Official Title of Study:

A Phase 2a, Open-label, Pilot Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-224 in Participants with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction (MERCUTIO)

NCT Number: NCT05556343

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CLINICAL PROTOCOL CV029009

A Phase 2a, Open-label, Pilot Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-224 in Participants with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction (MERCUTIO)

Brief Title:

Multiple Dose Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-224 in Participants with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Protocol Amendment 01

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EUDAMED: Not applicable
Other: Not applicable

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 01	05-Jul-2023	An optional 2-year, open-label extension following the initial titration period has been added [redacted]. The initial titration period is now referred to as Part A and the new open-label extension is referred to as Part B throughout the protocol. Additional minor edits (eg, to cardiac monitoring, echocardiography, adverse event collection) have been made based on site feedback, to reduce participant burden, or to improve clarity.
Original Protocol	02-Jun-2022	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

An optional 2-year, open-label extension following the initial titration period has been added [redacted] The initial titration period is now referred to as Part A and the new open-label extension is referred to as Part B throughout the protocol.

Additional minor edits (eg, to cardiac monitoring, echocardiography, adverse event collection) have been made based on site feedback, to reduce participant burden, or to improve clarity. The Protocol Summary has also been updated to align with the edits in the table below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Title Page	Added "(MERCUTIO)" to the end of the study title. Updated address for Medical Monitor.	Updated title to include new study name. Updated contact information.
Section 2: Schedule of Activities Table 9.4.5-1: Clinical Laboratory Assessments Section 9.8: Biomarkers	In Table 2-1, Table 2-2, Table 2-3, and Table 2-4, [redacted] In Section 9.8, added language for [redacted]	Updated to clarify that the [redacted] collected in this study will be used for exploratory research purposes to align with the study's objectives and endpoints (Table 4-1).
Section 2: Schedule of Activities Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information Table 10.4.2-1: Endpoints	In Table 2-1, Table 2-2, Table 2-3, Table 2-4, and Section 9.2.1, clarified that AEs and SAEs should be collected until 30 days after the final dose of MYK-224 *or the final study visit, whichever is longer.* In Table 10.4.2-1, updated timeframe of relevant endpoints to match this clarification.	Language updated to reflect the possibility that the last study visit may occur more than 30 days after the final dose.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Section 2: Schedule of Activities	In Table 2-1: • Removed Assessment of Signs/Symptoms/Clinical Complaints row. • The minimum required time for cardiac monitoring device data collection prior to dosing has been reduced to 10 days. In Table 2-2: • Additional detail and options were provided for the home visits at Titration Week 2 and Week 4. • Removed cardiac monitoring device-related activities at the [redacted] titration visit. • Updated notes for Drug Compliance row related to return of unused drug. In Table 2-3, removed Cardiac Monitoring Device row. In Table 2-4: • Added that post-exercise/stress transthoracic echocardiogram (TTE) is optional for unscheduled visits. • Removed end-of-treatment (EOT) visit for Cardiac Monitoring Device row. In Table 2-1, Table 2-2, Table 2-3, Table 2-4, updated table titles, column headers, and notes as needed to specify scheduled events are for Part A. Added on-treatment procedures (Table 2-5) and post-treatment visit activities (Table 2-6) for Part B.	These changes were made to: • To eliminate redundancy with other rows related to physical examination and adverse event monitoring. • Updated based on site feedback and confirmation that 10 days is sufficient to evaluate baseline cardiac function. These changes were made to: • Provide additional clarity on who may perform a home visit. The option to perform home visits as clinic visits was added. • [redacted] collection has been removed to reduce redundant data collection and participant burden. • Clarified expectations for return of unused drug. To align with removal of the patch at the end of dose titration through stable dosing. These changes were made to: • Update for clarity. • Remove unnecessary visit for cardiac monitoring device. To clarify the schedule of activities for Part A. To reflect the addition of an optional open-label extension (OLE) period.
Section 3.1: Study Rationale	Added sentence to note an optional OLE period (Part B) to follow the initial titration period (Part A).	Provided rationale for inclusion of an optional OLE period.
Table 3.3.1-1: Risk Assessment	Updated Summary of Data/Rationale for Risk for Reproductive row to expand description of relevant studies to date.	To clarify current clinical and non-clinical experience.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.1.1: Adverse Reactions or Loss of Response Due to Drug Interactions	• Updated description of potential clinical effects of drug-drug interaction (DDI) on MYK-224 concentrations. • Reduced study data requirement to initiate Cohort 2 from 80% of Cohort 1 at EOT to 50% of Cohort 1 at target dose.	• To reflect current understanding of the potential DDI relevant to the study. • [redacted]
Table 4-1: Objectives and Endpoints	Updated table to clarify symptomatic obstructive hypertrophic cardiomyopathy and which exploratory objectives and endpoints are for Part A and added exploratory objectives and endpoints for Part B.	To align objectives with the study population and reflect the addition of an optional OLE period.
Section 5: Study Design	Throughout Section 5 and related subsections and figures for study design, an optional OLE period (Part B) following the initial titration period (Part A) has been added to the study following the initial titration period (Part A).	An optional OLE period (Part B) following the initial titration period (Part A) has been added to the protocol to [redacted] of MYK-224.
Section 5.2: Number of Participants Section 10.2: Sample Size Determination	Modified text to include addition details on subgroups for each study cohort.	To clarify characteristics and number of participants for each cohort and subgroups.
Section 5.3: End of Study Definition	Defined study completion for Part A participants who do not continue in Part B.	To clarify study completion in the context of Part A and Part B.
Section 5.4: Scientific Rationale for Study Design Section 5.5: Justification for Dose	Added and/or modified language to include further rationale for study design and justification for dose in the context of each cohort and the OLE period.	To reflect current information based on clinical experience to date and the addition of an optional OLE period.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria Section 6.2: Exclusion Criteria	The following modifications were made: • Upper range of Age of Participant inclusion criterion was updated from 70 to 80 years. • Added "in the absence of dialysis" to inclusion criterion for Part A related to estimated glomerular filtration rate. • Inclusion and exclusion criteria were modified to note those applicable to Part A and add criteria for Part B. • Exclusion criteria were modified or added in Part A under Medical Conditions.	These changes were made to: • Increase the eligible age range for Part A in order to better align with age range of the target patient population. • Clarify eligibility related to estimated glomerular filtration rate. • Reflect the addition of an optional OLE period. • Clarify criteria based on questions from the clinical sites and align with expected conditions based on increased age range
Section 6.4: Screen Failures (Part A only) Section 6.4.1: Retesting During Screening or Lead-in Period (for all participants in Part A and as needed in Part B)	Updated section titles and/or text to clarify screening details for participants in Part A and Part B.	To reflect the addition of an optional OLE period.
Section 7.2: Method of Study Intervention Assignment	Added language related to maintaining participant numbers from Part A in Part B.	To clarify maintenance of participant numbers from Part A to Part B.
Section 7.4: Dosage Modification	Throughout Section 7.4 and related subsections content was added or modified for an optional OLE period (Part B) that has been added to the study following the initial titration period (Part A).	Updates to subsection headers and addition of new subsections were made to reflect the addition of an optional OLE period. Additional updates were made for clarity.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1: Prohibited and/or Restricted Treatments	Language related to background HCM therapy for Part B was added.	Changes made to reflect the addition of an optional OLE period.
Section 8.1.1.1: Echocardiographic Temporary Discontinuation Criteria	Modified to include additional details for Part A criteria and add criteria for Part B.	Updated for clarity and to reflect the addition of an optional OLE period.
Section 8.1.2.1: Criteria for Permanent Treatment Discontinuation	[redacted]	
Section 8.1.3: Post-study Intervention Study Follow-up	Language adjusted to clarify the use of EOT (end of treatment) vs ET (early termination) visits.	Updated for clarity.
Section 9.1.1.1: Echocardiography	Clarified echocardiography details related to use of contrast and echo views at specific visits and added language for Part B.	Updated for clarity and alignment with Inclusion Criteria and to reflect the addition of an optional OLE period.
Section 9.4.1: Physical Examinations	Added text to include other systems, as directed by interval history.	Clarified assessments included for physical examinations.
Section 9.4.3: Cardiac Monitoring Device	Updated section to clarify cardiac monitoring device details. Collection of cardiac monitoring data at screening reduced from 14 days to 10 days. Cardiac monitoring during Stable Dosing removed.	Description of the device updated to align with vendor information for the device. Collection days for screening reduced and removed use of cardiac monitoring device to reduce patient burden. These changes do not impact the ability to analyze the data as proposed.
Section 9.4.4: Electrocardiograms	Clarified expectations for investigator review and reporting of ECG results.	Updated for clarity.
Table 9.4.5-1: Clinical Laboratory Assessments	Added bicarbonate to chemistry panel and added details for pregnancy testing in the context of Part A and Part B.	Clarified pregnancy testing for participants in Part A and Part B.
Section 9.5: Pharmacokinetics	The following modifications were made: • Updated text to include details on dose timing, including expanded sample windows, and remove language related to treatment assignments example assessments and analyses. • Clarified that Table 9.5-1 pertains to Part A and added Table 9.5-2 to include a pharmacokinetic (PK) sampling schedule for Part B (optional OLE).	These changes were made to: • Align with study design and planned PK analyses. Sample collection windows for Part A have been expanded based on new PK data. • Reflect the addition of an optional OLE period.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.5.1: Pharmacokinetic Sample Collection Windows	[redacted]	To reflect the addition of an optional OLE period.
Section 9.8: Biomarkers	Updated language around example exploratory purposes [redacted] Updated section text, clarified that Table 9.8-1 pertains to Part A, and added Table 9.8-2 to include a biomarker sampling schedule for Part B.	To clarify exploratory biomarker sampling and to reflect the addition of an optional OLE period.
Section 10.4.1: General Considerations	Removed statement regarding data imputation.	Updated for clarity.
Section 10.4.4: Exploratory Endpoints	The following modifications were made: • Updated Table 10.4.4-1 to clarify which exploratory endpoints are for Part A and add exploratory endpoints for Part B. • Updated text in Description column as needed to align with Table 4-1. • Added language related to additional exploratory analyses that may be performed as specified in the Statistical Analysis Plan.	These changes were made to: • Reflect the addition of an optional OLE period. • Align with endpoints described in Section 4. • Clarify that exploratory analyses may be performed.
[redacted]		
Appendix 5: [redacted]	[redacted]	[redacted]
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2a, Open-label, Pilot Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-224 in Participants with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

Brief Title:

Multiple Dose Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-224 in Participants with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Rationale:

This is a proof-of-mechanism Phase 2a study in participants with obstructive hypertrophic cardiomyopathy (oHCM) to support future studies of MYK-224 (also known as BMS-986435) in this patient population. This study is supported by preclinical Good Laboratory Practices (GLP) toxicity and safety studies, as well as safety and tolerability data from the on-going first-in-human (FIH) study in healthy participants. The aim of this study is to characterize the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of MYK-224 in participants with oHCM. The current study was designed to generate multiple-dose data in participants using intra-patient dose titration (Part A). The initial titration will be followed by an optional open-label extension (OLE) to [redacted] (Part B). The results of this study are expected to facilitate future studies, including dose selection, in patient populations.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of MYK-224 in participants with symptomatic oHCM (Part A)	• AEs and SAEs (incidence, severity, causality), including cardiovascular events and hospitalizations • Incidence of arrhythmias, including atrial fibrillation/flutter (new from screening and recurrent), ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe) • Incidence of appropriate implantable cardioverter defibrillator therapy and resuscitated cardiac arrest • Results of vital signs, physical exams, 12-lead ECG (including HR), TTE, clinical laboratory tests (including hematology, clinical chemistry, and urinalysis)
Secondary	
• To evaluate the effect of MYK-224 on LVOT gradient in participants with symptomatic oHCM (Part A)	• Relief of obstruction as measured by change in LVOT peak gradient (post-exercise, resting, and Valsalva) from baseline to end of treatment (Part A) • Proportion of participants achieving a resting LVOT peak gradient of < 30 mm Hg and a Valsalva LVOT peak gradient < 50 mm Hg at end of treatment (Part A)
• To assess the PK/PD relationship of MYK-224 (Part A)	• Concentration-response relationship between MYK-224 PK and 1) LVOT peak gradients and 2) echocardiographic parameters of systolic and diastolic function
• To assess the PK of MYK-224 in participants with symptomatic oHCM (Part A)	• Summary of plasma concentrations

Abbreviations: AE, adverse events; ECG, electrocardiogram; HR, heart rate; LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event; TTE, transthoracic echocardiogram.

Overall Design:

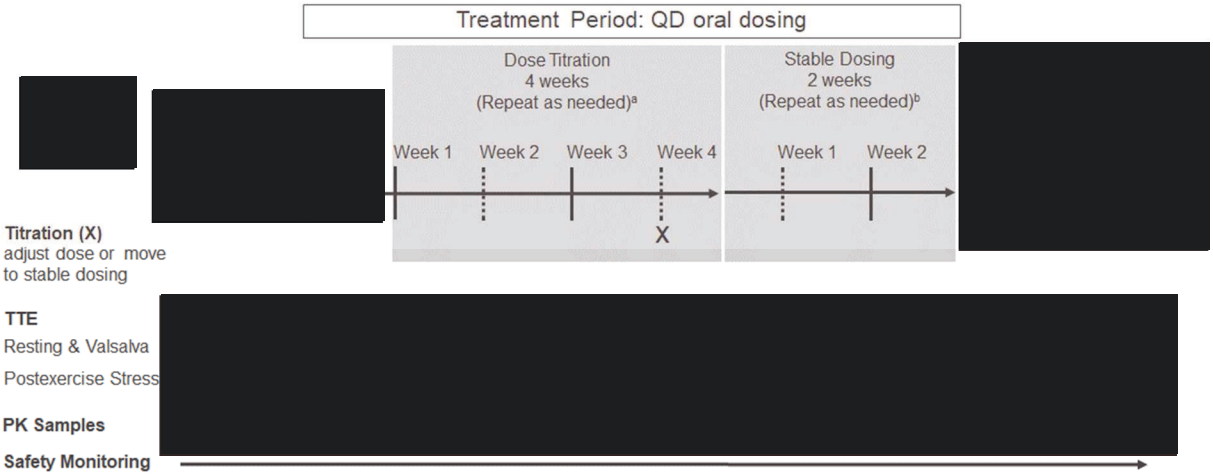
This is a proof-of-mechanism, open-label study of MYK-224 conducted in up to 2 cohorts with approximately [redacted] participants in each cohort:

- Cohort 1: Participants taking MYK-224 with beta-blockers as well as those taking no concomitant standard-of-care medications (MYK-224 monotherapy) will be included.
- Cohort 2: Participants taking MYK-224 with nondihydropyridine calcium channel-blockers or MYK-224 with disopyramide (in combination with either a calcium channel-blocker or beta-blocker) will be included.

- Both cohorts will use an intra-patient dose titration scheme designed to achieve safe and effective dosing for each participant by determining a target individual dose guided by their own response parameters (Part A). Dosing will consist of a once daily oral dose in tablet form. All participants will begin at an initial dose of 5-mg MYK-224, followed by dose decreases or increases for a total potential dose range of 2.5 mg to 50 mg. Dose titration will be based on TTE measures taken at 3 weeks post-initiation of each new dose. The same titration process will be followed for both Cohort 1 and Cohort 2, unless data from Cohort 1 support an alternative dosing regimen.
- The initial titration will be followed by an optional OLE to [redacted] (Part B). Dosing for participants in Part B will be based on the dose at which they completed their end of treatment visit from Part A.

The study design and dosing schemas for Part A are presented below in Figure 1-1 and Figure 1-2, respectively. The study design schema for Part B is presented in Figure 1-3.

Figure 1-1: Study Design Schema (Part A)



Grey boxes represent sections that may be repeated as needed prior to progressing to the next phase of the study.

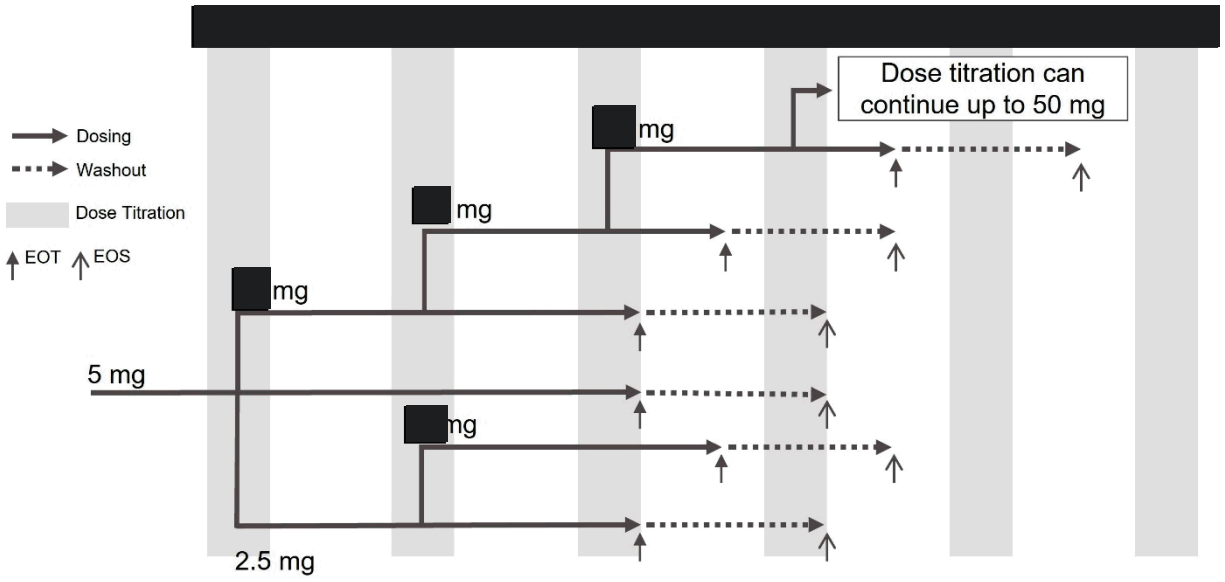
Abbreviations: [redacted] EOT, end of treatment; [redacted]; PK, pharmacokinetics; QD, once daily; TTE, transthoracic echocardiogram.

[a] Dose Titration: Repeat 4-week titration period until target dose is identified or maximum allowable dose is reached.

[b] Stable Dosing: Repeat 2-week dosing until participant has been on target dose/maximum allowable dose for at least 6 weeks AND dosed with MYK-224 at any dose for at least 12 weeks.

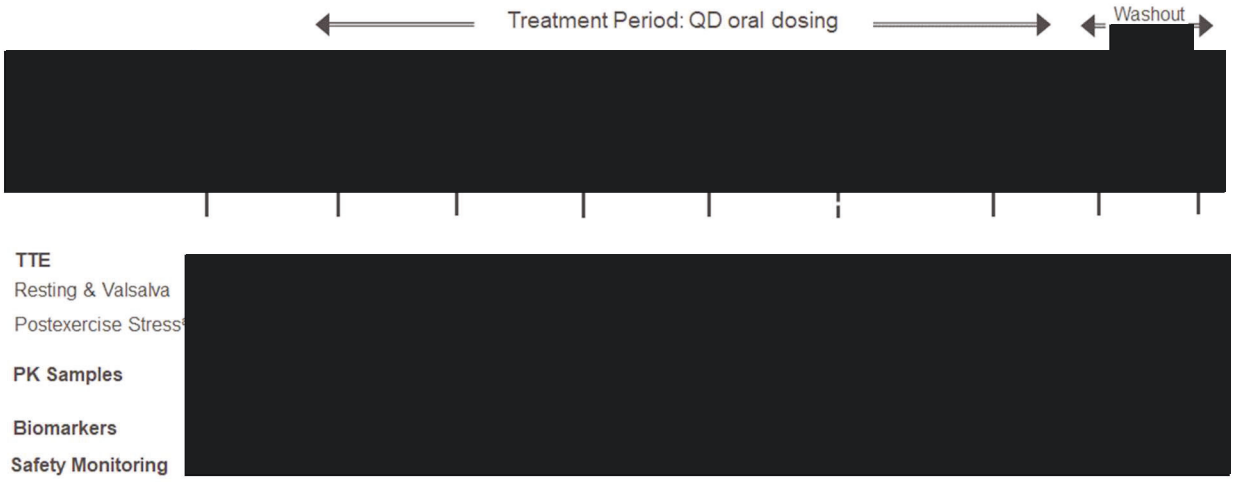
* TTE from Dose Titration Week 3 will be used to determine titration decision at Week 4.

Figure 1-2: Dosing Schematic (Part A)



Abbreviations: EOS, end of study; EOT, end of treatment; Wk, week.

Figure 1-3: Study Design Schema (Part B)



Abbreviations: [redacted]; PK, pharmacokinetics; QD, once daily; TTE, transthoracic echocardiogram.

Note: Phone visits will be conducted every [redacted] beginning at [redacted]). Clinic visits will be conducted every [redacted] beginning at [redacted] All visits have a [redacted] window.

- Postexercise stress TTE at Screening-B (if applicable), Weeks [redacted].
- Biomarker samples will be collected at [redacted]
- Screening visit as needed.

Number of Participants:

Approximately [redacted] participants will be enrolled (approximately [redacted] participants each in Cohort 1 and Cohort 2, respectively).

Study Population:

This study will include symptomatic male and female participants diagnosed with oHCM that are 18 to 80 years of age (inclusive).

Intervention Groups and Duration:

Participants will receive once daily oral doses of MYK-224 and dose continuously throughout the treatment period. In Part A, all participants will begin with a dose of 5-mg MYK-224, which will then be increased or decreased based on [redacted]. The potential doses of MYK-224 may range from 2.5 mg to 50 mg, with the goal of identifying an effective target dose for each participant guided by echocardiographic response parameters. Dose titrations will occur every 4 weeks and be based on the TTE data collected the week before. Once the target dose is identified or the participant has titrated up to the maximum allowable dose, participants will continue at that dose until they a) have completed a minimum of 6 weeks total dosing at their target dose/the maximum allowable dose; and b) have completed a minimum of 12 weeks of treatment with MYK-224 at any dose. The duration of study participation in Part A will depend on the number of titrations needed to identify each participant's target dose or reach the maximum allowable dose and could range from [redacted] including Screening and the mandatory [redacted] washout for all participants prior to the end of study. The same titration process will be followed for both Cohort 1 and Cohort 2, unless data from Cohort 1 support an alternative dosing regimen.

For Part B (optional OLE), participation will be up to [redacted] including any necessary screening time and the mandatory [redacted] washout period following [redacted] of treatment with MYK-224.

For all participants, down-titration to the last tolerated dose or discontinuation of dosing for safety may occur at any time during treatment (Part A and Part B) based on the clinical judgment of the investigator in consultation with the Sponsor Medical Monitor.

Study Intervention:

Study Intervention for CV029009		
Medication	**Potency**	**IMP/Non-IMP/AxMP**
MYK-224	[redacted] mg	IMP

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product.

Statistical Methods:

Primary analysis is to characterize the safety of MYK-224 in participants with oHCM. All the primary endpoints will be summarized descriptively. Descriptive summary statistics for continuous variables will include the number of participants, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Ninety percent exact confidence intervals will be presented, as appropriate.

Data Monitoring Committee: No

A Data Monitoring Committee will not be used in the study.

Other Committee: Yes

This study includes an Executive Committee.

Brief Summary:

The purpose of this study is to characterize the safety, tolerability, efficacy, PK, and PD of MYK-224 in participants with oHCM. Study details include the following:

Study Duration:

- Part A: Approximately [redacted]
- Part B: Approximately [redacted]

Study Intervention Duration:

- Part A: Approximately 12 to 45 weeks
- Part B: Approximately [redacted]

Study Visit Frequency:

- Part A: [redacted] clinic visits with phone visits on alternate weeks until end of treatment (EOT-A) followed by a [redacted] washout and end of study (EOS-A) visit.
- Part B: Clinic visits every [redacted] until [redacted], then every [redacted] until [redacted]) followed by a [redacted] washout and [redacted] visit.

Health Measurement/Observation: [redacted] that resolves the resting and Valsalva LVOT gradients [redacted]

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening/Day 1 Procedural Outline (Part A - All Participants)

Procedure[a]	Screening A[b]	Day 1A (5-mg dose)	Notes
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria (I/E)	X	X	Day 1 - review I/E and ensure participant still qualifies.
Medical History (MH)	X	X	MH should be reviewed and updated at each visit.
Safety Assessments			
Physical Examination (PE)	X	X	Height will be measured at screening only. Weight should be taken at every visit to calculate BMI. Full PE including a complete physical exam will be performed at screening, ET, and EOS. An abbreviated PE will be conducted at all other clinic visits. See Section 9.4.1.
Vital Signs	X	X	Vital signs, including temperature, heart rate (HR), respiratory rate (RR), and blood pressure (BP), will be obtained at screening, Day 1, EOT, and EOS visits. At all other visits, vital signs will include only HR, RR, and BP. See Section 9.4.2.
Concomitant Medication Use	X	X	Concomitant medications should be reviewed and updated at each visit.
12-lead ECG	X	X	12-lead ECGs will be performed in a supine position after 10 minutes of rest at Screening and at all onsite study visits. 12-lead ECGs should be obtained prior to dosing and before blood sampling at visits where those procedures are also performed. A post-dose 12-lead ECG will also be collected [redacted] after dosing on Day 1. See Section 9.4.4.

Table 2-1: Screening/Day 1 Procedural Outline (Part A - All Participants)

Procedure[a]	Screening A[b]	Day 1A (5-mg dose)	Notes
Cardiac Monitoring Device	X	X	Device will be applied at screening. It should be worn continuously and replaced as needed for a minimum of 10 days prior to dosing. The device will be removed on Day 1 prior to dosing. Participants will be trained on applying the patch, and additional supplies will be provided to each participant. See Section 9.4.3.
ICD Download	X		For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at Screening, EOT, EOS/ET, and any unscheduled visits, or as clinically indicated after any ICD discharge interrogation occurring during the study.
Laboratory Tests: participants should fast for 4 hours prior to arriving at clinic			
Hematology	X	X	
Chemistry	X	X	
Serology	X		Serology testing for infections: HIV and hepatitis.
SARS-CoV-2 Diagnostic Test	X		To be performed at screening according to the manner mandated by the study site and/or community where the trial is being conducted. Additional SARS-CoV-2 testing may be performed at other clinic visits following local guidance at each site.
Urinalysis	X	X	
Follicle Stimulating Hormone (FSH) (WNOCBP)	X		
Pregnancy Test (WOCBP)	X	X	Serum test at Screening and EOS or ET. Urine test at all other timepoints.

Table 2-1: Screening/Day 1 Procedural Outline (Part A - All Participants)

Procedure[a]	Screening A[b]	Day 1A (5-mg dose)	Notes
Adverse Event Reporting			
Monitor for Adverse Events (AEs) & Serious Adverse Events (SAEs)	X	X	All AEs and SAEs will be collected from the time of informed consent until 30 days after the final dose of MYK-224 or the final study visit, whichever is longer.
Efficacy Assessments			
Resting and Valsalva TTE	X	X	Resting and Valsalva TTE should be performed prior to post-exercise echocardiography. See Section 9.1.1.1 and Section 9.1.1.2.
Post-exercise/Stress TTE	X		Following a recommended 4-hour fast and prior to dosing. See Section 9.1.1.3. Post exercise TTE should be acquired the same day or within 72 hours of the resting TTE.
Clinical Outcome Assessments			
NYHA Functional Classification	X	X	
KCCQ-23		X	
[redacted]			
Pharmacokinetics			
PK Blood Sample		X	Day 1A: [redacted] baseline sample and a [redacted] sample at [redacted] post-MYK-224 administration.

Table 2-1: Screening/Day 1 Procedural Outline (Part A - All Participants)

Procedure[a]	Screening A[b]	Day 1A (5-mg dose)	Notes
Dosing			
MYK-224		X	Single initial dose of 5 mg - participants will be provided with sufficient MYK-224 supply for QD at-home dosing.

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ET, early termination; FSH, follicle stimulating hormone; [redacted]; HIV, human immunodeficiency virus; [redacted] HR, heart rate; I/E, inclusion/exclusion criteria; ICD, implantable cardioverter-defibrillator; KCCQ-23, Kansas City Cardiomyopathy Questionnaire (23-item version); MH, medical history; [redacted] NYHA, New York Heart Association; PE, physical examination; PK, pharmacokinetics; QD, once daily; RR, respiratory rate; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory coronavirus 2; TTE, transthoracic echocardiogram; WNOCBP, women not of childbearing potential; WOCBP, women of childbearing potential.

[a] The preferred order of study procedures is KCCQ-23, NYHA Functional Classification, 12-lead ECG, vital signs, PK, [redacted], clinical laboratory assessments, and TTE prior to dosing unless otherwise indicated.

[b] Screening may occur up to [redacted] prior to Day 1.

Table 2-2: Dose Titration (Part A)

Procedure[a,b]	Titration Week 1	Titration Week 2	Titration Week 3	Titration Week 4	Notes
Phone Visit		X		X	Site staff will schedule a phone visit with participants. A home visit (performed by an authorized vendor or the site staff) will also occur at [redacted] to provide participants with a new batch of MYK-224 and collect all unused drug from previous batch. This visit may be done as a clinic visit if preferred.
Clinic Visit	X		X		[redacted] There is a +7-day window for clinic visits. Participants should fast for 4 hours prior to arrival at clinic.
Safety Assessments					
Abbreviated Physical Examination (PE)	X		X		Weight and an abbreviated PE. See Section 9.4.1.
Vital Signs	X		X		HR, RR, and BP; see Section 9.4.2.
Concomitant Medication Use	X	X	X	X	Concomitant medications and medical history should be reviewed/updated at each clinic visit and during phone visits.
12-lead ECG	X		X		12-lead ECGs will be performed in a supine position after 10 minutes of rest at Screening and at all onsite study visits. 12-lead ECGs should be obtained prior to dosing and before blood sampling at visits where those procedures are also performed. A post-dose 12-lead ECG should be collected [redacted] after dosing at the [redacted] visit. See Section 9.4.4.
Cardiac Monitoring Device	X		X		Device will be applied at the [redacted] clinic visit and removed at the [redacted] visit. Additional supplies will be provided to each participant. See Section 9.4.3.

Table 2-2: Dose Titration (Part A)

Procedure[a,b]	Titration Week 1	Titration Week 2	Titration Week 3	Titration Week 4	Notes
Laboratory Tests					
Hematology			X		
Chemistry			X		
Urinalysis			X		
Pregnancy Test (WOCBP)			X		Urine test at [redacted]
Adverse Event Reporting					
Monitor for Adverse Events (AEs and SAEs)	X	X	X	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days after the final dose of MYK-224 or the final study visit, whichever is longer. SAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic (PK) Assessments					
PK Assessments	[redacted]		[redacted]		[redacted] samples will be taken at each clinic visit. A [redacted] sample will also be taken [redacted] after MYK-224 administration at the [redacted] visit. See Table 9.5-1 for PK sampling schedule.

[redacted]

Table 2-2: Dose Titration (Part A)

Procedure[a,b]	Titration Week 1	Titration Week 2	Titration Week 3	Titration Week 4	Notes
Efficacy Assessments					
Resting and Valsalva TTE	X		X		See Section 9.1.1.1 and Section 9.1.1.2.
Clinical Outcome Assessments					
NYHA Functional Classification	[redacted]				
KCCQ-23					
Study Intervention					
MYK-224 administered in clinic	X		X		Daily dose of MYK-224 will be administered in clinic to allow for predose sample collection.
Titration				X	The TTE assessment from Week 3 will be used to inform dose titration at Week 4. If dose is titrated, participant will repeat the 4-week Dose Titration phase. If current dose is determined to be the participant's target dose or no further increase is possible, the participant will move to the Stable Dosing phase [redacted]
Drug Compliance	X		X	X	Return dosing containers for tablet counts at clinic visits. Unused drug will be collected and returned at [redacted]

Abbreviations: AE, adverse event; BP, blood pressure; ECG, electrocardiogram; EDC, electronic data capture; EOS, end of study; EOT, end of treatment; [redacted] HR, heart rate; KCCQ-23, Kansas City Cardiomyopathy Questionnaire (23-item version); [redacted] NYHA, New York Heart Association; PE, physical examination; PK, pharmacokinetics; RR, respiratory rate; SAE, serious adverse event; TTE, transthoracic echocardiogram; WOCBP, women of childbearing potential.

[a] To be repeated if dose is adjusted, until target dose is identified or maximum allowable dose is reached.

[b] The preferred order of study procedures is KCCQ-23, NYHA Functional Classification, 12-lead ECG, vital signs, PK, [redacted], clinical laboratory assessments, and TTE prior to dosing unless otherwise indicated.

Table 2-3: Stable Dosing (Part A)

Procedure[a,b]	Stable Dose Week 1	Stable Dose Week 2	Notes
Phone Visit	X		Site staff will schedule a phone visit with participants.
Clinic Visit		X	At least [redacted] after initiation of dose, then approximately every [redacted] as needed to complete treatment period. Participants should fast for 4 hours prior to arrival at clinic (+7-day window).
Safety Assessments			
Abbreviated Physical Examination (PE)		X	Weight and an abbreviated PE. See Section 9.4.1.
Vital Signs		X	HR, RR, and BP; see Section 9.4.2.
Concomitant Medication Use	X	X	Concomitant medications and medical history should be reviewed/updated at each clinic visit and during phone visits.
12-lead ECG		X	See Section 9.4.4.
Laboratory Tests			
Hematology		X	
Chemistry		X	
Urinalysis		X	
Pregnancy Test (WOCBP)		X	Urine test
Adverse Event Reporting			
Monitor for Adverse Events (AEs and SAEs)	X	X	All AEs and SAEs will be collected from the date of participant's written consent until 30 days after the final dose of MYK-224 or the final study visit, whichever is longer. SAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic (PK) Assessments			
PK Assessments		[redacted]	See Table 9.5-1 for PK sampling schedule.

Table 2-3: Stable Dosing (Part A)

Procedure[a,b]	Stable Dose Week 1	Stable Dose Week 2	Notes
[redacted]			
Efficacy Assessments			
Resting and Valsalva TTE		X	See Section 9.1.1.1 and Section 9.1.1.2.
Clinical Outcome Assessments			
NYHA Functional Classification		[redacted]	
KCCQ-23			
Study Treatment			
MYK-224		X	Daily dose will be administered in clinic to allow for predose measurements and sample collection. See Section 7.4.
Drug Compliance		X	Return dosing containers for tablet counts.

Abbreviations: AE, adverse event; ECG, electrocardiogram; EDC, electronic data capture; EOT, end of treatment; [redacted] KCCQ-23, Kansas City Cardiomyopathy Questionnaire (23-item version); [redacted] NYHA, New York Heart Association; PE, physical examination; PK, pharmacokinetics; SAE, serious adverse event; TTE, transthoracic echocardiogram, WOCBP, women of childbearing potential.

[a] Repeat this phase until they either have been dosing at their "target dose" for 6 weeks (including the 4 in the titration period) OR been receiving study drug for 12 weeks, whichever is longest.

[b] The preferred order of study procedures is KCCQ-23, NYHA Functional Classification, 12-lead ECG, vital signs, PK, [redacted], clinical laboratory assessments, and TTE prior to dosing unless otherwise indicated.

[redacted]

Table 2-4: EOT/Washout Period/EOS/Unscheduled Visit/ET (Part A - All Participants)

Procedure[a]	[redacted]					Notes
Safety Assessments						
Physical Examination (PE)	X	X	X	X	X	Weight should be taken at every visit to calculate BMI. Full PE including a complete physical exam will be performed at [redacted] and for any [redacted] visit. An abbreviated PE will be conducted at all other clinic visits. See Section 9.4.1.
Vital Signs	X	X	X	X	X	Vital signs, including temperature, HR, RR, and BP, will be obtained at [redacted] and [redacted] visits. At all other visits, vital signs will include only HR, RR, and BP; see Section 9.4.2.
Concomitant Medication Use	X	X	X	X	X	Concomitant medications and medical history should be reviewed/updated at each clinic visit and during phone visits.
12-lead ECG	X	X	X	X	X	12-lead ECGs will be performed in a supine position after 10 minutes of rest at all onsite study visits. 12–lead ECGs should be obtained prior to dosing and before blood sampling at visits where those procedures are also performed. A [redacted] post-dose 12-lead ECG will also be performed at the [redacted] visit. See Section 9.4.4.
Cardiac Monitoring Device					X	If participant is wearing a device, it should be removed at [redacted], as applicable. See Section 9.4.3.
ICD Download	X		X	X	X	For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at Screening, [redacted], and any unscheduled visits, or as clinically indicated after any ICD discharge interrogation occurring during the study.
Laboratory Tests: Participants should fast for 4 hours prior to arriving at clinic.						
Hematology	X	X	X	X	X	

Table 2-4: EOT/Washout Period/EOS/Unscheduled Visit/ET (Part A - All Participants)

Procedure[a]	[redacted]					Notes
Chemistry	X	X	X	X	X	
Urinalysis	X		X	X	X	
Pregnancy Test (WOCBP)	X		X		X	Urine test at [redacted]. Serum test at [redacted]
Adverse Event Reporting						
Monitor for Adverse Events (AEs and SAEs)	X	X	X	X	X	All AEs and SAEs will be collected from the date of participant's written consent until 30 days after the final dose of MYK-224 or the final study visit, whichever is longer. SAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic (PK) Assessments						
PK Assessments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Table 9.5-1 for PK sampling schedule. [redacted] sample to be collected at [redacted].
[redacted]						
Efficacy Assessments						
Resting and Valsalva TTE	X	X	X	X	X	Resting and Valsalva TTE should be performed prior to post-exercise echocardiography. See Section 9.1.1.1 and Section 9.1.1.2.

Table 2-4: EOT/Washout Period/EOS/Unscheduled Visit/ET (Part A - All Participants)

Procedure[a]	[redacted]					Notes
Post Exercise/Stress TTE	X		X	X	X	Following a recommended 4–hour fast. See Section 9.1.1.3. Post-Exercise/Stress TTE is optional for unscheduled visits.
Clinical Outcome Assessments						
KCCQ-23	[redacted]					
NYHA Functional Classification						
Study Treatment						
MYK-224	X					Final dose will be given at the EOT-A visit to allow for a final set of PK samples. No MYK-224 will be provided during the washout period.
Drug Compliance	X			X	X	Return dosing containers for tablet counts.

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; ECG, electrocardiogram; EDC, electronic data capture; EOS, end of study; EOS-A, end of study for Part A; EOT, end of treatment; EOT-A, end of treatment for Part A; ET-A, early termination for Part A; ICD, implantable cardioverter-defibrillator; HR, heart rate; [redacted] KCCQ-23, Kansas City Cardiomyopathy Questionnaire (23-item version); [redacted]; NYHA, New York Heart Association; PE, physical examination; PK, pharmacokinetics; RR, respiratory rate; SAE, serious adverse event; TTE, transthoracic echocardiogram; WOCBP, women of childbearing potential.

[a] The preferred order of study procedures is KCCQ-23, NYHA Functional Classification, 12-lead ECG, vital signs, PK, [redacted], clinical laboratory assessments, and TTE prior to dosing unless otherwise indicated.

[redacted]

Table 2-5: On-Treatment Procedures (Part B - Optional OLE)

Procedure	[redacted]	Notes
Clinic Visit	X X X X X X	[redacted] Following Day 1, all clinic visits have a [redacted] day window.
Phone Visit	X	Site staff will schedule a phone visit with participants at [redacted] All phone visits have a [redacted] day window.
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X X	Review all I/E criteria on Day 1 to confirm eligibility prior to dosing.
Safety Assessments		
Complete Physical Examination (PE)	X X	Weight should be taken at every visit to calculate BMI. A complete PE will be performed at Screening and Day 1B. See Section 9.4.1. Any abnormal findings during the PE will be recorded as medical history in the participant's medical records and on the appropriate CRF.
Abbreviated PE	X X X X	Weight and abbreviated PE. See Section 9.4.1. Any abnormal findings from the PE will be reported on the AE CRF as appropriate.

Table 2-5: On-Treatment Procedures (Part B - Optional OLE)

Procedure	[redacted]							Notes
Vital Signs	X	X	X	X	X		X	Vital signs, including temperature, HR, RR, and BP, will be obtained at Screening, [redacted] At all other visits, vital signs will include only HR, RR, and BP.
Concomitant Medication Use	X	X	X	X	X	X	X	Concomitant medications should be reviewed and updated at each visit.
ICD Download	X							
12-lead ECG	X	X	X	X	X		X	12-lead ECGs will be performed in a supine position after 10 minutes of rest at all clinic visits. 12-lead ECGs should be obtained prior to dosing and before blood sampling. A post-dose 12-lead ECG will be [redacted] after dosing at [redacted]
Laboratory Tests: Participants should fast for 4 hours prior to arriving at clinic								
Hematology	X	X	X	X	X		X	
Chemistry	X	X	X	X	X		X	
Urinalysis	X	X		X			X	
Pregnancy Test (WOCBP Only)	X	X	X	X	X	X[e]	X	Urine pregnancy tests will be performed at home, at the site, or at a local lab every [redacted] when no clinic visit is scheduled. If performed at home or at a local lab, results will be requested by the site on a monthly basis and entered into the CRF.
Serology	X							Serology testing for infections: HIV and hepatitis.

Table 2-5: On-Treatment Procedures (Part B - Optional OLE)

Procedure	[redacted]	Notes
Pharmacokinetic (PK) Assessments		
PK Assessments	See Table 9.5-2 for PK sampling schedule.	
[redacted]		
Adverse Events Reporting		
Monitor for Non-serious and Serious AEs	X X X X X X X	All AEs and SAEs must be collected from the date of participant's written consent until [redacted] post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Efficacy Assessments		
Resting and Valsalva TTE	[redacted]	[redacted] See Section 9.1.1.2.
Post-exercise/Stress TTE	[redacted]	[redacted] See Section 9.1.1.3.

Table 2-5: On-Treatment Procedures (Part B - Optional OLE)

Procedure	[redacted]	Notes
Clinical Outcome Assessments		
NYHA Functional Classification	[redacted]	
KCCQ-23		
Study Intervention		
MYK-224	X X X X X	Daily dose of MYK-224 will be administered in clinic to allow for predose sample collection.
Drug Compliance	X X X X	Return dosing containers for tablet counts at all clinic visits.

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; CRF, Case Report Form; ECG, electrocardiogram; EOS, end of study; EOS-A, end of study for Part A, EOT, end of treatment; ET, early termination; HR, heart rate; [redacted] HIV, human immunodeficiency virus; ICD, implantable cardioverter-defibrillator; I/E, inclusion/exclusion; KCCQ-23, Kansas City Cardiomyopathy Questionnaire (23-item version); [redacted]; OLE, open-label extension; PE, physical examination; PK, pharmacokinetics; RR, respiratory rate; SAE, serious adverse event; [redacted]; WOCBP, women of childbearing potential.

[redacted]

The preferred order of study procedures is KCCQ-23, NYHA Functional Classification, 12-lead ECG, vital signs, PK, [redacted], clinical laboratory assessments, and TTE prior to dosing, unless otherwise indicated.

[e] Results from any at-home pregnancy tests conducted since the previous visit should be recorded at all phone visits.

Table 2-6: EOT/Washout Period/EOS/Unscheduled Visit/ET (Part B - Optional OLE)

Procedure[a]	[redacted]			Notes
Safety Assessments				
Physical Examination (PE)		X		Weight should be taken at every visit to calculate BMI. Full PE including a complete physical exam will be performed at [redacted] and for any ET visit. See Section 9.4.1.
Abbreviated PE	X		X	Weight should be taken at every visit to calculate BMI. See Section 9.4.1.
Vital Signs	X	X	X	Vital signs, including temperature, HR, RR, and BP, will be obtained at [redacted] visits. At all other visits, vital signs will include only HR, RR, and BP; see Section 9.4.2.
Concomitant Medication Use	X	X	X	Concomitant medications and medical history should be reviewed/updated at each clinic visit and during phone visits.
12-lead ECG	X	X	X	Single 12-lead ECGs will be performed in a supine position after 10 minutes of rest at all onsite study visits. 12–lead ECGs should be obtained prior to dosing and before blood sampling at visits where those procedures are also performed. A [redacted] post-dose 12-lead ECG will also be performed at the [redacted]. See Section 9.4.4.
ICD Download	X	X	X	For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at Screening, [redacted], and any unscheduled visits, or as clinically indicated after any ICD discharge interrogation occurring during the study.
Laboratory Tests: Participants should fast for 4 hours prior to arriving at clinic.				
Hematology	X	X	X	
Chemistry	X	X	X	
Urinalysis	X	X	X	
Pregnancy Test (WOCBP)	X	X		Urine test at [redacted]. Serum test at [redacted].

Table 2-6: EOT/Washout Period/EOS/Unscheduled Visit/ET (Part B - Optional OLE)

Procedure[a]	[redacted]			Notes
Adverse Event Reporting				
Monitor for Adverse Events (AEs and SAEs)	X	X	X	All AEs and SAEs will be collected from the date of participant's written consent until [redacted] after the final dose of MYK-224 or the final study visit, whichever is longer. SAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic (PK) Assessments				
PK Assessments	[redacted]	[redacted]	[redacted]	See [redacted] for PK sampling schedule. A sample will be collected [redacted] and [redacted] post dose at [redacted].
[redacted]				
Efficacy Assessments				
Resting and Valsalva TTE	[redacted]	[redacted]	[redacted]	[redacted] See Section 9.1.1.1 and Section 9.1.1.2.
Post Exercise/Stress TTE	[redacted]	[redacted]	[redacted]	[redacted]

Table 2-6: EOT/Washout Period/EOS/Unscheduled Visit/ET (Part B - Optional OLE)

Procedure[a]	[redacted]			Notes
Clinical Outcome Assessments				
KCCQ-23	[redacted]			
NYHA Functional Classification				
Study Treatment				
MYK-224	X			Final dose will be given at the EOT-B visit to allow for a final set of PK samples. No MYK-224 will be provided during the washout period.
Drug Compliance	X	X	X	Return dosing containers for tablet counts at EOT-B, ET-B, and any unscheduled visits.

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; ECG, electrocardiogram; EDC, electronic data capture; EOS, end of study; EOS-B, end of study for Part B; EOT, end of treatment; EOT-B, end of treatment for Part B; ET, early termination; ET-B, early terminatin visit for Part B; ICD, implantable cardioverter-defibrillator; HR, heart rate; [redacted]; KCCQ-23, Kansas City Cardiomyopathy Questionnaire (23-item version); [redacted]; NYHA, New York Heart Association; OLE, open-label extension; PE, physical examination; PK, pharmacokinetics; RR, respiratory rate; SAE, serious adverse event; TTE, transthoracic echocardiogram; WOCBP, women of childbearing potential.

[a] The preferred order of study procedures is KCCQ-23, NYHA Functional Classification, 12-lead ECG, vital signs, PK, [redacted], clinical laboratory assessments, and TTE prior to dosing unless otherwise indicated.

[redacted]

3 INTRODUCTION

3.1 Study Rationale

This is a proof-of-mechanism Phase 2a study in participants with obstructive hypertrophic cardiomyopathy (oHCM) to support future studies of MYK-224 in this patient population. This study is supported by preclinical Good Laboratory Practices (GLP) toxicity and safety studies, as well as safety and tolerability data from the on-going first-in-human (FIH) study in healthy participants. The current study was designed to generate multiple-dose data in participants using intra-patient dose titration (Part A). The initial titration will be followed by an optional open-label extension (OLE) [redacted] (Part B). The results of this study are expected to facilitate future clinical studies in patients with hypertrophic cardiomyopathy (HCM) and other potential indications.

There is no formal primary research hypothesis to be statistically tested. The purpose of this study is to characterize the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of MYK-224 (also known as BMS-986435) in participants with oHCM.

3.2 Background

Hypertrophic cardiomyopathy is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease. Hypertrophic cardiomyopathy is a chronic, progressive disease of the cardiomyocyte, and largely of the cardiac sarcomere, with a diverse clinical presentation and course. Over time, HCM results in tissue remodeling characterized histologically by myocyte hypertrophy and disarray, microvascular remodeling, and fibrosis.[1] Approximately 40% of affected individuals overall and 60% of those with a family history of clinical disease have a mutation in 1 or more sarcomeric structural genes.[2,3,4,5] Mutations in cardiac myosin and other sarcomeric proteins appear to increase net power generation by the sarcomere, which is consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in HCM.[6,7,8] Recent estimates of the prevalence of HCM using information from large administrative databases indicate that the prevalence of clinically diagnosed HCM ranges from 3 to 7 per 10,000.[9,10,11,12]

Two HCM phenotypes are recognized based on the presence or absence of obstruction of the LV outflow tract (LVOT), oHCM (also known as HOCM), and non-obstructive HCM (nHCM), where obstruction is defined as a peak LV outflow gradient ≥ 30 mm Hg at rest or with provocation.[3] Approximately 70% of individuals diagnosed with HCM have oHCM.[13] Therefore, the prevalence rate of oHCM is likely between 2 and 5 per 10,000, based on the recent estimates of HCM. The combination of the abnormal ventricular geometry caused by septal hypertrophy, reduced ventricular cavity size, and the pathologic elongation of the mitral valve are considered contributing factors, but the precise mechanism of LVOT obstruction is unknown.[14] Ventricular obstruction produces increased LV systolic pressure and an array of subsequent abnormalities, including prolongation of ventricular relaxation, elevation of LV diastolic pressure, mitral regurgitation (MR), atrial fibrillation, myocardial ischemia, and decreased forward cardiac output.[15] The presence of LVOT obstruction is an important prognostic factor in HCM and is

associated with an increased risk of disease progression, congestive heart failure, stroke, and death.[16,17] The risk of sudden cardiac death (SCD), which is one of the most common nontraumatic causes of death in young adults and sometimes the first manifestation of HCM, is also increased in the presence of LVOT obstruction.[3,18,19]

Current guidelines for the pharmacologic management of HCM rely on empirical use of established cardiovascular (CV) medications (including beta-blockers, verapamil, diltiazem, and disopyramide) that may improve LV outflow, but offer limited and variable relief in symptoms and functional status.[3,20] In oHCM, septal reduction therapy (SRT) may reduce obstruction and improve LV outflow, and an implantable cardioverter-defibrillator (ICD) may prevent SCD, but both involve invasive procedures, require specialized operators and clinic settings, and may not be available to all patients.[21] Cardiac transplant is the only option when pharmacologic options fail to adequately manage oHCM. None of these treatment options address the underlying etiology of HCM.

Recently, the first-in-class, cardiac myosin inhibitor mavacamten demonstrated improvements in exercise capacity, LVOT, symptoms, and health status in participants with oHCM, indicating a potential role for this novel therapeutic class in the treatment of participants with HCM.[22] Similar in mechanism to mavacamten, MYK-224 is a small molecule allosteric modulator of cardiac myosin that is being developed by BMS for the treatment of adults with symptomatic oHCM.

In nonclinical studies, MYK-224 was specific for striated muscle myosin and selective for the cardiac isoform. Its targeted mechanism of action and high degree of specificity were reflected in its pharmacology in vitro and in vivo, as well as in its nonclinical toxicology and safety pharmacology. The totality of the PD and tolerability data observed to date can be interpreted as direct or indirect consequences of altered cardiac contractility. For more detailed information on MYK-224, please refer to the most current Investigators Brochure (IB).

MYK-224 has been evaluated in 1 ongoing clinical trial: a Phase 1, blinded, first-in-human (FIH), randomized, placebo-controlled study evaluating the safety, tolerability, PK, and PD of single ascending doses (SAD) and multiple ascending doses (MAD) of MYK-224 in normal healthy participants. As of the clinical data safety cutoff date of 31-May-2022 for IB Version 3, [redacted] have received at least 1 dose of MYK-224 or placebo.[23]

[redacted]

3.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of MYK-224 may be found in the IB.

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Intervention(s): MYK-224		
Cardiac Failure and Systolic Dysfunction	MYK-224 has the potential to depress cardiac systolic function, which may result in hypotension, dizziness, and/or signs and symptoms of heart failure. This risk may be increased by combined administration with other negative inotropic agents, such as disopyramide, beta-blockers, or nondihydropyridine calcium channel-blockers, which also have the potential to reduce cardiac systolic function.	Eligibility requirement for a minimum level of LV systolic function; while on stable doses of concomitant HCM therapy (beta blockers, nondihydropyridine calcium channel blockers, and disopyramide) where applicable. Dosing will be tailored to each participant based on their own response parameters, with frequent monitoring of participant cardiac function and response to therapy by transthoracic echocardiography. Regular monitoring of vital signs, 12-lead ECG results, [redacted] levels will also be performed.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Reproductive	There is no clinical data available for pregnancy with exposure to the compound or other compounds in the same class. There is a potential risk of teratogenic and embryotoxic effects based on embryofetal development studies in animals with BMS-986435/MYK-224 at clinically-relevant exposures, as well as other compounds from the same class.	Male and female participants will be counseled by the site staff regarding reproductive risks, and all participants will be required to adhere to the contraceptive requirements.
[redacted]		
Adverse Reactions or Loss of Response due to Drug Interactions (see Section 3.3.1.1 below)	[redacted]	

Abbreviations: BP, blood pressure; [redacted] ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LV, left ventricular; [redacted].

3.3.1.1 Adverse Reactions or Loss of Response Due to Drug Interactions

[redacted]

3.3.2 Benefit Assessment

Hypertrophic cardiomyopathy is a global disease and is considered one of the most common genetic heart disorders with an estimated prevalence of between 1 in 200 to 1 in 500 people.[24] Patients with HCM commonly experience exertional dyspnea, which limits their daily activities and can be debilitating. Patients with HCM are also at increased risk for adverse clinical events, including overt heart failure, atrial fibrillation, syncope, malignant ventricular arrythmias, and sudden cardiac death.

Current medical treatment for HCM consists of beta-blockers, nondihydropyridine calcium channel-blockers, and disopyramide. For patients with more advanced disease, progressive systolic dysfunction may develop, in which case typical therapies for systolic heart failure are employed, although the evidence for the benefit of these therapies in this special subpopulation is lacking. Patients with oHCM may be candidates for SRT, such as surgical myectomy or percutaneous ASA. Although these procedures can be effective in reducing or eliminating outflow tract obstruction, it is unclear if they reduce overall morbidity or mortality.

BMS is developing MYK-224 to improve symptoms of dyspnea and exercise capacity in patients with HCM. MYK-224 selectively targets cardiac myosin and reversibly inhibits its binding to actin, reducing the aggregate force (and thus power output) of systolic contraction. This results in the reduction of sarcomeric contractility and is predicted to facilitate relaxation, which may improve both dynamic LVOT obstruction and LV compliance (diastolic dysfunction) in participants with HCM.

While there are no data available evaluating MYK-224 in patients with HCM, data with other agents in this class suggest the possibility that participants may benefit from participation by experiencing improvements in LV outflow tract obstruction and associated symptoms during treatment with MYK-224.

3.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to participants in this study, the potential risks identified in association with MYK-224 are justified by the anticipated benefits that may be afforded to participants with oHCM.

The Sponsor will evaluate the benefit/risk profile of the study on an ongoing basis. This evaluation will be based on all available data, with particular attention to 1) AEs or other safety trends in this or any other clinical study of MYK-224 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; 2) new nonclinical data suggesting unreasonable and significant risk of illness or injury.

If such evaluation suggests that the benefit/risk profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
• To assess the safety and tolerability of MYK-224 in participants with symptomatic oHCM (Part A)	• AEs and SAEs (incidence, severity, causality), including cardiovascular events and hospitalizations • Incidence of arrhythmias, including atrial fibrillation/flutter (new from screening and recurrent), ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe) • Incidence of appropriate implantable cardioverter defibrillator therapy and resuscitated cardiac arrest • Results of vital signs, physical exams, 12-lead ECG (including HR), TTE, clinical laboratory tests (including hematology, clinical chemistry, and urinalysis)
Secondary	**Secondary**
• To evaluate the effect of MYK-224 on LVOT gradient in participants with symptomatic oHCM (Part A)	• Relief of obstruction as measured by change in LVOT peak gradient (post-exercise, resting, and Valsalva) from baseline to end of treatment (Part A) • Proportion of participants achieving a resting LVOT peak gradient of < 30 mm Hg and a Valsalva LVOT peak gradient < 50 mm Hg at end of treatment (Part A)
• To assess the PK/PD relationship of MYK-224 (Part A)	• Concentration-response relationship between MYK-224 PK and 1) LVOT peak gradients; and 2) echocardiographic parameters of systolic and diastolic function
• To assess the PK of MYK-224 in participants with symptomatic oHCM (Part A)	• Summary of plasma concentrations

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Exploratory (Part A)	**Exploratory (Part A)**

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	
Exploratory (Part B)	**Exploratory (Part B)**
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

Abbreviations: [redacted] AE, adverse event; [redacted]; ECG, electrocardiogram; EOT, end of treatment; EOT-A, end of treatment for Part A; HCM, hypertrophic cardiomyopathy; [redacted]; HR, heart rate; [redacted]; [redacted]; LVOT, left ventricular outflow tract; [redacted]; oHCM, obstructive hypertrophic cardiomyopathy; OSS, overall summary score; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event; [redacted]; TTE, transthoracic echocardiogram.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2a, open-label, multicenter, proof-of-mechanism study of MYK-224 in participants with symptomatic oHCM. It will be conducted in up to 2 cohorts with approximately [redacted] participants with symptomatic oHCM in each cohort.

Cohort 1 will investigate MYK-224 administered as monotherapy or as an add on to SOC with beta-blockers

Cohort 2 will explore MYK-224 administered as an add on to SOC with nondihydropyradine calcium channel-blockers or SOC with disopyramide (combined with either a beta-blocker or a calcium channel-blocker).

All participants from Cohort 1 and 2 will participate in the main study (Part A). Following the main study period, the [redacted] of MYK-224 will be assessed via an optional OLE (Part B).

PART A:

All participants will participate in 3 study periods in Part A:

- Screening Period for Part A (up to [redacted]
- Treatment Period (variable between approximately 12 and 45 weeks)
  - Dose Titration period
  - Stable Dosing period
  - End of Treatment for Part A (EOT-A)

- Washout Period
  - Washout Visit for Part A (Washout A; [redacted]
  - End of Study Visit for Part A (EOS-A; [redacted]

PART B:

Participants who successfully complete Part A will then be eligible for an optional OLE (Part B). This will last for up to [redacted] and include the following:

- Screening B Period [redacted])
- Treatment Period ([redacted])
  - Day 1B through End of Treatment for Part B (EOT-B)

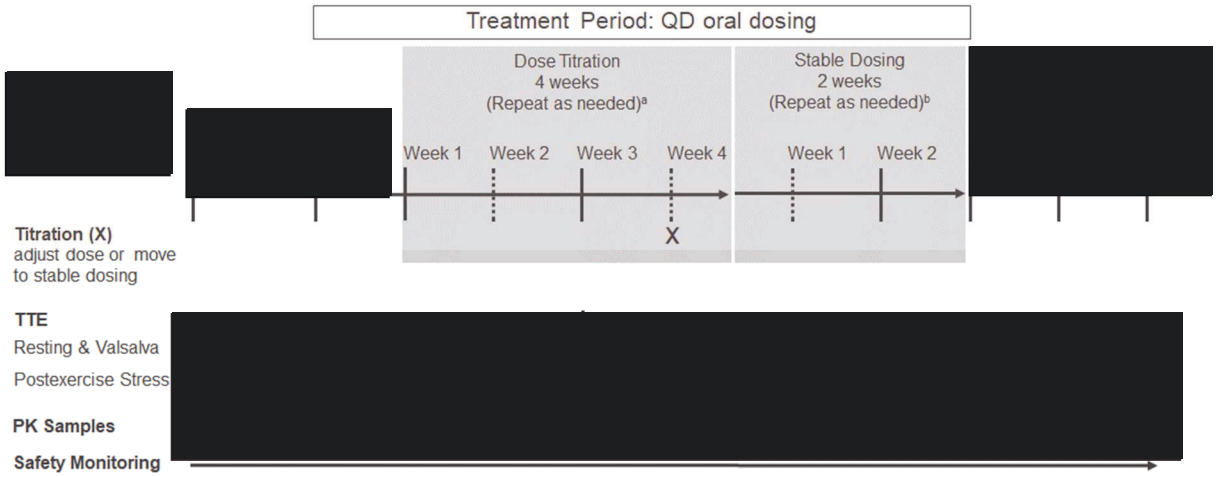
Washout B Period [redacted]

End of Study for Part B (EOS-B) visit following Washout

5.1.1 Part A - All Participants

The following procedures and study visits apply to all participants enrolled in the study. The study design schematic for Part A is presented in Figure 5.1.1-1.

Figure 5.1.1-1: Study Design Schema (Part A)



Grey boxes represent sections that may be repeated as needed prior to progressing to the next phase of the study.

Abbreviations: EOS-A, end of study for Part A; EOT, end of treatment; PK, pharmacokinetics; QD, once daily; TTE, transthoracic echocardiogram.

[a] Dose Titration: Repeat 4-week titration period until target dose is identified or maximum allowable dose is reached.

[b] Stable Dosing: Repeat 2-week dosing until participant has been on target dose/maximum allowable dose for at least 6 weeks AND dosed with MYK-224 at any dose for at least 12 weeks.

[*] TTE from Dose Titration Week 3 will be used to determine titration decision at Week 4.

5.1.1.1 Screening Period (Part A)

A screening visit will be conducted after participants provide signed informed consent. Participants will undergo a variety of general and laboratory assessments to assess eligibility (see Table 2-1). Key screening tests include 12-lead electrocardiograms (ECGs), assessment of New York Heart Association (NYHA) functional classification, and transthoracic echocardiogram (TTE) at rest, with Valsalva Maneuver and post-exercise. Screening test results reported by the echocardiography core laboratory will be used to confirm eligibility. A cardiac monitor will be applied and must be worn for at least 10 days prior to dosing on Day 1.

5.1.1.2 Treatment Period (Part A)

The treatment period is designed to identify the target individual dose for each participant. Dose titration will be based on measures taken at steady state (at least 21 days after dose initiation) and occur approximately every 4 weeks. Once the target individual dose has been identified for each participant, the participant will continue to the Stable Dosing period. The Dose Titration period and Stable Dosing period are described below.

Dose Titration Period

The study will include an intra-patient dose titration scheme designed to achieve safe and effective dosing for each participant by determining a target individual dose guided by their own response parameters. Participants who meet all eligibility criteria at Screening will begin study treatment with MYK-224. Dosing will consist of a once daily (QD) oral dose in the form of tablets. All participants will begin at an initial dose of 5 mg of MYK-224, followed by up- or down-titration to doses between 2.5 mg and 50 mg.

Participants will return to the investigational site for [redacted] clinic visits as outlined in Table 2-2 and Figure 5.1.1-1. These visits will include PK sample collection, [redacted], safety laboratory collection, 12-lead ECGs, clinical evaluations (eg, vital signs, clinical outcome assessments [COAs], concomitant medication use), and echocardiography.

Dose titration will be based on TTE measures taken at 3 weeks (at least 21 days) post-initiation of each new dose. Participants will repeat this 4-week period as needed to identify their individual target dose. Details on dose titration can be found in Section 7.4.1.1.

Stable Dosing Period

Once the individual target dose is identified, participants will continue dosing until 2 criteria are met: 1) 6 weeks (at least 42 days) total dosing at their target dose (including the 4-week titration period, if applicable); and 2) an overall minimum total treatment period of 12 weeks (at least 84 days) at any dose or combination of doses. See Section 7.4.1.2 for details regarding dose modification during stable dosing and the impact of any modification on the criteria for study completion. During this period, participants will have [redacted] clinic visits to collect PK samples, [redacted], 12-lead ECG and TTE measures, and safety assessments (see Table 2-3). The final dose of MYK-224 will be administered in clinic at an end-of-treatment visit.

5.1.1.3 Washout and End of Study (Part A)

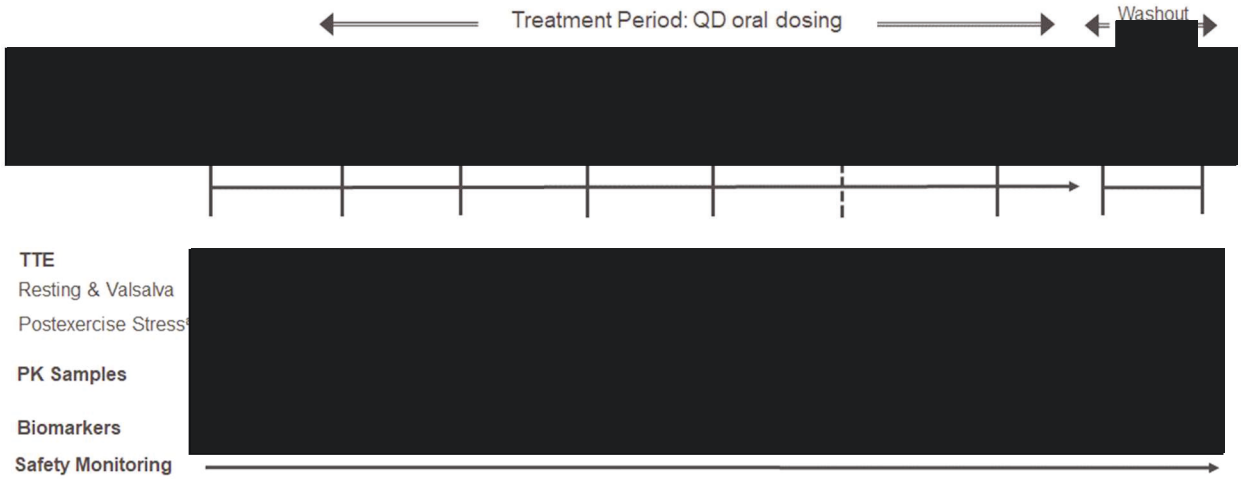
All participants will have a [redacted] washout period following the final dose of MYK-224. Participants will have a clinic visit at the second week (at least [redacted] after the last dose of MYK-224) of washout and an EOS-A clinic visit after the washout period is complete (at least [redacted] after the final dose of MYK-224). Refer to Table 2-4 for a list of assessments performed at these clinic visits.

An example dose titration schematic is presented in [redacted]

5.1.2 Part B - Optional Open-label Extension

The following procedures and study visits are optional for participants who successfully complete Part A. The study design schematic for Part B is presented in Figure 5.1.2-1.

Figure 5.1.2-1: Study Design Schema (Part B)



Abbreviations: [redacted]; PK, pharmacokinetics; QD, once daily; TTE, transthoracic echocardiogram.

Note: Phone visits will be conducted every [redacted] beginning at [redacted] Clinic visits will be conducted every [redacted] beginning at [redacted] All visits have a [redacted] day window. See Table 2-3.

a [redacted].

b Biomarker samples will be collected at Screening B (if applicable), Day [redacted]

c Screening visit as needed. See Section 5.1.2.1.

5.1.2.1 Screening Period (Part B)

Screening for Part B will be conducted at EOS-A **or** a separate Screening Visit as follows:

1) **EOS-A Visit as Screening Visit for Part B:** The assessments taken at the EOS-A visit maybe used in place of the Screening visit for Part B as long as the informed consent for Part B is signed and the Day 1B visit occurs within [redacted] of EOS-A.

2) **Separate Screening Visit for Part B:** Participants for whom the Day 1B visit will occur more than [redacted] past EOS-A will require a separate screening visit for Part B. The screening visit will be conducted after participants provide signed informed consent for Part B. Participants will undergo a variety of general and laboratory assessments to assess eligibility (see Table 2-5). Screening tests include, but are not limited to, 12-lead ECGs, assessment of [redacted], and TTE at rest, with Valsalva Maneuver, and post-exercise.

5.1.2.2 Treatment Period (Part B)

All participants will receive MYK-224. Dosing will consist of a QD oral dose in the form of tablets. Treatment will begin on Day 1B with each participant receiving either the dose at which they completed Part A or a dose of 5 mg if there have been certain modifications in a participant's background HCM therapy following completion of Part A (see Section 7.4.2 and Table 7.4.2-1 for details).

- Every effort should be made to continue all participants on the background therapy on which they completed the first part of the study.
- Participants that have had no change in background HCM therapy or those that have had a discontinuation of background therapy, or a decrease in the dose of background therapy, will start at the MYK-224 dose on which they completed Part A.
- Participants that completed Part A at a dose of 5 mg MYK-224 or higher and have begun a new permitted background HCM therapy (see Section 6.2 criteria 3) f) and 3) g)) or have had a dose increase in background HCM therapy may either:
  - Resume their prior HCM therapy with at least a [redacted] washout period prior to the screening visit for Part B (preferred) **or**
  - Continue current background HCM therapy (no dose adjustments within [redacted] of screening) and start Part B on a 5-mg dose of MYK-224.
- Participants who completed Part A at a dose of 2.5 mg of MYK-224 and have a subsequent dose increase in HCM therapy or new permitted HCM therapy must either resume prior background HCM therapy or discontinue new therapy prior to starting Part B at a 2.5-mg dose.
- Participants who have begun a background HCM therapy that is not permitted in Part B (see Section 6 [Study Population]) will need to discontinue these therapies for at least [redacted] prior to the Part B Screening visit to participate in the OLE part of the study.

Dose modification of MYK-224 is permitted (see Section 7.4.2 for details) and will be guided by site-read TTEs. Study investigators will not be blinded to the TTE results from these visits. Echocardiograms will also be sent to a core laboratory for future data analysis. Participants will continue QD dosing of MYK-224 at home, with the exception of clinic visit days, where the daily dose will be given at the clinic in order to collect predose samples. Where possible, participants should remain on the background HCM therapy on which they initiated the OLE part of the study (Part B). After [redacted] background therapy may be decreased or discontinued in consultation and agreement with the Medical Monitor.

Participants will return to the investigational site at [redacted] until EOT-B, as outlined in Table 2-5 and Table 2-6.These clinic visits will include PK sample collection, [redacted], safety laboratory collection, 12-lead ECGs, clinical evaluations (eg, vital signs, COAs, concomitant medication use), and echocardiography.

Telephone visits will be conducted starting at [redacted] thereafter ([redacted]) to assess for AEs, concomitant medication use, and results of any monthly at-home pregnancy tests that may occur outside of scheduled clinic visits, as outlined in Table 2-5.

The final dose of MYK-224 will be administered in the clinic at the EOT-B visit ([redacted]).

5.1.2.3 Washout and End of Study (Part B)

All participants will have a [redacted] washout period following the final dose of MYK-224. Participants will have an EOS-B clinic visit after the washout period is complete (at least [redacted] after the final dose of MYK-224). See Table 2-3 for a list of assessments performed at these clinic visits.

Participants who discontinue MYK-224 dosing prior to EOT-B (see Section 8.1) will be asked to complete the washout and end-of-study assessments, if possible. Participants who discontinue from the study (eg, withdraw consent; see Section 8.2) will be asked to complete an Early Termination (ET-B) visit.

5.1.3 Data Monitoring Committee and Other Committees

5.1.3.1 Data Monitoring Committee

A Data Monitoring Committee will not be used in the study.

5.1.3.2 Executive Committee

The Executive Committee will plan an active role in providing scientific guidance and advice to the sponsor related to the design, conduct, results analysis, and publication strategy for this study. The committee will be composed of a subset of study investigators who are experts in cardiovascular disease, including HCM, with relevant clinical and methodological expertise. Meeting frequency, membership, and specific responsibilities will be further described in the Executive Committee charter.

5.2 Number of Participants

The total number of participants enrolled in this study is approximately [redacted]. The sample size is based on practical considerations and previous experience with similar studies (see details in Section 10 Statistical Considerations). Participants who withdraw from the study or are discontinued for non-safety reasons may be replaced at the discretion of the Sponsor and PI.

Approximately [redacted] participants with symptomatic oHCM will be enrolled into each cohort. Each cohort has two subgroups:

- Cohort 1: MYK-224 monotherapy or MYK-224 with SOC using beta-blockers

- Cohort 2: MYK-224 with SOC using nondihydropyridine calcium channel-blockers or MYK-224 with SOC using disopyramide (combined with either a beta-blocker or a calcium channel-blocker)

The minimum size for each subgroup is [redacted]. The remaining [redacted] participants in each cohort can be enrolled into either subgroup within that cohort.

5.3 End of Study Definition

The start of the trial is defined as the first participant first visit.

End of trial is defined as the last participant last visit or scheduled procedure as shown as in the Schedule of Activities.

Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

A participant is considered to have completed the study if he/she has completed the last procedure shown in the Schedule of Activities. Participants who complete all visits for Part A but do not participate in Part B will still be considered to have completed the study.

5.4 Scientific Rationale for Study Design

This study will be conducted in adult participants with symptomatic oHCM. The study will be open-label, and all participants will receive MYK-224. The purpose of this study is to characterize the safety, tolerability, efficacy, and exposure-response relationship of MYK-224 in participants with oHCM. The optional OLE will additionally [redacted] of MYK-224.

Because individual patients may require higher or lower exposures to MYK-224 to achieve clinically relevant improvement in LVOT obstruction, Part A of this study will follow an individualized dose-titration strategy that is guided by clinical response. The study will use intra-participant dose titration to identify the individual target dose and assess the pharmacological effects of that dose at steady state. The initial dose selection and titration levels are based on pre-clinical data as well as data from the FIH trial in healthy volunteers (MYK-224-001). [redacted] See Section 5.5 for details on dose justification in this study.

Dose titration in this study (Part A) will be based on [redacted]. Specifically, [redacted] (Section 2). The core laboratory TTE data collected 3 weeks (at least 21 days) following the initiation of each dose will be used to determine dose titration, which if indicated, will occur the following week (4 weeks post-initiation).

In each participant, dose escalation will proceed [redacted] until both [redacted]. Dose reductions may occur [redacted] The individual target dose for this study is defined as the highest dose where these conditions are met (see Section 7.4).

Participants will enter the stable dosing period and continue to dose at their individual target dose for a minimum of 6 weeks (at least 42 days) of treatment with their target dose (or the maximum allowable dose), for a total treatment period of at least 12 weeks (at least 84 days). Transthoracic echocardiogram, PK samples, and safety labs will be collected [redacted] during the stable dosing period. This will provide sufficient time to evaluate the safety and efficacy of MYK-224 [redacted] for the highest tolerated dose in each participant. [redacted].

The objective of the study is to evaluate the safety, tolerability, and efficacy of MYK-224 alone and in combination with SOC therapies for HCM. The cohorts are staggered so that data from ongoing studies may be evaluated prior to imitating Cohort 2 to allow for modification of the starting dose or dose titration schedule if necessary. Cohort 2 includes participants with SOC consisting of either a nondihydropyramide calcium channel-blocker (verapamil or diltiazem) or disopyramide in combination with a beta-blocker or nondihydropyramide calcium channel-blocker. Both verapamil and diltiazem are moderate inhibitors of CYP3A4.

The initiation of Cohort 2 will be at the discretion of the Sponsor and will be informed by data obtained from Cohort 1, as well as from 2 on-going studies: 1) CV029005, a DDI study evaluating the effect of co-administration of MYK-224 and moderate (verapamil) and strong (itraconazole) [redacted] in healthy participants; 2) MYK-461-017 (VALOR-HCM), a clinical study evaluating mavacamten (a similar cardiac myosin inhibitor) in participants with oHCM who are eligible for septal reduction therapy, which includes the [redacted]. Cohort 2 will only be initiated once 50% of Cohort 1 participants have reached their target dose and the data from the CV029005 and VALOR-HCM study are available. The same dosing regimen as Cohort 1 will be use for Cohort 2 unless data from Cohort 1 and the indicated studies supports a change to this schedule.

Participants who successfully complete Part A will have the option to continue the study drug as a participant in Part B, a 2-year OLE study. In Part B, participants will start at the dose of MYK-224 on which they completed Part A with the exception of those who have had a change in background HCM therapy. In instances where participants have had adjustments in background HCM therapy following their completion of Part A, they may either resume the background therapy upon which they completed Part A at least [redacted] prior to screening for Part B or start Part B at a 5-mg dose (see Section 7.4). After the initial [redacted] of Part B, clinic visits will occur every [redacted] and will include clinical evaluation of symptoms, AE/SAE assessment, ECGs, TTEs, PK sampling, [redacted], and laboratory assessments. Dose modifications during Part B will be guided by local site-read TTEs (See Section 7.4.2 for details).

Part B is designed to generate long-term data in participants with oHCM, using an approach that conforms to established ethical standards of safe human experimentation and the requirements of Good Clinical Practice (GCP).

5.5 Justification for Dose

The current study design in Part A allows for a measured and stepwise exploration of doses, with the maximum dose for each participant limited by a normalization of cardiac contractility or resolution of clinical parameters of LVOT obstruction.

In a previous study with a similar compound (mavacamten), the exposure-response relationship for LVEF varied between healthy volunteers (HV) and HCM patients, with a higher baseline LVEF and a steeper slope for HCM patients. These observations are likely a manifestation of the underlying pathobiology of sarcomeric hypercontractility that is a hallmark of the disease. We anticipate a similar phenomenon with MYK-224 and have thus chosen a starting dose and an echocardiography-based dose titration scheme that will allow for safe and stepwise dose modification guided by each participant's response parameters. [redacted]. Additionally, given that HCM patients may exhibit relief of LVOT obstruction at lower exposures than at which effects on LVEF are observed, participants that demonstrate a clinical response at [redacted]

The starting dose of MYK-224 in the current study will be 5 mg, which has been shown to be safe and well-tolerated in the FIH study in normal healthy participants. [redacted]

[redacted]

Participants will resume dosing in Part B at the dose they had completed Part A. This serves as a reasonable starting point for further dosing since this is a dose that was selected according to each participant's echocardiographic response to the study drug and was a dose that was tolerated to study completion. In cases where background therapy was modified between study parts, participants will either resume previous therapy prior to screening and start at the dose they completed in Part A or start at a 5-mg dose (see Section 7.4 for details on starting dose for Part B). This will allow a safe starting point for subsequent dose titration to identify a new dose in the context of altered background therapy.

[redacted] (see Section 7.4 [Dose Modification]). The dose of MYK-224 may be decreased at any time during the study based on

the clinical judgement of the investigator in discussion with the Medical Monitor. [redacted] (see Section 8.1).

6 STUDY POPULATION

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

6.1 Inclusion Criteria

This study will include both male and female participants, including women of childbearing potential (WOCBP). Participants are eligible to be included in the study only if all of the following criteria apply:

PART A:

1) Signed Written Informed Consent

Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

2) Type of Participant and Target Disease Characteristics

a) Has adequate acoustic windows, to enable accurate TTEs as determined by the echocardiography core laboratory

b) Men or women diagnosed with oHCM consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines, satisfying both of the following criteria:

i) Has unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac (eg, hypertension, aortic stenosis) or systemic disease and with maximal LV wall thickness ≥ 15 mm (or ≥ 13 mm with positive family history of hypertrophic cardiomyopathy or with a known disease-causing mutation), as determined by core laboratory interpretation

AND

ii) Has a LVOT peak gradient during screening as assessed by echocardiography of ≥ 50 mm Hg at rest, or ≥ 30 mm Hg at rest and ≥ 50 mm Hg with Valsalva maneuver (confirmed by echocardiography core laboratory interpretation)

c) Has resting LVEF [redacted] at the Screening visit as determined by echocardiography core laboratory

d) Has a valid measurement of LVOT post-exercise peak gradient at screening as determined by echocardiography core laboratory

e) NYHA functional class II or III symptoms at screening

f) A body weight of at least 45 kg and a body mass index (BMI) 18 to 37 kg/m^2, inclusive, at the Screening visit, calculated using the institution's standard formula.

g) All safety laboratory parameters (chemistry, hematology, and urinalysis) within normal limits (laboratory reference range) at the Screening visit as assessed by the central laboratory, or if outside the limits must meet both of the following criteria:

i) Considered by the investigator to be clinically insignificant

ii) Alanine transaminase (ALT) or aspartate aminotransferase (AST) result must be < 1.5 x the upper limit of normal (ULN) of the laboratory reference range

iii) The body size-adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2, in the absence of dialysis

h) Must be able to complete the KCCQ-23 per established guidelines

3) Age of Participant

Participant must be 18 to 80 years of age inclusive, or the local age of majority provided it is over 18 years of age, at the time of signing the informed consent.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

i) Female participants must have documented proof that they are not of childbearing potential.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

iii) WOCBP must have a negative highly sensitive urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

iv) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

- WOCBP are not permitted to use hormonal contraception methods alone as a highly effective method (as described in Appendix 4).

v) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency (User Independent), as described in Appendix 4 during the intervention period and for at least 30 days after EOT and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period. The following methods are permitted (see Appendix 4):

(a) Intrauterine device (IUD) (eg, copper IUD)

(b) Intrauterine hormone-releasing system, in combination with a barrier method of birth control

(c) Bilateral tubal occlusion

(d) Vasectomized partner

(e) Sexual abstinence

b) Male Participants:

i) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

ii) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period and for at least 30 days after the last dose of study intervention.

iii) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 30 days after the last dose of study intervention in the male participant.

iv) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participants have undergone a successful vasectomy, during the intervention period and for at least 30 days after the last dose of study intervention.

v) Male participants must refrain from donating sperm during the intervention period and for at least 30 days after the last dose of study intervention.

vi) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

PART B:

Participants that have successfully completed Part A of the study may enroll in Part B, an optional, 2-year open-label extension study. Eligibility for Part B will be assessed following completion of informed consent. Participants that have completed Part A EOS assessments within the Part B 28-day screening window may use those assessments for eligibility determination. Where possible,

participants should enroll in Part B of the study on the same background therapy on which they completed Part A.

5) Signed Written Informed Consent

A separate informed consent will be collected for participation in Part B. Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

6) Type of Participant and Target Disease Characteristics

a) Must have successfully completed Part A through the EOS-A visit within 90 days of signing consent for Part B (participants who are beyond the 90-day window from the EOS-A visit may be included in this study pending Medical Monitor approval) and the investigator considers it to be in the participant's best interest to continue in the study.

b) Has adequate acoustic windows, to enable accurate TTEs as determined by the echocardiography core laboratory

c) Has documented resting LVEF [redacted] at the Screening visit as determined by local echocardiography

d) A body weight of at least 45 kg and a BMI 18 to 37 kg/m^2, inclusive, at the Screening visit, calculated using the institution's standard formula.

e) All safety laboratory parameters (chemistry, hematology, and urinalysis) within normal limits (laboratory reference range) at the Screening visit as assessed by the central laboratory, or if outside the limits must meet both of the following criteria:

vii) Considered by the investigator to be clinically insignificant

viii) ALT or AST result must be < 1.5 x the ULN of the laboratory reference range

ix) The body size-adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2, in the absence of dialysis

f) Must be able to complete the KCCQ-23 per established guidelines

7) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.
- Guidelines for both Female and Male participants outlined above in Part A (Section 6.1, criterion 4) should be followed in Part B.

6.2 Exclusion Criteria

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

PART A:

1) Medical Conditions

a) Presence of any medical condition that precludes exercise stress testing

b) History of syncope or sustained ventricular tachyarrhythmia within 6 months prior to Screening

c) Active infection

d) Known infiltrative or storage disorder causing cardiac hypertrophy that mimics HCM, such as Fabry disease, amyloidosis, or Noonan syndrome with left ventricular hypertrophy

e) Has been successfully treated with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation [ASA]) within 6 months prior to Screening or plans to have either of these treatments during the study (Note: Individuals with an unsuccessful myectomy or percutaneous ASA procedure performed > 6 months prior to Screening may be enrolled if study eligibility criteria for LVOT gradient criteria are met).

f) Implantable cardioverter-defibrillator (ICD) placement or pulse generator change within 2 months prior to screening or planned new ICD placement during the study (pulse generator changes, if needed during the study are allowed)

g) Has a history of resuscitated sudden cardiac arrest (any time) or known history of appropriate implantable cardioverter-defibrillator (ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to screening

h) Has paroxysmal atrial fibrillation with atrial fibrillation present per the Investigator's evaluation of the subject's ECG at the time of Screening

i) Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening and/or 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. Please see restricted therapies in Appendix 5).

j) Has QT interval with Fridericia correction (QTcF) > 500 msec when QRS interval < 120 msec or QTcF > 520 msec when QRS ≥ 120 msec if participant has left bundle branch block or any other 12-lead ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II)

k) Has known moderate or severe (per investigator's judgment) aortic valve stenosis at screening

l) History of LV systolic dysfunction (LVEF < 45%) at any time during their clinical course

m) Clinically significant pulmonary disease associated with exertional dyspnea

n) Has known significant unrevascularized obstructive coronary artery disease (> 70% stenosis in one or more main epicardial coronary arteries) or history of myocardial infarction

Note: participants with prior coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCIs) are allowed if the procedure was performed at least 12 weeks prior to Screening.

o) Positive serologic test at screening for infection with human immunodeficiency virus (HIV); hepatitis C virus (HCV); or hepatitis B virus (HBV), with the exception of hepatitis B s-antibody positive, which is a marker of immunity.

p) Known active infection with COVID-19 (polymerase chain reaction [PCR]+). If subject had a PCR+ test at screening, they must be symptom free for 14 days and have a negative antibody test prior to dosing.

q) **Not Applicable per Protocol Amendment 01:** History of malignancy of any type, with the following exceptions: in situ cervical cancer more than 5 years prior to Screening or surgically excised non-melanomatous skin cancers more than 2 years prior to Screening

r) Has a history or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion

s) Moderate to severe regurgitant or obstructive valvular heart disease in need of repair or other intracardiac procedure (or that may require it during study participation) or that may undermine the interpretation of clinical study data

t) Acute heart failure from 4 weeks prior to Screening up to study Day 1A

u) Heart transplant recipient or listed for heart transplant

v) Currently implanted with LV assist device

w) Any active or suspected malignancy or history of malignancy within 10 years of screening, except appropriately treated basal cell and non-metastatic squamous cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or low risk prostate cancer (participants with pretreatment prostate-specific antigen of < 10 ng/mL, and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)

2) Reproductive Status

a) Women who are pregnant or breastfeeding

3) Prior/Concomitant Therapy

a) Prior treatment with mavacamten or aficamten. An exception may be made in cases where myosin inhibitor use was not within 4 months of the Screening visit, and with the agreement of both the Investigator and the Medical Monitor.

b) Prior treatment with cardiotoxic agents such as anthracyclines (eg, doxorubicin) or similar

c) [redacted]

d)

e) Prior therapy with MYK-224. An exception is made for participants that have not received a dose of MYK-224 within 30 days of the Screening visit and with the agreement of both the investigator and the Medical Monitor.

f) **Cohort 1:**

i) The following are excluded:

(1) For individuals on beta-blockers, any dose adjustment of that medication < 14 days prior to screening or an anticipated change in regimen during the study

(2) Current (within 14 days prior to screening) or planned treatment during the study with nondihydropyridine calcium channel-blockers, disopyramide, cibenzoline, or ranolazine. Participants on any of these medications who, in the opinion of the investigator, can be safely withdrawn are eligible as long as medication is discontinued at least 14 days prior to the Screening visit.

g) **Cohort 2:**

i) The following are excluded:

(1) For individuals on verapamil, diltiazem, or disopyramide any dose adjustment of that medication < 14 days prior to screening or an anticipated change in regimen during the study

(2) Current treatment (within 14 days prior to screening) or planned treatment during the study with a combination of beta-blockers and verapamil, or a combination of beta-blockers and diltiazem or beta-blockers alone

(3) Current treatment (within 14 days prior to screening) or planned treatment during the study with cibenzoline or ranolazine

4) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population

5) Allergies and Adverse Drug Reaction

a) Hypersensitivity to MYK-224 or any of the components of the MYK-224 formulation, [redacted]

b) History of significant adhesive allergy that would preclude the use of the cardiac monitor and patch

c) History of any significant allergy (such as anaphylaxis or hepatotoxicity) to any food, drug, or other substance

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated.

b) Unable to comply with the study restrictions/requirements, including the number of required visits to the clinic site

c) Planned invasive procedure during the study period

d) Current or recent (within 3 months of study intervention administration) gastrointestinal disease that could impact upon the absorption of study intervention

e) Any major surgery within 4 weeks of study intervention administration

f) Any gastrointestinal surgery that could impact upon the absorption of study intervention

g) Donation of blood to a blood bank or in a clinical study (except at screening visit) within 4 weeks of study intervention administration (within 2 weeks for plasma only). Blood draws for routine medical purposes are acceptable.

h) Blood transfusion within 4 weeks of study intervention administration

i) Inability to tolerate oral medication

j) Inability to be venipunctured and/or tolerate venous access
k) 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 at least 5 times the respective elimination half-life (whichever is longer)
l) Recent (within 6 months of study intervention administration) drug or alcohol abuse as defined in DSM 5, Diagnostic Criteria for Drug and Alcohol Abuse
m) Is employed by, or is a relative of, someone employed by the Sponsor or the investigator
n) Any other sound medical, psychiatric, and/or social reason as determined by the investigator

PART B:

7) Medical Conditions

a) Presence of any medical condition that precludes exercise stress testing
b) Interval history of syncope or sustained ventricular tachyarrhythmia between the Part A EOS visit and the Part B Screening visit for participants that have a separate Screening visit for Part B
c) Active infection
d) Has been treated with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation [ASA]) following enrollment in Part A
e) Has an interval history of resuscitated sudden cardiac arrest or of appropriate implantable cardioverter-defibrillator (ICD) discharge for life-threatening ventricular arrhythmia between Part A EOS visit and Screening for Part B
f) Has paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the Investigator's evaluation of the subject's ECG at the time of Screening for Part B
g) Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening for Part B and/or not adequately rate controlled (Note: Participants with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed. Please see restricted therapies in Appendix 5).
h) Heart transplant or listed for heart transplant following enrollment in Part A
i) Currently implanted LV assist device
j) Clinically significant pulmonary disease associated with exertional dyspnea
k) Has known significant unrevascularized obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction since enrollment in Part A

   Note: participants with prior coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCIs) are allowed if the procedure was performed at least 12 weeks prior to Screening
l) Has QT interval with Fridericia correction (QTcF) > 500 msec when QRS interval < 120 msec or QTcF > 520 msec when QRS ≥ 120 msec or any other 12-lead ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II) at Screening for Part B

m) Has known moderate or severe (per investigator's judgment) aortic valve stenosis at Screening for Part B

n) Positive serologic test at the Part B screening visit for infection with human immunodeficiency virus (HIV); hepatitis C virus (HCV); or hepatitis B virus (HBV), with the exception of hepatitis B s-antibody positive, which is a marker of immunity

o) Known active infection with COVID-19 (polymerase chain reaction [PCR]+). If subject had a PCR+ test, they must be symptom free for 14 days prior to dosing

p) Interval development of significant malignant disease since enrollment in Part A, except appropriately treated basal cell and non-metastatic squamous cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or low risk prostate cancer (participants with pretreatment prostate-specific antigen of < 10 ng/mL, and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)

q) Has a history or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion

8) Reproductive Status

a) Women who are pregnant or breastfeeding

9) Prior/Concomitant Therapy

a) Interval treatment with mavacamten or aficamten between Part A EOS Visit and Screening for Part B

b) Prior treatment with cardiotoxic agents such as anthracyclines (eg, doxorubicin) or similar

c) [redacted]

d) [redacted]

[redacted]

10) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population

11) Allergies and Adverse Drug Reaction

a) Hypersensitivity to MYK-224 or any of the components of the MYK-224 formulation, [redacted]

b) Development any significant allergy (such as anaphylaxis or hepatotoxicity) to any food, drug, or other substance since participation in Part A

12) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated.

b) Unable to comply with the study restrictions/requirements, including the number of required visits to the clinic site

c) Planned invasive procedure during the study period

d) Current or recent (within 3 months of study intervention administration) gastrointestinal disease that could impact upon the absorption of study intervention

e) Any major surgery within 4 weeks of study intervention administration

f) Any gastrointestinal surgery that could impact upon the absorption of study intervention

g) Blood transfusion within 4 weeks of study intervention administration

h) Inability to tolerate oral medication

i) Inability to be venipunctured and/or tolerate venous access

j) Participated in a clinical trial where the participant received any investigational drug, other than MYK-224, (or is currently using an investigational device) within 30 days prior to Screening for Part B, or at least 5 times the respective elimination half-life (whichever is longer).

k) Recent (within 6 months of study intervention administration) drug or alcohol abuse as defined in DSM 5, Diagnostic Criteria for Drug and Alcohol Abuse

l) Is employed by, or is a relative of, someone employed by the Sponsor or the investigator

m) Any other sound medical, psychiatric, and/or social reason as determined by the investigator

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

- Starting 72 hours prior to the first dose until the EOS-A visit (or EOS-B visit, if applicable), participants should not engage in intensive exercise except during protocol-specified exercise tests.
- Starting at Screening for both Part A and Part B, participants will be required to abstain from blood or plasma donation until 3 months after the final study visit.

- [redacted]
- Daily dosing of MYK-224 should occur at approximately the same time every day.

6.4 Screen Failures (Part A and Part B)

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population.

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 (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-in Period (for all participants in Part A and as needed in Part B)

Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (eg, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

Participants who screen fail may be considered for rescreening based on the investigator's discretion, taking into consideration the reason(s) for screen fail. One attempt at rescreening will be allowed, and all procedures must be repeated. Further repeat assessments after rescreening may be conducted only after discussion with the Medical Monitor.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value). Additionally, repeat assessments are allowed if core labs require a repeat submission due to quality and to better assess inclusion/exclusion values.

The most current result prior to the first day of treatment in either Part A or Part B is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments at Screening may be repeated one time in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s) or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as Non-IMPs/AxMPs.

7.1 Study Interventions Administered

The initial dose and timing of dose titration for each participant is described in Section 5.1.

MYK-224 will be taken in a single oral daily dose, either administered at the investigation site or at home by the participant. Participants will take study drug as directed by the investigator/designee. Participants should be instructed to take the study drug at approximately the same time every day with approximately 8 ounces (240 mL) of water. If a participant forgets to take their daily dose at the usual time, they should take it as soon as they remember. Participants should never take more than 1 dose of study drug within an 8-hour period.

On study visit days, participants should fast for at least 4 hours prior to arrival at the clinical site and study drug dosing should be delayed until after study assessments are complete.

Table 7.1-1: Study Interventions

Cohort Name	Cohort 1 and Cohort 2
Intervention Name	MYK-224
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	[redacted] mg
Dosage Level(s)	Once daily oral dose between 2.5 and 50 mg
Route of Administration	Oral
Use	Experimental
IMP and Non-IMP/AxMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	MYK-224 BMS-986435

Abbreviations: AxMP, Auxiliary Medicinal Products; IMP, Investigational Medicinal Product.

7.2 Method of Study Intervention Assignment

Enrolled participants, including those not dosed, will be assigned sequential screening numbers starting with [redacted], (eg, [redacted]). Those enrolled participants meeting all inclusion and no exclusion criteria will be eligible to be dosed.

In the case of participant rescreening (see Section 6.4.1), the participant will be screened utilizing the screening transaction and will be assigned the next sequential number not associated to the previous screening number (eg, participant was screened under [redacted], another participant screening number assigned was [redacted], patient [redacted] is screened again under screening number [redacted]). All participant numbers from Part A will be maintained in Part B, even if a screening visit for Part B is performed.

Participant replacement is allowed under certain conditions as outlined in Section 8.2. Replacement participants will be screened and assigned the next sequential screening number.

7.3 Blinding

Not applicable as this is an open-label study; all participants will receive active study intervention; however, all dose adjustments will occur through interactive response technology (IRT) based on TTE data. The bioanalytical laboratory will receive treatment assignments in order to minimize unnecessary analysis of samples.

7.4 Dosage Modification

7.4.1 Part A Dosage Modification

The following dose modification instructions apply to all participants in Part A.

7.4.1.1 Dose Titration (Part A only)

All participants will receive a starting dose of 5-mg oral MYK-224. Dose titration will be based on the central read of each participant's TTE parameters collected 3 weeks (at least 21 days) after dose initiation during each dose titration cycle. [redacted], as outlined in [redacted]
Participants in Cohort 2 will follow the same titration scheme unless data from Cohort 1 or the ongoing CV029005 DDI study support an adjusted schedule.

In each participant, [redacted]

[redacted]

Once the target dose is reached, participants will proceed to the stable dosing period.

Left ventricular ejection fraction parameters for dose reductions as well as temporary and permanent dose discontinuation are also outlined in [redacted]. Both central and local TTE reads taken at any time may be used to guide these decisions as described in Section 8.1.1.1 and Section 8.1.2.1. In addition, a dose reduction to the last tolerated dose or dose interruption or discontinuation for safety may occur at any time during the dose titration period based on the clinical judgment of the investigator in consultation with the Medical Monitor. Following a dose reduction, participants will proceed to the stable dosing period and continue on the new dose for a minimum of 6 weeks.

[redacted]

[redacted]

7.4.1.2 Stable Dosing (Part A only)

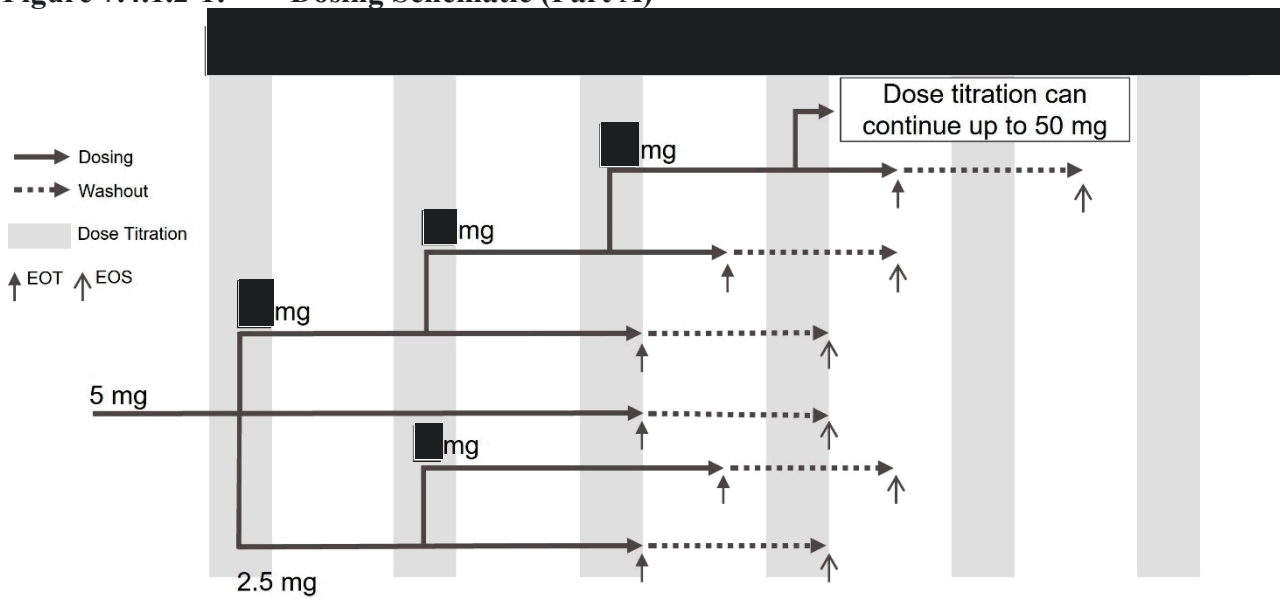
Participants should continue at stable dosing until the following criteria are met: 1) they have been at their target dose for at least 6 weeks (at least 42 days) AND 2) have received MYK-224 (at any dose or combination of doses) for a total of at least 12 weeks (at least 84 days).

During stable dosing, dose modification may still occur in the form of dose reduction to the last tolerated dose, dose interruption, or discontinuation as needed [redacted] This dose change would not affect the total time participants would need to stay on MYK-224 prior to EOT.

[redacted]

An example of a dosing schematic is shown below in Figure 7.4.1.2-1. Only planned down titrations are illustrated. Unplanned down titrations may occur at all dose levels as outlined above.

Figure 7.4.1.2-1: Dosing Schematic (Part A)



Abbreviations: EOS, end of study; EOT, end of treatment; Wk, week.

7.4.2 Part B Dosage Modification

The following dose modification guidelines apply only to participants in the optional OLE. Participants will return to the clinical site for monitoring as outlined in Table 2-5 and Table 2-6. TTE will be performed at each visit, and the results (local read) may be used to determine dose modification, as outlined below.

Initial Dosing (Day 1B)

Initial dosing for Part B will not exceed the dose at which each participant completed Part A (EOT-A dose) providing there was no change in background HCM therapy from Part A. If there have been modifications in a participant's background HCM therapy following completion of Part A, the initial dose will be 5 mg or less as outlined in [redacted] A lower initial dose may be selected at the discretion of the Investigator.

[redacted]

The dose of MYK-224 may be reduced or discontinued at any time during the study based on the clinical judgement of the investigator in discussion with the Medical Monitor. After [redacted] background therapy may be decreased or discontinued in consultation and agreement with the Medical Monitor.

Participants who have had a dose adjustment (either in MYK-224 or background HCM therapy) should return to the clinic approximately [redacted] days) for an unscheduled visit with AE and safety laboratory assessments, ECG, and resting TTE to confirm safety. Repeat of post-exercise echocardiographic assessment of LVOT gradient will be at the investigator's discretion. Based on results and clinical symptoms at follow-up visits, subsequent dose adjustments will be discussed with the Medical Monitor.

7.4.2.1 Dose Increase (Part B only)

Dose increases beyond the starting dose will be permitted at the investigator's discretion following a discussion with the Medical Monitor. At any visit subsequent to the initiation of Part B, [redacted]

[redacted]

Dose increases will be in 5-mg increments up to a maximum of 50 mg QD. [redacted]

7.4.2.2 Dose Reduction (Part B only)

[redacted]

7.5 Preparation/Handling/Storage/Accountability

The IP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/AxMP is only dispensed to study participants. The IP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

Study intervention not supplied by BMS will be stored in accordance with the package insert.

IP/AxMP documentation (whether supplied by BMS or not) must be maintained and must include all processes required to ensure the drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (eg, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

7.6 Treatment Compliance

- On clinic visit days, participants should wait to take study drug until after they reach the clinic and have a predose PK sample taken as indicated in the schedule of study procedures.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
- Compliance with study drug will be monitored by tablet count at all study visits. Participants should bring the study drug with them to all clinic visits. Refer to the Pharmacy Manual for details.
- When dose titration occurs, the new dose will be delivered directly to participants or be dispensed at the study site. Any remaining study drug from the previous dose will be collected and returned to the clinic site. A count of all returned study drug will be conducted by the site and recorded.
- Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.
- A record of the quantity of MYK-224 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

7.7 Concomitant Therapy

Concomitant therapy will be collected at all study visits from screening until the end of the study. Document all concomitant therapies on the appropriate eCRF, whether prescription or over-the-counter, vitamin and/or mineral supplements, herbs, and medications taken for an event or procedure (eg, biopsy). Include start/stop dates, dose, route, and indication.

The investigator should contact and confirm agreement with the Medical Monitor prior to the administration of any concomitant medications.

Medications taken within [redacted] prior to study intervention administration must be recorded on the CRF.

7.7.1 Prohibited and/or Restricted Treatments

- Treatments that are prohibited and/or restricted during the study are described below.
- Exposure to any investigational drug or placebo within 30 days of the Screening visit, or at least 5 times the respective elimination half-life (whichever is longer).
- Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar is prohibited.
- Background HCM therapy:
  - Use of cibenzoline or ranolazine are prohibited from 14 days before Screening to the final EOS visit
  - Cohort 1: Background HCM therapy using nondihydropyridine calcium channel-blockers and/or disopyramide is prohibited from 14 days before screening to the final EOS visit (see Section 6.2, exclusion criterion 3) f).
  - Cohort 2: Background HCM therapy using a combination of beta-blockers and verapamil, or a combination of beta-blockers and diltiazem, or beta-blockers alone is prohibited from 14 days before screening to the final EOS visit (see Section 6.2, exclusion criterion 3) g)).
  - Part A: Participants should be on optimal, tolerated HCM therapy as determined by the investigator and informed by HCM treatment guidelines[3] and as required for eligibility within the cohort in which they are enrolled. The treatment should be well-tolerated and the dosing stable for at least 2 weeks prior to screening and maintained through the EOS visit. Investigators are encouraged not to change the dosing of background HCM therapies while on study. However, investigators should nevertheless manage participants in accordance with their best clinical judgment.
  - Part B: Where possible, every effort should be made to have participants begin Part B on the same background HCM therapy on which they completed Part A. If adjustments are made to background therapy between Parts A and B the starting dose of the study medication in Part B may need to be adjusted as outlined in Section 7.4.2. After [redacted] of Part B, background therapy may be decreased or discontinued in consultation and agreement with the Medical Monitor.
- [redacted]
- [redacted]

7.7.2 Other Restrictions and Precautions

Participants are prohibited from joining another clinical trial while they are participating in this study.

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study intervention to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of MYK-224 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention (Part A and Part B)

8.1.1 Temporary Treatment Discontinuation

As a general rule, any discontinuation of study drug should be initially considered temporary unless permanent treatment discontinuation is mandated by the protocol (Section 8.1.2).

[redacted]

Temporary discontinuation may also be considered by the investigator in the case of an AE/SAE or for any other reason.

8.1.1.1 Echocardiographic Temporary Discontinuation Criteria

[redacted]

[redacted]

8.1.1.2 12-Lead ECG Temporary Discontinuation Criteria

Criteria for temporary discontinuation due to QTcF prolongation are as follows and depend on QRS width as determined by local ECG:

- If QRS is narrow (< 120 ms), QTcF ≥ 520 ms
- If QRS is wide (≥ 120 ms), QTcF ≥ 550 ms

If QTcF performed at the first follow-up visit persists as out of range, at the second follow-up visit, study drug will be discontinued permanently.

8.1.1.3 Potential Hepatotoxicity Temporary Discontinuation Criteria

MYK-224 should be withheld if ANY of the following criteria are met, and the participant should be evaluated for DILI:

- AST or ALT > 8 x ULN at any time
- AST or ALT > 5 x ULN and < 8 × ULN for ≥ 2 weeks
- AST or ALT > 5 x ULN and < 8 × ULN and unable to adhere to enhanced monitoring schedule
- ALT or AST > 3 x ULN and (total bilirubin [TBL]) > 2 × ULN or international normalized ratio (INR) > 1.5

  OR
- ALT or AST > 3 x 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%)

  OR
- TBL > 3 x ULN at any time

  OR
- Alkaline phosphate (ALP) > 8 x ULN at any time

MYK-224 should be withheld pending an investigation into alternative causes of DILI. If MYK-224 is withheld, the participant should be followed according to recommendations in Appendix 6 for possible DILI. Rechallenge may be considered if an alternative cause, such as acute hepatitis B infection, is discovered and the laboratory abnormalities resolve to normal or baseline.

The decision to rechallenge the participant should be discussed and unanimously agreed by the investigator and Sponsor.

If signs or symptoms recur with rechallenge, then MYK-224 will be permanently discontinued. Participants who clearly meet the criteria for permanent discontinuation (Section 8.1.2) should never be rechallenged.

In the case of discontinuation for an AE/SAE, the investigator should make a best effort to resume study drug as soon as practically possible, assuming there are no safety concerns (eg, the investigator is satisfied that in his or her medical judgment, the study drug is unlikely to be responsible for the event concerned).

In general, participants may resume dosing at the last tolerated dose, once the finding leading to interruption has resolved.

All temporary treatment interruptions should be recorded in the eCRF.

8.1.2 Permanent Treatment Discontinuation

After a temporary treatment discontinuation, if a safety concern has not resolved or stabilized or the investigator suspects that study drug is responsible, the investigator may consider a treatment discontinuation as permanent. The investigator should make best effort to contact the monitoring team before considering any treatment discontinuation as permanent. Permanent treatment discontinuation should be considered a last resort. Every effort should be made to collect important safety data if feasible and the study participant agrees.

There may be situations in which it is necessary for a participant to permanently discontinue study drug. In all cases, participants should be encouraged to discuss stopping study drug with the investigator/designee so that questions can be addressed, and concomitant therapy can be adjusted if needed. Investigators should contact the Medical Monitor prior to permanent study drug discontinuation to discuss the situation.

8.1.2.1 Criteria for Permanent Treatment Discontinuation

Study drug will be permanently discontinued in the event of any of the following:

- Pregnancy
- [redacted]

- MYK-224 should be discontinued permanently and the participant should be followed according to the recommendations in Appendix 6 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 (HF)
    - 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
    - Significant noncompliance with protocol (eg, procedures, assessments, medications, etc)

Participants MUST discontinue IP (and Non-IP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS

- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Pregnancy (refer to Section 9.2.5).
- The Sponsor requests that the participant permanently discontinues study drug.

All permanent treatment discontinuation should be recorded in the eCRF.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified washout and EOS procedures appropriate for the study part from which they are discontinuing as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.3 Post-study Intervention Study Follow-up

Participants who discontinue study intervention may continue to be followed.

- If a participant permanently discontinues treatment, the participant will be asked to undergo an EOT visit as soon as possible after stopping study drug, as outlined in Table 2-4 for Part A and Table 2-6 for Part B, and will remain on study to be evaluated for concomitant medications and clinical assessments through a [redacted] washout period and subsequent EOS assessment as outlined in Table 2-4 for Part A and Table 2-6 for Part B.
- If the participant is unwilling or unable to be followed for the duration of the study, they will undergo an ET visit as outlined in Table 2-4 for Part A and Table 2-6 for Part B.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study intervention

only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.

- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Participants who do not receive MYK-224 may be replaced. Participants who withdraw from the study for reasons other than AEs after receiving MYK-224 may be replaced at the discretion of the Sponsor.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

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

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If the investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before dosing on Day 1 for both Part A and Part B. 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

9.1.1.1 Echocardiography

Details are provided in the Echo Instruction Manual. Echocardiography assessments will take place as described in Section 2.

Images will be submitted to an echocardiography core laboratory for central review. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

Participants will undergo a screening echocardiography prior to enrollment to obtain the protocol required images. Images will be submitted to the central imaging vendor for review to confirm eligibility. The central imaging vendor will assess the quality of echocardiography images (including acoustic windows) and will assess the images to determine participant eligibility.

During Part A, echocardiography images will be sent to a central imaging laboratory. Results from the central imaging laboratory will be transmitted to the IRT to confirm eligibility and support dose titration and stopping criteria.

In Part B, images will be sent to a core imaging laboratory for analysis; however, study decisions will be guided by local echocardiography results.

The use of echo contrast is not recommended for this study and should only be used to optimize image quality in participants that exhibit technically limited echo windows. The use of contrast for screening is not allowed. If a participant requires contrast at an on-treatment visit, then contrast must be administered for all subsequent study-related TTE examinations. For further details, please refer to the Echo Instruction Manual.

The required echo views at specified visits (complete TTE or abbreviated TTE) will be detailed in the Echo Instruction Manual.

9.1.1.2 Resting Transthoracic Echocardiography

Resting TTE will be assessed prior to dosing during onsite visits as described in Section 2. Measures should be taken in a supine and/or left lateral decubitus position. Instantaneous peak LVOT gradient at rest and provoked peak LVOT gradient (Valsalva maneuver) will be assessed. The investigator should confirm during Screening that participant can adequately perform the Valsalva maneuver. Care should be taken to select the best window and angle when obtaining Doppler signal to assess the LVOT gradient and to avoid contamination by mitral regurgitation (MR) jet if present. Left ventricular ejection fraction (2-dimensional LVEF) and left ventricular fractional shortening will also be analyzed along with a variety of other echocardiographic measures (see Echo Instruction Manual).

9.1.1.3 Post-exercise/Stress Echocardiography

Participants will undergo standard post-exercise stress TTEs as outlined/described in Table 2-1 and Table 2-4. Participants should abstain from food for at least 4 hours prior to post-exercise stress TTEs. At all timepoints where both resting and post-exercise measures are taken, resting TTE should be performed prior to post-exercise echocardiography.

Post-exercise echocardiography needs to be acquired within 72 hours of Resting TTE. Instantaneous peak LVOT gradient will be assessed immediately post exercise by TTE. Care should be taken to select the best window and angle when obtaining Doppler signal to assess the LVOT gradient, obtain valid LVOT gradient value, and avoid contamination by MR jet if present (see Echo Instruction Manual). Participants on standard cardiomyopathy therapy (eg, beta-blockers or calcium channel-blockers) should be on the same dose whenever possible and this medication should be administered prior to exercise testing.

9.1.1.4 New York Heart Association Functional Classification

The NYHA Functional Classification of HF assigns participants to 1 of 4 categories based on the participant's symptoms (Table 9.1.1.4-1). Heart failure classification will be assessed by the investigator at every study visit (preferably before echocardiography assessment) and recorded as

indicated in the clinical database (see Section 10.4.4). Every effort should be made to have the same investigator evaluate the NYHA Functional Classification at all study visits.

Table 9.1.1.4-1: New York Heart Association Functional Classification of Heart Failure

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less-than ordinary-activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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

9.1.2 Patient-reported Outcomes

9.1.2.1 Kansas City Cardiomyopathy Questionnaire

[redacted]

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

Refer to Appendix 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the time of signing the consent until 30 days after the final dose of MYK-224 or the final study visit, whichever is longer.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 30 days following discontinuation of dosing. SAEs may be collected for more than 30 days following discontinuation of dosing if the final study visit occurs after this time.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure.

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 9.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 30 days after study product administration, the investigator must immediately notify the Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3. Dosing with MYK-224 must be discontinued immediately.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for 30 days after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE eCRF, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential DILI is defined as:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) and/or INR > 1.5
  AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 9.2.

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, x-ray filming, or any other potential safety assessment required or not required by the protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any dose of MYK-224 greater than prescribed for the participant per study protocol within a 24-hour time period [± 8 hours] will be considered an overdose. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

An overdose may be symptomatic or asymptomatic and may reflect enhanced on-target PD effects of MYK-224. In the event of symptomatic overdose or in the presence of significant symptoms and/or clinical compromise, including depressed cardiac contractility or asystole, the investigator should contact the Medical Monitor, and no additional study drug should be administered until further notice.

The participant should be closely monitored clinically for AEs/SAEs, with supportive measures undertaken as clinically indicated. There is no specific antidote for MYK-224. In acute overdose or toxic ingestion, gastrointestinal decontamination should be considered. If necessary, corrective measures, as described in the 2022 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline for the Management of Heart Failure[26] and in the 2021 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure,[27,28] should be implemented. Reintroduction of study drug must be approved by the Medical Monitor.

Symptomatic overdose is an adverse event of special interest (AESI). If a participant should experience symptomatic overdose, the investigator will report the symptomatic overdose to the 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.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to the Schedule of Activities.

Height will be taken at screening and used to calculate BMI throughout the study. Weight should be measured at every clinic visit.

The complete physical examination will include weight and calculated BMI, a neurological examination (gross motor and deep tendon reflexes), and an assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems, with other systems included, as directed by interval history.

For abbreviated physical examinations, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.

9.4.2 Vital Signs

Refer to the Schedule of Activities.

Vital signs, to be assessed at each study visit, include heart rate, respiratory rate, and blood pressure after resting for at least 5 minutes. Temperature will also be taken at select visits. Vital signs will be obtained with the participant in the same position at each visit. Blood pressure and heart rate

should be the mean of 3 measurements for all timepoints. Blood pressure should be taken via an automated recorder.

On Day 1A and Day 1B, vital signs will be taken predose and [redacted]. For all other clinic visits, vital signs will be taken prior to dosing.

9.4.3 Cardiac Monitoring Device (Part A only)

At Screening and in two-week intervals throughout the titration period for Part A, participants will wear a small data collection device that is FDA approved for collecting continuous HR and rhythm data (Table 2-1, Table 2-2, and Table 2-4). The self-contained device attaches to the skin using medical adhesive and contains surface electrodes, internal electronics to capture a continuous single-lead ECG waveform, sufficient solid-state memory to store up to 14 days of data, and a battery to power the device. It has no external wires or other connections and should be kept powered on continuously throughout the recording period. Following the period of data collection, the device will be returned to the study site where the continuous ECG waveforms record stored on the device will be retrieved and uploaded to the central ECG vendor for analysis. The device will be used to explore the pattern of HR and heart rhythm before and during treatment with MYK-224. Additional details regarding the use of this device will be provided in a separate manual.

The device will be applied at the Screening visit and collected at the Day 1A clinic visit. Participants should wear the device for a minimum of 10 days and a maximum of 14 days during screening prior to Day 1A. Each participant should be trained on applying the device and will be provided with additional single-use electrodes to be replaced if needed during the 14-day recording period. The device will be collected on Day 1A prior to dosing. During the titration period, participants will wear the device in two-week intervals. A new device will be applied at each Titration [redacted] visit and collected at the following Titration [redacted] visit (see Table 2-2).

9.4.4 Electrocardiograms

Refer to the Schedule of Activities.

Twelve-lead ECG evaluations will be performed in the supine position after 10 minutes of rest at Screening and at selected clinic visits prior to MYK-224 dosing and before any blood sample collection. All 12-lead ECG data will be sent to a central cardiac reader.

At each clinic visit, using a 12-lead ECG machine that automatically calculates heart rate (HR) and measures PR, QRS, QT, and QT interval with Fridericia correction (QTcF) intervals prior to dosing. Additional 12-lead ECGs will be performed post-dose at select time points as outlined in the Schedule of Activities. Each time a 12-lead ECG is completed, a 10-sec paper 12-lead ECG will be obtained and maintained in the participant's source documentation. The investigator will judge the overall interpretation as normal or abnormal with clinical significance. The investigator will review the 12-lead ECG results and correlate abnormal findings with any other clinical findings (including the reading by the central core lab reviewer), the participant's medical history, and laboratory data to determine the clinical importance of the finding.

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

9.4.5 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Participants should fast for at least 4 hours prior to sample collection. A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Table 9.4.5-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Fasting glucose	Total protein Albumin Sodium Potassium Chloride Bicarbonate Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance - screening only
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and -2 antibody (screening only)	
Other Analyses	

Table 9.4.5-1: Clinical Laboratory Assessments

Pregnancy test (WOCBP only): serum at screening and EOS or ET (for both Part A and Part B, as applicable), urine at all other timepoints. During Part B, testing should be done every [redacted] at home between clinic visits and the results reported to the site.
Follicle-stimulating hormone (at screening in Part A for women only)
Test for infection with SARS-CoV-2 (required at screening only, other timepoints based on local site regulations).

Abbreviations: EOS, end of study; ET, early termination; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

9.4.6 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

9.4.7 Other Safety Procedures and Assessments

Participants with ICDs will have their data downloaded at Screening, EOT, EOS/ET, and any unscheduled visits, or as clinically indicated whenever device discharge is interrogated and/or prior to device reset.

9.5 Pharmacokinetics

Plasma samples of MYK-224 will be collected for all participants as specified in Table 9.5-1 and Table 9.5-2. For all clinic visits during the treatment period, participants will be asked to take their daily dose of MYK-224 at the clinic to allow for [redacted] sample collection.

Plasma concentration analyses for MYK-224 will be performed by a validated bioanalytical method.

Bioanalytical samples designated for assessments [redacted] from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, etc).

Additionally, residual bioanalytical samples will be archived and may be used for [redacted] (including, but not limited to, metabolite analyses, etc) and or for additional method purposes (including, but not limited to, cross-validation, etc).

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

Table 9.5-1: Pharmacokinetic Sampling Schedule for Part A

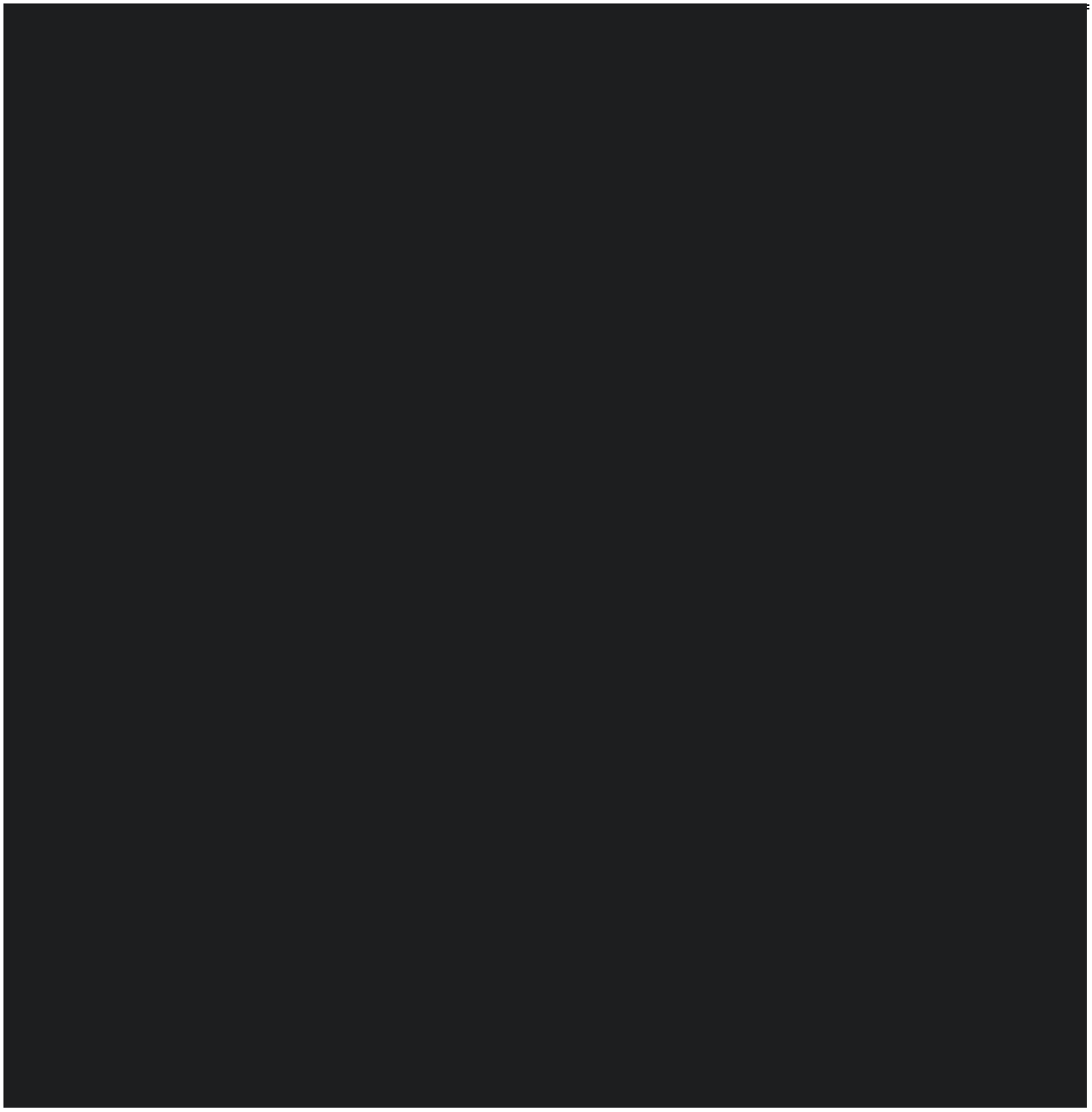
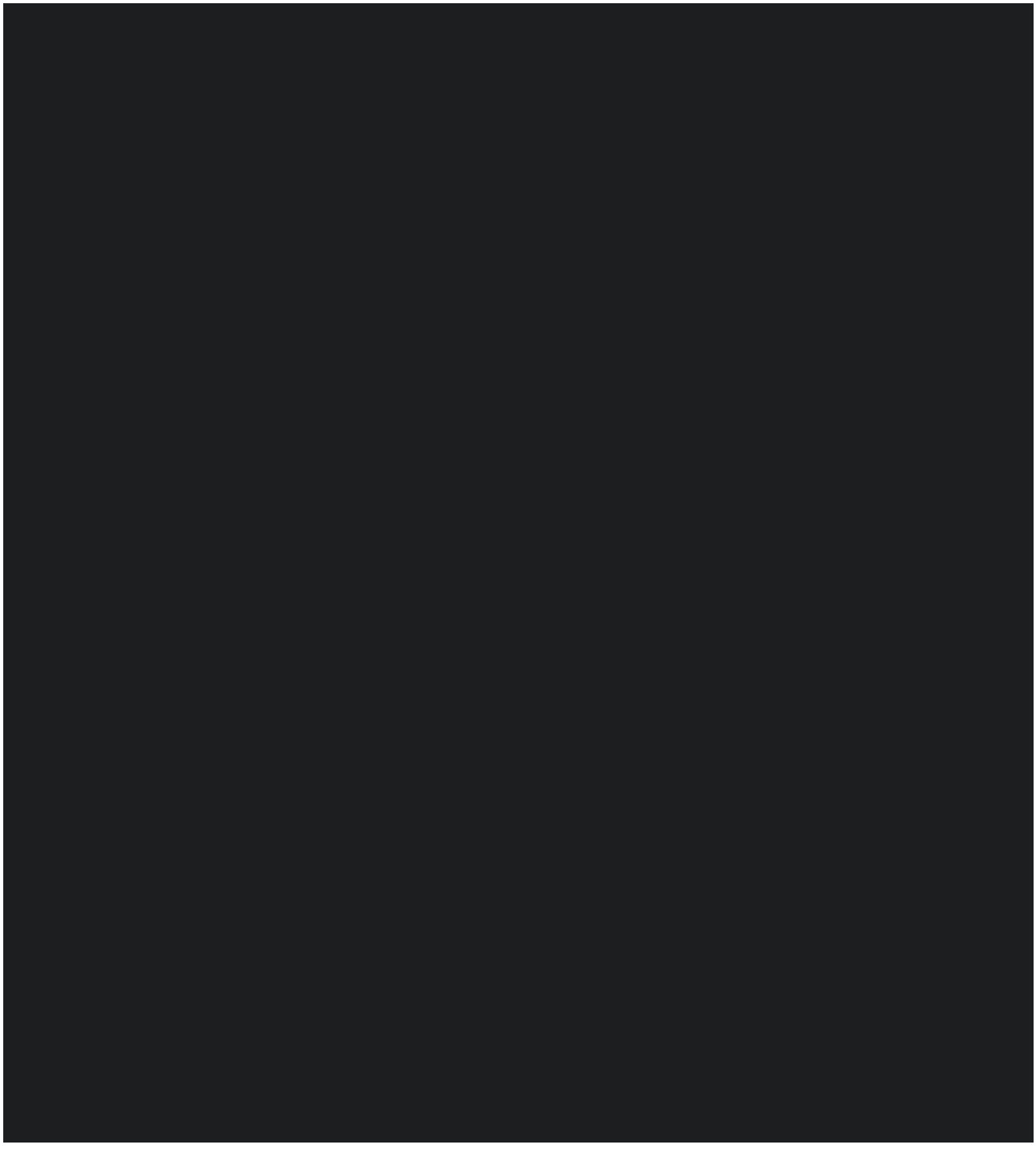


Table 9.5-2: Pharmacokinetic Sampling Schedule for Part B (optional OLE)



9.5.1 Pharmacokinetic Sample Collection Windows

It is expected that every effort will be made to collect PK samples at the times indicated. The following windows serve as a guideline for PK sample collection:

- [redacted] samples must be taken prior to drug administration preferably within 30 minutes of study drug administration.
- [redacted]

All samples should be collected using the time point labels provided even if they are outside the suggested window. Actual sample times must be recorded.

9.6 Immunogenicity Assessments

Not applicable.

9.7 Genetics

Not applicable.

9.8 Biomarkers

The following [redacted] biomarker samples will be collected in this study: [redacted] will be banked for [redacted]. If a sample is not collected as scheduled, it may be obtained on any study day.

A baseline [redacted] will also be collected for [redacted] and an additional DNA sample (baseline or any study day) will be banked for future research [redacted].

Blood samples for measuring [redacted] will be collected from all participants as noted in the Schedule of Activities from Parts A and Part B (see Section 2). [redacted] for [redacted], to potentially evaluate circulating markers including but not limited [redacted] or for [redacted] related to [redacted] diseases.

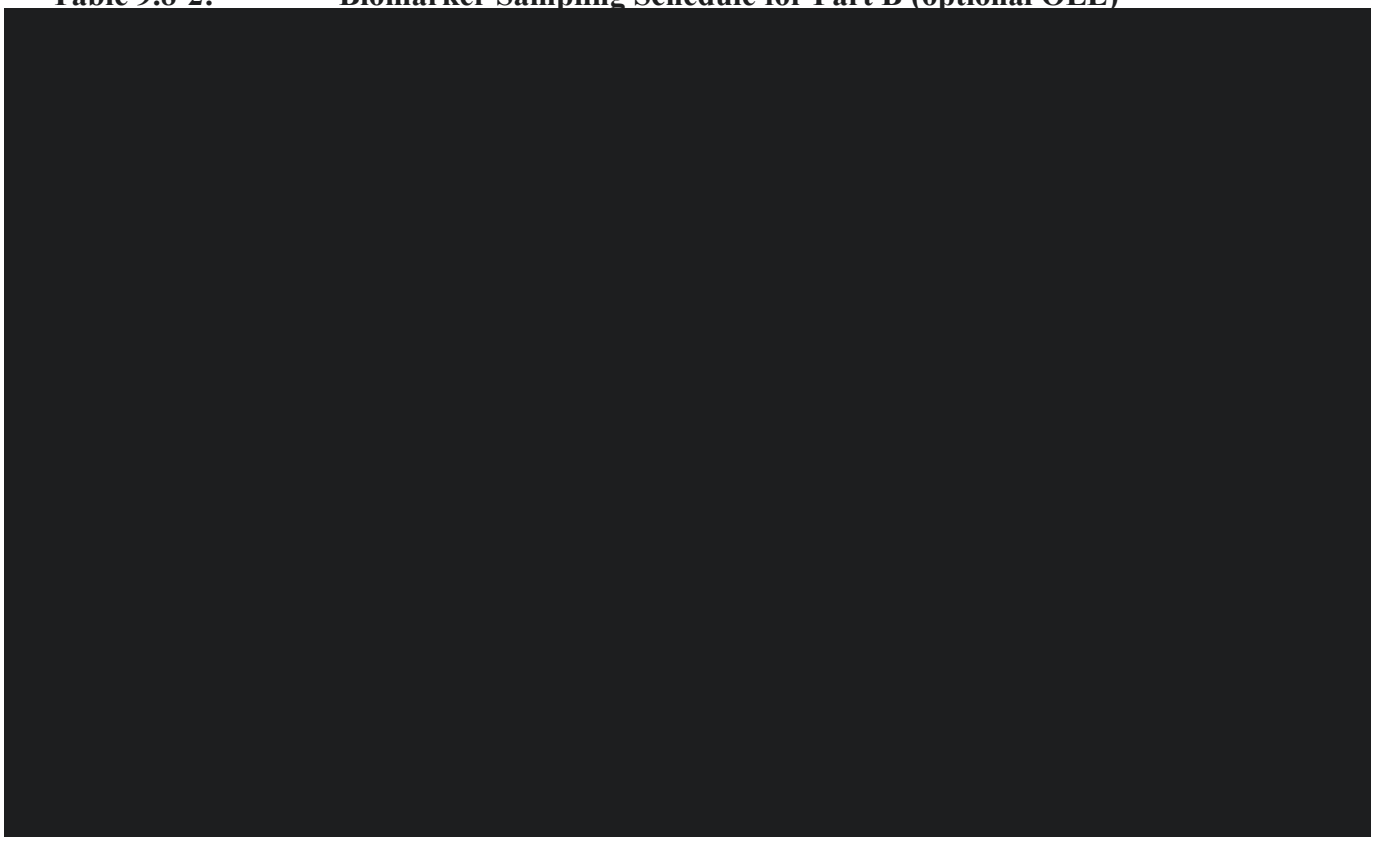
Table 9.8-1: Biomarker Sampling Schedule for Part A[a]

[redacted]

[a] All Biomarker samples should be collected predose.

[redacted]

Table 9.8-2: Biomarker Sampling Schedule for Part B (optional OLE)



9.9 Additional Research

This protocol will include residual sample storage for additional research (AR).

For All Sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

Additional research is intended to expand the R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

- [redacted], and PK collections (see Table 9.9-1) will also be retained for additional research purposes.

Samples kept for future research will be stored [redacted] or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be participant to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 9.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for Which Residual Samples Will Be Retained
[redacted]	[redacted]
PK	All

9.10 Other Assessments

Not applicable.

9.11 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

No hypothesis testing is planned for this study.

10.2 Sample Size Determination

The sample size is based on practical considerations and is consistent with this type of pilot study. Approximately [redacted] participants will be enrolled in the study. The minimum size for each subgroup (Cohort 1: MYK-224 monotherapy or SOC with beta-blockers; Cohort 2: SOC with

nondihydropyridine calcium channel-blockers or SOC with disopyramide in combination with beta-blockers or calcium channel-blockers) is [redacted].

[redacted] per cohort receiving MYK-224 will achieve a 91% power to detect a 30 mm Hg within-group change from baseline in post-exercise peak LVOT gradient and a > 99% power to detect a 50-mm Hg change. This assumed a 1-sided $\alpha = 0.05$ and a common standard deviation (SD) of [redacted]. The common SD of [redacted] is based on a previous study on a similar compound (MYK-461). Additionally, with smaller SD in both resting and Valsalva peak LVOT gradient, higher powers will be expected in detecting the same magnitude of changes.

The minimum subgroup size of [redacted] is determined based on post-exercise peak LVOT gradient. [redacted] per subgroup receiving MYK-224 will provide an 81% power to detect a 40 mm Hg within-group change from baseline and a 93% power to detect a 50-mm Hg change (see Table 10.2-1).

Table 10.2-1: Power for Detecting a Statistically Significant Within-Group Change in Post Exercise Peak LVOT Gradient

Subgroup Size	Power (%) to Detect 40-mm Hg Change From Baseline	Power (%) to Detect 50-mm Hg Change From Baseline
[redacted]	85	95
	81	93
	74	89

The precision of the sample size is addressed based on secondary endpoints as their precision is more challenging to achieve compared with the primary safety endpoints.

10.3 Analysis Sets

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

Population	Description
Enrolled	All participants who have agreed to participate in a clinical study following completion of the informed consent process.
Safety	All participants who received at least 1 dose of MYK-224
PK	All enrolled participants who receive at least 1 dose of MYK-224 and have at least 1 evaluable MYK-224 plasma concentration.
Efficacy/PD	All participants who receive at least 1 dose of MYK-224 and have primary or secondary endpoint data, including a baseline value and at least 1 post-baseline value.

[redacted]

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock (DBL), and it will include a more technical and detailed description of the statistical analyses described in this section.

10.4.1 General Considerations

Primary and secondary endpoints will be summarized descriptively. Descriptive summary statistics for continuous variables will include the number of participants, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Ninety percent exact confidence intervals will be presented, as appropriate. Baseline will be defined as the last observation recorded before the first dose of MYK-224.

10.4.2 Primary Endpoint(s)

Table 10.4.2-1: Endpoints

Primary Endpoint	Timeframe
Incidence, severity, and causality of AEs and SAEs	Up to 30 days after EOT-A or the final study visit, whichever is longer
Incidence of symptomatic resting LVEF [redacted]	Up to EOS-A
Incidence of resting LVEF [redacted]	Up to EOS-A
Incidence of MACE, including cardiovascular death, nonfatal stroke, nonfatal myocardial infarction	Up to 30 days after EOT-A or the final study visit, whichever is longer
Incidence of hospitalizations (due to cardiovascular and non-cardiovascular events)	Up to 30 days after EOT-A or the final study visit, whichever is longer
Incidence of HF events (including hospitalizations and urgent emergency room/outpatient visits for HF)	Up to EOS-A
Incidence of atrial fibrillation/flutter (new from screening and recurrent)	Up to EOS-A
Incidence of appropriate implantable cardioverter defibrillator therapy and resuscitated cardiac arrest	Up to EOS-A
Incidence of ventricular tachyarrhythmias (includes ventricular tachycardia, ventricular fibrillation, and Torsades de Pointes)	Up to EOS-A
Results of vital signs, physical exams, 12-lead ECG assessments (including HR), and clinical laboratory tests	Up to EOS-A

Abbreviations: AE, adverse events; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; SAE, serious adverse event; [redacted].

All safety analyses will be performed on the Safety Population. All recorded AEs and SAEs will be classified and listed by participant. All recorded AEs and SAEs will be summarized by system

organ class, preferred term, and subgroup. The incidence of cardiovascular events, hospitalizations, and arrhythmia will be listed by participants and summarized by subgroup. Clinical laboratory test results, vital sign measurements,12-lead ECG parameters, TTE parameters, weight, and PE findings will be listed by participants and summarized by planned time point and subgroup. Abnormal laboratory test results will be listed by participants and summarized by subgroup, and normal ranges will be included for reference.

The 12-lead ECG readings will be summarized by planned time point and subgroup and evaluated by the investigator. Abnormalities, if present, will be characterized as either clinically significant or non-clinically significant and listed by participant. HR, PR, QRS, and QTcF will be summarized using descriptive statistics. For each time point of measurement, the changes from baseline will be summarized using descriptive statistics. A categorical analysis of post-dose QTcF values by subgroup will also be performed.

10.4.3 Secondary Endpoint(s)

Table 10.4.3-1: Endpoints

Secondary Endpoint	Description	Timeframe
Effect on LVOT gradient	• Change from baseline to EOT-A in post-exercise LVOT peak gradient • Change from baseline to EOT-A in resting LVOT peak gradient, change from baseline to EOT-A in Valsalva LVOT peak gradient • Proportion of participants achieving a resting LVOT peak gradient of < 30 mm Hg and a Valsalva LVOT peak gradient < 50 mm Hg at EOT-A	Up to EOT-A
PK/PD relationship	Concentration response relationship between MYK-224 and resting, Valsalva, and post-exercise LVOT peak gradients. Concentration response relationship between MYK-224 and echocardiographic parameters of systolic and diastolic function including: • LV ejection fraction (LVEF) • LV fractional shortening • LVOT velocity time integral • LV global longitudinal strain (GLS) • LV stroke volume • E/A ratio • Lateral, septal, and average e' • Lateral, septal, and average E/e'	Up to EOS-A
PK concentrations	Summary of plasma concentrations	Up to EOS-A

Abbreviations: A, late diastolic mitral inflow velocity; E, early diastolic mitral inflow velocity; e', early diastolic mitral annular tissue velocity (note there is a lateral, septal and average of this parameter); E/A, early to late diastolic mitral inflow velocity ratio (or early diastolic mitral inflow velocity to late diastolic mitral inflow velocity ratio); E/e', early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity ratio (note: there is a lateral, septal and average of this parameter, depending on where the tissue velocity assessment is made lateral or septal [medial annulus]); EOS, end of study; EOT, end of treatment; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; PD, pharmacodynamic; PK, pharmacokinetics.

All secondary endpoint analyses will be performed on Efficacy/PD population or PK population. All endpoints related to the effect of MYK-224 on LVOT gradient parameters will be listed by participants and summarized by timepoint and subgroup. Ninety percent confidence interval will be presented, if possible. The PK/PD relationship parameters will be explored by graphical and regression analyses. All concentration-time data will be listed and summarized by timepoint and subgroup descriptively.

10.4.4 Exploratory Endpoint(s)

Table 10.4.4-1: Endpoints

Table 10.4.4-1: Endpoints

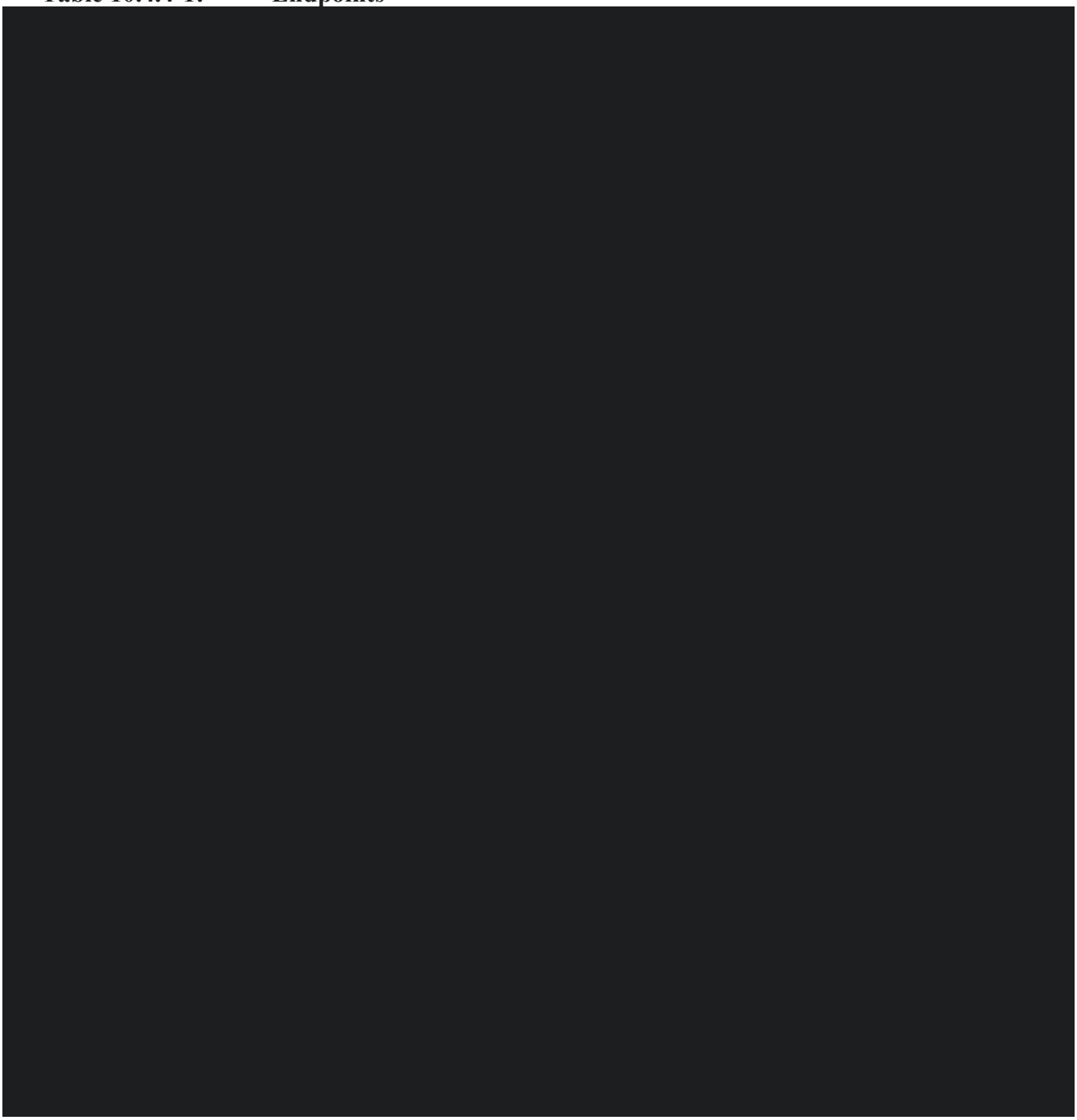


Table 10.4.4-1: Endpoints

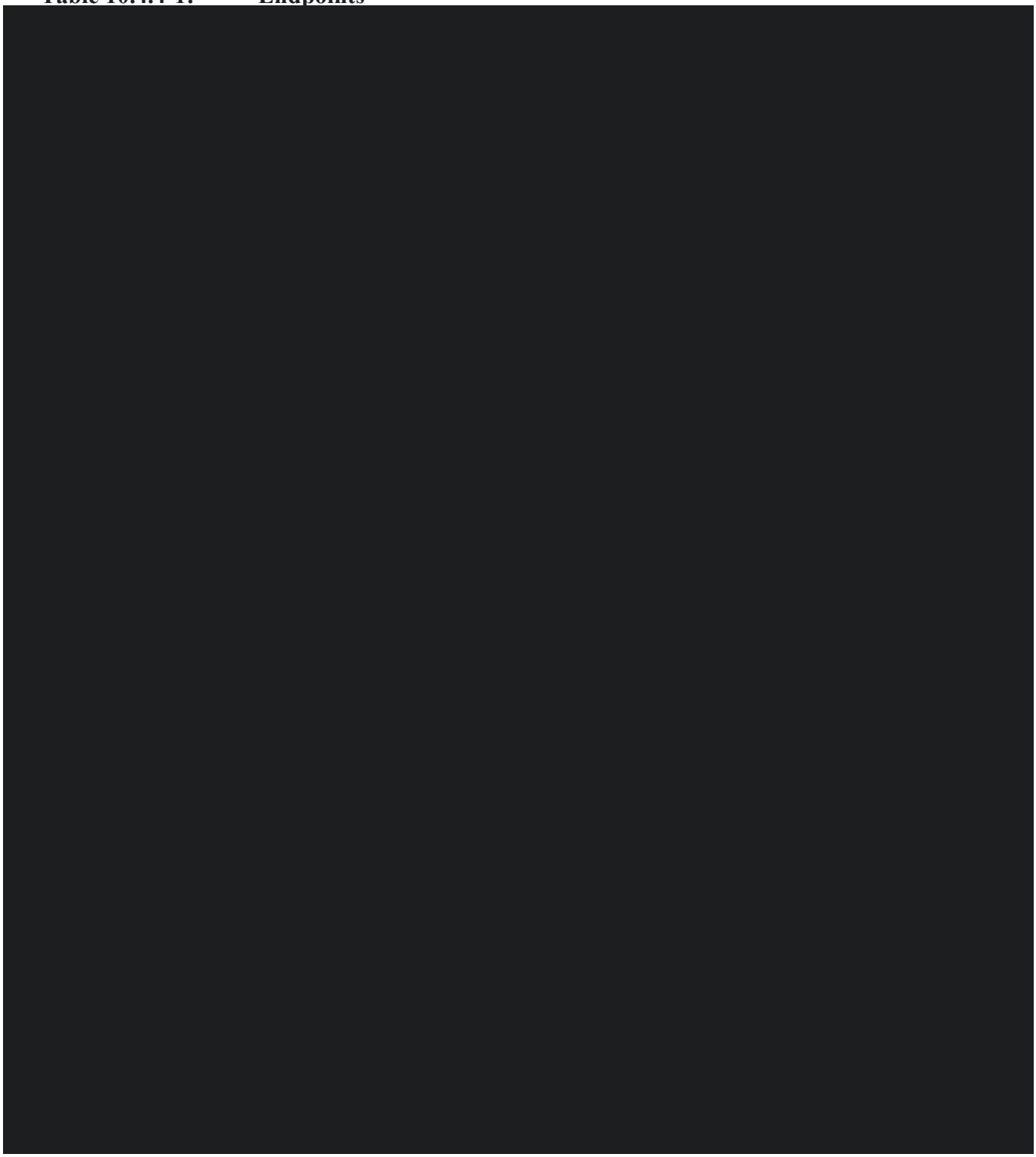


Table 10.4.4-1: Endpoints

10.4.5 Other Safety Analysis

Not applicable.

10.4.6 Other Analyses

Not applicable.

10.5 Interim Analyses

[redacted]

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
A	late diastolic mitral inflow velocity
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ADA	anti-drug antibodies
[redacted]	[redacted]
AED	automated external defibrillator
AE	adverse event(s)
AESI	adverse event(s) of special interest
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransaminase
[redacted]	[redacted]
AR	additional research
ASA	alcohol septal ablation
AST	aspartate transaminase
AT	ALT (alanine aminotransaminase) or AST (aspartate transaminase)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
AxMP	Auxiliary Medicinal Product
BICR	Blinded Independent Central Review
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BP	blood pressure
CABG	coronary artery bypass grafting
CIOMS	Council for International Organizations of Medical Sciences
[redacted]	[redacted]
CNS	central nervous system
[redacted]	[redacted]
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019

Term	Definition
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
[redacted]	
CTAg	clinical trial agreement
CTR	cardiothoracic ratio
Ctrough	trough observed plasma or serum concentration
CV	cardiovascular
CYP3A4	cytochrome P-450 3A family isozyme 4
DBL	database lock
DDI	drug-to-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSUR	Development Safety Update Report
E	early diastolic mitral inflow velocity
e’	early diastolic mitral annular tissue velocity (note there is a lateral, septal and average of this parameter)
E/A	early to late diastolic mitral inflow velocity ratio (or early diastolic mitral inflow velocity to late diastolic mitral inflow velocity ratio)
E/e’	early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity ratio (note: there is a lateral, septal and average of this parameter, depending on where the tissue velocity assessment is made lateral or septal [medial annulus])
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EF	ejection fraction
eGFR	estimate glomerular filtration rate
[redacted]	[redacted]
EOS	end of study
EOS-A	end of study for Part A

Term	Definition
EOS-B	end of study for Part B
EOT	end of treatment
EOT-A	end of treatment for Part A
EOT-B	end of treatment for Part B
ESC	European Society of Cardiology
ET	early termination
ET-A	early termination for Part A
ET-B	early termination for Part B
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
FPFV	first patient first visit
FS	Fractional Shortening
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GLS	global longitudinal strain
[redacted]	[redacted]
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCM	hypertrophic cardiomyopathy
HCV	hepatitis c virus
HF	heart failure
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HIV RNA	human immunodeficiency virus ribonucleic acid
HOCM	obstructive HCM
hr	hour
HR	heart rate
HRT	hormone replacement therapy
[redacted]	[redacted]
[redacted]	[redacted]
HV	healthy volunteer

Term	Definition
I/E	inclusion/exclusion
IB	Investigators Brochure
IC50	half-maximal inhibitory concentration
ICD	implantable cardioverter defibrillator
ICF	Informed Consent
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
IP/IMP	investigational [medicinal] product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intention to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
KCCQ-23	Kansas City Cardiomyopathy Questionnaire (23-item version)
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MACE	major adverse cardiovascular event
MAD	multiple ascending doses
MH	medical history
mm Hg	millimeters of mercury
MR	mitral regurgitation
[redacted]	[redacted]
MRI	magnetic resonance imaging
NA	not applicable
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect-level
[redacted]	[redacted]
NYHA	New York Heart Association
nHCM	non-obstructive hypertrophic cardiomyopathy

Term	Definition
oHCM	obstructive hypertrophic cardiomyopathy
OLE	open-label extension
OSS	overall summary score
PCI	percutaneous coronary interventions
PCR	polymerase chain reaction
PD	pharmacodynamics
PE	physical examination
PI	principal investigator
PK	pharmacokinetics
PL	physical limitation
PRO	patient-reported outcome
QD	once daily
QoL	quality of life
QRS	the interval between the beginning of the Q wave and the end of S wave in the electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's method
R&D	research and development
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event(s)
SAD	single ascending dose
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCD	sudden cardiac death
SD	standard deviation
SOC	standard of care
SRT	septal reduction therapy
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TB	tuberculosis
TBD	to be determined
TBL	total bilirubin level
Tmax	time at which maximum concentration (Cmax) occurs

Term	Definition
[redacted]	[redacted]
TTE	transthoracic echocardiogram
ULN	upper limit of normal
US	United States
USA	United States of America
UTN	universal trial number
vs	versus
WHO	World Health Organization
Wk	week
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential
WS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, also by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before 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.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible

adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

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 electronic CRF (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.
- Definitions of what constitutes source data can be found in the source data location list/map or equivalent document.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY INTERVENTION RECORDS

Records for study intervention MYK-224 (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be

reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

Each individual electronically signing eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS or a vendor or sourced by the investigator), such as partially used study treatment containers, vials, and syringes, may be destroyed on site.

If	Then
Study treatment supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. 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 the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor 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.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- Participant recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Those who make the most significant contributions, as defined above, will be considered by the BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.

Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • The investigator will also consult the Investigator’s Brochure and/or product information for marketed products in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission.

SAE Email Address: worldwide.safety@BMS.com

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgement in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

• Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.
• Vasectomized partner Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• Sexual abstinence. *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol..

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously. • Diaphragm with spermicide. • Cervical cap with spermicide. • Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and APPENDIX 3.

APPENDIX 5

[redacted]

APPENDIX 6 POTENTIAL DRUG-INDUCED LIVER INJURY REPORTING AND ADDITIONAL ASSESSMENTS REPORTING

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent aspartate/alanine (AST/ALT) and total bilirubin (TBL) elevation according to the criteria specified in Section 8.1.1 (3 × upper limit of normal [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 as a serious adverse event (SAE) within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

The appropriate electronic case report form (eCRF) (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to MyoKardia.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 9.2.

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, alkaline phosphatase [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.

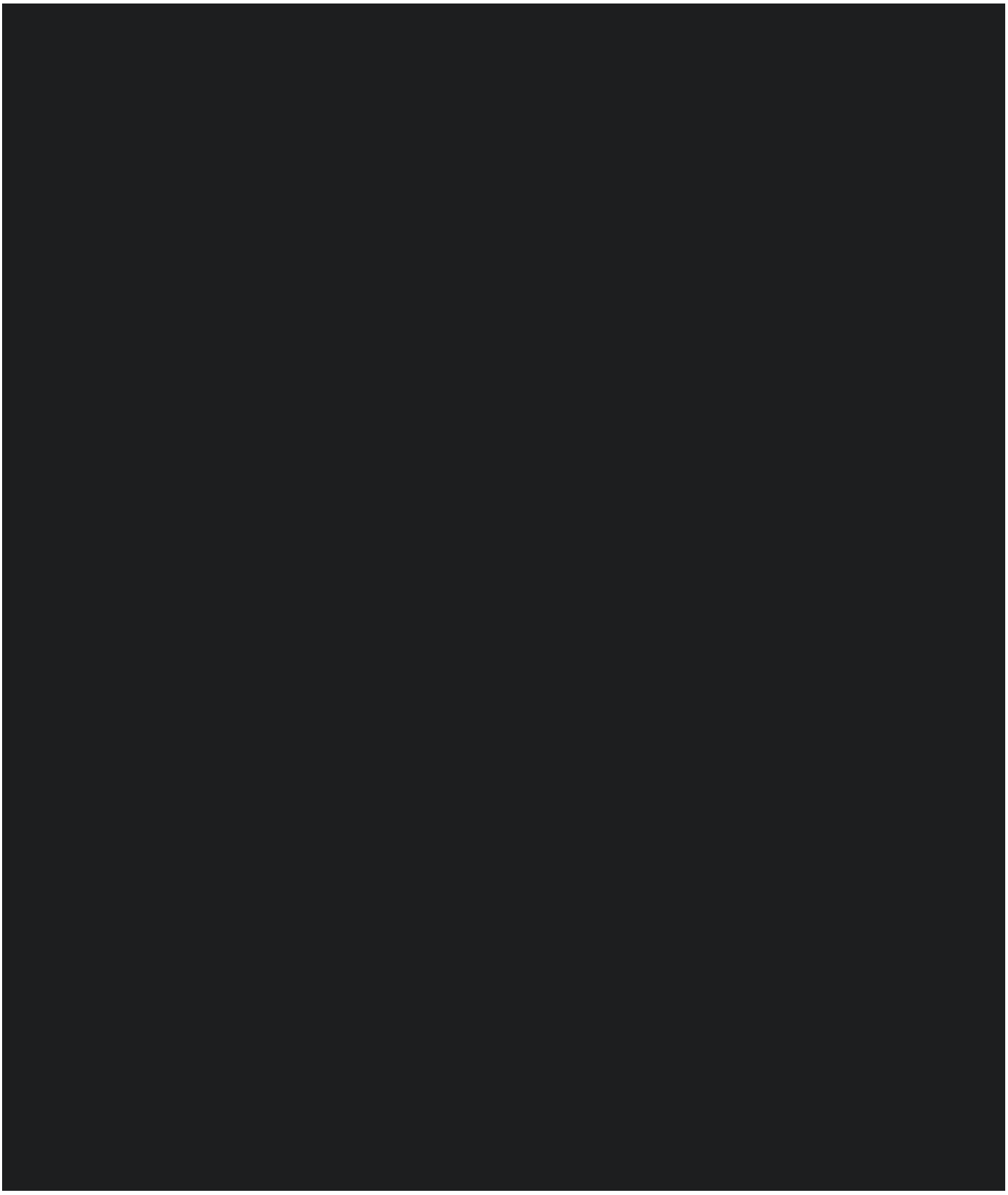
Participants are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the study drug or protocol-required therapies have been discontinued and the participant is asymptomatic.

- Obtain prothrombin time/international normalized ratio, fractionated bilirubin, and any other potentially relevant laboratory evaluations of liver function or disease.
- Obtain complete blood count with differential to assess for eosinophilia.
- Obtain appropriate blood sampling for pharmacokinetics analysis if this has not already been collected.

- Obtain a more detailed history of the following:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
  - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
  - Concomitant medications (including nonprescription medicines and herbal and dietary supplements).
    - Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr virus, herpes simplex virus, etc.); evaluate for other potential causes of DILI, including but not limited to: nonalcoholic steatohepatitis (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.

APPENDIX 7 KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE



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