Official Title of Study:

An Exploratory, Open-label, Proof-of-concept, Phase 2a Study of Mavacamten (MYK-461) in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Chronic Elevation of Cardiac Biomarkers

NCT Number: NCT04766892

Document Date (Date in which document was last revised): 01 Sep 2021

CLINICAL STUDY PROTOCOL

Protocol Title:	**AN EXPLORATORY, OPEN-LABEL, PROOF-OF-CONCEPT, PHASE 2A STUDY OF MAVACAMTEN (MYK-461) IN PARTICIPANTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF) AND CHRONIC ELEVATION OF CARDIAC BIOMARKERS**
Protocol Number:	MYK-461-019
Amendment Number:	1
Compound:	Mavacamten (MYK-461)
Study Phase:	2a
Acronym:	EMBARK-HFpEF
Sponsor Name	MyoKardia, Inc. (a Wholly-Owned Subsidiary of Bristol Myers Squibb)
Legal Registered Address:	1000 Sierra Point Parkway Brisbane, CA 94005
Medical Monitor:	[redacted] [redacted] Clinical Trial Physician [redacted]
Clinical Operations Contact:	[redacted] [redacted] Global Trial Manager [redacted]
Original Protocol Approval Date:	06 August 2020
Amendment 1	01 September 2021

Confidentiality Statement

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Protocol Amendment 1: 01 September 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary objectives of this amendment are to:

- Update the eligibility criteria for participants
- Change the primary endpoint from cardiac troponin I to cardiac troponin T
- [redacted]
- Streamline the Screening Visit (reduce from 3 visits to 1 visit) and make the Prescreening Visit optional
- Update the assessments to be completed at Prescreening, Screening, Day 1, and Weeks 18, 20, and 22
- [redacted]
- Update the pregnancy language to align with Investigator Brochure (IB) Edition 8.1
- Eliminate home visit options for study assessments
- Allow echocardiographic contrast agents

Changes are summarized in the table below. Additional changes were made for clarity, consistency, and accuracy throughout the document. Minor administrative and editorial changes were also made.

Location of Change	Summary of Change	Rationale for Change
Title Page Section 1.1. Section 12.	Updated title Cardiac ~~Troponin I and/or NT-proBNP~~ **Biomarkers**	Title was changed to reflect the change in eligibility criteria
Title Page	Updated Medical Monitor and Clinical Operations Manager	To reflect organizational staffing changes
Section 1.1.	Updated number of sites Approximately **3**~~2~~0 study sites	To support recruitment
Section 1.2. Section 1.3.	Initial Biomarker Assessment changed to **Optional Prescreening Up to** D -49	To streamline the screening process
Section 1.2. Section 1.3.	Screening Period **Up to D -28**	To align with change from 3 to 1 Screening Visit

Location of Change	Summary of Change	Rationale for Change
Section 1.1. Section 1.2. Section 1.3. Section 4.1.	• Cardiac troponins and NT-proBNP measured during Enrollment [redacted]	To simplify the acquisition of pre-dose blood and imaging biomarkers
[redacted]		
Section 1.3.	Adverse events, height, weight, and 12-lead ECG to be recorded during Optional Prescreening Up to Day -49	To increase the flexibility for acquiring eligibility data
[redacted]		
Section 1.3. Section 10.3.	Added collection of SPEP IMP compliance deleted from Wk 2, 4, 8, 10, 16, 18, 22, 24 (TC) columns.	Changed per the protocol clarification letter Removed since cannot be completed remotely via telephone call
Section 1.3.	Updated the footnotes for Table 1	To align with the changes made to the number of screening visits and changes in the assessments
[redacted]		
Section 1.1. Section 2.1.	Order of cardiac biomarkers was updated in the study rationale	To align with the new eligibility criteria. All participants will have a degree of NT-proBNP

Location of Change	Summary of Change	Rationale for Change
		elevation with or without elevation of hs-cTnT.
Section 1.1. Section 2.2. Section 4.1. Section 5.1. Section 8.1.1. Section 9.4.1.	Additional text to describe change in assessment from [redacted] to hs-cTnT with supporting rationale from the literature	hs-cTnT is a more sensitive prognostic biomarker than [redacted].
[redacted]		
Section 2.3.1 Section 6.8.4 Appendix 10.2.	Added information related to COVID-19 vaccines	To provide clarity on COVID-19 vaccination administration
Section 1.1. Section 3. Section 9.4.2.	The order of the primary objectives was rearranged and [redacted] was changed to cTnT	To align with the overall rationale of the study (evaluate safety of mavacamten and impact of mavacamten on levels of NT-proBNP and cTnT) and to replace [redacted] with the more sensitive prognostic biomarker hs-cTnT
Section 1.1. Section 3. Section 9.4.4.	The safety endpoint for vital sign was changed to vital sign abnormalities	To ensure consistency for the primary safety endpoints, data on vital sign abnormalities (not all vital signs) will be recorded
[redacted]		

Location of Change	Summary of Change	Rationale for Change
	[redacted]	
[redacted]		
Section 1.1. Section 5.1.	• Inclusion Criteria 5 for biomarker criteria clarified and participant restriction removed • Inclusion Criteria 6 to include LVEF ≤ 45% if not consistent with recovered HFrEF at discretion of study medical monitor • Inclusion Criteria 8 to include option to use echocardiographic contrast agents	To focus on elevated NT-proBNP; to prevent subject exclusion due to a spurious low LVEF; to correct an inconsistency, and interim review removed because enrollment will be almost complete [redacted]; to enhance study eligibility.

Location of Change	Summary of Change	Rationale for Change
Section 1.1. Section 5.1. Section 8.3.5. Section 10.4.4.2.	Updated the timing that contraception methods must be used from 3 to 4 months after the last dose of study drug	To align with updated pregnancy language in IB Edition 8.1
Section 1.1. Section 5.2.	• Exclusion Criteria 4 updated to further clarify positive serum immunofixation result • Exclusion Criteria 12 updated to define coronary artery disease as obstructive • Exclusion Criteria 27 updated to exclude acute decompensated heart failure events requiring treatment within 30 days prior to Screening • Exclusion Criteria 29 added to exclude subjects with hypersensitivity to or contraindication to intravenous electrocardiography contrast agents	To enable recruitment of subjects with positive results that do not represent a safety concern for entry into the study; to focus on significant coronary disease; to eliminate patients at increased risk of cardiovascular events during the study; to permit subjects to safely receive echocardiographic contrast agents
Section 5.4.	Individuals who do not meet the criteria for participation in this study **(prescreen or screen** failure) may be rescreened	To enhance the eligibility of subjects to enter the study
[redacted]		
Section 8.	Added text to describe that prescreening evaluations are optional and when they may be performed	To simplify the screening process
Footnotes to Schedule of Study Procedures Section 1.1. Section 5.1. [redacted].	Updated text on use of contrast echocardiograms [redacted]	To reduce screen failures due to poor image quality
Section 8.2.2.	Height (cm) and body weight (kg) will be measured at **Prescreening and/or** Screening, and body mass index (kg/m^2) will be calculated.	To increase the flexibility for acquiring eligibility data
Section 8.2.3.	Vital signs to be obtained with the participant at rest	To ensure consistency throughout the text, vital signs will be taken with participants at rest
Section 8.2.6.	Pregnancy tests to be conducted in clinic only	Home visit options are being removed

Location of Change	Summary of Change	Rationale for Change
[redacted]		
Section 9.4.4.1.	AEs will be mapped to SOCs and PTs using version 23.0 of theMedical Dictionary for Regulatory Activities (MedDRA).	To clarify that the same version number (23.0) of MedDRA will be used for the entire study
Section 9.4.4.1.1.	Updated text on data collected and listing provided for participant deaths during the study period	Clarify the analysis on death
Section 9.4.4.1.2.	Updated the pregnancy summaries that will be generated	Clarify the analysis on pregnancy summaries
Section 9.4.4.1.3.	Updated the summaries for reports of symptomatic overdose that will be generated	Clarify the analysis on symptomatic overdose
Section 9.4.4.3.1.	Deletion of normalization criteria for DILI and cross referenced to SAP	Simplify detailed text
Section 11.	**Gohar A, et al. Eur J Heart Fail. 2017** **Hoffmann J, et al. Ann Clin Biochem. 2019** [redacted]	References in bold added to support the rationale for focusing on hs-cTnT in this study. [redacted]

Abbreviations: [redacted]; BMI = body mass index; D = Day; DIL = drug-induced liver injury; ECG = electrocardiogram; EOS = End of Study; [redacted]; hs-cTnT = high sensitivity cardiac troponin T; [redacted]; IMP = investigational medicinal product; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NT-proBNP = N terminal pro b type natriuretic peptide; [redacted]; PT = preferred term; SAP = statistical analysis plan; SOC = system organ class; SPEP = serum protein electrophoresis; TC = telephone call; [redacted]; Wk = week.

1. PROTOCOL SUMMARY

1.1. Synopsis

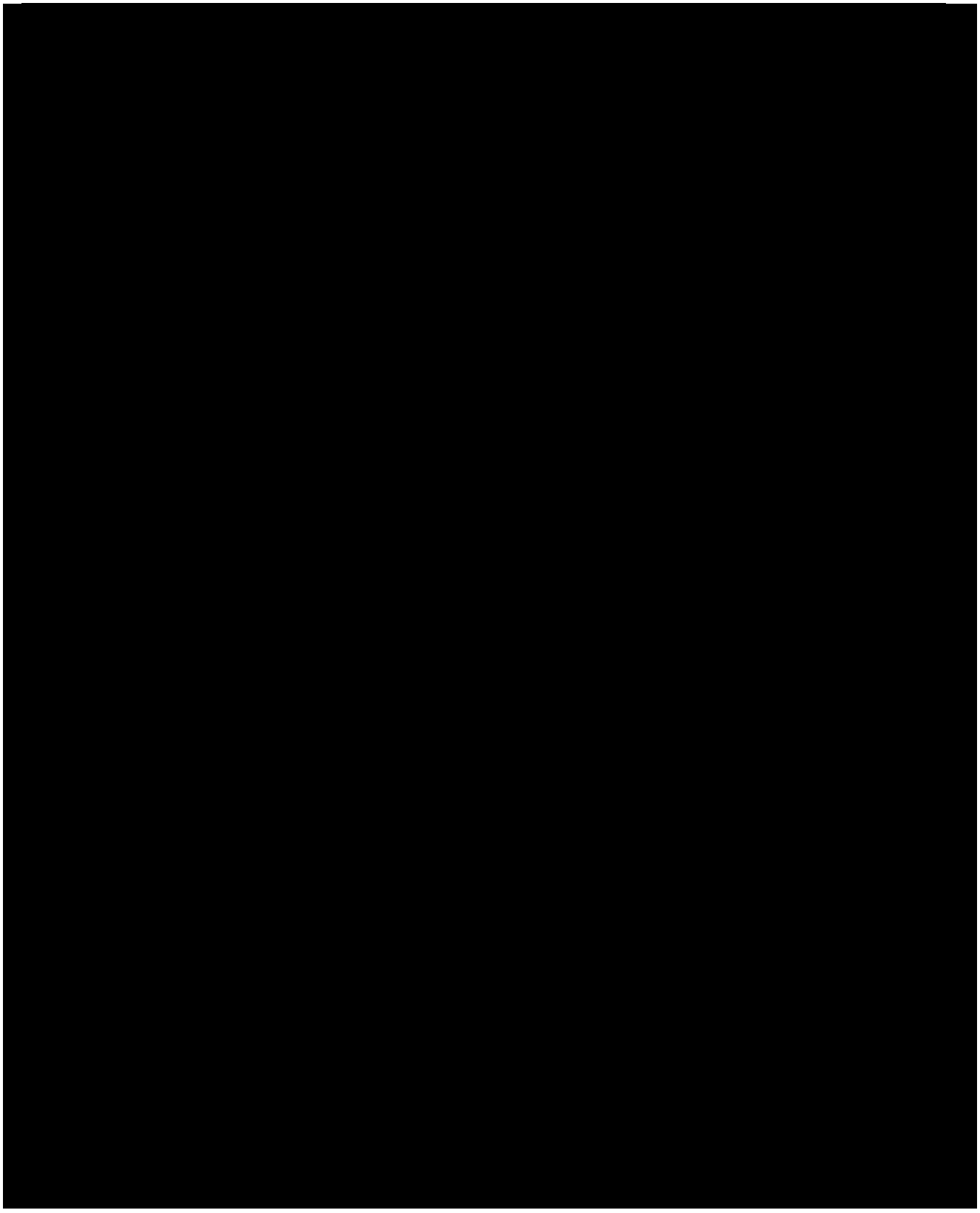
Protocol Title:	**AN EXPLORATORY, OPEN-LABEL, PROOF-OF-CONCEPT, PHASE 2A STUDY OF MAVACAMTEN (MYK-461) IN PARTICIPANTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) AND CHRONIC ELEVATION OF CARDIAC BIOMARKERS**

Rationale:

This is a Phase 2a proof-of-concept study to assess safety, tolerability, and preliminary efficacy of mavacamten treatment on N-terminal pro b-type natriuretic peptide (NT-proBNP) levels and high-sensitivity cardiac troponin T (hs-cTnT) levels in participants with heart failure with preserved ejection fraction (HFpEF) and chronic elevation of cardiac biomarkers. Data from this study will inform future study designs of mavacamten in participants with HFpEF.

Objectives and Endpoints: The primary, [redacted] objectives and endpoints of the study are as follows:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a 26-week course of mavacamten	• Frequency and severity of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs) [symptomatic overdose, outcomes of pregnancy, left ventricular ejection fraction (LVEF) ≤30%], and serious adverse events (SAEs); laboratory abnormalities; vital sign abnormalities; and cardiac rhythm abnormalities
• To evaluate the effect of a 26-week course of mavacamten on N-terminal pro b-type natriuretic peptide (NT-proBNP) levels (at rest)	• Change from baseline to Week 26 in NT-proBNP (at rest)
• To evaluate the effect of a 26-week course of mavacamten on cardiac troponin T (cTnT) levels (at rest)	• Change from baseline to Week 26 in cTnT (at rest), as assessed by a high-sensitivity assay



[redacted]

Overall Design: This is a multicenter, exploratory, open-label Phase 2a study to explore the safety, efficacy and/or pharmacodynamic effect, [redacted], and tolerability of mavacamten in approximately 35 ambulatory participants with symptomatic HFpEF and elevated NT-proBNP with or without elevation in hs-cTnT as defined in the inclusion/exclusion criteria. The study will include an up to 7-week screening period, a 26-week treatment period, and an 8-week posttreatment follow-up period. Participants will receive a 26-week course of mavacamten followed by an 8-week washout period. All participants will initially receive 2.5 mg orally each day. At Week 14, the dose for some participants may be [redacted] 5 mg orally each day as defined in the Study Procedures and Treatment section below. [redacted]	
Inclusion Criteria:	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. Is at least 50 years old at Screening. 3. Body weight is greater than 45 kg at Screening. 4. Documented prior objective evidence of heart failure as shown by 1 or more of the following criteria: a. Previous hospitalization for heart failure with documented radiographic evidence of pulmonary congestion. b. Elevated left ventricular (LV) end-diastolic pressure or pulmonary capillary wedge pressure at rest (≥15 mm Hg) or with exercise (≥ 25 mm Hg). c. Elevated level of NT-proBNP (> 400 pg/mL) or brain natriuretic peptide (BNP) (> 200 pg/mL). In the absence of qualifying historical NT-proBNP or BNP levels meeting this threshold, screening NT-proBNP meeting the threshold in inclusion criterion 5 will satisfy inclusion criterion 4. d. Echocardiographic evidence of medial E/e' ratio ≥15 or left atrial enlargement (left atrial volume index >34 mL/m^2)

	together with chronic treatment with spironolactone, eplerenone, or a loop diuretic. 5. Meets 1 or both of the following criteria: a. A screening hs-cTnT ≥ 99th percentile *AND* a screening NT-proBNP > 200 pg/mL (if not in atrial fibrillation or atrial flutter) or > 500 pg/mL (if in atrial fibrillation or atrial flutter) *OR* if the screened participant is of African descent or has a body mass index (BMI) ≥ 30.0 kg/m^2, a screening hs-cTnT ≥ 99th percentile, *AND* a screening NT-proBNP > 160 pg/mL (if not in atrial fibrillation or atrial flutter) or > 400 pg/mL (if in atrial fibrillation or atrial flutter). b. A screening NT-proBNP > 300 pg/mL (if not in atrial fibrillation or atrial flutter) or > 750 pg/mL (if in atrial fibrillation or atrial flutter) *OR* if the screened participant is of African descent or has a BMI ≥ 30.0 kg/m^2, a screening NT-proBNP > 240 pg/mL (if not in atrial fibrillation or atrial flutter) or > 600 pg/mL (if in atrial fibrillation or atrial flutter). 6. Has documented LVEF ≥60% at the Screening visit as determined by the echocardiography central laboratory and no history of prior LVEF ≤ 45% under stable conditions. If historical LVEF ≤ 45% is not consistent with recovered HFrEF medical history, the participant may be included after review of previous echocardiographic images and discussion with the study medical monitor. 7. Has maximal left ventricular wall thickness ≥ 12 mm *OR* documented elevated left ventricular mass index (LVMI) by 2-dimensional imaging (> 95 g/m^2 if female and > 115 g/m^2 if male) as determined by the echocardiography central laboratory. 8. Has adequate acoustic windows on screening resting TTE as determined by echocardiography central laboratory, to enable high likelihood of acquisition of high-quality TTEs throughout the study. Echocardiographic contrast agents may be used if the image quality of unenhanced echocardiographic images is deemed inadequate and there are no contraindications to the use of contrast agents [redacted]. 9. Has NYHA class II or III symptoms at Screening. 10. Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) within normal limits (according to the central laboratory reference range) at Screening; however, a participant with safety laboratory parameters outside normal limits may be included if he/she meets all of the following criteria: a. The safety laboratory parameter outside normal limits is considered by the investigator to be clinically unimportant. In this case, the investigator should discuss the result in question with the study medical monitor prior to enrollment.

	b. If there is an alanine aminotransferase or aspartate aminotransferase result, the value must be <3 × the upper limit of the laboratory reference range. c. The body size-adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2. 11. Female participants must not be pregnant or lactating and, if sexually active (and not postmenopausal or surgically sterile per the definition below), must be using one of the following highly effective birth control methods from the Screening visit through 4 months after the last dose of study drug. Male partners of female participants must also use a contraceptive (eg, barrier, condom, or vasectomy). a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration. b. Intrauterine device. c. Intrauterine hormone-releasing system. d. Female is surgically sterile or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion 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 levels are in the postmenopausal range.
Exclusion Criteria:	1. Previously participated in a clinical study in which mavacamten was received. 2. Hypersensitivity to any of the components of the mavacamten formulation. 3. Participated in a clinical trial where the participant received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening or 5 times the respective elimination half-life (whichever is longer). 4. Has a prior diagnosis of hypertrophic cardiomyopathy *OR* a known infiltrative or storage disorder which could cause HFpEF and/or cardiac hypertrophy, such as amyloidosis, Fabry disease, or Noonan syndrome with LV hypertrophy *OR* a positive serum immunofixation result unless a hematologist confirms the patient does not have amyloidosis or multiple myeloma. 5. Has any medical condition that precludes exercise stress testing (for stress echocardiogram). 6. Has a history of syncope within the last 6 months or sustained ventricular tachycardia with exercise within the past 6 months.

	7. Has a history of resuscitated sudden cardiac arrest at any time or known appropriate implantable cardioverter defibrillator discharge within 6 months prior to Screening. 8. Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening and/or is not adequately rate controlled within 6 months prior to Screening (note: participants with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed). 9. For participants on beta blocker, verapamil, or diltiazem, any dose adjustment < 14 days before Screening. 10. Currently treated or planned treatment during the study with either: (a) a combination of beta blocker and verapamil or a combination of beta blocker and diltiazem, (b) disopyramide, or (c) biotin or biotin-containing supplements/multivitamins. 11. Has any electrocardiogram (ECG) abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II). 12. Has either: (a) known unrevascularized obstructive coronary artery disease *OR* (b) acute coronary syndrome in the last 3 months. 13. Has known moderate or severe aortic valve stenosis, hemodynamically significant mitral stenosis, or severe mitral or tricuspid regurgitation at Screening (all in the investigator's judgment). 14. Has any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study. 15. Has severe chronic obstructive pulmonary disease, or other severe pulmonary disease, requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months. 16. Hemoglobin < 10.0 g/dL. 17. Body mass index (BMI) ≥ 45.0 kg/m^2. 18. Positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus. Positive hepatitis BsAb participants are allowed as this positive serologic test denotes presence of neutralizing, protective antibodies and does not denote chronic infection.

	19. Active coronavirus disease 2019 (COVID-19) infection and/or other acute respiratory infection at time of Screening or randomization. 20. History of clinically significant malignant disease within 5 years of Screening: a. Participants who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ can be included in the study. 21. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or study medical monitor, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion. 22. Currently taking, or has taken within 14 days prior to Screening, a prohibited medication (including over-the-counter medications) such as a cytochrome P450 (CYP) 2C19 inhibitor (eg, omeprazole, esomeprazole), a strong CYP3A4 inhibitor, or St. John's Wort. 23. Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar. 24. Unable to comply with the study requirements, including the number of required visits to the clinical site. 25. Employed by, or a relative of someone employed by MyoKardia, the investigator, or his/her staff or family. 26. Left ventricular global longitudinal strain by TTE in the range from 0 to -12.0 (assessed by central TTE reader). 27. Acute decompensated heart failure events requiring intravenous (IV) diuretics, IV inotropes, IV vasodilators, or a left ventricular assist device within 30 days prior to Screening. 28. NT-proBNP at Screening > 2000 pg/mL. 29. Known hypersensitivity or contraindication to the IV echocardiography contrast agent, if contrast echocardiography is required due to inadequate quality of unenhanced echocardiographic images.
Disclosure Statement: This is a single-arm, open-label, exploratory study.	
Number of Sites: Approximately 30 study sites within or outside the United States	
Number of Participants: Approximately 35 participants	
Study Procedures and Treatment:	

Doses of mavacamten used in this study will be 2.5 and 5 mg. Dose adjustments at Week 14 (described in greater detail below) will be based upon NT-proBNP and LVEF measured at the Week 12 visit.

Study visits will occur at Prescreening (optional), Screening, Day 1, Week 6, Week 12, Week 14, Week [redacted], Week [redacted], Week 26, and the End of Study (EOS) visit at Week 34. [redacted] Assessments during the treatment period will include vital signs, AEs, concomitant medications, abbreviated physical examination, weight, 12-lead ECG, [redacted], [redacted], safety laboratory assessments (chemistry, hematology, coagulation panel, and urinalysis), [redacted], hs-cTnT, NT-proBNP, urine pregnancy test (for women of childbearing potential only), [redacted]. In addition, participants will be contacted via telephone call at Weeks 2, 4, 8, 10, 16, [redacted], and 24 to collect information about AEs and concomitant medications. Participants who prematurely discontinue study drug at any time will attend an early drug discontinuation visit within 14 days of study drug discontinuation and the EOS visit at Week 34.

[redacted]

[redacted]

[redacted]

The dose may be [redacted] for safety at any time.

Safety will be monitored throughout the study.

Criteria for Evaluation:

Efficacy: The primary endpoint is change from baseline to Week 26 in NT-proBNP (at rest) and cTnT (at rest).

Safety: Safety assessments include monitoring of AEs and concomitant medications, safety laboratory assessments, physical examinations, vital sign measurements, TTEs, cardiac/activity monitoring, and ECGs.

Statistical Methods:

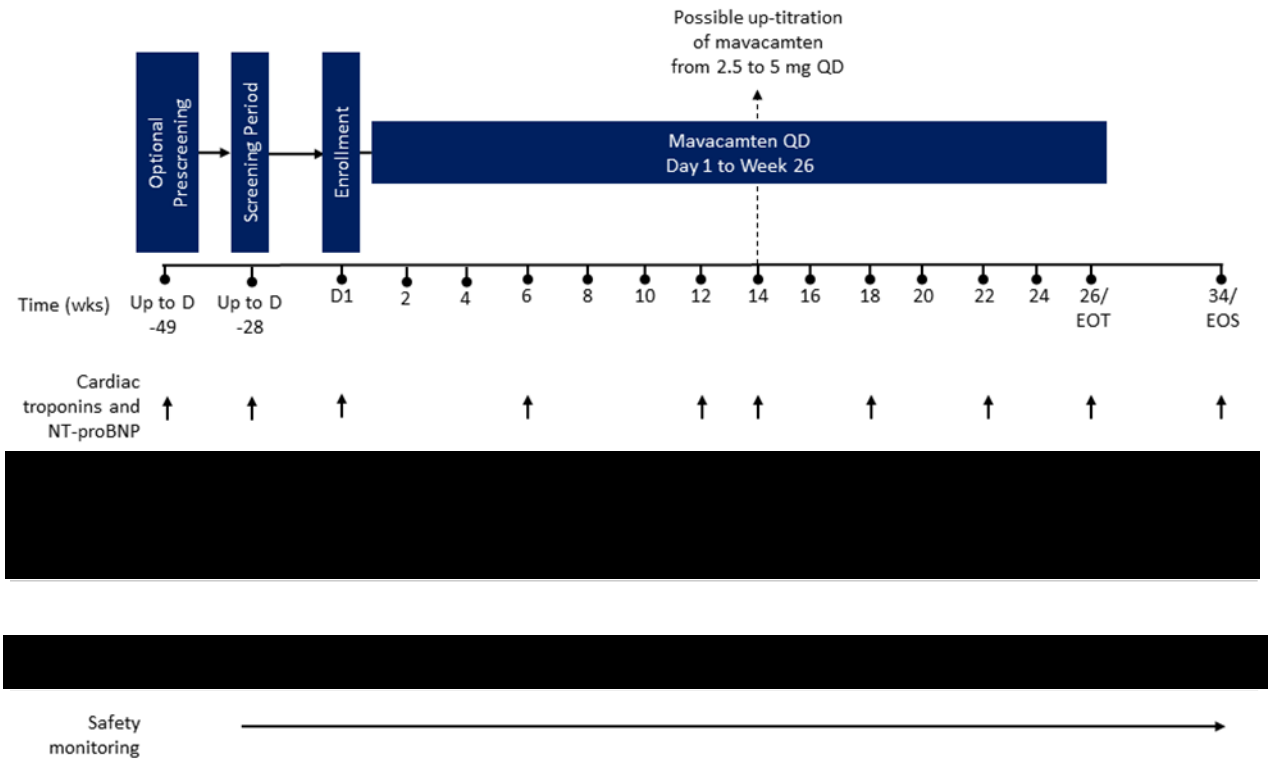
This exploratory study will include a total of approximately 35 participants.

In general, descriptive summaries will be presented at each visit. The descriptive summary for continuous variables will also be provided for the change from baseline. Summaries of continuous variables will include the number of participants, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum. For variables with highly skewed distribution (eg, log-normal distribution), such as hs-cTnT and NT-proBNP, geometric mean and percent coefficient of variation will also be reported in descriptive summaries. Descriptive summaries for categorical variables will include the number and percentage of participants. Unless otherwise stated, denominators for percentages will be the number of participants in the analysis population.

Study Committees: Independent Data Monitoring Committee

1.2. Schema

Figure 1: MYK-461-019 Study Schema



Abbreviations: D = Day; EOS = End of Study; EOT = End of Treatment; NT-proBNP = N-terminal pro b-type natriuretic peptide; QD = once daily; [redacted]; wks = weeks.

1.3. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

Assessment	Optional Prescreening: Up to Day -49[a]	Screening: Up to Day -28	D1[b]	Wk 2, 4, 8, 10, 16, [redacted], 24 (TC)[c]	Wk 6[c]	Wk 12[c]	Wk 14[c]	Wk [redacted]	Wk [redacted]	Wk 26/ EOT[c, e]	Early Discont. Visit[f]	Wk 34/ EOS[c]
Informed consent	X[g]	X										
Medical history		X										
Vital signs		X	X		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
Prior/concomitant medications		X	X	X	X	X	X	X	X	X	X	X
Full physical examination		X								X	X	X
Abbreviated physical examination[h]			X		X	X	X	X	X			
Height	X	X										
Weight	X	X	X		X	X	X	X	X	X	X	X
12-lead ECG	X	X	X		X	X	X	X	X	X	X	X
[redacted]												

Table 1: Schedule of Study Procedures (Continued)

Assessment	Optional Prescreening: Up to Day -49[a]	Screening: Up to Day -28	D1[b]	Wk 2, 4, 8, 10, 16, [redacted], 24 (TC)[c]	Wk 6[c]	Wk 12[c]	Wk 14[c]	Wk [redacted]	Wk [redacted]	Wk 26/ EOT[c,e]	Early Discont. Visit[f]	Wk 34/ EOS[c]
Hepatitis panel, HIV test[l]		X										
Serum free light chain ratio and SPEP w/immunofixation[l]		X										
[redacted]												
Chemistry[l]		X	X		X	X	X	X	X	X	X	X
Hematology[l]		X	X		X	X	X	X	X	X	X	X
Coagulation panel[l]		X	X		X	X	X	X	X	X	X	X
Urinalysis[l]		X								X	X	X
HbA1c[l]		X										
[redacted]												
NT-proBNP[l]	X	X	X[m,n]		X	X	X	X	X	X[n]	X	X[n]
hs-cTnT[l]	X	X	X[m,n]		X	X	X	X	X	X[n]	X	X[n]
TSH[l]		X										
FSH and serum pregnancy test (females)[l]		X										
Urine pregnancy test (females)[l]			X		X	X	X	X	X	X	X	X
[redacted]												

Table 1: Schedule of Study Procedures (Continued)

Assessment	Optional Prescreening: Up to Day -49[a]	Screening: Up to Day -28	D1[b]	Wk 2, 4, 8, 10, 16, [redacted], 24 (TC)[c]	Wk 6[c]	Wk 12[c]	Wk 14[c]	Wk [redacted]	Wk [redacted]	Wk 26/ EOT[c,e]	Early Discont. Visit[f]	Wk 34/ EOS[c]
[redacted]												
IMP QD			←	—	—	—	—	—	—	→		
Adjust dose							X					
IMP dosing at site			X							X		
IMP compliance					X	X	X	X	X	X	X	

D = Day; ECG = electrocardiogram; Discont. = discontinuation; eCRF = electronic case report form; EOS = End of Study; EOT = End of Treatment; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; [redacted]; hs-cTnT = high-sensitivity cardiac troponin T; [redacted]; IMP = investigational medicinal product; [redacted]; NT-proBNP = N-terminal pro b-type natriuretic peptide; [redacted]; [redacted]; QD = once daily; [redacted]; SPEP = serum protein electrophoresis; TC = telephone call; TSH = thyroid-stimulating hormone; [redacted]; Wk = Week.

[a] Although encouraged for all potential participants, the prescreen for initial biomarker data is not required to be performed at the investigator's discretion if prior NT-proBNP and/or cardiac troponin results from the ambulatory/outpatient setting indicate that the participant is likely to qualify for the study. In this case, the prior biomarker results should be documented in the eCRF (including assay type [high-sensitivity or not] and laboratory-specific upper limit of normal).

[redacted].

[c] Visit may be conducted in a window of ±3 days from the timepoint.

[redacted]

[e] EOT visit assessments may be performed over up to 3 consecutive days if needed for scheduling purposes given the number of assessments.

[f] The Early Discontinuation Visit may be utilized for the purposes of either permanent study drug discontinuation (without withdrawal from the study) or discontinuation/withdrawal from the study. In the former case, the EOS visit will still be conducted approximately 8 weeks after the Early Discontinuation Visit (and without functional testing [redacted]).

[g] There is a separate consent for the assessments completed at the optional prescreening visit.

[h] Abbreviated physical examination is an abbreviated cardiopulmonary physical examination, with other systems assessed as appropriate based on interval history at the investigator's discretion.

Table 1: Schedule of Study Procedures (Continued)

[redacted]

[l] Refer to the Study Laboratory Manual for details on how to complete the procedures.
[m] Sampling for [redacted], NT-proBNP, and hs-cTnT should be drawn predose.
[n] Sampling for [redacted], NT-proBNP, and hs-cTnT must be drawn prior to exercise [redacted]

[redacted]

2. INTRODUCTION

Mavacamten is a targeted cardiac-specific myosin inhibitor being developed for once-daily treatment of hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF) and chronic elevation of N-terminal pro b-type natriuretic peptide (NT-proBNP).

2.1. Study Rationale

This is a Phase 2a proof-of-concept study to assess safety, tolerability, and preliminary efficacy of mavacamten treatment on NT-proBNP levels and high-sensitivity cardiac troponin T (hs-cTnT) levels in participants with HFpEF and chronic elevation of cardiac biomarkers. The data from this study will complement results from the completed MYK-461-006 MAVERICK-HCM study in symptomatic participants with the related condition nonobstructive hypertrophic cardiomyopathy (nHCM). Data from this study will inform future study designs of mavacamten in participants with HFpEF.

2.2. Background

Heart failure with preserved ejection fraction is a clinical syndrome defined by current or prior heart failure symptoms, evidence of cardiac dysfunction as a cause of the symptoms, and a left ventricular ejection fraction (LVEF) ≥50%. Although HFpEF is a complex syndrome with multiple causes, left ventricular (LV) diastolic dysfunction with elevated filling pressures and impaired exercise capacity play an important role in the pathophysiology of the condition.

Mavacamten is a first-in-class, small molecule, selective allosteric inhibitor of cardiac myosin that reversibly inhibits its binding to actin. Mavacamten's profile of myosin modulation is predicted to reduce ventricular filling pressures in participants with HFpEF and LV hypertrophy by improving ventricular compliance.

A related condition, nHCM—which can present with the HFpEF phenotype (Pieske et al, 2019)—is characterized clinically by unexplained LV hypertrophy in the absence of known causes such as pressure overload, systemic diseases, or infiltrative processes (Gersh et al, 2011). The phenotypic hallmark of HCM, which is often caused by mutations in genes encoding cardiac sarcomere proteins, is myocardial hypercontractility accompanied by reduced LV compliance, often with reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. In the recent MAVERICK-HCM trial, mavacamten was shown to robustly reduce both NT-proBNP (an indicator of wall stress) and cardiac troponin I (cTnI) (an indicator of myocardial injury) in participants with symptomatic nHCM (Ho et al, 2020). Potentially beneficial effects of mavacamten were most pronounced in a combined subset of higher risk participants: those with either baseline cTnI greater than the 99th percentile (of a reference population) or with $E/e'_{average}$ (an echocardiogram surrogate for elevated LV filling pressures and ratio of early filling velocity of blood entering the left ventricle across the mitral valve during diastole to the velocity of motion of the myocardium in the region of the mitral annulus during the early filling portion of diastole) >14.

As the pathophysiology underlying nHCM and HFpEF is similar, this proof-of-concept study tests the hypothesis that an adjacent population of participants with HFpEF will experience similar salutary biomarker changes to those seen in participants with nHCM in the MAVERICK-HCM study. Primary efficacy biomarkers in this study focus on NT-proBNP and

hs-cTnT [redacted]. The focus on hs-cTnT is in light of published studies demonstrating several advantages of this cardiac troponin assay. First, hs-cTnT is a more sensitive prognostic marker [redacted]. Secondly, hs-cTnT, but not [redacted], has been shown to be a reliable biomarker to reflect echocardiographic stages of diastolic dysfunction [redacted], a hallmark of HFpEF. Furthermore, the latter study demonstrated that hs-cTnT concentrations corresponded with LV wall thickness and left atrial chamber size. Therefore, this study focuses on a segment of HFpEF characterized by LV hypertrophy, LVEF >60%, and chronically elevated NT-proBNP (elevated wall stress) with or without elevated hs-cTnT (indicating ongoing myocardial injury).

2.2.1. Clinical Studies

As of 31 October 2019, clinical conduct has been completed for 9 studies as follows:

- Study MYK-461-002, a single-ascending dose (SAD) study in 48 healthy participants
- Study MYK-461-003, a multiple-ascending dose study in 60 healthy participants
- Study MYK-461-009, a drug-interaction study with verapamil in 25 healthy participants
- Study MYK-461-010, a drug-interaction study with an oral contraceptive in 13 healthy women
- Study MYK-461-011, an ethnobridging pharmacokinetics (PK) study in 20 Japanese and 8 Caucasian participants
- Study MYK-461-012, an intrinsic factor PK study in 8 participants with cytochrome P450 (CYP) 2C19 poor metabolizers (PMs) and 8 participants identified as CYP2C19 normal metabolizers (NMs).
- Study MYK-461-013, a single-dose, mass balance study in 6 healthy participants
- Study MYK-461-001, a SAD study in 15 participants with HCM
- Study MYK-461-004 (PIONEER-HCM), a Phase 2 study in participants with obstructive hypertrophic cardiomyopathy (oHCM)

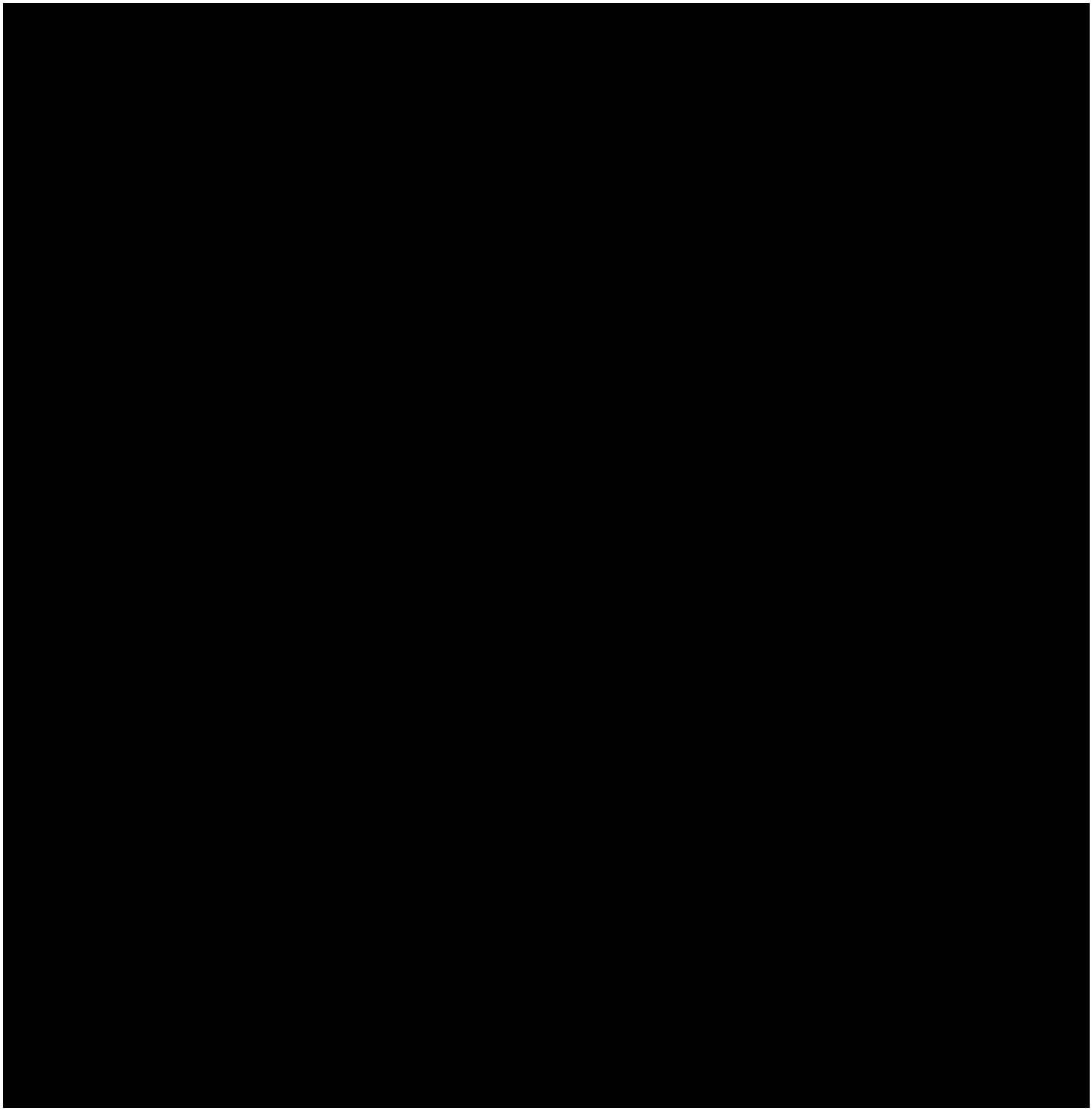
In total, 210 participants with HCM or healthy participants were enrolled across the completed studies, 188 of whom were exposed to at least 1 dose of mavacamten.

Additionally, more than 400 participants have been enrolled across 6 studies of mavacamten that were ongoing as of 31 October 2019:

- Study MYK-461-005 (EXPLORER-HCM), a Phase 3, multinational, randomized, double-blind, placebo-controlled study in participants with symptomatic oHCM
- Study MYK-461-006 (MAVERICK-HCM), a Phase 2 randomized, placebo-controlled, concentration-guided exploratory study in participants with symptomatic nHCM

- Study MYK-461-008 (PIONEER-OLE), an open-label extension study in participants with symptomatic oHCM who were previously enrolled in Study MYK-461 PIONEER-HCM
- Study MYK-461-007 (MAVA-LTE), an open-label extension study in participants with symptomatic HCM who were previously enrolled in Studies MYK-461-006 (MAVERICK-HCM) or MYK-461-005 (EXPLORER-HCM) studies
- Study MYK-461-014, a 3-period cross-over study in healthy participants to assess the relative bioavailability of the initial capsule formulation and the final commercial formulation of mavacamten, and the effect of food on the final commercial formulation
- Study MYK-461-015, an intrinsic factor study to assess PK of mavacamten on participants with the mild and moderate hepatic impairment and healthy controls

For a full list of studies, please reference the current Investigator's Brochure (IB).



2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of mavacamten may be found in the IB.

2.3.1. Risk Assessment

The safety profile of mavacamten treatment for participants with HCM is acceptable in the context of the observed clinical efficacy. Cumulatively (as of 30 October 2020), 97 total SAEs have been reported in 61 participants in the mavacamten clinical development program. Of these, 69 SAEs occurred in 45 participants treated with mavacamten and 28 SAEs occurred in 17 participants treated with placebo. Most serious and nonserious events reported for mavacamten-treated participants across the program were outcomes or symptoms of the underlying disease. No clinically significant off-target treatment effects were identified for mavacamten. In the pivotal Phase 3 study (MYK-461-005), dizziness was the most frequently reported AE and was more frequent in mavacamten-treated participants than placebo-treated participants. In the integrated safety summary, dizziness occurred in 15.5% of mavacamten treated participants and 12.2% of placebo treated participants. Given the absence of clear alternative etiology in a high proportion of participants, dizziness is proposed as an adverse drug reaction for mavacamten. Other proposed adverse drug reactions for mavacamten include heart failure and systolic dysfunction, which occurred in <5% of participants administered mavacamten. Systolic dysfunction with mavacamten has been reversible and has not resulted in a picture of progressive cardiac failure (recurrent hospitalizations and progressive LVEF reduction) as described in the literature associated with progression of underlying HCM.

Based on nonclinical data and the available clinical data, the most likely risks are those associated with higher exposures resulting in excessive decrease in cardiac contractility (decline in LVEF). Reduced tolerance might be reflected in nonspecific AEs such as fatigue or in reflex changes in resting heart rate (HR) or systolic blood pressure (BP). Higher exposures could result in the development of signs or symptoms of systolic heart failure, especially in the setting of simultaneous tachyarrhythmias or ischemia.

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

Teratogenicity is considered a potential risk due to findings in nonclinical studies conducted in 2 species (rabbits and rats) that resulted in postimplantation loss, decreased mean fetal body weight, and fetal malformations (visceral and skeletal) at doses that overlap with doses used in humans. However, there are no clinical data available for pregnancy with exposure to mavacamten. No pregnancies have been reported in participants exposed to mavacamten due to use of stringent contraceptive measures in all trials including use of oral contraceptives. Study MYK-461-010, a DDI study, confirmed that oral contraceptives are safe to use while on mavacamten.

Three important potential risks are described below. See the current IB for further details.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug		
Systolic dysfunction	Data across nonclinical toxicology studies have shown that plasma exposures associated with excess pharmacology likely to lead to reduced cardiac function, decreased blood pressure, and compensatory increases in heart rate. Clinical data have shown that dose-dependent on-target reductions in left ventricular ejection fraction (LVEF) have generally been well tolerated in healthy participants. Data from Study MYK-461-006, conducted in participants with nonobstructive hypertrophic cardiomyopathy (nHCM), demonstrated that those who experienced decreases in LVEF were returning to normal pretreatment levels after discontinuation of study treatment.	As this risk is related to excessive on-target pharmacology, [redacted]. Pharmacodynamic biomarkers (including N-terminal-pro B type natriuretic peptide, high sensitivity cardiac troponin and LVEF) by transthoracic echocardiography) will guide and should contribute to the safety [redacted]. Additionally, LVEF is assessed serially throughout the study and will lead to temporary and/or permanent discontinuation of study drug if safety thresholds are met [redacted]
Prolonged QTc	Consistent prolongation of corrected QT interval (QTc) with the typical QT measurements has been identified across all chronic dog studies. Clinical data from human exposure to mavacamten are mixed. Dose- and concentration-dependent QTc prolongation was observed in healthy participants in multiple ascending dose Study MYK-461-003. However, no QTc prolongations were observed in the single-dose studies or in healthy participants, in the 12-week study of participants with obstructive hypertrophic cardiomyopathy (Study MYK-461-004), or in the	QTc prolongation, where observed in either animal studies or in healthy volunteers in the multiple ascending dose Study MYK-461-003, has been dose and concentration dependent. As the dosing strategy in this study is conservative, with a maximum dose of 5 mg in this protocol, this should mitigate any risk of QTc prolongation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	nHCM (Study MYK-461-006) participants at the 16-week (End of Treatment) analysis.	
Teratogenicity	Oral administration of mavacamten in nonclinical studies conducted in 2 species (rabbits and rats) resulted in postimplantation loss, decreased mean body weight, skeletal malformations (rats) and visceral and skeletal malformations (rabbits), suggestive of a teratogenic potential of the compound. There are no clinical data on the safety of mavacamten during pregnancy, and highly effective contraception is required in the ongoing clinical studies. The risk of embryofetal toxicity due to paternal drug exposure in the semen was assessed based on preclinical data, actual semen concentrations of mavacamten in men dosed with mavacamten in Study MYK-461-003, and the potential for these concentration levels to cause maternal systemic exposures that could be teratogenic. It was concluded from the findings and estimates of maternal exposure by a man taking mavacamten that the risk of teratogenic effects caused by the drug transferred by semen or other body fluids is negligible.	Effective forms of contraception to mitigate this risk are specified in this protocol.

Nonlive COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of nonlive vaccines (including non-live COVID-19 vaccines) in participants receiving mavacamten is unknown.

2.3.2. Benefit Assessment

There is no currently known benefit of mavacamten to individuals with HFpEF; however, the results of the MAVERICK-HCM study of mavacamten in a high-risk subset of individuals with symptomatic nHCM suggest the potential for improvement of biomarkers related to LV wall stress (NT-proBNP) and myocardial injury (cardiac troponin) in HFpEF, in addition to E/e' as a

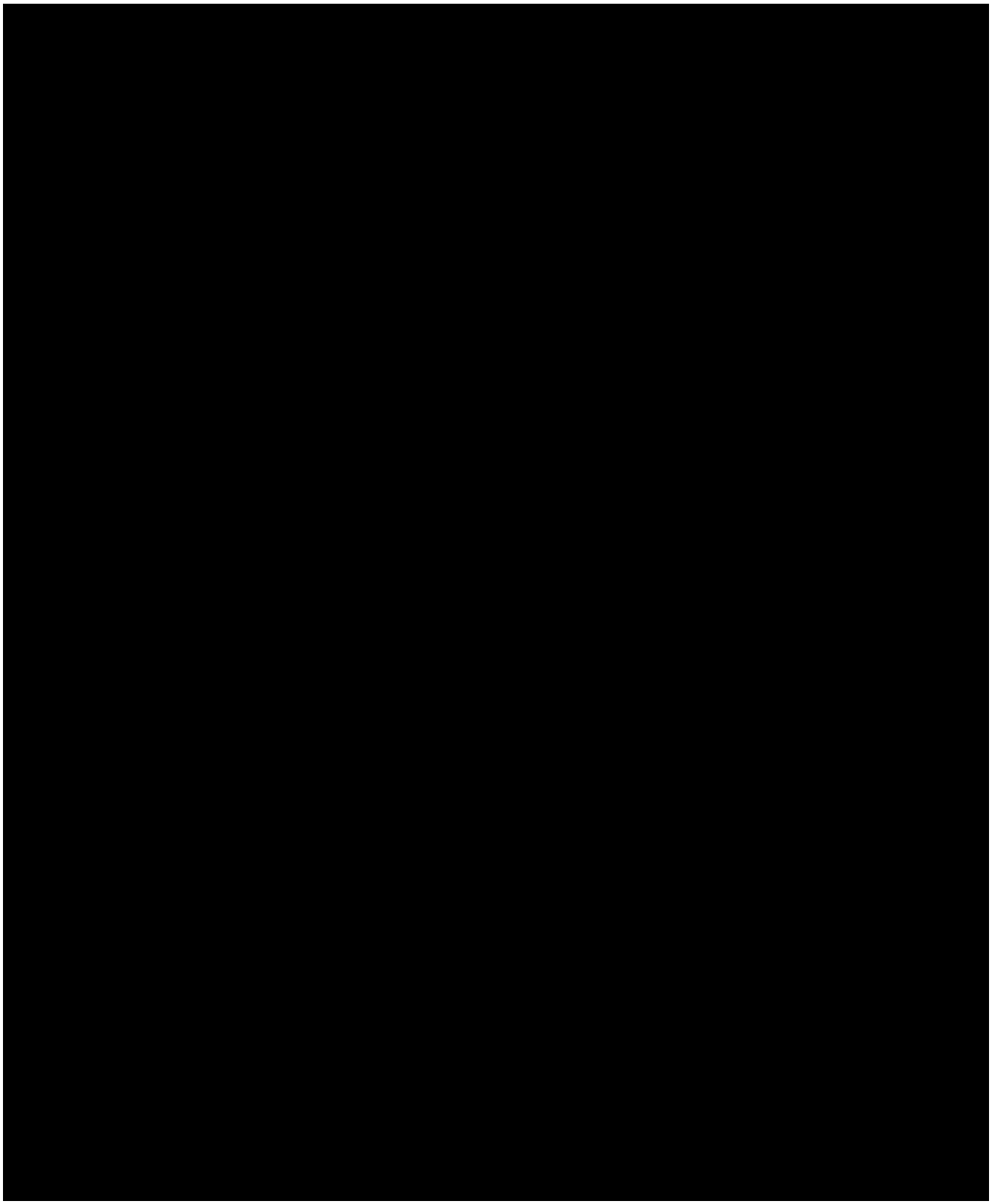
marker of diastolic function. Therefore, this study aims to test the hypothesis that mavacamten administration in HFpEF can improve biomarkers of cardiac wall stress and myocardial injury. The results have the potential to guide further development to more rigorously assess potential benefit in this segment of HFpEF patients.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to mitigate risk to participants in this study, the potential risks identified in association with mavacamten are justified by the anticipated potential benefits that may be afforded to participants with HFpEF.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a 26-week course of mavacamten	• Frequency and severity of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs) [symptomatic overdose, outcomes of pregnancy, left ventricular ejection fraction (LVEF) ≤30%], and serious adverse events (SAEs); laboratory abnormalities; vital sign abnormalities; and cardiac rhythm abnormalities
• To evaluate the effect of a 26-week course of mavacamten on N-terminal pro b-type natriuretic peptide (NT-proBNP) levels (at rest)	• Change from baseline to Week 26 in NT-proBNP (at rest)
• To evaluate the effect of a 26-week course of mavacamten on cardiac troponin T (cTnT) levels (at rest)	• Change from baseline to Week 26 in cTnT (at rest), as assessed by a high-sensitivity assay
[redacted]	



4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, exploratory, open-label, Phase 2a study to explore the safety, efficacy, pharmacodynamic effect, [redacted] and tolerability of mavacamten in approximately 35 ambulatory participants with symptomatic HFpEF and elevated NT-proBNP with or without elevation in hs-cTnT as defined in the inclusion/exclusion criteria.

The study will include an up to 7-week screening period, a 26-week treatment period, and an 8-week posttreatment follow-up period.

Study visits will occur at Prescreening (optional), Screening, Day 1, Week 6, Week 12, Week 14, Week 18, Week 22, Week 26, and the End of Study (EOS) visit at Week 34 (Table 1). [redacted]
Assessments during the treatment period will include vital signs, AEs, concomitant medications, abbreviated physical examination, weight, 12-lead electrocardiogram (ECG), [redacted], [redacted], safety laboratory assessments (chemistry, hematology, coagulation panel, and urinalysis), [redacted], NT-proBNP, hs-cTnT, urine pregnancy test (for women of childbearing potential only), [redacted]. In addition, participants will be contacted via telephone call at Weeks 2, 4, 8, 10, 16, [redacted], and 24 to collect information about AEs and concomitant medications. Participants who prematurely discontinue study drug at any time will attend an early drug discontinuation visit within 14 days of study drug discontinuation and the EOS visit at Week 34.

All participants will initially receive 2.5 mg mavacamten orally QD. At Week 14, the dose for some participants may be [redacted] 5 mg QD based on NT-proBNP and resting LVEF measured at the Week 12 visit. [redacted]

4.2. Scientific Rationale for Study Design

This study will test the hypothesis that mavacamten treatment can reduce biomarkers of cardiac wall stress and myocardial injury in a targeted segment of HFpEF participants that shares similar features to a subset of MAVERICK-HCM participants with symptomatic nHCM who experienced similar improvements in wall stress and myocardial injury. Additionally, the study

will provide a preliminary assessment of the tolerability and safety of mavacamten administration in this targeted HFpEF segment.

Assuming similar kinetics of NT-proBNP and troponin changes to those seen in nHCM, the open-label design will allow adequate assessment of biomarker reduction without a placebo group as individual and mean decreases in both NT-proBNP and troponin (if observed at Week 26) would be expected to return to approximately baseline by Week 34 (the end of the 8-week washout period).

The study additionally will explore several measures of symptoms and functioning in the participants with a goal of obtaining preliminary estimates of the effects of mavacamten on these parameters. These data may be useful in informing future study designs in HFpEF.

4.3. Justification for Dose

In the MAVERICK-HCM study, biomarker reductions (NT-proBNP and cardiac troponins) were noted in study participants at Week 4 of treatment when all participants were receiving 5 mg of mavacamten orally. [redacted].

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including the EOS visit shown in the Schedule of Study Procedures (Table 1).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

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. Is at least 50 years old at Screening.
3. Body weight is greater than 45 kg at Screening.
4. Documented prior objective evidence of heart failure as shown by 1 or more of the following criteria:
    a. Previous hospitalization for heart failure with documented radiographic evidence of pulmonary congestion.
    b. Elevated LV end-diastolic pressure or pulmonary capillary wedge pressure at rest (≥15 mm Hg) or with exercise (≥ 25 mm Hg).
    c. Elevated level of NT-proBNP (> 400 pg/mL) or brain natriuretic peptide (BNP) (>200 pg/mL). In the absence of qualifying historical NT-proBNP or BNP levels meeting this threshold, screening NT-proBNP meeting the threshold in inclusion criterion 5 will satisfy inclusion criterion 4.
    d. Echocardiographic evidence of medial E/e' ratio ≥ 15 or left atrial enlargement (left atrial volume index >34 mL/m^2) together with chronic treatment with spironolactone, eplerenone, or a loop diuretic.
5. Meets 1 or both of the following criteria:
    a. A screening hs-cTnT ≥ 99th percentile *AND* a screening NT-proBNP > 200 pg/mL (if not in atrial fibrillation or atrial flutter) or > 500 pg/mL (if in atrial fibrillation or atrial flutter) *OR* if the screened participant is of African descent or has a BMI ≥ 30.0 kg/m^2, a screening hs-cTnT ≥ 99th percentile, *AND* a screening NT-proBNP > 160 pg/mL (if not in atrial fibrillation or atrial flutter) or > 400 pg/mL (if in atrial fibrillation or atrial flutter). *OR*
    b. A screening NT-proBNP > 300 pg/mL (if not in atrial fibrillation or atrial flutter) or > 750 pg/mL (if in atrial fibrillation or atrial flutter) *OR* if the screened participant is of African descent or has a BMI ≥ 30.0 kg/m^2, a screening NT-proBNP > 240 pg/mL (if not in atrial fibrillation or atrial flutter) or > 600 pg/mL (if in atrial fibrillation or atrial flutter).
6. Has documented LVEF ≥ 60% at the Screening visit as determined by the echocardiography central laboratory and no history of prior LVEF ≤ 45% under stable conditions. If historical LVEF ≤ 45% is not consistent with recovered HFrEF medical history, the participant may be included after review of previous echocardiographic images and discussion with the study medical monitor.
7. Has maximal left ventricular wall thickness ≥ 12 mm *OR* documented elevated left ventricular mass index (LVMI) by 2-dimensional imaging (>95 g/m^2 if female and >115 g/m^2 if male) as determined by the echocardiography central laboratory.
8. Has adequate acoustic windows on screening resting TTE as determined by echocardiography central laboratory, to enable high likelihood of acquisition of high quality TTEs throughout the study. Echocardiographic contrast agents may be used if the image quality of unenhanced echocardiographic images is deemed inadequate and there are no contraindications to the use of contrast agents [redacted].
9. Has NYHA Class II or III symptoms at Screening.

10. Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) within normal limits (according to the central laboratory reference range) at Screening; however, a participant with safety laboratory parameters outside normal limits may be included if he/she meets all of the following criteria:
    a. The safety laboratory parameter outside normal limits is considered by the investigator to be clinically unimportant. In this case, the investigator should discuss the result in question with the study medical monitor prior to enrollment.
    b. If there is an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) result, the value must be <3 × the upper limit of the laboratory reference range.
    c. The body size-adjusted estimated glomerular filtration rate is ≥30 mL/min/1.73 m^2.
11. Female participants must not be pregnant or lactating and, if sexually active (and not postmenopausal or surgically sterile per the definition below), must be using one of the following highly effective birth control methods from the Screening visit through 4 months after the last dose of study drug. Male partners must also use a contraceptive (eg, barrier, condom, or vasectomy).
    a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration.
    b. Intrauterine device.
    c. Intrauterine hormone-releasing system.
    d. Female is surgically sterile or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion 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.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Previously participated in a clinical study in which mavacamten was received.
2. Hypersensitivity to any of the components of the mavacamten formulation.
3. Participated in a clinical trial where the participant received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening or 5 times the respective elimination half-life (whichever is longer).
4. Has a prior diagnosis of HCM *OR* a known infiltrative or storage disorder which could cause HFpEF and/or cardiac hypertrophy, such as amyloidosis, Fabry disease, or Noonan syndrome with LV hypertrophy *OR* a positive serum immunofixation result unless a hematologist confirms the patient does not have amyloidosis or multiple myeloma.
5. Has any medical condition that precludes exercise stress testing (for stress echocardiogram).
6. Has a history of syncope within the last 6 months or sustained ventricular tachycardia with exercise within the past 6 months.

7. Has a history of resuscitated sudden cardiac arrest at any time or known appropriate implantable cardioverter defibrillator discharge within 6 months prior to Screening.
8. Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening and/or is not adequately rate controlled within 6 months prior to Screening (note: participants with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed).
9. For participants on beta blocker, verapamil, or diltiazem, any dose adjustment <14 days before Screening.
10. Currently treated or planned treatment during the study with either: (a) a combination of beta blocker and verapamil or a combination of beta blocker and diltiazem, (b) disopyramide, or (c) biotin or biotin-containing supplements/multivitamins.
11. Has any ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II).
12. Has either: (a) known unrevascularized obstructive coronary artery disease *OR* (b) acute coronary syndrome in the last 3 months.
13. Has known moderate or severe aortic valve stenosis, hemodynamically significant mitral stenosis, or severe mitral or tricuspid regurgitation at Screening (all in the investigator's judgment).
14. Has any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study.
15. Has severe chronic obstructive pulmonary disease, or other severe pulmonary disease, requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months.
16. Hemoglobin < 10.0 g/dL.
17. Body mass index (BMI) ≥ 45.0 kg/m^2.
18. Positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus. Positive hepatitis BsAb participants are allowed as this positive serologic test denotes presence of neutralizing, protective antibodies and does not denote chronic infection.
19. Active COVID-19 infection and/or other acute respiratory infection at time of Screening or randomization.
20. History of clinically significant malignant disease within 5 years of Screening:
    a. Participants who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ can be included in the study.
21. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or

study medical monitor, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion.

22. Currently taking, or has taken within 14 days prior to Screening, a prohibited medication (including over-the-counter medications) such as CYP2C19 inhibitor (eg, omeprazole, esomeprazole), a strong CYP3A4 inhibitor, or St. John's Wort.
23. Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar.
24. Unable to comply with the study requirements, including the number of required visits to the clinical site.
25. Employed by, or a relative of someone employed by MyoKardia, the investigator, or his/her staff or family.
26. Left ventricular global longitudinal strain (GLS) by TTE in the range from 0 to -12.0 (assessed by central TTE reader).
27. Acute decompensated heart failure events requiring intravenous (IV) diuretics, IV inotropes, IV vasodilators, or a left ventricular assist device within 30 days prior to Screening.
28. NT-proBNP at Screening > 2000 pg/mL.
29. Known hypersensitivity or contraindication to the IV echocardiography contrast agent, if contrast echocardiography is required due to inadequate quality of unenhanced echocardiographic images.

5.3. Lifestyle Considerations

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

- Starting 72 hours prior to the first dose of study drug until the final follow-up visit, participants should not engage in unaccustomed intensive exercise except during protocol-specified exercise tests.
- Starting at Screening, participants will be required to abstain from blood or plasma donation until 3 months after the final study visit.
- Starting on Day 1 until the final follow-up visit, participants will be asked to abstain from grapefruit or grapefruit juice, Seville oranges, and quinine (eg, tonic water).
- Starting at the time of signing informed consent, participants must abstain from taking biotin and biotin-containing supplements/multivitamins.

Contraception requirements are discussed in the inclusion criteria in Section 5.1.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of

Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (prescreen or screen failure) may be rescreened.

5.5. Criteria for Temporarily Delaying

With consideration to unforeseen circumstances (including those related to the COVID-19 pandemic), randomization and/or initial study drug administration may be delayed, if necessary, upon documented mutual agreement by the study physician and MyoKardia or their designee.

6. STUDY DRUG

Study drug is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

6.1. Study Drug Administered

The study drug administered in this study is mavacamten supplied as 2.5 and 5 mg capsules. Mavacamten capsules of both strengths are identical in appearance.

Participants will receive a mavacamten capsule (either 2.5 or 5 mg) once daily for 26 weeks (Day 1 to Week 26). [redacted]

Study drug will be supplied to participants in 30-count high-density polyethylene bottles that are appropriately labeled. Participants will be instructed to store study drug in a cool, dry place.

Participants will take study drug as directed by the investigator/designee. Participants should be instructed to take study drug at approximately the same time every day. Study drug should be taken with approximately 8 ounces of water. Participants should never take > 1 dose of study drug within an 8-hour period. On study visit days, study drug dosing should be delayed until after study assessments are complete and the study staff instruct the participant to take their daily dose.

Table 2 provides an overview of the study drug.

Table 2: Study Drug

Intervention Name	Mavacamten
Type	Drug
Dose Formulation	Capsule
Unit Dose Strength(s)	2.5 mg and 5 mg
Dosage Level(s)	2.5 mg or 5 mg once daily
Route of Administration	Oral
Use	Experimental

Table 2: Study Drug (Continued)

Intervention Name	Mavacamten
Investigational Medicinal Product	Mavacamten
Sourcing	Provided by the sponsor
Packaging and Labeling	See Section 6.2

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. At the study site and site pharmacy all study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1. Formulation, Packaging, and Labeling of Study Drug

Mavacamten capsules are provided as size 2, blue opaque capsules printed with a yellow band on the body and a black band on the cap. Each capsule contains white to off-white powder.

Mavacamten capsules are supplied in 2.5 and 5 mg strengths. Mavacamten capsules of both strengths are identical in appearance.

Mavacamten is manufactured according to current Good Manufacturing Practice regulations. It is supplied in high-density polyethylene bottles with induction seals and child-resistant caps with 30 capsules in each bottle. All bottles are labeled according to applicable local regulatory guidelines.

Mavacamten capsules must be stored at 36°F to 77°F (2°C to 25°C) in the packaging supplied by MyoKardia.

6.2.2. Direct-to-Participant Study Drug Shipment (At Selected Sites)

In certain circumstances, it may be necessary to ship study drug directly to a participant to accommodate the participant's schedule through Week 26. Study sites should contact the participant by telephone to confirm study drug delivery. Refer to the Pharmacy Manual for details.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. There will be no blinding at the site level.

6.4. Study Drug Compliance

Participant compliance with study drug dosing will be monitored by capsule count at all study visits from Week 2 through the end of study treatment. Refer to the Pharmacy Manual for details.

6.6. Continued Access to Study Drug After the End of the Study

Not applicable. Currently, there is no continued access to study drug after the end of the study.

6.7. Treatment of Overdose

An overdose is defined as taking more capsules of study drug than directed. An overdose may be suspected by the investigator or spontaneously reported by the participant. An overdose may be symptomatic or asymptomatic. Only symptomatic overdoses should be reported as AEs/adverse events of special interest (AESI).

In the event of symptomatic overdose or in the presence of significant symptoms and/or clinical compromise, the investigator should contact the study medical monitor, and the study drug should be temporarily discontinued. The participant should be closely monitored clinically for AEs/SAEs, with supportive measures undertaken as clinically indicated. If necessary, corrective measures, as described in the 2013 American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure (Yancy et al, 2013) and in the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (Ponikowski et al, 2016), should be implemented. Resumption of study drug must be approved by the study medical monitor.

6.7.1. Reporting and Follow-up of Overdose

Symptomatic overdose is an AESI as defined in Section 8.3.6. If a participant should experience symptomatic overdose, the investigator will report the symptomatic overdose to the study medical monitor and complete the required information in the electronic data capture (EDC)

system within 24 hours of study staff becoming aware of the overdose. Follow-up on the participant's condition will be conducted by the investigator and study staff.

6.8. Prior and Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements a participant is taking will be monitored at all study visits from Screening until the end of the study and documented on the appropriate electronic case report form (eCRF), including start/stop dates, dose, route of administration, and indication.

6.8.1. Prior Medication

At the time of providing signed informed consent, participants will be asked about medication use during the previous 30 days, including prescription and nonprescription medications, herbal medications, vitamins, and minerals. Any prohibited medication and restricted food items must be discontinued for ≥14 days before screening may proceed.

6.8.2. Background HFpEF Medication

As results of clinical trials to date in HFpEF have generally been neutral, management of the condition is primarily focused on associated symptoms (eg, edema) and/or conditions (eg, hypertension and atrial fibrillation). Background medications for HFpEF and related conditions and symptoms (eg, antihypertensives and mineralocorticoid antagonists) are allowed during the study unless specifically excluded by eligibility criteria. The treatment should be well tolerated for at least 2 weeks prior to screening and should generally be maintained through the EOS visit. In this context, investigators are encouraged not to change background medications (including dose) from Day 1 to Week 34; however, investigators should manage participants appropriately using their clinical judgment. Any change in medications must be entered into the eCRF with the rationale for the change.

6.8.3. Prohibited Medication

Medications that are prohibited during the study are outlined in Section 10.2. Prior or concomitant treatment with cardiotoxic agents, such as doxorubicin or similar, is prohibited.

The study medical monitor should be contacted for any questions regarding prior or concomitant medications.

6.8.4. COVID-19 Vaccine Considerations

Locally authorized or approved COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of mavacamten study treatment and after the last administration of mavacamten study treatment.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

Temporary treatment discontinuation:

- Will be implemented when a predefined safety threshold [redacted] has been met.
- May be considered by the investigator in the case of an AE/SAE or for another reason.

As a general rule, any discontinuation of study drug should be initially considered temporary unless permanent treatment discontinuation is mandated.

In rare instances, it may be necessary for a participant to permanently discontinue study drug. If study drug is permanently discontinued, the participant will be encouraged to remain in the study to be evaluated for safety and study endpoints as appropriate through the EOS visit. See the Schedule of Study Procedures (Table 1) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

Participants with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL], or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for withholding of study drug or other protocol-required therapies. Withholding is either permanent or conditional depending on the clinical circumstances discussed below as specified in the United States (US) Food and Drug Administration (FDA) Guidance for Industry–Drug Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.1.1.1. Criteria for Permanent Withholding of Mavacamten Due to Potential Hepatotoxicity

Mavacamten should be discontinued permanently and the participant should be followed according to the recommendations in Section 10.5 for possible drug-induced liver injury (DILI), if all the criteria below are met:

- TBL > 2 × ULN or INR > 1.5.
- AND increased AST or ALT, if the baseline value was <ULN and AST or ALT elevation is > 3 × ULN.
- AND no other cause for the combination of laboratory abnormalities is immediately apparent. Important potential causes for abnormal AST/ALT or TBL values include, but are not limited to, the following:
  - Obstructive gall bladder or bile duct disease.
  - Viral or alcoholic hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella).
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure.

- Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements.
- Heritable disorders causing impaired glucuronidation (eg, Gilbert syndrome); α-1 antitrypsin deficiency.
- Autoimmune hepatitis.
- Nonalcoholic steatohepatitis (NASH) or other fatty liver disease.

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

7.1.1.2. Criteria for Conditional Withholding of Mavacamten Due to Potential Hepatotoxicity

For participants who do not meet the criteria for permanent withholding of study medication outlined in Section 7.1.1.1, mavacamten should be withheld if ANY of the following criteria are met, and the participant should be evaluated for DILI:

- AST or ALT > 8 × ULN at any time.
- AST or ALT > 5 × ULN and < 8 × ULN for ≥2 weeks.
- AST or ALT > 5 × ULN and < 8 × ULN and unable to adhere to enhanced monitoring schedule.
- ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR >1.5).
- ALT or AST > 3 × ULN and clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%).
- TBL > 3 × ULN at any time.
- ALP > 8 × ULN at any time.

Mavacamten should be withheld pending an investigation into alternative causes of DILI. If mavacamten is withheld, the participant should be followed according to recommendations for possible DILI (Section 10.5). Rechallenge may be considered if an alternative cause, such as acute hepatitis B infection, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 7.1.1.3).

7.1.1.3. Criteria for Rechallenge of Mavacamten After Potential Hepatotoxicity

The decision to rechallenge a participant should be discussed and unanimously agreed upon by the investigator, the study co-coordinating investigators, and MyoKardia or their designee.

If signs or symptoms recur with rechallenge, then mavacamten will be permanently discontinued. Participants who clearly meet the criteria for permanent discontinuation (as described in Section 7.1.1.1) should never be rechallenged.

[redacted]

[redacted]

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator or MyoKardia or their designee for safety, behavioral, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early drug discontinuation visit should be conducted, as shown in the Schedule of Study Procedures (Table 1). See the Schedule of Study Procedures for data to be collected at the time of study discontinuation.

The participant will be permanently discontinued both from the study drug and from the study at that time.

If the participant withdraws consent for disclosure of future information, MyoKardia or their designee may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at minimum 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all enrolled participants, including those who did not receive study drug. Public sources may be searched for

vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempt to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 in Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Study Procedures (Table 1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with MyoKardia or their designee immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in the Schedule of Study Procedures, is essential and required for study conduct.

Prescreening evaluations are optional and may be performed to assess chronic values of cardiac biomarkers if no historical values of chronic NT-proBNP or cardiac troponins are available. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

At the investigator's discretion or per the request of MyoKardia or their designee, unscheduled visits may be conducted for reasons including, but not limited to, assessment of AEs, new or worsening symptoms, physical examinations, vital signs, laboratory tests, ECGs, [redacted]. ECGs [redacted] conducted at unscheduled visits will be sent to the respective core laboratory for central reading.

8.1. Pharmacodynamic Assessments

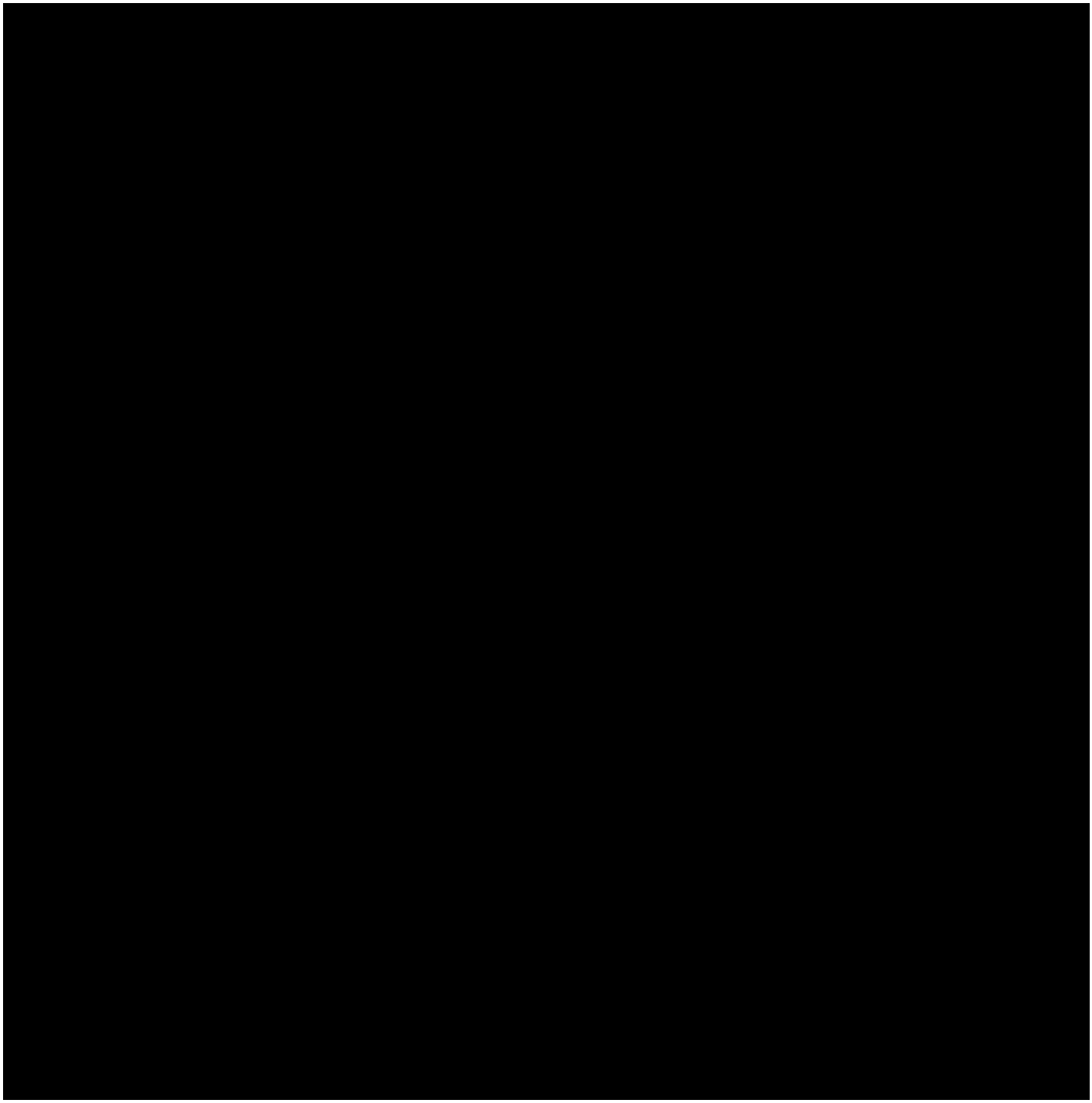
Planned time points for all pharmacodynamic assessments are provided in the Schedule of Study Procedures (Table 1).

8.1.1. Cardiac Biomarkers

Blood samples will be collected to evaluate NT-proBNP, hs-cTnT, [redacted] concentrations as outlined in Table 1.

With the exception of post-exercise cardiac biomarker samples, where indicated in the Schedule of Study Procedures, all blood draws for cardiac biomarkers must be drawn at rest and prior to exercise. Unscheduled or additional blood samples may be collected if appropriate in the opinion of the investigator (eg, for medical management of heart failure) and/or MyoKardia or their designee. Whenever possible, discussion with the study medical monitor is encouraged.

[redacted]



8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Study Procedures (Table 1).

8.2.1. Medical History

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

8.2.2. Physical Examinations

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

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

Body weight will be recorded as indicated in Table 1.

8.2.3. Vital Signs

Complete vital signs including temperature, HR, respiratory rate (RR), and BP will be assessed as in indicated in Table 1.

Vital signs will be obtained with the participant in the same position; BP will be taken after at least 5 minutes of rest via an automated recorder.

At all visits, vital signs will be taken prior to dosing. Alert values will be flagged. Refer to the Study Laboratory Manual for additional details.

8.2.4. 12-Lead Electrocardiograms

Central read, single 12-lead ECG evaluations will be performed after 10 minutes of rest as indicated in Table 1. At clinic visits during the treatment period, ECGs will be taken prior to dosing.

The investigator may perform 12-lead ECG safety assessments if he/she considers it is required for any other safety reason. These assessments should be recorded as an unscheduled assessment.

8.2.5. Clinical Safety Laboratory Assessments

Safety laboratory results will be assessed in an ongoing manner. See Section 10.3 for the list of clinical laboratory tests to be performed and to the Schedule of Study Procedures (Table 1) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests considered clinically significant abnormal values during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and MyoKardia or their designee notified.
  - All protocol-required laboratory tests, as defined in Section 10.3, must be conducted in accordance with the laboratory manual and the Schedule of Study Procedures (Table 1).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.6. Pregnancy Testing

Serum pregnancy testing will be performed at Screening for all females of childbearing potential. In addition, urine pregnancy testing in clinic will be conducted every 4 to 6 weeks throughout the study. Confirmatory serum testing will be performed if any urine test is positive.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The investigator should refer to Section 10.4 for detailed definitions of AEs and SAEs and additional information regarding AE reporting.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs, including SAEs, will be collected from the signing of the informed consent form (ICF) until 56 days after the last dose of study drug (Table 1).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as pretreatment adverse events (PTAEs), as detailed in Section 10.4.

All SAEs/AESIs will be recorded and reported to MyoKardia or their designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4. The investigator will submit any updated SAE data to MyoKardia or their designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify MyoKardia or their designee (via paper SAE form).

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AESIs (as defined in Section 8.3.6), and AEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3), including being considered lost to follow-up at the end of the study. Further information on follow-up procedures is provided in Section 10.4.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to MyoKardia or their designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met. All SAEs occurring during the treatment-emergent period (defined as the period from the first dose of study drug to the last dose of study drug + 56 days), regardless of causality, will be reported by the investigator or designee to MyoKardia or their designee within 24 hours of knowledge of the event or sequelae. Deaths and SAEs occurring after the treatment-emergent period and considered related to study drug or study procedure must also be reported. SAE reporting instructions are provided in the Study Reference Manual.

Medical records may be requested to support documentation of an SAE. The investigator is responsible for summarizing the pertinent aspects of the event (including discharge summaries, diagnostic procedures, laboratory data, and interventions) and for updating the SAE eCRF with this information.

MyoKardia or their designee retains the right to request additional information for any participant with any ongoing AEs/SAEs at the end of the study, if judged necessary.

Spontaneously reported SAEs that are considered related to study drug after completion of the study should be promptly reported by the investigator to MyoKardia or their designee.

Prompt notification by the investigator to MyoKardia or their designee of SAEs is essential so that legal obligations and ethical responsibilities for the safety of participants and the safety of a study intervention under clinical investigation are met. MyoKardia or their designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about

the safety of a study drug under clinical investigation. MyoKardia or their designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from MyoKardia or their designee will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Female participants of childbearing potential must use appropriate methods of contraception as listed in the inclusion criteria (Section 5.1). Female participants of nonchildbearing potential are defined as those who are permanently (surgically) sterilized or are postmenopausal. Permanent sterilization includes hysterectomy, bilateral oophorectomy, and bilateral tubal occlusion or ligation. Female participants 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.

- All pregnancies in female participants and female partners of male participants who received at least one dose of study drug must be reported if they occur anytime from the first dose of study drug to 4 months after the last dose of study drug.
- The investigator is responsible for informing MyoKardia or their designee within 24 hours of knowledge of the pregnancy even if no AE has occurred. If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to MyoKardia or their designee within 24 hours of learning of the pregnancy of the female participant or the female partner of a male participant (after obtaining the necessary signed informed consent from the female partner).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant or pregnant female partner of a male participant will be followed to determine the outcome of the pregnancy. The participant will be asked to provide information on the outcome of the pregnancy through 6 months after birth or details of premature termination of the pregnancy. The investigator will collect follow-up information on the participant or pregnant female partner of a male participant and the neonate for 6 months after birth and the information will be forwarded to MyoKardia or their designee
- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to MyoKardia or their designee, as described in Section 8.3.4. While the investigator is not obligated to actively seek this

information in former study participants or pregnant female partners of male participants, he/she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study drug.

8.3.6. Adverse Events of Special Interest

Symptomatic overdose, teratogenicity, and LVEF ≤30% as determined by local site read or centrally read echocardiogram are considered AESIs.

AESIs are required to be reported by the investigator to MyoKardia or their designee within 24 hours, irrespective of regulatory seriousness criteria. If a participant should experience symptomatic overdose, LVEF ≤30%, or if pregnancy outcome becomes known, the investigator will report the information to the study medical monitor and complete the required information in the EDC system within 24 hours of study staff becoming aware of the AESI.

[redacted]

[redacted]

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no formal statistical hypothesis testing in this exploratory Phase 2a study.

9.2. Sample Size Determination

Given the exploratory nature of the study, no formal sample size calculation was done. The sample size will be approximately 35 participants.

9.3. Analysis Sets

For the purpose of analysis, the following analysis populations are defined:

Table 4: Analysis Populations Definitions

Analysis Population	Definition
ITT	All enrolled participants regardless of whether they receive study drug.
Safety	All enrolled participants who receive at least 1 dose of study drug, with analyses conducted by actual treatment received.

[redacted]

ITT = intention-to-treat; [redacted].

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary [redacted] endpoints.

9.4.1. General Considerations

In general, descriptive summaries will be presented at each visit. The descriptive summary for continuous variables will also be provided for the change from baseline. Summaries of continuous variables will include the number of participants, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum. For variables with a highly skewed distribution (eg, log-normal distribution), such as hs-cTnT and NT-proBNP, geometric mean and percent coefficient of variation will also be reported in descriptive summaries. Descriptive summaries for categorical variables will include the number and percentage of participants. Unless otherwise stated, denominators for percentages will be the number of participants in the analysis population.

9.4.2. Primary Pharmacodynamic Endpoints

The primary pharmacodynamic endpoints are the following:

- Change from baseline to Week 26 in NT-proBNP (at rest)
- Change from baseline to Week 26 in hs-cTnT (at rest), as assessed by a high-sensitivity assay

Further details for these analyses will be specified in the study SAP.

[redacted]

Further details for these analyses will be specified in the study SAP.

9.4.4. Safety Endpoints

The safety endpoints are the following:

- Frequency and severity of treatment-emergent adverse events (TEAEs), AESIs (symptomatic overdose, teratogenicity, and LVEF ≤30% as determined by local site read or centrally read echocardiogram), and SAEs; laboratory abnormalities; vital sign abnormalities; and cardiac rhythm abnormalities

All safety analyses will be performed for the Safety Analysis Population using the following common rules:

- The baseline value is defined generally as the last available value before the first administration of study drug, unless specified otherwise.
- For quantitative safety parameters based on central laboratory measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group; changes may be presented in shift tables or scattergrams.
- The analysis of the safety variables will be descriptive, and no hypothesis testing is planned.

The safety analysis will focus on the treatment-emergent period, which is defined as the time from the first dose of study drug to the last dose of study drug + 56 days.

9.4.4.1. Adverse Events

AEs will be mapped to system organ classes (SOC) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) v23.0. AEs will be monitored during the study and the data analyzed with respect to overall incidence, as well as severity and potential relationship of AEs to study drug. AEs with onset during the treatment-emergent period (ie, TEAEs) or with an onset before the first dose of study drug that increase in severity or become serious during the treatment-emergent period will be considered TEAEs.

AE incidence tables will present the number and percentage of participants experiencing at least one TEAE by SOC, high-level group term (HLGT), high-level term (HLT), and PT in alphabetical order for each treatment group. Multiple occurrences of the same event in the same participant will be counted only once within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

AE incidence tables will be provided for TEAEs, including all TEAEs, all treatment-emergent SAEs, all treatment-emergent treatment-related AEs, all treatment-emergent treatment-related SAEs, TEAEs by severity, and all TEAEs leading to permanent treatment discontinuation.

9.4.4.1.1. Death

The number and percent of participants who died by study period (TEAE, on-study) will be summarized for the safety population, and a listing will be provided for all events involving a participant death, if applicable.

9.4.4.1.2. Pregnancy

The following pregnancy summaries will be generated, if applicable:

- Number of female participants or female partners of male participants who become pregnant
- Outcomes of the pregnancies and analysis of the outcomes
- TEAEs experienced during the pregnancy by primary SOC, HGLT, HLT, and PT showing the number and percent of participants sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

9.4.4.1.3. Symptomatic Overdose

The following summaries for reports of symptomatic overdose will be generated, if applicable:

- Number of participants who experienced symptomatic overdose summarized by treatment received
- Analysis of the cause and occurrence of the symptomatic overdose
- TEAE experienced during the symptomatic overdose by primary SOC, HGLT, HLT, and PT showing the number and percent of participants sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

9.4.4.2. 12-Lead Electrocardiogram

The RR, pulse rate (PR), QRS, and QT intervals will be measured and read by a central laboratory. [redacted].

9.4.4.2.1. Correction for Heart Rate

Corrected QT interval (QTc) will be calculated using the manually over-read QT values. Each individual ECG QT value will be corrected for HR. [redacted]

9.4.4.2.2. ECG Numeric Variables

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

9.4.4.2.3. Categorical Analysis

The number and percentage of participants with any postdose QTcF values of >450 msec, >480 msec, and >500 msec will be summarized. Participants with QTc values >500 msec will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The incidence count and percentage of participants with a ΔQTcF increase from baseline of >30 msec and >60 msec will be summarized.

9.4.4.2.4. Morphology Findings

New ECG morphologies for each participant not present on any ECG at baseline for that participant will be summarized for all observation time points combined.

The number and percentage of participants 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.

9.4.4.3. Laboratory Data

The summary statistics (including number of participants, mean, median, SD, minimum and maximum) of all laboratory variables (laboratory values and changes from baseline), will be summarized at all baseline and postbaseline time points.

Listings of participants with laboratory values that are outside of the reference range will be produced.

9.4.4.3.1. Potential Drug-Induced Liver Injury

The liver function tests, namely ALT, AST, ALP, and TBL, are used to assess possible drug-induced liver toxicity.

[redacted]

9.4.4.4. Vital Signs Data

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all vital sign variables (values and changes from baseline) will be summarized at all baseline and postbaseline time points.

Listings of participants with vital sign values that are outside of the reference range will be produced.

9.4.4.5. Other Safety Analyses

Abnormal physical examination results will be listed. Concomitant medications will be summarized.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Consideration

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The study, inclusive of protocol amendments, will be conducted in accordance with local health authority requirements. Changes to the study conduct will not be

implemented without health authority notification or approval, as required, except as necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of US Title 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide MyoKardia or their designee with sufficient, accurate financial information as requested to allow MyoKardia or their designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of US Title 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The study record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 calendar days from the previous ICF signature date.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by MyoKardia or their designee. Any participant records or datasets that are transferred to MyoKardia or their designee will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by MyoKardia or their designee in accordance with the local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by MyoKardia or their designee, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will meet at regular intervals to review ongoing study data. The role of the IDMC will be to act in an advisory capacity to MyoKardia or their designee with respect to safeguarding the interest of study participants, assessing interim safety data, and advising MyoKardia or their designee on important emerging study conduct issues. The IDMC may formulate recommendations in relation to the evaluation procedures and methodologies being employed to survey and detect potential safety signals. Meeting frequency, membership, and conduct will be described in the IDMC charter.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic case report forms (CRFs) unless transmitted to MyoKardia or their designee or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details, strategy, methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques will be delineated in the Monitoring Plan.
- MyoKardia or designee is responsible for the data management of this study including quality checking of the data.
- MyoKardia or their designee assumes accountability for actions delegated to other individuals (eg, contract research organizations).

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified (unless local regulations or institutional policies require a longer retention period). No records may be destroyed during the retention period without the written approval of MyoKardia or their designee. No records may be transferred to another location or party without written notification to MyoKardia or their designee.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

Study Start Date and First Act of Recruitment

The study start date is the date of informed consent for the first enrolled participant.

The first act of recruitment is the screening of the first potential participant (after informed consent is obtained).

Study/Site Termination

MyoKardia or designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by MyoKardia or their designee or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, MyoKardia's or their designee's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants enrolled earlier than expected

If the study is prematurely terminated or suspended, MyoKardia or their designee shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Sponsor's Responsibilities

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

- Request by a regulatory agency or health authority to terminate the study
- Unsatisfactory participant enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on participants, 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

10.1.9.1. Participant 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 or their designee 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 participant.

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

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

10.1.9.2. Study Supplies

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

- Mavacamten active capsules in 2 strengths (2.5 mg, 5 mg,) in 30-count bottles
- Cardiac/activity monitoring devices, including accelerometers and ECG machines
- Supplies for laboratory assessments
- Study Reference Manual
- Laboratory Manual
- Pharmacy Manual
- IXRS (Interactive Response System) Manual
- IB

10.1.9.3. Investigator Training

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

10.1.9.4. Ongoing Communication of Safety Information During the Study

MyoKardia or their designee will provide investigators with documentation of SAEs from this study and other studies that are related to mavacamten and are unexpected, as appropriate. Investigators must forward this documentation to the IRB/IEC.

MyoKardia or their designee will also notify investigators of any other significant safety findings that could alter the safety profile of the investigational medicinal product (IMP) from what is

described in the protocol and significantly affect the safety of participants, affect the conduct of the study, or alter the IRB/IEC opinion regarding continuation of the study.

10.1.9.5. Study Monitoring

MyoKardia, or their designee, and a contracted clinical research organization 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 investigators and clinical site staff are expected to provide adequate space for monitoring visits and allocate sufficient time to permit adequate review of the study's progress. The investigators will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections, providing direct access to source data/documents and study-related facilities (eg, pharmacy, diagnostic laboratories).

10.1.9.6. Study Auditing and Inspecting

MyoKardia or their designee may audit the study conduct, compliance with the protocol, and accuracy of the data at 1 or more study centers.

The investigators/institutions will permit study-related monitoring, audits, and inspections by MyoKardia or their designee, IRBs/IECs, government regulatory authorities, and MyoKardia or their designee quality assurance personnel/designees by providing direct access to source data/documents after appropriate notification from MyoKardia or their designee.

10.1.10. Publication Policy

- The results of this multisite study may be published or presented at scientific meetings. Publication or presentation of the results of the study conducted at each individual site will not be made before the first multisite publication.
- The investigator agrees to submit all manuscripts or abstracts to MyoKardia or their designee before submission. This allows MyoKardia or their designee to protect proprietary information and to provide comments.
- MyoKardia or their designee will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, MyoKardia or their designee will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Prohibited Medications

The following medications are prohibited during the study. Generally, this directive should include the washout period (between Week 26 and Week 34). If a compelling clinical necessity to administer one of these medications arises, the investigator should contact the study medical monitor in advance to discuss a plan including whether/when to discontinue study drug.

Cardiotoxic Agents

Prior or concomitant treatment with cardiotoxic agents, such as doxorubicin, or similar, is prohibited.

Moderate and Potent CYP2C19 Inhibitors and Potent CYP3A4 Inhibitors

Potent and moderate CYP2C19 inhibitors and potent CYP3A4 inhibitors are prohibited from 14 days prior to Screening through the end of the study. Examples are listed below.

- Efavirenz (antiviral)
- Etravirine (antiviral)
- Fluconazole (antifungal)
- Fluvoxamine (selective serotonin reuptake inhibitor [SSRI]/antidepressant)
- Fluoxetine (SSRI/antidepressant)
- Moclobemide (monoamine oxidase inhibitor/antidepressant)
- Omeprazole (proton pump inhibitor)
- Esomeprazole (proton pump inhibitor)
- Ticlopidine (platelet inhibitor)
- Voriconazole (antifungal)

St. John's Wort

Use of St. John's Wort is prohibited from 14 days prior to Screening through the end of the study.

Live COVID-19 Vaccines

Live COVID-19 vaccines should not be administered to a participant during the study, including during the treatment period and within 3 months following the last dose of IMP. In addition, the administration of a live COVID-19 vaccine is prohibited up to 30 days prior to initiation of study treatment.

10.3. Appendix 3: Safety Laboratory Tests

- The tests detailed in Table 5 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study drug administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 5: Protocol-required Safety Laboratory Tests

Laboratory Test	Parameters		
Hematology	WBC count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: • Mean corpuscular volume • Mean corpuscular hemoglobin • %Reticulocytes
Coagulation	International normalized ratio	aPTT	
Clinical chemistry[a]	Sodium	Blood urea nitrogen	Creatine phosphokinase
	Potassium	Creatinine	Glucose (fasting)
	Chloride	ALP[b]	Total protein
	Bicarbonate	ALT/serum glutamic-pyruvic transaminase	Albumin
	Calcium	AST/serum glutamic-oxaloacetic transaminase	
	Magnesium	Total bilirubin	
Routine Urinalysis	• Specific gravity • pH, protein, glucose, leukocyte esterase, blood, nitrite by dipstick • Microscopic examination (if blood or protein is abnormal)		
Pregnancy testing	• Highly-sensitive serum or urine β-hCG pregnancy test (as needed for women of childbearing potential)		

Table 5: Protocol-required Safety Laboratory Tests (Continued)

Laboratory Test	Parameters
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of non-childbearing potential only to confirm postmenopausal status) • Thyroid-stimulating hormone • Estimated glomerular filtration rate • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Serum free light chain ratio and SPEP w/immunofixation

β-hCG = beta-human chorionic gonadotropin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial prothrombin time; AST = aspartate aminotransferase; HIV = human immunodeficiency virus; IEC = independent ethics committee; INR = international normalized ratio; IRB = institutional review board; RBC = red blood cell; SPEP = serum protein electrophoresis; ULN = upper limit of normal; WBC = white blood cell.

[a] Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 and Section 10.5. All events of ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and INR >1.5, (if INR measured) which may indicate severe liver injury (possible Hy's Law), must be reported to MyoKardia or their designee in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

[b] If ALP is elevated, consider fractionating.

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.4. Appendix 4: Evaluation, Recording, and Reporting of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

Safety assessments will consist of monitoring and recording of AEs, including SAEs and AESIs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

10.4.1. Definitions of Pretreatment Adverse Events, Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

10.4.1.1. Pretreatment Adverse Events

A PTAE is an AE that occurs in a participant who has signed informed consent to participate in a study but has not received any study drug. A PTAE may result from a protocol-mandated procedure (eg, phlebotomy, invasive procedure, such as biopsy) but does not necessarily have to have a causal relationship with study participation.

10.4.1.2. Adverse Events

- According to the ICH guideline for GCP, an AE is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product; it does not necessarily have to have a causal relationship with this treatment.
- An AE can therefore be any unfavorable and unintended sign (eg, tachycardia, enlarged liver, clinically important or abnormal laboratory finding), symptom (eg, nausea, chest pain), or evidence of disease activity temporally associated with the use of a study medication, whether or not related to the study medication.
- Each AE should be recorded as a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should not be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as a PTAE or AE.
- Any new disease or exacerbation of an existing disease (eg, a worsening in the character, frequency, or severity of a known condition) is an AE, except as described below:
  - Preexisting medical conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should not be recorded as PTAEs or AEs. However, if the participant experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTAE (worsening or complication occurs before the first dose of study drug) or an AE (worsening or complication occurs after the first dose of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of ….").
- Recurrence of an intermittent medical condition (eg, headache) not present prior to the first dose of study drug is an AE.

- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug is an AE.

The following additional points should be considered for PTAEs and AEs:

- Preplanned medical or surgeries or procedures
  - Preplanned surgeries or procedures that were scheduled prior to signing of informed consent are not considered PTAEs or AEs. However, if a planned procedure is performed early (eg, as an emergency) due to worsening of a preexisting condition, the worsening of the condition should be captured appropriately as a PTAE or AE.
- Hospitalization for elective surgeries or procedures
  - Elective procedures performed for which there is no change in the participant's medical condition should not be recorded as PTAEs or AEs.
  - A hospitalization that was planned prior to the study or was scheduled during the study when the elective surgery or procedure became necessary because of the expected normal progression of the disease should not be recorded as PTAEs and AEs.
- Insufficient clinical response (lack of efficacy)
  - Insufficient clinical response, efficacy, or pharmacologic action should not be recorded as an AE. The investigator must make the distinction between exacerbation of preexisting medical condition and lack of therapeutic efficacy.
- Overdose
  - Cases of overdose with any medication without manifested side effects are not considered PTAEs or AEs.

The following should not be recorded as PTAEs or AEs:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the disease/disorder being studied, unless judged by the investigator to be more severe than expected for the participant's condition
- 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
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

10.4.1.3. Serious Adverse Event

An SAE is defined as any untoward medical occurrence at any dose that:

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

PTAEs that fulfill any of the criteria above are also to be considered SAEs and should be reported and followed up in the same manner.

- The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (eg, rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).
- 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.
- Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the investigator to MyoKardia or their designee within 24 hours after learning of the event.

10.4.1.4. Adverse Events of Special Interest

Symptomatic overdose, pregnancy, and LVEF ≤ 30% as determined by local site read echocardiogram are considered AESIs.

AESIs are required to be reported by the investigator to MyoKardia or their designee within 24 hours, irrespective of regulatory seriousness criteria.

10.4.2. Collection and Reporting of Adverse Events

10.4.2.1. Pretreatment Adverse Events and Adverse Events Collection Periods

Collection of PTAEs will commence from the time the participant signs the informed consent to participate in the study and continue until the participant receives the first dose of study drug. For participants who discontinue prior to study drug administration, PTAEs are collected until the participant discontinues study participation.

Collection of TEAEs will commence at the time the participant receives the first dose of study drug. Routine collection of TEAEs will continue until the end of the study. Assessments of the relationship of AEs to study drug will be captured for TEAEs and not PTAEs.

10.4.2.2. Pretreatment Adverse Events and Adverse Events Reporting Periods

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Participants may report AEs occurring at any other time during the study.

All participant experiencing PTAEs or TEAEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to screening levels or until there is a satisfactory explanation for the changes observed. All PTAEs and TEAEs will be documented in the PTAE/AE page of the eCRF, whether or not the investigator concluded that the event is related to the study drug. The information to be documented for each event is described in the following sections.

10.4.2.2.1. Event Description

When collecting PTAEs and TEAEs, 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. In this situation, the event that led to the death is the name of the event.

10.4.2.2.2. Start Date/Time and Stop Date/Time

The date (and time during the period of residency) that the PTAE or TEAE started and the date (and time during the period of residency) that the event ended will be recorded. For events that continue for long periods of time, recording the end date as the day the event stabilized will be acceptable.

10.4.2.2.3. Relationship to Study Drug (Suspected Adverse Reactions)

The investigator will 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?"

10.4.2.2.4. Severity/Intensity

The intensity or severity of the PTAE or TEAE will be recorded using the following guidance:

- 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)

10.4.2.2.5. Seriousness

A PTAE or TEAE that meets any of the criteria for an SAE outlined in Section 10.4.1.3 will be recorded as an SAE, along with the criteria that were met.

It is important to distinguish between seriousness (PTAE or AE compared with SAE) and severity/intensity (mild, moderate, severe, life-threatening, or fatal) of AEs as outlined in Section 10.4.1.3.

10.4.2.2.6. Outcome

The outcome of a PTAE or TEAE will be recorded according to the options provided on the eCRF.

10.4.2.3. Reporting of Serious Adverse Events

All SAEs occurring during the treatment-emergent period (defined as the period from the first dose of study drug to the last dose of study drug + 56 days), regardless of causality, will be reported by the investigator or designee to MyoKardia or their designee within 24 hours of knowledge of the event or sequelae. Deaths and SAEs occurring after the treatment-emergent period and considered related to study drug or study procedure must also be reported. SAE reporting instructions are provided in the Study Reference Manual.

Medical records may be requested to support documentation of an SAE. The investigator is responsible for summarizing the pertinent aspects of the event (including discharge summaries, diagnostic procedures, laboratory data, interventions) and updating the SAE eCRF with this information.

MyoKardia or their designee retains the right to request additional information for any participant with any ongoing AEs/SAEs at the end of the study, if judged necessary.

Spontaneously reported SAEs after completion of the study should be promptly reported by the investigator to MyoKardia or their designee.

Prompt notification by the investigator to MyoKardia or their designee of SAEs is essential so that legal obligations and ethical responsibilities for the safety of participants and the safety of a study intervention under clinical investigation are met.

10.4.2.4. Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AESIs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is considered lost to follow-up at the end of the study.

10.4.3. Safety Reporting to Investigators, Institutional Review Boards, Independent Ethics Committees, and Regulatory Authorities

MyoKardia or their designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. MyoKardia or their designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from MyoKardia or their designee will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4.4. Pregnancy

10.4.4.1. Avoidance of Pregnancy

Female participants of childbearing potential must use appropriate methods of contraception as listed in the inclusion criteria (Section 5.1). Female participants of nonchildbearing potential are defined as those who are permanently (surgically) sterilized or are postmenopausal. Permanent sterilization includes hysterectomy, bilateral oophorectomy, and bilateral tubal occlusion or ligation. Female participants 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.

10.4.4.2. Reporting and Follow-up of Pregnancies

All pregnancies in female participants and female partners of male participants who received at least 1 dose of study drug must be reported if they occur anytime from the first dose of study drug to 4 months after the last dose of study drug. The investigator is responsible for informing MyoKardia within 24 hours of knowledge of the pregnancy, even if no AE has occurred. The participant will be asked to provide information on the outcome of the pregnancy through 6 months after birth or details of premature termination of the pregnancy. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

10.5. Appendix 5: Potential Drug-induced Liver Injury Reporting and Additional Assessments Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL elevation according to the criteria specified in Section 7.1.1.2 (3 × ULN for AST/ALT and 2 × ULN for TBL in participants 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 or their designee as an SAE within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to MyoKardia or their designee.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 10.4.1.3.

Additional Clinical Assessments and Observation

All participants from whom study drug or protocol-required therapies are withheld (either permanently or conditionally) due to potential DILI or who experience AST/ALT elevations > 3 × ULN are to undergo a period of "close observation" until abnormalities return to normal or to the participant's baseline levels. Assessments to be performed during this period include the following:

- Repeat liver chemistries within 24 to 48 hours (ALT, AST, ALP, TBL); in cases of TBL > 2 × ULN or AST/ALT much greater than 3 × ULN, retesting is to be performed within 24 hours.

For participants who are far from the study center, it may be difficult to return promptly to the study center. In this case, the participant should be retested locally, but normal laboratory ranges should be recorded, results should be made available to the study investigator immediately, and the data should be included in the eCRF.

Participants are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the study drug or protocol-required therapies have been discontinued and the participant is asymptomatic.

- Obtain prothrombin time/INR, 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 [redacted] analysis if this has not already been collected.
- Obtain a more detailed history of the following:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents

  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
  - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
  - Concomitant medications (including nonprescription medicines and herbal and dietary supplements).
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr virus, herpes simplex virus, etc.); evaluate for other potential causes of DILI, including but not limited to NASH, hypoxic/ischemic hepatopathy, and biliary tract disease.
- Obtain gastroenterology or hepatology consult.
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation.
- Follow the participant 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 the appropriate eCRFs.

10.6. Appendix 6: Abbreviations and Definitions

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CFR	Code of Federal Regulations
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CRF	case report form
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CYP	cytochrome P450
DDI	drug drug interaction
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLS	global longitudinal strain
HCM	hypertrophic cardiomyopathy
HFpEF	heart failure with preserved ejection fraction
HLGT	high-level group term
HLT	high-level term
HR	heart rate
[redacted]	[redacted]
hs-cTnT	high-sensitivity cardiac troponin T
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug

INR	international normalized ratio
IRB	institutional review board
IV	intravenous
[redacted]	[redacted]
LV	left ventricular
LVEF	left ventricular ejection fraction
LVMI	left ventricular mass index
MedDRA	Medical Dictionary for Regulatory Activities
NASH	nonalcoholic steatohepatitis
nHCM	nonobstructive hypertrophic cardiomyopathy
NM	Normal metabolizer
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PASP	pulmonary artery systolic pressure
PK	pharmacokinetic(s)
PM	poor metabolizer
PR	pulse rate
PT	preferred term
PTAE	pretreatment adverse event
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction
RR	respiratory rate
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
[redacted]	[redacted]
SOC	system organ class
SPEP	serum protein electrophoresis
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life
t_{max}	Time to reach maximum concentration
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States

11. REFERENCES

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12. PROTOCOL ACCEPTANCE PAGE

I have read and understood the contents of the clinical protocol, MYK-461-019 (An Exploratory, Open-label, Proof-of-concept, Phase 2a Study of Mavacamten [MYK-461] in Participants with Heart Failure with Preserved Ejection Fraction [HFpEF] and Chronic Elevation of Cardiac Biomarkers), 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 or their designee
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the ethics committee (ie, central or institutional review board [IRB] or independent ethics committee [IEC]) for the study protocol, written informed consents, consent form updates, participant recruitment procedures, and any other written information to be provided to the participants before initiating this clinical study
- Not to implement any changes to, or deviations from, the protocol without prior agreement from MyoKardia and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the participants or when changes involve only logistical or administrative aspects of the clinical study
- To permit direct monitoring and auditing by MyoKardia or their designee 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 their designee, including, but not limited to, the current Investigator's Brochure
- 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 the conduct of 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: _____

Protocol Version: _____ Protocol Date: