A Phase 2 Open-label Pilot Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction (PIONEER-HCM)

24 OCTOBER 2017

Statistical Analysis Plan

Version 2.0

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

Approved by: __________________________    Date: __________

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List of Abbreviations

2D 2-dimensional
3D 3-dimensional
AE adverse event
ALP alkaline phosphatase
ALT alanine aminotransferase
AST aspartate aminotransferase
BLQ Below the limit of quantitation
BMI body mass index
BP blood pressure
CPET cardiopulmonary exercise testing
CRF case report form
CV coefficient of variation
DILI drug-induced liver injury
DNA deoxyribonucleic acid
ECHO echocardiogram
EOS End of Study
ECG Electrocardiogram
HCM hypertrophic cardiomyopathy
HR heart rate
HSE Hemodynamic stress echocardiography
IB Investigator’s Brochure
ICH International Council for Harmonisation
IMP investigational medicinal product
KCCQ Kansas City Cardiomyopathy Questionnaire
LME linear mixed effects
LS least squares
LVEF left ventricular ejection fraction
LVFS left ventricular fractional shortening
LVOT left ventricular outflow tract
MedDRA Medical Dictionary for Regulatory Activities
MMRM mixed effect model with repeated measures
NRS numeric rating scale
NT-proBNP N-terminal pro B-type natriuretic peptide
NYHA New York Heart Association
OSS overall summary score
PD pharmacodynamic(s)
PK pharmacokinetic(s)
PT preferred term
pVO2 peak oxygen uptake
QTc  corrected QT interval
QTcB  QTc Bazett
QTcF  QTc Fridericia
RR    respiratory rate
SAE   serious adverse event
SE    standard error
SD    standard deviation
SOC   system organ class
TBL   total bilirubin
TEAE  treatment-emergent adverse event
TTE   transthoracic echocardiography, transthoracic echocardiogram
VCO2  carbon dioxide production
VE    volume expired
WHO   World Health Organization
MyoKardia, Inc.  
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1. Introduction

Hypertrophic cardiomyopathy (HCM), an autosomal dominant genetic disease, is defined clinically as unexplained left ventricular (LV) hypertrophy in the absence of known causes such as pressure overload, systemic diseases, or infiltrative processes (Gersh et al., 2011). The phenotypic hallmark of HCM is myocardial hypercontractility accompanied by reduced LV compliance, reflected clinically as reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. Mutations in cardiac myosin and other sarcomere proteins in patients with HCM appear to increase net power generation by the sarcomere (Chuan et al., 2012; Sommese et al., 2013; Sung et al., 2012), which is consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in patients with HCM.

MYK-461 is a first-in-class small molecule allosteric modulator of striated muscle myosin that selectively targets cardiac myosin and reversibly inhibits its binding to actin. MYK-461’s profile of myosin modulation is predicted to reduce dynamic left ventricular outflow tract (LVOT) obstruction in patients with obstructive HCM by reducing systolic hypercontractility and dynamic obstruction in the near term, and reducing ventricular hypertrophy with chronic treatment. MyoKardia is developing MYK-461 for the treatment of adults with symptomatic obstructive HCM to relieve obstruction, improve symptoms, and increase exercise capacity.

In nonclinical studies, MYK-461 was specific for striated muscle myosin and selective for the cardiac isoform (see the MYK-461 Investigator’s Brochure [IB]). Its targeted mechanism of action and high degree of specificity were reflected in its pharmacology in vitro and in vivo, as well as in the toxicology and safety pharmacology. In a feline model of HCM with LVOT obstruction, treatment with MYK-461 reduced contractility and relieved obstruction in an exposure-dependent manner (Stern et al., under review). The totality of the pharmacodynamic (PD) and tolerability data observed to date can be interpreted as direct or indirect consequences of altered cardiac contractility.

Please refer to the IB for more detailed information on MYK-461.

2. Objectives

2.1. Primary Objective

The primary objective of this study is:

- To characterize the effect of 12 weeks of MYK-461 treatment on reducing post-exercise peak LVOT gradient in subjects with symptomatic HCM and LVOT obstruction.

2.2. Secondary Objectives

The secondary objectives of this study are:
• To assess the proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 30 mm Hg
• To assess the effects of 12 weeks of MYK-461 treatment on dyspnea symptom score, peak oxygen uptake (pVO2), and volume expired (VE)/carbon dioxide production (VCO2) slope
• To evaluate the pharmacokinetic (PK) of MYK-461
• To evaluate the PD of MYK-461 as assessed by a variety of echocardiographic imaging parameters
• To evaluate the safety and tolerability of MYK-461
• To evaluate the posttreatment reversibility of the effects of MYK-461 after 4 weeks of washout

in subjects with symptomatic HCM and LVOT obstruction.

2.3. Exploratory Objectives
The exploratory objectives of this study are:
• To assess the proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 10 mm Hg
• To assess the effects of 12 weeks of MYK-461 treatment on New York Heart Association (NYHA) functional class, N-terminal pro B-type natriuretic peptide (NT-proBNP), and the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score (OSS)
• To assess the effects of MYK-461 treatment on arterial pulse wave morphology assessed using an optical biosensor
• To assess the effect of MYK-461 treatment on heart rate (HR) and heart rhythm as assessed using a cardiac monitoring skin patch

in subjects with symptomatic HCM and LVOT obstruction.

3. Investigational Plan

3.1. Overall Study Design and Plan
This is a non-randomized, phase 2 open-label pilot study to evaluate the efficacy, PK, PD, safety, and tolerability of MYK-461 in subjects with symptomatic HCM and LVOT obstruction. Approximately 20 adult subjects with symptomatic HCM, a resting LVOT gradient ≥ 30 mm Hg, and post-exercise peak LVOT gradient ≥ 50 mm Hg will be enrolled. Approximately 10 subjects will participate in Part A and approximately 10 subjects will participate in Part B. The study will have a 12-week treatment phase and a 4-week washout phase (Figure 1).
At Screening, subjects will undergo transthoracic echocardiography (TTE) in the supine or left lateral decubitus position. In addition to a standardized complete TTE, both resting instantaneous peak LVOT gradient (baseline) and provoked peak LVOT gradient (Valsalva maneuver) will be collected. Subjects will then undergo a standard symptom-limited exercise test (hemodynamic stress echocardiography). Subjects will be assessed systematically for symptoms of dyspnea and/or angina. Instantaneous peak LVOT gradient will be assessed immediately post-exercise by TTE.

On Day 1, resting TTE will be performed, blood samples will be drawn for PK, and subjects will have an assessment of pVO2, VE/VCO2, and other variables via cardiopulmonary exercise testing (CPET). After CPET, subjects will be dosed with open-label oral MYK-461 at the investigational site and will be observed for at least 1 hour after dosing, with assessment of vital signs and electrocardiograms (ECGs) at 1 hour postdose. Subjects will then be supplied with MYK-461 sufficient for once daily (QD) dosing at home.

Subjects will be evaluated at the investigational site at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 12, and 16. At each of these visits, resting TTE will be performed and blood samples will be drawn for PK. On study visit days, study medication will be administered at the investigational site in order to collect blood samples for PK ≤ 2 hours prior to dosing. At Weeks 4, 12, and 16, hemodynamic stress echocardiography will be performed and peak LVOT gradient will be assessed. CPET will be conducted between Weeks 10 and 12 (inclusive).
Part A:
The MYK-461 starting dose will be 10 mg for subjects who weigh ≤ 60 kg and 15 mg for subjects who weigh > 60 kg. At the end of Week 4 (Day 28), each subject’s left ventricular ejection fraction (LVEF) will be evaluated, and the subject’s dose may be increased, decreased, or remain unchanged based on the predetermined criteria in Table 1, in consultation between the investigator and the medical monitor. If MYK-461 plasma concentration exceeds 750 ng/mL at Week 2, no dose increase is allowed, regardless of LVEF data at Week 4; however, dose decrease per LVEF data is allowed in this circumstance. The subject will subsequently receive that dose from Week 5 through Week 12.

<table>
<thead>
<tr>
<th>Percent Decrease From Baseline in LVEF at the End of Week 4 (Day 28)</th>
<th>Action for MYK-461 Dose Week 5-Week 12$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>increase dose by 10 mg</td>
</tr>
<tr>
<td>≥ 10 and &lt; 15</td>
<td>increase dose by 5 mg</td>
</tr>
<tr>
<td>≥ 15 and &lt; 20</td>
<td>no change in dose</td>
</tr>
<tr>
<td>≥ 20</td>
<td>decrease dose by 5 mg</td>
</tr>
</tbody>
</table>

$^1$LVEF, left ventricular ejection fraction

$^a$ No dose increase allowed if plasma concentration of MYK-461 > 750 ng/mL at Week 2.

Part B:
The MYK-461 starting dose will be 2 mg. At the end of Week 4 (Day 28), each subject’s resting (non-provoked) peak instantaneous LVOT gradient and LVEF from the Week 4 TTE will be evaluated. The subject’s dose will be increased to 5 mg or remain unchanged based on the predetermined criteria in Table 2 below, in consultation between the investigator and the medical monitor. If MYK-461 plasma concentration exceeds 300 ng/mL at Week 2, no dose increase is allowed. The subject will subsequently receive that dose from Week 5 (Day 29) through Week 12.

For all subjects who provide consent, blood will be drawn prior to dosing on Day 1 for assessment of HCM genotype and potentially additional deoxyribonucleic acid (DNA) sequencing.

In addition, subjects may consent separately to collection of pharmacogenetic samples that will be stored for potential future analysis of genetic biomarkers of efficacy, safety-related, PD, or PK parameters as determined by future studies using clinically meaningful endpoints, through DNA sequencing or other genetic testing.

Blood samples will be collected from all subjects prior to dosing on Day 1 and at Week 12 and stored for exploratory circulating biomarker analysis, e.g., proteomic analysis related to disease activity, metabolic pathways, efficacy measures, or safety measures.

The expected study duration is approximately 8 months (4 months for recruitment and 4 months for study conduct) for Part A and approximately 10 months for Part B (18 months in total). Each subject is expected to be in the study no more than 140 days: up to 28 days for screening and up to 112 days for study conduct.
Table 2: Part B Week 4 Dose Adjustment Criteria

<table>
<thead>
<tr>
<th>Percent Decrease From Day 1 in Resting TTE Instantaneous Peak LVOT gradient at the End of Week 4 (Day 28)</th>
<th>Action for MYK-461 Dose Week 5-Week 12*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50%</td>
<td>increase dose to 5 mg</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>no change in dose</td>
</tr>
</tbody>
</table>

LVOT, left ventricular outflow tract; TTE, transthoracic echocardiogram; No dose increase allowed if plasma concentration of MYK-461 > 300 ng/mL at Week 2.

3.2. Study Endpoints

3.2.1 Primary Endpoint

- Change in post-exercise peak LVOT gradient from baseline to Week 12

3.2.2 Secondary Endpoints

- Proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 30 mm Hg
- Change in dyspnea symptom score from baseline to Week 12
- Change in pVO2 and VE/VCO2 from baseline to Week 12
- Change from baseline in LVEF 2-dimensional (2D) and 3-dimensional (3D), global longitudinal strain, and left ventricular fractional shortening (LVFS) from baseline to Week 12
- Change from Week 12 to Week 16 in post-exercise peak LVOT gradient
- Plasma PK profile of MYK-461 treatment

3.2.3 Exploratory Endpoints

- Proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 10 mm Hg
- Change in NYHA functional classification from baseline to Week 12
- Change in NT-proBNP from baseline to Week 12
- Change in KCCQ OSS from baseline to Week 12
- Change from baseline in arterial pulse wave morphology assessed using an optical biosensor
- Change from baseline in HR and heart rhythm assessed using a cardiac monitoring skin patch

3.2.4 Safety Endpoints

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Changes from baseline in laboratory values and vital signs
• Changes from baseline in ECGs

3.3. Treatments
All subjects will receive MYK-461 in an open-label manner.

Investigational medicinal product (IMP) is defined as MYK-461. Study medication is used throughout this protocol to refer to IMP as well as any other protocol-required medications (note that for this protocol there are no other required study medications).

3.4. Dose Adjustment/Modifications
All subjects in Part A will be assigned to a starting dose of oral MYK-461 based on body weight for doses ≥ 10 mg, which they will receive QD for 4 weeks. Subjects in Part B will be assigned a starting dose of 2 mg. At the Week 4 visit, dose adjustment may be performed based on the predetermined criteria in Section 3.1, Table 1 (Part A) and Table 2 (Part B). The subject will subsequently receive that dose from Week 5 (Day 29) through Week 12.

Subjects with abnormal hepatic laboratory values (e.g., 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.

4. General Statistical Considerations
All statistical analyses and programming of tables, figures, and listings will be performed by PPD using the SAS® Version 9.2 or higher (SAS Institute Inc., Cary, North Carolina, USA).

Unless otherwise specified, all tables will be presented with the columns labeled with the combination of ‘initial dose’/’adjusted dose’.

Descriptive summaries will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, standard deviation (STDEV), first and third quartiles, minimum and maximum for continuous variables. For the analysis of primary endpoint using a mixed-effect model with repeated measures (MMRM), LS mean with standard error (SE) will also be provided. Standard error formatting should be presented to 4 more decimal places than the measured value.

P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as ‘< 0.0001’ and p-values that round to 1.000 will be presented as ‘> 0.9999’. Confidence intervals (CIs) will be estimated based on the MMRM for the analysis of the primary endpoint, a two-sided 90% significance level.

All mean and quartile values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value. All percentages will be rounded to 1 decimal point. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses.

All analysis and summary tables will have the analysis population sample size (i.e., number of subjects) in the column heading. All listings will be sorted for presentation in order of study site, subject identification and date of procedure or event.
The day of the first dose of study drug will be defined as Day 1.
Baseline value will be defined as the last non-missing value in date/time before the first dose of study drug is administered.

Missing data handling will be described in Section 7, 8, 9 and 10. All laboratory data will be reported using International System of Units (SI).

The planned analysis visit window for weekly visits will consider +/- 3 days of the scheduled visit date based on the date of first exposure to the study drug. For a missed visit, the evaluation will be rescheduled as close as possible to the original planned visit, thus analysis windows have been designed to be all-inclusive. If more than one result is available for a particular visit window and results are equidistant from the analysis target date, the later result will be selected to break the tie. The associated visit window with corresponding visit is tabulated below.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Scheduled Visit Day</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 1</td>
<td>[1, 4]</td>
</tr>
<tr>
<td>Week 1</td>
<td>Day 8</td>
<td>[5, 11]</td>
</tr>
<tr>
<td>Week 2</td>
<td>Day 15</td>
<td>[12, 18]</td>
</tr>
<tr>
<td>Week 3</td>
<td>Day 22</td>
<td>[19, 25]</td>
</tr>
<tr>
<td>Week 4</td>
<td>Day 29</td>
<td>[26, 32]</td>
</tr>
<tr>
<td>Week 5</td>
<td>Day 36</td>
<td>[33, 39]</td>
</tr>
<tr>
<td>Week 6</td>
<td>Day 43</td>
<td>[40, 46]</td>
</tr>
<tr>
<td>Week 7</td>
<td>Day 50</td>
<td>[47, 53]</td>
</tr>
<tr>
<td>Week 8</td>
<td>Day 57</td>
<td>[54, 64]</td>
</tr>
<tr>
<td>Week 10*</td>
<td>Day 71</td>
<td>[65, 78]</td>
</tr>
<tr>
<td>Week 12*</td>
<td>Day 85</td>
<td>[79, 99]</td>
</tr>
<tr>
<td>Week 16</td>
<td>Day 113</td>
<td>[100, 116]</td>
</tr>
</tbody>
</table>

*CPET may be conducted between study visits 10 and 12, therefore the planned analysis window ranges from Day 65 to Day 99 with Day 85 set to the scheduled visit day. Note: The window is adjusted for visit 12; visit 10 will not be presented.

For any subjects who discontinued treatment prior to Week 4 dose adjustment, the subjects will not be presented in the treatment columns (initial dose/adjusted dose), however will be presented in the total column in the table.

If the “seconds” portion of the date/time variable is missing or not collected, it will be imputed as “:00”, as needed.

### 4.1. Sample Size

Approximately 10 subjects will be dosed in Part A and in Part B. The sample size is based on practical considerations and is consistent with this type of study. Ten subjects per group receiving MYK-461 will provide 80% power to detect a 30 mm Hg within-group change from baseline in post-exercise peak LVOT gradient and a > 99% power to detect a 50 mm Hg change (Table 3). This assumes a 1-sided $\alpha = 0.05$ and a common standard deviation of 35 mm Hg. The common standard
deviation of 35 mm Hg is based on observed data in patients with HCM and provocable LVOT (Nistri et al., 2012).

4.2. Randomization, Stratification, and Blinding

Subjects will not be randomized to treatment in this study, and treatment will not be blinded.

4.3. Analysis Set

4.3.1. All Enrolled
The All Enrolled Population includes every subject who signed informed consent. Subjects in the all enrolled population will be analyzed according to the planned dose combination.

4.3.2. Efficacy Analysis Population
The Efficacy Analysis Population is defined as all subjects who receive at least 1 dose of MYK-461 and have primary or secondary endpoint data, including a baseline value and at least one post baseline value. All efficacy analyses will be performed on the Efficacy Analysis Population. Subjects in the efficacy population will be analyzed according to the planned dose combination.

4.3.3. Safety Analysis Population
The Safety Analysis Population is defined as all subjects who receive at least 1 dose of MYK-461. Safety analyses will be performed on the Safety Analysis population. Subjects in the safety population will be analyzed according to the actual dose combination.

4.3.4. Pharmacokinetic (PK) Analysis Population
The PK Analysis Population is defined as all subjects who received at least 1 dose of MYK-461 and have at least one detectable PK concentration. PK analyses will be performed on the PK Analysis Population.

4.3.5. PK/ECG Analysis Population
The PK/ECG Analysis Population is defined as all subjects who received at least 1 dose of MYK-461 and have detectable PK concentration and ECG data pre-dose.

5. Subject Disposition
Subject disposition will be summarized for the all enrolled population. A disposition of subjects includes the number and percentage of subjects for the following categories: subjects who were enrolled, subjects who failed screening, subjects who completed the study, subjects who discontinued from the study, will be summarized. Besides, number of subjects in safety set,
efficacy set, PK set and in PK/ECG set will be summarized as well. All percentages will be based on the number of subjects enrolled.

The reasons for study discontinuation will also be summarized in this table. The reason for study discontinuation includes the following: adverse event, death, lost to follow-up, non-compliance with study procedures/restrictions, pregnancy, study terminated by sponsor, withdrawal by subject and other.

Subject disposition data will be presented in a listing.

All protocol deviations, extracted from the clinical trial management system, will be presented in a listing. Significant protocol deviations will be further subset in a separate listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline information will be presented. The demographic characteristics consist of age (years), sex, race, and ethnicity. The baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2).

Age is calculated as (date of informed consent – date of birth)/365.25.

Age (years), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of subjects by age category (<=65, >65), sex (Male, Female), BMI category (<25.0, 25.0-29.9, ≥30.0 kg/m^2), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino), will also be reported. Percentages will be based on the total number of subjects in the enrolled set. In addition, reproductive status and Pregnancy test will be also summarized.

Subject demographic and baseline characteristics will be presented in a listing.

6.2. Medical History

Medical History will be mapped to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA Version 19 or higher). The number and percentage of subjects with any medical history will be summarized overall and by decreasing frequency of MedDRA SOC. Within each SOC, PT will be sorted by alphabetical order. Percentages will be calculated based on number of subjects in the safety population.

Subject medical history data including specific details will be presented in a listing.

6.3. Inclusion and Exclusion Criteria
Subjects who failed inclusion and exclusion criteria will be presented in a listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All medications used within 30 days prior to the date of informed consent through the end of study (EOS) will be collected on the case report form (CRF). All medications will be coded according to the World Health Organization drug dictionary (WHODRUG June 2016 or later).

A prior medication is defined as any medication that is taken within 30 days prior to the first dose of study drug. A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study drug.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date;
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date.

Missing stop dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

If start date is completely missing and end date is not prior to the first dose, then the medication will be classified as both prior and concomitant. If the start date is completely missing and the end date is prior to the first dose of study drug, then the medication will be classified as prior. If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as prior and concomitant.
7.1.1. Prior Medications
The total number of prior medications and the number and percentages of subjects with at least one prior medication will be summarized by preferred term and by alphabetical order. All summaries will be performed using the safety set.

7.1.2. Concomitant Medications and Procedures
The total number of concomitant medications and the number and percentages of subjects with at least one concomitant medication will be summarized and presented by preferred term and will be sorted in alphabetical order. All summaries will be performed using the safety set.

Concomitant procedures will be mapped to SOCs and PTs using the MedDRA Version 19 or later and will be presented in a listing.

7.2. Study Treatments
Study medication will consist of MYK-461 immediate-release oral tablets, 2mg, 5mg, 10mg, and 20mg. All subjects in Part A will be assigned to a starting dose of oral MYK-461 based on body weight for doses ≥ 10 mg. Subjects who weigh ≤ 60 kg will start at 10 mg and subjects who weigh > 60 kg will start at 15 mg. Subjects in Part B will be assigned a starting dose of 2 mg. Each subject will receive oral MYK-461 at their determined starting dose QD beginning on Day 1 and continuing through Week 4. At Week 4, and individual subject’s daily dose may be adjusted based on predetermined criteria. The subject will subsequently receive that dose from Week 5 through Week 12.

7.2.1. Extent of Exposure
Duration of treatment (days) is defined as the total number of days a subject is exposed to any study drug and will be presented as the total number of days from the first dose date (Day 1) to the last dose date (date of last dose minus the date of first dose + 1) as recorded on the Study Completion/Termination page on the CRF. If the last dose date on the Study Completion/Termination page is missing, or if a subject is lost to follow-up, but the study drug exposure at investigation site form confirms that the subject has taken study drug at a visit, the latest date of the exposure at investigation site on the CRF will be used.

Because study drug reduction may occur during the study, the exposure to study drug will also be characterized by cumulative dose (mg), which is defined as the cumulative number of dose taken by subjects.

The duration of treatment to study drug will be summarized for all subjects in the Safety set and will be presented in a table by summary statistics. The duration of treatment will then be classified into the following categories: > 0 week, ≥ 2 weeks, ≥ 4 weeks, ≥ 6 weeks, ≥ 8 weeks, ≥ 10 weeks, and ≥ 12 weeks and will be presented as the number and percentage of subjects in each duration category. Percentages will be computed from the number of subjects in the Safety set.
The total cumulative dose (mg) will be defined as the sum of the actual dose taken across all study days. Average daily dose is cumulative dose divided by total days on study drug. The average daily dose and cumulative dose will be summarized by descriptive summary statistics.

A summary of each subject’s exposure will be presented in a listing.

7.2.2. Treatment Compliance

Study drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of study drug as instructed. The number of tablets taken will be calculated by subtracting the number of tablets returned from the number of tablets dispensed.

The overall study drug compliance (%) will be calculated by dividing the actual cumulative dose taken at all visits by the planned cumulative dose prescribed for all visits and then multiplying by 100. The overall study drug compliance will be summarized.

Summary statistics on percentage of treatment compliance as well as the number and percentage of subjects in each compliance category (<75%, 75-85%, and greater than 85% compliant) will be presented overall. Percentages will be calculated out of the number of subjects who were dosed in the Safety set. A subject is considered compliant if overall study drug compliance is greater than or equal to 80%.

8. Efficacy Analysis

All efficacy analyses will be performed on the Efficacy Analysis Population.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 in post-exercise peak LVOT gradient. Baseline is defined as the last non-missing measurement of post-exercise LVOT gradient prior to the first dose. Post-exercise peak LVOT gradient will be analyzed using a mixed-effect model with repeated measures (MMRM). All data available from baseline (Screening) to Week 16 (EOS) will be included and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effects of timepoint: baseline, Week 4, Week 12 (end of treatment), and Week 16 (EOS). An unstructured covariance structure will be assumed unless model diagnostics suggest otherwise.

This model will provide least-squares (LS) mean estimates with their corresponding standard errors at each time point. Comparison between baseline and Week 12 (end of treatment) will be based on the LS mean difference obtained from the MMRM, and will be presented with its associated two-sided 90% confidence interval. Statistical significance of the difference versus baseline will be evaluated at the two-sided 0.10 level. The primary efficacy endpoint will also be descriptively summarized by each timepoint.
8.2. Secondary and Exploratory Efficacy Endpoint

The proportion of subjects achieving LVOT gradient responses of < 30 mm Hg and < 10 mm Hg will be summarized at each post-baseline visit as well as across all post-baseline visits. In case of missing data at a given visit, it will be assumed that the subject had not achieved an LVOT gradient response.

Figures presenting mean +/- SE of resting, post-exercise and provoked LVOT gradient by timepoint will be included in the analyses.

Quantitative endpoints, including the Dyspnea numeric rating scale (NRS), pVO2, VE/CO2, LVEF, NYHA functional classification, NT-proBNP, and KCCQ OSS will be analyzed using the same MMRM model as for the primary efficacy endpoint. The list of timepoints included in the MMRM will be adjusted according to the visits at which each endpoint will be measured. All efficacy endpoint will also be descriptively summarized by each timepoint.

Change from baseline in heart rate and heart rhythm using a cardiac monitoring skin patch will be analyzed descriptively. Resting echocardiogram (ECHO) and hemodynamic stress echocardiography (HSE) parameters will be presented in a listing.

9. Safety Analysis

All safety analyses will be performed on the Safety Analysis population.

9.1. Adverse Events

AEs will be mapped to SOCs and PTs using the MedDRA Version 19 or later. 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.

A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:
- begins on or after the first dose of study drug and before the stop of study drug + 28 days;
- begins before the first dose of study drug and worsens in severity on or after the first dose of study drug and before the stop of study drug + 28 days;
- is completely missing an onset date and end date;
- is completely missing an onset date and the end date is on or after the first dose of study drug.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):
• UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

• DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):
• UK-MMM-YYYY: Assume the last day of the month;
• DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, study drug-related TEAE, study drug-related serious TEAE, TEAE leading to treatment discontinuation, TEAE leading to study termination, TEAE leading to treatment interruption and AE leading to death will be provided.

### 9.1.1. Incidence of Adverse Events

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided. Treatment-emergent AEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety set.

A summary of TEAEs will also be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any two or more Socs is equal, the Socs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

All AEs will be presented in a listing.

### 9.1.2. Relationship of Adverse Events to Study Drug

A summary of TEAEs by relationship to study drug will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Not Related”, “Unlikely”, “Possible”, “Probable”, and “Definite”. In the TEAE relationship table, if a subject reports multiple occurrences of the
same TEAE, only the most closely related occurrence will be presented. Treatment –emergent AEs that are missing a relationship will be presented in the summary table as “Definite” but will be presented in the data listing with a missing relationship or the actual relationship respectively. Percentages will be calculated out of the number of subjects in the Safety set.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

9.1.3. Severity of Adverse Event
A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are “Mild,” “Moderate,” and “Severe.” In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are missing severity will be presented in tables as “Severe” but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the Safety set.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.1.

9.1.4. Serious Adverse Events
The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. A serious AE (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, is a congenital anomaly/birth defect, requires in-patient hospitalization or prolongation, or results in significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs will be summarized by MedDRA SOC and PT in a table.

9.1.5. Adverse Events Leading to Treatment Discontinuation
All TEAEs with a study drug action taken of “Drug Withdrawn” will be presented in a data listing.

9.1.6. Adverse Events Leading to Study Discontinuation
A summary of TEAEs where the answer to “Caused Study Discontinuation” is “Yes” will be presented in a data listing.

9.1.7. Death
All subjects who have an AE with an outcome of “Death Related to Adverse Event” will be presented in a listing.
9.2. Clinical Laboratory Evaluations

Safety laboratory data including hematology, chemistry, and urinalysis will be evaluated by visit for the Safety Analysis Population using descriptive statistics.

Laboratory assessments will be performed by a PPD central laboratory. All summaries will be based on the standard units provided by the central laboratory, no conversions will be attempted. Drug-induced liver injury (DILI) will be identified, according to the criteria in the protocol Section 7.4, and summarized. Subjects who met each of the DILI criteria, TBL > 2 X ULN or > 3 X ULN for AST/ALT with baseline < ULN will be summarized descriptively.

9.2.1. Hematology

The following laboratory tests will be included: red blood cell count (RBC), hemoglobin, hematocrit (HCT), platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red blood cell distribution width (RDW), WBC count, total neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Baseline values and change from baseline at each scheduled post-baseline timepoint will be descriptively summarized. All hematology data by subject will be presented in a listing, with the measurements outside of the reference range flagged.

For the schedule of hematology laboratory tests, please refer to Appendix 1.

9.2.2. Serum Chemistry

The following laboratory tests will be included: blood urea nitrogen (BUN), calcium, creatinine, sodium, potassium, chloride, magnesium, bicarbonate, protein, albumin, bilirubin (TBL), alkaline phosphatase (ALP), aspartate aminotransferase (AST), creatinine phosphokinase (CPK), and alanine aminotransferase (ALT).

Baseline values and change from baseline at each scheduled post-baseline timepoint will be descriptively summarized. All chemistry data by subject will be presented in a listing, with the measurements outside of the reference range flagged.

For the schedule of serum chemistry laboratory tests, please refer to Appendix 1.

9.2.3. Urinalysis

The following laboratory tests will be included: specific gravity, pH, protein, glucose, leukocyte esterase, and blood.

Baseline values and change from baseline at each scheduled post-baseline timepoint will be descriptively summarized. All urinalysis data by subject will be presented in a listing.
For the schedule of urinalysis laboratory tests, please refer to Appendix 1.

9.3. Vital Sign Measurements

Vital signs, to be assessed at each study visit, include temperature, HR, respiratory rate, and blood pressure (BP) after resting for at least 5 minutes. Vital signs will be obtained with the subject in the same position; BP and HR should be the mean of 3 measurements taken ≥ 5 minutes apart. BP should be taken via an automated recorder.

On Day 1 of dosing, vital signs will be taken predose and at 1 hour postdose. At all other visits, vital signs will be taken prior to dosing.

Summary tables presenting observed values and changes from baseline will be presented for vital sign data, including systolic BP (mmHg), diastolic BP (mmHg), temperature (°C), pulse (bpm), and respiration (breaths/minute) for subjects in the Safety set.

Changes from baseline at each scheduled post-baseline visit will be presented. All vital sign data by subject will be presented in a listing.

9.4. Physical Examination

At Screening, Day 1, Week 12, and Week 16, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height (Screening only) and weight, and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.

Physical examination results will be presented in a listing.

9.5. Electrocardiogram

Triplicate ECG recordings will be obtained at each scheduled timepoint and the average of the three readings will be used to determine ECG intervals, including QRS, heart rate, PR, QT, Corrected QT interval using Fridericia’s formula (QTcF), Corrected QT interval using Bazett’s formula (QTcB) and RR. Missing ECG data will not be imputed. If one or two replicates are missing, the average will be calculated on the available replicates.

ECG Numeric Variables

HR, PR, QRS, QT, QTcF, QTcB, and RR will be summarized using descriptive statistics. The change from baseline of these ECG parameters at each timepoint will be listed for each subject. For each timepoint of measurement, the changes from baseline will be summarized using descriptive statistics.
Categorical Analysis
The cumulative 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 will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The cumulative incidence count and percentage of subjects with ΔQTcF increase of > 30 msec and > 60 msec will be tabulated. Also subjects with QTcB/QTcF > 480 ms and/or change from baseline in QTcB/QTcF > 60 ms will also be listed in a separate listing.

Morphology Findings
New ECG morphologies for each subject not present on any ECG at baseline for that subject will be summarized for all observation timepoints combined.

The number and percentage of subjects having new morphology changes from baseline will be reported, and summarized as QTc Prolongation, ST depression, ST elevation, T-waves biphasic, T-waves flat, T-wave inversion, or U-wave abnormality.

ECG overall interpretation by visit will be presented in a listing.

For the schedule of ECG test, please refer to Appendix 1.

10. Pharmacokinetics
Blood samples for plasma PK analysis of MYK-461 will be collected within 2 hours prior to dosing at the following timepoints: Day 1, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 12 and Week 16 or End of Study (End of Treatment + 4 Week) for Part A and Part B.

Concentrations that are BLQ will be treated as zero for descriptive statistics. All missing concentrations will be treated as missing for descriptive statistics.

Plasma concentration data of MYK-461 will be listed by subject and summarized by MYK-461 dose level and nominal time point using descriptive statistics (number of subjects (n), arithmetic mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum).

Arithmetic mean plasma concentration data of MYK-461 versus nominal time (days) will be plotted by MYK-461 dose level on linear and semi-logarithmic scales. Individual plasma concentration data of MYK-461 versus actual times will also be presented on linear and semi-logarithmic scales. Overlay plot of individual plasma concentration data of MYK-461 versus actual times will also be presented on linear and semi-logarithmic scales.

11. PK-QTc Analyses
A concentration-QTc regression analysis, based on data collected from the ECG recordings after drug administration and MYK-461 concentration values for each subject at each matching timepoint will be performed. A linear mixed effects (LME) model will be fitted on change from
baseline QTcF, with baseline QTcF, MYK-461 concentration as an independent variable and subject as a random effect. Baseline QTcF is defined as the average of the last assessment prior to start of study treatment. A corresponding scatter plot will be provided. The analyses will be performed on PK/ECG set.

12. Pharmacogenomic/HCM Genotype
For all subjects who provide consent, blood will be drawn on prior to dosing Day 1 for assessment of HCM genotype and potentially additional deoxyribonucleic acid (DNA) sequencing.

In addition, subjects may consent separately to collection of pharmacogenetic samples that will be stored for potential future analysis of genetic biomarkers of efficacy, safety-related, PD, or PK parameters as determined by future studies using clinically meaningful endpoints, through DNA sequencing or other genetic testing.

Data collected for Pharmacogenomic and HCM Genotype will be listed and summarized as requested by the sponsor.

13. Interim Analysis
There will be an interim analysis for Part A subjects, when the last subject for Part A completes the study. The Part A interim analysis will include: demographics, disposition, adverse events, drug exposure, vital signs, laboratory evaluations, ECG, PK, primary and secondary efficacy endpoints.

14. Changes in the Planned Analysis
14.1.1. References


Appendices
## APPENDIX 1 SCHEDULE OF STUDY PROCEDURES

| Timepoint (Day/Week)
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* Footnotes and abbreviations defined on last page of table.
APPENDIX 1  SCHEDULE OF STUDY PROCEDURES (continued)

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AE, adverse event; BP, blood pressure; CPET, cardiopulmonary exercise testing; D, day; ECG, electrocardiogram; eCRF, electronic case report form; EOS, end of study; ET, early termination; FSH, follicle-stimulating hormone; HCM, hypertrophic cardiomyopathy; HIV, human immunodeficiency virus; HR, heart rate; ICF, informed consent form; IMP, investigational product; KCCQ, Kansas City cardiomyopathy questionnaire; LVFS, left ventricular fractional shortening; LVOT, left ventricular outflow tract; NRS, numerical rating scale; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetic; QD, once daily; SAE, serious adverse event; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiography; VCO₂, carbon dioxide production; VE, volume expired; VO₂, oxygen uptake; VIT, velocity time integral; W, week.

* At the investigator’s discretion, unscheduled visits may be conducted at the investigative site for the assessment of AEs, physical examinations, vital signs, laboratory tests, ECGs, and/or TTEs. All information collected from unscheduled visits will be recorded on the eCRF and included in the clinical database.

* A complete medical history will be recorded at the Screening visit, which will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal, liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse, or any other diseases or disorders as well as participation in clinical studies (study medication and or device or other therapy).

* Approximately on Day 4 and approximately at Week 10, subjects will be contacted via telephone to determine the subject’s status and whether the subject is experiencing any AEs. Information on concomitant medications will also be collected.
Vital signs include temperature, HR, respiratory rate, and BP after resting for at least 5 minutes. Obtain vital signs with subject in the same position; BP and HR should be the mean of 3 measurements taken ≥ 5 min apart. BP should be taken via an automated recorder. On Day 1, vital signs will be taken predose and at 1 hour postdose. At all other visits, vital signs will be taken predose.

Any changes in baseline conditions that occur after the ICF is signed are recorded on the medical history eCRF, unless the change is related to a study procedure, in which case it is considered an AE. All changes that occur after the administration of the study medication are recorded as AEs.

At Screening, Day 1, Week 12, and Week 16, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height (Screening only) and weight, and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.

A 12-lead ECG (triplicate) will be performed after 10 minutes of rest at Screening and at all study visits. On Day 1, ECG will be performed within 2 hours predose and at 1 hour postdose. At all other visits, ECGs will be taken predose.

Instantaneous peak LVOT gradient (baseline) and provoked peak LVOT gradient (Valsalva maneuver) will be assessed. Ejection fraction (2-dimensional and 3-dimensional), LVFS, global longitudinal strain by speckle tracking, and VTI will be analyzed. Resting TTE should be performed prior to hemodynamic stress echocardiography or CPET.

CPET after a 4-hour fast (water is allowed) by standardized treadmill with assessment of LVOT peak gradient. CPET should be conducted prior to dosing with study medication. The following will be assessed: VO2, VCO2, VE, VE/VO2, VE/VCO2, and respiratory exchange ratio (RER).

CPET may be conducted at the Week 12 visit or anytime between Weeks 10 and 12. If CPET and hemodynamic stress echocardiography are conducted at the same visit, the hemodynamic stress echocardiography should be conducted first, followed by the CPET.

Subjects will undergo a standard symptom-limited exercise test. Instantaneous peak LVOT gradient will be assessed immediately post-exercise by TTE. Post Screening, hemodynamic stress echocardiography should be conducted prior to dosing with study medication.

For participating sites, an optical biosensor may be fastened to the subject’s wrist for several minutes to collect data on pulse wave morphology. This assessment is optional and will be conducted only if the subject provides consent.

The cardiac monitoring adhesive skin patch is to be applied at Screening visit and removed at the Day 1 visit. Additional patches should be applied and retrieved at the timepoints shown. Each subject should be trained on applying the patch and should be provided with an additional patch for the subject to apply if a patch comes off after less than 14 days.

At Week 8, the subject should be provided with an additional cardiac monitoring skin patch. At Week 10, the subject is to remove the patch applied at Week 8 and mail the patch using a preaddressed, postage-paid envelope. The subject will then apply the additional patch that was supplied at Week 8.

Collect PK samples ≤ 2 hours prior to dosing.

FSH testing at Screening for postmenopausal women to confirm postmenopausal status.

Pregnancy test (serum or urine) for women of childbearing potential, based on standard at institution.

For subjects who consent, blood will be drawn on Day 1 for assessment of HCM genotype.

For subjects who consent, blood sample will be drawn for potential future exploratory pharmacogenetic analysis on Day 1.

Blood samples for potential exploratory biomarker analysis predose on Day 1 and at Week 12.

At the end of Week 4, each subject’s dose may be increased, decreased, or remain unchanged based on predetermined criteria.

All subjects will return their IMP dosing containers to the site pharmacy for tablet counts. Refer to the Pharmacy Manual for details.
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