruction in the near term and may reduce ventricular hypertrophy with long-term treatment. Therefore, mavacamten may provide an additional pharmacologic therapy to comply with guideline-recommended maximal medical therapy prior to considering an invasive SRT procedure and reduce the need for myectomy or ASA procedures.

Study MYK-461-017 (VALOR-HCM) is a Phase 3, double-blind, placebo-controlled, randomized study of subjects with drug-refractory, symptomatic oHCM who are eligible for SRT according to ACCF/AHA and/or European Society of Cardiology (ESC) guidelines (per the country in which the site is located) (Gersh et al. 2011; Elliott et al. 2014). The primary analysis at 16 weeks has already been reported (Desai et al. 2022). And mavacamten's effects in reducing the need for SRT in patients with highly symptomatic oHCM persist through 32 weeks (Desai et al. 2022).

The purpose of this analysis is to investigate the effect of mavacamten through 56 weeks of active treatment in subjects originally randomized to the mavacamten group (Day 1 to Week 56) and through 40 weeks of active treatment in the subjects originally randomized to the placebo group (Week 16 to Week 56).

1. ORIGINAL STUDY DESIGN AND PLAN

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of males and females ≥ 18 years with oHCM who meet 2011 ACCF/AHA criteria for SRT and have been referred for an invasive procedure. After completing screening assessments, eligible subjects will be randomized 1:1 to the mavacamten or placebo treatment groups. Randomization will be stratified by the type of SRT procedure recommended (myectomy or ASA) and New York Heart Association (NYHA) functional class.

The study duration will be up to 138 weeks, including a 2-week screening period (Week –2), 128 weeks of treatment, and an 8-week posttreatment until the EOS visit (Week 136).

There will be 3 dosing periods as follows:

- Placebo-controlled dosing period (Day 1 to Week 16): Subjects will receive double-blind mavacamten or placebo once daily for 16 weeks
- Active-controlled dosing period (Week 16 to Week 32): All subjects will receive mavacamten once daily for 16 weeks. Dose will be blinded.
- Long-term extension (LTE) dosing period (Week 32 to Week 128): All subjects will receive mavacamten once daily for 96 weeks. During the LTE period, mavacamten dose will remain blinded.

This SAP covers data included through Week 56.

2. TREATMENT GROUPS

Patients will be classified according to their original randomization, but will focus on the exposure time to mavacamten. The two treatment groups will be labeled as:

- Mavacamten exposure for 56 weeks (Day 1 to Week 56)
- Placebo subjects with mavacamten exposure for 40 weeks (Week 16 to Week 56)

3. STUDY OBJECTIVES

The objectives of this study is to describe the longer term effect of mavacamten on the following:

- Need for septal reduction therapy (SRT)
- Cardiac biomarkers
- Hemodynamic parameters
- Quality of life (QoL) parameters

4. SAMPLE SIZE

A total of 112 patients were randomized into the study. This sample size provided adequate power to determine the superiority of mavacamten in reducing eligibility for SRT procedures at the end of the 16-week treatment period. The original power calculation assumed that a clinically meaningful relative reduction of 50% in the primary endpoint between subjects in the mavacamten and placebo groups. It was assumed that 70% of the subjects receiving placebo would meet the 16-week endpoint versus 35% of subjects receiving mavacamten. The proposed sample size of 50 subjects in each treatment group provided 95% power at a 2-sided 5% statistical significance level. Subjects who underwent SRT, terminated the study early, died, or could not otherwise be assessed for SRT eligibility at the end of the 16-week placebo-controlled treatment period were classified as eligible for an SRT procedure.

5. GENERAL STATISTICAL CONSIDERATIONS

This analysis will be based on the 56-week follow-up period for all patients. Data collected through this time point will be cleaned and locked prior to conducting the primary analysis.

The presentation of data will be categorized by 56 weeks of exposure to mavacamten (patients randomized to mavacamten) and by 40 weeks of exposure to mavacamten (patients randomized to placebo).

In general, descriptive summaries will be presented by treatment group for values at each visit. The descriptive summary for continuous variables will also be provided for the change from baseline as appropriate. 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.

5.1. Study Endpoints

Efficacy Endpoints

The efficacy endpoints to be evaluated in this study include:

1. Need for SRT during exposure to mavacamten
    a. Decision to proceed with SRT
    b. SRT guideline eligible based on the 2011 ACCF/AHA HCM Guidelines
2. Change from baseline in post-exercise left ventricular outflow tract (LVOT) gradient during exposure to mavacamten
3. Change from baseline in patient symptoms during exposure to mavacamten:
    – NYHA functional class (at least 1 class improvement)

- Kansas City Cardiomyopathy Questionnaire 23-item version Clinical Summary Score (KCCQ-23, CSS)

4. Change from baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac troponin I during exposure to mavacamten
5. Change in echo parameters measured in the core lab, including: LVOT gradient at rest and induced by Valsalva, LVEF, left ventricular (LV) filling pressures, LV stroke volume index, left atrial volume index, LV end-systolic volume index, LV end-diastolic volume index, and LV mass
6. Change from baseline in LVOT gradients measured using site-read echo parameters.
7. Final mavacamten dosing at the end of 56 weeks exposure and at the end of 40 weeks exposure to mavacamten

Safety Endpoints:

- Incidence of LVEF < 50% determined by transthoracic echocardiography (TTE)
- Incidence and severity of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), and laboratory abnormalities
- Incidence of major adverse cardiac events (MACE; death, stroke, acute myocardial infarction, heart failure hospitalization)
- Incidence of ventricular tachyarrhythmias (includes ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe)
- Incidence of adverse events of special interest (AESIs; symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30% as reported on AESI CRF page)
- Other adverse events of clinical importance

Analysis Populations

Analysis Set: Efficacy endpoints will be analyzed on the Analysis Set. All randomized subjects that received at least one dose of mavacamten will be categorized according to original randomized treatment assignment. The analysis window is day 0 to 56 weeks in the mavacamten group and week 16 to week 56 in the placebo group.

In this Analysis Set, subjects originally randomized to placebo that either have SRT or withdraw from the study prior to the Week 16 visit are excluded from this population.

Safety Set: All randomized subjects that received at least one dose of study drug, categorized according to original randomized treatment assignment. Safety endpoints will be analyzed using this population. The analysis window is through day 0 to week 56 for both treatment groups.

Definition of Baseline

Baseline is defined as the last non-missing value prior to the first dose of mavacamten. For the subjects randomized to mavacamten, baseline is defined as the last available value before the first mavacamten treatment administration. For the subjects randomized to placebo, baseline will occur at the Week 16 visit.

6. EFFICACY ANALYSES

All analyses will be based on the Analysis Set unless otherwise noted. Descriptive summaries for each treatment group will be provided, but there will be no statistical testing performed. The primary purpose of this analysis is to provide information on the longer term exposure (56 weeks active drug exposure) to mavacamten and to describe the experience in the placebo group after switching to mavacamten (approximately 40 weeks mavacamten exposure).

6.1. SRT ENDPOINT

The SRT endpoint for this study is the composite of:

1) Decision to proceed with SRT during exposure to mavacamten

2) SRT guideline eligibility based on the 2011 ACCF/AHA HCM Guidelines during exposure to mavacamten

The decision to proceed with SRT is based on the patient's decision as recorded on the CRF. The SRT guideline eligibility will be derived using the NYHA class and LVOT assessments per the 2011 ACCF/AHA guideline clinical and hemodynamic criterion below:

- Clinical criteria: NYHA Class III or IV or for the purposes of the Valor Study, subjects who are NYHA Class II with exertion-induced syncope or near syncope, AND
- Hemodynamic criteria: dynamic LVOT gradient at rest or with provocation (ie, Valsalva or exercise) >= 50 mmHg

Specifically, for subjects with NYHA Class II at follow-up, the following rules will be applied to determine the SRT eligibility:

- If a subject is NYHA Class II with history of exertional syncope or syncope at baseline and is still NYHA Class II at follow-up, they remain SRT eligible IF their maximal LVOT gradient is ≥ 50mmHg
- If a subject is NYHA Class III/IV at baseline and has improved to Class II at follow-up, they are no longer SRT eligible UNLESS they have AE of exertional syncope or pre-syncope during the follow-up period.

6.1.1. Estimand for the SRT Endpoint

Treatment	- *Mavacamten exposure for 56 weeks (study period Day 0 through Week 56)*

	- *Mavacamten exposure for 40 weeks (study period Week 16 through Week 56)*
Population	*Adult patients with symptomatic obstructive hypertrophic cardiomyopathy who are eligible for SRT*
Variable	*Whether proceed to SRT or are guideline eligible during exposure period to mavacamten*
Intercurrent events/strategy	*Early termination from the study or lost to follow up during mavacamten exposure leading to missing data/treatment policy* *Missed visit or inadequate imaging quality or other clerical reason that led to missing assessment/treatment policy;* *Early termination from the treatment or change in cardiac medication but stayed on the study/treatment policy*
Population level summary	- *Proportion of mavacamten randomized patients who proceed to SRT prior to Week 56 or are SRT eligible at Week 56.* - *Proportion of placebo randomized patients who proceed to SRT between week 16 and week 56 or are SRT eligible at week 56* **see note below*

For intercurrent events of early termination or lost to follow up prior to week 56 that lead to missing data, it is assumed that these subjects are likely not benefiting from treatment. Thus, these cases will be imputed as “meeting the SRT endpoint” under the “treatment policy”.

For other intercurrent events that led to missing data (e.g. visit outside analysis window, unevaluable ECHO images or other clerical reason), it is also assumed that these subjects are likely not benefitting from treatment, thus these cases will be imputed as "meeting the SRT endpoint" under the treatment policy.

For the intercurrent events that do not lead to missing data such as discontinuation of treatment or change in cardiac medication, all data collected will be included for analysis using the treatment policy strategy.

*** Note:**

- Subjects randomized to mavacamten: if the subject decides to proceed with SRT prior to the Week 56 visit (Day 0 to Week 56, inclusive), they are considered meeting the SRT endpoint based on the endpoint definition.
- Subjects randomized to placebo: subjects that underwent SRT during the placebo-controlled period (Day 0 to Week 16), will not be included in this analysis. Only subjects that reach Week 16 and start treatment with mavacamten will be included for analysis.

The primary estimand will be the proportion of subjects meeting the SRT endpoint. The observed proportions will be presented for each group.

6.2. Secondary Efficacy Endpoints

Five secondary endpoints will also be examined for each treatment group:

1. Change from baseline in post-exercise LVOT gradient
2. Proportion of subjects who had at least 1 class of NYHA improvement from baseline
3. Change from baseline in patient-reported health-related QoL as assessed by the KCCQ-23, CSS
4. Change from baseline in NT-proBNP
5. Change from baseline in cardiac troponin I

6.2.1. Analysis Method for the Secondary Endpoints

Secondary endpoints will be summarized for each treatment group at each visit using descriptive statistics.

- The proportion of subjects who have at least 1 class of improvement from baseline in NYHA class will be presented by treatment exposure group
- Change from baseline to the end of the mavacamten exposure period in NT-proBNP, cardiac troponin I, and KCCQ-23 CSS will be summarized using means, standard deviation, median and interquartile range (Q1, Q3).

6.2.2. Handling of Missing Data

Missing data for secondary and exploratory efficacy analyses will not be imputed.

6.3. Exploratory Efficacy Analysis

6.3.1. General Analysis Methods

All the exploratory endpoints described in this section will be summarized for each treatment group using descriptive summary statistics. P-values for changes from baseline in echo parameters and laboratory may be generated but are not to be considered confirmatory.

6.3.2. Hemodynamic Parameters, Cardiac Biomarkers, and Quality of Life

Change from baseline to follow-up in the following parameters will be analyzed as exploratory efficacy endpoints and presented by treatment group.

- Hemodynamic parameters
  - LVOT gradient at rest
  - LVOT gradient induced by Valsalva
  - LVEF
  - LV filling pressures (E/e')
  - LV stroke volume index

- Left atrial volume index
- LV end-systolic volume index
- LV end-diastolic volume index
- LV mass index
-

6.3.3. Site-Read LVOT Gradients

The mean and standard deviation (SD) for site-read LVOT gradients will be summarized for each visit. Change from baseline at each visit will be calculated and presented as mean, standard deviation and 95% confidence interval.

The mean and SD of the site-read LVOT gradients and the core-lab LVOT gradients at each visit will be plotted on the same graph, with visit on the x-axis and mean gradient on the y-axis.

6.3.4. Type and Dose of Study Medication and Cardiac Medications of Interest

Last dose level of mavacamten given at Week 56 will be provided in the following categories: 2.5mg, 5mg, 10mg, and 15mg. The number and percentage of patients in each category will be presented by treatment group.

For each cardiac medication of interest (beta-blocker, calcium-channel blocker, and disopyramide), the number of patients who had change(s) in their cardiac medication will be summarized by treatment group.

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