Official Title of Study:

A Phase 3, Open-label, Single Arm, Clinical Study to Evaluate Efficacy, Safety and Tolerability of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy (HORIZON-HCM)

NCT Number: NCT05414175

Document Date (Date in which document was last revised): 18 October 2022

CLINICAL PROTOCOL CV027004

A Phase 3, Open-label, Single Arm, Clinical Study to Evaluate Efficacy, Safety and Tolerability of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy (HORIZON-HCM)

Compound: BMS-986427

Brief Title: Mavacamten in Obstructive Hypertrophic Cardiomyopathy

Protocol Amendment 03
Incorporates Administrative Letter 01

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REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: NA
EudraCT/EU Trial Number: N/A
NCT: N/A
UTN: N/A
EUDAMED: N/A
Other: N/A

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	18-Oct-2022	• Increase the screening period [redacted] • Clarify pregnancy testing at screening, prior to dosing, and during the study • Clarify inclusion and exclusion criteria • Update safety laboratory test schedule [redacted] • Clarify management of overdose language • Update additional resesarch of residual samples to be optional • Clarify fasting requirements prior to exercise testing • Correct other typographical errors identified
Administrative Letter 01	22-Aug-2022	• Updated contact information for the clinical trial physician and clinical scientist
Protocol Amendment 02	23-Mar-2022	• Correction of typographical errors
Protocol Amendment 01	17-Mar-2022	• Clarification of temporary/permanent discontinuation criteria [redacted] • Updated language describing prohibited medications, dietary restrictions, and allowable concomitant medications • Clarified required contraceptive methods that are approved in Japan. • Removed SARS-CoV-2 serology testing • Corrected other typographical errors and removed redundancies
Original Protocol	18-Jan-2022	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The primary purpose of this amendment is to increase the Screening Period; [redacted] clarify pregnancy testing at Screening, prior to dosing, and during the study; clarify inclusion and exclusion criteria; update safety laboratory test schedule [redacted] clarify management of overdose language; update additional resesarch of residual samples to be optional; clarify fasting requirements prior to exercise testing; and correct other typographical errors identified.

These revisions are specified below and have been incorporated into the Protocol Summary.

Administrative Letter 01, which updated contact information for the clinical trial physician and clinical scientist, has also been incorporated.

Revisions apply to future participants enrolled in the study and, where applicable, to all participants currently enrolled.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
Table 2-1: Screening Procedural Outline	Lengthened duration of Screening Period from 28 to 35 days.	To allow more time for Screening assessments to be performed.
Table 2-1: Screening Procedural Outline Table 2-2: On-Treatment - Schedule of Activities for All Participants (Primary Analysis Treatment Period) Table 2-3: On-Treatment - Schedule of Activities for All Participants (Long-Term Treatment Period)	Reduced number of hours from 4 to 3 for recommended fasting prior [redacted] and Post exercise/Stress [redacted]	To align [redacted] testing requirements.
	Added to Notes that [redacted] can be completed on Day 1 prior to dosing, and hematology must be collected within 7 days of the [redacted] assessments (preferably on the day [redacted]). In the event that a visit hematology sample is collected more than 7 days before or after [redacted] is performed, an unscheduled hematology sample must be collected on the same day as the [redacted] assessment.	To allow for more flexibility [redacted] and clarify the need for hematology to be performed.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline Table 2-2: On-Treatment - Schedule of Activities for All Participants (Primary Analysis Treatment Period) Table 2-3: On-Treatment - Schedule of Activities for All Participants (Long-Term Treatment Period) Table 2-4: Follow-Up Procedural Outline	Added to Notes that electrocardiogram (ECG) should be completed prior to blood draws.	To provide more flexibility and clarity.
	Revised footnote regarding order of assessments.	
Table 2-2: On-Treatment - Schedule of Activities for All Participants (Primary Analysis Treatment Period)	Added to Notes and footnote that Kansas City Cardiomyopathy Questionnaire (KCCQ) should be completed prior to any other study procedure taking place, when possible.	To avoid bias in KCCQ.
	Revised pregnancy test requirements in Notes.	To clarify requirement for serum pregnancy test during Screening and negative urine pregnancy test prior to dosing.
Table 2-3: On-Treatment - Schedule of Activities for All Participants (Long-Term Treatment Period)	Added Week 90 and Week 114 safety laboratory tests including hematology, chemistry, and coagulation assessments.	To add additional safety assessments.
	Removed Week 102 safety laboratory tests to align with [redacted] collection schedule.	To align laboratory test collections [redacted].
Table 2-2: On-Treatment - Schedule of Activities for All Participants (Primary Analysis Treatment Period) Table 2-3: On-Treatment - Schedule of Activities for All Participants (Long-Term Treatment Period)	[redacted]	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On-Treatment - Schedule of Activities for All Participants (Primary Analysis Treatment Period) Table 2-3: On-Treatment - Schedule of Activities for All Participants (Long-Term Treatment Period) Table 2-4: Follow-Up Procedural Outline	Added footnote for visit windows.	To clarify that the ± 7 day visit window does not apply to Day 1.
Section 3.2: Background	Updated cutoff date and the number of sites and participants in mavacamten clinical studies.	To align with current Investigator's Brochure.
Table 4-1: Objectives and Endpoints	[redacted]	
Section 5.1: Overall Design Figure 5.1-1: Study Design Schema Section 5.1.1: Screening Period Section 6.5.1: Retesting During Screening Section 7.7.1: Prior Therapy	Adjusted all timeframes to account for addition of 7 days to Screening and/or changed 28-day Screening window to 35-day Screening window.	To align with change in Screening duration.
Section 5.1.2.1: Treatment Period for Primary Analysis	Removed pregnancy status from Week 2 phone call to participants.	Pregnancy testing is required every 4 weeks and is already performed at Day 1 and Week 4.
Section 5.1.3: Post-Treatment Follow-up Period	Added clarification if participant is a cytochrome P450 (CYP) 2C19 poor metabolizer (PM) and requires additional follow-up.	To communicate when sites will be notified if participants are CYP 2C19 PMs.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.4: Description of Other Procedures and Assessments	Corrected the second implantable cardioverter-defibrillator (ICD) data download to Week 12.	Fixed typographical error.
	Added that participants who meet all inclusion/exclusion criteria [redacted] requirements will undergo [redacted] during Screening or Day 1 pre-dose or up to 5 days before each visit after Day 1.	To allow for more flexibility [redacted] and clarify [redacted] will only be performed at sites willing to participate in the assessments.
Section 5.3: End of Study Definition	Revised definition of end of Treatment Period for Primary Analysis and added definition of end of treatment (EOT).	To provide more clarity.
Section 6.1: Inclusion Criteria	4)a)iii): Clarified requirement for negative urine pregnancy test at Day 1 prior to start of study treatment.	To clarify a negative urine pregnancy test is required at Day 1 prior to dosing in addition to required negative serum pregnancy test during Screening.
Section 6.2: Exclusion Criteria Section 7.7.2: Background HCM Therapy Section 7.7.4: Prohibited and/or Restricted Treatments Appendix 5: Prohibited Medications	Added "assessments" after "Screening" throughout the protocol.	To clarify that with regards to prior/ concomitant therapy affecting eligibility, the timing is in relation to when Screening assessments begin, not at the beginning of the Screening Period.
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1: Prior Therapy	Clarified that participants who have taken prohibited medications within 14 days prior to signing the informed consent form (ICF) must discontinue treatment for at least 14 days prior to Screening assessments. Principal Investigator to determine if participant can discontinue prohibited treatments.	To clarify timing when Screening assessments begin in relation to prior/ concomitant therapy affecting eligibility.
Section 7.7.4: Prohibited and/or Restricted Treatments	Added that "if a compelling clinical necessity to administer one of these medications arises," the investigator and medical monitor should discuss whether/when the participant would discontinue study drug.	To clarify that investigators should discuss how to safely administer prohibited concomitant medications with the medical monitor in cases where clinical necessity requires their use.
Section 8.1.3.1: Temporary Discontinuation in Treatment Period for Primary Analysis (Day 1 through Week 30) Section 8.1.3.2: Temporary Discontinuation in Long-Term Treatment Period (Week 30 to Week 138)	Removed the possibility of lengthening temporary discontinuation for CYP 2C19 PMs.	To clarify that all participants will follow the same criteria with respect to temporary discontinuations and must meet the same requirements to restart treatment after a temporary discontinuation.
Section 9: Study Assessments and Procedures	Revised text regarding order of assessments.	To provide more flexibility and clarity.
Section 9.1.1: Efficacy Assessment for the Study [redacted]	Added "and/or operational" to "technical capabilities" of conducting [redacted].	To allow flexibility where operational challenges may prevent [redacted] from being performed.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.1: Efficacy Assessment for the Study	Reduced number of hours from 4 to 3 for recommended fasting prior [redacted] and Post exercise/ Stress [redacted]	To align with [redacted] echocardiography manuals.
	Added participant requirements for withholding caffeine, nicotine, alcohol, food, and exercise prior to [redacted] procedures.	To clarify participant requirements [redacted].
Section 9.1.2.1: Echocardiography	Reduced number of hours from 4 to 3 for recommended fasting prior to Post exercise/Stress [redacted]	To align with echocardiography manual.
	Added that the exercise test should be performed within the site's standard protocol; if not available, the [redacted] exercise protocol must be utilized.	To clarify options for the exercise test protocol.
[redacted]		
Section 9.2.5: Pregnancy	Increased time for follow-up of pregnancy outcome from 6 months to 1 year after birth or premature termination.	To update follow-up time in line with Sponsor requirements.
	Removed requirement that the pregnancy of a male participant's female partner be followed up.	Pregnant partner follow-up is no longer required per asset-level guidance.
Section 9.3: Overdose	Added detail regarding management of overdoses and instructions for investigators.	To align overdose language with the Investigator's Brochure.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4.3.2: Cardiac Monitoring Device	Corrected text regarding memory cards.	To correct cardiac monitoring device information.
Section 9.4.4: Clinical Safety Laboratory Assessments	Clarified that participants must have a negative urine pregnancy test at Day 1 prior to initiating study therapy.	To clarify a negative urine pregnancy test is required prior to dosing.
	Added details to pregnancy test requirements during the Long-Term Treatment Period.	To clarify requirement for serum pregnancy test during Screening and negative urine pregnancy test prior to dosing.
[redacted]		
Section 9.7.2: Pharmacogenetic Assessments Table 9.8-1: Biomarker Sampling Schedule for All Participants	Removed "panel" from text regarding gene testing.	Only CYP 2C19 pharmacogenetic testing is being performed.
Section 9.9: Additional Research	Updated language to reflect that participation in additional research on residual samples is optional.	To provide more flexibility and clarity.
Section 10.1: Statistical Hypotheses	Revised text to clarify how results of safety and efficacy will be assessed to support registration in Japan.	To provide more clarity of the assessment approach.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3: Analysis Sets	[redacted]	To align with statistical analysis plan.
Section 10.5: Interim Analyses	Added that an additional analysis will be conducted when all participants complete the Week 54 visit or permanently discontinue treatment.	
Appendix 2: Study Governance Considerations	Added 2 new sections.	To reflect BMS' commitment to diversity and providing data protection, privacy, and security in clinical trials.
Appendix 5: Prohibited Medications	Removed grapefruit juice from prohibited medications because it is listed in Section 6.4.1, Meals and Dietary Restrictions.	To provide consistent guidance regarding grapefruit juice.
All	Minor formatting and typographical corrections.	Minor and therefore have not been summarized.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title: A Phase 3, Open-label, Single-arm, Clinical Study to Evaluate Efficacy, Safety and Tolerability of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Brief Title: Mavacamten in Obstructive Hypertrophic Cardiomyopathy

Rationale:

Mavacamten (BMS-986427, also known as MYK-461) is a first-in-class, small-molecule, selective allosteric inhibitor of cardiac myosin ATPase specifically developed to target the underlying pathophysiology of hypertrophic cardiomyopathy by reducing actin–myosin cross-bridge formation, thereby reducing contractility and improving myocardial energetics.

In EXPLORER-HCM, a Phase 3, randomized, double-blind, placebo-controlled trial, treatment with mavacamten improved exercise capacity, left ventricular outflow tract (LVOT) obstruction, New York Heart Association (NYHA) functional class, and health status in patients with obstructive hypertrophic cardiomyopathy (HCM).

This Phase 3 open-label, single-arm, study is designed to evaluate the efficacy, safety, and tolerability of a 30-week course of mavacamten and the long-term effects of mavacamten in Japanese participants with symptomatic obstructive HCM.

Objectives and Endpoints:

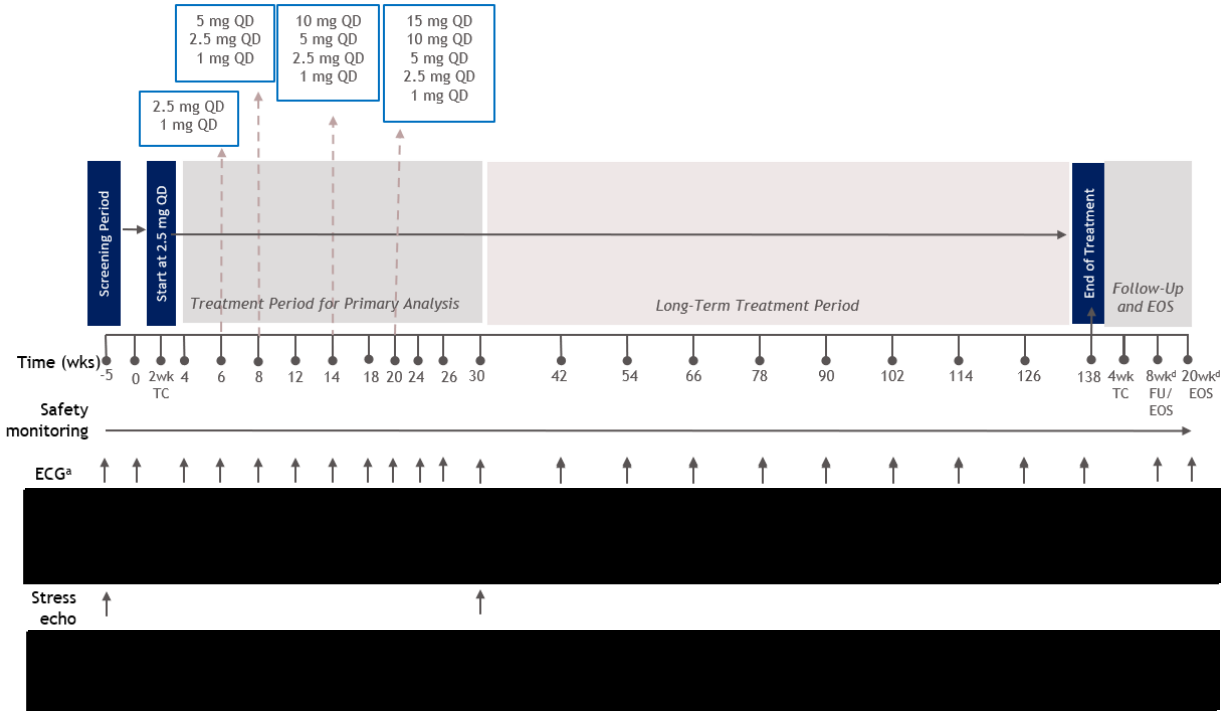
Objectives	Endpoints
Primary	
• To evaluate the effect of a 30-week course of mavacamten on post exercise peak LVOT gradient as determined by Doppler echocardiography.	• Change from baseline to Week 30 in post exercise LVOT peak gradient.
Secondary	
• To assess the effect of a 30-week course of mavacamten on health status.	• Change from baseline to Week 30 in KCCQ CSS.
• To assess the effect of a 30-week course of mavacamten on symptoms.	• Proportion of participants with at least 1 class improvement in NYHA functional class from baseline to Week 30.
• To assess the effect of a 30-week course of mavacamten on cardiac biomarkers.	• Change from baseline to Week 30 in NT-proBNP. • Change from baseline to Week 30 in cardiac troponins.
[redacted]	
[redacted]	

Objectives	Endpoints
[redacted]	

Abbreviations: [redacted] CSS, Clinical Summary Score; [redacted] KCCQ, Kansas City Cardiomyopathy Questionnaire; [redacted] LVOT, left ventricular outflow tract; [redacted] NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; [redacted]

Overall Design:

Study Design Schema



Abbreviations: [redacted] CYP, cytochrome P450; ECG, electrocardiogram; EOS, end of study; FU, follow-up; [redacted] PM, poor metabolizer; QD, once daily; stress echo, post exercise stress echocardiography; TC, telephone call; Time 0, Day 1 (start of Treatment Period for Primary Analysis); [redacted] wks, weeks.

a In addition to pre-dose ECG, post-dose ECG is to be performed around time of maximum observed concentration (Tmax) (0.5 to 3 hours post-dose) at Day 1 and Weeks 8, 14, and 20.

[redacted]

d Follow-up or EOS visit at Week 8 for all participants, and at Week 20 if cytochrome P450 (CYP) 2C19 PM.

Screening Period (Day -35 to Day -1):

Participants will undergo a variety of general and laboratory assessments to assess eligibility. Key screening tests include electrocardiogram (ECG); [redacted] conducted

at rest, with Valsalva maneuver, and post exercise; [redacted] A goal of at least 25% of the participants will be NYHA functional Class III at Screening.

The following Screening assessments may be repeated, as long as they are within the 35-day screening window: blood tests, ECG, [redacted]. Repeat assessments are allowed if central core laboratories require a repeat submission due to quality and in order to better assess inclusion/exclusion values. Participants who fail screening may be considered for rescreening based on the investigator's discretion, taking into consideration the reason(s) for screening failure. One attempt at rescreening will be allowed, and all procedures must be repeated.

Participants who meet all eligibility criteria will be treated.

Treatment Period:

Treatment Period for Primary Analysis (Day 1 Through Week 30)

The initial treatment period (Day 1 through Week 30) for primary efficacy analysis will include dose titration designed to achieve safe and effective dosing for each participant based on their own response parameters. Participants will receive treatment with mavacamten at a 2.5-mg starting dose once daily (QD). The permissible doses during Day 1 through Week 30 are 1, 2.5, 5, 10, and 15 mg mavacamten. Assessments including ECG, [redacted] will be performed at study visits and read by core laboratories. The dose will be adjusted or temporarily discontinued as described in the Study Treatment and Administration section. The dose may be reduced or discontinued at any time during the Treatment Period based on the clinical judgment of the investigator in discussion with the Medical Monitor.

At Week 30, participants will complete [redacted] at rest, with Valsalva maneuver, and post exercise; [redacted]

Long-Term Treatment Period (Week 30 to Week 138)

Participants will continue on the dose received at Week 30.

After the initial 30 weeks of the study, visits will occur every 12 weeks and will include but are not limited to clinical evaluation of symptoms, AE/serious adverse event assessments, ECGs, [redacted] and laboratory assessments including N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac troponins.

The dose may be reduced or discontinued at any time during the Long-Term Treatment Period based on the clinical judgment of the investigator in discussion with the Medical Monitor.

The permissible doses during Week 30 to Week 138 are 1, 2.5, 5, 10, and 15 mg mavacamten.

Post-treatment Follow-up Period (End of Treatment to End of Study):

Participants who prematurely discontinue the study will attend an early termination visit, be contacted by telephone 4 weeks later, and return to the study site 8 weeks later for an end of study (EOS) visit. CYP 2C19 poor metabolizers (PMs) will also return to the study site for an 8-week follow-up visit and a 20-week EOS visit. After the participant completes the EOT visit, the site

will be contacted by the Sponsor to notify the investigator if the participant is a CYP 2C19 PM and requires an additional 20-week EOS visit.

Participants who complete 138 weeks of the study and do not roll over to commercially available mavacamten will attend an EOT visit, be contacted by telephone 4 weeks later, and return to the study site 8 weeks later for an EOS visit. CYP 2C19 PMs will also return to the study site for the 8-week follow-up visit and a 20-week EOS visit. After the participant completes the EOT visit, the site will be contacted by the Sponsor to notify the investigator if the participant is a CYP 2C19 PM and requires an additional 20-week EOS visit.

Participants who roll over to commercially available mavacamten at any time will be contacted by telephone 4 weeks and 8 weeks later for an EOS follow-up to assess AEs, concomitant medications, and pregnancy status. CYP 2C19 PMs will be contacted by telephone at Weeks 4, 8, and 20 post EOT.

Safety Monitoring:

Safety monitoring will be ongoing at scheduled study visits during the study through EOS. Clinic visits will include but are not limited to monitoring of AEs and concomitant medications, safety laboratory assessments, physical examinations, vital sign measurements, [redacted] and ECGs.

[redacted] will be performed by study site sonographers at scheduled visits as per protocol following enrollment. If left ventricular ejection fraction (LVEF) of ≤ 30% is measured at the site, then mavacamten will be permanently discontinued as described within the protocol.

Assessments obtained during clinic visits will be used to guide dose reduction or temporary discontinuation, based on predefined criteria detailed within the protocol.

Number of Participants:

Approximately 30 participants will be treated.

It is estimated that approximately 50 screened participants will be required to achieve the 30 treated participants.

Study Population:

Japanese participants with symptomatic obstructive HCM.

Intervention Groups and Duration:

Intervention groups: All participants will be treated with mavacamten.

Study duration: The study duration is a maximum of 151 weeks (163 weeks if CYP 2C19 PM): Screening Period (up to 5 weeks); Treatment Period for Primary Analysis (Day 1 through Week 30), Long-Term Treatment Period (Week 30 to Week 138), and Post-treatment Follow-up Period (8 weeks [and 20 weeks if CYP 2C19 PM]) or until mavacamten becomes commercially available (at the discretion of the Sponsor).

The EOS is defined as the date of the last visit on the Schedule of Activities of the last participant.

Study Intervention:

Study Intervention for CV027004		
Medication	**Potency**	**IMP/Non-IMP/AxMP**
BMS-986427/MYK-461 immediate-release capsules	1, 2.5, 5, 10, and 15 mg	IMP

Abbreviations: AxMP, auxiliary medicinal product IMP, investigational medicinal product.

Dosing: Treatment Period for Primary Analysis (Day 1 through Week 30)

Participants will begin treatment with mavacamten immediate-release capsules 2.5 mg QD for the first 6 weeks of the dosing period.

All dose adjustments will occur through the interactive response system, based on core laboratory read [redacted] data entered by the core laboratory. Participants will receive mavacamten in 30 count high-density polyethylene bottles that are appropriately labeled. Mavacamten is administered QD by mouth.

Scheduled dose adjustments will occur at Weeks 6, 8, 14, and 20 based on the core read echocardiography laboratory measurements of LVOT gradient with Valsalva maneuver [redacted]

If at Week 4 Valsalva LVOT gradient is < 30 mm Hg and LVEF is ≥ 50%, the dose will be decreased to 1 mg at Week 6. There are 3 opportunities for up-titration: at Week 8 based on Week 6 assessments, at Week 14 based on Week 12 assessments, and at Week 20 based on Week 18 assessments. Up-titration requires LVEF ≥ 55% and LVOT gradient with Valsalva maneuver ≥ 30 mm Hg. Dose may be down-titrated by 1 dose level or discontinued for safety at any time during the study based on the clinical judgment of the investigator in consultation with the Medical Monitor.

Dose increases are designed to be stepwise and are not allowed to skip doses (eg, from 2.5 mg to 10 mg). The permissible doses after dose adjustment at Week 8 will be 1, 2.5, or 5 mg. The permissible doses after dose adjustment at Week 14 will be 1, 2.5, 5, or 10 mg. The permissible doses after dose adjustment at Week 20 will be 1, 2.5, 5, 10, or 15 mg.

Dosing: Long-Term Treatment Period (Week 30 to Week 138)

Dose adjustments will occur on the day of the visit, based on site-read measurement of LVOT gradient with Valsalva maneuver [redacted]. The permissible doses during Week 30 to Week 138 are 1, 2.5, 5, 10, and 15 mg mavacamten.

At any visit subsequent to Week 30, if the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mm Hg and resting LVEF is ≥ 55%, then a dose increase may be considered, up to a maximum of 15 mg QD, after discussion with the Medical Monitor.

If dose adjustment occurs, the participant should return to the clinic approximately 28 days later (± 7 days) for an unscheduled visit with resting [redacted] to confirm safety. Post exercise echocardiographic assessment of LVOT gradient during this period will be at the investigator's discretion.

The dose may be reduced or discontinued at any time during the Long-Term Treatment Period based on the clinical judgment of the investigator in discussion with the Medical Monitor. Participants who have had a dose reduction should return to the clinic approximately 28 days later (± 7 days) for an unscheduled visit with AE and safety laboratory assessments, ECG, and resting [redacted] to confirm safety. 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.

Temporary Discontinuation

Dosing will be temporarily discontinued if results as reported by the central laboratories from any visit during the first 30 weeks of study (or site-read [redacted] from Week 30 to Week 138) show resting LVEF < 50%, [redacted] or the QT interval with Fridericia correction (QTcF) stopping criterion is met (if baseline QRS is narrow [< 120 msec], the stopping criterion is the smaller of a 15% increase from baseline in QTcF or QTcF ≥ 520 msec; if baseline QRS is wide [≥ 120 msec], the stopping criterion is the smaller of a 15% increase from baseline in QTcF or QTcF ≥ 550 msec).

Upon receipt of this information, the study site/investigator will contact the participant and instruct the participant to discontinue mavacamten. If LVEF is ≥ 50%, [redacted] and/or QTcF duration is below programmed discontinuation rules, then mavacamten will be restarted at a lower dose.

Statistical Methods:

Approximately 30 participants will be treated. Assuming the mean (SD) of the primary endpoint, the change from baseline to Week 30 in post exercise LVOT gradient is -40 (45) mm Hg, a sample size of 30 participants will have approximately 94% probability to observe a mean change of ≤ -27 mm Hg, with an observed 95% CI of (-43, -11) mm Hg.

To determine the similarity of the results between this study and EXPLORER-HCM study, we consider the following 2 criteria:

1) The observed mean change in post exercise LVOT gradient in this study should be ≤ -27 mm Hg, which is at least 57% of the change shown in the mavacamten arm of EXPLORER-HCM study.
2) The CI of the mean change in this study should exclude the mean change from baseline to Week 30 in placebo arm of EXPLORER-HCM study, ie, upper limit of the CI < -10.

When all participants complete the Week 30 visit or terminate the study treatment prior to week 30, primary analysis will be performed to assess the efficacy and safety of mavacamten treatment for the 30-week period. When all participants complete the Week 54 visit or permanently

discontinue treatment, an additional analysis will be conducted. Final analysis will be performed when all participants complete the EOS visit.

Efficacy Analyses

Descriptive statistics will be presented for all efficacy endpoints. Descriptive summary will be based on all data available. Missing data will not be imputed. In case the primary and secondary endpoints have missing data that are more than expected (eg, 10%), data imputation may be performed, and detailed methods will be discussed in the statistical analysis plan.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint of post exercise LVOT peak gradient change from baseline to Week 30 will be summarized along with 95% CIs.

Secondary [redacted] Efficacy Endpoints Analyses

The general analytical rules for the secondary [redacted] efficacy endpoints are the following:

- Change from baseline endpoints will be summarized with descriptive statistics, including mean, SD, minimum, median, maximum, and 95% CI. There is no formal testing for secondary [redacted] endpoints.
- Response rate for the categorical endpoints will be summarized with number and percentage with 95% CI, and no formal testing will be performed.

Safety Analyses

Safety data will be analyzed using descriptive statistics without formal statistical testing. The safety analysis will focus on the Treatment-emergent Adverse Event Period. This period is defined as the time from the first administration of mavacamten to the last administration of mavacamten + 56 days (or 140 days if CYP 2C19 PM).

[redacted]

Data Monitoring Committee: No

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

Other Committee: No

Other review committee will not be used in the study.

Brief Summary:

Condition/Disease: Patients with obstructive hypertrophic cardiomyopathy (HCM).

Study Hypothesis: This Phase 3 open-label, single-arm, study is designed to evaluate the efficacy, safety, and tolerability of a 30-week course of mavacamten and the long-term effects of mavacamten in Japanese participants with symptomatic obstructive HCM.

Study Duration: The study duration is a maximum of 151 weeks (163 weeks if CYP 2C19 PM).

Study Intervention Duration: Treatment Period for Primary Analysis (Day 1 through Week 30), Long-Term Treatment Period (Week 30 to Week 138).

Health Measurement/Observation: The primary efficacy endpoint will evaluate the effect of a 30-week course of mavacamten on post exercise peak LVOT gradient as determined by echocardiography.

Study Visit Frequency: Visits will occur every 2 to 4 weeks during the Treatment Period for Primary Analysis. All visit dates will be scheduled based on Day 1. All visits after Day 1 should occur within the visit window (± 7 days) scheduled based on the projected study date. After the initial 30 weeks of the study, visits will occur every 12 weeks.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures for screening are presented in Table 2-1, and schedules of activities for on-treatment and follow-up are presented in Table 2-2, Table 2-3, and Table 2-4.

Table 2-1: Screening Procedural Outline (CV027004)

Procedure[a]	Screening Period[b] (Day -35 to Day -1)	Notes
Informed Consent	X	Informed consent must be signed prior to initiating any study procedures.
Inclusion/Exclusion Criteria	X	See Sections 6.1 and 6.2.
Medical History	X	All medical history relevant to disease under study.
ICD Download	X	For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs.
[redacted]		

Table 2-1: Screening Procedural Outline (CV027004)

Procedure[a]	Screening Period[b] (Day -35 to Day -1)	Notes
[redacted]		
NYHA Functional Class	X	
Physical Examination (PE)	X	A complete physical examination will be conducted, including a neurological examination.
Weight	X	
Height	X	
Vital Signs	X	Complete vital signs including temperature, HR, respiratory rate, and BP will be obtained. Vital signs should be taken with the study participant in the same position at all visits. BP should be taken via an automated recorder after resting for at least 5 minutes.
Concomitant Medication Use	X	
ECG	X	12-lead ECGs will be performed after 10 minutes of rest. After the ECG is completed, a 10-second paper ECG will be obtained and maintained in the study participant's source documentation. ECG should be completed prior to blood draws.
Cardiac Monitoring Device	X	A cardiac monitoring device will be applied at Screening.
Laboratory Tests	See Table 9.4.4-1.	
Hematology	X	
Chemistry	X	
Urinalysis	X	
Follicle-stimulating Hormone (FSH)	X	FSH testing for postmenopausal women to confirm postmenopausal status.
Pregnancy Test (β-hCG)	X	Serum pregnancy testing for all females of childbearing potential.

Table 2-1: Screening Procedural Outline (CV027004)

Procedure[a]	Screening Period[b] (Day -35 to Day -1)	Notes
Coagulation Panel	X	
Serology	X	Includes hepatitis C antibody, hepatitis B surface antigen, and HIV-1 and -2 antibody.
Adverse Event Reporting		
Monitor for Serious Adverse Events (SAEs)	X	All SAEs will be collected starting after the signed consent and at each visit through Follow-up Period. See Section 9.2.
Biomarker Assessments		
Biomarkers	See Table 9.8-1 for biomarker sample collection.	

Abbreviations: β-hCG, human chorionic gonadotropin; BP, blood pressure; [redacted] ECG, electrocardiogram; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; HR, heart rate; ICD, implantable cardioverter-defibrillator; [redacted] NYHA, New York Heart Association; PE, physical examination; SAE, serious adverse event; [redacted].

[a] All assessments should be performed prior to mavacamten dosing unless otherwise specified. ECG should be completed prior to blood draws. Blood draws (for biomarkers and laboratory tests) should be performed prior to exercise.

[b] Screening may require more than one visit to accommodate all study procedures.

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
Physical Examination (PE)	X		X	X	X	X	X	X	X	X	X	X	At Week 30 and ET, a complete physical examination will be conducted, including a neurological examination. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.
Weight												X	
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	At Week 30 and ET, complete vital signs including temperature, HR, respiratory rate, and BP will be obtained. At all other visits, only HR and BP are required. If [redacted] is conducted at a visit, vital signs should be collected before [redacted]. Vital signs should be taken with the study participant in the same position at all visits. BP should be taken via an automated recorder after resting for at least 5 minutes.
Concomitant Medication Use	X	X	X	X	X	X	X	X	X	X	X	X	

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
ECG	X		X	X	X	X	X	X	X	X	X	X	12-lead ECGs will be performed after 10 minutes of rest prior [redacted] at most on-site study visits. At Day 1, Weeks 8, 14, and 20, post-dose ECG will also be performed around Tmax (0.5 – 3 hours after study drug dose) in addition to the pre-dose ECG. Each time an ECG is completed, a 10 second paper ECG will be obtained and maintained in the study participant's source documentation. ECG should be completed prior to blood draws.
Cardiac Monitoring Device						X					X		A cardiac monitoring device will be applied at Weeks 12 and 26.
ICD Download						X						X	For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at Week 12, Week 30, and ET, or as clinically indicated after any ICD discharge interrogation occurring during the study.
KCCQ	X			X		X		X				X	The KCCQ should be completed by participants prior to any other study procedure taking place, when possible.
Laboratory Tests	See Table 9.4.4-1.												
Hematology						X						X	

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
Chemistry	X			X		X		X				X	
Urinalysis												X	
Pregnancy Test	X		X	X	X	X	X	X	X	X	X	X	Urine pregnancy testing for all females of childbearing potential. Negative Day 1 urine pregnancy test is required prior to initiating study treatment. If a urine test is positive or 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. Refer to Section 9.2.5.
Coagulation Panel	X			X		X		X				X	
Adverse Event Reporting													
Monitor for Adverse Events (AEs)	Continuously												Nonserious AEs will be collected starting with the first dose of study drug and at each visit through Follow-up Period. See Section 9.2.
Monitor for Serious Adverse Events (SAEs)	Continuously												All SAEs will be collected starting after the signed consent and at each visit through Follow-up Period. See Section 9.2.
[redacted]													

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
Biomarker Assessments													
Biomarkers	See Table 9.8-1 for biomarker sampling schedule.												
Efficacy Assessments													
[redacted]													

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
[redacted]													

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
[redacted]													

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
[redacted]													
NYHA Functional Class	X		X	X	X	X	X	X	X	X	X	X	
Study Treatment QD	Continuously												
Dose Adjustment Assessment				X	X		X		X				
Study Treatment Administered at Site	X		X	X	X	X	X	X	X	X	X	X	At all on-site visits, mavacamten will be administered at the investigational site to facilitate collection of [redacted] sample ≤ 4 hours prior to dosing. Mavacamten will be administered at the end of the visit when all other assessments have completed, including any drawing of blood.

Table 2-2: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Primary Analysis Treatment Period (Day 1 through Week 30)												Notes
	D1	Wk 2 TC, D15	Wk 4 D29	Wk 6 D43	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 20 D141	Wk 24 D169	Wk 26 D183	Wk 30[c] D211	
Study Treatment Compliance			X	X	X	X	X	X	X	X	X	X	All participants will return their mavacamten dosing containers to the site pharmacy for capsule counts. Refer to the Pharmacy Manual for details.

Abbreviations: AE, adverse event; BP, blood pressure; [redacted] d, day; ECG, electrocardiogram; ET, early termination; HCM, hypertrophic cardiomyopathy; HR, heart rate; ICD, implantable cardioverter-defibrillator; [redacted] KCCQ, Kansas City Cardiomyopathy Questionnaire; [redacted] NYHA, New York Heart Association; [redacted] QD, once daily; SAE, serious adverse event: TC, telephone call; Tmax, time of maximum observed concentration; [redacted] Wk, week; Wt, weight.

[a] All visit dates will be scheduled based on Day 1. All visits after Day 1 should occur within the visit window (± 7 days) scheduled based on the projected study date.

[b] All assessments should be performed prior to mavacamten dosing unless otherwise specified. The KCCQ should be completed by participants prior to any other study procedure taking place, when possible. ECG should be completed prior to blood draws. Blood draws (for [redacted] biomarkers, and laboratory tests) should be performed prior to exercise.

[c] In case of unforeseen medical conditions preventing ability to perform procedures at Week 30, these procedures may be completed at the earliest possible time point based on investigator assessments of medical status (outside of the ± 7-day window).

[redacted]

Table 2-3: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Long-Term Treatment Period (Week 30 to Week 138)										Notes[d]
	Wk 42 D295	Wk 54 D379	Wk 66 D463	Wk 78 D547	Wk 90 D631	Wk 102 D715	Wk 114 D799	Wk 126 D883	Unscheduled Visit[c]	Wk 138 EOT	ET	
Physical Examination (PE)	X	X	X	X	X	X	X	X	X	X	X	At ET and/or Week 138, a complete physical examination will be conducted, including a neurological examination. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.
Weight			X			X				X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	At ET and/or Week 138, complete vital signs including temperature, HR, respiratory rate, and BP will be obtained. At all other visits, only HR and BP are required. If [redacted] conducted at a visit, vital signs should be collected before [redacted] sampling. Vital signs should be taken with the study participant in the same position at all visits. BP should be taken via an automated recorder after resting for at least 5 minutes.
Concomitant Medication Use	X	X	X	X	X	X	X	X	X	X	X	

Table 2-3: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Long-Term Treatment Period (Week 30 to Week 138)										Notes[d]
	Wk 42 D295	Wk 54 D379	Wk 66 D463	Wk 78 D547	Wk 90 D631	Wk 102 D715	Wk 114 D799	Wk 126 D883	Unscheduled Visit[c]	Wk 138 EOT	ET	
ECG	X	X	X	X	X	X	X	X	X	X	X	12-lead ECGs will be performed after 10 minutes of rest prior [redacted] at most on-site study visits. Each time an ECG is completed, a 10-second paper ECG will be obtained and maintained in the study participant's source documentation. ECG should be completed prior to blood draws.
Cardiac Monitoring Device			X			X		X				A cardiac monitoring device will be applied at Weeks 66, 102, and 126.
ICD Download			X			X				X	X	For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at Weeks 66, 102, ET, and/or Week 138, or as clinically indicated after any ICD discharge interrogation occurring during the study.
KCCQ		X	X	X			X			X	X	
Laboratory Tests	See Table 9.4.4-1.											
Hematology		X		X	X		X			X	X	
Chemistry		X		X	X		X			X	X	
Urinalysis			X							X	X	

Table 2-3: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Long-Term Treatment Period (Week 30 to Week 138)											Notes[d]
	Wk 42 D295	Wk 54 D379	Wk 66 D463	Wk 78 D547	Wk 90 D631	Wk 102 D715	Wk 114 D799	Wk 126 D883	Unscheduled Visit[c]	Wk 138 EOT	ET	
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	Urine pregnancy testing for all females of childbearing potential. A pregnancy test will be taken every 4 weeks at home, at the site, or at a local laboratory when no clinic visit is scheduled until the end of the study. Refer to Section 9.2.5. Conduct serum test if any urine test is positive.
Coagulation Panel		X		X	X		X			X	X	
Monitor for Adverse Events (AEs)	See Notes.											Nonserious AEs will be collected starting with the first dose of study drug and at each visit through Follow-up Period. See Section 9.2.
Monitor for Serious Adverse Events (SAEs)	See Notes.											All SAEs will be collected starting after the signed consent and at each visit through Follow-up Period. See Section 9.2.
[redacted]												
Biomarker Assessments												
Biomarker Assessments	See Table 9.8-1 for biomarker sampling schedule.											

Table 2-3: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Long-Term Treatment Period (Week 30 to Week 138)											Notes[d]
	Wk 42 D295	Wk 54 D379	Wk 66 D463	Wk 78 D547	Wk 90 D631	Wk 102 D715	Wk 114 D799	Wk 126 D883	Unscheduled Visit[c]	Wk 138 EOT	ET	
Efficacy Assessments												
[redacted]												

Table 2-3: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Long-Term Treatment Period (Week 30 to Week 138)											Notes[d]
	Wk 42 D295	Wk 54 D379	Wk 66 D463	Wk 78 D547	Wk 90 D631	Wk 102 D715	Wk 114 D799	Wk 126 D883	Unscheduled Visit[c]	Wk 138 EOT	ET	
[redacted]												

Table 2-3: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Long-Term Treatment Period (Week 30 to Week 138)											Notes[d]
	Wk 42 D295	Wk 54 D379	Wk 66 D463	Wk 78 D547	Wk 90 D631	Wk 102 D715	Wk 114 D799	Wk 126 D883	Unscheduled Visit[c]	Wk 138 EOT	ET	
[redacted]												
NYHA Functional Class	X	X	X	X	X	X	X	X	X	X	X	
Study Treatment QD	Continuously											

Table 2-3: On-Treatment - Schedule of Activities for All Participants (CV027004)

Week Visits (± 7 d)[a,b]	Long-Term Treatment Period (Week 30 to Week 138)										Notes[d]
	Wk 42 D295	Wk 54 D379	Wk 66 D463	Wk 78 D547	Wk 90 D631	Wk 102 D715	Wk 114 D799	Wk 126 D883	Unscheduled Visit[c]	Wk 138 EOT	ET	
Study Treatment Administered at Site	X	X	X	X	X	X	X	X	X	X		At all on-site visits, mavacamten will be administered at the investigational site to facilitate collection of [redacted] sample ≤ 4 hours prior to dosing. Mavacamten will be administered at the end of the visit when all other assessments have completed, including any drawing of blood.
Study Treatment Compliance	X	X	X	X	X	X	X	X	X	X	X	All participants will return their mavacamten dosing containers to the site pharmacy for capsule counts. Refer to the Pharmacy Manual for details.

Abbreviations: AE, adverse event; BP, blood pressure; [redacted] CYP, cytochrome P450; d, day; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ET, early termination; HR, heart rate; Ht, height; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; [redacted] NYHA, New York Heart Association; [redacted] PM, poor metabolizer; QD, once daily; SAE, serious adverse event; [redacted] Wk, week.

[a] All visits after Day 1 should occur within the visit window (± 7 days) scheduled based on the projected study date.

[b] All assessments should be performed prior to mavacamten dosing unless otherwise specified. The KCCQ should be completed by participants prior to any other study procedure taking place, when possible. ECG should be completed prior to blood draws. Blood draws (for [redacted] biomarkers, and laboratory tests) should be performed prior to exercise.

[c] Participants who have any dose adjustment should return to the clinic approximately 28 days later (± 7 days) for an unscheduled visit with AE and safety laboratory assessments, and ECG [redacted] to confirm safety (see Section 7.4.1.2).

[d] Participants who prematurely discontinue study treatment will attend an ET visit and be contacted by site 4 weeks later for a telephone call. They will return to the study site 8 weeks later for an EOS visit. CYP 2C19 PMs will return to the study site for the Week 8 follow-up visit and a Week 20 EOS visit.

Table 2-4: Follow-Up Procedural Outline (CV027004)

Week Visits (± 7 d)[a,b]	Week 4 Follow-up Telephone Call	Week 8 Follow-up/EOS[c]	Week 20 Follow-up/EOS[c]	Notes
Physical Examination (PE)		X	X	An abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.
Vital Signs		X	X	Only HR and BP are required. If [redacted] sampling is conducted at a visit, vital signs should be collected before [redacted] sampling. Vital signs should be taken with the study participant in the same position at all visits. BP should be taken via an automated recorder after resting for at least 5 minutes.
Concomitant Medication Use	X	X	X	
ECG		X	X	12-lead ECGs will be performed after 10 minutes of rest prior [redacted]. Each time an ECG is completed, a 10-second paper ECG will be obtained and maintained in the study participant's source documentation. ECG should be completed prior to blood draws.
Laboratory Tests	See Table 9.4.4-1.			
Hematology		X	X	
Chemistry		X	X	
Urinalysis		X	X	
Pregnancy test	X	X	X	Urine pregnancy testing for all females of childbearing potential. A pregnancy test will be taken every 4 weeks at home, at the site, or at a local laboratory when no clinic visit is scheduled until the end of the study. Conduct serum test if any urine test is positive
Coagulation Panel		X	X	

Table 2-4: Follow-Up Procedural Outline (CV027004)

Week Visits (± 7 d)[a,b]	Week 4 Follow-up Telephone Call	Week 8 Follow-up/EOS[c]	Week 20 Follow-up/EOS[c]	Notes
Adverse Event Reporting				
Monitor for Adverse Events (AEs)	Continuously			Nonserious AEs will be collected starting with the first dose of study drug and at each visit through Follow-up Period. See Section 9.2.
Monitor for Serious Adverse Events (SAEs)	Continuously			All SAEs will be collected starting after the signed consent and at each visit through Follow-up Period. See Section 9.2.
[redacted]				
Biomarker Assessments				
Biomarker Assessments	See Table 9.8-1 for biomarker sampling schedule.			
Efficacy Assessments				
[redacted]				
NYHA Functional Class		X	X	

Abbreviations: AE, adverse event; BP, blood pressure; CYP, cytochrome P450; d, day; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; FU, follow-up; HR, heart rate; [redacted] NYHA, New York Heart Association; PE, physical examination; [redacted] PM, poor metabolizer; SAE, serious adverse event; [redacted]

[a] All visits after Day 1 should occur within the visit window (± 7 days) scheduled based on the projected study date.

[b] All assessments should be performed prior to mavacamten dosing unless otherwise specified. The KCCQ should be completed by participants prior to any other study procedure taking place, when possible. ECG should be completed prior to blood draws. Blood draws (for [redacted] biomarkers, and laboratory tests) should be performed prior to exercise.

[c] Follow-up visit/EOS will be completed at 8 weeks (and 20 weeks if CYP 2C19 PM).

3 INTRODUCTION

HORIZON-HCM (CV027004), a Phase 3 open-label, single-arm, study, is designed to evaluate the efficacy, safety, and tolerability of a 30-week course of mavacamten and the long-term effects of mavacamten in Japanese participants with symptomatic obstructive hypertrophic cardiomyopathy (HCM).

3.1 Study Rationale

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease. HCM 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 one 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,[6,7,8] which is consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in HCM. 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), obstructive HCM (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 obstructive hypertrophic cardiomyopathy.[13] Therefore, the prevalence rate of obstructive hypertrophic cardiomyopathy 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,[14] but the precise mechanism of LVOT obstruction is unknown. 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)[3,20] that may improve LV outflow, but offer limited and variable relief in symptoms and functional status. In obstructive hypertrophic cardiomyopathy, septal reduction therapy 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 nHCM. None of these treatment options address the underlying etiology of HCM.

Mavacamten is a small-molecule selective allosteric inhibitor of cardiac myosin that reversibly inhibits its binding to actin, thereby relieving systolic hypercontractility and improving ventricular compliance. BMS is developing mavacamten for the treatment of HCM and heart failure with preserved ejection fraction (HFpEF).

3.2 Background

Clinical Experience with Mavacamten

To date, 19 clinical studies have been initiated to investigate the safety and tolerability of mavacamten. As of 31-Aug-2021, a total of 599 participants with HCM, HFpEF, or healthy participants were exposed to at least 1 dose of mavacamten. Participants who received treatment in both parent and extension studies are only counted once. Please refer to the Investigator's Brochure (IB) for more details.

In the EXPLORER-HCM (MYK-461-005) Phase 3, randomized, double-blind, placebo-controlled study, patients with obstructive hypertrophic cardiomyopathy were assigned (1:1) to receive mavacamten (starting at 5 mg) or placebo for 30 weeks.[22] Treatment with mavacamten was superior to placebo across the primary endpoint and all secondary endpoints in a study population with 92% of participants on either beta blocker or non-dihydropyridine calcium channel blocker therapy. Participants treated with mavacamten demonstrated twice the response rate of those in the placebo group on the composite functional primary endpoint (36.6% vs 17.2%), with a highly statistically significant between-group difference (19.4% [95% CI: 8.67, 30.13], P = 0.0005). Additionally, 20.3% of participants treated with mavacamten met the criteria of ≥ 3.0 mL/kg/min increase in peak oxygen consumption (peak VO_2) and ≥ 1 New York Heart Association (NYHA) class improvement compared with 7.8% of participants on placebo. Mavacamten treatment was also effective in reducing LVOT gradients and improving symptoms, exercise performance, and health status, as shown by significant improvement in all secondary endpoints.[23]

The safety of mavacamten has been evaluated for single and multiple doses in healthy participants and participants with HCM.

Treatment with mavacamten was well tolerated in the EXPLORER-HCM (MYK-461-005) study through 30 weeks of treatment. Overall, treatment-emergent adverse events (TEAEs) were higher in the mavacamten group compared with the placebo group during the on-treatment (Day 1 through Week 30) period (87.8% vs 78.9%) and treatment-emergent (Day 1 through Week 38) period (87.8% and 81.3%). It is notable that the TEAE rate did not increase in the mavacamten group with 8 weeks of additional observation during study drug washout. The proportion of participants in the mavacamten group with treatment discontinuations due to TEAEs was 1.6% (2 of 123 participants). No participants in the placebo group discontinued treatment due to TEAEs,

although one participant experienced sudden death. Serious adverse events (SAEs) were balanced between treatment groups: on-treatment rates of SAEs were 8.1% in the mavacamten group versus 8.6% in the placebo group, and rates of treatment-emergent SAEs through washout were 11.4% and 9.4%, respectively.[23]

The pharmacokinetic (PK) profile of mavacamten is characterized by a biphasic profile with a rapid absorption (time of maximum observed concentration [Tmax] generally between 1 and 2 h) and a long terminal half-life (t1/2) with a mean of 6 to 9 days in cytochrome P450 (CYP) 2C19 normal metabolizers (NMs). In cytochrome P450 (CYP) 2C19 poor metabolizers (PMs), t1/2 is approximately 23 days and the area under the concentration-time curve (AUC) is increased up to approximately 3-fold and maximum observed concentration (Cmax) by 50% compared to NMs (ie, *1/*1 genotype). Based on population PK studies, the exposure is largely dose proportional between 2.5 and 15 mg. At steady state, the peak-to-trough plasma concentration ratio with once daily (QD) dosing is very low (1.5 to 1). Clearance and volume of distribution have not been determined in humans, as they require intravenous (IV) administration; however, data are consistent with a low clearance and high volume of distribution, as shown in nonclinical studies. Only minor metabolites have been detected in human plasma from the multiple ascending dose clinical trial (MYK-461-003). The systemic exposure of the most abundant metabolite in human plasma was less than 2% of the exposure of mavacamten. This was confirmed in a human ^{14}C absorption, metabolism, and excretion (AME) study where all plasma metabolites were < 4% of the mavacamten exposure. The available data indicate that approximately 74% of the metabolism occurs through CYP 2C19, 18% through CYP 3A4/5, and the rest through CYP 2C9 liver enzymes. Less than 3% of the administered drug is found unchanged in the urine. A dedicated food effect study (MYK-461-014) showed that while absorption is delayed, the overall bioavailability is not affected to a clinically significant degree. An ethno-bridging study (MYK-461-011) indicated no important PK differences between Japanese and Caucasian CYP 2C19 NMs. In most cases, the between-participant variability (coefficient of variation) for exposure is moderate (in the 30% to 50% range).

Because proton pump inhibitors such as omeprazole may be used by many HCM patients, and several of them are CYP 2C19 inhibitors, the effect of over-the-counter-strength omeprazole (20 mg) on mavacamten exposure was determined in a dedicated drug-drug interaction (DDI) study (MYK-461-018). The coadministration of a weak CYP 2C19 inhibitor like omeprazole 20 mg increased the mavacamten AUC by 50% with no change in C_{max} after a single dose of mavacamten. The data from the omeprazole DDI study and from the PM versus NM study (MYK-461-012) indicate that CYP 2C19 inhibitors may increase mavacamten exposure from approximately 1.5-fold for a weak inhibitor to at most 3.4-fold for a strong inhibitor. In this study, omeprazole and esomeprazole are prohibited.

A drug-interaction study with the moderate CYP 3A4 inhibitor verapamil, which is frequently used in obstructive hypertrophic cardiomyopathy patients, revealed no changes in AUC and a 50% increase in C_{max} after a single dose of mavacamten. These changes are not considered clinically significant, especially when using a dosing strategy of starting every participant on a low dose of

mavacamten and increasing the dose as needed. Physiologically based PK modeling indicates that a strong CYP 3A4 inhibitor may be expected to increase mavacamten exposure up to 1.6-fold.

Because of the potential for mavacamten to cause induction of CYP 3A4, a drug-interaction study was conducted with a typical oral contraceptive consisting of ethinyl estradiol and norethindrone (Ortho-Novum®), which was administered before and after a 17-day course of mavacamten (25 mg on Days 1 and 2, followed by 15 mg daily for 15 days). Mavacamten did not decrease the exposure to either ethinyl estradiol or norethindrone, thus ruling out a drug interaction with oral contraceptives. Another dedicated CYP 3A4 induction study with the more sensitive probe midazolam confirmed overall no clinically meaningful induction by mavacamten. These data indicate that therapeutic levels of mavacamten do not result in clinically significant CYP 3A4 induction. The individualized, clinically guided dosing approach addresses sources of inter-individual variability.

3.3 Benefit/Risk Assessment

The potential clinical benefit of mavacamten in this study is to provide therapeutic effect in patients with symptomatic obstructive hypertrophic cardiomyopathy.

3.3.1 Risk Assessment

Based on nonclinical data and the available clinical data, cardiac failure due to systolic dysfunction (symptomatic left ventricular ejection fraction; LVEF <50%), has been identified as an important known risk. Heart failure (HF) due to drug-drug interactions with CYP 2C19 and potent 3A4 inhibitors, embryofetal toxicity, and arrhythmia due to QT prolongation have been identified as important potential risks.

3.3.1.1 Important Known Risks for Mavacamten

Cardiac Failure due to Systolic Dysfunction

In the mavacamten program, systolic dysfunction associated with mavacamten was observed as episodes of reversible LVEF reduction below the normal range. This systolic dysfunction ranged from drops in LVEF (either symptomatic or asymptomatic), and contrasted with LVEF reductions in the setting of clinical events of cardiac failure observed in complex clinical scenarios with other acute conditions such as stress cardiomyopathy, atrial fibrillation, anaphylactic shock, or other intercurrent acute conditions that confounded the causality assessment for mavacamten. Systolic dysfunction with mavacamten has been reversible and has not resulted in a picture of progressive cardiac failure (recurrent hospitalizations and progressive LVEF reduction) as described in the literature associated with progression of underlying HCM. However, the serious risk of cardiac failure due to systolic dysfunction (defined as symptomatic LVEF < 50%) is an important identified risk, and cardiac failure and systolic dysfunction are considered adverse drug reactions for mavacamten.

3.3.1.2 Important Potential Risks for Mavacamten

Heart Failure due to Interaction with CYP 2C19 and Potent 3A4 Inhibitors

Mavacamten is metabolized primarily by CYP 2C19 (74%) and CYP 3A4 (18%). CYP 2C19 inhibitors and potent CYP 3A4 inhibitors have the potential to increase mavacamten concentrations. Mavacamten exposures (AUC) increase by about 2-fold when it is taken with moderate CYP 2C19 inhibitors. Higher mavacamten concentrations may contribute to new events of systolic dysfunction, which may lead to heart failure.

Embryofetal Toxicity

There are no clinical data available on the safety of mavacamten during human pregnancy. However, in nonclinical reproductive toxicology studies, mavacamten was found to cause external, visceral, and skeletal fetal abnormalities, and developmental abnormalities occurred at exposure levels that were less than the maximum recommended human exposures. The risk of embryofetal toxicity due to paternal exposure in semen was assessed based on preclinical data, actual semen concentrations in healthy male volunteers, and the potential for these concentration levels to cause maternal systemic exposures that could be teratogenic. Based upon measurements of mavacamten in semen of 4 male participants who received 18.5 mg and 6 male participants who received 25 mg of mavacamten for 28 days, it was concluded that the risk of teratogenic effects caused by mavacamten transferred by semen or other body fluids is negligible. Highly effective contraception is required for females of childbearing potential in the ongoing clinical studies.

Arrhythmia due to QT Prolongation

In healthy hearts, modest dose-dependent and concentration-dependent corrected QT interval (QTc) prolongation has been observed. However, nonclinical data demonstrated that QTc prolongation in healthy hearts is not torsadogenic and did not result from an off-target direct effect of mavacamten; instead, the findings are attributed to an adaptive response to myosin inhibition in hearts with normal LV contractility. No torsadogenic clinical events (eg, malignant ventricular arrhythmias, seizures, or sudden death) have been observed to date in the mavacamten clinical program other than 1 event of sudden death (study MYK-005) observed on placebo treatment. In patients with obstructive hypertrophic cardiomyopathy, centrally read ECG results were consistent with a regression analysis demonstrating a negative correlation between mavacamten plasma concentrations and changes in QT interval with Fridericia correction (QTcF).

Based on the findings in healthy hearts, and due to abnormalities of QTcF in HCM patients in clinical practice (eg, interventricular conduction delay, bundle branch block, or repolarization changes due to underlying disease; use of implantable cardioverter-defibrillators/pacemakers; or concomitant use of proarrhythmic drugs), as well as the limited experience of concomitant use of mavacamten with known QT prolonging drugs commonly used in the HCM population, QTc interval change remains an important potential risk for mavacamten.

More detailed information about benefits and risks is provided in the Investigator's Brochure.

3.3.2 Benefit Assessment

The potential clinical benefit of mavacamten in this study is to provide therapeutic effect in patients with symptomatic obstructive hypertrophic cardiomyopathy.

4 OBJECTIVES AND ENDPOINTS

Table 4-1 summarizes the primary, secondary, [redacted] objectives and endpoints of the study.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of a 30-week course of mavacamten on post-exercise peak LVOT gradient, as determined by Doppler echocardiography.	• Change from baseline to Week 30 in post exercise LVOT peak gradient.
Secondary	
• To assess the effect of a 30-week course of mavacamten on health status.	• Change from baseline to Week 30 in KCCQ CSS.
• To assess the effect of a 30-week course of mavacamten on symptoms.	• Proportion of participants with at least 1 class improvement in NYHA functional class from baseline to Week 30.
• To assess the effect of a 30-week course of mavacamten on cardiac biomarkers.	• Change from baseline to Week 30 in NT-proBNP. • Change from baseline to Week 30 in cardiac troponins.
[redacted]	
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

Abbreviations: [redacted] CSS, Clinical Summary Score; [redacted] KCCQ, Kansas City Cardiomyopathy Questionnaire; [redacted] LVOT, left ventricular outflow tract; [redacted] NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; [redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 3, open-label, single-arm, study to evaluate the safety, tolerability, and efficacy of mavacamten in Japanese patients with symptomatic obstructive hypertrophic cardiomyopathy. Approximately 30 participants will be treated.

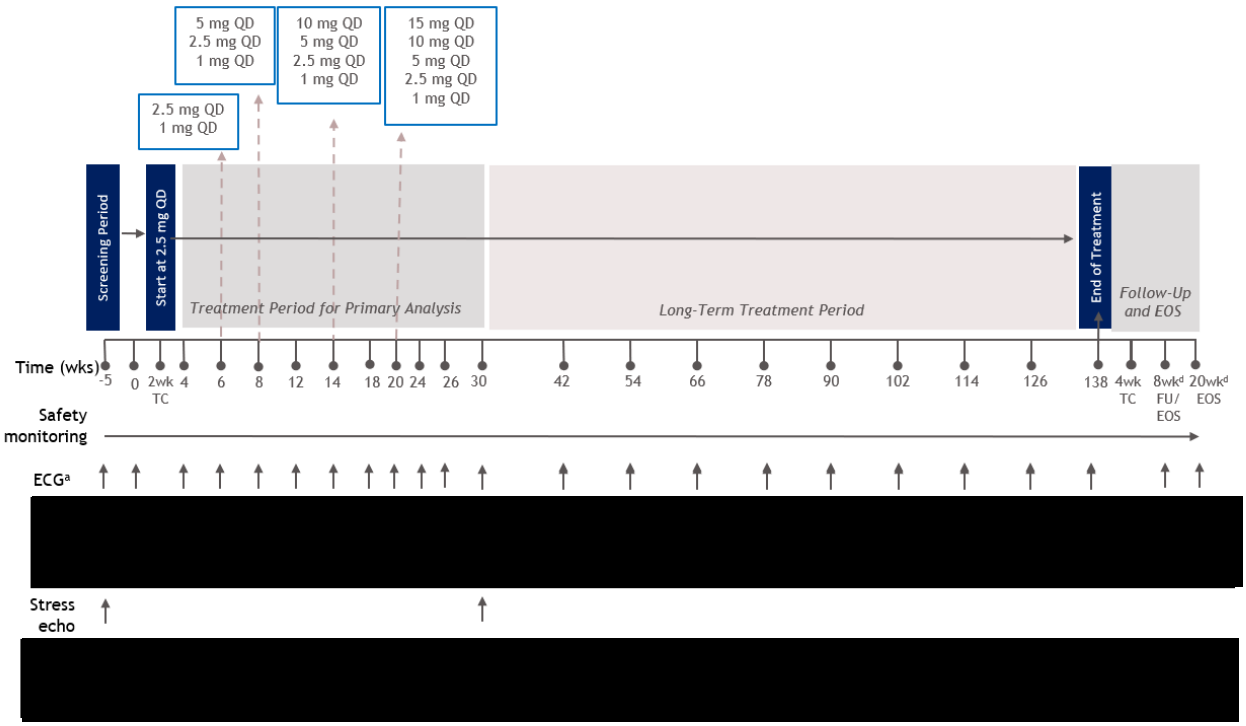
The study duration is a maximum of 151 weeks (163 weeks if CYP 2C19 PM).

The study will comprise 3 periods:

- Screening Period (up to 5 weeks)
- Treatment Period
  - Treatment Period for Primary Analysis (Day 1 through Week 30)
  - Long-Term Treatment Period (Week 30 to Week 138)
- Post-treatment Follow-up Period (8 weeks [and 20 weeks if CYP 2C19 poor metabolizer {PM}]), or until mavacamten becomes commercially available (at the discretion of the Sponsor).

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schema



Abbreviations: [redacted]
CYP, cytochrome P450; ECG, electrocardiogram; EOS, end of study; FU, follow-up; [redacted]
PM, poor metabolizer; QD, once daily; stress echo, post exercise stress echocardiography; TC, telephone call; Time 0, Day 1 (start of Treatment Period for Primary Analysis); [redacted] wks, weeks.

[a] In addition to pre-dose ECG, post-dose ECG is to be performed around Tmax (0.5 to 3 hours post-dose) at Day 1, and Weeks 8, 14, and 20.

[redacted]

[d] Follow-up or EOS visit at Week 8 for all participants, and at Week 20 if CYP 2C19 PM.

5.1.1 Screening Period

Participants will undergo a variety of general and laboratory assessments to assess eligibility (see Figure 5.1-1 and Table 2-1). Key screening tests include ECG; [redacted] A goal of at least 25% of the participants will be NYHA functional Class III at Screening.

The following Screening assessments may be repeated, as long as they are within the 35-day screening window: blood tests, ECG, [redacted]. Repeat assessments are allowed if central core laboratories require a repeat submission due to quality and in order to better assess inclusion/exclusion values. Participants who fail screening may be considered for rescreening based on the investigator's discretion, taking into consideration the reason(s) for screening failure. One attempt at rescreening will be allowed, and all procedures must be repeated.

Screening test results as reported by core laboratories (ECG core laboratory and echocardiography core laboratory) will be used to confirm eligibility.

Participants who meet all eligibility criteria may be treated.

5.1.2 Treatment Period

In the context of coronavirus disease 2019 (COVID-19) or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend on-site study visits for scheduled assessments and dispensation of mavacamten. Guidance on participant management in these situations is outlined in Appendix 7.

5.1.2.1 Treatment Period for Primary Analysis

The initial treatment period (Day 1 through Week 30) for primary efficacy analysis will include dose titration designed to achieve safe and effective dosing for each participant based on their own response parameters. Participants who meet all eligibility criteria at Screening will be entered into the study via an interactive response system (IXRS), and will receive treatment with mavacamten 2.5 mg starting dose once daily (QD). The permissible doses during Day 1 through Week 30 are 1, 2.5, 5, 10, and 15 mg mavacamten. Assessments including ECG, [redacted] will be performed at study visits and read by core laboratories (Table 2-2 and Table 2-3). The dose will be adjusted or temporarily discontinued as described in Section 7.4.1. The dose may be reduced or discontinued at any time during the Treatment Period based on the clinical judgment of the investigator in discussion with the Medical Monitor.

After the Day 1 visit, participants will be contacted by telephone at Week 2 to check on AEs and concomitant medications. Participant will first be seen at Week 4 for an initial evaluation of clinical tolerability and safety. [redacted]

Participants will subsequently be seen at Weeks 6, 8, 12, 14, 18, 20, 24, 26, and 30 for repeat evaluation. Core read assessments [redacted] of LVEF and LVOT gradient with Valsalva will be performed to guide dose adjustment via the IXRS. At Week 6, dose may be decreased or remain unchanged based upon results of Week 4 assessments. At Weeks 8, 14, and 20, the dose will be adjusted (dose increase, dose decrease, dose unchanged) based upon results of Week 6, 12, and 18 assessments, respectively, as specified in Section 7.4.1.

After Week 20, there are no additional scheduled dose titrations. Assessments at any visit can inform dose reduction or temporary discontinuation of mavacamten based on predefined criteria detailed in Section 8.1.3.1.

All clinic visits will include but are not limited to clinical evaluation (symptoms, [redacted] AE/SAE assessments, concomitant medications). Assessments including ECG, [redacted] will be performed at study visits and read by core laboratories (see Section 2). If LVEF ≤ 30% is measured at the site, then the investigator will be notified and mavacamten will be permanently discontinued (Section 8.1.4).

At Week 30, participants will complete [redacted] at rest, with Valsalva maneuver, and post exercise; [redacted]

For any participant permanently discontinuing treatment prior to Week 30, an early termination (ET) visit should be conducted as soon as possible after stopping study drug. Participants who prematurely discontinue the study will attend an ET visit and should return to the study site 8 weeks later for an end of study (EOS) visit as outlined in Section 5.1.3. CYP 2C19 PMs will also return to the study site for an 8-week follow-up (FU) visit and a 20-week EOS visit.

5.1.2.2 Long-Term Treatment Period

Participants will continue on the dose received at Week 30.

After the initial 30 weeks of the study, visits will occur every 12 weeks and will include but are not limited to clinical evaluation of symptoms, AE/SAE assessments, ECGs, [redacted] laboratory assessments including N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac troponins.

At any visit subsequent to Week 30, a dose increase may be considered, up to a maximum of 15 mg QD. Site-read assessments [redacted] of LVEF and LVOT gradient with Valsalva will be performed to guide dose adjustment via the IXRS. The dose may be reduced or discontinued at any time during the Long-Term Treatment Period based on the clinical judgment of the Investigator in discussion with the Medical Monitor (Section 7.4.1.2). The permissible doses during Week 30 to Week 138 are 1, 2.5, 5, 10, and 15 mg mavacamten.

All participants will receive mavacamten QD for a duration of 108 weeks during the Long-Term Treatment Period, or until mavacamten becomes commercially available, whichever comes first.

Data from central laboratories and electrocardiography core laboratories will be used for safety (eg, monitor criteria for temporary discontinuation, down-titration, and/or permanent discontinuation); see Section 8.1.3.2.

For any participant permanently discontinuing treatment prior to Week 138, an early termination (ET) visit should be conducted as soon as possible after stopping study drug. Participants who prematurely discontinue the study will attend an ET visit and should return to the study site 8 weeks later for an EOS visit as outlined in Section 5.1.3. CYP 2C19 PMs will also return to the study site for an 8-week follow-up visit and a 20-week EOS visit.

5.1.3 Post-treatment Follow-up Period

Participants who prematurely discontinue the study will attend an early termination visit, be contacted by telephone 4 weeks later, and return to the study site 8 weeks later for an EOS visit. CYP 2C19 PMs will also return to the study site for an 8-week follow-up visit and a 20-week EOS visit. After the participant completes the EOT visit, the site will be contacted by the Sponsor to notify the investigator if the participant is a CYP 2C19 PM and requires an additional 20-week EOS visit.

Participants who complete 138 weeks of the study and do not roll over to commercially available mavacamten will attend an EOT visit, be contacted by telephone 4 weeks later, and return to the study site 8 weeks later for an EOS visit. CYP 2C19 PMs will also return to the study site for the 8-week follow-up visit and a 20-week EOS visit. After the participant completes the EOT visit, the site will be contacted by the Sponsor to notify the investigator if the participant is a CYP 2C19 PM and requires an additional 20-week EOS visit.

Participants who roll over to commercially available mavacamten at any time will be contacted by telephone 4 weeks and 8 weeks later for an EOS follow-up to assess AEs, concomitant medications, and pregnancy status. CYP 2C19 PMs will be contacted by telephone at Weeks 4, 8, and 20 post EOT.

Telephone Assessments

Telephone assessments will be conducted at the 4-week follow-up (FU)/telephone call (TC) to assess AEs, concomitant medications, and results of pregnancy test.

5.1.4 Description of Other Procedures and Assessments

Participants with ICDs will have their data downloaded at Screening, Week 12, Week 30, Week 66, Week 102, ET and/or Week 138 (EOT), or as clinically indicated whenever device discharge is interrogated and/or prior to any device reset.

Participants who meet all inclusion and exclusion criteria [redacted] requirements will undergo [redacted] during Screening or Day 1 prior to dosing, Week 30, Week 90, ET and/or Week 138 (EOT) (or up to 5 days before each visit after Day 1) [redacted]

The KCCQ assessment will be completed at Baseline/Day 1, Week 6, 12, 18, 30, 54, 66, 78, 114, and ET (and/or Week 138/EOT) (Section 9.1.1).

Participants may consent separately to have blood drawn for assessment of HCM genotype (Table 9.8-1), preferably on Day 1 or any visit thereafter. This assessment is optional.

In addition, blood samples will be collected for analysis of biomarkers of efficacy, safety, [redacted] parameters. [redacted]

5.1.5 Data Monitoring Committee and Other Committees

Not applicable.

5.2 Number of Participants

Assuming a 40% screen failure rate, it is estimated that approximately 50 screened participants will be required to achieve approximately 30 treated participants.

Approximately 30 participants will be treated with mavacamten.

5.3 End of Study Definition

The start of the study is defined as the first participant first screening visit.

End of Treatment Period for Primary Analysis is defined as last participant has completed Week 30 visit or terminated the initial 30-week treatment period prematurely.

End of treatment (EOT) is defined as last participant has completed Week 138 visit or has terminated early.

End of study (EOS) is defined as the last participant last visit on the Schedule of Activities.

A participant is considered to have completed the study if he/she has completed the last visit shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

Sponsor is developing mavacamten, a novel, small-molecule, allosteric inhibitor of cardiac-specific myosin, for the treatment of patients with symptomatic obstructive hypertrophic cardiomyopathy, a condition with significant unmet medical need, with the goals of improving exercise capacity, functional capacity, and symptoms including fatigue and dyspnea. This Phase 3 open-label study is designed to evaluate the efficacy, safety, and tolerability of a 30-week course of mavacamten and the long-term effects of mavacamten in Japanese patients with symptomatic obstructive hypertrophic cardiomyopathy. The study is designed [redacted]. The results of efficacy and safety in this study will be assessed comprehensively and are intended to be used in combination with the EXPLORER-HCM study to support its registration in Japan.

In preclinical and early clinical studies, treatment with mavacamten successfully relieved LVOT gradients and improved parameters of left ventricular filling. In the Phase 2, open-label PIONEER-HCM study, mavacamten was well tolerated and significantly reduced post exercise LVOT gradients in obstructive hypertrophic cardiomyopathy.[24] The EXPLORER-HCM study demonstrated a mean change in post exercise LVOT gradient of -47 (40.3) mm Hg at Week 30 in the mavacamten group vs -10 (29.6) mm Hg in the placebo group (between-group difference based on analysis of covariance model is -35 mm Hg [-43.2, -28.1], $P < 0.0001$).[23]

The primary endpoint in HORIZON-HCM is the change from baseline to Week 30 in post exercise LVOT peak gradient. Assuming the mean (SD) of the primary endpoint, the change from baseline to Week 30 in post exercise LVOT gradient, is -40 (45) mm Hg, a sample size of 30 participants will have approximately 94% probability to observe a mean change of ≤ -27 mm Hg, with an observed 95% CI of (-43, -11) mm Hg. (Section 10.2).

Since patients to be enrolled in HORIZON-HCM remain symptomatic despite optimal medical therapy, an important additional measure of the benefit of mavacamten will be to assess its effect on improvement of their symptoms, a benefit that is related but different from improvement in functional capacity.[25] NYHA classification is the functional status classification used most commonly in patients with CV disease, especially HF and HCM, in both clinical practice and research studies. For an individual patient, a change in NYHA Class of 1 or more represents a clinically meaningful improvement.

In PIONEER Cohort A, 70% of patients achieved an improvement of at least 1 in NYHA class. In the EXPLORER-HCM study, more than twice the proportion of patients in the mavacamten group compared with the placebo group showed an improvement from baseline of ≥ 1 NYHA class at Week 30 (80 [65.0%] in the mavacamten group vs 40 [31.3%] in the placebo group; $P < 0.0001$ for stratified and unstratified analyses).[23] In a cohort of 44 HCM patients followed for 2 to 4 years, a symptomatic improvement was observed with a mean decrease in NYHA Class of 0.9 and 0.6, observed in surgical myectomy and alcohol septal ablation (ASA), respectively.[26] In another larger cohort of 223 HCM patients followed for up to 20 years, treatment with invasive septal reduction therapy was associated with long-term patient symptom relief, with an observed mean decrease in NYHA class ranging from 1.2 to 1.49, with myectomy and ASA, respectively.[27]

[redacted]

Participants will begin treatment with mavacamten 2.5 mg, with scheduled dose increases at 3 time points in the first 30 weeks. After 30 weeks of treatment, participants will continue on the dose received at Week 30, into the Long-Term Treatment Period. During this Long-Term Treatment Period, NYHA functional class, [redacted] Kansas City Cardiomyopathy Questionnaire (KCCQ), and safety of mavacamten will be assessed to determine long-term outcomes of participants receiving mavacamten.

5.4.1 Participant Input Into Study Design

Participants did not provide input into study design.

5.5 Justification for Dose

The starting dose of 2.5 mg/day was selected using integrated clinical data within a population pharmacokinetic (PPK) and exposure-response (E-R) modeling and simulation framework (PPK/ER M&S).

An ethno-bridging study (MYK-461-011) compared exposure in Japanese versus Caucasian healthy participants with normal CYP 2C19 metabolizer status after single-dose administration of mavacamten and demonstrated that no significant differences in PK, safety, and tolerability were observed. The PPK analysis and covariate effects modeling showed that mavacamten PK was most influenced by dose level, CYP 2C19 genotype, and body weight. Japanese patients generally exhibit a lower body weight and higher CYP 2C19 prevalence compared to the EXPLORER-HCM study population. Adjustment of these participant characteristics in the simulated population was expected to better reflect the Japanese obstructive hypertrophic cardiomyopathy population.

Based on PPK/ER M&S, a 2.5 mg starting dose with a 3-step up-titration scheme to 15 mg in the Treatment Period for Primary Analysis suggested acceptable safety and efficacy profiles based on LVOT and LVEF outcomes compared to the 5 mg starting dose in the EXPLORER-HCM study. Therefore, a 2.5 mg starting dose has been selected to assure safety among Japanese patients who generally exhibit a lower body weight and higher CYP 2C19 prevalence compared to the EXPLORER-HCM study population. The recommended 2.5 mg starting dose is appropriate for all Japanese patients, regardless of covariates identified as affecting mavacamten exposure (eg, body weight, CYP 2C19 genotype).

Furthermore, the individualized, clinically guided dosing approach addresses sources of inter-individual variability. The fact that individual patients may require higher or lower mavacamten exposure to achieve a clinically relevant improvement in LVOT obstruction supports

an individualized dose-titration strategy that is guided by clinical response. The permissible doses are 1, 2.5, 5, 10, and 15 mg mavacamten.

Based on the results from the PPK/ER M&S, it was determined [redacted]

6 STUDY POPULATION

Participants eligible for the study include both male and females, at least 18 years old, with obstructive HCM diagnosis.

A total of approximately 30 participants are expected to be treated with mavacamten in the study.

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

6.1 Inclusion Criteria

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

1) Signed Written Informed Consent

Participants, or their legally acceptable representative (refer to Appendix 2), 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) Body weight is greater than 35 kg at Screening.

b) Has adequate acoustic windows to enable accurate TTEs (refer to Echocardiography Site Instruction Manual).

c) Diagnosed with obstructive hypertrophic cardiomyopathy consistent with current American College of Cardiology Foundation/American Heart Association, European Society of Cardiology, and Japanese Circulation Society guidelines, ie, satisfy all criteria below (criteria to be documented by the echocardiography core laboratory):

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).

ii) Has LVOT peak gradient ≥ 50 mm Hg during Screening as assessed [redacted] at rest, after Valsalva maneuver, or post exercise.

iii) Has LVOT gradient with Valsalva at Screening [redacted] of ≥ 30 mm Hg.

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

e) Has documented LVEF ≥ 60% by echocardiography core laboratory read of Screening [redacted] at rest.

f) Has NYHA Class II or III symptoms at Screening.

g) Not applicable per Protocol Amendment 01, [redacted].

3) Age of Participant

Participant must be at least 18 years of age inclusive at the time of signing the informed consent.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- 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.
  - **Note:** Intravaginal and transdermal combined hormonal contraception are not approved by Japan Health Authority. Also, progestogen-only hormonal contraception is not approved by Japan Health Authority.

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 serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]). A negative urine pregnancy test result is required at Day 1 prior to the start of study treatment.

- 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 permitted to use hormonal contraception methods (as described in Appendix 4).

i) 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, as described in Appendix 4, during the intervention period (starting from Screening) and for at least 4 months

after the last dose of mavacamten and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

b) Male Participants:

i) No additional contraceptive measures are required to be used.

6.2 Exclusion Criteria

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

1) Medical Conditions

a) Known infiltrative or storage disorder causing cardiac hypertrophy that mimics obstructive hypertrophic cardiomyopathy, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy.

b) Has any condition that precludes upright exercise stress testing.

c) Has a history of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to Screening.

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

e) Has paroxysmal atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's ECG at the time of Screening.

f) 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).

g) 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).

h) ICD placement within 2 months prior to Screening or planned ICD placement during the study.

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

j) Has documented obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction.

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

l) Has any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study.

m) Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation.

n) History of malignant disease within 10 years of Screening:

i) Participants who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma, or have been adequately treated for cervical carcinoma in situ or breast ductal carcinoma in situ may be included in the study.

ii) Participants with other malignancies who are cancer free for more than 10 years before Screening can be included in the study.

o) 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.

2) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7.4 (refer to Appendix 5).

b) Current treatment (within 14 days prior to Screening assessments) or planned treatment during the study with cibenzoline, disopyramide, or ranolazine.

c) Current treatment (within 14 days prior to Screening assessments) or planned treatment during the study with a combination of beta blockers and verapamil or a combination of beta blockers and diltiazem. Combination treatment with beta blockers and dihydropyridine calcium channel blockers is allowed.

d) For individuals on any beta blockers or any calcium channel blockers, any dose adjustment of these medications < 14 days prior to Screening assessments or any anticipated change in treatment regimen during the first 30 weeks of the study.

e) Is currently taking, or has taken within 14 days prior to Screening assessments, a prohibited medication, such as a cytochrome P450 (CYP) 2C19 inhibitor (eg, omeprazole or esomeprazole), a strong CYP 3A4 inhibitor, or St. John's Wort (see Section 7.7.4 and refer to Appendix 5). Alternatives such as pantoprazole are allowed and may be discussed with the Medical Monitor.

f) Prior treatment with cardiotoxic agents such as doxorubicin or similar agents.

g) Is currently taking, or has taken within 14 days prior to Screening assessments, biotin supplements (multivitamins that contain < 1000 mg QD of biotin are allowed during the study but must be stopped 24 hours prior to each study visit).

3) Physical and Laboratory Test Findings

a) Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) outside normal limits (according to the central laboratory reference range) at Screening as assessed by the central laboratory; however, a participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:

i) The safety laboratory parameter outside normal limits is considered by the investigator to be clinically not significant.

ii) If there is an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) result, the value must be < 3 × the upper limit of the laboratory reference range.

iii) The body size-adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2.

b) Has a positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or human immunodeficiency virus 1 (HIV-1) and HIV-2 antibody at Screening. Note: participants

with a treated and completely resolved hepatitis C infection without any sequelae are permitted.

c) Known active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease of 2019) polymerase chain reaction positive (PCR+) within 30 days of Screening.

4) Allergies and Adverse Drug Reaction

a) Hypersensitivity to any of the components of the mavacamten formulation.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated.

b) Previously participated in a clinical study with mavacamten.

c) Participated in a clinical trial in which 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 of the investigational drug (whichever is longer).

d) Is unable to comply with the study requirements, including the number of required visits to the clinical site.

e) Is a first degree relative of personnel directly affiliated with the study at the clinical study site, any study vendor, or the study sponsor.

f) Inability to comply with restrictions as listed in Section 6.4 (Lifestyle Restrictions).

g) Not Applicable per Protocol Amendment 01, [redacted].

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.

[redacted]

6.4 Lifestyle Restrictions

6.4.1 Meals and Dietary Restrictions

- Refrain from consumption of Seville oranges, grapefruit or grapefruit juice and quinine (eg, tonic water) from Day 1 before the start of study intervention until after the final follow-up visit.
- Biotin supplements are prohibited from 14 days prior to screening through the EOS visit. Multivitamins that contain < 1000 mg QD of biotin are allowed during the study but must be stopped 24 hours prior to each study visit.

6.4.2 Other Restrictions

- Starting 72 hours prior to the first dose until the final follow-up visit, participants should not engage in unaccustomed intensive exercise except during protocol-specified exercise tests.
- Starting at Screening, participants will be required to abstain from blood or plasma donation until 3 months after the final study visit.

6.5 Screen Failures

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.

6.5.1 Retesting During Screening

Assessments that are out of range at Screening may be repeated once. 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.

The following Screening assessments may be repeated, as long as they are within the 35-day screening window: blood tests, ECG, [redacted]. Repeat assessments are allowed if central core laboratories require a repeat submission due to quality and in order to better assess inclusion/exclusion values.

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 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.

In this study, investigational product is mavacamten, which is supplied as 1, 2.5, 5, 10, and 15 mg capsules.

Participants will receive mavacamten (1, 2.5, 5, 10, or 15 mg capsule) QD during the Treatment Period for Primary Analysis, and the Long-Term Treatment Period, for up to a total of 138 weeks of treatment. During the study, there is an opportunity for mavacamten dose titration as described in Section 7.4.

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-IPs/AxMPs.

7.1 Study Interventions Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Study Intervention

ARM Name	**Mavacamten**
Intervention Name	Mavacamten (BMS-986427/MYK-461)
Type	Study drug
Dose Formulation	Immediate-release capsule
Unit Dose Strength(s)	1, 2.5, 5, 10, and 15 mg
Dosage Level(s)	1, 2.5, 5, 10, or 15 mg once daily
Route of Administration	Oral
Use	Experimental
IMP and Non-IMP/AxMP	IMP
Sourcing	Sponsor
Packaging and Labeling	Study intervention will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Mavacamten (BMS-986427/MYK-461)

Abbreviations: AxMP, auxiliary medicinal product IMP, Investigational Medicinal Product.

Mavacamten will be supplied to participants via the IXRS in 30 count high-density polyethylene bottles that are appropriately labeled. See Table 7.1-1 for the complete schedule of mavacamten administration. The participants will be instructed to store the mavacamten capsules and bottles in a cool, dry place.

Participants will take mavacamten as directed by the study investigator.

Each participant will receive a single oral dose of mavacamten at approximately the same time every day (± 8 hours).

At the time of dosing, 240 mL of water will be administered to the participant along with his/her dose of study intervention. If the dosing window is missed, the participant should not take mavacamten that day. In the event of vomiting, dose should not be repeated, but taken again the next day. Restrictions related to food and fluid intake are described in Section 6.4.

7.2 Method of Study Intervention Assignment

Study using IXRS: All participants will be centrally assigned to treatment using IXRS. Before the study is initiated, each user will receive log-in information and directions on how to access the IXRS.

Study intervention will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted] (eg, [redacted]). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed. Sequential numbering may restart at [redacted] for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and participant number (eg, [redacted]).

Participants who withdraw from the study after receiving an initial dose of treatment will not be replaced. If a participant withdraws after enrollment and before dosing, that participant may be replaced. The replacement participant will undergo the same enrollment procedures as a new participant.

7.3 Blinding

This is a nonrandomized, open-label, single-arm study. It has been determined that blinding is not required to meet study objectives. Blinding procedures are not applicable and access to treatment assignment information is unrestricted. The specific treatment to be taken by a participant will be assigned using IXRS. The site will contact the IXRS prior to the start of study intervention administration for each participant. The site will record the treatment assignment on the applicable Case Report Form (CRF), if required.

7.4 Dosage Modification

All dose adjustments will occur using the IXRS. During the first 30 weeks of the study, dose adjustments will occur via IXRS based on the echocardiogram core read data. After 30 weeks, all dose adjustments will occur via IXRS on the day of the visit based on site-read echocardiogram data entered by the site. The tables in this section outline how the dose may be adjusted and the IXRS will be programmed.

7.4.1 Dose Adjustments During Treatment Period

7.4.1.1 Dose Titration Period for Primary Analysis (Day 1 through Week 30)

The initial treatment period (Day 1 through Week 30) for primary efficacy analysis will include dose titration designed to achieve safe and effective dosing for each participant based on their own response parameters. Participants who meet all eligibility criteria at Screening will be entered into the study via an interactive response system (IXRS) and will receive treatment with mavacamten 2.5 mg starting dose once daily (QD). This Treatment Period will include a 3-step dose up-titration scheme at Weeks 8, 14, and 20 (see Figure 5.1-1).

In this study, the starting dose of study drug is mavacamten 2.5 mg QD.

If at Week 4, core read [redacted] Valsalva LVOT gradient < 30 mm Hg and LVEF ≥ 50%, the dose will be decreased to 1 mg at Week 6 via IXRS.

At Weeks 8, 14, and 20, participants will undergo dose adjustment (dose increase, dose decrease, or dose unchanged) based on their results from core read [redacted] Valsalva LVOT gradient assessments at Weeks 6, 12, and 18, respectively. Up-titration requires LVEF ≥ 55% and LVOT gradient with Valsalva maneuver ≥ 30 mm Hg (Table 7.4.1.1-1). Sites and investigators will not be actively adjusting doses. All dose adjustments will occur via IXRS.

Mavacamten dose may be down-titrated by 1 dose level or discontinued for safety at any time during the study based on the clinical judgment of the Investigator in consultation with the Medical Monitor.

Table 7.4.1.1-1: Dose Titration (Day 1 through Week 30)

Time of Assessment[a]	Valsalva LVOT Gradient	LVEF	Dose Titration	Time and Dose
Week 4	≥ 30 mm Hg	≥ 50%	No change	Week 6 Dose remains at 2.5 mg
	< 30 mm Hg	≥ 50%	Decrease	Week 6 Dose decrease from: • 2.5 mg to 1 mg
Week 6	≥ 30 mm Hg	≥ 55%	Increase	Week 8 Dose increase from: • 1 mg to 2.5 mg • 2.5 mg to 5 mg
	< 30 mm Hg	≥ 50%	No change	Week 8 Dose remains at 1 mg or 2.5 mg
	≥ 30 mm Hg	50% ≤ LVEF < 55%	No change	Week 8 Dose remains at 1 mg or 2.5 mg
Week 12	≥ 30 mm Hg	≥ 55%	Increase	Week 14 Dose increase from: • 1 mg to 2.5 mg • 2.5 mg to 5 mg • 5 mg to 10 mg
	< 30 mm Hg	≥ 50%	No change	Week 14 Dose remains at 1, 2.5, or 5 mg
	≥ 30 mm Hg	50% ≤ LVEF < 55%	No change	Week 14 Dose remains at 1, 2.5, or 5 mg

Table 7.4.1.1-1: Dose Titration (Day 1 through Week 30)

Time of Assessment[a]	Valsalva LVOT Gradient	LVEF	Dose Titration	Time and Dose
Week 18	≥ 30 mm Hg	≥ 55%	Increase	Week 20 Dose increase from: • 1 mg to 2.5 mg • 2.5 mg to 5 mg • 5 mg to 10 mg • 10 mg to 15 mg[b]
	< 30 mm Hg	≥ 50%	No change	Week 20 Dose remains at 1, 2.5, 5, or 10 mg
	≥ 30 mm Hg	50% ≤ LVEF < 55%	No change	Week 20 Dose remains at 1, 2.5, 5, or 10 mg

Abbreviations: IXRS, interactive response system; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; [redacted].

[a] Dose adjustments will also be communicated directly to the IXRS based on Week 4, 6, 12, and 18 assessments including measures of [redacted] peak Valsalva LVOT gradient reported by the core laboratory.

[b] 15 mg once daily is the maximum allowable dose of mavacamten.

Note: Table is provided for IXRS programming.

7.4.1.2 Dose for Long-Term Treatment Period (Week 30 to Week 138)

After Week 30, participants will return to the clinical site for monitoring at every 12 weeks until Week 138. At each visit, AEs, concomitant medications, and symptoms will be assessed, and ECG, [redacted] will be performed for ongoing safety monitoring. Compliance with mavacamten will also be monitored by capsule count at each visit.

At any visit subsequent to Week 30, if the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mm Hg and resting LVEF is ≥ 55%, then a dose increase may be considered, up to a maximum of 15 mg QD, after discussion with the Medical Monitor (Table 7.4.1.2-1). Any dose adjustments will occur on the day of the visit, based on site-read measurement of LVOT gradient with Valsalva maneuver and LVEF [redacted]. Mavacamten dose may be reduced or discontinued at any time during the Long-Term Treatment Period based on the clinical judgment of the investigator in discussion with the Medical Monitor.

Participants who have any dose adjustment should return to the clinic approximately 28 days later (± 7 days) for an unscheduled visit with AE and safety laboratory assessments, ECG, [redacted] to confirm safety. 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.

Table 7.4.1.2-1: Optional Dose Titration Guidelines for Week 42 to Week 126[a]

Time of Assessment	Valsalva LVOT gradient	LVEF	Dose Titration	Dose
Week 42 – Week 126	≥ 30 mm Hg	50% ≤ LVEF < 55%	Dose remains unchanged	Dose remains at: 1, 2.5, 5, 10, or 15 mg
	≥ 30 mm Hg	LVEF ≥ 55%	Dose increase	• 1 mg to 2.5 mg • 2.5 mg to 5 mg • 5 mg to 10 mg • 10 mg to 15 mg[a]
	< 30 mm Hg	LVEF ≥ 50%	Dose remains unchanged	Dose remains at: 1, 2.5, 5, 10, or 15 mg

Abbreviations: IXRS, interactive response system; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; [redacted].

[a] 15 mg once daily is the maximum allowable dose of mavacamten.
Note: Table is provided for IXRS programming.

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 that includes 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.
- Only participants enrolled into the study may receive study drug, and only authorized study staff may supply or administer study drug. All study drug must be stored in a secure and monitored area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

7.5.1 Formulation, Packaging, and Labeling of Study Drug

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

Mavacamten capsules are supplied in 1, 2.5, 5, 10, and 15 mg strengths. Mavacamten capsules of all strengths are identical in appearance.

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

Mavacamten capsules must be stored in the packaging supplied by the Sponsor (refer to the label for storage condition details).

7.5.2 Direct-to-Participant Study Drug Shipment (at Selected Sites)

In certain circumstances, it may be necessary to ship study drug directly to a participant (refer to Appendix 7). When study drug is shipped directly to the participant, a qualified individual who is contracted by the Sponsor/contract research organization (CRO) or study site will open the package of study drug, review temperature monitoring data, and confirm receipt. Study sites should contact participants by telephone to confirm study drug delivery. The study drug bottle(s) from the previous study visit will be returned to the site. Refer to the Pharmacy Manual for details.

7.6 Treatment Compliance

Compliance with study drug will be monitored by capsule count at all study visits. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit. Refer to the Pharmacy Manual for details.

On study visit days, participants should wait to take study drug until after they reach the clinic [redacted] as indicated in the schedule of study procedures [redacted]
Any concomitant medication may be administered prior to all exercise testing.

7.7 Concomitant Therapy

7.7.1 Prior Therapy

At the time of signing the ICF, participants will be asked about their medication history over the previous 28 days, including prescription and nonprescription medications, herbal medications, vitamins, and minerals. Prior medications are those with a stop date within the Screening Period (35 days prior to the first dose of study drug).

If the participants have taken prohibited medications within 14 days prior to signing the ICF, they may sign the ICF and then must discontinue treatment for at least 14 days before proceeding to the Screening assessments. If participants have not taken any prohibited medications in the past 14 days prior to signing the ICF, they may proceed to Screening assessments. The Principal Investigator will determine if the participant can discontinue prohibited treatments.

7.7.2 Background HCM Therapy

Background cardiomyopathy therapy (eg, beta blocker, verapamil, or diltiazem) is allowed, (although not a combination of beta blockers and verapamil or a combination of beta blockers and diltiazem, per exclusion criteria). Participants should be on optimal medical therapy as determined by the investigator and informed by HCM treatment guidelines.[32] The treatment should be well tolerated for at least 2 weeks prior to Screening assessments, and the investigators are encouraged to maintain this treatment unchanged (ie, at a stable dose) during the first 30 weeks of the study. After Week 30, investigators should manage background HCM medications (eg, beta blocker, verapamil, or diltiazem) as clinically appropriate in conjunction with the Medical Monitor. Any change in HCM medications must be entered into the electronic Case Report Form (eCRF) with the rationale for the change.

COVID-19 vaccination status will be collected from all study participants.

7.7.3 Concomitant Therapy

Concomitant medications are those with a stop date on or after the first dose of study drug of analysis interest or that were ongoing at the end of the analysis period.

Concomitant therapy will be collected at all clinic visits from the first dose 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.

7.7.4 Prohibited and/or Restricted Treatments

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

Use of disopyramide, cibenzoline, or ranolazine is prohibited from 14 days before Screening assessments to the EOS.

Potent and moderate CYP 2C19 inhibitors and potent CYP 3A4 inhibitors are prohibited from 14 days before Screening assessments through the EOS.

If a compelling clinical necessity to administer one of these medications arises, the investigator should contact the study medical monitor in advance to discuss a plan including whether/when to discontinue study drug.

Additional prohibited medications are listed in Appendix 5.

[redacted]

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 mavacamten 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

- In general, every effort should be made to keep a participant on treatment for as long as possible during the study unless a safety concern arises. Treatment discontinuation may either be temporary or permanent and if permanent, the degree to which a study participant withdraws can vary. Each of these circumstances is described below.

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 prior to Week 30 or Week 138, an early termination visit should be conducted as soon as possible after stopping study drug. Participants who prematurely discontinue the study will attend an ET visit and should return to the study site 8 weeks later for an EOS visit as outlined in Section 5.1.3. CYP 2C19 PMs will return to the study site for an 8-week follow-up visit and a 20-week EOS visit. 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.

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 early termination (ET) procedures 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.

8.1.1 Temporary Treatment Discontinuation

Temporary treatment discontinuation

- Will be implemented when a predefined safety threshold has been met (Section 8.1.3)
- May be considered by the investigator in the case of an AE/SAE or for another reason

As a general rule, any discontinuation of study drug should be initially considered temporary unless permanent treatment discontinuation is mandated by the protocol (Section 8.1.4).

If a temporary treatment discontinuation was caused by a safety threshold being met, treatment will be resumed approximately 4 to 6 weeks later at a lower dose, transmitted via IXRS (Section 8.1.3).

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 (ie, the investigator is satisfied that in his or her medical judgment, the study drug is unlikely to be responsible for the event concerned).

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 a 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.

In all cases, participants should be encouraged to discuss stopping study drug with the investigator or the investigator's designee so that questions can be addressed, concomitant therapy can be adjusted if needed, and a follow-up assessment can be arranged.

All permanent treatment discontinuation should be recorded in the eCRF.

8.1.3 Criteria for Temporary Treatment Discontinuation

In addition to the dose adjustments described in Section 7.4.1, at any time (T) during the Treatment Period, dosing will be temporarily discontinued in the case of systolic dysfunction (LVEF < 50%), [redacted], or excessive QTcF prolongation as described below.

If participant has a resting LVEF < 50%, [redacted], or QTcF stopping criteria described below, as determined by the echocardiography central laboratory in the Treatment Period for Primary Analysis and the site-read echocardiography in the Long-Term Treatment Period, or ECG core laboratory, respectively, it will be communicated to the investigator and Medical Monitor that a criterion for temporary discontinuation has been met. Criteria for temporary discontinuation due to QTcF prolongation are as follows and depend on QRS width as determined by the ECG core laboratory:

- If QRS is narrow (< 120 msec), then temporary discontinuation criteria are the smaller of: a 15% increase from baseline QTcF OR QTcF ≥ 520 msec
- If QRS is wide (≥ 120 msec), then temporary discontinuation criteria are the smaller of: a 15% increase from baseline QTcF OR QTcF ≥ 550 msec

8.1.3.1 Temporary Discontinuation in Treatment Period for Primary Analysis (Day 1 through Week 30)

Upon receipt of information that participant has a resting LVEF < 50% [redacted] or QTcF stopping criteria, as determined by the core-read echocardiography results and ECG core laboratory, respectively, the study site/investigator will contact the participant and instruct the participant to discontinue mavacamten and to return for an on-site visit within 2 to 4 weeks (T + 2 to 4 weeks). This could correspond to a scheduled or unscheduled visit.

At the follow-up visit (T + 2 to 4 weeks), ECG, [redacted] will be repeated and another scheduled/unscheduled visit will be planned for 2 weeks later (T + 4 to 6 weeks). If LVEF ≥ 50% AND [redacted] AND QTcF duration is below programmed discontinuation rules, then mavacamten will be restarted at a lower dose (at T + 6 weeks) as follows (previous dose → restart dose):

Mavacamten Dose Reduction Guide:

- 15 mg → 10 mg
- 10 mg → 5 mg
- 5 mg → 2.5 mg

- 2.5 mg → 1 mg
- 1 mg → none (permanent treatment discontinuation)

If LVEF, [redacted] and/or QTcF persist out of range at the follow-up visit, then mavacamten will be discontinued.

8.1.3.2 Temporary Discontinuation in Long-Term Treatment Period (Week 30 to Week 138)

Temporary Discontinuations Due to LVEF < 50% Only

If the reason for temporary discontinuation is LVEF < 50% only, as determined by site-read echocardiography results, sites will be notified.

In this case, at the first follow-up visit (T + 2 to 4 weeks), [redacted] will be repeated to confirm if the LVEF is ≥ 50%. The QTcF [redacted] do not need to be repeated. If the LVEF is ≥ 50% at this visit, then mavacamten may be restarted at a lower dose as described below (see Dose Reduction Guide below).

If at the first follow-up visit (T + 2 to 4 weeks), the LVEF is < 50%, then the second follow-up visit will be planned for 2 weeks later (T + 4 to 6 weeks). Mavacamten will be restarted at a lower dose if the LVEF is ≥ 50% at this visit.

If LVEF performed at the follow-up visit persists out of range, mavacamten will be discontinued permanently.

Temporary Discontinuations Due to QTcF Alone [redacted] or [redacted] in Combination with LVEF < 50%:

If the reason for temporary discontinuation is QTcF as determined by ECG core laboratory and/or [redacted] in combination with LVEF < 50%, as determined by site-read echocardiography results, sites will be notified. At the first follow-up visit (T + 2 to 4 weeks), ECG, [redacted] will be repeated and another unscheduled visit will be planned for 2 weeks later (T + 4 to 6 weeks).

If LVEF ≥ 50% AND [redacted] QTcF duration are below programmed discontinuation rules, then mavacamten will be restarted at a lower dose as follows (previous dose → restart dose):

Mavacamten Dose Reduction Guide:

- 15 mg → 10 mg
- 10 mg → 5 mg
- 5 mg → 2.5 mg
- 2.5 mg → 1 mg
- 1 mg → none (permanent discontinuation)

If LVEF, [redacted] and/or QTcF persist out of range at the follow-up visit, then mavacamten will be discontinued.

If participants are on 1 mg mavacamten and meet permanent discontinuation criteria, it will be communicated to the investigator and Medical Monitor.

8.1.4 Criteria for Permanent Treatment Discontinuation

The following reasons will lead to permanent treatment discontinuation:

- Pregnancy
- LVEF ≤ 30% as determined by local site

  Note: If LVEF ≤ 30% is measured at the site for any participant, the sonographer should review and re-measure the findings with at least one other professional qualified in echocardiography assessment (eg, the investigator, echocardiogram laboratory director, another experienced sonographer, or cardiologist). If the result is confirmed (LVEF ≤ 30%), the investigator will be notified immediately, and mavacamten will be discontinued. The site must report [redacted] within 24 hours.
- Continued administration of study drug is considered by the investigator to be detrimental to the participant's safety or well-being
- If all the criteria are met for possible drug-induced liver injury (DILI) (Section 9.2.7.1)
- The participant requests to discontinue study drug
- The Sponsor requests that the participant permanently discontinue study drug

8.1.5 Management of Participants After Permanent Treatment Discontinuation

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.

If a participant permanently discontinues treatment prior to Week 138, the participant will be asked to undergo an ET visit as soon as possible after stopping study drug, using the procedure normally planned for the EOT and EOS assessments as outlined in Section 2.

For participants who do not withdraw consent for ongoing study participation but fail to return to the site, the investigator should make every effort to contact the participant (eg, contacting participant's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, particularly vital status. Attempts to contact such participants must be documented in the participant's records (eg, number of attempts and dates of attempted telephone contact and receipt for sending a registered letter).

8.1.6 Rechallenge

8.1.6.1 Hepatotoxicity Rechallenge

Participants with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL], or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for withholding of mavacamten or other protocol-required therapies.

If mavacamten is withheld, the participant should be followed according to recommendations in Section 9.2.7 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.

8.1.6.2 Criteria for Rechallenge of Mavacamten After Potential Hepatotoxicity

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 mavacamten will be permanently discontinued. Participants who clearly meet the criteria for permanent discontinuation (Section 9.2.7.1) should never be rechallenged.

8.1.7 Post-study Intervention Study Follow-up

Participants who discontinue study intervention may continue to be followed.

Participants who prematurely discontinue the study will attend an early termination visit, be contacted by telephone 4 weeks later, and return to the study site 8 weeks later for an EOS visit. CYP 2C19 PMs will also return to the study site for an 8-week follow-up visit and a 20-week EOS visit.

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.

8.2.1 Withdrawal From the Study

8.2.1.1 Withdrawal of Consent for Ongoing Study Participation

Participants may withdraw from the study before study completion if they decide to do so, at any time and for any reason. Withdrawal of consent for treatment (permanent treatment discontinuation) described above should be distinguished from withdrawal of consent for ongoing study participation with scheduled visits and from withdrawal of consent for non-participant contact follow-up (eg, medical records check).

Participants who withdraw from the study should be explicitly asked about the reason and the contribution of any AE(s) that led to their decision, and any AE information elicited should be documented. The participant may withdraw consent verbally or in writing. If the consent is withdrawn verbally, the site should document it appropriately.

All study withdrawals should be recorded by the investigator in the appropriate eCRF and in the participant's medical records when considered as confirmed. The date of the withdrawal and the reason should be documented.

The statistical analysis plan (SAP) will specify how these participants lost to follow-up will be considered for their primary endpoints.

Participants who have withdrawn from the study cannot be retreated in the study. Their inclusion and treatment numbers must not be reused.

8.2.1.2 Replacement of Participants Who Withdraw from the Study

Participants who withdraw from the study after receiving an initial dose of treatment will not be replaced. If a participant withdraws after enrollment and before dosing, that participant may be replaced. The replacement participant will undergo the same enrollment procedures as a new participant.

8.2.2 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, 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 (see Section 2).

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

The following describes the study procedures to be performed during the study. Additional details are provided in Table 2-2 and Table 2-3 of this document. All assessments should be performed prior to mavacamten dosing unless otherwise specified. The KCCQ should be completed by participants prior to any other study procedure taking place, when possible. ECG should be completed prior to blood draws. Blood draws (for [redacted] biomarkers, and laboratory tests) should be performed prior to exercise. The order of assessments may vary slightly at specific time points to facilitate the most contemporaneous performance of the required assessments. Unscheduled or additional safety assessments may be performed if necessary, in the opinion of the investigator. Whenever possible, discussion with the Medical Monitor is encouraged.

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

Visit Scheduling

All visits after Day 1 should occur within the visit window (± 7 days) scheduled based on the projected study date. If an evaluation is missed, reschedule and perform it as close as possible to the original date.

In case of unforeseen medical conditions preventing ability to perform procedures at Week 30, these procedures may be completed at the earliest possible time point based on investigator assessments of medical status (outside of the ± 7-day window).

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

New York Heart Association Functional Class

The NYHA Functional Classification of HF assigns participants to 1 of 4 categories based on the participant's symptoms (Table 9.1.1-1). 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. A goal of at least 25% of the participants will be NYHA functional Class III at Screening.

Table 9.1.1-1: 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.

Kansas City Cardiomyopathy Questionnaire (23-item Version)

The Kansas City Cardiomyopathy Questionnaire (23-item version) (KCCQ) is a patient-reported questionnaire that measures the impact of patients' CV disease or its treatment on 6 distinct domains using a 2-week recall: symptoms/signs, physical limitations, quality of life, social limitations, self-efficacy, and symptom stability. [33] [redacted]

[redacted] The KCCQ will be administered to participants as indicated. The KCCQ should be completed by participants at study visits as outlined in Section 2, prior to any other study procedure taking place, when possible.

[redacted]

9.1.2 Imaging Assessment for the Study

9.1.2.1 Echocardiography

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

During Screening echocardiography results will be sent to a central imaging laboratory and transmitted to the IXRS to confirm eligibility.

In the Treatment Period for Primary Analysis, all echocardiography data will be sent to a central imaging laboratory.

In the Long-Term Treatment Period, echocardiograms will be site-read. All echocardiography data will be sent to the IXRS for LVEF stopping criteria (LVEF < 50% by local site read). Echocardiograms will also be sent to a core laboratory for future assessment during data analysis.

If necessary, contrast may be administered to ensure that good quality echocardiogram images are obtained.

Resting [redacted]

Resting [redacted] will be assessed prior to dosing during on-site visits as described in Section 2. 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).

At Screening and Week 30, resting [redacted] should be performed prior to post exercise echocardiography [redacted].

Post exercise/Stress Echocardiography

Participants will undergo a standard symptom-limited exercise test (after a recommended 3-hour fast) at Screening and Week 30 (see Section 2) prior to study drug dosing. The exercise test should be performed per the institution's standard exercise protocol. If the site does not have a standard protocol, the study [redacted] exercise protocol must be utilized. This test may be performed on a different day [redacted]; however, if both procedures are performed on the same day, participants must exercise only once for both tests, with the participant undergoing first [redacted] and then post exercise stress echocardiography. Post exercise echocardiography needs to be acquired within 72 hours of resting [redacted] post exercise gradient can be done on 2 different days, but the same sequence of visits must be used for both screening and EOT. Instantaneous peak LVOT gradient will be assessed immediately post exercise by [redacted] 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. Participants on standard cardiomyopathy therapy (eg, beta blockers or calcium channel blocker) should be on the same dose at Screening and Week 30 stress echocardiogram whenever possible, and this medication should be administered prior to exercise testing. Biomarker sampling should be performed prior to exercise.

[redacted]

[redacted]

9.2 Adverse Events

The definitions of an AE, SAE, or [redacted] can be found in Appendix 3.

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

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 SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 56 days (to 140 days for CYP 2C19 PM) following discontinuation of dosing.

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, SAEs, and AESIs, 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 judgement 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 EOS 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 and Appendix 3) 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 4 months after the last dose of study product administration, the investigator must immediately notify the BMS 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.

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. The participant will be asked to provide information on the outcome of the pregnancy through 1 year after birth or details of premature termination.

Pregnancy in a female participant will lead to permanent treatment discontinuation.

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 refer to Appendix 3 for reporting details).

Potential DILI is defined as:

- Aminotransaminase (AT:ALT or AST) elevation > 3× upper limit of normal (ULN)
  AND
- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
  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.

9.2.7.1 Criteria for Permanent Withholding of Mavacamten due to Potential Hepatotoxicity

Mavacamten should be discontinued permanently, and the participant should be followed according to the recommendations in Appendix 6 for possible drug-induced liver injury (DILI), if all of the criteria below are met:

- TBL > 2× upper limit of normal (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 gallbladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, hepatitis A/B/C/D/E), Epstein-Barr virus, cytomegalovirus, herpes simplex virus, or varicella
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right-sided 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

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

9.2.7.2 Criteria for Conditional Withholding of Mavacamten Due to Potential Hepatotoxicity

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

- AST or ALT > 8× ULN at any time
- AST or ALT > 5× ULN and < 8× ULN for ≥ 2 weeks
- AST or ALT > 5× ULN and < 8× ULN and unable to adhere to enhanced monitoring schedule
- ALT or AST > 3× ULN and TBL > 2× ULN or INR > 1.5

- OR: ALT or AST > 3× ULN and clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%).
- OR: TBL > 3× ULN at any time
- OR: ALP > 8× ULN at any time

Mavacamten should be withheld pending an investigation into alternative causes of DILI. If mavacamten is withheld, the participant should be followed according to recommendations 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.

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 mavacamten greater than once daily (QD) 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 Section 9.2 and refer to Appendix 3).

An overdose is defined as taking more capsules of study intervention than directed. An overdose may be suspected by the investigator or spontaneously reported by the participant. An overdose may be symptomatic or asymptomatic. Only symptomatic overdoses should be reported as AEs. 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 BMS Medical Monitor, and no further study intervention 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 mavacamten. In acute overdose or toxic ingestion, gastrointestinal decontamination should be considered. If necessary, corrective measures, as described in the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of Heart Failure and in the 2016 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure should be implemented. Based on its almost exclusive hepatic metabolism through the CYP2C19 and CYP3A4 enzymes, administration of inducers of CYP2C19 and CYP3A4 may be helpful.

Nonclinical experiments have established that beta adrenergic agonists and dobutamine can counteract mavacamten's modulation of myosin activity, providing the rationale for the use of these widely used clinical agents to support individuals who may be inadvertently overexposed.

The efficacy of other measures of elimination has not been established. Reintroduction of study intervention must be approved by the BMS Medical Monitor.

In the event of an overdose, the investigator should:

- Closely monitor the participant for AEs/SAEs and laboratory test result abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Please refer to the Investigator's Brochure (IB) for more details.

9.4 Safety

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

Safety will be assessed throughout the study. Safety assessments include medical history, physical examinations, ECGs, vital signs, observed and participant-reported AEs, pregnancy testing, and safety laboratory results. Any abnormal findings judged by the investigator to be clinically important will be recorded as an AE.

Safety data will be monitored on an ongoing basis by the study Sponsor.

9.4.1 Physical Examinations

See Schedule of Activities (Section 2).

At Screening, Week 30, ET, and/or Week 138 (EOT), a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height (Screening only) and weight, and assessment of the following: general appearance; skin; head and neck; mouth; lymph nodes; thyroid; abdomen; musculoskeletal, CV, and respiratory systems. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.

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

Body weight will be captured in clinic at Screening, Weeks 30, 66, 102, ET, and/or Week 138/EOT.

9.4.2 Vital Signs

See Schedule of Activities (Section 2).

Vital signs are to be assessed at each on-site study visit. At Screening, Week 30, ET, and/or Week 138/EOT, complete vital signs including temperature, HR, respiratory rate, and blood pressure (BP) will be obtained. At all other visits, only HR and BP are required.

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

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

9.4.3 Electrocardiograms and Cardiac Monitoring Device

See Schedule of Activities (Section 2).

9.4.3.1 Electrocardiograms

12-lead ECG evaluations will be performed after 10 minutes of rest at Screening and at the on-site study visits every 2 to 4 weeks through Week 30, then every 12 weeks until the EOT, Week 8 EOS, and Week 20 EOS (if CYP 2C19 PM). At Day 1, Weeks 8, 14, and 20, post-dose ECG will also be performed around Tmax (0.5 to 3 hours after study drug dose) in addition to the pre-dose ECG. On visits during the Treatment Period, ECGs will be taken prior to dosing. All ECG data will be sent to a central cardiac laboratory and transmitted to IXRS.

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

9.4.3.2 Cardiac Monitoring Device

At 6 time points during the study, participants will wear a small device to collect continuous HR and rhythm data for approximately 48 hours. The monitoring device uses surface electrodes, internal electronics to capture a continuous ECG waveform, a removable memory card to store data over 48 hours, and a battery to power the device. Following a period of data collection, the memory card will be uploaded to a core laboratory where the continuous ECG waveforms will be analyzed. The analysis will provide full disclosure capabilities for HR and heart rhythm over the period during which the device was properly applied and functioning. The device will be used to explore the pattern of HR and heart rhythm before and during treatment with study drug.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Serum pregnancy testing will be performed at Screening for all females of childbearing potential. Participants must have a negative urine pregnancy test result at Day 1 prior to initiating study treatment.

In addition, urine pregnancy testing will be conducted in the clinic at every on-site visit throughout the study. During the Long-Term Treatment Period, pregnancy testing will be performed every 4 weeks at the clinic, or at home when no on-site visit is scheduled, until the end of the study. During the Long-Term Treatment Period, the site will contact the participant every 4 weeks in between clinic visits to confirm at-home pregnancy test results. If a participant has a positive urine pregnancy test at home, they will be instructed to notify the site immediately. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Confirmatory serum testing will be performed if any urine test is positive.

Safety laboratory results will be assessed in an ongoing manner. A central safety laboratory will perform the analyses and will provide reference ranges for these tests. The following safety laboratory parameters will be measured by the central laboratory.

Table 9.4.4-1: Clinical Safety Laboratory Assessments

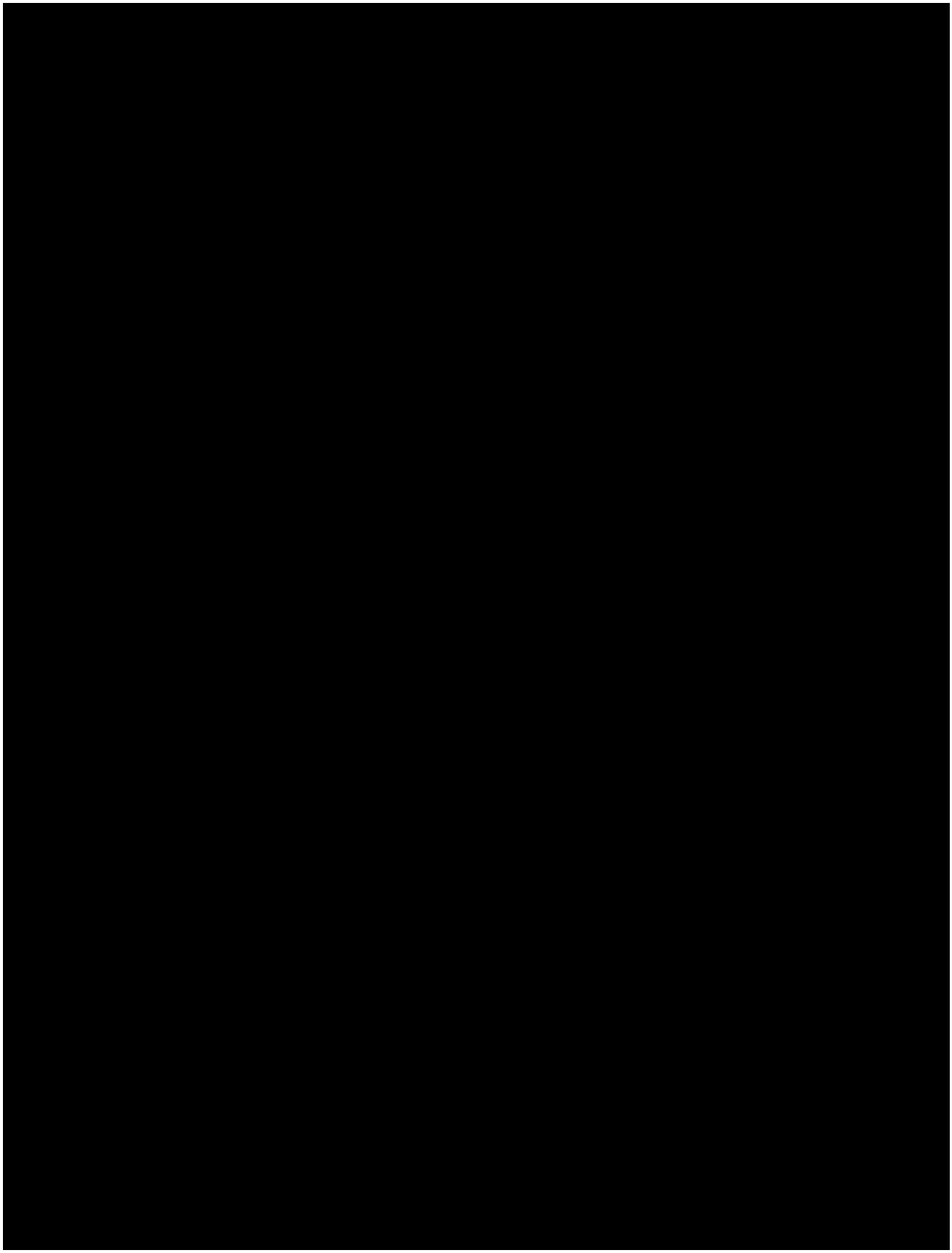
Hematology/Coagulation	Serum Chemistry	Urinalysis[a]
CBC, including differential count	Sodium	Specific gravity
	Potassium	pH
Platelet count	Chloride	Protein
INR	Bicarbonate	Glucose
aPTT	Calcium	Leukocyte esterase
	Magnesium	Blood
	BUN	
	Creatinine	
	ALP	
	ALT	
	AST	
	TBL	
	CPK	
	Glucose	
	Protein	
	Albumin	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CPK, creatine phosphokinase; INR, international normalized ratio; TBL, total bilirubin.

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

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

[redacted]



9.6 Immunogenicity Assessments

Not applicable.

9.7 Genetics

9.7.1 HCM Genotyping

For participants who provide consent for HCM genotyping, blood will be drawn preferably on Day 1 or any visit thereafter for assessment of HCM genotype. See Table 9.8-1 for sample collection schedule.

9.7.2 Pharmacogenetic Assessments

Blood will be drawn preferably on Day 1 for commercially available testing of gene(s) encoding for drug metabolism enzymes and drug transporters (DMET). Genetic variations in DMET have the potential to significantly impact an individual's metabolic capacity. For mavacamten, genetic variations for CYP 2C19 are known to have particular significance and will be assessed in this study. See Table 9.8-1 for sample collection schedule.

9.8 Biomarkers

Table 9.8-1: Biomarker Sampling Schedule for All Participants

Study Day of Sample Collection (1 week = ± 7 days)[a]	Blood Sample for HCM Genotyping[b]	Pharmacogenetic Assessments[c]	[redacted]	Cardiac Biomarkers
Screening				X
Day 1	X	X		X
Week 6 Day 43				X
Week 12 Day 85				X
Week 18 Day 127				X
Week 30 Day 211				X
Week 42 Day 295				X
Week 54 Day 379				X
Week 66 Day 463				X
Week 78 Day 547				X
Week 90 Day 631				X
Week 102 Day 715				X
Week 114 Day 799				X
Week 126 Day 883				X
Unscheduled Visit				
Week 138/EOT				X
ET				X
Follow-up Period				
Week 8 Follow-up EOS				X
Week 20 Follow-up EOS				X

Abbreviations: EOS, end of study; EOT, end of treatment; ET, early termination; HCM, hypertrophic cardiomyopathy.

[a] All blood draws must be drawn at rest and prior to any exercising.

[b] Blood for assessment of HCM genotype will be drawn preferably on Day 1 or any visit thereafter.

[c] The pharmacogenetic testing will include CYP 2C19 genotyping and will be obtained preferably on Day 1.

9.8.1 Cardiac Biomarkers

Blood samples will be collected for cardiac biomarkers NT-proBNP and cardiac troponins (troponin I and troponin T) concentrations. All blood draws for these cardiac biomarkers must be drawn at rest and prior to any exercising. Concentrations of NT-proBNP and cardiac troponins will be analyzed for efficacy. Unscheduled or additional blood samples may be collected if appropriate in the opinion of the investigator (eg, for medical management of HF) and/or Sponsor. Whenever possible, discussion with the Medical Monitor is encouraged.

[redacted]

9.9 Additional Research

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

For All sites:

Additional research is optional for all study participants, except where retention is prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements.

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

- Residual blood samples from [redacted] pharmacogenetic, or HCM genotyping, cardiac biomarker, [redacted] collections (see Table 9.9-1) will also be retained for additional research purposes

Samples kept for future research will be stored at the BMS Biorepository in [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 subject 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

Sample Type	Time points for which residual samples will be retained
[redacted]	
Pharmacogenetic	All
HCM Genotyping	All
Cardiac Biomarkers	All
[redacted]	

Abbreviations: HCM, hypertrophic cardiomyopathy; [redacted].

9.10 Other Assessments

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

- Hepatitis panel (HBV and HCV)
- HIV test
- FSH

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

To support registration in Japan, the results of efficacy and safety in this study will be assessed comprehensively, and to further aid in the interpretation of these findings, the results from the EXPLORER-HCM study will be used.

10.2 Sample Size Determination

Approximately 30 participants will be treated with mavacamten. Assuming the mean (SD) of the primary endpoint, the change from baseline to Week 30 in post exercise LVOT gradient is -40 (45) mm Hg, a sample size of 30 participants will have approximately 94% probability to observe a mean change of ≤ -27 mm Hg, with an observed 95% CI of (-43, -11) mm Hg.

To determine the similarity of the results between this study and EXPLORER-HCM study, we consider the following 2 criteria:

1) The observed mean change in post exercise LVOT gradient in this study should be ≤ -27 mm Hg, which is at least 57% of the change shown in the mavacamten arm of EXPLORER-HCM study.
2) The CI of the mean change in this study should exclude the mean change from baseline to Week 30 in placebo arm of EXPLORER-HCM study, ie, upper limit of the CI < -10.

10.3 Analysis Sets

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

Population	Description
ITT Population	All participants past screening or assigned study drug.
Safety Analysis Population	All participants who receive at least one dose of study drug.
[redacted]	

Abbreviations: [redacted] ITT, intent-to-treat; [redacted].

10.4 Statistical Analyses

The statistical analysis plan (SAP) will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is an outline of the intended methodology for key endpoints.

10.4.1 General Considerations

Descriptive summary statistics for continuous variables will include the number of participants, mean, SD or standard error, median, first quartile, third quartile, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

Baseline is defined as the last non-missing assessment before the first dose of study drug.

All efficacy analyses will be performed on the ITT Population. Descriptive statistics will be presented for all efficacy endpoints.

Missing AE start date will be imputed for the purpose of determining whether the AE is treatment emergent. Missing concomitant medication start date will be imputed when determining whether the medication is prior or concomitant. Imputation rule will be specified in the SAP.

All other analyses will be based on observed data with no imputations. In case the primary and secondary endpoints have missing data which are more than expected (eg, 10%), data imputation

may be performed, and detailed methods will be discussed in the SAP. Otherwise, missing data will generally not be imputed unless specified in SAP.

10.4.1.1 Participant Disposition

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

10.4.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

10.4.1.3 Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the Safety Population.

The duration of study drug exposure is defined as last dose date – first dose date + 1 day, regardless of intermittent discontinuations. Adjusted duration will also be derived by taking protocol-defined interruptions into account.

Compliance will be calculated based on the total cumulative dose received divided by the total expected cumulative dose. Compliance of taking pills will be calculated based on the total number of pills taken divided by the adjusted duration. Treatment exposure and compliance will be summarized descriptively (number [n], mean, SD, median, minimum, and maximum). The compliance of participants with compliance < 80% and those with compliance > 100% will be summarized.

10.4.2 Primary Endpoint

The primary efficacy endpoint is change from baseline to Week 30 in post exercise LVOT peak gradient. The change from baseline to Week 30 in post exercise LVOT peak gradient will be summarized with descriptive statistics, including mean, SD, minimum, maximum, and 95% CIs.

To determine the similarity of the results between this study and EXPLOER-HCM study, we consider the following two criteria:

1) the observed mean change in post exercise LVOT gradient in this study should be ≤ -27 mm Hg, which is at least 57% of the change shown in the mavacamten arm of EXPLORER-HCM study
2) the CI of the mean change in this study should exclude the mean change from baseline to Week 30 in placebo arm of EXPLORER-HCM study, ie, upper limit of the CI < -10.

10.4.3 Secondary Endpoints

The secondary endpoints are:

- Change from baseline to Week 30 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS)
- Proportion of participants with at least 1 class improvement in NYHA functional class from baseline to Week 30

- Change from baseline to Week 30 in N-terminal pro b-type natriuretic peptide (NT-proBNP)
- Change from baseline to Week 30 in cardiac troponins

The general analytical rules for the secondary efficacy endpoints are the following:

- Change from baseline endpoints will be summarized in a similar way as primary endpoint, where descriptive statistics, including mean, SD, minimum, median, maximum, and 95% CI will be presented. There is no formal testing for secondary endpoints.
- Response rate for the categorical endpoints will be summarized with number and percentage with 95% CI, and no formal testing will be performed.

[redacted]

10.4.5 Other Safety Analysis

10.4.5.1 Adverse Events

All safety analyses will be performed on the Safety Analysis Population using descriptive statistics without formal statistical testing. The safety analysis will focus on the Treatment-emergent Adverse Event Period. This period is defined as the time from the first administration of mavacamten to the last administration of mavacamten + 56 days (140 days for CYP 2C19 PM).

AEs will be mapped to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be monitored during the study and the data analyzed with respect to overall incidence as well as severity and potential relationship of AEs to study medication. AEs with onset during the treatment-emergent period, or with an onset before the first dose of study medication that increases in severity or becomes serious during the treatment-emergent period, will be considered treatment emergent.

Adverse event incidence tables will present the number and percentage of participants experiencing at least one TEAE by SOC and PT in alphabetical order. Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the Safety Population.

Adverse event incidence tables will be provided for all types of TEAEs: all TEAEs, all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

All deaths will be listed for the event time relative to the first study dose and the relevant AE descriptions, if applicable.

[redacted]

10.4.5.3 Overdose

The following summaries for reports of overdose will be generated:

- Number of participants who experienced overdose
- Analysis of the cause and occurrence of the overdose
- TEAE experienced during the overdose by primary SOC and PT showing the number and percent of participants sorted by SOC and PT

10.4.6 Other Analyses

10.4.6.1 12-lead Electrocardiogram

The RR, PR, QRS, and QT intervals will be measured and read by a central laboratory. HR will be calculated as 60/ (RR × 1000) (with RR expressed in msec) and rounded to the nearest integer.

Correction for Heart Rate

Corrected QT interval (QTc) will be calculated using the manually over-read QT values. Each individual ECG QT value will be corrected for HR. The measured QT data will be corrected for HR using QTcF as per the following formulae/method (with QT, RR, and QTc expressed in msec):

Fridericia's Correction:

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

ECG Numeric Variables

HR, PR, QRS, and QTcF will be summarized using descriptive statistics. QRS duration, manually over-read, will be used to determine which threshold criterion rules to apply for temporary discontinuation based on QTcF (eg, QRS duration < 120 msec or QRS duration ≥ 120 msec) (see Section 8.1.3). The change from baseline of these ECG parameters at each time point will be listed for each participant. For each time point of measurement, the changes from baseline will be summarized using descriptive statistics.

Categorical Analysis

The incidence count and percentage of participants with any QTcF values of > 450 msec, > 480 msec, > 500 msec, > 520 msec, and > 550 msec will be tabulated for all participants. Participants with QTcF values > 500 msec will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The incidence count and percentage of participants with QTcF increase from baseline of > 30 msec and > 60 msec will be tabulated.

Morphology Findings

ECG morphologies for each participant will be listed.

Concentration-QTc Analyses

A concentration-QTc regression analysis, based on data collected from the ECG recordings after drug administration and concentration values for each participant at each matching time point, will be performed. Linear or nonlinear models will be implemented to estimate the slope and 95% CI of the relationship. Predictions at selected concentration values will be computed within the model.

10.4.6.2 Laboratory Data

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all laboratory variables (laboratory values and changes from baseline) will be calculated for each visit (baseline and post-baseline time points).

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

Potential Drug-induced Liver Injury

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

A graph of distribution of peak values of ALT versus peak values of TBL will be presented. Note that the ALT and TBL values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3× ULN for ALT and a horizontal line corresponding to 2× ULN for TBL.

The number and percentage of participants with elevated liver function tests (based on safety laboratory data) during the TEAE period will be summarized by categories of elevation (> 3× ULN, > 5× ULN, > 10× ULN, and > 20× ULN for ALT and AST; > 1.5× ULN for ALP; and > 1.5× ULN and > 2× ULN for TBL). Potential Hy's law cases will be investigated by summarizing the number of participants with elevated ALT or AST (> 3× ULN) and with elevated TBL (> 2× ULN) where transaminase elevation coincides with or precedes bilirubin elevation.

10.4.6.3 Vital Signs Data

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all vital sign variables (values and changes from baseline) will be calculated for each visit (baseline and post-baseline time points).

[redacted]

10.5 Interim Analyses

No formal interim analysis will be performed. When all participants complete the Week 30 visit or terminate the treatment prematurely, the primary analysis will be performed to assess the efficacy and safety of mavacamten treatment for the 30-week period.

When all participants complete the Week 54 visit or permanently discontinue treatment, an additional analysis will be conducted.

Final analysis will be performed when all participants complete the EOS visit.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AME	absorption, metabolism, and excretion
aPTT	activated partial thromboplastin time
ASA	alcohol septal ablation
AST	aspartate aminotransferase
AT	aminotransaminase
AUC	area under the concentration-time curve
AxMP	auxiliary medicinal product
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLT	total body clearance
cm	centimeter
Cmax	maximum observed concentration
[redacted]	
COVID-19	coronavirus disease 2019
[redacted]	
CRF	Case Report Form, paper or electronic
CRO	contract research organization
CSR	Clinical Study Report
CSS	Clinical Summary Score
CTAg	Clinical Trial Agreement
CV	cardiovascular
CYP	cytochrome P450
DDI	drug-drug interaction

Term	Definition
DILI	drug-induced liver injury
dL	deciliter
DMET	drug metabolism enzymes and drug transporters
DSM 5	Diagnostic and Statistical Manual of Mental Disorders (5th Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
[redacted]	
EHR	electronic health record
EMR	electronic medical record
EOS	end of study
EOT	end of treatment
E-R	exposure-response
ET	early termination
FSH	follicle-stimulating hormone
FU	follow-up
g	gram
GCP	Good Clinical Practice
h	hour
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
HFpEF	heart failure with preserved ejection fraction
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	implantable cardioverter-defibrillator
ICF	informed consent form

Term	Definition
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IU	international unit
IUS	intrauterine hormone-releasing system
IV	intravenous
IXRS	interactive response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	kilogram
L	liter
LAM	lactation amenorrhea method
[redacted]	
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
M&S	modeling and simulation
[redacted]	
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR	mitral regurgitation
[redacted]	
µg	microgram
N/A	not applicable

Term	Definition
NASH	nonalcoholic steatohepatitis
[redacted]	
nHCM	non-obstructive hypertrophic cardiomyopathy
NM	normal metabolizer
Non-IMP	Non-investigational Medicinal Product
NP	nurse practitioner
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PA	physician assistant
[redacted]	
PK	pharmacokinetic(s)
PM	poor metabolizer
PPK	population pharmacokinetic
PT	preferred term
pVO_2	peak oxygen consumption
QD	once daily
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	
SCD	sudden cardiac death
SD	standard deviation
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected, unexpected serious adverse reaction
T	time
TBL	total bilirubin
TC	telephone call
TEAE	treatment-emergent adverse event

Term	Definition
T1/2	half-life
Tmax	time of maximum observed concentration
TR_Cmax	Cmax treatment ratio
TTE	transthoracic echocardiography, transthoracic echocardiogram, transthoracic echocardiography
ULN	upper limit of normal
[redacted]	
VO_2	oxygen consumption
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential

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 1 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 or his/her legally acceptable representative and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or his/her legally acceptable representative 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 or his/her legally acceptable representative to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant or his/her legally acceptable representative 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 or his/her legally acceptable representative 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.

In situations where consent cannot be given by participants, their legally acceptable representatives (as per country regulation) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Participant unable to give their written informed consent (eg, stroke or participants with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the ICF as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

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 systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol-required assessments, and/or drug accountability records. Also, see "Guidelines for good clinical practices, ICH-GCP, 2015".

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 (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.

Certain CRF pages and/or electronic files may serve as the source documents.

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 treatments 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. But 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.

If	Then
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, health care 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.

CLINICAL STUDY REPORT

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

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); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

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 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.)

Adverse Events of Special Interest

[redacted]

AESIs are required to be reported by the investigator to the Sponsor within 24 hours, irrespective of regulatory seriousness criteria, and recorded as AEs. The required information in the electronic data capture (EDC) system will be completed 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.

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, SAEs, and AESIs

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: [redacted]

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

Note: Intravaginal and transdermal combined hormonal contraception are not approved by Japan Health Authority. Also, progestogen-only hormonal contraception is not approved by Japan Health Authority.

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

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used from Screening through 4 months after the last dose of mavacamten.

A vasectomy is a highly effective contraception method provided that the participant is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- 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 7.7.4 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 7.7.4 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 PROHIBITED MEDICATIONS

Cardiotoxic Agents

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

Disopyramide, cibenzoline, or ranolazine

Use of disopyramide, cibenzoline, or ranolazine is prohibited from 14 days before Screening assessments to the end of study (EOS).

Moderate and Potent CYP 2C19 Inhibitors and Potent CYP 3A4 Inhibitors

Potent and moderate CYP 2C19 inhibitors and potent CYP 3A4 inhibitors are prohibited from 14 days before Screening assessments through the EOS. Examples are listed below. For any medication in question, ask the Sponsor/CRO medical monitor.

CYP 2C19 Inhibitors

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

CYP 3A4 Inhibitors

- Boceprevir (antiviral)
- Ceritinib (kinase inhibitor)
- Clarithromycin (antibiotic)
- Cobicistat (GS-9350)
- Conivaptan (diuretic)
- Idelalisib (kinase inhibitor)
- Indinavir (protease inhibitor)
- Itraconazole (antifungal)
- Josamycin (antibiotic)
- Ketoconazole (antifungal)
- LCL161 (cancer treatment)

- Mibefradil (calcium channel blocker)
- Mifepristone (antiprogestin)
- Nefazodone (antidepressant)
- Nelfinavir (protease inhibitor)
- Posaconazole (antifungal)
- Ribociclib (kinase inhibitor)
- Ritonavir (protease inhibitor)
- Saquinavir (protease inhibitor)
- Telaprevir (antiviral)
- Telithromycin (antibiotic)
- Tipranavir (protease inhibitor)
- Troleandomycin (antibiotic)
- Tucatinib (kinase inhibitor)
- Viekira Pak (antiviral)

St. John's Wort

Use of St. John's Wort is prohibited from 14 days before Screening assessments to EOS.

Biotin Supplements

Biotin supplements are prohibited from 14 days prior to screening assessments through the EOS visit. Multivitamins that contain < 1000 mg QD of biotin are allowed during the study but must be stopped 24 hours prior to each study visit.

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 9.2.7 (> 3 times upper limit of normal [ULN] for AST/ALT and > 2 times 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 Sponsor as an SAE within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, AE CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Appendix 3.

Additional Clinical Assessments and Observation

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

- Repeat liver chemistries within 24 to 48 hours (ALT, AST, alkaline phosphatase [ALP], total bilirubin [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 that are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the participants should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports

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 investigational product(s) 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 [redacted] analysis if this has not already been collected
- Obtain a more detailed history of the following:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents

  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type reactions, fatigue, nausea, vomiting, and fever
  - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
  - Concomitant medications (including nonprescription medicines and herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr virus, herpes simplex virus, etc.); evaluate for other potential causes of DILI, including but not limited to: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation as specified in Section 9.2.7.
- 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 corresponding CRFs.

APPENDIX 7 MANAGEMENT OF PARTICIPANTS WHO ARE UNABLE TO ATTEND ONSITE STUDY VISITS (DUE TO COVID-19 OR OTHER PANDEMICS OR NATURAL DISASTERS)

The following provisions may be made to accommodate participants who are unable to attend on-site study visits for scheduled assessments and dispensation of mavacamten:

- Study visits may be performed at a remote location by a visiting health care service provider. Service providers must be approved by the Sponsor before performing study assessments.
- Participants who are unable to be seen at the clinic or at home by a visiting health care service provider may be required to temporarily discontinue mavacamten.
- Participants may be tested for COVID-19 at the discretion of the investigator and/or Sponsor.

Remote Health Assessment

- Protocol-specified assessments listed below may be conducted in the participant's home by a visiting health care professional or via telemedicine.
  - NYHA may be assessed by the Principal Investigator via telemedicine
  - Physical examination may be done by a home health care professional who is a licensed NP/PA
  - [redacted] may be acquired at home by a qualified sonographer who has been certified by the echocardiography core lab.
  - ECG may be acquired by home health care professional
  - Holter Monitor may be applied and removed at participant's home by a home health care professional.
  - Phlebotomy may be done by a home health care professional

Under certain circumstances the site may choose to contract with a community-based facility (with Sponsor/CRO medical monitor approval) for the above assessments (eg, vital signs, ECG, echocardiography upon certification by core echocardiography lab, application and removal of Holter).

Drug Dispensation

- Mavacamten may be shipped by Direct-to-Subject Study Drug Shipment (Section 7.5.2)

Temporary Discontinuation of Study Drug

Participants in Treatment Period for Primary Analysis (Day 1 through Week 30)

Under unusual circumstances such as a pandemic or natural disaster, if participants in the first 30 weeks of the study (Day 1 through Week 30) cannot be monitored for safety within 1 week of their scheduled study assessment, as they cannot be seen at the site or by a home health care provider, the participant will be contacted by the site at the end of the 1-week period and instructed to stop taking mavacamten.

Participants who discontinue mavacamten should be contacted by the site every 2 to 4 weeks from the time of discontinuing mavacamten to assess for AEs and to document concomitant medications until the next study visit.

When the participant can return to the study site, he/she will receive a new participant ID and undergo rescreening to re-enter the study. All screening assessments need to be repeated.

- Participants will restart study drug (mavacamten 2.5 mg QD) at Day 1 and resume study visits from Day 1.
- Participants who do not qualify based on re-screening assessments, on Principal Investigator consultation with the Sponsor/CRO Medical Monitor, may be scheduled for repeat screening at a later time. There is no limit to the number of times re-screening can occur when the participant discontinued IP due to a pandemic or natural disaster.

Participants in Long-Term Treatment Period (Week 30 through Week 138)

Under unusual circumstances such as a Pandemic or Natural Disaster, if participants in the long-term treatment period of the study (Week 30 through Week 138) cannot be monitored for safety within 1 week of their scheduled study assessment, as they cannot be seen at the site or by a home health care provider, the participant will be contacted by the site at the end of the 1-week period and instructed to stop taking mavacamten.

Participants who discontinue mavacamten should be contacted by the site every 2 to 4 weeks from the time of discontinuing mavacamten to assess for AEs and to document concomitant medications until the next study visit.

When the participant can return to the study site, he/she will receive a new participant ID and undergo re-screening to re-enter the study. All screening assessments need to be repeated.

- Resume mavacamten at the dose they were taking when they temporarily discontinued, following completion of an unscheduled safety visit.
- Resume study visits at time (T) + x weeks (where T is the study week at discontinuation and x is the number of weeks discontinued).
- Participants who have discontinued and resumed treatment according to these guidelines may repeat the discontinuation/resumption cycle as often as necessary.
- Participants who do not qualify based on re-screening assessments, on Principal Investigator consultation with the Sponsor/CRO Medical Monitor, may be scheduled for repeat screening at a later time. There is no limit to the number of times re-screening can occur when the participant discontinued IP due to a pandemic or natural disaster.

APPENDIX 8 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 02, 23-Mar-2022

This amendment corrects findings [redacted].

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.2 Exclusion Criteria, 2) Prior/Concomitant Therapy, c)	c) Removal of "non" from non-dihydropyridine	Correction of typo. Combination treatment with beta blockers with dihydropyridine calcium channel blockers is permitted.
All	Minor typographical errors corrected throughout	Clarification

Overall Rationale for the Protocol Amendment 01, 17-Mar-2022

The main reason for revising the protocol [redacted]. The revised protocol applies to all future participants of the study.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	[redacted] Clinical Scientist Bristol-Myers Squibb Company Route 206 & Province Line Road Lawrenceville, NJ 08543 Phone: [redacted] email: [redacted]	Updated name and contact information for Clinical Scientist
Table 2-1: Screening Procedural Outline (CV027004)	Removed SARS-CoV-2 Serology Test	SARS-CoV-2 serology test no longer required

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1.2.1 Treatment Period for Primary Analysis	Removed exception from criteria for permanent treatment discontinuation.	To avoid ambiguity, study drug is required to be discontinued, regardless of potential confounding factors, when LVEF ≤ 30%.
[redacted]		
6.1 Inclusion Criteria, 4) Reproductive Status; Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	• Note: Intravaginal and transdermal combined hormonal contraception are not approved by Japan Health Authority. Also, progestogen-only hormonal contraception is not approved by Japan Health Authority.	Added to clarify
6.2 Exclusion Criteria, 1) Medical Conditions, e)	• Has paroxysmal atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's ECG at the time of Screening.	Removal of 'intermittent' to be consistent with JCS guideline for Cardiac Arrhythmias.
6.2 Exclusion Criteria, 2) Prior/Concomitant Therapy, c) and d)	c) 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. Combination treatment with beta blockers and non-dihydropyridine calcium channel blockers is allowed. d) For individuals on any beta blockers or any calcium channel blockers, any dose adjustment of these	c) Added text to clarify that combination of beta blockers + non-dihydropyridine calcium channel blockers are prohibited but combination with dihydropyridine calcium channel blockers are allowed d) added "any" for clarification

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	medications < 14 days prior to Screening or any anticipated change in treatment regimen during the first 30 weeks of the study.	
6.2 Exclusion Criteria 3), c)	Timing of SARS infection updated to 30 days of screening.	Participants with history of SARS-CoV-2 infection greater than 30 days from Screening will be eligible.
[redacted]		
6.4.1 Meals and Dietary Restrictions	• Refrain from consumption of Seville oranges, grapefruit or grapefruit juice and quinine (eg, tonic water) from Day 1 before the start of study intervention until after the final follow-up visit.	Clarification.
Table 7.4.1.1-1 and Table 7.4.1.2-1	Updated Valsalva LVOT gradient	Updates made to clarify LVOT gradient.
[redacted]		
7.7.2 Background HCM Therapy	Added collection of COVID-19 vaccination status of all participants	To ensure understanding of COVID-19 medical history.
8.1.3 Criteria for Temporary Treatment Discontinuation	Updated to clarify language on temporary dose discontinuation.	Added “will” and “or” to clarify language of temporary discontinuation criteria

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
8.1.4 Criteria for Permanent Treatment Discontinuation	Updated to specify discontinuation required if LVEF ≤ 30%.	To avoid ambiguity, study drug is required to be discontinued, regardless of potential confounding factors, when LVEF ≤ 30%.
[redacted]		
9.4.4 Clinical Safety Laboratory Assessments; Table 9.8.1 Biomarker Assessments; 9.10 Other Assessments;	Removal of SARS-CoV-2 Serology.	Blood samples for SARS-CoV-2 Serology are no longer required.
9.7.1 HCM Genotyping	Redundant text removed.	Clarification.
All	Minor typographical errors corrected throughout.	Clarification.