

CLINICAL STUDY PROTOCOL

Protocol Number MYK-461-004

Protocol Title: 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)

Indication: Hypertrophic Cardiomyopathy

Phase: 2

Investigational Medicinal Product MYK-461

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PROTOCOL SYNOPSIS

Protocol Number and Title:

MYK-461-004: 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)

Name of Investigational Product: MYK-461

Sponsor: MyoKardia, Inc.

Phase: 2

Study Objectives:**Primary Objective:**

- To characterize the effect of 12 weeks of MYK-461 treatment on reducing post-exercise peak left ventricular outflow tract (LVOT) gradient in subjects with symptomatic hypertrophic cardiomyopathy (HCM) and LVOT obstruction

Secondary Objectives:

- To assess the proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 30 mm Hg in subjects with symptomatic HCM and LVOT obstruction
- 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 in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the pharmacokinetics (PK) of MYK-461 in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the pharmacodynamics (PD) of MYK-461 in subjects with symptomatic HCM and LVOT obstruction as assessed by a variety of echocardiographic imaging parameters in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the safety and tolerability of MYK-461 in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the posttreatment reversibility of the effects of MYK-461 after 4 weeks of washout in subjects with symptomatic HCM and LVOT obstruction

Exploratory Objectives:

- To assess the proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 10 mm Hg in subjects with symptomatic HCM and LVOT obstruction
- 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) in subjects with symptomatic HCM and LVOT obstruction
- To assess the effects of MYK-461 treatment on arterial pulse wave morphology assessed using an optical biosensor in subjects with symptomatic HCM and LVOT obstruction
- To assess the effect of MYK-461 treatment on heart rate and heart rhythm as assessed using a cardiac monitoring skin patch in subjects with symptomatic HCM and LVOT obstruction

Eligibility Criteria:**Inclusion Criteria:**

Each subject must meet the following criteria to be included in this study.

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure.
2. Men or women 18 to 70 years of age at the Screening visit.
3. Diagnosed with HCM (hypertrophied and non-dilated left ventricle in absence of systemic or other known cause), with left ventricular [LV] wall thickness ≥ 15 mm at time of initial diagnosis or ≥ 13 mm with a positive family history of HCM.
4. Body mass index (BMI) 18 to 37 kg/m², inclusive, at the Screening visit, calculated using the institution's standard formula.
5. All safety laboratory parameters (chemistry, hematology, and urinalysis) within normal limits (laboratory reference range) at the Screening visit as assessed by the central laboratory, or if outside of the limits must meet both of the following criteria:
 - considered by the investigator to be clinically unimportant
 - if a liver function test result, must be $< 1.5 \times$ the upper limit of the laboratory reference range.
6. Has documented left ventricular ejection fraction (LVEF) $\geq 55\%$ at the Screening visit as determined by the investigator and the investigational site's echocardiography laboratory.
7. Resting LVOT gradient ≥ 30 mm Hg and post-exercise peak LVOT gradient ≥ 50 mm Hg at the Screening visit as determined by the investigator and the investigational site's echocardiography laboratory.

8. NYHA functional class II or higher, judged by the investigator to be due to LVOT obstruction.
9. Has adequate acoustic windows, in the judgment of the investigator and the investigational site's echocardiography laboratory, to enable accurate transthoracic echocardiograms (TTEs).
10. Female subjects must not be pregnant or lactating and, if sexually active, must be using one of the following acceptable birth control methods from the Screening visit through 3 months after the last dose of investigational medicinal product (IMP). Hormonal contraceptives are not considered highly effective contraception for this study because MYK-461 could reduce the effectiveness of hormonal contraceptives.
 - Double-barrier method (e.g., vasectomy or male using a condom and female using a diaphragm or cervical cap)
 - Barrier (e.g. male using a condom) plus non-hormonal intrauterine device (IUD) or intrauterine system (IUS)
 - Female is surgically sterile for 6 months or postmenopausal for 2 years. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to Screening. Females are considered postmenopausal if they have had amenorrhea for at least 2 years or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
11. Male subjects with female partners (including postmenopausal partners) must agree to use highly effective contraceptive measures from the Screening visit through 3 months after the last dose of study medication. Highly effective contraception includes documented vasectomy, abstaining from sexual intercourse, double-barrier method (e.g., male using a condom and female using a diaphragm or cervical cap), or barrier plus hormonal contraception (e.g., male using a condom and female using hormonal contraception). As there may be a risk of drug being secreted in the ejaculate, male subjects (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and for 3 months after the last dose of study medication. In addition, male subjects with sexual partners should use condoms for the duration of the study and for 3 months after the last dose of study medication, even if the partner is not pregnant or capable of becoming pregnant, in order to prevent passing MYK-461 to the partner in the ejaculate.
12. Must be able to complete the Dyspnea Numeric Rating Scale (NRS) and the KCCQ per established guidelines.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from the study.

1. Hypersensitivity to MYK-461 or any of the components of the MYK-461 formulation.

2. Presence of any medical condition that precludes exercise stress testing.
3. History of sustained ventricular tachyarrhythmia.
4. History of syncope with exercise within past 6 months.
5. Active infection.
6. Persistent atrial fibrillation or atrial fibrillation at Screening or history of paroxysmal atrial fibrillation with resting rate documented >100 bpm within 1 year of screening.
7. Has QTc Fridericia (QTcF) > 500 ms, or any other electrocardiogram (ECG) abnormality considered by the investigator to pose a risk to subject safety (e.g., second degree atrioventricular block type II).
8. Aortic stenosis or fixed subaortic obstruction.
9. History of LV systolic dysfunction (LVEF < 45%) at any time during their clinical course.
10. History of obstructive coronary artery disease (stenosis of >70% of luminal diameter in one or more coronary arteries).
11. History of malignancy of any type, with the following exceptions: in situ cervical cancer more than 5 years prior to Screening or surgically excised non-melanomatous skin cancers more than 2 years prior to Screening.
12. Positive serologic test at Screening for infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
13. Positive test for alcohol or drugs of abuse at Screening.
14. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or MyoKardia physician, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
15. Participated in a clinical trial where the subject received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening, or at least 5 times the respective elimination half-life (whichever is longer).
16. Current use of tobacco- or nicotine-containing products exceeding 10 cigarettes per day or equivalent.
17. Part A: Subjects who in the opinion of the investigator require ongoing therapy with β -blockers, calcium channel blockers, or disopyramide. Subjects on any of these medications who, in the opinion of the investigator, can safely be withdrawn are eligible as long as medication is discontinued at least 14 days prior to the Screening visit.

Part B: Subjects who in the opinion of the investigator require ongoing therapy with calcium channel blockers or disopyramide. Subjects on any of these medications who, in the opinion of the investigator, can safely be withdrawn are eligible as long as medication is discontinued at least 14 days prior to the Screening visit.

18. Prior treatment with cardiotoxic agents such as doxorubicin or similar, or current treatment with antiarrhythmic drugs that have negative inotropic activity, e.g., flecainide or propafenone.
19. Unable to comply with the study restrictions/requirements, including the number of required visits to the clinical site.
20. Is employed by, or is a relative of someone employed by MyoKardia, the investigator, or his/her staff or family.

Study Treatment:

Study medication will consist of MYK-461 immediate-release oral tablets, 2 mg, 5 mg, 10 mg, and 20 mg.

Part A:

Subjects on β -blockers who, in the opinion of the investigator, can safely be withdrawn are eligible for this part of the study as long as medication is discontinued at least 14 days prior to the Screening visit. The starting dose will vary based on individual subjects' weight. Subjects who weigh ≤ 60 kg will start at 10 mg and subjects who weigh > 60 kg will start at 15 mg. Each subject will receive oral MYK-461 at their determined starting dose once daily (QD) beginning on Day 1 and continuing through Week 4. At Week 4, an individual subject's daily dose may be adjusted based on predetermined criteria (see Study Design). The subject will subsequently receive that dose from Week 5 through Week 12.

Part B:

Subjects not currently taking beta blockers and subjects on a stable dose of β -blockers for at least 14 days, who in the opinion of the investigator require ongoing therapy with β -blockers at the same dose, are eligible for this part of the study. This includes patients treated with β -blockers for rate control of paroxysmal atrial fibrillation. The starting dose will be 2 mg MYK-461 QD beginning on Day 1 and continuing through Week 4. At Week 4, an individual subject's daily dose may be adjusted based on predetermined criteria (see Study Design). The subject will subsequently receive that dose from Week 5 through Week 12.

Number of Subjects Planned: Approximately 20 (10 in Part A, 10 in Part B)

Number/Location of Investigational Sites: Approximately 7 sites in the United States

Study Duration: Approximately 18 months

Study Design:

This is a 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. The study will have a 12-week treatment phase and a 4-week washout phase.

At Screening, subjects will undergo 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 ECGs at 1 hour postdose. Subjects will then be supplied with MYK-461 for 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 \leq 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 \leq 60 kg and 15 mg for subjects who weigh $>$ 60 kg. At the end of Week 4 (Day 28), each subject's LVEF will be evaluated, and the subject's dose may be increased, decreased, or remain unchanged based on the predetermined criteria below, 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.

Percent Decrease From Baseline in LVEF at the End of Week 4 (Day 28)	Action for MYK-461 Dose Week 5-Week 12^a
< 10	increase dose by 10 mg
\geq 10 and < 15	increase dose by 5 mg
\geq 15 and < 20	no change in dose
\geq 20	decrease dose by 5 mg

^a LVEF, left ventricular ejection fraction 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 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.

Percent Decrease From Day 1 in Resting TTE Instantaneous Peak LVOT gradient at the End of Week 4 (Day 28)	Action for MYK-461 Dose Week 5-Week 12^a
< 50%	increase dose to 5 mg
≥ 50%	no change in dose

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

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.

Study Assessments and Procedures:

The efficacy of MYK-461 will be evaluated using TTE and CPET. The primary endpoint will be the change from baseline to Week 12 in post-exercise peak LVOT gradient.

Secondary endpoints include the proportion of subjects achieving a LVOT gradient response of post-exercise peak gradient < 30 mm Hg; change from baseline to Week 12 in the dyspnea symptom score, pVO₂, VE/VCO₂, LVEF (2-dimensional [2D] and 3-dimensional [3D]), global longitudinal strain, and left ventricular fractional shortening (LVFS); and change from Week 12 to Week 16 in post-exercise peak LVOT gradient. The plasma PK profile of MYK-461 is also a secondary endpoint.

Exploratory endpoints include the proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 10 mm Hg; change from baseline to Week 12 in NYHA functional class, NT-proBNP, and KCCQ OSS; change from baseline in arterial pulse wave morphology assessed using an optical biosensor; and change from baseline in heart rate and heart rhythm as assessed using a cardiac monitoring skin patch.

Safety endpoints include treatment-emergent AEs and serious adverse events (SAEs), and changes from baseline in laboratory test results, vital signs, and ECGs. Any abnormal ECG or vital sign finding judged by the investigator to be clinically important will be recorded as an AE.

End of Study

Subjects will be followed through completion of End of Study (EOS) procedures. All AEs, including SAEs and deaths, will be collected for the duration of the study, up to and including the EOS visit.

If there is a significant clinical abnormality or a clinically significant laboratory abnormality in need of monitoring, the subject will be followed until resolution of the abnormality or until it is considered stable in the opinion of the investigator.

Sample Size and Statistical Considerations:

Sample Size:

Approximately 10 subjects will be dosed in Part A and approximately 10 in Part B. The sample size is based on practical considerations and is consistent with this type of study. Ten subjects receiving MYK-461 will provide 80% power to detect a 30 mm Hg difference versus baseline in post-exercise LVOT peak gradient and a > 99% power to detect a 50 mm Hg difference. This assumes a 1-sided $\alpha = 0.05$ and a common standard deviation of 35 mm Hg.

Statistical Analyses:

All efficacy and PD analyses will be performed on the Efficacy/PD Analysis Population, which comprises 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 measured during the on-treatment period.

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). 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 95% confidence interval. Statistical significance of the difference versus baseline will be evaluated at the 1-sided 0.05 level.

The proportion of subjects achieving LVOT gradient responses of < 30 mm Hg and < 10 mm Hg will be summarized at each post-baseline visit. In case of missing data at a given visit, it will be assumed that the subject had not achieved an LVOT gradient response. Quantitative endpoints, including the Dyspnea 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. Data collected from the optical biosensor and cardiac monitoring skin patch will be analyzed descriptively.

Plasma concentrations of MYK-461 will be determined and summarized descriptively.

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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
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
cGMP	Current Good Manufacturing Practices
CPET	cardiopulmonary exercise testing
CRF	case report form
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee; refers to an IRB or IEC or equivalent.
EOS	End of Study
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
FSH	follicle-stimulating hormone
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HCM	hypertrophic cardiomyopathy
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

IMP	investigational medicinal product
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LS	least-squares
LV	left ventricular
LVEF	left ventricular ejection fraction
LVFS	left ventricular fractional shortening
LVOT	left ventricular outflow tract
MAD	multiple ascending-dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model with repeated measures
NASH	nonalcoholic steatohepatitis
NRS	numeric rating scale
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
QD	once daily
QTc	corrected QT interval
QTcF	QTc Fridericia
OSS	overall summary score
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
pVO ₂	peak oxygen uptake
RER	respiratory exchange ratio
SAD	single ascending-dose
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
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
VTI	velocity time integral

1 INTRODUCTION

1.1 Background

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, 2016](#)). 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.

1.2 Clinical Studies

Three clinical studies have investigated the safety and tolerability of MYK-461 to date. A double-blind, placebo-controlled, single ascending-dose study (SAD) (MYK-461-002) was conducted in healthy men. Subjects received single doses ranging from 1 mg to 48 mg. Conduct of an open-label sequential-group SAD study in subjects with clinically stable HCM (MYK-461-001) is also complete; single doses of up to 144 mg were administered. In addition, a double-blind, placebo-controlled, multiple ascending-dose (MAD) study (MYK-461-003) is being conducted in which healthy adult subjects have received multiple doses of MYK-461 up to 25 mg once daily (QD) for up to 28 days.

1.2.1 MYK-461-002

In Study MYK-461-002, single doses from 1 mg to 48 mg were administered as an oral suspension to healthy men. All dose levels were well tolerated, with no serious adverse events (SAEs), deaths, or withdrawals from study due to adverse events (AEs) reported. The incidence of treatment-emergent AEs did not appear to increase with dose. The pharmacokinetic (PK) profile of MYK-461 displayed rapid absorption and subsequent distribution followed by a long elimination phase, with a mean elimination half-life of approximately 8 days. Single doses of ≥ 12 mg of MYK-461 were associated with detectable reductions in LV contractility from baseline as assessed by 3 independent echocardiographic measures (left ventricular ejection fraction [LVEF], LV fractional shortening (LVFS), and LVOT velocity time integral [VTI]). At the highest dose studied in healthy subjects (48 mg), mean reduction in LVEF at any timepoint was -6% relative to baseline. No changes in systolic blood pressure (BP) or heart rate (HR) were detected at any of the dose levels tested in this study.

1.2.2 MYK-461-001

In Study MYK-461-001, single doses of up to 144 mg were administered to 15 subjects with HCM. All dose levels were well tolerated without deaths, withdrawals due to AEs, or dose-related treatment-emergent AEs, except for 1 of 5 subjects who received the 144 mg dose. This subject experienced an SAE described as a vasovagal reaction characterized by a period of asystole and hypotension that spontaneously resolved without sequelae. In terms of causality assessment, there are no nonclinical or other clinical data to implicate MYK-461 in cardiac ion channel current modulation, or cardiac impulse generation or conduction. MYK-461 has no documented vasoactive properties and is biochemically inactive against smooth muscle myosin. Other potential contributions to the event include chronic β -blockade with metoprolol succinate 150 mg QD, and the observation that the subject inadvertently performed the Valsalva maneuver during the handgrip strength assessment immediately prior to the event.

Preliminary PK analysis in Study MYK-461-001 revealed a PK profile in subjects with HCM similar to that of healthy subjects. All subjects with HCM demonstrated proof of mechanism in terms of documenting reduced LV contractility by at least 1 of 3 independent echocardiographic measures. In 2 subjects, measurable LVOT gradients following Valsalva were reduced to < 10 mm Hg following a single 96 mg dose of MYK-461.

1.2.3 MYK-461-003

In Study MYK-461-003, 4 cohorts of healthy adult subjects have been dosed, each scheduled to dose for 28 days. MYK-461 was well tolerated at multiple doses up to 25 mg QD. All AEs were mild or moderate in severity, and there were no SAEs. In cohort 3, 3 of 12 subjects who received blinded treatment (either MYK-461 12.5 mg or placebo QD) had diarrhea and/or abdominal cramps. One of these subjects was discontinued due to recurrence of diarrhea upon rechallenge, and the other 2 subjects were successfully restarted on study medication. The investigator considered these gastrointestinal AEs either mild or moderate in severity

and likely related to study medication. No gastrointestinal AEs were reported in cohort 4 (MYK-461 25 mg or placebo).

Dosing in cohort 4 was stopped on Day 25 by the investigator, because 5 of 12 subjects who received blinded treatment (either MYK-461 25 mg or placebo QD) achieved the predefined stopping criterion for dose ascension of $\geq 20\%$ reduction in LVEF. All subjects remained asymptomatic.

PD evidence of reduced contractility was apparent in the higher dose-level groups (12.5 mg QD and 25 mg QD). These data, along with the PK and PD data from all subjects in all studies to date, have been incorporated into a robust PK-PD model to help inform a safe dosing strategy for the current study that is also likely to be efficacious.

1.3 Known and Potential Benefits and Risks

Potential clinical benefit for the subjects who participate in this study is unclear at this stage of development.

Little is known regarding the risks of administering repeat daily doses of MYK-461 to humans. Of 3 clinical studies with MYK-461 ([Section 1.2](#)), conduct of 2 single-dose studies is complete (one in healthy subjects and one in subjects with HCM), and conduct of 1 multiple-dose study in healthy subjects is complete. Doses higher than 25 mg QD are not planned in the current study, as this was the highest dose tested to date in the repeat-daily-dose study in healthy subjects. In that study, 5 of 12 subjects who received blinded treatment (MYK-461 25 mg or placebo QD) for 25 days exceeded the prespecified 20% relative decrease from baseline in LVEF, which precluded further dose escalation in that healthy subject study. Single doses up to 48 mg were well tolerated in 36 healthy adult subjects. Single doses of up to 144 mg were administered to subjects with HCM; 1 of 5 subjects who received 144 mg experienced a vasovagal reaction characterized by a period of asystole and hypotension that spontaneously resolved in the setting of a reduction in LVEF that also satisfied the prespecified stopping rules ($> 20\%$ relative reduction) for further dose escalation in that study.

Safety testing in other mammalian species has demonstrated that dose-limiting toxicity is related to exaggerated pharmacologic effect, and not to off-target adverse effects. Experiments with isolated adult rat ventricular myocytes in vitro and with anesthetized rats in vivo have established that the pharmacological effects of MYK-461 can be counteracted by β -adrenergic agonists (isoproterenol and dobutamine, respectively).

2 RATIONALE FOR THE STUDY AND FOR DOSE AND DOSING SCHEDULE

2.1 Rationale for the Study

MyoKardia has studied MYK-461 extensively across a variety of pharmacological activity and nonclinical safety evaluation platforms. In clinical studies ([Section 1.2](#)), single doses of MYK-461 up to 48 mg were well tolerated in healthy subjects (MYK-461-002), and single doses of up to 144 mg have been well tolerated (except for a vasovagal reaction with asystole and hypotension in 1 of 5 subjects at the 144 mg dose) in a study in subjects with HCM (MYK-461-001). Daily doses of 25 mg were well tolerated clinically in healthy subjects for a period of 25 days, after which time dosing was suspended by the investigator secondary to concerns regarding the degree of pharmacological activity observed (MYK-461-003). The predefined stopping criterion for dose escalation (reduction in LVEF by $\geq 20\%$) was satisfied in both the single-dose study (MYK-461-001) at 144 mg and in the 28-day multiple-dose study (MYK-461-003) at 25 mg QD.

MyoKardia has designed the current study to generate multiple-dose (steady-state) data in subjects with obstructive, symptomatic HCM using an approach that conforms to established ethical standards of safe human experimentation and the requirements of Good Clinical Practice (GCP).

2.2 Rationale for Dose and Dosing Schedule

Part A

The starting dose of MYK-461 will be 10 mg for subjects who weigh ≤ 60 kg and 15 mg for subjects who weigh > 60 kg. Each subject will receive oral MYK-461 at the starting dose QD from Day 1 through Week 4. At Week 4, an individual subject's daily dose may be decreased by 5 mg, increased by 5 to 10 mg, or remain the same based on predetermined criteria (see [Section 4](#)). The subject will subsequently receive that dose from Week 5 through Week 12. The dose selection was based on PK/PD modeling and analysis of PD and safety data from all 3 MYK-461 clinical studies (MYK-461-001, MYK-461-002, and MYK-461-003).

Part B

The starting dose of MYK-461 in Part B will be 2 mg. The dose selected for this part is intended to describe the dose and concentration response for gradient reduction and exercise tolerance at lower drug exposures than those achieved in Part A. An individual subject's daily dose may be increased to 5 mg based on predetermined criteria (see [Section 4](#)). The subject will subsequently receive that dose from Week 5 (day 29) through Week 12.

3 STUDY OBJECTIVES

3.1 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

3.2 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 in subjects with symptomatic HCM and LVOT obstruction
- To assess the effects of 12 weeks of MYK-461 treatment on dyspnea symptom score, peak oxygen uptake (pVO_2), and volume expired (VE)/carbon dioxide production (VCO_2) slope in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the PK of MYK-461 in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the PD of MYK-461 in subjects with symptomatic HCM and LVOT obstruction as assessed by a variety of echocardiographic imaging parameters in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the safety and tolerability of MYK-461 in subjects with symptomatic HCM and LVOT obstruction
- To evaluate the posttreatment reversibility of the effects of MYK-461 after 4 weeks of washout in subjects with symptomatic HCM and LVOT obstruction

3.3 Exploratory Objectives

The exploratory objectives of this study are:

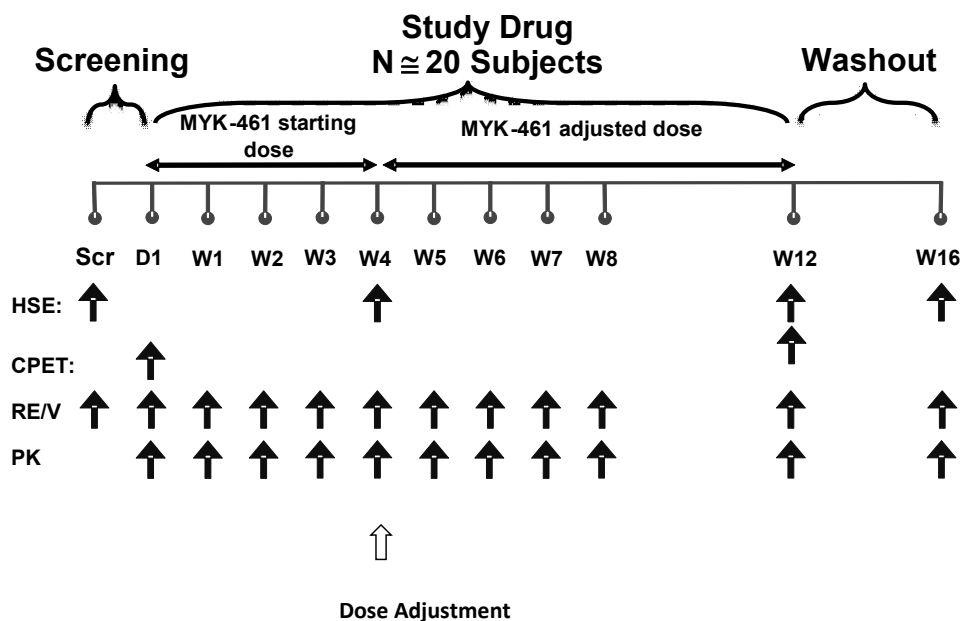
- To assess the proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient < 10 mm Hg in subjects with symptomatic HCM and LVOT obstruction
- To assess the effects of 12 weeks of MYK-461 treatment on New York Heart Association (NYHA) functional class, N-terminal pro B-type natriuretic peptide (NT-proBNP), and the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score (OSS) in subjects with symptomatic HCM and LVOT obstruction

- To assess the effects of MYK-461 treatment on arterial pulse wave morphology assessed using an optical biosensor in subjects with symptomatic HCM and LVOT obstruction
- To assess the effect of MYK-461 treatment on heart rate and heart rhythm as assessed using a cardiac monitoring skin patch in subjects with symptomatic HCM and LVOT obstruction

4 OVERALL STUDY DESIGN AND PLAN

This is a 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).

Figure 1 Study Schema



CPET, cardiopulmonary exercise training; D, day; HSE, hemodynamic stress echocardiography; N, number PK, pharmacokinetic sample; RE/V, resting echocardiography/Valsalva; W, week

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 ECGs at 1 hour postdose. Subjects will then be supplied with MYK-461 sufficient for 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 \leq 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 \leq 60 kg and 15 mg for subjects who weigh $>$ 60 kg. At the end of Week 4 (Day 28), each subject's 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 1 Part A Week 4 Dose Adjustment Criteria

Percent Decrease From Baseline in LVEF at the End of Week 4 (Day 28)	Action for MYK-461 Dose Week 5-Week 12 ^a
< 10	increase dose by 10 mg
\geq 10 and < 15	increase dose by 5 mg
\geq 15 and < 20	no change in dose
\geq 20	decrease dose by 5 mg

LVEF, left ventricular ejection fraction

^b 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.

Table 2 Part B Week 4 Dose Adjustment Criteria

Percent Decrease From Day 1 in Resting TTE Instantaneous Peak LVOT gradient at the End of Week 4 (Day 28)	Action for MYK-461 Dose Week 5-Week 12 ^a
< 50%	increase dose to 5 mg
≥ 50%	no change in dose

; LVOT, left ventricular outflow tract;

^a No dose increase allowed if plasma concentration of MYK-461 > 300 ng/mL at Week 2.

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.

4.1 Study Duration

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.

4.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will regularly review study data. The role of the IDMC will be to help identify and manage any emerging safety issues, advise the investigators and Sponsor on any important emerging study conduct issues, and serve in an advisory role concerning the evaluation procedures and methodologies being employed to survey and detect potential safety signals.

5 SELECTION AND WITHDRAWAL OF STUDY POPULATION

5.1 General Study Population and Clinical Sites

Approximately 20 subjects with symptomatic HCM and LVOT obstruction are expected to enroll in this study at 7 clinical sites in the United States (US).

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure.
2. Men or women 18 to 70 years of age at the Screening visit.
3. Diagnosed with HCM (hypertrophied and non-dilated left ventricle in absence of systemic or other known cause), with LV wall thickness ≥ 15 mm at time of initial diagnosis or ≥ 13 mm with a positive family history of HCM.
4. Body mass index (BMI) 18 to 37 kg/m², inclusive, at the Screening visit, calculated using the institution's standard formula.
5. All safety laboratory parameters (chemistry, hematology, and urinalysis) within normal limits (laboratory reference range) at the Screening visit as assessed by the central laboratory, or if outside of the limits must meet both of the following criteria:
 - considered by the investigator to be clinically unimportant
 - if a liver function test result, must be $< 1.5 \times$ the upper limit of the laboratory reference range.
6. Has documented LVEF $\geq 55\%$ at the Screening visit as determined by the investigator and the investigational site's echocardiography laboratory.
7. Resting LVOT gradient ≥ 30 mmHg and post-exercise peak LVOT gradient ≥ 50 mm Hg at the Screening visit as determined by the investigator and the investigational site's echocardiography laboratory.
8. NYHA functional class II or higher, judged by the investigator to be due to LVOT obstruction.
9. Has adequate acoustic windows, in the judgment of the investigator and the investigational site's echocardiography laboratory, to enable accurate TTEs.
10. Female subjects must not be pregnant or lactating and, if sexually active, must be using one of the following acceptable birth control methods from the Screening visit through 3 months after the last dose of investigational medicinal product (IMP). Hormonal contraceptives are not considered highly effective contraception for this study because MYK-461 could reduce the effectiveness of hormonal contraceptives.
 - Double-barrier method (e.g., vasectomy or male using a condom and female using a diaphragm or cervical cap)

- Barrier (e.g. male using a condom) plus non-hormonal intrauterine device (IUD) or intrauterine system (IUS)
 - Female is surgically sterile for 6 months or postmenopausal for 2 years. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to Screening. Females are considered postmenopausal if they have had amenorrhea for at least 2 years or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
11. Male subjects with female partners (including postmenopausal partners) must agree to use highly effective contraceptive measures from the Screening visit through 3 months after the last dose of study medication. Highly effective contraception includes documented vasectomy, abstaining from sexual intercourse, double-barrier method (e.g., male using a condom and female using a diaphragm or cervical cap), or barrier plus hormonal contraception (e.g., male using a condom and female using hormonal contraception). As there may be a risk of drug being secreted in the ejaculate, male subjects (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and for 3 months after the last dose of study medication. In addition, male subjects with sexual partners should use condoms for the duration of the study and for 3 months after the last dose of study medication, even if the partner is not pregnant or capable of becoming pregnant, in order to prevent passing MYK-461 to the partner in the ejaculate.
12. Must be able to complete the Dyspnea Numeric Rating Scale (NRS) and the KCCQ per established guidelines.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Hypersensitivity to MYK-461 or any of the components of the MYK-461 formulation.
2. Presence of any medical condition that precludes exercise stress testing.
3. History of sustained ventricular tachyarrhythmia.
4. History of syncope with exercise within past 6 months.
5. Active infection.
6. Persistent atrial fibrillation or atrial fibrillation at Screening or history of paroxysmal atrial fibrillation with resting rate documented >100 bpm within 1 year of screening.
7. Has QTc Fridericia (QTcF) > 500 ms, or any other ECG abnormality considered by the investigator to pose a risk to subject safety (e.g., second degree atrioventricular block type II).
8. Aortic stenosis or fixed subaortic obstruction.
9. History of LV systolic dysfunction (LVEF < 45%) at any time during their clinical course.

10. History of obstructive coronary artery disease (stenosis of >70% of luminal diameter in one or more coronary arteries).
11. History of malignancy of any type, with the following exceptions: in situ cervical cancer more than 5 years prior to Screening or surgically excised non-melanomatous skin cancers more than 2 years prior to Screening.
12. Positive serologic test at Screening for infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
13. Positive test for alcohol or drugs of abuse at Screening.
14. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or MyoKardia physician, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
15. Participated in a clinical trial where the subject received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening, or at least 5 times the respective elimination half-life (whichever is longer).
16. Current use of tobacco- or nicotine-containing products exceeding 10 cigarettes per day or equivalent.
17. Part A: Subjects who in the opinion of the investigator require ongoing therapy with β -blockers, calcium channel blockers, or disopyramide. Subjects on any of these medications who, in the opinion of the investigator, can safely be withdrawn are eligible as long as medication is discontinued at least 14 days prior to the Screening visit.
18. Part B: Subjects who in the opinion of the investigator require ongoing therapy with calcium channel blockers or disopyramide. Subjects on any of these medications who, in the opinion of the investigator, can safely be withdrawn are eligible as long as medication is discontinued at least 14 days prior to the Screening visit. Prior treatment with cardiotoxic agents such as doxorubicin or similar, or current treatment with antiarrhythmic drugs that have negative inotropic activity, e.g., flecainide or propafenone.
19. Unable to comply with the study restrictions/requirements, including the number of required visits to the clinical site.
20. Is employed by, or is a relative of someone employed by MyoKardia, the investigator, or his/her staff or family.

5.4 Screening and Enrollment

An informed consent form (ICF) must be signed and dated by the subject before the subject is asked to discontinue HCM background therapy and before any study-specific tests or procedures may be performed.

Each subject will be assigned an identification number when informed consent has been obtained. This number will be used to identify the subject throughout the study and should appear on all study-related documentation.

Subjects that fail to meet all inclusion criteria or present with an exclusion criterion may be re-screened. Refer to Study Reference Manual for re-screening criteria.

5.5 Withdrawal and Replacement of Subjects

5.5.1 *Withdrawal from the Study*

Study participants may withdraw from further participation in the study at any time and for any reason. The degree to which a study participant withdraws can vary, and efforts will be made to collect important safety data if feasible and the study participant agrees. Study participants can:

- Withdraw from treatment and agree to participate in the Early Termination and End of Study (EOS) visits
- Withdraw from treatment and agree to participate in the Early Termination visit
- Withdraw from treatment and all follow-up

The investigator or MyoKardia may withdraw a study participant from treatment in the study for any of the following (or other) reasons:

- AE
- Noncompliance with study procedures/restrictions
- Study termination by MyoKardia

In all cases, the reason(s) for study withdrawal will be recorded in the source document and on the appropriate electronic case report form (eCRF).

5.5.2 *Replacement of Subjects*

Subjects who do not receive MYK-461 may be replaced. Subjects who drop out of the study for reasons other than AEs after receiving study medication may be replaced at the discretion of MyoKardia.

All data from subjects who receive at least 1 dose of IMP will be documented and maintained in the clinical trial database.

6 RANDOMIZATION AND BLINDING PROCEDURES

6.1 Randomization

Subjects will not be randomized to treatment in this study.

6.2 Blinding

Treatment will not be blinded in this study.

7 STUDY TREATMENT

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

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).

7.1 MYK-461, Administration, and Schedule

Study medication will consist of MYK-461 immediate release oral tablets, supplied in 4 strengths: 2 mg, 5 mg, 10 mg, and 20 mg. MYK-461 tablets are uncoated and plain and white in appearance. The 2 mg and 5 mg tablets are round-convex in shape and of different sizes, while the 10 mg and 20 mg tablets are oval shaped of different sizes.

MYK-461 tablets are manufactured according to current Good Manufacturing Practice (cGMP) regulations. They will be supplied in high-density polyethylene bottles with induction seals and child resistant caps at 30 count per bottle. All study medication will be labeled according to applicable local regulatory guidelines.

The MYK-461 tablets must be stored at controlled room temperature at 20°C to 25°C (68°F to 77°F) in the packaging supplied by MyoKardia. Study medication at the investigational site will be stored in a secure area with access limited to authorized study personnel.

IMP will be supplied to subjects at least every 4 weeks in 30-count high-density polyethylene bottles that are appropriately labeled, with written instructions for daily dosing. The subjects will be instructed to store the MYK-461 tablets/bottles in a cool dry place. Drug should be taken with approximately 8 ounces of water.

7.2 Treatment Compliance

All subjects will return their IMP dosing containers, including unused study medication, to the site for tablet counts. Refer to the Pharmacy Manual for details.

Subjects should be instructed to take the study medication at approximately the same time every day (\pm 4 hours). If the dosing window is missed, the subject should not take study medication that day. Subjects should never receive 2 doses of MYK-461 within a 12-hour period.

On study visit days, subjects should wait until they reach the clinic to take their study medication.

7.3 Dose Adjustment

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 4, Table 1 \(Part A\) and Table 2 \(Part B\)](#). The subject will subsequently receive that dose from Week 5 (Day 29) through Week 12.

7.4 Hepatotoxicity Stopping and Rechallenge Rules

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 below (as specified in the US Food and Drug Administration (FDA) Guidance for Industry–Drug Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

7.4.1 *Criteria for Permanent Withholding of MYK-461 Due to Potential Hepatotoxicity*

MYK-461 should be discontinued permanently and the subject should be followed according to the recommendations in [Appendix 3](#) for possible drug-induced liver injury (DILI), if all of the criteria below are met:

- $TBL > 2 \times$ upper limit of normal (ULN) or international normalized ratio > 1.5
- AND increased AST or ALT, if the baseline value was $< ULN$ and AST or ALT elevation is $> 3 \times ULN$
- AND no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to the following:
 - obstructive gall bladder or bile duct disease
 - viral or alcoholic hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella)
 - hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
 - concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir, irinotecan) or herbal or dietary supplements
 - heritable disorders causing impaired glucuronidation (e.g., Gilbert syndrome); α -1 antitrypsin deficiency
 - autoimmune hepatitis
 - nonalcoholic steatohepatitis (NASH) or other “fatty liver disease”

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what is noted above, determine whether study medication and other protocol-required therapies should be permanently or temporarily discontinued based on subject population and/or severity of the hepatotoxicity or event, as deemed appropriate for the safety of the subject.

7.4.2 *Criteria for Conditional Withholding of MYK-461 Due to Potential Hepatotoxicity*

For subjects who do not meet the criteria for permanent withholding of study medication outlined above, MYK-461 should be withheld if ANY of the following criteria are met, and the subject should be evaluated for DILI:

- Elevation of either AST or ALT, regardless of baseline AST or ALT value, if:
 - $> 8 \times \text{ULN}$ at any time
 - $> 5 \times \text{ULN}$ and $< 8 \times \text{ULN}$ for ≥ 2 weeks
 - $> 5 \times \text{ULN}$ and $< 8 \times \text{ULN}$ and unable to adhere to enhanced monitoring schedule
- OR: clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia $> 5\%$). If such signs or symptoms are coupled with ALT or AST elevations $> 3 \times \text{ULN}$, study medication should be withheld.
- OR: TBL $> 3 \times \text{ULN}$ at any time
- OR: ALP $> 8 \times \text{ULN}$ at any time

MYK-461 should be withheld pending investigation into alternative causes of DILI. If study medication is withheld, the subject should be followed according to recommendations in [Appendix 3](#) for possible DILI. Rechallenge may be considered if an alternative cause, such as acute hepatitis B infection, is discovered and the laboratory abnormalities resolve to normal or baseline ([Section 7.4.3](#)).

7.4.3 *Criteria for Rechallenge of MYK-461 After Potential Hepatotoxicity*

The decision to rechallenge the subject should be discussed and unanimously agreed by the investigator, IDMC, and Sponsor.

If signs or symptoms recur with rechallenge, then MYK-461 should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in [Section 7.4.1](#)) should never be rechallenged.

7.5 *Guidelines for the Management of an Exaggerated Pharmacologic Effect*

Beta-adrenergic agonists are known to counteract the pharmacologic activity of MYK-461 in nonclinical studies. If a subject experiences AEs potentially related to reduced cardiac output,

administration of therapeutic doses of a β -adrenergic agonist (e.g., 5 to 10 $\mu\text{g}/\text{kg}/\text{min}$ dobutamine infusion) should be considered. Additional supportive measures, e.g., intravenous volume supplementation and/or the use of arterial vasoconstrictor agents (α -adrenergic agonists) may complement the use of a β -adrenergic agonist. Aside from this specific advice regarding the role of a β -adrenergic agonist, appropriate care will be determined by the treating medical personnel.

7.6 Overdose

There is no human overdose experience with MYK-461. The consequences of higher exposures achieved in nonclinical species are directly related to the pharmacologic activity of MYK-461, and consideration of interventions that might ameliorate the effects of unintentionally high exposures in human subjects provide the available guidance in suspected overdose.

Experiments with isolated adult rat ventricular myocytes in vitro and with anaesthetized rats in vivo have established that the pharmacologic effects of MYK-461 can be counteracted by β -adrenergic agonists (isoproterenol and dobutamine, respectively). The ability of dobutamine (10 $\mu\text{g}/\text{kg}/\text{min}$ by continuous intravenous infusion) to counteract the effects of MYK-461 in the rat was fully effective up to exposures causing a 60% reduction in cardiac contractility. Beyond this level of effect, dobutamine was only partially effective in counteracting the effects of MYK-461. There are no known direct-acting antidotes.

In the event of dosing resulting in suspected overexposures (subsequently documented based on PK sampling, which may be assessed at a scheduled or unscheduled visit) that do not appear to be well tolerated, the subject should be closely monitored clinically with supportive measures undertaken as indicated, including initiation of inotropic support with dobutamine and/or α -adrenergic agonists and other supportive measures, in a suitably well-monitored, acute-care environment.

It is unknown whether MYK-461 can be safely removed by dialysis. Attempts to employ these measures should be avoided until more information is available.

7.7 Prior and Concomitant Treatment

7.7.1 Prior Therapy

At the time of signing the ICF, subjects will be asked about their medication history over the previous 30 days, including prescription and nonprescription medications, herbal medications, vitamins, and minerals.

If subjects have not taken any prohibited medications in the past 14 days they may proceed to Screening. Subjects taking prohibited medications must discontinue treatment for 14 days before proceeding to the Screening assessments.

7.7.2 Concomitant Therapy

Document all concomitant therapies on the appropriate eCRF, whether prescription or over-the-counter, vitamin and/or mineral supplements, herbs, and medications taken for an event or procedure (e.g., biopsy). Include start/stop dates, route and indication.

7.7.3 Prohibited Therapy

Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar is prohibited, as is prior or concomitant treatment with antiarrhythmic drugs with negative inotropic activity, e.g., flecainide or propafenone.

Part A: Use of β -blockers, calcium channel blockers, and disopyramide are prohibited within 14 days of the Screening visit and throughout the study.

Part B: Use of calcium channel blockers and disopyramide are prohibited within 14 days of the Screening visit and throughout the study. Subjects enrolled in Part B may be on a stable dose of β -blockers (for at least 14 days before Screening) and should remain on a stable dose throughout the study.

8 RISKS AND PRECAUTIONS

8.1 General

Little is known regarding the risks of administering repeat daily doses of MYK-461 to humans. Of 3 clinical studies with MYK-461 ([Section 1.2](#)), conduct of 2 single-dose studies is complete (one in healthy subjects and one in subjects with HCM), and 1 multiple-dose study is ongoing in healthy subjects. Doses higher than 25 mg QD are not planned in the current study, as this was the highest dose tested to date in the repeat-daily-dose study in healthy subjects. In that study, 3 of 10 subjects treated with 25 mg QD for 25 days exceeded the prespecified 20% relative decrease from baseline in LVEF, which precluded further dose escalation in that healthy subject study. Single doses up to 48 mg were well tolerated in 36 healthy adult subjects. Single doses of up to 144 mg were administered to subjects with HCM; 1 of 5 subjects who received 144 mg experienced a vasovagal reaction characterized by a period of asystole and hypotension that spontaneously resolved in the setting of a

reduction in LVEF that also satisfied the prespecified stopping rules (> 20% relative reduction) for further dose escalation in that study.

Safety testing in other mammalian species has demonstrated that dose-limiting toxicity is related to exaggerated pharmacological effect, and not to off-target adverse effects. Experiments with isolated adult rat ventricular myocytes in vitro and with anesthetized rats in vivo have established that the pharmacological effects of MYK-461 can be counteracted by β -adrenergic agonists (isoproterenol and dobutamine, respectively).

8.2 Pregnancy

8.2.1 Avoidance of Pregnancy

Women of childbearing potential must use appropriate methods of birth control as listed in [Section 8.2.3](#). Women of non-childbearing potential are defined as women who are permanently (surgically) sterilized or are postmenopausal. Permanent sterilization includes hysterectomy, bilateral oophorectomy, and bilateral tubal occlusion or ligation at least 6 months prior. Women are considered postmenopausal if they have had amenorrhea for at least 2 years or more following cessation of all exogenous hormonal treatments and FSH levels are in the postmenopausal range.

8.2.2 Restrictions for Male Subjects

There is no information about effects that MYK-461 could have on the development of the fetus in humans. Therefore, it is important that the partners of male subjects do not become pregnant during the study and for a total period of 3 months after the male subject has taken the last dose of study medication. As a precaution, all male subjects should avoid fathering a child by using appropriate methods of birth control, as listed in [Section 8.2.3](#), for the duration of the study and for 3 months after the last dose of study medication. This is to ensure that the fetus is not potentially exposed to the study medication in the ejaculate.

In addition, male subjects with partners should use condoms for the duration of the study and for 3 months after the last dose of study medication, even if the partner is not pregnant or capable of becoming pregnant, in order to prevent passing MYK-461 to the partner in the ejaculate.

Male subjects should be advised not to donate sperm for 3 months after the last dose of study medication.

8.2.3 Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those that result in a low failure rate (< 1% per year) when used consistently and correctly. Hormonal contraceptives are not considered highly effective contraception for this study because MYK-461 could reduce the effectiveness of hormonal contraceptives. From the time of Screening through 3 months after the last dose of study medication, subjects should practice true abstinence or use effective means of contraception as follows:

- Double-barrier method (e.g., vasectomy or male using a condom and female using a diaphragm or cervical cap)
- Barrier (e.g. male using a condom) plus non-hormonal intrauterine device (IUD) or intrauterine system (IUS)
- Female is surgically sterile or postmenopausal as defined in [Section 8.2.1](#).

For male subjects only (but not partners of female subjects), documented vasectomy is also an accepted method of birth control.

8.2.4 *Reporting and Follow-up of Pregnancies*

All pregnancies in female subjects and female partners of male subjects receiving at least 1 dose of study medication will be reported if they occur anytime from first dose to 3 months after the last dose of study medication. The investigator is responsible for informing MyoKardia of the pregnancy. The subject will be asked to provide information on the outcome of the pregnancy, including premature termination. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

9 **STUDY ASSESSMENTS AND PROCEDURES**

The investigator is responsible for ensuring that all staff involved in the study are familiar and comply with the content of this section.

The following describes the study procedures to be performed during the study. Additional details are provided in [Appendix 1](#) of this document. When several assessments are to be conducted at the same timepoint, the preferred order of assessments is ECG, vital signs, laboratory assessments (including PK), then TTE. The order of assessments may vary slightly at specific timepoints (e.g., 1 hour postdose) to facilitate the most contemporaneous performance of the required assessments. Unscheduled or additional safety assessments may be performed if necessary in the opinion of the investigator.

For assessments that require the subjects to be in a semi-recumbent or supine position, assessments should be conducted with subjects in the same position at all timepoints.

9.1 **Efficacy and Pharmacodynamic Assessments**

9.1.1 *Echocardiography and Cardiopulmonary Exercise Testing*

Details are provided in the Study Reference Manual. Echocardiography and CPET should be performed prior to dosing. All echocardiography data will be sent to a central imaging laboratory. CPET data will also be sent to a central laboratory.

9.1.1.1 Resting Transthoracic Echocardiography

Resting TTE will be assessed throughout the study. Instantaneous peak LVOT gradient (baseline) and provoked peak LVOT gradient (Valsalva maneuver) will be assessed. Ejection fraction (2-dimensional [2D] and 3-dimensional [3D]), LVFS, global longitudinal strain by speckle tracking, and LVOT VTI will be analyzed, along with a variety of other echocardiographic measures (see Study Reference Manual).

Resting TTE should be performed prior to hemodynamic stress echocardiography or CPET.

9.1.1.2 Hemodynamic Stress Echocardiography

Subjects will undergo a standard symptom-limited exercise test (hemodynamic stress echo) after a 4-hour fast (water is allowed) at designated visits ([Appendix 1](#)). Instantaneous peak LVOT gradient will be assessed immediately post-exercise by TTE.

9.1.1.3 Cardiopulmonary Exercise Testing

CPET and exercise ECGs will be conducted using a treadmill at designated visits ([Appendix 1](#)). Symptom-limited exercise tests will be performed after a 4-hour fast (water is allowed). Subjects will be encouraged to perform maximally to achieve their expected HR. The following will be assessed: oxygen uptake (VO_2), VCO_2 , VE, VE/VO_2 , VE/VCO_2 , and respiratory exchange ratio (RER).

9.1.2 *Dyspnea Numeric Rating Scale*

The Dyspnea NRS is a validated measure of present dyspnea ([Gift and Narsavage, 1998](#)). Patients rate their shortness of breath by designating a number from 0 to 10, with 0 being “no shortness of breath” and 10 being “shortness of breath as bad as can be.”

9.1.3 *Kansas City Cardiomyopathy Questionnaire*

The KCCQ is a self-administered 23-item questionnaire that quantifies physical limitation, symptoms, quality of life, social interference, and self-efficacy ([Green et al, 2000](#)). The OSS is derived from the physical limitation, symptom, quality of life, and social interference domains. Scores range from 0 to 100, with higher scores reflecting better health status.

9.1.4 *New York Heart Association Class*

The NYHA functional classification of heart failure assigns patients to 1 of 4 categories based on the patient’s symptoms and objectives assessments ([Table 3](#)).

Table 3 **New York Heart Association (NYHA) Functional Classification of Heart Failure**

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.VrtuzPkrKU1

9.1.5 ***Exploratory Assessments***

9.1.5.1 **Pulse Wave Optical Biosensor**

An experimental noninvasive optical biosensor resembling a wristwatch may be fastened to the subject's wrist for several minutes to collect data on arterial pulse wave morphology. This assessment is optional and will be performed only if the subject provides consent.

9.1.5.2 **Cardiac Monitoring Skin Patch**

Throughout the study, subjects will wear a small data collection device that is FDA-approved for collecting HR and rhythm data. The self-contained device attaches to the skin using medical adhesive and contains 2 surface electrodes, internal electronics to capture a continuous single-lead ECG waveform, an accelerometer to capture physical activity, sufficient solid-state memory to store up to 14 days' data, and a battery to power the device. It has no external wires or other connections. Following a period of data collection, the device will be transported to a core laboratory where the continuous ECG waveforms and activity record stored on the device will be uploaded for analysis. The analysis will provide full disclosure capabilities for HR, heart rhythm, and physical activity over the period during which the device was properly applied and functioning. The device will be used to explore the pattern of HR, heart rhythm, and physical activity before, during, and after treatment with MYK-461.

9.2 Pharmacokinetic, Pharmacogenetic, and Biomarker Assessments

9.2.1 Pharmacokinetic Assessments

Blood samples will be collected for PK assessments at all post-Screening visits. Plasma concentrations of MYK-461 will be evaluated. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor.

At all visits from Day 1 to Week 12 (inclusive), MYK-461 will be administered at the investigational site to facilitate collection of PK samples \leq 2 hours prior to dosing.

9.2.2 Genotype/Pharmacogenetic/Biomarker Assessment

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.

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.

9.3 Safety Assessments

Safety will be assessed throughout the study. Safety assessments include medical history, physical examinations, ECGs, vital signs, observed and subject-reported AEs, and safety laboratory results.

Any abnormal findings judged by the investigator to be clinically important will be recorded as an AE.

9.3.1 Medical History

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).

9.3.2 *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.

Height (cm) and body weight (kg) will be measured at Screening, and BMI (kg/m^2) will be calculated. Subjects will be required to remove their shoes and wear clothing as specified by the clinical site.

9.3.3 *12-Lead ECG*

Triplicate 12-lead ECG evaluations will be performed after 10 minutes of rest at Screening and at all study visits. All ECG data will be sent to a central cardiac laboratory.

On Day 1, ECG will be performed within 2 hours predose and at 1 hour postdose. At all other visits, ECGs will be taken prior to dosing.

The investigator will judge the overall interpretation as normal or abnormal with clinical significance. Only the overall evaluation (normal/abnormal) will be recorded in the eCRF. The investigator will review the ECG and correlate abnormal findings with any other clinical findings, subject's medical history, and laboratory data to determine the clinical importance of the finding.

The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be recorded as an unscheduled assessment.

9.3.4 *Vital Signs*

Vital signs, to be assessed at each study visit, include temperature, HR, respiratory rate, and 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. Alert values ([Section 7.3](#)) will be flagged. Refer to the Study Reference Manual for additional details.

9.3.5 *Other Safety Assessments*

Refer to [Section 10](#) for information on AE assessment and [Section 7.7](#) for concomitant therapy assessments.

Safety laboratory results will be assessed in an ongoing manner. A central safety laboratory will be used. Laboratory parameters are provided in [Appendix 2](#).

9.4 Subject Restrictions During This Study

The following restrictions apply for the specified times during the study period. If a subject does not comply with these restrictions or tests positive in any laboratory tests (e.g., drug, alcohol, pregnancy), they may be excluded or withdrawn from the study.

- Starting 72 hours prior to the first dose until the final follow-up visit, subjects should not engage in unaccustomed intensive exercise except during protocol-specified exercise tests.
- Starting at Screening, subjects will be required to abstain from blood or plasma donation until 3 months after the final study visit.
- Starting on Day 1 until the final follow-up visit, subjects will be asked to abstain from alcohol, grapefruit or grapefruit juice, Seville oranges, and quinine (e.g., tonic water).
- Contraception requirements are discussed in [Section 8.2](#).

9.5 Study Procedures by Visit

This section lists study procedures by visit. Every effort should be made to avoid protocol deviations.

After providing written informed consent, potential subjects will undergo screening procedures to confirm eligibility to participate in the study. The investigator or appropriately trained designee will perform the screening procedures within 28 days prior to Day 1 (administration of MYK-461). All results from the screening procedures needed to evaluate study eligibility, including safety laboratory results, must be available prior to the administration of study medication.

9.5.1 Screening (Day -28 to Day -1)

- Informed consent
- Medical history; includes participation in prior investigational clinical studies (IMP and/or device or other therapy)
- Withdraw subject from β -blockers (Part A Only), calcium channel blockers (Part A and B), or disopyramide (Part A and B) as necessary, at least 14 days prior to further Screening assessments.
- Complete physical examination; includes neurological examination, height, and weight
- 12-lead ECG (triplicate)

- Vital signs: temperature, HR, respiratory rate, and BP after resting for at least 5 minutes
- Blood samples for
 - Hematology and serum chemistry
 - FSH testing for postmenopausal women to confirm FSH is in the postmenopausal range
 - Hepatitis panel and HIV test
 - Thyroid stimulating hormone (TSH) test
 - Testing for drugs of abuse
- Urine sample for urinalysis
- Alcohol test based on standard at institution
- Pregnancy test (blood or urine) for women of childbearing potential, based on standard at institution
- Full resting TTE
- Hemodynamic stress echocardiography after 4 hour fast
- Prior and concomitant therapy assessment
- Assessment of NYHA class
- AE assessment (pretreatment symptoms that are an ongoing medical condition are recorded with the medical history, and signs and/or symptoms associated with a study procedure are recorded as an AE)
- Apply cardiac monitoring skin patch
- Optical biosensor pulse wave analysis (consenting subjects)

9.5.2 *Day 1*

Complete the following procedures before administering the oral dose of study medication.

- Complete physical examination; includes neurological examination and weight
- 12-lead ECG (triplicate) within 2 hours predose
- Vital signs after resting for at least 5 minutes
- Pregnancy test (blood or urine) for women of childbearing potential, based on standard at institution
- Full resting TTE

- CPET after a 4-hour fast (water is allowed)
- Blood samples for
 - Hematology and serum chemistry
 - HCM genotyping (consenting subjects)
 - Potential future exploratory pharmacogenetic analysis (consenting subjects)
 - Potential exploratory biomarker analysis
 - NT-proBNP
 - PK, within ≤ 2 hours prior to dosing
- Urine sample for urinalysis
- Concomitant therapy assessment
- AE assessment (pretreatment symptoms that are an ongoing medical condition are recorded with the medical history and signs, and/or symptoms associated with a study procedure are recorded as an AE)
- Dyspnea NRS
- KCCQ
- Verify subject remains eligible
- Retrieve previous cardiac monitoring skin patch and apply a new one
- Optical biosensor pulse wave analysis (consenting subjects)

Open-label administration of MYK-461 at site.

Complete the following procedures postdose (when indicated, timing of assessments is approximate):

- Resting vital signs at 1 hour postdose
- 12-lead ECG (triplicate) at 1 hour postdose
- AE assessment

9.5.3 Day 4

- Contact subject via telephone to determine the subject's status and ascertain whether the subject is experiencing any AEs. Information on concomitant medications should also be collected.

9.5.4 Weeks 1, 2, 3, 4, 5, 6, 7, and 8

Complete the following procedures before administering the oral dose of study medication.

- Abbreviated cardiopulmonary physical examination, with other systems assessed as directed by interval history
- 12-lead ECG (triplicate)
- Vital signs after resting for at least 5 minutes
- Resting TTE
- Hemodynamic stress echocardiography (Week 4 only) after 4 hour fast
- Blood samples for
 - hematology, serum chemistry (Weeks 4 and 8 only)
 - NT-proBNP (Weeks 4 and 8 only)
 - PK, within ≤ 2 hours prior to dosing
- Pregnancy test (blood or urine) for women of childbearing potential, based on standard at institution (Weeks 4 and 8 only)
- Retrieve previously applied cardiac monitoring skin patch (Weeks 2, 4, 6, and 8 only) and apply a new patch. At Week 8 only, the subject should be provided with an additional patch to be applied at Week 10.
- Optical biosensor pulse wave analysis (consenting subjects) (Weeks 1, 2, 4, and 8 only)
- Concomitant therapy assessment
- AE assessment
- Dyspnea NRS
- Study medication compliance
- Potential dose adjustment (Week 4 only)
- Open-label MYK-461 administration at site

9.5.5 Week 10

- Contact subject via telephone to determine the subject's status and ascertain whether the subject is experiencing any AEs. Information on concomitant medications should also be collected.

9.5.6 Week 12/Early Termination

- Complete physical examination; includes neurological examination and weight
- 12-lead ECG (triplicate)
- Vital signs after resting for at least 5 minutes
- Resting TTE
- Hemodynamic stress echocardiography after 4 hour fast
- CPET after a 4-hour fast (water is allowed). 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.
- Blood samples for
 - Hematology and serum chemistry
 - NT-proBNP
 - Potential exploratory biomarker analysis
 - PK (within ≤ 2 hours prior to dosing)
- Pregnancy test (blood or urine) for women of childbearing potential, based on standard at institution
- Urine sample for urinalysis
- Retrieve previously applied cardiac monitoring skin patch and apply a new patch. The skin patch is only required for up to 2 weeks of wear time.
- Optical biosensor pulse wave analysis (consenting subjects)
- Concomitant therapy assessment
- AE assessment
- Study medication compliance
- Dyspnea NRS
- KCCQ
- NYHA class
- Open-label MYK-461 administration at site

9.5.7 ***Week 16/End of Study***

- Complete physical examination; includes neurological examination and weight
- 12-lead ECG (triplicate)
- Vital signs after resting for at least 5 minutes
- Resting TTE
- Hemodynamic stress echocardiography after 4 hour fast
- Blood samples for
 - Hematology and serum chemistry
 - NT-proBNP
 - PK
- Urine sample for urinalysis
- Pregnancy test (blood or urine) for women of childbearing potential, based on standard at institution
- Retrieve cardiac monitoring skin patch
- Optical biosensor pulse wave analysis (consenting subjects)
- Concomitant therapy assessment
- AE assessment
- Dyspnea NRS
- KCCQ
- NYHA class

9.5.8 ***Unscheduled Visits***

At the investigator's discretion, unscheduled visits may be conducted 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.

9.6 **Visit Window and Missed Visits**

Weekly visits should occur within the visit window (\pm 1 day). If an evaluation is missed, reschedule and perform it as close as possible to the original date. If rescheduling becomes, in the investigator's opinion, medically unnecessary because the evaluation would occur too close to the next scheduled evaluation, it may be omitted.

10 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event

An AE is any untoward medical occurrence, or the deterioration of a preexisting medical condition (other than the condition that is being treated by the study) associated with the use of a study medication in humans, whether or not it is considered related to the study medication. An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver, clinically important abnormal laboratory result or diagnostic procedure), subject-reported symptom (e.g., nausea, chest pain), or evidence of any disease activity temporally associated with the use of a study medication, whether or not related to the study medication.

In clinical studies, an AE can include an undesirable medical condition occurring at any time after the subject has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

Preexisting medical conditions (other than natural progression of the disease being studied) judged by the investigator or subject to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period will be reported as AEs or SAEs as appropriate.

Imaging-based assessments of decrease in contractility are not considered AEs unless associated with symptoms or signs of clinical concern on the part of the investigator. Such events should be categorized as an AE defined in terms of those symptoms or signs.

An AE or SAE can also be a complication that occurs as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies).

For MyoKardia to collect additional information about clinically important laboratory results or diagnostic tests (e.g., blood, ECG, imaging), at a minimum, the following abnormalities should be captured on the AE eCRF:

- Any test result that meets the definition of an SAE
- Any clinically important test abnormality that suggests a disease and/or organ toxicity that has worsened or is new (e.g., $>3\times$ deviation from the upper or lower limit of the analyzing laboratory reference range, or as otherwise specified in the protocol)
- Any test abnormality that required the subject to have study medication discontinued or interrupted or in the clinical judgment of the investigator.
- Any test abnormality that required the subject to receive specific corrective therapy, close observation, more frequent follow-up assessment, or further diagnostic investigation.

The term AE is used generally to include any AE whether serious or non-serious.

10.1.2 *Serious Adverse Event*

An SAE is an AE that fulfils one or more of the following criteria in the opinion of the investigator or MyoKardia:

- Results in death
- Is immediately life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent one of the outcomes listed above.

10.2 Adverse Event Reporting and Descriptions

10.2.1 *Reporting Period and Follow-Up*

AEs will be assessed from the time the subject provides informed consent through the duration of the study. Preexisting medical conditions that increase in severity from the first dose of study medication will be reported as AEs. Preexisting medical conditions that increase in severity after providing informed consent but before the first dose of study medication will be reported as medical history.

Any AEs that are unresolved at the subject's last visit in the study are followed by the investigator until resolved, or stabilized and are considered irreversible, or the subject has died.

MyoKardia retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

10.2.2 *Adverse Event Attributes*

The following attributes will be recorded for each AE. Additional attributes may be collected as required by MyoKardia

10.2.2.1 Description

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *“Have you had any health problems since you were last asked?”*, or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms (e.g., anemia, not low hemoglobin). However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Death is an outcome and not the name of the event. In this situation, the event that led to the death is the name of the event. If the cause of death is unknown, “found dead” is an acceptable description.

10.2.2.2 Start Date/Time and Stop Date/Time

Record the date (and time during period of residency) the AE started and the date (and time during period of residency) the event ended. For events that continue for long periods of time, it is acceptable to record the end date as the day the event stabilized.

10.2.2.3 Relationship to Study Treatment (Suspected Adverse Reactions)

The investigator should assess causality by answering either “yes” or “no” to the following question, “is there a reasonable possibility that the event may have been caused by the IMP/study medication?”

10.2.2.4 Intensity

Record the intensity or severity of the event using the following guide:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)
- life-threatening (urgent intervention indicated)
- fatal (event lead to death)

10.2.2.5 Seriousness

Record SAE criteria described in [Section 10.1.2](#) or indicate that the AE is not serious.

It is important to distinguish between category (AE vs SAE) and intensity (mild, moderate or severe) of AEs.

Severity is a measure of intensity (Section 10.2.2.4), whereas seriousness is defined by the criteria in Section 10.1.2.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

10.2.2.6 Outcome

Record the outcome of the event based on the options provided on the eCRF.

10.3 Reporting and Evaluation of Serious Adverse Events

All SAEs regardless of causality will be reported by the investigator or designee to MyoKardia/designee through the last visit or 30-day period after the last dose of study medication, whichever is longer, within 24 hours of knowledge of the event or sequelae. Deaths and SAEs occurring beyond this timepoint and considered related to study medication or study procedure must also be reported. SAE reporting instructions are provided in the Study Reference Manual.

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (i.e., not defined as expected in the current IB, clinical protocol, or approved labeling for marketed products). In this case, MyoKardia or designee will report to the relevant regulatory authority(ies) and forward a formal notification describing the SUSAR to investigators, according to regulatory requirement. Each investigator must then notify his/her ethics committee (EC) of the SUSAR as required by local regulatory authorities and in accordance with their EC policy.

11 STATISTICAL METHODS

11.1 Determination of 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 4). 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 provokable LVOT (Nistri et al, 2012).

Table 4 **Power for Detecting a Statistically Significant Within Group Change With 10 Subjects^a**

Difference Versus Baseline In Peak LVOT Gradient (mm Hg)	Power (%)
50	> 99
40	95
30	80
20	50

LVOT, left ventricular outflow tract

^a Calculations were made using nQuery 7.0 Advisor software.

11.2 Study Endpoints

11.2.1 Primary Endpoint

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

11.2.2 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 (2D and 3D), global longitudinal strain, and 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

11.2.3 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

11.2.4 Safety Endpoints

- Treatment-emergent AEs and SAEs
- Changes from baseline in laboratory values and vital signs
- Changes from baseline in ECGs

11.3 Statistical Analysis

Before database lock, a final statistical analysis plan (SAP) for clinical data and PK analyses will be prepared that will contain full details of all planned analyses. The analyses presented here represent an outline of the intended methodology.

11.3.1 Analysis Populations

Three analysis populations are defined in this study.

The Efficacy/PD 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 and PD analyses will be performed on the Efficacy/PD 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.

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

11.3.2 General Considerations

Descriptive summary statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Ninety-five percent confidence intervals will be presented, as appropriate.

The two groups from Part A and Part B, respectively, will be analyzed separately and not statistically compared with one another for effect sizes. They may be compared side-by-side with respect to demographic and baseline characteristics to evaluate whether they were drawn from the same overall population.

11.3.3 Subject Disposition

The number and percentage of subjects who complete and discontinue as well as reasons for early discontinuation will be presented.

11.3.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

11.3.5 Efficacy/Pharmacodynamic Analyses

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

11.3.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 in post-exercise peak LVOT gradient.

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).

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 95% confidence interval. Statistical significance of the difference versus baseline will be evaluated at the 1-sided 0.05 level.

11.3.5.2 Secondary and Exploratory Efficacy Endpoints

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

Quantitative endpoints, including the Dyspnea 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.

Data collected from the optical biosensor and cardiac monitoring skin patch will be analyzed descriptively.

11.3.6 Pharmacokinetic Analyses

Plasma concentrations of MYK-461 will be determined and summarized descriptively. Population PK and PK/PD analyses will be conducted.

11.3.7 *Interim Analysis*

No formal interim analysis is planned.

11.3.8 *Safety Analyses*

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

11.3.8.1 Adverse Events

AEs will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). 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 on or after the first dose of study medication, or with an onset before the first dose of study medication that increase in severity on or after the first dose of study medication, will be considered treatment-emergent. Treatment-emergent AEs will be summarized for the Safety Analysis Population by system organ class and preferred term, and by severity and relationship to treatment. Severe and life-threatening AEs, SAEs, and AEs leading to study withdrawal, if any, will be presented in data listings.

11.3.8.2 12-lead Electrocardiogram

The RR, PR, QRS, and QT intervals will be measured. HR will be calculated as $60/(RR \times 1000)$ (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 the Fridericia method (QTcF) as per the following formulae/method (with QT, RR and QTc expressed in msec):

Fridericia's Correction:

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

ECG Numeric Variables

HR, PR, QRS, and QTcF will be summarized using descriptive statistics. The change from baseline of these ECG parameters at each 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 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, Δ QTcF, and baseline and treatment HR. The incidence count and percentage of subjects with Δ QTcF increase of > 30 msec and > 60 msec will be tabulated.

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 T-wave morphology changes and/or the occurrence of abnormal U-waves that represent the appearance or worsening of the morphological abnormality from baseline will be reported.

Concentration-QTc Analyses

A concentration-QTc regression analysis, based on data collected from the ECG recordings after drug administration and concentration values for each subject at each matching timepoint, will be performed.

11.3.8.3 Other Safety Analyses

Safety laboratory data including hematology, chemistry, and vital signs will be evaluated by visit for the Safety Analysis Population using descriptive statistics. Changes from baseline at each post-Day 1 timepoint will also be assessed. Listings of subjects with laboratory, and/or vital sign values that are out of the reference range will be produced. Abnormal physical examination results will be listed. Concomitant medications will be summarized.

11.3.9 *Exploratory Analyses*

Additional exploratory analyses may be performed. Detailed planned exploratory analyses will be specified in the SAP.

12 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

12.1 Compliance Statement

This study will be conducted in accordance with the International Conference on Harmonisation (ICH) GCP guidelines; US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; European Union (EU) GCP; cGMP; the principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in the countries where the study is to be conducted.

12.2 Informed Consent

The ICFs used for the study must comply with the Declaration of Helsinki, US 21 CFR Part 50, ICH GCP guidelines, and any other local regulations. The investigator, or a person delegated by the investigator, must explain the medical aspects of the study including the nature of the study and the treatment, orally and in writing, in such a manner that the potential subject is aware of potential benefits and risks. Potential subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects, or a legal guardian if the subject is unable to, must give informed consent in writing.

Prior to participation in any study-related procedures, subjects must sign and date an ethics-committee (EC)-approved written ICF in a language the subject can understand. The informed consent process must be conducted, documented in the source document (including the date), and the form must be signed before the subject undergoes any study-specific procedures.

The language in the written information about the study should be as non-technical as practical and should be understandable to the potential subject. Before informed consent is obtained, the investigator should provide the potential subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. All subjects will receive a copy of his/her signed and dated ICF.

12.3 Ethics Committee

The term EC used in this document refers to an Institutional Review Board (IRB) or Independent Ethics Committee (EC) or equivalent. The EC must review and, if appropriate, approve the following documents, as applicable:

- Study protocol and amendment(s)
- Written ICF(s) and consent form updates
- Subject recruitment procedures/documents (e.g., advertisements)
- Written information to be provided to subjects
- IB and available safety information (Note: ECs do not approve IBs but are responsible for acknowledging receipt)
- Information about payments and compensation available to subjects

The EC approval must be in writing, clearly identifying the study (by protocol date and/or version), the documents reviewed, including informed consent, and date of the review. The

investigator has the responsibility to provide MyoKardia with the written EC approval prior to initiating any study-related procedures.

The investigator also has the responsibility to inform the EC of the following according to the EC's policy:

- All SUSARs (as described in [Section 10.3](#))
- Any new information that may affect adversely the safety of the subjects or the conduct of the trial
- Protocol deviations
- A synopsis of the study report upon study completion

Documentation of subsequent reviews of the study must also be forwarded to MyoKardia.

13 ADMINISTRATIVE PROCEDURES

13.1 Sponsor's Responsibilities

MyoKardia reserves the right to terminate the study at any time. MyoKardia and the investigators will assure that adequate consideration is given to the protection of the subjects' interests. MyoKardia retains the right to terminate the study and remove all study materials from a clinical site at any time. Specific circumstances that may precipitate such termination are:

- Request by Health Authority to terminate the study
- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects, maintain adequate study records or inaccurate, incomplete, or late data recording on a recurrent basis
- The incident or severity of AEs in this or other studies indicating potential health hazard caused by the study treatment

13.1.1 Subject Confidentiality

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study medications used in this study. These data will be processed with adequate precautions to ensure confidentiality according to applicable laws.

MyoKardia ensures that the personal data are:

- Collected for a specified and legitimate purpose
- Processed fairly and lawfully
- Accurate and up to date

Explicit consent for the processing of personal data will be obtained prospectively from the participating subject.

MyoKardia, whose responsibilities require access to personal data, agrees to keep the identity of subjects confidential. This confidentiality will be maintained throughout the complete data processing.

Subjects will be entitled to request confirmation of the existence of personal data held by MyoKardia and will have the right to rectify erroneous or inaccurate data up until database lock.

13.1.2 Study Supplies

MyoKardia will supply or ensure the coordination of sufficient quantities of the following materials to each clinical site:

- MYK-461 tablets of 4 strengths in 30-count bottles
- Cardiac monitoring skin patches
- Optical biosensors
- Supplies for laboratory assessments

13.1.3 Investigator Training

All clinical sites will have a center-specific study initiation meeting to ensure the center staff understands the protocol, study requirements, and data capture processes. This training will take place before the first subject is enrolled. Each clinical site will be provided with information regarding GCP and regulations specific to the conduct of the clinical studies. Each clinical site will be responsible for ensuring that new team members are adequately trained and the training is documented.

13.1.4 Ongoing Communication of Safety Information during the Study

MyoKardia will provide the investigator with documentation of SAEs from the study and other studies that are related to MyoKardia study medication and are unexpected (refer to [Section 10.3](#)), as appropriate. The investigator must forward this documentation to the EC as described in [Section 10.3](#).

MyoKardia will also notify the investigator about any other significant safety findings that could alter the safety profile of the IMP from what is described in the protocol and significantly affect the safety of subjects, affect the conduct of the study, or alter the EC's opinion about the continuation of the study.

13.1.5 Study Monitoring

MyoKardia will monitor this clinical study through remote data checks and monitoring visits to check the adequacy of clinical site staff and facilities, and to ensure adherence to the protocol, study procedures, and applicable regulations. The clinical site monitor will also assess proper eCRF completion and source document retention. The investigator and clinical site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The investigator will permit study-related monitoring, audits, EC review, and regulatory inspection(s), providing direct access to source data/documents and study-related facilities (e.g., pharmacy, diagnostic laboratories).

13.1.6 Study Auditing and Inspecting

MyoKardia may audit the study conduct, compliance with the protocol, and accuracy of the data in 1 or more clinical sites.

The investigator(s)/institution(s) will permit study-related monitoring, audits and inspections by MyoKardia, EC, government regulatory authority(ies), and MyoKardia's quality assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from MyoKardia.

13.2 Investigator's Responsibilities

13.2.1 Screening Log

The investigator must keep a record that lists all subjects who signed an informed consent and the reason for non-inclusion if the potential subject does not ultimately enroll and receive IMP.

13.2.2 MYK-461 Accountability

The investigator must ensure that the study medications at the investigational site are kept secured and accounted for with access limited to only those individuals authorized by the investigator. The investigator, his/her designee, or pharmacist must also maintain adequate records of distribution, dispensing, and return of all study medication to be able to reconcile the study medication records (i.e., accountability or dispensing logs) at the end of the study. The study medication records must be readily available for inspection by the site monitor and/or auditor. In general, no study medication can be returned to MyoKardia/clinical site or disposed of at the clinical site until the clinical site monitor has verified the accuracy of the study medication records at the clinical site and indicated whether the medication should be destroyed at the clinical site or returned to MyoKardia/designee.

13.2.3 *Reporting and Recording of Study Data*

Data will be captured and compiled using procedures developed by MyoKardia or designee. Electronic data capture (EDC) technology will be used for this study. Clearly record all requested study data on the eCRF and other forms as required. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study personnel responsibility/signature log and who have received appropriate training on the EDC system may enter or correct data in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries that require resolution by the investigator or designee. Corrections to the eCRF, including the reason for change, will be automatically documented through the EDC system's audit trail.

Subject source data must be maintained as original records or a certified copy (i.e., copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original). The investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Data collected on the eCRF must match the source documents.

An eCRF must be completed for each subject who receives at least 1 dose of IMP. All entries into the eCRF are ultimately the responsibility of the investigator before approving them via an electronic signature. The investigator is responsible for ensuring accurate, authentic and complete records for each subject.

An electronic copy of the eCRF casebooks will be sent to the clinical site for retention with other study documents after full completion of the study.

13.2.4 *Source Data and Source Documents*

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the company and clinical site staff. The source documents are to be accessible for verification by the clinical site monitor.

Source documents should at minimum include the following information for each subject:

- Subject identification and contact information (name, date of birth, sex, address, phone)
- Documentation verifying subject eligibility (i.e., medical history, physical examination)
- Informed consent process documentation and ICF
- Record of all visits and other contacts
- Record of all AEs and other safety parameters and all event attributes
- Record of all concomitant therapy (including start/stop dates, indication for use, dose)
- Date of study completion and reason for early discontinuation, if applicable

The author of an entry in the source documents should be identifiable as well as the date of the entry. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. The investigator will provide certified copies of the subject's medical records in the event that clinical site's policy does not permit direct access to the electronic medical records.

13.2.5 *Subject Identification Information*

To permit easy identification of the individual subject during and after the study, the investigator is responsible for keeping an updated log that contains the subject identification information. This document will be reviewed by the clinical site monitor for completeness. However, to ensure the subject's confidentiality, the document will be maintained at the clinical site and no copy will be made.

13.2.6 *Records Retention*

MyoKardia will inform the investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or MyoKardia, the investigator agrees to keep records, including the identity of all subjects (e.g., subject identification code list and all source documents), all original signed ICFs, copies of all eCRFs, original laboratory reports, detailed records of study medication disposition, and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, the investigator may need to retain these documents for a longer period if required by the local regulatory requirements or by an agreement with MyoKardia.

13.2.7 *Protocol Deviations*

Protocol waivers will not be allowed.

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the investigator or designee must document and explain the reason for any deviation from the approved protocol. The investigator or the medical monitor may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to subjects without prior EC approval. Immediately after the implemented deviation or change, the investigator must submit a report explaining the reasons for the protocol deviation to the EC and MyoKardia, if required. If a protocol deviation may result in inadequate subject data, MyoKardia may determine that the subject should be replaced. The medical monitor will notify the study monitor(s) of the decision.

13.2.8 *Blood Sample Collection/Storage*

Blood samples that are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for PK or PD analyses.

After the study, samples may be used for additional investigation to help identify factors that may influence response to therapy. Such samples will be used in compliance with guidelines defined by US FDA Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens That are Not Individually Identifiable (issued 25Apr2006) and European Medicines Agency's (EMA's) Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMA/Committee for Medicinal Products for Human Use [CHMP] 2007).

13.3 Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating clinical sites upon request.

13.4 Protocol Amendments and Study Administrative Letters

Study procedures will not be changed without the mutual agreement of the investigator and MyoKardia.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol.

The amendment should be approved by the EC and the appropriate regulatory authority(ies), before implementation, as appropriate. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the ICF, the EC will need to approve the revised ICF before the revised form is used.

If there are nonsubstantial changes such as clarification of statement or corrections to obvious errors/typos/inconsistencies in the protocol, or change to logistical or administrative aspects, then MyoKardia may issue an Administrative Letter. If local regulations require, any administrative change will be communicated to or approved by the EC.

14 DATA QUALITY ASSURANCE

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by MyoKardia, as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH E6 GCP: Consolidated Guidance and the applicable regulatory requirements.

15 ADMINISTRATIVE CONSIDERATIONS

15.1 Use of Computerized Systems

This study will require the use of the following electronic data collection methods:

- EDC system to capture protocol-required subject data: clinical sites will enter data from source documents onto eCRFs for each study visit using a web-based interface. Study monitors and data management personnel will use this system to review data and generate queries and reports as needed.
- Cardiac clinical data management systems will be used to analyze ECG, CPET, and echocardiographic data from digital equipment used by clinical site personnel to collect subject data.

In addition, other central data management systems/databases and software may be used to collect and analyze study data:

- Laboratory Information Systems or proprietary systems will be used by laboratories for storing and/or analyzing bioanalytical laboratory data collected throughout the study.
- Statistical software will be used for the statistical analysis of the study data as outlined in the SAP.

Information on the above systems will be provided to the investigator, clinical site personnel, and other personnel as appropriate. Measures will be taken to ensure data security and accuracy, including but not limited to user training, granting of user accounts and privileges to trained and authorized personnel in a role-based manner, username/password/electronic signature requirements enforcement, programmed and manual edit checks as outlined in data validation specifications, computer generated audit trails, centralized data management, and routine study monitoring. The systems used will be compliant with US 21 CFR Part 11 and Annex 11 to the Rule Governing Medicinal Products in the European Union and the data collected will be archived (at minimum) for the period specified by applicable regulatory requirements.

15.2 Study Records

The investigator and affiliated institution shall maintain the study documents and records as specified in “Essential Documents for the Conduct of a Clinical Trial” (ICH E6 Section 8), and as required by the applicable regulatory requirement(s). This includes, but is not limited to, the protocol, eCRFs, AE reports, subject source data (original records or certified copies), correspondence with health authorities and EC, consent forms, investigator’s curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The eCRF must be completed at the time of, or shortly after the subject’s visit or upon receipt of test results. Information will be provided to clinical site staff on the proper way to complete the eCRF.

A copy of each subject’s eCRF will be maintained by the investigator.

16 PUBLICATION

The data and results of the study will be owned solely by MyoKardia and shall be confidential information of MyoKardia, subject to the investigator's publication rights, all as outlined in the agreement between the investigator/institution and MyoKardia regarding the conduct of the clinical study (the "Clinical Study Agreement"). It is understood by the investigator that MyoKardia may use the information developed in this study in connection with the development of MyoKardia's proprietary IMP and, therefore, may disclose such information as necessary or useful to other clinical investigators or regulatory agencies. To allow for the use of the information derived from the study, the investigator understands that he/she has an obligation to provide and disclose all study results and all data developed during this study to MyoKardia.

Any publication or presentation of the results or data of this clinical study by the investigator may only be made in strict compliance with the provision of the Clinical Study Agreement. The investigator understands that it is not MyoKardia's intention to prevent publication of the data generated in the study; rather, MyoKardia reserves the right to control the form and timing of such publication for commercial reasons and desires to confirm the scientific accuracy of such information prior to such publication or presentation.

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Footnotes and abbreviations defined on last page of table.

APPENDIX 1 SCHEDULE OF STUDY PROCEDURES (continued)

Timepoint (Day/Week) ^a	Screen D -28 to D -1	D1	W1	W2	W3	W4	W5	W6	W7	W8	W12/ET	W16/EOS or ET + 4W
<i>Laboratory (continued)</i>												
NT-proBNP		X				X				X	X	X
FSH ^p	X											
Pregnancy test (women) ^q	X	X				X				X	X	X
HCM genotyping ^r		X										
Pharmacogenetic ^s		X										
Biomarkers (blood) ^t		X									X	
<i>Symptom Assessment</i>												
Dyspnea NRS		X	X	X	X	X	X	X	X	X	X	X
KCCQ		X									X	X
NYHA class	X										X	X
<i>Investigational Medical Product</i>												
Open-label MYK-461 administration at site		X	X	X	X	X ^u	X	X	X	X	X	
Open-label MYK-461 QD		←										→
Study medication compliance ^v			X	X	X	X	X	X	X	X	X	

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.

- ^a At the investigator’s discretion, unscheduled visits may be conducted at the investigational 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.
- ^b 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).
- ^c 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.

- ^d 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.
- ^e 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.
- ^f 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.
- ^g 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.
- ^h 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.
- ⁱ 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: VO_2 , VCO_2 , VE, VE/VO_2 , VE/VCO_2 , and respiratory exchange ratio (RER).
- ^j 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.
- ^k 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 and after a 4 hour fast.
- ^l 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.
- ^m 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.
- ⁿ 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.
- ^o Collect PK samples ≤ 2 hours prior to dosing.
- ^p FSH testing at Screening for postmenopausal women to confirm postmenopausal status.
- ^q Pregnancy test (serum or urine) for women of childbearing potential, based on standard at institution.
- ^r For subjects who consent, blood will be drawn on Day 1 (predose) for assessment of HCM genotype.
- ^s For subjects who consent, blood sample will be drawn for potential future exploratory pharmacogenetic analysis on Day 1 (predose).
- ^t Blood samples for potential exploratory biomarker analysis predose on Day 1 and Week 12.
- ^u At the end of Week 4, each subject's dose may be adjusted based on predetermined criteria.
- ^v All subjects will return their IMP dosing containers to the site for tablet counts. Refer to the Pharmacy Manual for details.

APPENDIX 2 LABORATORY ASSESSMENTS

The following safety laboratory parameters will be measured by the central laboratory:

Hematology	Serum Chemistry	Urinalysis^a
CBC, including differential count	• Sodium	• Specific gravity
	• Potassium	• pH
Platelet count	• Chloride	• Protein
	• Bicarbonate	• Glucose
	• Calcium	• Leukocyte esterase
	• Magnesium	• Blood
	• BUN	
	• Creatinine	
	• ALP	
	• ALT	
	• AST	
	• Total bilirubin	
	• CPK ^b	
	• Glucose	
	• Protein	
	• Albumin	

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CPK, creatine phosphokinase.

^w Urine microscopy will be performed if there is a significant abnormality in the dipstick.

^x If CPK is high, troponin I will be performed and reported.

At the investigator's discretion, safety laboratory assessments may be repeated on Day -1 to confirm study eligibility before dosing of study medication.

The following non-safety laboratory parameters will be measured at Screening:

- Hepatitis panel (HVB and HVC)
- HIV test
- FSH
- TSH
- Testing for alcohol and drugs of abuse

APPENDIX 3 POTENTIAL DRUG-INDUCED LIVER INJURY REPORTING AND ADDITIONAL ASSESSMENTS REPORTING

To facilitate appropriate monitoring for signals of DILI, cases of concurrent aspartate AST/ALT and TBL elevation according to the criteria specified in [Section 7.4](#) ($3 \times$ ULN for AST/ALT and $2 \times$ ULN for TBL in subjects with no underlying liver disease and eligibility criteria requiring normal liver function at baseline) require the following:

- The event is to be reported to MyoKardia as an SAE within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded).
- The appropriate case report form (CRF) (e.g., Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to MyoKardia.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in [Section 10.1.2](#).

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI or who experience AST/ALT elevations $> 3 \times \text{ULN}$ are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include the following:

- Repeat liver chemistries within 24-48 hours (ALT, AST, ALP, TBL); in cases of TBL $> 2 \times \text{ULN}$ or AST/ALT much greater than $3 \times \text{ULN}$, retesting is to be performed within 24 hours.
 - Subjects are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the investigational product(s) or protocol-required therapies have been discontinued AND the subject is asymptomatic.
- Obtain prothrombin time/international normalized ratio, fractionated bilirubin, and any other potentially relevant laboratory evaluations of liver function or disease.
- Obtain complete blood count with differential to assess for eosinophilia.
- Obtain appropriate blood sampling for PK analysis if this has not already been collected.
- Obtain a more detailed history of the following:
 - prior and/or concurrent diseases or illness
 - exposure to environmental and/or industrial chemical agents
 - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
 - prior and/or concurrent use of alcohol, recreational drugs, and special diets
 - concomitant medications (including nonprescription medicines and herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr virus, herpes simplex virus, etc.); evaluate for other potential causes of

DILI, including but not limited to: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease.

- Obtain gastroenterology or hepatology consult.
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation as specified in [Section 7.4](#).
- Follow the subject until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after investigational product(s) or protocol-required therapies discontinuation.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

APPENDIX 4 INVESTIGATOR’S SIGNATURE

I have read and understand the contents of the clinical protocol, MYK-461-004, 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), and I agree to the following:

- To assume responsibility for the proper conduct of this clinical study at this clinical site and to conduct the study in compliance with this protocol, any future amendments and with any other study conduct procedures provided by MyoKardia/designee.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirement to obtain written and dated approval for the Ethics Committee (e.g., Institutional or Central Review Board [IRB] or Independent Ethics Committee [IEC]) for the study protocol, written informed consents, consent form updates, study participant recruitment procedures and any other written information to be provided to the study participants before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from MyoKardia and review and documented approval from the EC, except to eliminate an immediate hazard to the study participants, or when change(s) involves only logistical or administrative aspect of the clinical study.
- To permit direct monitoring and auditing by MyoKardia or MyoKardia’s representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the Investigational Medicinal Product (IMP) and other study medication(s) (if applicable), as described in this protocol, and any other information provided by MyoKardia or designee, including, but not limited

to the current Investigator's Brochure (IB) or equivalent document and marketed prescription information (if applicable).

- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, IMP/study medication(s) and their clinical study-related duties and functions.

Signed: _____ Date: _____
(*sign name with credentials*)

Printed Name: _____

APPENDIX 5 INVESTIGATOR'S SIGNATURE AMENDMENT 1

I have read and understand the contents of the clinical protocol, MYK-461-004 Amendment 1, 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), and I agree to the following:

- To assume responsibility for the proper conduct of this clinical study at this clinical site and to conduct the study in compliance with this protocol, any future amendments and with any other study conduct procedures provided by MyoKardia/designee.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirement to obtain written and dated approval for the Ethics Committee (e.g., Institutional or Central Review Board [IRB] or Independent Ethics Committee [IEC]) for the study protocol, written informed consents, consent form updates, study participant recruitment procedures and any other written information to be provided to the study participants before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from MyoKardia and review and documented approval from the EC, except to eliminate an immediate hazard to the study participants, or when change(s) involves only logistical or administrative aspect of the clinical study.
- To permit direct monitoring and auditing by MyoKardia or MyoKardia's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the Investigational Medicinal Product (IMP) and other study medication(s) (if applicable), as described in this protocol, and any other information provided by MyoKardia or designee, including, but not limited to the current Investigator's Brochure (IB) or equivalent document and marketed prescription information (if applicable).

- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, IMP/study medication(s) and their clinical study-related duties and functions.

Signed: _____ Date: _____
(sign name with credentials)

Printed Name: _____