Official Title of Study:

Randomized, Double-blind, Placebo-controlled, Two-Part, Adaptive Design Study of Safety, Tolerability, Preliminary Pharmacokinetics, and Pharmacodynamics of Single and Multiple Ascending Oral Doses of MYK-491 in Patients With Stable Heart Failure With Reduced Ejection Fraction

NCT Number: NCT03447990

Document Date (Date in which document was last revised): March 19, 2019

CLINICAL TRIAL PROTOCOL

Protocol Number:	MYK-491-003 (HF-SAD/MAD)
Study Title:	Randomized, Double-blind, Placebo-controlled, Two-Part, Adaptive Design Study of Safety, Tolerability, Preliminary Pharmacokinetics, and Pharmacodynamics of Single and Multiple Ascending Oral Doses of MYK-491 in Patients with Stable Heart Failure with Reduced Ejection Fraction
Indication:	Heart Failure with Reduced Ejection Fraction
Phase:	1b/2a
Investigational Medicinal Product:	MYK-491
Sponsor:	MyoKardia, Inc. 333 Allerton Avenue South San Francisco, CA 94080
EudraCT Number	2018-002239-11
Key Sponsor Contacts:	[redacted]
Edition Number:	5
Release Date:	19 March 2019
Replaces Previous Edition Number:	4
Date:	14 December 2018

Confidentiality Statement

SYNOPSIS

Sponsor: MyoKardia, Inc.
Investigational Medicinal Product: MYK-491
Study Title: Randomized, Double-blind, Placebo-controlled, Two-Part, Adaptive Design Study of Safety, Tolerability, Preliminary Pharmacokinetics, and Pharmacodynamics of Single and Multiple Ascending Oral Doses of MYK-491 in Patients with Stable Heart Failure with Reduced Ejection Fraction
Study Number: MYK-491-003
Study Phase: 1b/2a
Primary Objective: To establish preliminary safety and tolerability of single- and multiple-ascending oral doses of MYK-491 in ambulatory patients with stable heart failure with reduced ejection fraction (HFrEF)
Secondary Objectives: • To establish preliminary human pharmacokinetics (PK) of MYK-491 after single- and multiple-ascending oral doses of MYK-491 in patients with HFrEF • To determine changes in left ventricular stroke volume [LVSV] derived from left ventricular outflow tract-velocity time integral [LVOT-VTI]), left ventricular ejection fraction (LVEF) and change in left ventricular fractional shortening [LVFS] with MYK-491 after ascending single and multiple doses compared with Baseline and placebo as measured by transthoracic echocardiography (TTE) • To determine changes in systolic ejection time (SET) with MYK-491 after ascending single and multiple doses compared with Baseline and placebo as measured by TTE • To determine changes in pharmacodynamics (PD) dose/concentration effects (change in LVSV [derived from LVOT-VTI], LVEF, LVFS) with MYK-491 compared with Baseline and placebo after ascending single and multiple doses, as measured by TTE
[redacted]

[redacted]

Main Criteria for Inclusion:

Inclusion Criteria:

This study is to be performed in patients with HFrEF due to any etiology. Each patient 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 80 years of age at the Screening visit.
3. Body mass index (BMI) 18 to 40 kg/m^2, inclusive, at the Screening visit and all required assessments can be reliably performed.
4. Sinus rhythm or stable atrial pacing with mean resting heart rate (HR) 50-95 beats per minute (bpm), inclusive. (Patient will be ineligible to dose if, on Day 1, the predose HR measurement is ≥ 95 bpm. Heart rate is the mean of 3 measurements taken 1 minute apart. A single measurement would not make a patient ineligible).
5. Has stable, chronic HFrEF of moderate severity as defined by all of the following:
   - For the first 3 patients in each multiple-ascending dose (MAD) cohort testing a new (higher) daily dose: documented LVEF 25% to 35% during Screening (as confirmed by ECHO Central Lab)
   - For other patients in the MAD Cohorts (and all patients in SAD Cohorts): documented LVEF 15% to 35% during Screening (as confirmed by ECHO Central Lab)
   - LVEF must be confirmed with second screening ECHO to be performed at least 7 days after initial screening ECHO. Results of both must meet inclusion criteria and must be received from core lab prior to dosing. In the event of extended screening windows due to SRC reviews, effort should be made to ensure second ECHO is near planned time of randomization.
   - Chronic medication for the treatment of heart failure consistent with current guidelines that has been given at stable doses for ≥ 2 weeks with no plan to modify during the study. This includes treatment with at least one of the following unless not tolerated or contraindicated: beta-blocker, angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB)/angiotensin receptor neprilysin inhibitor (ARNI)

6. Female patients must not be pregnant or lactating. Male patients (including men who have had vasectomies), as there may be a risk of drug being secreted in the ejaculate, should use barrier methods for the duration of the study and for 3 months after the last dose of study medication. All patients, if sexually active, must be using one of the following highly-effective birth control methods from the Screening visit through 3 months after the last dose of investigational medicinal product (IMP):

    - Hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), or intrauterine hormone-release system (IUS) plus barrier (eg, male using condom or female using diaphragm or cervical cap).
    - Vasectomy plus barrier.
    - Female is surgically sterile for 6 months or postmenopausal for 1 year. 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 1 year or more following cessation of all exogenous hormonal treatments, and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
    - Male patients with postmenopausal partners.

Exclusion Criteria:

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

1. Inadequate echocardiographic acoustic windows.
2. Any of the following ECG abnormalities (a) QTcF > 480 ms (Fridericia's correction, not attributable to pacing or prolonged QRS duration, average of triplicate Screening ECGs) or (b) second-degree atrioventricular block type II or higher in a patient who has no pacemaker.
3. Hypersensitivity to MYK-491 or any of the components of the MYK-491 formulation.
4. Active infection as indicated clinically as determined by the investigator.
5. History of malignancy of any type within 5 years prior to Screening, with the exception of the following surgically excised cancers occurring more than 2 years prior to Screening: in situ cervical cancer, nonmelanomatous skin cancers, ductal carcinoma in situ, and nonmetastatic prostate cancer.
6. Positive serologic test at Screening for infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
7. Hepatic impairment (defined as alanine aminotransferase [ALT]/ aspartate aminotransferase [AST] > 3 times upper limit of normal [ULN] and/or total bilirubin [TBL] > 2 times ULN).

8. Severe renal insufficiency (defined as current estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2 by simplified Modification of Diet in Renal Disease equation [sMDRD]).
9. Serum potassium < 3.5 or > 5.5 mEq/L.
10. Any persistent out-of-range safety laboratory parameters (chemistry, hematology, urinalysis), considered by the investigator and medical monitor to be clinically significant.
11. History or evidence of any other clinically significant disorder, condition, or disease (including substance abuse) that, in the opinion of the investigator or MyoKardia physician would pose a risk to patient safety or interfere with the study evaluation, procedures, completion, or lead to premature withdrawal from the study.
12. Participated in a clinical trial in which the patient 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).
13. Previous participation in a clinical trial with MYK-491, with the exception that patients that participated or were screen failures in one part of this trial may participate in the other part, ie patients may enroll in Part 1 (SAD) followed by Part 2 (MAD) or Part 2 (MAD) followed by Part 1 (SAD), with the following caveats:
    - If the patient has an ongoing adverse event (AE), has had a serious adverse event (SAE), or has met any stopping criteria, the investigator should contact the Sponsor prior to enrolling the patient in a subsequent cohort.
    - Patients must have at least 1 week washout after the end of MAD dosing prior to SAD dosing, or at the end of SAD dosing prior to MAD dosing.
    - Patients do not need to rescreen if MAD screening occurred within 12 weeks of the first SAD dosing, or if SAD screening occurred within 12 weeks of the first MAD dosing. Investigators should verify that patients are clinically stable and no exclusions have occurred during the interim; if > 12 weeks have elapsed or there is clinical instability, then patients should be rescreened.
14. Unable to comply with the study restrictions/requirements, including, in particular, the number of required overnight stays at the clinical site.
15. Is employed by, or is a first-degree relative of someone employed by, MyoKardia or Sanofi, the investigator, or his/her staff or family.
16. At Screening, symptomatic hypotension, or systolic blood pressure (BP) > 170 mmHg or < 90 mmHg, or diastolic BP > 95 mmHg, or HR < 50 bpm. Heart rate and BP will be the mean of 3 measurements taken at least 1 minute apart.
17. Current angina pectoris.

18. Recent (< 90 days) acute coronary syndrome.
19. Coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) within the prior 3 months.
20. Recent (< 90 days) hospitalization for heart failure, use of chronic IV inotropic therapy or other cardiovascular event (e.g., cerebrovascular accident).
21. Uncorrected severe valvular disease.
22. Elevated troponin I (> 0.15 ng/mL) at Screening, based on Central Laboratory assessments. Note: Central Laboratory Troponin I assay ULN is 0.03 ng/mL.
23. Presence of disqualifying cardiac rhythms that would preclude study ECG or echocardiographic assessments, including: (a) Current atrial fibrillation, (b) recent (< 2 weeks) persistent atrial fibrillation, or (c) frequent premature ventricular contractions. Note: Patients with active cardiac resynchronization therapy (CRT) or pace-maker (PM) are eligible if initiated at least 2 months prior with no plan to change CRT or PM settings during the study.
24. A life expectancy of < 6 months.

Study Treatment:

Part 1-Single, ascending doses (SAD Cohorts): Each patient will be enrolled into either Cohort 1 or Cohort 2. Four to 8 patients will first be enrolled into Cohort 1 and then up to 8 patients will be enrolled into Cohort 2. The Safety Review Committee (SRC) will determine the number of patients enrolled into each cohort. Patients enrolled in Cohort 1 will participate in 3 to 4 dosing periods, while patients enrolled in Cohort 2 will participate in 2 to 4 dosing periods. For both cohorts, patients will receive sequential, ascending single oral doses of MYK-491 and a randomly assigned period with matching placebo. For Cohort 1, all patients will receive the first dose of MYK-491, which will be 175 mg, and the second dose of MYK-491, which will be 350 mg. Some patients in Cohort 1 may receive a third dose of MYK-491, given open label, that will be determined by the SRC after review of data from the first 2 doses. The SRC will select the number of dosing periods and the doses that will be administered to patients enrolled in Cohort 2 based on review of safety and PK/PD data from Cohort 1 and any other newly available MYK-491 data. Doses may be split into 2 aliquots. Patients will receive the placebo in random order along with the doses of active drug (see Figure 1). Sequential dosing for an individual patient can occur after a minimum period of 5 days and a maximum period of 14 days from the time of the ingestion of the previous dose, except for the open-label dose in Cohort 1 which will be completed after the SRC meets and provides dosing instructions. Further details are available in Section 4.4.1.

Part 2—Multiple, ascending doses (MAD Cohorts): The duration of dosing with blinded study drug will be 9 days. All patients will initially receive placebo twice a day (BID) in single-blinded manner for 2 days (Days 1 through 2). Patients will then be randomized to receive either placebo or active MYK-491 for 7 days (Days 3 through 9). Patients will be enrolled into sequential, dose-escalation cohorts with a low dose (Dose-Escalation Cohort A), medium dose (Dose-Escalation Cohort B), or high dose (Dose-Escalation Cohort C). The same dose will be given to all patients in a single cohort randomized to active drug. Based on prior testing, the low dose to be given in the first Cohort (Cohort A)

is intended to be at the lower end of the exposure range that produces a discernable pharmacodynamic effect in order to ensure safety and evaluate steady-state PK. [redacted]

The low dose of MYK-491 for Cohort A will be 75 mg administered orally every 12 hours. [redacted] The planned medium dose of MYK-491 for Cohort B will be [redacted] every 12 hours. The planned high dose of MYK-491 for Cohort C will be [redacted] every 12 hours. The actual medium and high doses will be determined and confirmed by the SRC after data from prior cohorts are reviewed. Dose escalation between cohorts will not exceed a 2-fold increase in dose from the prior cohort if the prior cohort demonstrated acceptable safety and tolerability.

In addition, optional Cohorts D and E, and possible additional cohorts, may be enrolled to evaluate the feasibility of a once daily dosing regimen given for 7 days or to explore additional every day (QD) or BID dosing regimens. The total daily dose for the optional cohorts will not exceed a total daily dose already evaluated in this study, [redacted].

Note: For Cohorts A, B and C testing a BID regimen, only one dose (active or placebo) will be given in the morning on Day 9 (Dosing Day 7) to allow for 72 hours of serial PK/PD assessments.

Number of Patients Planned:

Part 1-Single, ascending doses (SAD Cohorts): Enrollment of at least 4 and no more than 8 patients are planned for Cohort 1, with 1 patient randomized to each sequence of dose escalation and placebo administration (see Figure 1). For Cohort 2, 4 patients are planned, and no more than 8 patients will be enrolled, with up to 2 patients randomized to each sequence of dose escalation.

There will be an option for the SRC to expand Cohort 1 or Cohort 2 to meet study objectives. Decision to expand the number of patients or not will be made by the SRC. Two additional patients may be enrolled as replacements for drop-outs in each cohort, so the maximum number of patients that may be enrolled, including cohort expansions, will be approximately 32.

Part 2-Multiple, ascending doses (MAD Cohorts): Enrollment of a total of a minimum of 24 patients is planned, with 8 patients enrolled the low-dose group (Cohort A), 8 patients enrolled in the medium-dose group (Cohort B), and 8 patients enrolled in the high-dose group (Cohort C). The SRC may expand any cohort up to 24 patients. In addition, the initial planned size of Cohorts D and E, and possible additional cohorts, will be 8 patients each. The final total sample size for Part 2 will not exceed 96 patients. In addition, up to 2 additional patients may be enrolled per cohort as replacements for drop-outs or patients non-evaluable for PK-PD at steady state.

Cohorts will be randomized 3:1 to each sequence of active drug and placebo administration.

Number/Location of Investigational Sites:
Approximately 18 sites in North America and Europe

Study Duration:
The overall expected study duration is approximately 24 months.

Part 1-Single, ascending doses (SAD Cohorts): Each patient is expected to be in the study no more than 77 days: up to 28 days for Screening plus up to 42 days for dosing including 7 days for follow up after the last dose (or longer if clinically indicated). Patients returning for an additional dosing period in Cohort 1 may have prolonged participation. Patients will be resident at the clinical site for each dosing period, each consisting of check-in on Day -1, dosing the following morning (Day 1) followed by ~24 hours of serial PD and ~48 hours of serial PK assessments, followed by discharge the following morning (Day 3). An additional outpatient plasma PK sample will be taken on the morning of Day 4 at 72 hours postdose.

Part 2: Multiple, ascending doses (MAD Cohorts): Patients are expected to be in the study no more than 56 days: up to 28 days for Screening plus up to 28 days for (a) scheduling (b) 11 days of dosing and associated assessments, and (c) 7 days of follow up after the last dose (or longer if clinically indicated). Patients who are in Screening while dosing is on hold due to SRC meeting may have participation extended to allow dosing to be scheduled after SRC has convened. While waiting for a cohort to open to patients with LVEF < 25%, these patients may be in Screening up to 12 weeks (if the patient remains stable) while the SRC convenes.

Total time in the study may be longer for patients who participate in both Part 1 (SAD) and Part 2 (MAD).

Study Design:
This is a two-part study. Part 1 will evaluate single-ascending doses of MYK-491 (SAD Cohorts) and Part 2 will evaluate multiple, ascending doses of MYK-491 (MAD Cohorts). Note: Part 2 (MAD portion) of the study is planned to start before Cohort 2 of Part 1 (SAD Cohort) is complete. If a patient at a site qualifies for enrollment in either Part 1 (SAD) or Part 2 (MAD), Part 2 (MAD) will generally take priority; however, a patient may enroll in both, ie Part 1 (SAD) followed by Part 2 (MAD) or Part 2 (MAD) followed by Part 1 (SAD). In such cases, sites should consult with the monitoring team to discuss details.

Part 1-Single, ascending doses (SAD Cohorts): This is a randomized, crossover, double-blind (DB), placebo-controlled, two-cohort, sequential ascending (oral) single-dose study in ambulatory patients with heart failure. All patients will receive placebo and 2 or 3 active doses of MYK-491. Each patient will undergo sequential, single-dose treatment events separated by no fewer than 5 days and no more than 14 days. Patients in Cohort 1 may also return for a fourth dosing period (open label) after the SRC reviews available data and recommends the dose. Patients enrolled prior to the implementation of Amendment 1 may be offered the opportunity to return for the open-label period. Patients who return for this additional period must sign the amended informed consent form (ICF). Patients in Cohort 2 may participate in 2-4 dosing periods, based on SRC decision. Patients will be randomized to 1 of the different dosing sequences outlined in Figure 1. Multiple patients

can be dosed at the same time or during the same week depending on administrative issues, ie, capacity and scheduling.

For each dosing period, patients will be admitted to the clinical site on Day -1, (the day before dosing). Patients will be assessed for absence of exclusion criteria (eg, new lab abnormalities based on local labs and/or conditions that indicate the patient is clinically unstable). They will receive MYK-491 or placebo in the morning of Day 1 followed by serial PK and PD assessments, as well as serial safety assessments. Patients will be discharged on Day 3 (ie, ~48 hours following Day 1 dosing). An additional outpatient plasma PK sample will be taken on the morning of Day 4 at 72 hours postdose.

Before administering a dose, the investigator or the subinvestigator will review all available safety data, including vital signs, safety laboratory values including locally assayed troponin concentrations, TTEs, ECGs, and ECG telemetry. Dosing with DB treatment will take place at the same time each of the dosing days. Background concomitant medications, including diuretic if applicable, should also be administered at same time each of the dosing day. Prior to dosing, any patient with a predose resting HR $\geq$ 95 bpm will be considered ineligible and not treated. HR is the mean of 3 measurements.

A full PK profile and multiple TTEs and ECGs will be obtained at Baseline and after each dose. Patients will return for a final safety Follow-up visit 7 days (±1 day) following the last dose.

During the study, the patients should continue to ingest their medications for the treatment of their congestive heart failure and other medical conditions at the same doses and as close to the same times as usual.

Part 2: Multiple, ascending doses (MAD Cohorts): This is a randomized, parallel-group, DB, placebo-controlled, adaptive design, sequential ascending (oral) multiple-dose study in stable patients with heart failure. Three MAD Cohorts (A, B, C) are initially planned (with additional optional cohorts) with 8 patients each (2 placebo, 6 active). An SRC will review results from each cohort and will determine the dose and confirm initial sample size for the subsequent cohort. Additionally, the first 3 patients in each cohort must have a $\geq$ 25% LVEF; the SRC will review preliminary safety data from these patients and decide whether to open cohort enrollment to patients with LVEF < 25%.

After Screening and qualification, patients will be confined to a clinical testing facility from Day 1 (Check-in) to Day 11. This includes an initial 2-day placebo dosing period (Days 1-2), followed by a 7-day randomized treatment period (Days 3-9) and 48 hours of monitoring following the last dose of study drug (Days 10-11). An additional outpatient plasma PK sample will be taken on the morning of the day following discharge at 72 hours after the last dose (Day 12).

Note: **Confinement is not required for patients with an implantable cardioverter defibrillator (ICD)**: Patients with an ICD may reside for some or all of the period from Day 1 to Day 12 in close proximity to the Clinical Testing Unit, eg, at a hotel, provided they can return for all study drug dosing and all study assessments, including but not limited to all serial PK and TTEs. Alternatively, patients may be visited by a home health nurse for selected study drug administration and for any assessments that can be performed away from the clinical site.

Each patient will initially receive placebo BID for 2 days (Days 1-2) in single-blinded manner ("run-in" during acclimatization to confinement in the Clinical Testing Unit) prior to receiving the randomized DB study drug treatment on Day 3. All patients will then receive either placebo or active MYK-491 for 7 days (Days 3-9). More than one patient can be dosed in a cohort at the same time or during the same week depending on administrative issues, i.e., capacity and scheduling.

Patients will be dosed twice daily (every 12 hours). Doses may occur ± 2 hours from scheduled dosing times as long as doses are separated by at least 10 hours and by no more than 14 hours. The exception to the twice daily dosing is on Day 9 (last dose of randomized DB study drug treatment). On Day 9, a single morning dose will be administered followed by 72 hours of PK and PD assessments.

Before each dosing event, all available safety data from the previous days will be reviewed (for non-confined patients, if a home health nurse is utilized, the nurse and site will be in daily communication to ensure safety). Dosing of DB treatment will take place at approximately the same time each day.

A full PK profile and multiple TTEs and ECGs will be obtained on Days 3 and 9 (corresponding to first and last day of DB treatment respectively) before and after the morning dose. In case of premature permanent treatment discontinuation, perform end-of-treatment visit (same assessments as Day 9) as close as possible to last DB dose (ie, on day of last dose or next day).

Patients will return for a Follow-up visit 7 days following the last dose of study drug. In case of premature permanent treatment discontinuation, perform end-of-treatment visit (same assessments as Day 9) as close as possible to last DB dose (ie, on day of last dose or next day).

Note: Screening may continue during planned and unplanned SRC meetings. The protocol-specified Screening window may be extended to account for delays due to SRC meetings.

Recommendations by the SRC will include, but not be limited to: (a) evaluation of dose-modification and dose stopping criteria, (b) doses to be given in specified cohorts, (c) size of specified cohorts and (d) modification of the number and timing of PK and PD assessments (see Section 4.4.1).

Study Assessment and Procedures: Efficacy Assessments:
There are no therapeutic efficacy assessments in this study. Pharmacodynamic assessments will serve as surrogates for efficacy.

Pharmacokinetic Assessments:
For each cohort, blood samples to measure MYK-491 [redacted] plasma concentration will be drawn on each dosing day predose and postdose at serial timepoints as defined in the schedule of assessments. After review of the data, the SRC may decide that up to 2 additional blood samples should be obtained after each dosing period, or the timing of the samples should be modified to allow for acquisition of robust PK profiles. [redacted]

Pharmacodynamics Assessments:
The PD effect of MYK-491 will be evaluated throughout this study by serial TTE examination in accordance with a standardized imaging protocol at Screening, before first DB dose (on Day 1, Day 2, and Day 3 morning predose), during DB treatment (Day 3 to Day 9), and during follow up (Day 10, Day 11) at defined timepoints (predose and/or 7h postdose) as defined in the schedule of assessments. The intent is to obtain a TTE at a timepoint close to the anticipated peak effect following each dose based on the PK profile. Throughout the study, in order to minimize variability of cardiac loading conditions for detecting changes in TTE assessments from DB treatment, every effort should be made to maintain stable background HF treatment and to administer such treatments (including diuretic as applicable) at the same time every day throughout the duration of the study. After review of the data, the SRC may decide to obtain up to 2 additional TTEs for each dosing period or the timing of the TTEs may be modified to obtain robust PD profiles. The primary echocardiographic variables of interest are LVSV (derived from LVOT-VTI), LVEF, LVFS, and SET. The sonographers will be trained and certified to perform the TTE by the Imaging Core Laboratory.

[redacted]

Safety Assessments:
Serum troponin and ECGs will be obtained as part of the Screening visit, before and/or after dosing on selected days. Refer to Schedule of Events for timing.

Safety assessments include medical history, physical examinations, SET as determined by TTE, 12-lead ECGs, continuous ECG monitoring by (a) telemetry, (b) Holter monitor recording or (c) equivalent technology, vital signs, observed and patient-reported AEs, serum troponin concentrations, and safety laboratory tests. Any abnormal findings judged by the investigator to be clinically relevant will be recorded as AEs.

Suspected ischemic events, new or worsening episodes of ventricular arrhythmias and troponin elevations will be sent for review by a Central Safety Adjudication Committee (see Section 4.5).

Statistical Analyses:
General Considerations:
Clinical data will be analyzed separately for the SAD and MAD parts of the study. In Part 1, the placebo dosing periods will be pooled across cohorts to form a placebo group. Placebo subjects from all MAD Cohorts will be pooled to form one combined placebo group for analyses. No formal statistical hypothesis testing will be performed. Descriptive summary statistics for continuous variables will include the number of participants, mean, standard deviation (SD), median, 1st and 3rd quartiles, minimum, and maximum. Categorical variables will be summarized using counts and percentages. The 95% confidence intervals may be presented as well.

Safety Analyses:
SET, as determined by TTE, will be assessed using summary statistics. Observations and change from Baseline will be summarized by treatment at each timepoint and the

maximum change from Baseline will be determined for each patient. [redacted]

The number of patients with abnormal and/or rising troponin levels (taking into account potential troponin elevation at Baseline) will be determined.

Continuous ECG recordings by telemetry or Holter monitor (or equivalent) will be used to assess the nature, frequency, and severity of any ventricular arrhythmias or other significant cardiac rhythm abnormalities.

AEs, ECGs, vital signs, and laboratory values will be analyzed using descriptive statistics.

Pharmacokinetic Analyses:

The PK population will include all patients who receive MYK-491, have detectable plasma concentration data, and have no major or critical protocol deviations related to IMP (eg, incomplete ingestion of the drug, vomiting up to 8 hours after drug administration). In addition, a single plasma sample near the predicted time of maximum observed plasma concentration (T_{max}) of MYK-491 will be evaluated to confirm lack of circulating MYK-491 for the dosing period(s) when the patients received placebo.

Plasma concentration [redacted] data for MYK-491 will be summarized using descriptive statistics, including mean or geometric mean, as appropriate, SD, median, minimum and maximum values, and coefficient of variation (CV%). Other PK parameters include (but are not limited to) maximum observed plasma drug concentration (C_{max}), T_{max}, area under the plasma concentration-time curve over the dosing interval (AUC_{0-t}), AUC_{0-12}, AUC_{0-24}, AUC_{0-inf} after the single dose on Day 1 in Part1 or Days 3 and 9 in Part 2 (in appropriate patients), trough concentration (C_{trough}), apparent first-order terminal elimination rate constant (λ_z)(on Day 1 in Part 1 and Day 9 in Part 2 only), and mean residence time (MRT). PK parameters at steady-state will be compared to those observed after the first dose in this study, and the accumulation ratios determined (with the appropriate confidence intervals) based on C_{max} and AUC_{0-t} after a single dose and at steady-state as well as λz. Additionally, the apparent terminal-phase elimination half-life ($t_{1/2z}$) will be calculated after each dosing day in Part 1 and on Day 7 in appropriate patients. [redacted]

Pharmacodynamic Analyses:

The PD Analysis population will include patients who have any interpretable TTE data. TTE data for LVSV (derived from LVOT-VTI), LVEF, LVFS, and SET will be analyzed using descriptive statistics. Observations by timepoint and change from Baseline (predose in that dosing period) for each timepoint will be summarized by treatment arms. Change from Baseline will be analyzed with attention to relationship to time postdose, dose level, and comparison with placebo. For SAD Cohorts, placebo-adjusted change from Baseline will be calculated for each subject at each postbaseline timepoint and then summarized at each dose level. In addition, for SAD and MAD Cohorts, least square means of placebo-adjusted change from Baseline for the key PD parameters (LVSV [derived from

LVOT-VTI], LVEF, LVFS, SET) at each postbaseline time point at each dose level may be estimated using mixed model.

Pharmacokinetic/Pharmacodynamic Analyses:
Correlations of LVSV (derived from LVOT-VTI), LVEF, LVFS, SET, and/or vital signs with MYK-491 dose and/or plasma concentration may be assessed. [redacted]

Sample Size Considerations:
No formal statistical hypothesis testing will be performed. In Part 1, enrollment of 4-8 patients per cohort is planned and in Part 2, 8 patients per cohort with the potential to expand to 24 patients, with up to an additional 2 replacements per cohort, in order to meet study objectives. Based on the study design, the sample size is considered appropriate to explore tolerability and safety parameters, PK profile, and PD effects of MYK-491.

Compliance Statement:
This study will be conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines; US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; European Union (EU) GCP and Good Manufacturing Practices (GMP); and the principles enunciated in the Declaration of Helsinki and all human clinical research regulations where the study is to be conducted.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

λ_z	apparent first-order terminal elimination rate constant
ACE	angiotensin converting enzyme
ADP	adenosine diphosphate
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
[redacted]	[redacted]
CK-MB	creatine kinase-MB
C_{max}	maximum observed plasma concentration
CRT	cardiac resynchronization therapy
CV	cardiovascular
[redacted]	[redacted]
[redacted]	[redacted]
DB	double-blind
[redacted]	[redacted]
DILI	drug-induced liver injury
EC	ethics committee; refers to an IRB or IEC or equivalent
ECG	electrocardiography, electrocardiogram
eCRF	electronic case report form

EDC	electronic data capture
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LVEF	left ventricular ejection fraction
LVFS	left ventricular fractional shortening
LVOT-VTI	left ventricular outflow tract-velocity time integral
LVSV	left ventricular stroke volume
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
NOAEL	no observable adverse effect level
QTc	heart rate-corrected QT interval

QTcF	QT interval, corrected using Fridericia's formula
PD	pharmacodynamic(s)
[redacted]	[redacted]
PI	principal investigator
PK	pharmacokinetic(s)
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SET	systolic ejection time
sMDRD	simplified Modification of Diet in Renal Disease
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent first-order terminal elimination half-life
$t_{1/2z}$	the apparent terminal-phase elimination half-life
TBL	total bilirubin
T_{max}	time of maximum observed plasma drug concentration
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States

1 INTRODUCTION

This is the first administration of MYK-491 to patients with heart failure. Heart failure affects about 6.5 million people in the United States (US) and its prevalence is increasing due to the aging of the population. Despite therapeutic advances made over the past 10 to 20 years, it remains a major source of morbidity and mortality, comparable to cancer, with more than 50% of heart failure patients dying within 5 years. Heart failure is the leading cause of hospitalization in Medicare patients in the US and represents a major financial burden to society (Braunwald 2013; Yancy et al, 2013; Benjamin et al, 2017). New, innovative therapies are therefore desperately needed for this condition.

Contemporary medical therapy for HFrEF centers on counteracting the effects of neurohormonal activation with β-adrenergic blockers, diuretics, and modulators of the renin-angiotensin-aldosterone-system. Although these drugs attenuate some of the maladaptive consequences and improve clinical outcomes, none address the underlying causal pathways of myocardial dysfunction.

Several inotropic agents are used in clinical practice to augment cardiac contractility by increasing intracellular calcium or cyclic adenosine monophosphate, mechanisms that increase myocardial oxygen demand. Their use is limited to short-term therapy in patients with refractory or end-stage heart failure because chronic studies with these drugs have demonstrated increased mortality due to arrhythmias and ischemia. However, these drugs do improve hemodynamics and symptoms.

An alternative approach to improving hemodynamics is to target the contractile apparatus directly. Omecamtiv mecarbil is a small-molecule myosin ATPase allosteric activator currently in clinical development for patients with chronic heart failure. It enhances cardiac contractility by increasing the number of actin/myosin crossbridges, effectively increasing calcium sensitivity at the level of the sarcomere. Clinically, this mechanism is reflected in a prolongation of the systolic ejection time (SET). Initial studies in patients with chronic heart failure treated with omecamtiv mecarbil suggest that modulation of the sarcomere by myosin activation increases stroke volume and promotes beneficial cardiac reverse remodeling. In the Phase 2 COSMIC Trial conducted in HFrEF patients, omecamtiv was associated with

increased stroke volume and beneficial cardiac reverse remodeling. Although high exposures have been associated with myocardial ischemia in a few subjects (Teerlink et al, 2011), in the vast majority of patients, the treatment was well-tolerated. A low-level increase in troponin was commonly observed without associated clinical ischemia or ECG changes (Teerlink et al, 2016). A large randomized cardiovascular (CV) Outcome Phase 3 trial, GALACTIC-HF, is currently ongoing in HFrEF patients (ClinicalTrials.gov Identifier: NCT02929329).

MyoKardia undertook detailed biochemical and biophysical studies to understand the mechanistic contributors to increased SET by myosin activators. The focus was on 2 steps within the actin/myosin chemomechanical cycle: phosphate release (a measure of crossbridge formation) and adenosine diphosphate (ADP) release (a measure of crossbridge detachment). It was hypothesized that enhanced crossbridge formation increases contractility, whereas impaired detachment contributes to further prolongation of ejection time to achieve a given degree of contraction. Based on this premise, MyoKardia identified MYK-491, a myosin modulator that increases crossbridge formation (measured as phosphate release) without inhibition of crossbridge detachment (measured as ADP release).

[redacted]

MyoKardia considers that nonclinical data and preliminary data from healthy volunteers support the safe initiation of clinical pharmacology studies of MYK-491 in patients with heart failure. [redacted]

1.1 Background

1.1.1 In Vitro Studies

MYK-491 reversibly binds to myosin, increasing the number of myosin/actin crossbridges available to participate in the strongly bound state of the chemomechanical cycle, thereby increasing contraction. MYK-491 does not affect any of the other states of the cycle, nor does it affect calcium homeostasis.

MYK-491 is biochemically specific for striated muscle myosin and selective for the slow-twitch isoform found in the heart. Studies in skinned fibers confirm activity in slow-twitch fibers (skeletal or cardiac) with minimal effect on fast-twitch skeletal fibers. Studies in adult rat cardiac ventricular myocytes demonstrated exposure-dependent increase in contraction and confirm that MYK-491 does not modulate calcium homeostasis. Studies in skinned cardiac myofibers have demonstrated exposure-dependent increased sensitivity to calcium.

[redacted]

1.1.3 Drug Metabolism

Pharmacokinetics of MYK-491 were determined following single oral and intravenous (IV) doses of MYK-491 to FVB mouse, Sprague-Dawley rat, cynomolgus monkey, beagle dog, and farm pig (IV only). [redacted]

No unanticipated accumulation in plasma or tissues has been observed in nonclinical studies performed to date. Metabolic profiles were generated using rat, monkey, dog, and human liver microsomes and hepatocytes. All of the identified metabolites formed from incubations with human hepatocytes were also formed in incubations with either rat or dog hepatocytes. These results thereby validated the use of rat and dog for toxicology studies.

[redacted]

[redacted]

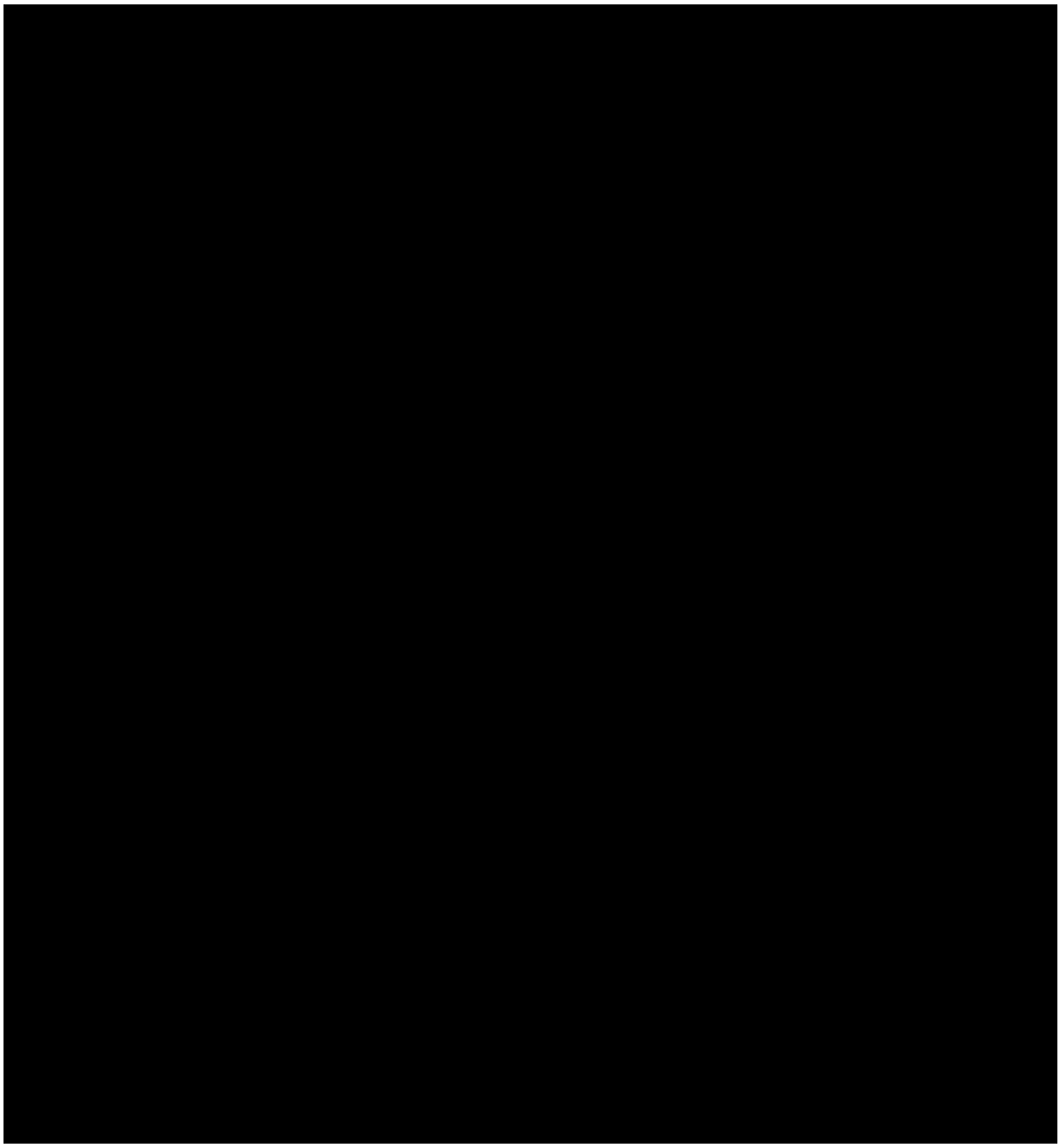
1.1.5 MYK-491

Please refer to the Investigator's Brochure (IB) for more detailed information on MYK-491.

1.2 Clinical Studies

A single-ascending dose, double-blind (DB), placebo-controlled tolerance, PK, and PD study in healthy volunteers has been completed (MYK-491-001). A total of 64 subjects were enrolled across 8 cohorts, each consisting of 8 healthy volunteers (6 receiving MYK-491 and 2 receiving placebo). [redacted]
No additional Dose-Escalation Cohort(s) are planned.

In general, MYK-491 has been well-tolerated at all doses. [redacted]



1.3 Known and Potential Risks and Benefits

There is no expectation of clinical benefit for the patients who volunteer to participate in this study. The risks of administering MYK-491 to humans are unknown, but based on nonclinical observations and the administration to healthy volunteers, MyoKardia considers that it can safely be administered if patients are carefully observed. Safety testing in other mammalian species demonstrates that dose-limiting toxicity is related only to on-target exaggerated pharmacology with development of myocardial ischemia and heart failure at high doses and after prolonged exposures. No off-target adverse effects were observed in the toxicology studies. The initial doses of MYK-491 given in this study have already been

administered as a single dose to healthy volunteers in a previous study (MYK-491-001) and shown to be well-tolerated (see above Section 1.2).

In Part 1 (single-ascending dose), patients will be admitted to the clinical research facility for dosing and will remain confined for a total of 3 days and 3 nights for each of 3 or 4 dosing periods or longer if the Safety Review Committee (SRC) believes it is important to assure the safety of the patients or to obtain robust PK and/or PD data. In no case will the patients remain confined for more than 5 days after the administration of the last dose of MYK-491.

In Part 2 (multiple-ascending doses), patients will be confined to the clinical research facility for the duration of the dosing and 2 days after dosing unless they have an ICD. Patients with the ICD will be observed frequently either in the research facility or by a home health nurse for all of the dosing, and the collection of the study parameters (plasma samples, safety labs, vital signs, and TTEs). Thus, all patients will be under close supervision, and the clinic staff will be responsible for the ongoing safety and well-being of the patients while they are confined for during the dosing periods. If a home health nurse is utilized, the nurse and site will be in daily communication to ensure safety. The initial dose for the MAD Cohort is predicted to reach exposures that have previously been observed in patients in Part 1. [redacted]

2 RATIONALE FOR THE STUDY AND FOR DOSE AND DOSING SCHEDULE

2.1 Rationale for the Study

MYK-491 was well-tolerated in healthy volunteers after the administration of single doses (see Section 1.2) and has been studied extensively preclinically across a variety of pharmacological activity and nonclinical safety evaluation platforms. The purpose of this study is to determine the safety, tolerability, PK profile, and PD activity of MYK-491 in patients with HFrEF. In animal studies, paced dogs with heart failure were found to be more sensitive to the positive inotropic effects of MYK-491 compared to healthy dogs. Patients suffering from HFrEF have reduced cardiac output and reduced organ perfusion. It is therefore important to understand any potential differences in the safety, tolerability, PK, and PD inotropic effects of MYK-491 in patients with HFrEF compared to healthy volunteers. This study will allow for the initial assessment of the therapeutic dose/concentration range of MYK-491 and guide the choice of doses to be studied in subsequent trials in HFrEF patients.

Randomization and blinding are employed to minimize bias in ascertainment of potential causality with respect to overall tolerability and adverse clinical and laboratory events. A placebo control is used to provide a degree of assay sensitivity with respect to these parameters.

2.2 Rationale for Dose and Dosing Schedule

2.2.1 Part 1 (SAD) Cohort 1 Dose Levels

2.2.1.1 Low-Dose Level Cohort 1

[redacted]

[redacted] the 175 mg dose has been selected as the initial dose level in Cohort 1.

2.2.1.2 Second Dose Level Cohort 1

The second dose that will be studied in Cohort 1 is 350 mg. [redacted]

[redacted]

2.2.1.3 Third Dose Level Cohort 1

A third active dose may be administered to some patients in Cohort 1. The third active dose will be determined for individual patients by the SRC after reviewing data for the first and second doses. The third dose may be different for each subject based on individual PK (or dose/exposure) [redacted].

2.2.2 Part 1 (SAD) Cohort 2 Dose Levels

The selection of the 3 doses for Cohort 2 will be determined based on SRC review of data from Cohort 1 together with other available data on MYK-491.

[redacted] Cohort 2 could also include less than 3 doses.

The SRC may determine that some or all of the doses in Cohort 2 may be given in 2 aliquots as a split dose, in order to achieve higher exposure. The SRC will determine the timing of the administration of the second half of the dose relative to the first.

2.2.3 Part 2 (MAD) Cohort A Dose

The dose level chosen for Cohort A in Part 2 of the study is 75 mg given twice daily.

[redacted]

2.2.4 Part 2 (MAD) Cohorts B and C Doses

[redacted] The actual medium and high doses will be determined and confirmed by the Safety Review Committee (SRC) after data from prior cohorts are reviewed. [redacted]

2.3 Rationale for Exceeding NOAEL

It should be noted that achieving plasma concentrations in humans exceeding the NOAEL maximum observed plasma concentration (C_{max}) values [redacted] is likely to be necessary in order to adequately evaluate the safety and tolerability of pharmacologically active single doses of MYK-491 in humans (healthy subjects and heart failure patients), in light of the following considerations:

- MYK-491 is expected to have a PD effect in humans because the primary pharmacology studies establishing the biochemical mechanism of action confirmed its activity using recombinant human myosin (IB, Sections 4.1.2 and 4.2.1). However, differences in free fraction/protein binding and in potency on cardiac tissue may account for observed interspecies differences.
- [redacted]
- In the definitive toxicology studies (IB, Sections 1.6 and 4.4), all toxicities above the NOAEL were consistent with on-target exaggerated pharmacological effects of MYK-491. No evidence of off-target toxicity was observed.
- The PK profile observed in humans is generally in line with the one predicted from nonclinical PK and toxicokinetic data, which provide confidence in the exposures with further dose escalation.

- Both studies (491-001 and 491-003) were/will be conducted under the surveillance of Study Safety Review Committees (1 each for 491-001 and 491-003 studies).
- In addition, Study 491-003 includes adequate safeguards to maximize patient safety. These include but not are limited to: close patient monitoring with serial assessments of vital signs, AEs, safety labs (including troponin), serial ECGs, continuous real-time telemetry and/or Holter, and PK data. Also, Study 491-003 includes clear stopping criteria for both individual patients and for the overall study based on observed safety/tolerability, AEs, and predefined levels of on-target TTE PD activity.

All the above features provide a strong rationale to identify, in a safe manner and with appropriate safeguards, a clear pharmacologically active dose for MYK-491, a new and innovative oral positive inotropic agent for heart failure patients.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to establish preliminary safety and tolerability of single- and multiple-ascending oral doses of MYK-491 in ambulatory patients with stable HFrEF.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To establish preliminary human PK of MYK-491 after single- and multiple-ascending oral doses of MYK-491 in patients with HFrEF
- To determine changes in left ventricular stroke volume [LVSV] derived from left ventricular outflow tract-velocity time integral [LVOT-VTI]), left ventricular ejection fraction (LVEF) and change in left ventricular fractional shortening [LVFS] with MYK-491 after ascending single and multiple doses compared with Baseline and placebo as measured by transthoracic echocardiography (TTE)
- To determine changes in SET with MYK-491 after ascending single and multiple doses compared with Baseline and placebo as measured by TTE
- To determine changes in PD dose/concentration effects (change in LVSV [derived from LVOT-VTI], LVEF, LVFS) with MYK-491 compared with Baseline and placebo after ascending single and multiple doses, as measured by TTE

4 OVERALL STUDY DESIGN AND PLAN

4.1 Study Design

This is a two-part study. Part 1 will evaluate single-ascending doses of MYK-491 (SAD Cohorts) and Part 2 will evaluate multiple-ascending doses of MYK-491(MAD Cohorts).

Note: Part 2 (MAD portion) of the study is planned to start before Cohort 2 of Part 1 (SAD Cohort) is complete. If a patient at a site qualifies for enrollment in either Part 1 (SAD) or Part 2 (MAD), Part 2 will generally take priority; however, a patient may enroll in both, ie Part 1 (SAD) followed by Part 2 (MAD) or Part 2 (MAD) followed by Part 1 (SAD). In such cases, sites should consult with the monitoring team to discuss details.

4.1.1 Part 1 Study Design

Part 1 is a randomized, crossover, DB, placebo-controlled, two-cohort, sequential ascending (oral) single-dose study in ambulatory patients with heart failure. All patients will receive placebo and 2 or 3 active doses of MYK-491. Each patient will undergo sequential, single-dose treatment events separated by no fewer than 5 days and no more than 14 days. Patients in Cohort 1 may also return for a fourth dosing period (open label) after the SRC reviews available data and recommends the dose. Patients enrolled prior to the implementation of Amendment 1 may be offered the opportunity to return for the open-label period. Patients who return for this additional period must sign the amended informed consent form (ICF). Patients in Cohort 2 may participate in 2 to 4 dosing periods, based on SRC decision. Patients will be randomized to 1 of the different dosing sequences outlined in Figure 1. Multiple patients can be dosed at the same time or during the same week depending on administrative issues, ie, capacity and scheduling.

For each dosing period, patients will be admitted to the clinical site on Day -1. Patients will be assessed for absence of exclusion criteria (eg, new lab abnormalities and/or conditions that indicate the patient is clinically unstable). They will receive MYK-491 or placebo in the morning of Day 1 followed by serial PK and PD assessments, as well as serial safety assessments. Patients will be discharged on Day 3 (ie, ~48 hours following Day 1 dosing). An additional outpatient plasma PK sample will be taken on the morning of Day 4 at 72 hours postdose.

Before administering a dose, the investigator or the subinvestigator will review all available safety data, including vital signs, safety laboratory values including locally assayed troponin concentrations, TTEs, ECGs, and ECG telemetry. Dosing with DB treatment will take place at the same time each of the dosing days. Background concomitant medications, including diuretic if applicable, should also be administered at same time each of the dosing days. Prior to dosing, any patient with a predose resting HR ≥ 95 bpm will be considered ineligible and not treated. HR is the mean of 3 measurements.

A full PK profile and multiple TTEs and ECGs will be obtained at Baseline and after each dose. Patients will return for a final safety Follow-up visit 7 days (± 1 day) following the last dose.

During the study, the patients should continue to ingest their medications for the treatment of their congestive heart failure and other medical conditions at the same doses and as close to the same times as usual.

4.1.2 Part 2 Study Design

This is a randomized, parallel-group, DB, placebo-controlled, adaptive design, sequential ascending (oral) multiple-dose study in stable patients with heart failure. Three MAD Cohorts (A, B, C) are initially planned (with additional optional cohorts) with 8 patients each (2 placebo, 6 active). An SRC will review results from each cohort and will determine the dose and confirm initial sample size for the subsequent cohort. Additionally, the first 3 patients in each cohort must have LVEF ≥ 25%; the SRC will review preliminary safety data from these patients and decide whether to open cohort enrollment to patients with LVEF < 25%.

After Screening and qualification, patients will be confined to a clinical testing facility from Day 1 (Check-in) to Day 11. This includes an initial 2-day placebo dosing period (Days 1 and 2), followed by a 7-day randomized treatment period (Days 3 through 9) and 48 hours of monitoring following the last dose of study drug (Days 10 and 11). An additional outpatient plasma PK sample will be taken on the morning of the day following discharge at 72 hours after the last dose (Day 12).

Note: **Confinement is not required for patients with an ICD**: Patients with an ICD may reside for some or all of the period from Day 1 to 12 in close proximity to the Clinical Testing Unit, eg, at a hotel, provided they can return for all study drug dosing and all study assessments, including but not limited to all serial PK and TTEs. Alternatively, patients may be visited by a home health nurse for study drug administration and for any assessments that can be performed away from the clinical site.

Each patient will initially receive placebo BID for 2 days (Days 1 and 2) in single-blinded manner ("run-in" during acclimatization to confinement in the Clinical Testing Unit) prior to receiving the randomized DB study drug treatment on Day 3. All patients will then receive either placebo or active MYK-491 for 7 days (Days 3 through 9). More than one patient can be dosed in a cohort at the same time or during the same week depending on administrative issues, i.e., capacity and scheduling.

Patients will be dosed twice daily (every 12 hours). Doses may occur ± 2 hours from scheduled dosing times as long as doses are separated by at least 10 hours and by no more than 14 hours. The exception to the twice daily dosing is on Day 9 (last dose of randomized DB study drug treatment). On Day 9, a single morning dose will be administered followed by 72 hours of PK and PD assessments.

Before each dosing event, all available safety data from the previous days will be reviewed (for non-confined patients, if a home health nurse is utilized, the nurse and site will be in daily communication to ensure safety). Dosing of DB treatment will take place at approximately the same time each day.

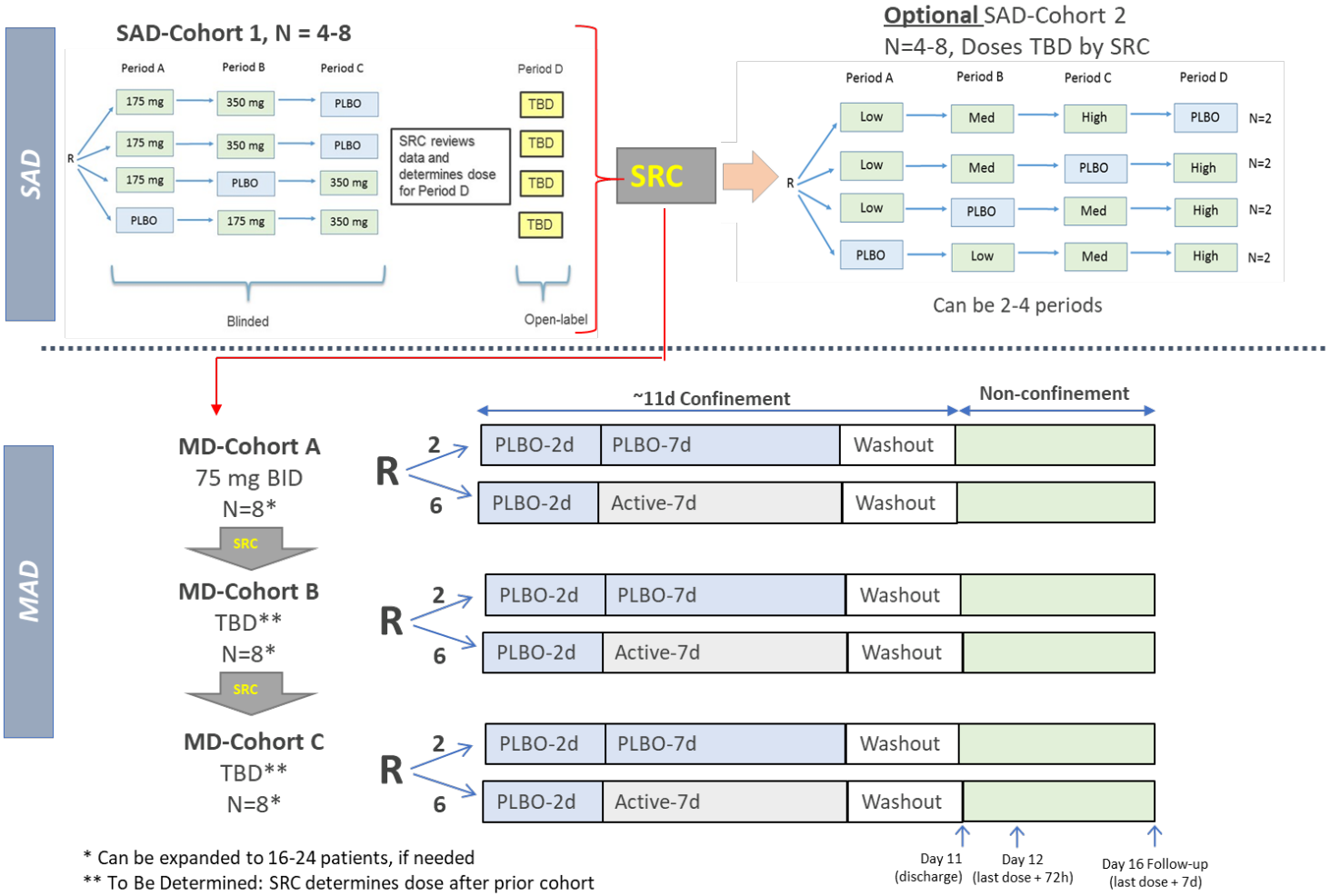
A full PK profile and multiple TTEs and ECGs will be obtained on Days 3 and 9 (corresponding to first and last day of DB treatment respectively) before and after the morning dose.

Patients will return for a Follow-up visit 7 days following the last dose of study drug. In case of premature permanent treatment discontinuation, end-of-treatment visit (same assessments as Day 9) will be performed as close as possible to last DB dose (ie, as best as possible on day of last dose or next day). This visit should include (but is not limited to) the following assessments: TTE, PK, 12-lead ECG, safety labs, troponin and adverse events.

Note: Screening may continue during planned and unplanned SRC meetings. The protocol-specified Screening window may be extended to account for delays due to SRC meetings.

Recommendations by the SRC will include, but not be limited to: (a) evaluation of dose-modification and dose-stopping criteria; (b) doses to be given in specified cohorts; (c) size of specified cohorts; and (d) modification of the number and timing of PK and PD assessments (see Section 4.4.1).

Figure 1 Study Schema



BID, twice daily; MAD, multiple-ascending doses; PLBO, placebo; QD, once daily; R, randomization; SAD, single-ascending doses; SRC, Safety Review Committee; TBD, to be determined (Period D is optional, based on SRC evaluation).
NOTE: Additional Cohorts D and E, and possible additional cohorts, may be enrolled, eg to explore QD dosing or an alternative BID regimen.

4.2 Stopping Criteria

For Part 1, as each patient will receive several, ascending single doses, there are stopping criteria for which further dosing of an individual patient must be suspended, and also stopping criteria for the study to be considered by SRC.

For Part 2, as each patient will receive 9 days of study drug treatment (including 2 days of single-blind placebo and 7 days of DB active or placebo), there are dose-modification criteria and stopping criteria for individual patients, as well as stopping criteria for the study to be considered by SRC.

4.2.1 Stopping Criteria for an Individual Participant in Part 1 (SAD)

If the following events occur, as determined by investigator assessment, dosing of a patient must be suspended, AE/SAE forms completed as applicable, and the event reviewed by the SRC. The SRC may decide to perform selected unblinding pertaining to one or several periods for a given patient or recommend that further dosing of the patient be suspended. The following is a list of possible criteria for suspension of dosing of an individual and review of the data by the SRC:

- A patient has drug-related cardiac ischemia, as determined by investigator (Note: The whole context [ie, clinical symptoms, ECG, and cardiac biomarkers such as troponin, CK-MB, cardiac imaging, and coronary angiograms, if applicable] should be taken into account by the investigator in making that determination since patients enrolled in the study are likely to have an abnormal ECG and/or elevated and/or fluctuating troponin at Baseline in relation to their heart failure condition. This information will also be submitted for subsequent central adjudication.
- A patient has an increase in the maximal SET > 75 ms on 2 sequential TTE recordings based on site evaluations.
- A patient has clinically significant and drug-related changes in his/her vital signs that are persistent over a period of time such as a new arrhythmia, systolic BP < 90 or > 170 mm Hg, or HR < 40 or > 100 bpm. The diagnosis and clinical significance of a new arrhythmia will be adjudicated by the SRC as it relates to this stopping criterion, including core lab assessments as appropriate.
- A patient experiences a drug-related SAE (including, but not limited to, serious unexpected suspected adverse reactions [SUSARs] or coronary ischemic events).
- A patient has a QTc interval > 500 ms (Fridericia's correction, average of triplicate ECGs) not attributable to pacing or prolonged QRS duration.
- Any patient fulfills the criteria for potential drug-induced liver injury (Hy's Law). These include:
  - Aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) are > 3 times ULN with an associated elevation of total bilirubin (TBL) > 2 times ULN without evidence of hemolysis, or

- ALT or AST activity that is > 5 times ULN, or
- TBL > 3 times ULN.

- A patient has 2 successive echocardiograms that show a > 50% relative increase from Baseline in at least 2 contractility indices (LVSV [derived from LVOT-VTI], LVEF, or LVFS).

4.2.2 Criteria for Unscheduled SRC Review of the Study in Part 1 (SAD)

If any of the following events occur at any time during the study, an ad hoc SRC review will be performed. Dosing may be paused for SRC review; eg, in case of drug-related SAEs, SUSAR, or coronary ischemic events (see Section 4.2.1). Based on the review of the data, the SRC may decide to unblind selected patients, terminate the study, continue dosing the patients using a modified dose-escalation scheme, or continue the dosing of the patients.

- The dosing of 2 patients who received MYK-491 is suspended because they reached the individual stopping criteria. The SRC will adjudicate stopping criteria.
- During the planned review by the SRC after the initial 4 patients in Cohort 1, evidence of PD activity will be considered to have been observed and dose escalation will be terminated if there is a Baseline-corrected, group mean relative increase of > 40% in 2 successive timepoints in 2 contractility indices (LVSV [derived from LVOT-VTI], LVEF, LVFS) in patients receiving MYK-491. Placebo-adjusted evaluation may be considered. The study may continue with the enrollment of Cohort 2, but the daily doses to be administered will not be greater than the daily dose that demonstrated the PD activity that terminated dose escalation.
- Any patient receiving MYK-491 experiences a drug-related SAE (including, but not limited to, a SUSAR or coronary ischemic event) that has not also occurred in a patient receiving placebo.
- Two or more patients receiving MYK-491 have QTc prolongation defined as > 500 ms (Fridericia's correction, average of triplicate ECGs) not attributable to pacing or prolonged QRS duration.
- Any patient receiving MYK-491 fulfills the definition for Hy's law:
  - Aminotransferases (ALT or AST) are > 3 times ULN with an associated elevation of TBL > 2 times ULN without evidence of hemolysis, or
  - ALT or AST activity that is > 5 times ULN, or
  - TBL > 3 times ULN.

Note: Screening may continue during an unscheduled SRC meeting, and if dosing is paused, Screening windows may be extended until dosing resumes.

4.2.3 Dose-Modification Criteria for an Individual Participant in Part 2 (MAD)

If the following events occur, as determined by investigator assessment, dosing of a patient should be modified by skipping one dose of study drug and resuming dosing at a lower dose (25% to 50% lower). The lower dose to be administered for a given cohort will be determined by SRC and communicated along with starting dose. [redacted]

- An increase in the maximal SET > 75 ms on 2 sequential TTE recordings based on site evaluations
- A patient has 2 successive echocardiograms that show a > 50% relative increase from Baseline in at least 2 contractility indices (LVSV [derived from LVOT-VTI], LVEF, or LVFS).

  Note: Day 3, predose echo in the morning should be used as Baseline for local site evaluation.

In addition, in case of an AE, DB treatment may be temporarily suspended, as determined by the investigator. In such cases, the Sponsor medical monitor should be contacted without delay.

4.2.4 Stopping Criteria for an Individual Participant in Part 2 (MAD)

If the following events occur, as determined by investigator assessment, dosing of a patient must be terminated, AE/SAE forms completed as applicable, and Sponsor should be informed without delay:

- Drug-related coronary ischemia, as determined by investigator

  Note: Whole context ie, clinical symptoms, ECG, cardiac biomarkers such as troponin, CK-MB, cardiac imaging, and coronary angiograms, if applicable, should be taken into account by the investigator in making that determination since patients enrolled in the study are likely to have elevated and/or fluctuating troponin and/or abnormal ECGs at Baseline in relation to their heart failure condition. This information will also be submitted for subsequent central adjudication.
- The patient has clinically significant and drug-related changes in his/her vital signs that are persistent over a period of time such as a new arrhythmia, systolic BP < 90 or > 170 mm Hg, or HR < 40 or > 100 bpm. The diagnosis and clinical significance of a new arrhythmia will be adjudicated by the SRC as it relates to this stopping criterion.
- A patient experiences a drug-related SAE (including, but not limited to, SUSARs or coronary ischemic events).
- A patient has a QTcF interval > 500 ms (Fridericia's correction, average of triplicate ECGs) not attributable to pacing or prolonged QRS duration.
- Any patient fulfills the criteria for potential drug-induced liver injury (Hy's Law). These include:

- Aminotransferases (ALT or AST) are > 3 times ULN with an associated elevation of TBL > 2 times ULN without evidence of hemolysis, or
- ALT or AST activity that is > 5 times ULN, or
- TBL > 3 times ULN.

4.2.5 Criteria for Unscheduled SRC Review of the Study in Part 2 (MAD)

If any of the following events occur at any time during the study, an ad hoc SRC review will be performed. Dosing may be paused until SRC review; eg, in case of drug-related SAEs, SUSAR, or coronary ischemic events. Based on the review of the data, the SRC may decide to unblind selected patients, terminate the study, continue dosing the patients using a modified dose-escalation scheme or continue the dosing of the patients.

- Two patients in a cohort receiving MYK-491 reached individual dose-modification and/or stopping criteria. The SRC will adjudicate stopping criteria.
- Any patient receiving MYK-491 experiences a drug-related SAE (including, but not limited to, a SUSAR or coronary ischemic event) that has not also occurred in a patient receiving placebo.
- Any patient receiving MYK-491 fulfills the definition for Hy's law
  - Aminotransferases (ALT or AST) are > 3 times ULN with an associated elevation of TBL > 2 times ULN without evidence of hemolysis, or
  - ALT or AST activity that is > 5 times ULN, or
  - TBL > 3 times ULN.

Note: Screening and dosing may be paused or may continue during an unscheduled SRC meeting.

4.3 Study Duration

The overall expected study duration is approximately 24 months.

In Part 1 (SAD), each patient is expected to be in the study no more than 77 days: up to 28 days for Screening plus up to 42 days for dosing including 7 days for follow up after the last dose (or longer if clinically indicated). Patients returning for an additional dosing period in Cohort 1 may have prolonged participation. Patients will be resident at the clinical site for each dosing period, each consisting of check-in on Day -1, dosing the following morning (Day 1) followed by ~24 hours of serial PD and ~48 hours of serial PK assessments, followed by discharge the following morning (Day 3). An additional outpatient plasma PK sample will be taken on the morning of Day 4 at 72 hours postdose.

In Part 2 (MAD), patients are expected to be in the study no more than 56 days: up to 28 days for Screening plus up to 28 days for (a) scheduling, (b) 11 days of dosing and associated assessments, and (c) 7 days of follow up after the last dose (or longer if clinically indicated). Patients who are in Screening while dosing is on hold due to SRC meeting may have

participation extended to allow dosing to be scheduled after SRC has convened. While waiting for a cohort to open to patients with LVEF < 25%, these patients may be in Screening up to 12 weeks (if the patient remains stable) while the SRC convenes.

Total time in the study may be longer for patients who participate in both Part 1 (SAD) and Part 2 (MAD).

4.4 Safety Review Committee

4.4.1 Safety Review Committee Meetings

In Part 1 (SAD), the SRC will meet to review the data after each patient in Cohort 1 has completed the first 3 dosing periods (175 mg, 350 mg, and placebo). The SRC will determine if the subject will receive a third active dose level (open-label Period D) and what the dose should be. The SRC will also meet at the conclusion of Cohort 1 and after all of the patients have completed the study. The SRC will review all relevant data to select the dosing levels for Cohort 2. During Cohort 2 dosing, the SRC will meet to review the data after every 2 to 4 patients have completed all dosing periods. The SRC may recommend dose modification for the remainder of the cohort.

In Part 2 (MAD), the SRC will review data after at least 4 to 8 patients from a cohort have been dosed. The SRC will then confirm the sample size, dose, and regimen (BID or QD) for next MAD Cohort, or may decide to expand current MAD Cohort. Additionally, the SRC will review preliminary safety data after the first 3 patients in each cohort, with LVEF ≥ 25%, to decide whether to open cohort enrollment to patients with LVEF < 25%.

A Notification Letter with the rationale for the choice of doses selected by the SRC will be sent to the investigator, who will inform the appropriate Institutional Review Boards (IRBs) as necessary.

Refer to Section 4.2.2 and Section 4.2.5 for criteria leading to ad hoc SRC meetings.

SRC data review will be based on unblinded data summary (see Section 6.2).

4.4.2 Composition of Safety Review Committee

The SRC will be composed of at least 5 members including 2 Sponsor representatives and 3 independent cardiologists. The Sponsor's medical monitor will act as chair of the committee. Sponsor representatives (including the Sponsor's medical monitor) will not be voting members. The 3 independent cardiologists will be the only voting members. Three members including the Sponsor's medical monitor and 2 independent cardiologists need to be present for a quorum, with at least 2 independent cardiologists available for voting. In case of a tie, all 3 independent cardiologists should vote. Other individuals may attend the meeting to share data, but they will not be voting members. All dosing recommendations for individual patients in Period D in SAD Cohort 1 will be discussed with the investigators whose patient it is.

Following review of the existing study data, the SRC may consider recommending changes to the protocol intended to enhance patient safety, data integrity, data robustness, or efficiency of study conduct. As part of the review process, the SRC may need to review the unblinded data. SRC members should consider the possible scenarios and the nature of the decision on study continuation or dose level and what they would consider the appropriate next step (eg, repeat the dose level, continue the dose escalation with reduced dose-escalation steps, or terminate the study).

- All substantial changes to the study protocol will be captured in the meeting minutes, and a protocol amendment will be instituted if needed.
- Nonsubstantial changes to the study approved by the SRC may be implemented immediately without a protocol amendment, and the IRB/Ethics Committee (EC) (as defined in Section 12.3) will be immediately notified in writing of the change. Examples of these changes are: reducing the dose of the study medication, expanding enrollment, or adjusting timepoints for procedures. Additional blood samples for PK may be obtained but no more than 2 additional timepoints for each dosing period (a maximum increase of 36 mL of blood in total) will be requested. An increase in the number of TTEs, ECGs, or vital sign determinations that may be obtained will also be considered a nonsubstantial change, as these are noninvasive procedures, but no more than 2 additional TTEs will be obtained per dosing period.

For Part 2 (MAD), the SRC will review data after at least 4 to 8 patients from a cohort have been dosed. The SRC will then confirm the sample size, dose, and regimen (BID or QD) for next MAD Cohort, or may decide to expand current MAD Cohort.

All decisions of the SRC will be documented and provided as appropriate to parties involved with the study.

4.5 Independent Safety Adjudication

Suspected cardiac ischemia (new chest pain or angina equivalent, or new ECG changes suggestive of ischemia), new or worsening ventricular arrhythmia, and troponin elevations will be reviewed centrally by an independent safety Adjudication Committee. Adjudication package will include relevant associated clinical data and source documents including but not limited to ECGs.

5 SELECTION AND WITHDRAWAL OF STUDY POPULATION

In Part 1 (SAD), enrollment of at least 4, and no more than 8, patients is planned for Cohort 1, with 1 patient randomized to each sequence of dose escalation and placebo administration (see Figure 1). For Cohort 2, at least 4, and no more than 8, patients will be enrolled and 2 patients will be randomized to each sequence of dose escalation.

There will be an option for the SRC to expand Cohort 1 or Cohort 2 to meet study objectives. Decision to expand the number of patients or not will be made by the SRC. Two additional patients may be enrolled as replacements for drop-outs in each cohort, so the maximum number of patients that may be enrolled will be approximately 32.

In Part 2 (MAD), enrollment of a total of a minimum of 24 patients is planned, with 8 patients enrolled the low-dose group (Cohort A), 8 patients enrolled in the medium-dose group (Cohort B) and 8 patients enrolled in the high-dose group (Cohort C). In addition, the planned size of Cohorts D and E, and possible additional cohorts, will be 8 patients each. The final total sample size for Part 2 will not exceed 96 patients if the SRC decides to expand one or more cohorts up to 24 patients. In addition, up to 2 additional patients may be enrolled per cohort as replacements for drop-outs or patients non-evaluable for PK-PD at steady-state.

Cohorts in Part 2 will be randomized 3:1 (active drug: placebo). Additional patients may be enrolled in each cohort as replacements for drop-outs.

Note: Part 2 (MAD portion) of the study is planned to start before Cohort 2 of Part 1 (SAD Cohort) is complete. If a patient at a site qualifies for enrollment in either Part 1 (SAD) or Part 2 (MAD), Part 2 will generally take priority. However, a patient may also enroll in both; ie, Part 1 (SAD) followed by Part 2 (MAD) or Part 2 (MAD) followed by Part 1 (SAD). If a patient will cross over, sites should consult with the monitoring team to discuss prior to randomization.

5.1 Inclusion Criteria

This study is to be performed in patients with HFrEF due to any etiology. Each patient 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 80 years of age at the Screening visit
3. Body mass index (BMI) 18 to 40 kg/m^2, inclusive, at the Screening visit and all required assessments can be reliably performed.
4. Sinus rhythm or stable atrial pacing with mean resting HR 50-95 beats per minute (bpm), inclusive (Patient will be ineligible to dose if, on Day 1, the predose HR measurement is $\geq$ 95 bpm. Heart rate is the mean of 3 measurements taken 1 minute apart. A single measurement would not make a patient ineligible.)
5. Has stable, chronic HFrEF of moderate severity as defined by all of the following:

- For the first 3 patients in each MAD Cohort testing a new (higher) daily dose: documented LVEF 25% to 35% during Screening (as confirmed by ECHO Central Lab)
- For other patients in the MAD Cohorts (and all patients in SAD Cohorts): documented LVEF 15% to 35% during Screening (as confirmed by ECHO Central Lab)
    - LVEF must be confirmed with second screening ECHO to be performed at least 7 days after initial screening ECHO. Results of both must meet inclusion criteria and must be received from core lab prior to dosing. In the event of extended screening windows due to SRC reviews, effort should be made to ensure second ECHO is near planned time of randomization.
- Chronic medication for the treatment of heart failure consistent with current guidelines that has been given at stable doses for ≥ 2 weeks with no plan to modify during the study. This includes treatment with at least one of the following unless not tolerated or contraindicated: beta-blocker, angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB)/angiotensin receptor neprilysin inhibitor (ARNI).

6. Female patients must not be pregnant or lactating. Male patients (including men who have had vasectomies), as there may be a risk of drug being secreted in the ejaculate, should use barrier methods for the duration of the study and for 3 months after the last dose of study medication. All patients, if sexually active, must be using one of the following highly-effective birth control methods from the Screening visit through 3 months after the last dose of investigational medicinal product (IMP):
    - Hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), or intrauterine hormone-release system (IUS) plus barrier (eg, male using condom or female using diaphragm or cervical cap)
    - Vasectomy plus barrier
    - Female is surgically sterile for 6 months or postmenopausal for 1 year. 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 1 year or more following cessation of all exogenous hormonal treatments, and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
    - Male patients with postmenopausal partners

5.2 Exclusion Criteria

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

1. Inadequate echocardiographic acoustic windows
2. Any of the following ECG abnormalities: (a) QTcF > 480 ms (Fridericia's correction, not attributable to pacing or prolonged QRS duration, average of triplicate Screening ECGs)

or (b) second-degree atrioventricular block type II or higher in a patient who has no pacemaker

3. Hypersensitivity to MYK-491 or any of the components of the MYK-491 formulation
4. Active infection as indicated clinically as determined by the investigator
5. History of malignancy of any type within 5 years prior to Screening, with the exception of the following surgically excised cancers occurring more than 2 years prior to Screening: in situ cervical cancer, nonmelanomatous skin cancers, ductal carcinoma in situ, and nonmetastatic prostate cancer
6. Positive serologic test at Screening for infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)
7. Hepatic impairment (defined as alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) > 3 times ULN and/or total bilirubin (TBL) > 2 times ULN)
8. Severe renal insufficiency (defined as current estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2 by simplified Modification of Diet in Renal Disease equation [sMDRD])
9. Serum potassium < 3.5 or > 5.5 mEq/L
10. Any persistent out-of-range safety laboratory parameters (chemistry, hematology, urinalysis), considered by the investigator and medical monitor to be clinically significant
11. History or evidence of any other clinically significant disorder, condition, or disease (including substance abuse) that, in the opinion of the investigator or MyoKardia physician, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion, or lead to premature withdrawal from the study
12. Participated in a clinical trial in which the patient 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)
13. Previous participation in a clinical trial with MYK-491, with the exception that patients that participated or were screen failures in one part of this trial may participate in the other part, ie patients may enroll in Part 1 (SAD) followed by Part 2 (MAD) or Part 2 (MAD) followed by Part 1 (SAD), with the following caveats:
    - If the patient has an ongoing AE, has had an SAE, or has met any stopping criteria, the investigator should contact the Sponsor prior to enrolling the patient in a subsequent cohort.
    - Patients must have at least 1 week washout after the end of MAD dosing prior to SAD dosing, or at the end of SAD dosing prior to MAD dosing.
    - Patients do not need to rescreen if MAD screening occurred within 12 weeks of the first SAD dosing, or if SAD screening occurred within 12 weeks of the first MAD dosing. Investigators should verify that patients are clinically stable and no exclusions have occurred during the interim; if > 12 weeks have elapsed or there is clinical instability, then patients should be rescreened.

14. Unable to comply with the study restrictions/requirements, including, in particular, the number of required overnight stays at the clinical site
15. Is employed by, or is a first-degree relative of someone employed by, MyoKardia or Sanofi, the investigator, or his/her staff or family
16. At Screening, symptomatic hypotension, or systolic BP > 170 mmHg or < 90 mmHg, or diastolic BP > 95 mmHg, or HR < 50 bpm. HR and BP will be the mean of 3 measurements taken at least 1 minute apart.
17. Current angina pectoris
18. Recent (< 90 days) acute coronary syndrome
19. Coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) within the prior 3 months
20. Recent (< 90 days) hospitalization for heart failure, use of chronic IV inotropic therapy or other cardiovascular event (e.g., cerebrovascular accident)
21. Uncorrected severe valvular disease
22. Elevated Troponin I (> 0.15 ng/mL) at Screening, based on Central Laboratory assessments. Note: Central Laboratory Troponin I assay ULN is 0.03 ng/mL
23. Presence of disqualifying cardiac rhythms that would preclude study ECG or echocardiographic assessments, including: (a) Current atrial fibrillation, (b) recent (< 2 weeks) persistent atrial fibrillation, or (c) frequent premature ventricular contractions. Note: Patients with active cardiac resynchronization therapy (CRT) or pacemaker (PM) are eligible if initiated at least 2 months prior with no plan to change CRT or PM settings during the study.
24. A life expectancy of < 6 months

5.3 Withdrawal and Replacement of Patients

The investigator will make every reasonable attempt to retain patients so that they complete the study. Two additional patients may be enrolled in each cohort as replacements for drop-outs as long as the patients did not permanently discontinue treatment because of drug-related AEs, or for patients non-evaluable for PK-PD at steady state.

5.3.1 Withdrawal from the Study

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

Patients can:

- Withdraw from treatment and agree to participate in the Early Termination (Safety Follow-up) visit
- Withdraw from treatment and all follow up

The investigator or MyoKardia may withdraw a patient 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).

5.3.2 Follow-up Procedures After Withdrawal

The investigator will make every effort to complete the protocol-specified follow-up procedures as specified in Appendix 1 and Appendix 2, including the follow up of any unresolved AEs until the AE is resolved or stabilized.

If patient discontinues DB treatment prematurely, every effort should be made to have an end-of-treatment visit conducted as soon as possible (ie, as best as possible same day or next day) after the last dose of DB treatment, and perform PK, safety labs, and TTE assessments.

5.3.3 Replacement of Patients

Patients who do not receive MYK-491 or placebo will be replaced. Patients who withdraw/are withdrawn permanently due to a drug-related AE may not be replaced. Patients who drop out of the study after receiving study medication for reasons other than drug-related AEs or patients who are not evaluable for PK-PD at steady state may be replaced at the discretion of MyoKardia in consultation with the investigator, but no more than 2 patients per cohort may be replaced.

All data from patients who receive IMP will be documented and maintained in the clinical trial database.

6 RANDOMIZATION AND BLINDING PROCEDURES

6.1 Randomization

In Part 1 (SAD), eligible patients will be randomized to 1 of 3 (Cohort 1) or 4 (Cohort 2) different treatment sequences (Figure 1).

In Part 2 (MAD), eligible patients will be randomized in a 3:1 ratio to receive active drug or placebo, respectively (Note: All patients will receive placebo on Days 1 and 2).

After reconfirming eligibility, each patient will be randomized within 24 hours of the planned first dose of study medication. If a randomized patient withdraws/is withdrawn from the study, the randomization code cannot be reused. The randomization list will provide replacement randomization codes.

Patients who fail to meet all inclusion criteria or meet any exclusion criterion will not, under any circumstances, be enrolled into the study. There can be no exceptions to this rule. Patients who do not meet the inclusion criteria or meet any exclusion criterion at initial Screening but, in the opinion of the investigator may be eligible for the study upon rescreening, may be rescreened for eligibility.

If a patient who does not meet the selection criteria is enrolled in error and this is identified before dosing, the patient should be withdrawn from the study. If a patient is withdrawn prior to dosing, they will be replaced.

If a patient who does not meet the selection criteria is dosed before the error is identified, the PI will inform the medical monitor of the error, and a joint decision will be made as to whether the patient should continue in the study or be replaced.

6.2 Blinding

All staff at the clinical center, with the exception of the study pharmacist and other pharmacy staff who ensure accurate study medication preparation and dispensation for each patient, will be blinded to the assigned treatment. Any unblinded clinical staff involved in the preparation of the IMP cannot serve in other roles for the study. The randomization list should be kept in a secure location at the site until the database is locked.

In addition, each patient, clinical site monitor, central cardiac core laboratory staff, safety laboratory staff, and CROs responsible for clinical monitoring will also be blinded to the assigned treatment. An unblinded monitor will be assigned to review IMP accountability records throughout the study. Designated MyoKardia pharmacovigilance members will be unblinded for SUSAR reporting purposes. Designated MyoKardia biostatisticians, statistical programmers, pharmacologists, and a Quality representative are unblinded. The biostatisticians and statistical programmers will create the randomization list and statistical analysis to support SRC meetings, and the unblinded Quality representative will communicate with the unblinded pharmacist at the site. These unblinded personnel will take appropriate precautions to ensure no other personnel are unblinded. The SRC may review

unblinded data prior to database lock. Each cohort may be locked and unblinded independently upon its completion.

If an emergency unblinding is required, the investigator will have immediate access to individual sealed patient codes. In addition, if required, the site pharmacist or his/her delegate who will have dispensed the medication can release the code to the investigator and other medical personnel as appropriate. In the event of a medical emergency when management of a patient's condition requires knowledge of the study medication, the treatment received may be revealed by personnel authorized by the PI. When possible, such emergencies are to be discussed with MyoKardia prior to disclosure of the treatment allocation. If the treatment assignment is revealed, the following must be recorded in the subject's source documents: the reason(s) and justification(s) for breaking a code, the date and time when the code was broken, the identity of the person responsible and other unblinded personnel. Information that would lead to further unblinding in the eCRF or source documents should not be recorded.

The bioanalyst assaying the PK samples will be unblinded so only the appropriate samples will be analyzed. On days in which the patients received placebo, only 1 sample obtained at about the time of the predicted maximum plasma concentration will be assayed to ensure that the patient received placebo.

7 STUDY TREATMENT

IMP is defined as MYK-491 or placebo. In Part 1 (SAD), study patients will receive separate ascending doses of MYK-491 (2 to 3 doses) and a single dose of matching placebo.

In Part 2 (MAD), study patients will receive single-blind placebo BID for Days 1 and 2 and will then receive DB treatment (either placebo or MYK-491) for 7 days (Days 3 through 9). In Cohorts A, B, and C, on Day 9 patients will receive a single dose of placebo or MYK-491 in the morning for serial PK/PD assessments, while on Days 3 through 8 patients in these cohorts will receive placebo or MYK-491 BID.

In optional Cohorts D and E, and possible additional cohorts, patients may receive placebo or MYK-491 QD or BID dosing as determined by SRC.

7.1 Investigational Medicinal Product

MYK-491 drug substance is a [redacted] synthetic molecule with a molecular weight of 435.4 g/mol. [redacted]

MYK-491 will be provided as a tablet. Placebo will be provided as matching tablet.

7.1.1 Supply of Investigational Medical Product

The clinical trial material for the MYK-491-003 study will be manufactured, packaged, labeled, and distributed by [redacted]. MyoKardia will provide 25 mg tablets, 100 mg tablets, and matching placebo tablets for this study. The tablets will be blistered and then carded, Each blister card will contain either only 25 mg, only 100 mg, or only placebo. There will be no mixed strength blister cards. Each blister card will be labeled as required by local regulations and will be “open” in labeling, ie, the label will identify the contents of the blister card. The blister cards will be packaged into “Kit Boxes.” Each kit box will be labeled as required by local regulations and will be “open” in labeling, ie, the label will identify the contents of the kit box.

The pharmacist, who is unblinded in this protocol for purposes of dose preparation, will prepare blinded doses, which he/she will provide to the clinician, who will administer it to the patient. Both the clinician and the patient will not know what dose it contains.

7.1.2 Storage and Handling Procedures

MYK-491 must be stored in accordance with the labeled storage conditions in the packaging supplied by MyoKardia. IMP at the investigational site will be stored in a secure area with access limited to authorized study personnel.

7.1.3 Packaging and Labeling

MYK-491 and the matching placebo tablets will be shipped in appropriately labeled containers. Blinding will occur at the site by the unit’s pharmacists or qualified delegated

staff. All study medication will be labeled according to applicable local regulatory guidelines.

7.2 Study Medication, Administration, and Schedule

Study medication will consist of MYK-491 25 mg tablets, 100 mg tablets, or matching placebo tablets.

MYK-491 tablets and matching placebo tablets will be manufactured according to current Good Manufacturing Practice (cGMP) regulations.

In Part 1 (SAD), MYK-491 or placebo will be administered after an overnight fast (at least 6 hours), while in Part 2 (MAD) MYK-491 will be administered after a 2 hour fast. The dose should be ingested with a minimum of 240 mL of water, but more water may be ingested as needed. The entire dose should be administered over a period of up to 15 minutes. The time of dose used to determine future assessments will be the time the last tablet is taken.

In Part 1 (SAD), if the SRC specifies that the total dose should be split for selected periods, all dosing should be completed before approximately 12 noon so that the expected peak drug effect occurs before bedtime and when there is adequate staffing present. The exact timing may be determined by the site based on scheduling needs. For example, the first half of the dose may be given between 6 and 8 AM and the second half given between 10 AM and 12 noon. Appendix 1 provides a schedule of assessments to be followed in the event of a split dose. Four hours is the expected interval for split dose but timing may be modified based on emerging PK data.

In the initial cohorts for Part 2 (MAD), a BID regimen will be used (see Section 4.1.2). **Patients with ICD who are not confined in the Clinical Testing Unit** should return to the Clinical Testing Unit for dosing with IMP. Alternatively, patients may be visited by a home health nurse for study drug administration and for any assessments that can be performed away from the clinical site. Only a single dose may be dispensed at one time to the home health nurse in this manner.

7.2.1 Administration Relative to Meals

In Part 1 (SAD), patients will fast overnight (approximately 6 hours) through 4 hours postdose. With the exception of the water consumed with the dose, water may be ingested until approximately 1 hour prior to dosing and approximately 1 hour after dosing. If doses are split, subjects should fast 6 hours prior to the first half-dose. A light, low-fat snack may be consumed 2 hours after the first half-dose and a fast continued through 2 hours after the second half-dose.

In Part 2 (MAD), patients will fast for 2 hours before and 2 hours after dosing. For example, if morning dosing will occur at 8 AM, patients can have a snack at 6 AM and a full breakfast at 10 AM. If afternoon dosing will occur at 8 PM, patients can have dinner at 6 PM and a snack at 10 PM. These times may be adjusted based on local scheduling preferences, but doses should be separated by at least 10.5 hours. The fasting requirement may be eliminated

or modified during the conduct of this study if the results of a planned food effect study become available.

Patients with ICD who are not confined in the Clinical Testing Unit should be educated with respect to meal and fasting requirements for the study. In particular, it is important also to remind patients who will not be taking their meal in the Clinical Testing Unit to maintain a stable diet throughout the study, to continue to remain adherent to their usual diet recommended for their heart failure condition (low to moderate salt diet) and to take their meals at about the same time every day from Day 1 until Day 11.

7.3 Treatment Compliance

MYK-491 or placebo will be administered by a qualified member of the clinical staff. Study staff will verify that each patient ingests the entire dose of the study medication with at least 240 mL of water. Clinical site staff will be responsible for accurately completing the patient's study medication records.

Patients with ICD who are not confined in the Clinical Testing Unit should return to the Clinical Testing Unit for dosing or be administered the study drug by a home health nurse.

7.4 Guidelines for the Management of an Exaggerated Pharmacological Effect

Based on the nonclinical pharmacological characteristics, exaggerated effects of MYK-491 may lead to myocardial ischemia. The duration of effect would follow the PK profile of MYK-491 [redacted]. The clinical signs and symptoms, which may include chest pain, lightheadedness, diaphoresis, and ECG changes should start to abate over a short period of time. Any patient with signs and/or symptoms that may be secondary to cardiac ischemia should be immediately evaluated by the physician for the possibility of cardiac ischemia and additional ECGs and serial troponins obtained as part of the evaluation as appropriate. If evidence of cardiac ischemia is present, then the patient should receive standard therapy for ischemia as appropriate, including supplemental oxygen and nitrates. [redacted]

7.5 Overdose

There is no antidote for MYK-491. Patients who receive a greater dose than planned should be supported as appropriate. If there is an exaggerated pharmacologic effect, the patients should be supported as described in Section 7.4.

If a subject should experience an overdose, the investigator will report the overdose within 24 hours, even if there are no signs or symptoms associated with the overdose in the subject. Follow up on the subject's condition will be conducted.

7.6 Concomitant Therapy

During the study, the patients should continue to ingest their medications for the treatment of their congestive heart failure and other medical conditions at the same doses and as close to the same times as usual, in order to maintain as best as possible similar preload and afterload conditions throughout the study in order to minimize confounding factors for the assessment of the effects of MYK-491. ***In particular, if patient is treated with diuretics, time of administration of diuretic relative to DB treatment should be kept similar throughout the study. Times of administration of diuretics, if applicable, will be collected in the eCRF. If patient is not confined, instruct patient to maintain timing of daily administration of medications constant, including diuretic if applicable. Patients should record the time of administration of diuretics.***

All prescription and over-the-counter medications must be reviewed by the investigator. Questions concerning enrollment or medications should be discussed with the medical monitor. [redacted]

If the patient has an AE requiring treatment (including the ingestion of acetaminophen or ibuprofen), the medication should be recorded in the appropriate section of the eCRF; including time of the administration (start/stop), date, dose, and indication.

8 RISKS AND PRECAUTIONS

8.1 General

The risks of administering MYK-491 to patients with heart failure are unknown, but single doses administered to healthy volunteers were well-tolerated (Section 1.2). Safety testing in other mammalian species demonstrates that dose-limiting toxicity is related to an exaggerated pharmacological effect, and not to off-target adverse effects. Dose/exposure/effect relationships based on data from the single-dose study in healthy volunteers have been taken into consideration in the selection of the initial and subsequent dose levels. In addition, stopping criteria, to ensure that MYK-491 will be administered safely, are part of this study.

8.2 Pregnancy

8.2.1 Avoidance of Pregnancy

Women of childbearing potential will be allowed to participate if they are not currently pregnant and/or breastfeeding and agree to not become pregnant for up to 3 months after the last dose of study medication. Women must use appropriate methods of birth control as listed in Section 8.2.3. Women of nonchildbearing potential are defined as women who are permanently (surgically) sterilized or are postmenopausal. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and bilateral tubal occlusion or ligation at least 6 months prior. Women are considered postmenopausal if they have had amenorrhea for at least 1 year following cessation of all exogenous hormonal treatments and FSH levels are in the postmenopausal range. Pregnancy tests (urine or blood determined by local requirements [eg, only serum is acceptable in the UK]) should be performed on all females.

8.2.2 Restrictions for Male Patients

There is no information about effects that MYK-491 could have on the development of the fetus in humans. Therefore, it is important that the partners of male patients do not become pregnant during the study and for a total period of 3 months after the male patient has taken the last dose of study medication. As a precaution, all male patients 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 patients 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-491 to the partner in the ejaculate.

Male patients 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. From the time of Screening through 3 months after the last dose of study medication, patients should practice true abstinence or use effective means of contraception as follows:

- Hormonal contraception associated with inhibition of ovulation, IUD, or intrauterine hormone-release system (IUS) plus barrier (eg, male using condom or female using diaphragm or cervical cap)
- Vasectomy plus barrier
- Female is surgically sterile for 6 months or postmenopausal for 1 year. 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 1 year or more following cessation of all exogenous hormonal treatments, and FSH levels are in the postmenopausal range.
- Male partners of postmenopausal females

8.2.4 Reporting and Follow up of Pregnancies

All pregnancies in female patients and female partners of male patients 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 patient 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.

Procedures to be performed during the study are detailed in Appendix 1 and Appendix 2 of this document. Refer to the appropriate schedule(s) of assessments, as indicated in Table 1.

Table 1 Schedules of Assessments

Study Part	Table
Part 1 (SAD): Screening, Dosing Periods, and Follow up – High-Level	Table 2
Part 1 (SAD): Dosing Periods and Follow up – Detailed	Table 3
Part 1 (SAD): Split Dose Screening, Dosing Periods, and Follow up – Detailed	Table 4
Part 2 (MAD): Screening, Dosing Periods, and Follow up – High-Level	Table 5
Part 2 (MAD): Dosing Periods and Follow up – Detailed for Days 3 and 9	Table 6

MAD, multiple-ascending dose; SAD, single-ascending dose

The timelines in Appendix 1 and Appendix 2 should be followed by patients enrolled in Cohort 1 and Cohort A, respectively. Subsequently, the SRC will review all available data. The committee may modify the timing of the assessments or increase or decrease the number of assessments, based on the accumulating data.

Screening values and assessments will be made by the Central Laboratory/reader; in Part 1 (SAD), Day -1 assessments will be split with one sample assayed locally for review by the investigator and one sample assayed centrally.

When several assessments are to be conducted at the same timepoint, the preferred order of assessments is ECG, vital signs, PK, and then TTE. The order of assessments may vary slightly at specific timepoints (eg, 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 patients to be in a semirecumbent or supine position, assessments should be conducted with the patient in the same position at all timepoints.

9.1 Efficacy Assessments

There are no efficacy assessments in this study.

9.2 Pharmacodynamic Assessments

9.2.1 Transthoracic Echocardiography

TTE evaluations of LVSV (derived from LVOT-VTI), LVEF, LVFS, SET, and other parameters will be PD assessments at the timepoints indicated in Appendix 1 and Appendix 2 (with a window of ± 1 hour). The patients should be at bed rest for 10 minutes before the

TTEs are obtained. The actual timing of TTE should be modified and/or additional TTEs obtained at other timepoints based on the review of data from prior treatment periods by the SRC. In Part 2 (MAD), TTEs are usually obtained before the morning dose and/or at 7 hours postdose (ie, close to the anticipated peak effect based on the PK profile from the healthy volunteer studies). Up to an additional 2 observations may be requested per treatment period by the SRC after review of the data from previous treatment periods.

Echocardiograms will be evaluated locally for changes that might affect dosing decisions for subsequent doses in one patient or others in the cohort, but the official reading will be done centrally by experts in a core laboratory in a blinded manner with results provided to the SRC.

The sonographers to be used in the study will complete echo protocol training and submit an example of a study to the core laboratory for evaluation. The core TTE lab will certify that the sonographer is able to perform the TTEs at a level satisfactory for obtaining the required protocol data. All echocardiography data will be sent to a central imaging laboratory.

9.3 Pharmacokinetic [redacted] Assessments

9.3.1 Pharmacokinetic Assessments

Blood samples will be collected for PK assessments as indicated in Appendix 1 and Appendix 2. It is important that PK sampling occurs as close as possible to the scheduled time. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor. Timing of the samples may be modified and an additional 2 samples per treatment period requested by the SRC following review of the data from previous time periods. [redacted] If an unscheduled echocardiogram is requested by the investigator, serum PK should also be collected at this timepoint.

[redacted]

9.4 Safety Assessments

Safety will be assessed throughout the study as indicated in Appendix 1 and Appendix 2. Safety assessments include medical history, physical examinations, SET as determined by TTE, 12-lead ECGs, ECG telemetry (in confined patients), Holter ECG (in Part 2), vital signs, observed and patient-reported AEs, serum troponin concentrations, and safety laboratory tests. [redacted]

The actual timing of the assessment of ECGs, TTEs, and vital signs may be modified or up to an additional 2 sets of observations or samples per treatment period may be requested by the SRC after review of the data from previous treatment periods.

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

9.4.1 Medical History

A complete medical history will be recorded at the Screening visit, which will include evaluation (past or present) of the cardiovascular and heart failure medical history as well as the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, 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). The medical history will be updated at admission if needed.

9.4.2 Vital Signs

Vital signs are to be assessed throughout the study as indicated in Appendix 1 and Appendix 2. The actual timing of the vital sign measurements may be modified and/or additional sets per treatment period may be requested by the SRC. Clinically significant abnormal values will be flagged. On days with multiple vital sign assessments, temperature needs to be assessed once, unless clinically indicated.

9.4.3 Physical Examination

Height (cm) will be measured at Screening and body weight (kg) will be measured at Screening and admission (first dosing period only in Part 1 [SAD]) BMI (kg/m^2) will be calculated. Patients will be required to remove their shoes and wear indoor clothing as specified by the clinical site.

At Screening and admission, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), 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 timepoints, an abbreviated physical examination (pulmonary, cardiac, abdominal, and other systems related to symptoms) will be conducted.

9.4.4 Systolic Ejection Time

See Section 9.2 for a description of assessment of SET using TTE.

[redacted]

[redacted]

9.4.5 Electrocardiograms (12-Lead ECG)

The 12-lead ECG should be obtained as indicated in Appendix 1 and Appendix 2. The actual timing of the ECGs may be modified and/or up to an additional 2 ECGs per treatment period may be requested by the SRC after review of the data from previous patients or treatment periods. In addition, the investigator may add extra 12-lead ECG assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. If the patient has a new troponin abnormality (see Section 9.4.9) or any signs or symptoms suggestive of possible cardiac ischemia, additional ECGs should be obtained. These assessments should be recorded as unscheduled assessments. All ECG data will be sent to a central cardiac laboratory.

The investigator will judge the overall interpretation as (a) normal, (b) abnormal without clinical significance, or (c) abnormal with clinical significance. If clinically significant, the abnormality will be recorded. In addition, before each treatment period, the investigator or subinvestigator should review the available ECGs from the previous treatment periods looking for signs of ischemia. If there are signs of ischemia, continued dosing should be withheld until there is full understanding of the possible ischemic changes. 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, patient's medical history, and laboratory data to determine the clinical importance of the finding.

The 12-lead ECG abnormalities suggestive of ischemia (eg, new or worsened ST depression or new T-wave inversions), as determined by investigator, will be reviewed centrally by an Adjudication Committee.

9.4.6 Electrocardiogram Telemetry

Real-time telemetry ECG (at least 3-lead) will be displayed starting at least 1 hour predose and continuing through 48 hours postdose (in Part 2 [MAD], postfinal dose on Day 9). The investigator or designee will monitor the continuous ECG telemetry data and correlate the finding(s) with any other clinical findings, study participant's medical history, study participant's clinical status, and laboratory data to determine the clinical importance of the finding. Clinically significant findings that are new or worsened (compared to baseline), as determined by investigator, will be reported in CRF as AEs (see Section 10).

If the investigator notes an event as clinically significant, the relevant strip should be printed and sent to the central ECG cardiac laboratory. The investigator should modify/stop dosing based on local assessment if indicated but the final read will be made centrally. A copy of the event and subsequent central cardiac ECG laboratory analysis should be kept in the subject's source documentation.

New or worsening ventricular arrhythmia observed on ECG telemetry or on a 12-lead ECG, as determined by investigator, will be reviewed centrally by an Adjudication Committee.

Worsened ventricular arrhythmia would include but is not limited to increase over baseline in the frequency or complexity of premature ventricular contractions (PVCs).

9.4.7 Holter Electrocardiogram

In Part 2 (MAD), Holter ECG recordings (or equivalent technology) will be acquired as indicated in Appendix 2. During the 48-hour Holter ECG, site staff should periodically verify that Holter device is adequately functioning ie, that continuous recording is occurring as intended. If alternative comparable technology is identified by the Sponsor, the device used and the length of recording may be modified.

9.4.8 ICD Download (For Patients with ICD)

An ICD download should be performed at the end of the study (Day 16 ± 1 week) unless the site encounters significant technical difficulties and is required in case of shock(s) delivered by the ICD during the study.

9.4.9 Troponin Levels

Troponin samples will be collected at timepoints as indicated in Appendix 1 and Appendix 2. Samples for troponin should be split with one sample assayed locally in order to be locally reviewed by the investigator. The local troponin evaluated can be either Troponin I or Troponin T, based on local site access to assays. The other sample will be analyzed at a Central Laboratory. The Central Laboratory will analyze Troponin I and Troponin T.

Results of troponin assays from the local lab should guide patient evaluation. Results of troponin assays from Central Lab will be used for further research purposes by the Sponsor, and will not be communicated back to the Investigator (with the exception of Central Lab Troponin I values which will be communicated to determine patient eligibility).

Abnormal and/or rising troponin values (as per investigator's judgment and taking into account potential baseline troponin elevation frequently observed in heart failure) should lead to patient being clinically evaluated for possible myocardial ischemia. Also, if the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional serial troponin (and other safety labs, including creatine kinase-MB [CK-MB] samples) should be obtained and continued dosing should be withheld until there is full understanding of the possible ischemic event. The investigator will evaluate the entire clinical context (eg, signs, symptoms, new ECG changes, new troponin, and CK-MB abnormalities) and correlate with any other relevant clinical findings, patient's medical history, and laboratory data to determine the clinical significance of the findings.

Troponin results performed on Day 2 of Part 1 (SAD) and Day 10 of Part 2 (MAD) at local lab should be reviewed prior to patient being discharged the next day.

All elevated levels of troponin above the upper limit of normal from either the local or Central Lab, regardless of baseline levels, will be centrally reviewed by an independent adjudicator (Section 4.5).

If the investigator assessment is that an AE has occurred, the event should also be reported as an AE according to Section 10.

9.4.10 Adverse Events

Please see Section 10 for information on evaluating, recording, and reporting AEs.

9.4.11 Safety Laboratory Tests (Other Than Troponin)

Samples will be drawn for safety laboratory tests at the timepoints indicated in Appendix 1 and Appendix 2. At Screening, assessments will be made by the Central Laboratory. Safety laboratory samples should be split for one sample to be analyzed locally and one sample processed centrally. Local lab results should be reviewed, and eligibility confirmed, prior to dosing. If the investigator has any questions regarding eligibility, the Sponsor should be contacted.

9.5 Missed Evaluations

Evaluations should occur within the assessment window specified by the protocol. If an evaluation is missed, it should be performed as close as possible to the original time.

9.6 Patient Restrictions During the Study

The following restrictions apply for the specified times during the study period. If a patient does not comply with these restrictions or they may be excluded or withdrawn from the study.

- Throughout the study, starting at Screening, patients should maintain stable medications, activity levels, fluid intake, and meals.
    - During the confinement period at the clinical site, meals will be served at scheduled times. If patient is not confined, instruct patients to have meals at consistent times.
    - From 72 hours prior to the first dose through the final Follow-up visit, patients should not engage in unaccustomed intensive exercise.
    - From the time of Screening through the Follow-up visit, every effort should be taken to maintain concomitant medications at stable doses. To minimize variability in cardiac loading conditions for cardiac echo assessments, medications (including diuretics) should be taken at the same time every day and timing of diuretics if applicable will be recorded. Patients not confined should be advised to take all medications, including diuretics if applicable, at the same time every day.
- In Part 1 (SAD), the patients will fast overnight (at least 6 hours) prior to the morning dosing. In Part 2 (MAD), the patients will fast 2 hours prior and 2 hours after dosing. With the exception of the water consumed with the dose, patients may ingest water up to 1 hour before and 1 hour after ingestion of the dose. Fasting and fluid restriction periods can be made shorter or eliminated at the discretion of the SRC.

- Starting at Screening, patients will be required to abstain from blood or plasma donation until 3 months after the final study visit.
- From Screening through the final Follow-up visit, patients will be asked to abstain from grapefruit or grapefruit juice, Seville oranges, and quinine (eg, tonic water).
- Contraception requirements are discussed in Section 8.2.
- **Patients with ICD who are not confined in the Clinical Testing Unit** should be educated about all above requirements, including but not limited to: fasting instructions and following their physician-recommended diet (ie, low to moderate salt diet, taking their medications, and meals at consistent times every day). Patients should be advised to avoid alcohol or excessive caffeine consumption.

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 (eg, tachycardia, enlarged liver, clinically important abnormal laboratory result or diagnostic procedure), patient-reported symptom (eg, 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 patient 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 patient 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 (eg, invasive procedures such as biopsies).

For MyoKardia to collect additional information about clinically important laboratory results or diagnostic tests (eg, 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 (eg, > 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 requires the patient to have study medication discontinued or interrupted or in the clinical judgment of the investigator
- Any test abnormality that requires the patient 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 nonserious.

10.1.2 Serious Adverse Event

An SAE is an AE that fulfills 1 or more of the following criteria in the opinion of the investigator or MyoKardia:

- Results in death
- Is immediately life-threatening (places the patient at immediate risk of death from the event as it occurred)
- Requires in-patient 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 1 of the outcomes listed above

10.2 Events NOT Meeting the Definition of an Adverse Event

If an event is not an AE then it cannot be an SAE, even if the event outcome meets the definition for seriousness defined by the criteria in Section 10.1.2. Instances where an event is not an AE include

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or hospital admission/extension for convenience)
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) that are present or detected at the start of the study that do not worsen

10.3 Adverse Event Reporting and Descriptions

10.3.1 Reporting Period and Follow Up

All AEs will be reported from the time the patient provides informed consent through the last visit or 30-day period after last dose of study medication, whichever is longer. SAEs occurring after providing informed consent but before the first dose of study medication will

be reported as SAEs only if they are considered related to protocol or study procedure. 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. Overdose should be reported using the same method as SAE reporting.

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

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

All SAEs regardless of causality will be reported by the investigator or designee to MyoKardia or its designee within 24 hours of knowledge of the event. All follow-up information for previously reported SAEs will also be reported to MyoKardia or its designee within 24 hours of knowledge. Deaths and SAEs occurring beyond this timepoint and considered related to study medication or study procedure must also be reported.

10.3.1.1 Recording and Assessing Adverse Events

10.3.1.2 Description

All AEs spontaneously reported by the patient 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 (eg, 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.

10.3.1.3 Relationship to Study Treatment

The investigator should assess causality by answering either "yes" or "no" to the question *"Is there a reasonable possibility that the event may have been caused by the IMP/study medication?"*

The following factors can be used in consideration of causality assessment:

- Dechallenge/rechallenge: Did the event abate after study medication was reduced or interrupted? Did the event reappear after study medication was reintroduced?
- Temporal relationship and time to onset plausibility

- Confounding risk factors
- Amount and duration of study drug exposure
- Concomitant medications

10.3.1.4 Severity

Severity can be assessed as follows:

- 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 led to death)

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

Severity is a measure of intensity, whereas seriousness is defined by the criteria stated above.

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.

All SAEs regardless of causality will be reported by the investigator or designee to MyoKardia or its designee per the reporting period defined in Section 10.3.1 within 24 hours of knowledge of the event. All follow-up information for previously reported SAEs will also be reported to MyoKardia or its designee within 24 hours of knowledge. Deaths and SAEs occurring beyond this timepoint and considered related to study medication or study procedure must also be reported.

10.3.1.5 Pregnancy

Pregnancy, or if a partner of a male patient becomes pregnant during the study or for a period of 3 months after the male patient has taken the last dose of study medication, must be reported within the same timelines of an SAE. Pregnancies will be followed until final outcome and live births will be followed for 6 months after birth. SAE reporting instructions are provided in the Investigator Site File.

11 STATISTICAL METHODS

11.1 Determination of Sample Size

Part 1 is a single-ascending (oral) dose study and Part 2 is a multiple-ascending (oral) dose study to evaluate safety and tolerability of MYK-491. No formal statistical hypothesis testing will be performed.

In Part 1 (SAD), enrollment of at least 4 patients is planned for Cohort 1, with 1 patient randomized to each sequence of dose escalation and placebo administration. For Cohort 2, 4 to 8 patients will be enrolled and randomized to each sequence of dose escalation. There will be an option for the SRC to expand Cohort 1 or Cohort 2 to meet study objectives. Decision to expand or not the number of patients will be made by the SRC. Two additional patients may be enrolled as replacements for drop-outs in each cohort, so the maximum number of patients that may be enrolled will be approximately 32.

In Part 2 (MAD), enrollment of a total of a minimum of 24 patients is planned, with 8 patients enrolled the low-dose group (Cohort A), 8 patients enrolled in the medium-dose group (Cohort B) and 8 patients enrolled in the high-dose group (Cohort C). In addition, the planned size of additional optional Cohorts will be 8 patients each. The final total sample size for Part 2 will not exceed 96 patients if the SRC decides to expand one or more cohorts up to 24 patients. In addition, up to 2 additional patients may be enrolled per cohort as replacements for drop-outs or for patients non-evaluable for PK-PD at steady state.

Based on the study design, the sample is considered appropriate to explore tolerability and safety parameters, PK profile, and pharmacodynamic effects of MYK-491 in patients with heart failure.

11.2 Study Endpoints

11.2.1 Primary Endpoint

Primary safety measures will include the following:

- Treatment-emergent AEs and SAEs
- ECG recordings (Central Laboratory manual over-read), interpretation, and intervals
- Vital signs
- Serum Troponin I concentrations
- Laboratory abnormalities
- Physical examination abnormalities

11.2.2 Secondary Endpoints

The following are secondary endpoints:

- The human PK profile of MYK-491. The analysis includes at a minimum the following PK parameters. Additional PK parameters may be determined as appropriate.
  - C_{max} for each dose level
  - T_{max} for each dose level
  - AUC for each dose level dose
  - Apparent first-order terminal elimination half-life ($t_{1/2}$)
  - Mean residence time (MRT) for each dose level
  - Accumulation ratios determined (with the appropriate confidence intervals) for C_{max} and AUC_{0-t} (Part 2 only)
- SET as determined using TTE. The main parameters are the change from Baseline at each timepoint by treatment levels and the maximum change from Baseline.
- The following as assessed by TTE:
  - Change from Baseline in LVSV (derived from LVOT-VTI)
  - Change from Baseline in LVEF
  - Change from Baseline in LVFS
  - Change from Baseline in SET

[redacted]

11.3 Statistical Analysis

Before database lock, a statistical analysis plan (SAP) for clinical data and an analysis plan for PK 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 Safety population, the PK Analysis population, and the PD Analysis population.

The Safety population is defined as patients who are randomized and receive any amount of study medication (MYK-491 or placebo), including patients who prematurely withdraw from the study. Except as noted, all safety analyses, including demographic and Baseline characteristics, will be performed based on the Safety population.

The PK Analysis population is defined as patients who are randomized and receive any amount of MYK-491, have detectable plasma concentration data, and have no major or critical protocol deviations related to IMP (eg, incomplete ingestion of the drug, vomiting up to 8 hours after drug administration). During the placebo dosing period, a single plasma sample will be evaluated near the predicted T_{max} of MYK-491 to confirm lack of circulating MYK-491 and will not be included in the PK Analysis population.

The PD Analysis population is defined as patients who are randomized and receive any amount of study medication (MYK-491 or placebo), have any interpretable PD data, and have no critical or major protocol deviations related to IMP (eg, incomplete ingestion of the drug, vomiting up to 8 hours after drug administration). The PD analyses will be performed based on the PD Analysis population.

The PK/PD analysis will be performed based on MYK-491-treated patients that are in both the PK Analysis population and the PD Analysis population and/or Safety population depending on which parameters are to be included in the PK/PD analysis.

11.3.2 General Considerations

Clinical data will be summarized by treatment group. Descriptive summary statistics for continuous variables will include the number of patients, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

11.3.3 Patient Disposition

The number and percentage of patients who complete or discontinue the study, 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 Pharmacokinetic Analyses

Plasma [redacted] concentration data for MYK-491 will be summarized using descriptive statistics, including mean or geometric mean as appropriate, SD, median, minimum, and maximum values and CV%. PK parameters will include (but are not limited to) C_{max}, T_{max}, AUC, apparent first-order terminal elimination rate constant (λ_z), and MRT. In addition, the accumulation ratios will be calculated with C_{max} and $AUC_{0\text{-}t}$ (t = dose interval or τ) after dose on Day 9 (at steady-state) and Day 3 (1st dose). Additionally, the apparent terminal-phase elimination half-life ($t_{1/2z}$) will be calculated. [redacted]

[redacted]

11.3.6 Pharmacodynamic Analyses

TTE data for LVEF, SET, LVFS, LVSV will be analyzed using descriptive statistics. No inferential analysis will be performed. Observations by timepoint and change from Baseline (either absolute or percent relative change) at each timepoint will be summarized by treatment period (Part 1) and treatment group (Part 2). Change from Baseline will be analyzed with attention to the relationship to time postdose, dose level, and comparison with placebo. For SAD Cohorts, placebo-adjusted change from Baseline will be calculated for each subject at each postbaseline timepoint and then summarized at each dose level. In addition, for SAD and MAD Cohorts, least square means of placebo-adjusted change from Baseline for the key PD parameters (LVEF, LVFS, LVSV, SET) at each postbaseline time point at each dose level may be estimated using mixed model.

The relationship between the TTE endpoints and MYK-491 plasma concentration will be assessed using linear or nonlinear correlations.

[redacted]

11.3.7 Safety Analyses

All safety analyses except SET as determined by TTE will be performed on the Safety Analysis population. Analyses of SET as determined by TTE will be performed on the PD Analysis population.

11.3.7.1 Systolic Ejection Time

SET as determined by TTE will be assessed using summary statistics. Observations and change from Baseline will be summarized by treatment at each timepoint and the maximum change from Baseline will be determined for each patient. [redacted]

11.3.7.2 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 also be monitored. Treatment-emergent AEs will be summarized for the Safety Analysis population by MedDRA system organ class and preferred term, and by severity and relationship to treatment. Severe and life-threatening AEs, SAEs, AEs leading to study withdrawal, if any, will be presented in data listings.

11.3.7.3 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 ms) and rounded to the nearest integer.

QTc will be calculated using the manually over-read QT values per the standard procedures of the central ECG laboratory. 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 ms):

$$QTcF = \frac{QT}{\frac{RR}{1000}^{0.33}}$$

11.3.7.3.1 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 patient. For each timepoint of measurement, the changes from Baseline will be summarized. The relationship between HR/ECG intervals and time will be plotted.

Separate analyses will be performed in patients who are not paced and have no prolonged QRS at Baseline.

11.3.7.3.2 Categorical Analysis

The incidence count and percentage of patients with any postdose QTcF values of > 450 ms, > 480 ms, and > 500 ms will be tabulated for all patients. Patients with QTc values > 500 ms will be listed with corresponding Baseline values, ΔQTcF, and Baseline and treatment HR. The incidence count and percentage of patients with ΔQTcF increase of > 30 ms and > 60 ms will be tabulated.

A separate QTcF analysis will be performed in patients who are not paced and have no prolonged QRS at Baseline.

11.3.7.3.3 Morphology Findings

New ECG morphologies for each patient not present on any ECG at Baseline for that patient will be summarized for all observation timepoints combined.

The number and percentage of patients 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.

11.3.7.3.4 Concentration-QTc Analyses

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

11.3.7.4 Holter Electrocardiograms

The interpretation and analysis of the Holter ECG data will be performed by the central ECG laboratory. Data from the 12-lead Holter recorder digital flashcard will be transmitted to the central ECG laboratory using a digital uploading system. The recordings will be reviewed for the presence of any clinically significant arrhythmias. The actual time of dosing will be communicated to the central ECG laboratory by the clinical site.

Analysis of blinded Holter recordings will be performed to assess the nature, frequency, and severity of any ventricular arrhythmias. Parameters evaluated will include but not be limited to total number of premature ventricular complexes (PVCs) during the recording period, average number of PVCs per hour, maximum number of PVCs per hour, total number of PVC pairs, total number of PVC triplets, total number of ventricular tachycardia (VT) runs (4 or more PVCs in a row), longest VT run, maximum HR during a VT run, minimum HR during a VT run, PVCs per 1000. Additional ECG abnormalities will be noted, including supraventricular arrhythmias and instances of heart block.

11.3.7.5 Other Safety Analyses

Safety laboratory data including hematology, chemistry, ECG telemetry, and vital signs will be evaluated by timepoint for the Safety Analysis population using descriptive statistics. Changes from Baseline at each postbaseline timepoint will also be assessed. Listings of patients with laboratory and/or vital sign values that are observed to be out of the reference range will be produced. Abnormal physical examination results will be listed. Concomitant medications will be summarized.

12 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

12.1 Compliance Statement

This study will be conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (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 patient is aware of potential benefits and risks. Potential patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Patients must give informed consent in writing.

Prior to participation in any study-related procedures, patients must sign and date an EC-approved written ICF in a language the patient 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 patient undergoes any study-specific procedures.

The language in the written information about the study should be as nontechnical as practical and should be understandable to the potential patient. Before informed consent is obtained, the investigator should provide the potential patient 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 patient. The written ICF should be signed and personally dated by the patient and by the person who conducted the informed consent discussion. All patients 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 IRB or Independent Ethics Committee (IEC) 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
- Patient recruitment procedures/documents (eg, advertisements)
- Written information to be provided to patients

- IB and available safety information (Note: ECs do not approve IBs but are responsible for acknowledging receipt)
- Information about payments and compensation available to patients

The EC approval must be in writing, clearly identifying the study (by protocol date and/or version), the documents reviewed (including informed consent), and the 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
- Any new information that may affect adversely the safety of the patients 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 for any reason or for no reason. MyoKardia and the investigators will assure that adequate consideration is given to the protection of the patients' 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 include:

- Request by Health Authority to terminate the study
- Unsatisfactory patient enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on patients, 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 Patient 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 patient.

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

Patients 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-491 tablets and the corresponding placebo
- IB for MYK-491
- ECG equipment
- [redacted]

13.1.3 Investigator Training

A site-specific study initiation meeting and/or an Investigator Meeting will be held to ensure the center staff understands the protocol, study requirements, and data capture processes. This training will take place before the first patient is enrolled. The clinical site will be provided with information regarding GCP and regulations specific to the conduct of the clinical studies. The 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 with MYK-491 that 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 patients, 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.

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 patients who signed an informed consent and the reason for noninclusion if the potential patient does not ultimately enroll and receive IMP.

13.2.2 MYK-491 and Matching Placebo 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 (ie, accountability or dispensing logs) at the end of the study. The study medication records must be readily available for inspection by the (unblinded) 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. All requested study data must be clearly recorded on the eCRF and other forms as required. Whenever possible, the reason for missing data in the source document must be recorded. Only individuals who are identified on the study personnel responsibility/signature log and who have received appropriate training on the electronic data capture (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 documented.

Patient source data must be maintained as original records or a certified copy (ie, 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 patient who receives at least 1 dose of IMP. All entries into the eCRF are ultimately the responsibility of the investigator. The investigator is responsible for ensuring accurate, authentic, and complete records for each patient.

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 MyoKardia 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 patient:

- Patient identification and contact information (name, date of birth, sex, address, phone)
- Documentation verifying patient eligibility (ie, 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 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 patient's medical records in the event that the clinical site's policy does not permit direct access to the electronic medical records.

13.2.5 Patient Identification Information

To permit easy identification of the individual patient during and after the study, the investigator is responsible for keeping an updated log that contains the patient identification information. This document will be reviewed by the clinical site monitor for completeness. However, to ensure the patient'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 patients (eg, patient

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 applications 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

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 may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to patients without prior EC approval. If required, 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 a protocol deviation results in inadequate patient data, MyoKardia may determine that the patient should be replaced. The medical monitor will notify the study monitor 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.

[redacted]

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/typographical errors/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 *Good Clinical Practice: 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 patient data: the clinical site will enter data from source documents onto eCRFs for each study timepoint 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 echocardiographic data from digital equipment used by clinical site personnel to collect patient 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 EU 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, *Good Clinical Practice*, Section 8), and as required by the applicable regulatory requirement(s). This includes, but is not limited to, the protocol, eCRFs, AE reports, patient 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 patient'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 patient'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.

17 REFERENCE LIST

Benjamin E, Blaha M, Chiuve S, Cushman M, Das S, Deo R, et al. Heart disease and stroke statistics – 2017 update: A report from the American Heart Association. Circulation. 2017;135(10):e146-603.

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Teerlink J, Clarke C, Saikali K, Lee J, Chen M, Escandon R, et al. Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study. Lancet. 2011;378(9792):667-75.

Teerlink J, Felker G, McMurray J, Solomon S, Adams K Jr, Cleland J, et al. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. Lancet. 2016;388(10062):2895-2903.

Yancy C, Jessup M, Bozkurt B, Butler J, Casey D, Drazner M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.

APPENDIX 1 PART 1 SCHEDULE OF STUDY PROCEDURES – SINGLE, ASCENDING DOSES

Table 2 Part 1 (SAD): Screening, Dosing Periods, and Follow up – High-Level

		Dosing Periods																				
Period	**Screen**	**A**					**B**					**C**					**D[a]**					**Follow-up[b]**
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**7 ± 1**
Informed consent	X																					
Confinement in the unit[c]		AD	X	X	D/C		AD	X	X	D/C		AD	X	X	D/C		AD	X	X	D/C		
IMP Administration			X					X					X					X				
Medical history[d]	X	X																				
Physical examination[e]	X	X	X				X	X				X	X				X	X				X
Body height	X	X																				
Body weight	X	X					X					X					X					X
Vital signs[f]	X	X	X	X			X	X	X			X	X	X			X	X	X			X
12-lead ECGs[g]	X	X	X	X			X	X	X			X	X	X			X	X	X			X
AEs/SAEs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TTE[i]	X		X	X				X	X				X	X				X	X			
[redacted]																						
ECG telemetry[k]			X	X	X			X	X	X			X	X	X			X	X	X		
Serology[l]	X																					
Pregnancy test[m]	X	X					X					X					X					X
FSH level[n]	X																					
Hematology[o]	X	X		X			X		X			X		X			X		X			X
Chemistry[o]	X	X		X			X		X			X		X			X		X			X
Urinalysis[o]	X	X		X			X		X			X		X			X		X			X
Troponin[p]	X	X	X	X			X	X	X			X	X	X			X	X	X			X
[redacted]																						

		Dosing Periods																				
Period	**Screen**	**A**					**B**					**C**					**D[a]**					**Follow-up[b]**
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**-1**	**1**	**2**	**3**	**4**	**7 ± 1**
[redacted]																						
Plasma for PK[r]			X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	
[redacted]																						

AD, admission; AE, adverse event; BP, blood pressure; bpm, beats per minute; [redacted] eCRF, electronic case report form; D/C, discharge; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, heart rate; ICF, informed consent form; IMP, investigational medicinal product; PK, pharmacokinetic; SAD, single-ascending dose; SAE, serious adverse event; SRC, Safety Review Committee; TTE, transthoracic echocardiography.

[a] Dosing Period D is optional, based on SRC evaluation.

[b] Follow-up visits should take place after Period C. If the patient is scheduled for Period D, a second Follow-up visit will be performed. Follow-up assessments should be performed if a patient withdraws. A TTE should be obtained at follow up if the patient's last locally reviewed TTE has not returned to Baseline.

[c] The patient will be discharged from the site on the morning of Day 3 of each dosing period after all procedures have been completed and the investigator deems it safe.

[d] A complete medical history 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. Update medical history at Day -1, if needed.

[e] At Screening and Day -1, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height and weight, and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems. All other timepoints can be abbreviated physical examination (pulmonary, cardiac, abdominal, and other systems related to any symptoms).

[f] Vital signs include temperature, HR, and BP after resting for at least 5 minutes. HR and BP taken predose, 6 hours, and 24 hours postdose will be obtained with the patient in the supine position 1 time after standing for 2 minutes and 1 time after standing for 5 minutes. All other HR and BP measurements should be the mean of 3 measurements taken in supine position, and BP should be taken via an automated recorder. Throughout Day 1, assessment of vital signs may be initiated up to 5 minutes before the assigned timepoint. On Day 1, patient will be ineligible to dose if HR $\geq$ 95 bpm at predose.

[g] Triplicate 12-lead ECG evaluations taken within a 20-minute window will be performed in the supine position after 10 minutes of rest. The predose ECG on Day 1 should be performed within 2 hours of dosing. The timing of the 12-lead ECGs in this table applies to patients enrolled in Cohort 1. The actual timing of the ECGs may be modified and/or up to an additional 2 ECGs may be requested by the SRC after review of the data from previous cohorts. The

investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it required for any other safety reason. If the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional ECGs should be obtained. These assessments should be recorded as unscheduled assessments.

[h] Changes in a Baseline condition after the ICF is signed but before IMP is administered are recorded on the medical history eCRF unless the change is considered an AE related to a study procedure. All changes that occur after administration of the study medication are recorded as AEs.

[i] A full TTE must be performed at Screening. Two TTEs will be performed during screening, no fewer than 7 days apart. Eligibility must be confirmed by core laboratory for both TTEs. Effort should be made for the second TTE to be performed as close to time of dosing as is feasible, taking into account core laboratory processing time and patient availability. After the Screening assessment, abbreviated TTEs will be performed. It is important that the TTEs are completed as close as possible to the scheduled time. TTEs will be evaluated locally for changes that might affect dosing decisions for others in the cohort, but the official reading will be done centrally by experts in a core laboratory in a blinded manner with results provided to the SRC. The SRC may modify the timing of the TTEs after the initial cohort so that for each subsequent cohort a TTE is obtained at the time of the predicted peak pharmacological effect. This will be based on the PK and TTE profiles from the previous cohorts. If appropriate, the SRC can request up to 2 additional TTEs be obtained.

[redacted]

[k] ECG telemetry will be initiated at least 1 hour predose and continued through at least 48 hours. Additional monitoring may be needed based on data and/or patient's tolerance to the treatment.

[l] Blood sample for HIV, HCV, and HBV will be collected at Screening.

[m] Pregnancy tests, urine or blood based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the UK), should be performed on all females at Screening, Day-1, and Follow-up.

[n] FSH tests will be included for potentially postmenopausal women.

[o] Samples for safety laboratory tests will be taken at Screening, Day -1, 24 hours postdose, and Follow up. Screening values and assessments will be made by the Central Laboratory; Day -1 assessments will be split with one sample assayed locally for review by the investigator and one sample assayed centrally. Safety laboratory tests may be added at the discretion of the investigator.

[p] Samples for troponin should be split with 1 sample assayed locally in order to be locally reviewed by the investigator. The other sample will be assayed in Central Lab. Troponin testing performed at the Central Laboratory will be used for research purposes and will not be communicated to the study site except for Troponin I at Screening. If the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional serial troponin samples should be obtained as appropriate to evaluate the possibility of ischemia. Lab results should be reviewed prior to patient discharge.

[redacted]

[r] It is important that PK sampling occurs as close as possible to the scheduled time. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor.

[redacted]

Table 3 Part 1 (SAD): Dosing Periods and Follow up – Detailed

		Detailed Treatment and Observation for Each of 4 Dosing Periods A, B, C, and D															
Day	**-1**	**1**												**2**		**3**	**4**
Hour		**Predose[a]**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**12**	**18**	**24**	**36**	**48**	**72**
Confinement in the unit[b]	AD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	D/C	
IMP Administration			X														
Medical history[c]	X																
Physical examination[d]	X								X								
Body Height	X																
Body weight	X																
Vital signs[e]	X	X				X			X			X		X			
12-lead ECGs[f]	X	X				X		X			X	X		X	X		
AEs/SAEs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TTE[h]		X				X			X		X			X			
ECG telemetry[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[k]	X																
Hematology[l]	X													X			
Chemistry[l]	X													X			
Urinalysis[l]	X													X			
Troponin[m]	X					X		X			X	X		X	X-		
Plasma for PK[o]		X		X	X	X	X	X	X		X	X	X	X	X	X	X

AD, admission; AE, adverse event; BP, blood pressure; CK-MB, creatine kinase-MB; eCRF, electronic case report form; D/C, discharge; ECG, electrocardiogram; HR, heart rate; ICF, informed consent form; IMP, investigational medicinal product; PK, pharmacokinetic; SAE, serious adverse event; SRC, Safety Review Committee; TTE, transthoracic echocardiography.

[a] All predose assessments should be performed within 2 hours of administering the oral dose of MYK-491 or placebo, with the following exceptions: predose or trough PK blood samples should be taken within 1 hour predose, and ECG telemetry monitoring should be initiated at least 1 hour prior to dosing.

[b] The patient will be discharged from clinical research unit on Day 3 after all procedures have been completed and the investigator deems it safe.

[c] Update medical history at Day -1, if needed.

[d] At Screening and Day -1, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height 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 6 hours postdose and at the Follow-up visit, an abbreviated physical examination (pulmonary, cardiac, abdominal, and other systems related to any symptoms) will be conducted.

[e] Vital signs will be taken at Screening, at Day -1, predose, and at 3, 6, 12, and 24 hours postdose, and at the Follow-up visit. Vital signs include temperature, HR, and BP after resting for at least 5 minutes. HR and BP taken predose, 6 hours, and 24 hours postdose will be obtained with the patient in the supine position, 1 time after standing for 2 minutes and 1 time after standing for 5 minutes. All other HR and BP measurements should be the mean of 3 measurements taken in supine position, and BP should be taken via an automated recorder. On Day1, patient will be ineligible to dose if HR $\geq$ 95 bpm at predose.

[f] Triplicate 12-lead ECG evaluations taken within a 20-minute window will be performed in the supine position after 10 minutes of rest at Screening, Day -1, predose, and at 3, 5, 9, 12, 24, and 36 hours postdose. The predose ECG on Day 1 should be performed within 2 hours of dosing. The timing of the 12-lead ECGs in this table applies to patients enrolled in Cohort 1. The actual timing of the ECGs may be modified and/or up to an additional 2 ECGs may be requested by the SRC after review of the data from previous cohorts. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it required for any other safety reason. If the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional ECGs should be obtained. These assessments should be recorded as unscheduled assessments.

[g] Changes in a Baseline condition after the ICF is signed but before IMP is administered are recorded on the medical history eCRF unless the change is considered an AE related to a study procedure. All changes that occur after administration of the study medication are recorded as AEs.

[h] A full TTE must be performed at Screening. After the Screening assessment, abbreviated TTEs will be performed predose, and at 3, 6, 9, and 24 hours postdose. It is important that the TTEs are completed as close as possible to the scheduled time. TTEs will be evaluated locally for changes that might affect dosing decision for others in the cohort, but the official reading will be done centrally by experts in a core laboratory in a blinded manner with results provided to the SRC. The SRC may modify the timing of the TTEs after the initial cohort so that for each subsequent cohort a TTE is obtained at the time of the predicted peak pharmacological effect. This will be based on the PK and TTE profiles from the previous cohorts. If appropriate, the SRC can request up to 2 additional TTEs be obtained.

[i] [redacted]

[j] ECG telemetry will be initiated at least 1 hour predose and continued through at least 48 hours. Additional monitoring may be needed based on data and/or patient's tolerance to the treatment.

[k] Pregnancy tests, urine or blood based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the UK), should be performed on all females.

[l] Samples for safety laboratory tests will be taken at Screening, Day -1, 24 hours postdose, and Follow up. Screening values and assessments will be made by the Central Laboratory; Day -1 assessments will be split with one sample assayed locally for review by the investigator and one sample assayed centrally. Safety laboratory tests may be added at the discretion of the investigator.

[m] Troponin samples will be collected at Screening, Day -1, and at 3, 5, 9, 12, 24, and 36 hours postdose. Samples for troponin should be split with one sample assayed locally in order to be locally reviewed by the investigator. The other sample will be analyzed at a Central Laboratory. Troponin testing performed at the Central Laboratory will be used for research purposes and will not be communicated to the study site except for Troponin I at Screening. Results of troponin from local lab should guide patient evaluation. Abnormal and/or rising troponin values (as per investigator's judgment and taking into account potential Baseline troponin elevation) should lead to patient being clinically evaluated for possible myocardial ischemia. Also, if the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional serial troponin (and other safety labs, including CK-MB samples) should be obtained. Last troponin result performed at local lab (36h postdose) should be reviewed prior to patient discharge.

[redacted]

[o] Plasma PK samples will be obtained within 1 hour predose and at 1, 2, 3, 4, 5, 6, 9, 12, 18, 24, 36, and 48 hours postdose during confinement, as well as an additional outpatient sample taken during an ambulatory visit 72 hours postdose. It is important that PK sampling occurs as close as possible to the scheduled time. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor.

[redacted]

Table 4 Part 1 (SAD): Split Dose Screening, Dosing Periods, and Follow up – Detailed

This Table should be followed for any dosing period when a single dose is split.

		Detailed Treatment and Observation for Each of 4 Dosing Periods A, B, C, and D																
Day	**-1**	**1**												**2**		**3**		**4**
Hour		**Predose[a]**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**10**	**12**	**18**	**24**	**36**	**48**	**72**
Confinement in the unit[b]	AD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	D/C	
IMP Administration			X				X[c]											
Medical history[d]	X																	
Physical examination[e]	X								X									
Body Height	X																	
Body weight	X																	
Vital signs[f]	X	X				X			X		X		X		X			
12-lead ECGs[g]	X	X				X		X			X		X		X	X		
AEs/SAEs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TTE[i]		X		-		X			X		X				X			
[redacted]																		
ECG telemetry[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[l]	X																	
Hematology[m]	X														X			
Chemistry[m]	X														X			
Urinalysis[m]	X														X			
Troponin[n]	X					X		X			X		X		X	X		
[redacted]																		
Plasma for PK[p]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		

AD, admission; AE, adverse event; BP, blood pressure; CK-MB, creatine kinase-MB; eCRF, electronic case report form; D/C, discharge; ECG, electrocardiogram; HR, heart rate; ICF, informed consent form; IMP, investigational medicinal product; PK, pharmacokinetic; SAE, serious adverse event; SRC, Safety Review Committee; TTE, transthoracic echocardiography.

[a] All predose assessments should be performed within 2 hours of administering the oral dose of MYK-491 or placebo, with the following exceptions: predose or trough PK blood samples should be taken within 1 hour predose, and ECG telemetry monitoring should be initiated at least 1 hour prior to dosing.

[b] The patient will be discharged from clinical research unit on Day 3 after all procedures have been completed and the investigator deems it safe.

[c] Four hours is the expected interval for split dosing, but timing may be modified based on emerging PK data.

[d] Update medical history at Day -1, if needed.

[e] At Screening and Day -1, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height 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 6 hours postdose and at the Follow-up visit, an abbreviated physical examination (pulmonary, cardiac, abdominal, and other systems related to any symptoms) will be conducted.

[f] Vital signs will be taken at Screening, at Day -1, predose, and at 3, 6, 9, 12, and 24 hours postdose, and at the Follow-up visit. Vital signs include temperature, HR, and BP after resting for at least 5 minutes. HR and BP taken predose, 6 hours, and 24 hours postdose will be obtained with the patient in the supine position, 1 time after standing for 2 minutes and 1 time after standing for 5 minutes. All other HR and BP measurements should be the mean of 3 measurements taken in supine position, and BP should be taken via an automated recorder. On Day1, patient will be ineligible to dose if HR $\geq$ 95 bpm at predose.

[g] Triplicate 12-lead ECG evaluations taken within a 20-minute window will be performed in the supine position after 10 minutes of rest at Screening, Day -1, predose, and at 3, 5, 9, 12, 24, and 36 hours postdose. The predose ECG on Day 1 should be performed within 2 hours of dosing. The timing of the 12-lead ECGs in this table applies to patients enrolled in Cohort 1. The actual timing of the ECGs may be modified and/or up to an additional 2 ECGs may be requested by the SRC after review of the data from previous cohorts. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it required for any other safety reason. If the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional ECGs should be obtained. These assessments should be recorded as unscheduled assessments.

[h] Changes in a Baseline condition after the ICF is signed but before IMP is administered are recorded on the medical history eCRF unless the change is considered an AE related to a study procedure. All changes that occur after administration of the study medication are recorded as AEs.

[i] A full TTE must be performed at Screening. After the Screening assessment, abbreviated TTEs will be performed predose, and at 3, 6, 9, and 24 hours postdose. It is important that the TTEs are completed as close as possible to the scheduled time. TTEs will be evaluated locally for changes that might affect dosing decision for others in the cohort, but the official reading will be done centrally by experts in a core laboratory in a blinded manner with results provided to the SRC. The SRC may modify the timing of the TTEs after the initial cohort so that for each subsequent cohort a TTE is obtained at the time of the predicted peak pharmacological effect. This will be based on the PK and TTE profiles from the previous cohorts. If appropriate, the SRC can request up to 2 additional TTEs be obtained.

[redacted]

[k] ECG telemetry will be initiated at least 1 hour predose and continued through at least 48 hours. Additional monitoring may be needed based on data and/or patient's tolerance to the treatment.

[l] Pregnancy tests, urine or blood based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the UK), should be performed on all females.

[m] Samples for safety laboratory tests will be taken at Screening, Day -1, 24 hours postdose, and Follow up. Screening values and assessments will be made by the Central Laboratory; Day -1 assessments will be split with one sample assayed locally for review by the investigator and one sample assayed centrally. Safety laboratory tests may be added at the discretion of the investigator.

[n] Troponin samples will be collected at Screening, Day -1, and at 3, 5, 9, 12, 24, and 36 hours postdose. Samples for troponin should be split with one sample assayed locally in order to be locally reviewed by the investigator. The other sample will be analyzed at a Central Laboratory. Troponin testing performed at the Central Laboratory will be used for research purposes and will not be communicated to the study site except for Troponin I at Screening. Results of troponin from local lab should guide patient evaluation. Abnormal and/or rising troponin values (as per investigator's judgment and taking into account potential Baseline troponin elevation) should lead to patient being clinically evaluated for possible myocardial ischemia. Also, if the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional serial troponin (and other safety labs, including CK-MB samples) should be obtained. Last troponin result performed at local lab (36h postdose) should be reviewed prior to patient discharge.

[redacted]

[p] Plasma PK samples will be obtained within 1 hour predose and at 1, 2, 3, 4 (before second dose of IMP), 5, 6, 8, 9, 10, 12, 18, 24, 36, and 48 hours postdose during confinement, as well as an additional outpatient sample taken during an ambulatory visit 72 hours postdose. It is important that PK sampling occurs as close as possible to the scheduled time. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor.

[redacted]

APPENDIX 2 PART 2 SCHEDULE OF STUDY PROCEDURES - MULTIPLE, ASCENDING DOSES

Table 5 Part 2 (MAD): Screening, Dosing Periods, and Follow up – High-Level

		High-level Treatment and Observation												
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16± 1**
Period	**Screen[a]**	**Baseline Single-blind Placebo BID**		**Double-blind Treatment BID**							**Follow Up**			
CONFINED:														
Confinement in the unit[b] with telemetry		Admission ◄										Discharge		
NON-CONFINED[b]:														
Clinic visit mandatory[c]	X	AM, 3PM	AM, 7h	X (all day)	7h			AM		X (all day)	AM	AM	X	X
Clinic visit (optional) or HHN visit[d]		PM	PM		AM, PM	AM, PM	AM, PM	PM	AM, PM					
All Dosing and Assessments below apply to both CONFINED or NON-CONFINED Patients														
Informed consent	X													
Single-blind placebo administration		X Q12h	X Q12h											
Randomized DB IMP administration[e]				X Q12h	X Q12h	X Q12h	X Q12h	X Q12h	X Q12h	X Once (AM)				
Assessment of dose-modification/stopping criteria[f]		◄								►				
Medical history	X													
Physical examination[g]	X	X		X				X±1d		X	X	X		X
Body height	X													
Body weight	X			X								X		
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

		High-level Treatment and Observation												
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16± 1**
Period	**Screen[a]**	**Baseline Single-blind Placebo BID**		**Double-blind Treatment BID**							**Follow Up**			
AEs/SAEs[i]	←	←	←	←	←	←	←	←	←	←	←	←	←	←
Prior/concomitant therapy (incl. stable HF background treatment)[j]	←	←	←	←	←	←	←	←	←	←	←	←	←	←
TTE[k]	X	X 3pm	X 0, 7h	X 0, 7h	X 7h			X 0h		X 0, 7hr	X 24h	X 48h		
ECG telemetry[l]		←	←	←	←	←	←	←	←	←	←	←		
Holter ECG[m]		←	←	→				←	←	→				
12-lead ECGs[n]	X		X 0h	X 0, 7h	X 7h			X±1d		X 0h	X 24h	X 48h		X
ICD download[o]														X (± 1w)
Serology[p]	X													
Pregnancy test[q]	X													X
FSH level[r]	X													
Hematology[s]	X		X		X 7h			X±1d		X		X		X
Chemistry[s]	X		X		X 7h			X±1d		X		X		X
Urinalysis[s]	X									X				
Troponin[t]	X		X 0h	X 0,7h	X 7h			X±1d		X 0h	X 24h	X 48h		X
NT-proBNP	X		X	X						X				X
[redacted]														

		High-level Treatment and Observation												
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16± 1**
Period	**Screen[a]**	**Baseline Single-blind Placebo BID**		**Double-blind Treatment BID**							**Follow Up**			
[redacted]														
PK (plasma)[w]				X Mult	X 0, 7h			X 0h		X Mult	X 24h	X 48h	X 72h	
[redacted]														

AE, adverse event; BP, blood pressure; bpm, beats per minute; CK-MB, creatine kinase-MB; DB, double-blind, [redacted] ECG, electrocardiogram; eCRF, electronic case report form; HF, heart failure; HHN, home health nurse; HR, heart rate; ICD, implantable cardioverter defibrillator; ICF, informed consent form; IMP, investigational medicinal product; PK, pharmacokinetic; Pk/Tr, peak/trough; Q12h, every 12 hours; SAE, serious adverse event; SRC, Safety Review Committee; TTE, transthoracic echocardiography.

[a] Patients with LVEF < 25% may be screened for up to 12 weeks to accommodate SRC review of first 3 patients of each cohort. Patients must remain clinically stable to meet eligibility.

[b] **If a patient has an ICD, confinement is not required**. The patient may elect to stay in close proximity to the investigational site (eg, at a nearby hotel), but must return to the clinic for all IMP administrations and assessments. Alternatively, patients may be visited by a home health nurse for IMP administrations and assessments not requiring central equipment.. For all patients, ECGs, TTEs, and PK blood draws will be performed at the study site. If a patient is not confined, it is expected that the home health nurse will be in daily contact with the study site. All patients will be discharged from clinical research unit on Day 11 after all procedures have been completed and the investigator deems it safe.

[c] For Day 3 and Day 9, a clinic visit from morning AM (pre-dose) until evening PM dose (12h later) is required. Refer to Table 6 for a detailed schedule

[d] Randomization will occur on Day 3 following local labs on Day 2. For patients who are not confined, some IMP administrations and assessments could be completed by a HHN. Days 1, 2, 4, 7 could have a HHN visit for the PM dose. Days 5, 6, 8 could utilize a HHN for both doses. Day 3 will require an in-clinic visit for both doses. Day 9 visit will be in-clinic and no evening dose and, therefore, no HHN visit. Days 10-12 assessments will be done on site.

[e] For Cohorts D and E, and any additional cohorts, all IMP administration may be QD or BID for each dosing day, as determined by the SRC.

[f] Further detail regarding dose-modification and stopping criteria are described in Section 4.2.

[g] At Screening, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height 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 time points an abbreviated physical examination (pulmonary, cardiac, abdominal, and other systems related to any symptoms) will be conducted. Physical exams should be conducted prior to the morning dose on dosing days.

[h] Vital signs will be taken at Screening, every day prior to the morning dose, and at the Follow-up visit. See detailed level of assessments for Day 3 and 9 in Table 6 for additional times vital signs are taken. Vital signs include temperature, HR, and BP after resting for at least 5 minutes. On Day 2 and once on Day 9 (see Table 6 for Day 9 instructions), vitals should include HR and BP taken in the supine position, one standing for 2 minutes, and one time standing for 5 minutes. All other HR and BP measurements should be the mean of 3 measurements taken in supine position, and BP should be taken via an automated recorder during confinement or during a clinic visit, and, if available, during home health nurse visits. On Day 1, patient will be ineligible to dose if HR ≥ 95 bpm at predose, if the average of 3 readings is higher than 95 bpm.

[i] Changes in a Baseline condition after the ICF is signed but before IMP is administered are recorded on the medical history eCRF unless the change is considered an AE related to a study procedure. All changes that occur after administration of the study medication are recorded as AEs.

[j] Every effort should be made to maintain stable background HF treatment and to administer such treatments (including diuretic as applicable) at the same time every day throughout the duration of the study.

[k] Two TTEs will be performed during screening, no fewer than 7 days apart. Eligibility must be confirmed by core laboratory for both TTEs. Effort should be made for the second TTE to be performed as close to time of dosing as is feasible, taking into account core laboratory processing time and patient availability. A full TTE should be performed at all time points indicated (with morning '0h' TTE on Day 3, Day 7 and Day 9 to be performed pre-dose). It is important that the TTEs are completed as close as possible to the scheduled time (±1 hour). TTEs will be evaluated locally for changes that might affect stopping criteria and/or dose modification, but the official reading for final results will be done centrally by experts in a core laboratory in a blinded manner. For all patients, TTEs will be performed at the study site.

[l] ECG telemetry will be initiated at least 1 hour prior to first dose (single-blind) on Day 1 and continued through Day 11 (ie, until about 48 hours post final double-blind dose on Day 9). Additional monitoring may be needed based on data and/or patient's tolerance to the treatment. Note: ECG telemetry is not required **for patients who are not confined**.

[m] Continuous Holter monitoring will be acquired in 2 timepoints, first from Day 1 until Day 3 morning (before first dose of DB treatment, 48 hours total) and from Day 7 until Day 9 . Holter may be set up any time on Day 7 and should be removed 48 hours later on Day 9. Holter may be set up by a trained home health nurse or at the study site. All patients, whether confined or not confined, must have Holter monitoring during the required times.

[n] Triplicate 12-lead ECG evaluations will be performed in the supine position after 10 minutes of rest at Screening and at Follow-up visit. See detailed schedule for Days 3 and 9. On Day 2, ECGs should be taken prior to the morning dose. On Day 4 ECG should be taken 7 hours post morning dose. On Day 7 (±1 day) ECGs should be taken prior to morning dose. On Day 10, ECG is 24 hours post final dose and on Day 11 ECG is post 48 hours final dose. All predose ECGs should be taken within 2 hours of dose, and all other ECGs should be taken plus or minus 2 hours of time point indicated. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it required for any other safety reason. If the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional ECGs should be obtained. These assessments should be recorded as unscheduled assessments. For all patients, ECGs will be performed at the study site.

[o] ICD download to be performed unless site encounters significant technical difficulties and is required in case of shock(s) delivered by the ICD during the study.

[p] Blood sample for HIV, HCV, and HBV will be collected at Screening.

[q] Pregnancy tests, urine or blood based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the UK), should be performed on all females.

[r] FSH tests will be included for potentially postmenopausal women.

[s] Safety laboratory tests should be split and one sample evaluated by local lab and the other sent to Central Lab. Samples will be taken on days indicated prior to morning dose (except on Day 4, where labs will be taken at 7 hours post-dose). Day 2 local lab results must be evaluated prior to dosing on Day 3. If needed to accommodate local laboratory time tables, Day 2 samples may be taken on Day 1. Safety laboratory tests may be added at the discretion of the investigator. NOTE: Day 7 safety laboratory assessments can be performed ±1 day if the assessments would fall on a weekend.

[t] Troponin samples will be collected as indicated. The 0 hour assessment samples should be taken prior to dosing. On Day 10, samples should be taken 24 hours post last dose. On Day 11, samples should be taken 48 hours post last dose. Samples for troponin should be split, with one sample assayed locally in order to be locally reviewed by the investigator. Troponin I or Troponin T is acceptable for local troponin, based on availability of assay at site. The other sample will be analyzed at a Central Laboratory. Results of troponin from local lab should guide patient evaluation. Abnormal and/or rising troponin values (as per investigator judgment and taking into account potential Baseline troponin elevation) should lead to patient being clinically evaluated for possible myocardial ischemia. Also, if the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional serial troponin (and other safety labs, including CK-MB samples) should be obtained. NOTE: Day 7 troponin samples can be taken ±1 day if the assessments would fall on a weekend. Troponin testing performed at the Central Laboratory will be used for research purposes and will not be communicated to the study site except for Troponin I at Screening.

[redacted]

[w] Refer to Table 6 for Day 3 and Day 9 timepoints. On Day 10, samples should be taken 24 hours post final dose. On Day 11 samples should be taken 48 hours post final dose and Day 12 at 72 hours post final dose. It is important that PK sampling occurs as close as possible to the scheduled time. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor. For all patients, PK blood draws will be performed at the study site.

[redacted]

Table 6 Part 2 (MAD): Dosing Periods and Follow up – Detailed for Days 3 and 9

		Detailed Treatment and Observation for Randomized Study Drug on Days of First and Last Double-blind Dose (All-Day In Clinic Days 3 and 9)									
		Study Hour									
Hour	**Predose[a]**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**12**
Vital signs[b]	X								X		
12-lead ECGs[c]	X								X (Day 3 only)		
Troponin[d]	X								X (Day 3 only)		
[redacted]											
PK (plasma)[e]	X		X	X	X	X	X	X	X	X	X
[redacted]											
TTE[g]	X								X		
[redacted]											

AE, adverse event; BP, blood pressure; CRF, case report form; ECG, electrocardiogram; HR, heart rate; ICD, implantable cardioverter defibrillator; IMP, investigational medicinal product; PK, pharmacokinetic; SAE, serious adverse event; SRC, Safety Review Committee; TTE, transthoracic echocardiography.

[a] All predose assessments should be performed within 2 hours of administering the oral dose of MYK-491 or placebo, with the following exceptions: predose or trough PK blood samples should be taken within 1 hour predose, and ECG telemetry monitoring should be initiated at least 1 hour prior to the first dose.

[b] Vital signs include temperature, HR, and BP after resting for at least 5 minutes. On Day 9, in the morning (predose), HR and BP should be taken once in the supine position, once after 2 minutes standing, once after 5 minutes standing. All other HR and BP measurements should be the mean of 3 measurements taken in supine position, and BP should be taken via an automated recorder.

[c] Triplicate 12-lead ECG evaluations will be performed in the supine position after 10 minutes of rest at Screening, predose, and at 7 hours postdose. The predose ECG on Day 1 should be performed within 2 hours of dosing. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it required for any other safety reason. If the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional ECGs should be obtained. These assessments should be recorded as unscheduled assessments. For all patients, ECGs will be performed at the study site.

[d] Samples for troponin should be split with one sample assayed locally in order to be locally reviewed by the investigator. The other sample will be analyzed at a Central Laboratory. Results of troponin from local lab should guide patient evaluation. Abnormal and/or rising troponin values (as per investigator's judgment and taking into account potential Baseline troponin elevation) should lead to patient being clinically evaluated for possible myocardial ischemia.

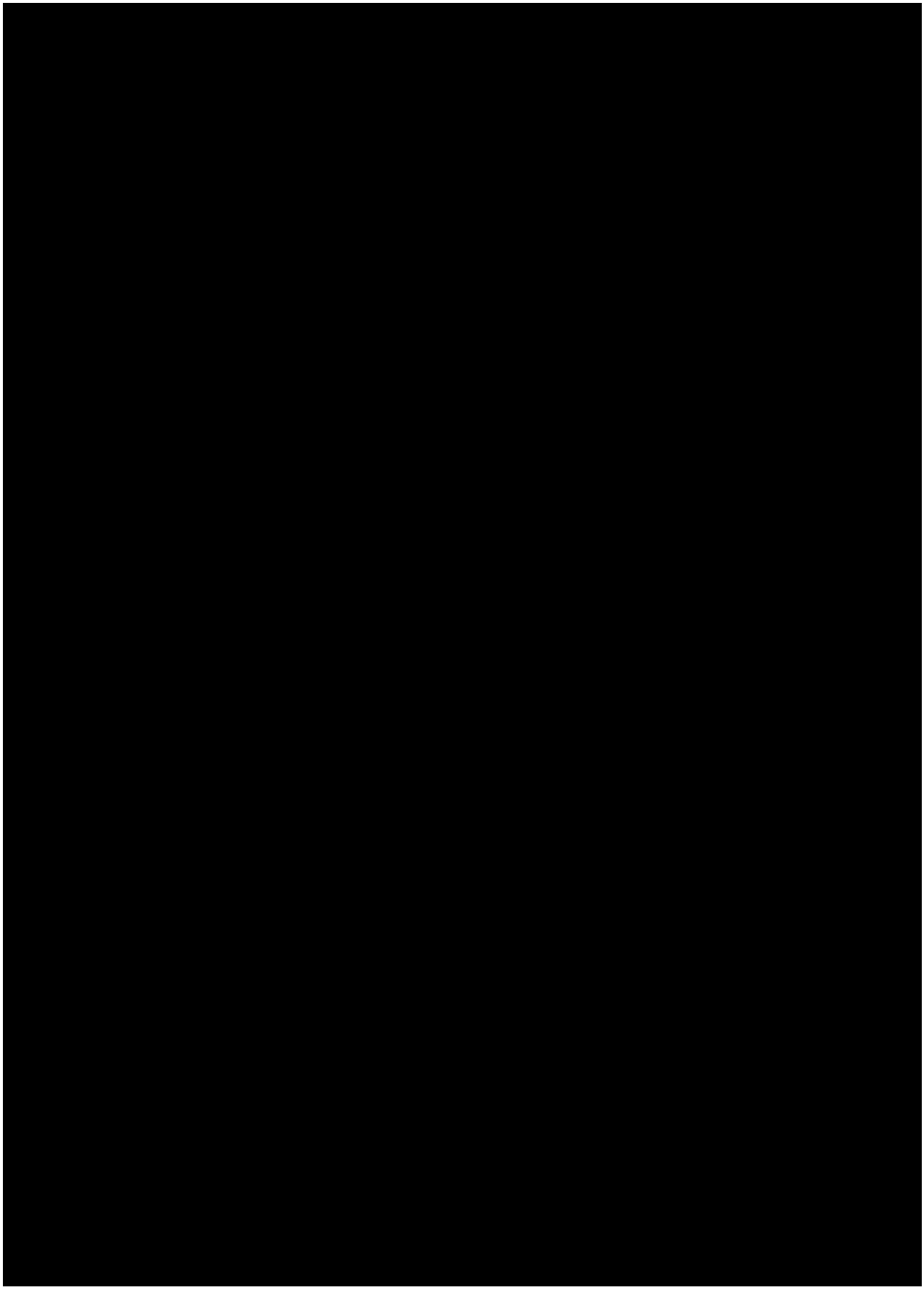
Also, if the patient has any signs or symptoms suggestive of possible cardiac ischemia, additional serial troponin (and other safety labs, including CK-MB samples) should be obtained. Troponin testing performed at the Central Laboratory will be used for research purposes and will not be communicated to the study site except for Troponin I at Screening.

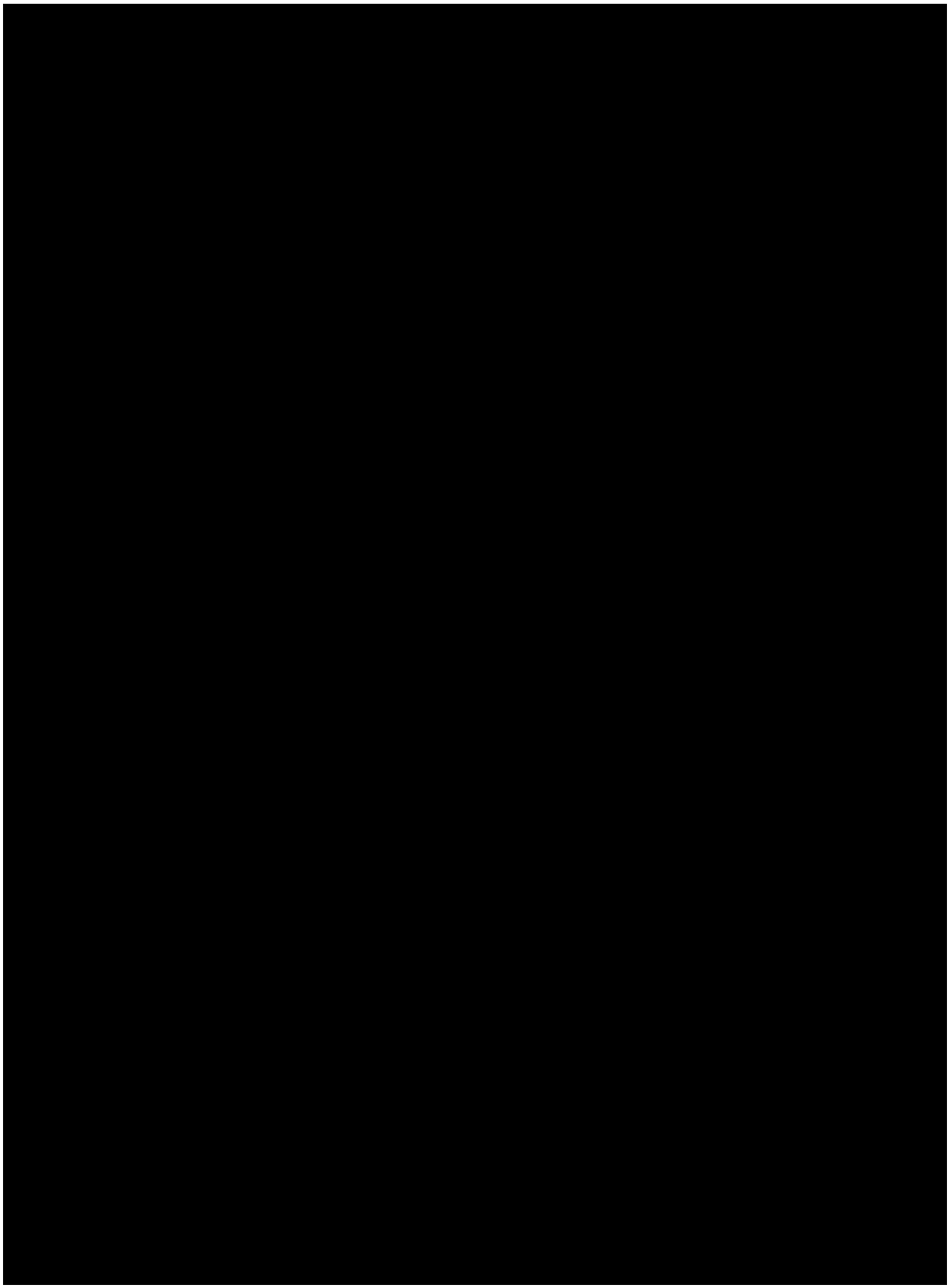
[e] Plasma PK samples will be obtained at time points indicated. The 12-hour time point should be collected prior to evening dose on Day 3. It is important that PK sampling occurs as close as possible to the scheduled time. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor. For all patients, PK blood draws will be performed at the study site.

[redacted]

[g] It is important that the TTEs are completed as close as possible to the scheduled time (±1 hour). TTEs will be evaluated locally for changes that might affect dosing decision for others in the cohort, but the official reading will be done centrally by experts in a core laboratory in a blinded manner with results provided to the SRC. For all patients, TTEs will be performed at the study site.

[redacted]





APPENDIX 4 LABORATORY ASSESSMENTS

The following safety laboratory parameters will be measured.

Table 9 Safety Laboratory Parameters

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

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

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

Troponin I, Troponin T, [redacted] will also be assessed (Appendix 1 and Appendix 2).

The following nonsafety laboratory parameters will be measured in this study:

- Serology (HIV, hepatitis panel)
- FSH
- Pregnancy, assessed in urine or blood based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the UK)

APPENDIX 5 POTENTIAL DRUG-INDUCED LIVER INJURY REPORTING AND ADDITIONAL ASSESSMENTS REPORTING

To facilitate appropriate monitoring for signals of drug-induced liver toxicity (DILI), cases of concurrent AST/ALT and TBL elevation according to the criteria specified in Section 4.2 (3 times ULN for AST/ALT and 2 times ULN for TBL in patients 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 (ie, before additional etiologic investigations have been concluded).
- The appropriate eCRFs (eg, Adverse Event eCRFs) that capture 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 patients 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 ULN are to undergo a period of close observation until abnormalities return to normal or to the patient's Baseline levels. Assessments that are to be performed during this period include the following:

- Repeat liver chemistries within 24-48 hours (ALT, AST, alkaline phosphatase, TBL); in cases of TBL ≥ 2 times ULN or AST/ALT much greater than 3 × ULN, retesting is to be performed within 24 hours.
  - Patients 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 patient 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: nonalcoholic steatohepatitis, 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 4.2.
- Follow the patient 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 eCRFs.

APPENDIX 6 INVESTIGATOR'S SIGNATURE

MYK-491-003 (HF-SAD/MAD), Edition 5, Release date: 19 March 2019

I have read and understand the contents of the clinical protocol, MYK-491-003, a Randomized, Double-blind, Placebo-controlled, Two-Part, Adaptive Design Study of Safety, Tolerability, Preliminary Pharmacokinetics, and Pharmacodynamics of Single and Multiple Ascending Oral Doses of MYK-491 in Patients with Stable Heart Failure with Reduced Ejection Fraction, 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 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 requirements to obtain written and dated approval for the Ethics Committee (EC) (eg, 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 reviewed 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 aspects 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: _____