Cover Page for Statistical Analysis Plan

Sponsor Name: MyoKardia, Inc.
NCT Number: NCT03442764
Sponsor Trial ID: MYK-461-006 (MAVERICK-HCM)
Study Title: A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction
Document Description: Statistical Analysis Plan (Version 1.0)
Document Date: 28 August 2019

STATISTICAL ANALYSIS PLAN

Protocol Number:	MYK-461-006 (MAVERICK-HCM)
Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction
Indication:	Hypertrophic Cardiomyopathy
Phase:	2
Investigational Medicinal Product:	Mavacamten (MYK-461)
Sponsor:	MyoKardia, Inc. [redacted]
Protocol Version	Amendment 1
Date	April 4, 2018
SAP Version	Version 1.0
Date	August 28, 2019
Author	[redacted]

SIGNATURE PAGE

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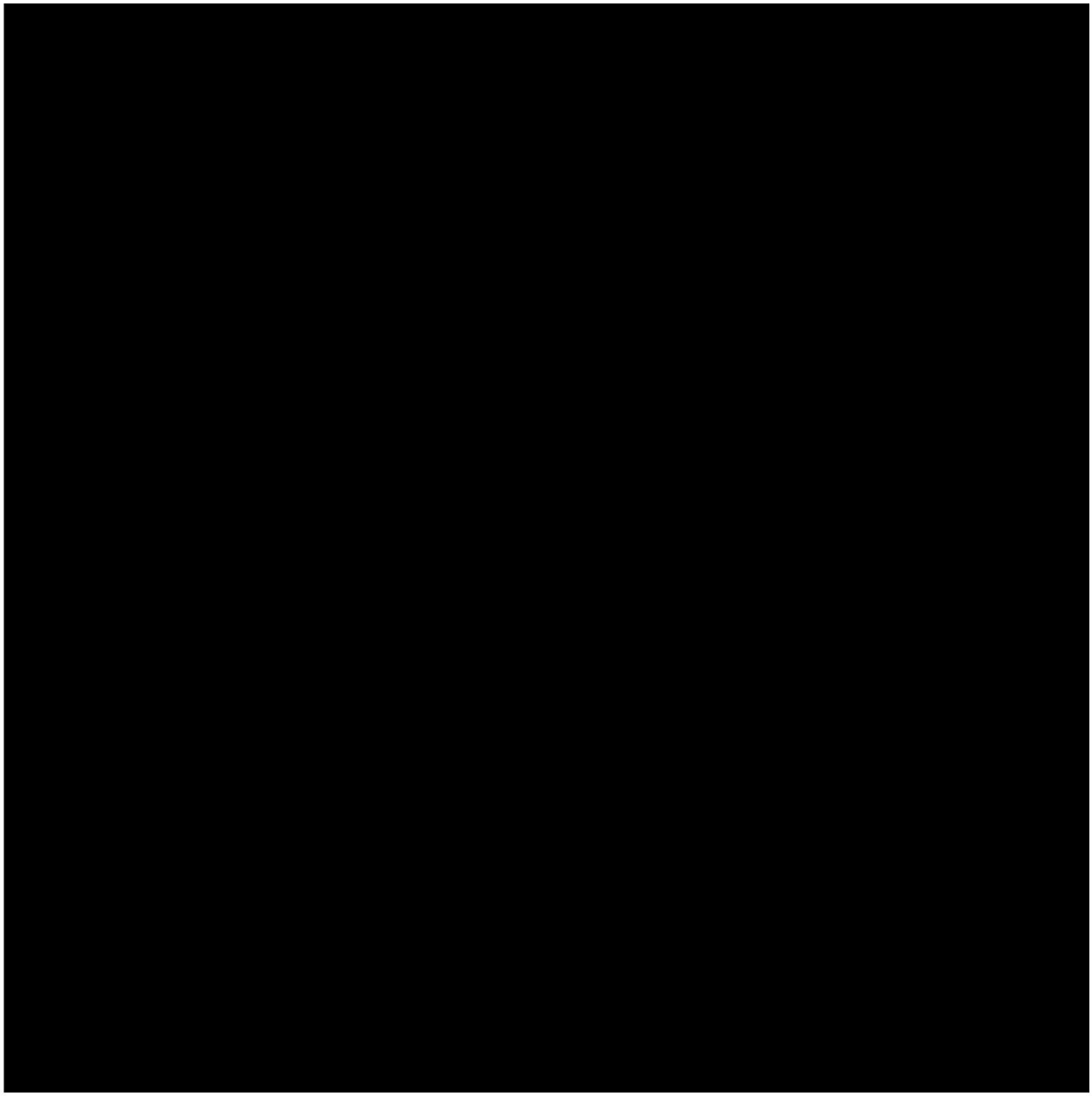

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LIST OF ABBREVIATIONS

A	peak velocity of late transmitral flow
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
CPET	cardiopulmonary exercise test or testing
CYP	cytochrome P450
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
E	peak velocity of early diastolic transmitral flow
e'	peak velocity of early diastolic septal and lateral mitral annular motion
EC	ethics committee; refers to an IRB or IEC or equivalent
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	
EOS	end of study
ET	early termination
FDA	The United States Food and Drug Administration
GCP	Good Clinical Practice
HCM	hypertrophic cardiomyopathy
[redacted]	
HR	heart rate
IB	Investigator's Brochure
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine system
IXRS	interactive response system
[redacted]	
LLOQ	lower limit of quantification
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
nHCM	non-obstructive hypertrophic cardiomyopathy
NSVT	non-sustained ventricular tachycardia
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PD	pharmacodynamic(s)
[redacted]	
[redacted]	
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
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SRT	septal reduction therapy
SUSAR	suspected unexpected serious adverse reactions

TBL	total bilirubin
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States
VCO_2	carbon dioxide production
VE	volume expired
VO_2	oxygen uptake

[redacted]

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of a 16-week course of mavacamten in individuals with symptomatic nHCM.

[redacted]

[redacted]

3. OVERALL STUDY DESIGN AND PLAN

This is a Phase 2, multicenter, exploratory, randomized, double-blind study to evaluate the safety, tolerability, preliminary efficacy, PD, and PK of 2 target drug concentrations of mavacamten compared with placebo in patients with symptomatic nHCM.

Approximately 60 patients with symptomatic nHCM will be enrolled. Patients will be randomized in a 1:1:1 ratio to receive a 16-week course of mavacamten doses titrated to achieve 1 of 2 target drug concentrations (Group 1: ~200 ng/mL; Group 2: ~500 ng/mL) or placebo once daily (QD). Randomization will be stratified according to current treatment with beta blocker (yes or no) and type of exercise testing (treadmill or bicycle). Patients will be treated for 16 weeks and then followed up approximately 8 weeks after the last dose of study drug. At Week 6, all patients will undergo blinded dose adjustment based on Week 4 assessments. Patients who are treated for their HCM condition (eg, beta blocker or calcium channel blocker) should receive a stable dose of such treatment for at least 2 weeks prior to Screening, and every effort should be made to keep such treatment unchanged (ie, at the same dose) throughout the entire study duration until the EOS visit at Week 24.

During the Screening process, patients will undergo a variety of general, cardiopulmonary, laboratory, exploratory biomarker, patient-reported outcomes (PRO), and symptom assessments. Patients will receive their first dose of study drug on Day 1. Patients will then undergo a variety of assessments every 2 weeks through Week 16. Assessments will be conducted at the clinical site at Weeks 4, 6, 8, 12, and 16; assessments will be conducted via telephone call at Weeks 2, 10, and 14. At Week 24, patients will undergo EOS procedures.

PRO questionnaires will be completed either on paper or on an electronic device provided to each patient during the Screening period or on an app installed on the patient's own electronic device.

[redacted]

3.1. Study Duration

The expected study duration is approximately 28 weeks: up to 4 weeks for Screening and 16 weeks (± 7 days) for study conduct, and 8-week posttreatment follow-up period.

3.2. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will meet at regular intervals to review study data. The role of the IDMC will be to act in an advisory capacity to the Sponsor with respect to safeguarding the interest of study patients, assessing interim safety data, and advising the Sponsor and investigators on important emerging study conduct issues. The IDMC may formulate recommendations in relation to the evaluation procedures and methodologies being employed to survey and detect potential safety signals. Meeting frequency and membership is described in the IDMC Charter.

3.3. Treatment Withholding and Discontinuation

Patients with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL], or international normalized ratio) or signs/symptoms of hepatitis may meet the criteria for withholding of study medication or other protocol-required therapies. Withholding is either permanent or conditional depending on the clinical circumstances discussed in the protocol.

Patients with exaggerated pharmacologic effect (systolic dysfunction), higher than expected plasma concentration, or excessive QT prolongation, may discontinue study treatment as described in the protocol

4. RANDOMIZATION AND BLINDING PROCEDURES

4.1. Randomization

Patients who meet the inclusion/exclusion criteria will be randomized via an IXRS to 1 of 3 groups in a 1:1:1 ratio: 2 active treatment groups and 1 matching placebo group. Randomization will be stratified according to current treatment with beta blocker (yes or no) and type of exercise testing (treadmill or bicycle).

4.2. Study Blinding

Patients will be randomized to 1 of 3 groups via the IXRS. All patients receive either 5 mg mavacamten or matching placebo daily from Day 1 to Week 6. Blinded dose adjustment (to 2.5,

5, 10, or 15 mg mavacamten or placebo daily) via the IXRS will begin at Week 6 based on PK measurements at Week 4. Study drug administration will occur in a double-blind manner via the IXRS such that the investigator, site staff, the pharmacist, and the patient 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. Echocardiography results (eg, LVEF) performed at clinic visits will be blinded to the investigator and study staff. The 4 different doses of mavacamten and matching placebo will be identical in appearance in order to preserve the blind. Study drug (2.5, 5, 10, or 15 mg mavacamten or matching placebo) will be labeled with a unique identifying number that will be assigned to a patient through the IXRS.

Members of the pharmacovigilance team will be unblinded for suspected unexpected serious adverse reaction (SUSAR) reporting. The IDMC may also review unblinded safety and efficacy data.

4.3. Methods for Unblinding

Unblinding by the investigator independently of the Sponsor also may occur if an AE or toxicity necessitates identification of the medication for the welfare of the patient. Please refer to the IXRS Manual for the unblinding process.

5. DETERMINATION OF SAMPLE SIZE

This study will include a total of approximately 60 patients, or approximately 20 patients per treatment group. Such a sample size will be sufficient to obtain sound variability estimates while yielding reasonable effect size estimates for future planning purposes.

6. GENERAL STATISTICAL CONSIDERATIONS

The primary analysis will be conducted through the 16-week treatment period. Data collected through this timepoint will be cleaned and locked prior to analysis.

Once all subjects have completed their Week 24/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, Group 1, Group 2, and overall active]. Summaries of continuous variables will utilize the number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Descriptive summaries for categorical variables will utilize counts and percentages. Unless otherwise stated, denominators for percentages will be the number of patients in the analysis population with non-missing variable of interest for the column of interest.

The between-group comparisons focus on the comparative performance of Group 1 (target concentration of ~200 ng/mL) vs placebo and Group 2 (target concentration of ~500 ng/mL) vs

placebo. An overall active vs placebo comparison will also be conducted where appropriate. Any statistical test will be conducted at a two-sided significance level of 0.05 using the exact method unless otherwise stated.

In general, baseline is defined as the last non-missing result on or before the first dose date, and time where applicable. For certain data types (e.g., accelerometer, PROs, cardiac rhythm monitoring, etc.), special considerations may be required; please refer to the specific data section for details. Unless otherwise noted, non-safety (ie. efficacy, 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 visits will also be mapped to analysis visits. The analysis day for purposes of the visit windows are derived as follows (reference date is the study drug initiation date for the safety population or the randomization date for the ITT population):

- If date of information is missing, analysis day cannot be calculated and leave as missing
- If date of information < reference date, analysis day = analysis date – reference date. If date of information >= reference date, analysis day = (analysis date – reference date) + 1

Safety information will be summarized by the nominal visit (per protocol), and unscheduled visits will be presented in listings only.

The visit windows for efficacy and PD assessments will be as follows, unless otherwise noted in the specific data sections below:

Table 1: Analysis Windows

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Day 1 (Baseline*)	Screening <= analysis day <=1	1
Week 4	15 < analysis day <= 42	28
Week 8	43 <= analysis day <= 70	56
Week 12	71 <= analysis day <= 98	84
Week 16	99 <= analysis day <= 126	112
Week 24	155 <= analysis day <= 182	168

Note: CPET only collected on Day 1 and Week 16.
* Per the baseline definition in this section.

When more than one result is available within the same analysis visit, the result collected closest to the target visit day will be used for analysis. If two values tie as closest to the time point (for example, one value is before and the other value is after the target day), then the latest value will be selected as the analysis value. If for a specific analysis window, the last collected time point has 2 or more values collected, for continuous and ordinal (scale) data, the average among these results will be derived. If the data are categorical (eg, Yes/No) then the clinically 'worse' measurement will be affiliated with the visit of interest.

If a measurement does not fall into an analysis window it will not be included in efficacy summary. However, these measurements will be included in data listings and SAS data sets.

6.1. Study Endpoints

Safety Endpoints:

- Frequency and severity of treatment-emergent AEs, AEs of special interest, and SAEs
- Frequency of laboratory abnormalities
- Change from baseline vital signs
- Frequency of cardiac rhythm abnormalities

[redacted]

[redacted]

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 the 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 study [redacted]

6.3. Covariates and Subgroups

The study is not adequately powered to detect treatment differences in any subgroup analysis. Any subgroup analyses performed will be considered exploratory.

[redacted]

[redacted]

6.4. Missing Data

In general, no imputation of missing data will be done in the study unless specifically stated in this SAP. For mixed model repeated measure analyses, missing data are handled by the model implicitly. For responder analyses, if the patient's responder status cannot be determined due to missing data, the patient will be treated as non-responder. For other analyses, missing data will not be included in the analyses.

Handling of Missing Data:

- In general, missing result values will not be imputed unless otherwise specified.
- For values below the lower limit of quantitation (LLOQ), 1/2 of LLOQ will be imputed unless otherwise specified.
- In general, for missing or partial dates the following noted:
    - Start Dates:
        - If day is missing, then impute it to be the start of the month (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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.

6.5. Multiplicity Control

Due to the exploratory nature of the study, multiplicity adjustment is not planned.

7. SUBJECT DISPOSITION

The number and percentage of subjects who complete and discontinue the treatment and study as well as reasons for early discontinuation will be summarized by randomized treatment assignment using the ITT population.

7.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by randomized treatment assignment using the ITT population.

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

CYP2C19 genotypes and phenotypes will be summarized as part of the baseline characteristics summary table and listing.

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 within the safety population.

The duration of study drug exposure is defined as last dose date – first dose date + 1 day, regardless of intermittent discontinuations.

Compliance will be calculated based on the total cumulative dose received divided by the total planned cumulative dose. Imputation will be performed for subjects with missing or incomplete data.

Treatment compliance and above-planned and under-planned dosing percentages will be summarized descriptively (number [n], mean, SD, median, minimum, and maximum). The subjects with compliance < 80% will be fully described and summarized. In addition, number and percentage of subjects with at least 1 dosing administration will be given, as well as the number and percentage of subjects with 0, 0 to 20%, and greater than 20% under-planned dosing administrations.

Actual dose adjustments that occurred in the study and expected dose adjustments based on the criteria per protocol will be listed by subject and timepoint. Any inconsistencies will be flagged.

7.3. Protocol Deviations

Prior to database lock, all protocol deviations will be reviewed and confirmed by the Sponsor. All protocol deviations will be presented in a by-subject data listing. Important Protocol Deviations (IPD) (ie. CSR Reportable PDs) will be identified by the Sponsor and summarized in table. ICH E3 defines important protocol deviations 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 subject's rights, safety, or well-being.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

13. SAFETY ANALYSES

All safety analyses will be performed on the Safety 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 analysis 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 + 56 days.

13.1. Adverse Events

AEs will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA v21.0). AEs will be monitored during the study and the data analyzed with respect to overall incidence as well as severity and potential relationship of AEs to study medication. AEs with onset during the treatment-emergent period or with an onset before the first dose of study medication that increases in severity or becomes serious during the treatment-emergent period, will be considered treatment-emergent.

Adverse event incidence tables will present the number (n) and percentage (%) of subjects experiencing at least one treatment-emergent AE (TEAE) by system organ class (SOC) and preferred term (PT). Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment group. In addition, the adverse event incident table will also be presented by SOC, PT, and severity grade. When there are multiple occurrences of the same event in the same patient, only the most severe one will be included in the tables.

Adverse event incidence tables will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent serious AEs, drug related AEs, AEs of Special Interest (AESI; per protocol), all TEAEs leading to permanent treatment discontinuation, and all TEAEs leading to death.

AE may also be summarized by Standardised MedDRA Queries (SMQs) deemed relevant based on AESIs and SAEs observed in the study.

A by-subject listing of all AEs, SAEs, and TEAEs leading to treatment discontinuation will also be provided.

Deaths

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

- Number and percent of subjects who died by study period (TEAE, on-study) summarized on the safety population by treatment received
- Death in non-randomized subjects or randomized and not treated subjects
- TEAE 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 percent of subjects

Pregnancy

The following pregnancy information will be provided in a by-subject data listing:

- Number of subjects or partners of subjects who became pregnant summarized by treatment received
- 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 subjects

Overdose

If overdoses occur, the following overdose information will be provided in a by-subject data listing:

- Number of subjects who experienced overdose summarized by treatment received
- Analysis of the cause and occurrence of the overdose
- TEAE, if any, experienced during the overdose by primary SOC, high-level group term, high-level term, and PT showing the number and percent of subjects

13.2. 12-lead Electrocardiogram

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.

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 QTcF as per the following formulae/method (with QT, RR and QTc expressed in msec):

Fridericia's Correction:

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

ECG Numeric Variables

HR, PR, QRS, and QTcF will be summarized using descriptive statistics. The change from baseline of these ECG parameters at each time point will be listed for each patient. For each time point of measurement, the changes from baseline will be summarized using descriptive statistics.

Categorical Analysis

The incidence count and percentage of subjects with any postdose QTcF values of > 450 msec, > 480 msec, and > 500 msec will be tabulated for all subjects. Subjects with QTc values > 500 msec will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The incidence count and percentage of subjects with ΔQTcF increase from baseline of > 30 msec and > 60 msec will be tabulated.

Morphology Findings

ECG morphologies for each patient will be listed.

Concentration-QTc Analyses

The concentration-QTc relationship will first be evaluated by a scatterplot of time-matched QTcF and concentration data to investigate any potential delayed or sustained effects and to explore the shape of the relationship. Linear or nonlinear mixed models may then be applied, if appropriate, to estimate the slope and 95% CI of the concentration-QTc relationship. For linear mixed effects models, concentration and sex will be included as fixed effects, subject as random effect, and compound symmetry will be implemented for the variance-covariance structure.

13.3. Safety Laboratory Data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all safety laboratory tests (ie. hematology and chemistry panels) will be calculated for each visit (baseline and post-baseline time points) and presented by treatment group.

Shift tables reflecting changes from baseline (i.e., normal to low, high, etc.) will be presented in lieu of descriptive statistics of changes from baseline. Listings of subjects with laboratory values that are out of the reference range will be produced.

Potential drug-induced liver injury

The liver function tests, namely ALT, AST, ALP (alkaline phosphatase), and TBL (total bilirubin), will be used to assess possible drug-induced liver toxicity.

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

The number of subjects with elevated liver function tests will be summarized in a table 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 (to ≤ 1 × ULN or return to baseline if baseline > ULN): never normalized,

normalized after permanent discontinuation of study drug. Note that a patient will be counted only under the maximum elevation category (1-3 × ULN, 3-5 × ULN, 5-10 × ULN, 10-20 × ULN, > 20 × ULN).

If identified, the number of subjects with concurrent ALT/AST of 3 x ULN or higher, TBL of 2 x ULN or higher, and ALP below 2 x ULN (possible Hy's Law cases) will also be summarized in this table and included in a by-subject listing as well.

13.4. Vital Signs Data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all vital signs variables (values and changes from baseline) will be calculated for each visit (baseline and post-baseline time points) and presented by treatment group.

Shift tables reflecting changes from baseline may be presented in lieu of descriptive statistics of changes from baseline.

13.5. Cardiac Rhythm Monitoring (including Holter Monitor)

The summary statistics (including mean, median, SD, minimum and maximum) of atrial fibrillation (AF), nonsustained ventricular tachycardia (NSVT) will be calculated for each visit (baseline and post-baseline time points) and presented by treatment group. For each cardiac event type, the number of subjects with at least one occurrence, the number of episodes per subject per day, and the duration of each episode will also be summarized. Additional parameters may be summarized as appropriate.

13.6. Other Safety Analyses

Abnormal physical examination results will be listed by subject, and clinical significance. Medical history, concomitant, and prior medications will be summarized in tables and listings.

HCM history, including frequency of SRT (septal reduction therapy) will be summarized in a separate table by treatment and overall.

The number of subjects who met each IMP stopping criteria per protocol will be summarized by treatment and overall.

15. INTERIM ANALYSIS

No interim analysis is planned.

16. SUMMARY OF CHANGES FROM PROTOCOL DEFINED ANALYSES

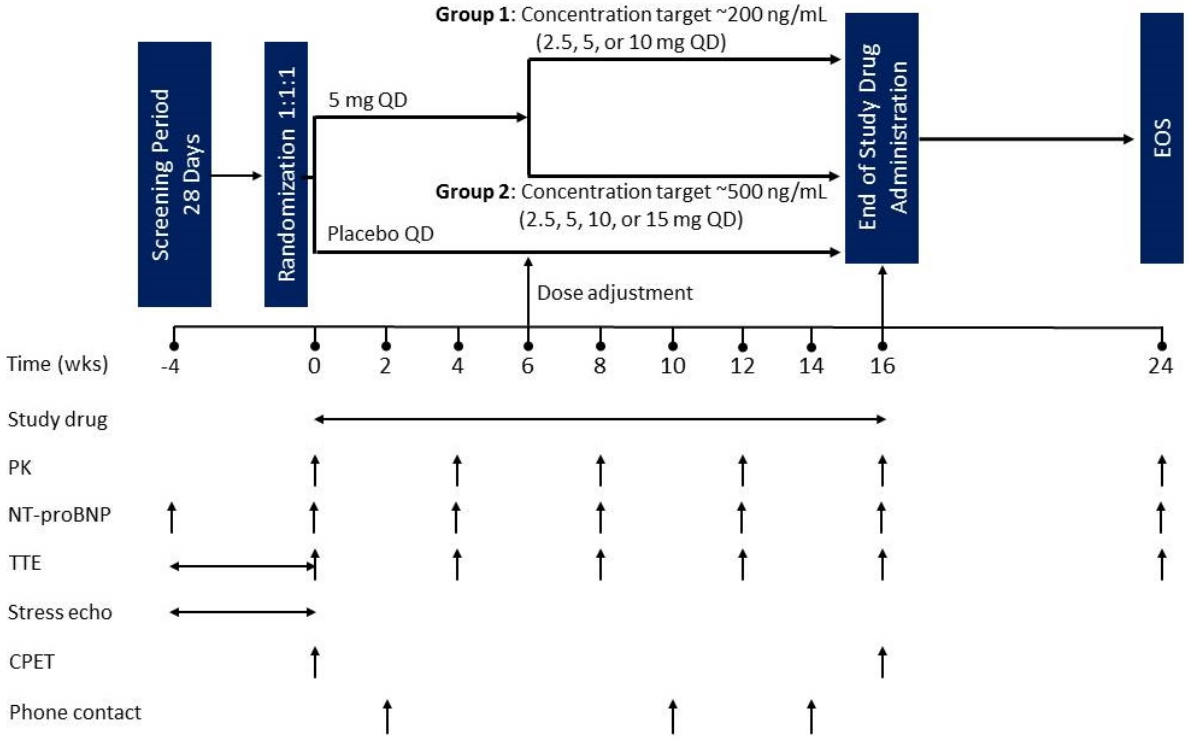
[redacted]

[redacted]

Biophysical J. 2012;102(3 suppl 1):613a-614a. Available at:
[redacted]

APPENDIX A.

Figure 1: Study Schema



Abbreviations: CPET, cardiopulmonary exercise testing; EOS, end of study; NT-proBNP, N-terminal pro b-type natriuretic peptide; PK, pharmacokinetic blood sample taken; QD, once daily; stress echo, stress echocardiography; TTE, transthoracic echocardiogram.

Table 1: Schedule of Study Procedures

Assessment[a]	Screening[b] Day -28 to Day -1	Day 1	Week 2 (telephone call)[c]	Week 4[c]	Week 6[c]	Week 8[c]	Week 10 (telephone call)[c]	Week 12[c]	Week 14 (telephone call)[c]	Week 16[c]/ET	Week 24[c]/EOS
General Procedures											
Informed consent	X										
Medical history[d]	X										
Vital signs[e]	X	X		X		X		X		X	X
AEs[d]	X	X	X	X	X	X	X	X	X	X	X
ICD information downloaded[f]	X									X	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Physical examination including height and weight[g]	X	X		X		X		X		X	X
ECG[h]	X	X		X		X		X		X	X
Resting TTE[i]	X	X		X		X		X		X	X
Post-exercise stress echocardiography[j]	X										
CPET[k]		X								X	
Accelerometer attached[l]	X							X			
Apply cardiac monitoring skit patch[m]	X							X			
Randomization		X									
Laboratory											
Hepatitis panel, HIV test	X										
[redacted]				X		X		X		X	X
Coagulation panel	X	X		X		X		X		X	X

Table 1: Schedule of Study Procedures (cont'd)

Assessment[a]	Screening[b] Day -28 to Day -1	Day 1	Week 2 (telephone call)[c]	Week 4[c]	Week 6[c]	Week 8[c]	Week 10 (telephone call)[c]	Week 12[c]	Week 14 (telephone call)[c]	Week 16[c]/ET	Week 24[c]/EOS
Laboratory (continued)											
Chemistry	X	X		X		X		X		X	X
Hematology	X	X		X		X		X		X	X
Urinalysis	X	X									X
hs-cardiac troponin I		X		X		X		X		X	X
NT-proBNP[o]	X[o]	X[o]		X		X		X		X[o]	X
TSH	X										
FSH[p] /Serum pregnancy test (women)[q]	X										
Urine pregnancy test (women)[q]		X		X		X		X		X	X
[redacted]		X									
[redacted]		X									
[redacted]		X								X	X
Symptom Assessments											
NYHA class	X	X		X		X		X		X	X
PRO Assessments											
[redacted]		X								X	X
[redacted]	X[v]		←		→		X[w]		X[w]	X[w]	X[w]
[redacted]	X[x]				X		X		X	X	X
[redacted]					X		X		X	X	X

Footnotes and abbreviations are defined on last page of table.

Table 1: Schedule of Study Procedures (cont'd)

Assessment[a]	Screening[b] Day -28 to Day -1	Day 1	Week 2[c] (telephone call)	Week 4[c]	Week 6[c]	Week 8[c]	Week 10 (telephone call)[c]	Week 12[c]	Week 14 (telephone call)[c]	Week 16[c]/ET	Week 24[c]/EOS
Investigational Medical Product											
IMP QD		←	—	—	—	—	—	—	—	→	
IMP administered at site		X								X	
IMP compliance[y]				X	X	X		X		X	

Abbreviations: AE, adverse event; BP, blood pressure; CPET, cardiopulmonary exercise testing; DNA, deoxyribonucleic acid; ECG, electrocardiogram; eCRF, electronic case report form; EOS, end of study; [redacted]; ET, early termination; FSH, follicle-stimulating hormone; HCM, hypertrophic cardiomyopathy; [redacted] HIV, human immunodeficiency virus; HR, heart rate; hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; ICF, informed consent form; IMP, investigational medicinal product; [redacted] LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; [redacted]; PK, pharmacokinetic; PRO, patient-reported outcomes; QD, once daily; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiography.

[a] Preferred order of assessments is symptom questionnaires; the following 3 assessments in any order: ECG, vital signs, and TTE; pre-exercise blood draws; exercise test; and post-exercise blood draws.

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

[c] All post–Day 1 study visits have a window of ± 7 days. At Weeks 2, 10, and 14, patients will be contacted by telephone to collect AE and concomitant medication data.

[d] Changes in baseline conditions from once the ICF is signed are recorded on the medical history eCRF unless the change is related to a study procedure, which is then considered an AE. All changes that occur after the administration of the IMP are recorded as AEs.

[e] At Screening, ET (if applicable), Week 16 (end of treatment), and Week 24 (end of study), complete vital signs including temperature, HR, respiratory rate, and BP will be obtained. At all other onsite visits except Week 6, 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 patient in the same position at all visits. BP should be taken via an automated recorder after the patient rests for at least 5 minutes.

[f] For patients who have ICDs, information including rhythm strips and events will be downloaded from the ICDs.

[g] At Screening, Week 16, and Week 24, a complete physical examination will be conducted, including a neurological examination. At Week 4, Week 8, and Week 12, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history. Physical examinations will also include height (at Screening only) and weight (at all onsite visits at which a physical examination is performed).

[h] 12-lead ECGs will be performed at Screening and all onsite visits except for the Week 6 visit after 10 minutes of rest. Each time an ECG is completed, a 10-second paper ECG will be obtained and maintained in the study patient's source documentation. On Day 1, an ECG will be performed predose.

[i] Resting TTE should be performed prior to post-exercise stress echocardiography or CPET. Instantaneous peak LVOT gradient at rest and provoked peak LVOT gradient (Valsalva maneuver) will be assessed only at Screening.

[j] After a 4-hour fast, patients will undergo a standard symptom-limited exercise test by standardized treadmill or bicycle ergometer. Instantaneous peak LVOT gradient will be assessed immediately post-exercise by TTE.

[k] CPET by standardized treadmill or bicycle ergometer will be performed on both Day 1 and at Week 16/ET prior to dosing. CPET is done after a 4-hour fast. Obtain CPET with study patient in the same position at Week 16 as done on Day 1.

[l] The accelerometer is to be distributed during Screening and at the Week 12 visit and retrieved at the Day 1 and Week 16 visits.

[m] The cardiac monitoring adhesive skin patch is to be applied during Screening and at the Week 12 visit and retrieved at the Day 1 and Week 16 visits.

[n] Blood samples for PK will be collected at all post-Screening onsite visits except for the Day 1 and Week 6 visits. The time of each blood draw will be recorded. At Week 16, a PK sample will be collected before dosing as well as within 2 hours postdose. On other PK sampling days, the PK blood samples can be taken at any time that best facilitates conduct of all scheduled study procedures. The date and time of the last dose of IMP taken prior to the PK sample collection will be recorded.

[o] At Screening, the blood draw for NT-proBNP will occur prior to post-exercise stress echocardiography. At the Day 1 and Week 16 visits, the blood draw for NT-proBNP will be obtained both prior to and immediately after CPET.

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

[q] Pregnancy testing for all females of childbearing potential. Conduct serum test at Screening and a urine pregnancy test at all other visits shown; conduct serum test if a urine test is positive. At Week 20, a urine pregnancy test will be conducted at home.

[r] Separate consent is required for HCM genotyping. Note that if a patient with a prior HCM clinical genotype test that was positive for pathogenic HCM-causing mutation(s) consents to provide their results, then no further genotype assessment will be performed. However, patients who have not been tested, patients who have tested negative for pathogenic HCM-causing mutation(s) on clinical panels, and patients 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 prior to the first dose of IMP for assessment of HCM genotype.

[s] Patients may also consent separately to have blood drawn prior to dosing on Day 1 for assessment of pharmacogenetics and potentially additional DNA sequencing.

[t] Patients will have blood samples drawn on Day 1 and Week 16 prior to dosing and at Week 24 for potential exploratory biomarker analysis.

[redacted].

[y] All patients will return their IMP dosing containers to the site for capsule counts. Refer to the Pharmacy Manual for details.