

Official Title of Study:

A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

NCT Number: NCT05582395

Document Date (Date in which document was last revised): 25 Jul 2024

Page: 1  
Protocol Number: CV027031  
Date: 29-Jun-2022  
Revised Date: 25-Jul-2024

## **CLINICAL PROTOCOL CV027031**

A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in  
Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

### **Brief Title:**

Mavacamten in non-obstructive HCM

### **Protocol Amendment Number 03**

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IND: 121904  
EU CT Number: 2023-506352-24  
UTN: U1111-1269-8581

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## DOCUMENT HISTORY

| Document              | Date of Issue | Summary of Change                                                                                                                                                                                                                                                               |
|-----------------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Protocol Amendment 03 | 25-Jul-2024   | The rationale for Protocol Amendment 03 is to remove the incidence of cardiac arrhythmias sub-study [REDACTED]                                                                                                                                                                  |
| Protocol Amendment 02 | 02-Aug-2023   | The 3 key changes in this amendment are: 1) removal of the extended double-blind treatment period, 2) addition of a long-term extension period, and 3) [REDACTED] the Kansas City Cardiomyopathy Questionnaire-23 clinical summary score threshold at screening from [REDACTED] |
| Protocol Amendment 01 | 10-Apr-2023   | The rationale for Protocol Amendment 01 is [REDACTED] to clarify sections of the protocol based on input from investigators, the clinical research organization, and the executive committee.                                                                                   |
| Original Protocol     | 29-Jun-2022   | Not applicable                                                                                                                                                                                                                                                                  |

### OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

This protocol was amended [REDACTED] regarding statistical analyses, including the method of analyses, [REDACTED]

[REDACTED] The cardiac arrhythmias sub-study was removed due to operational challenges. Several minor updates were included to provide clarity and consistency.

The protocol summary is updated to reflect the changes made in the protocol amendment.

This protocol amendment applies to all participants.

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03                                                                                      |                       |                 |
|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------------|
| Section Number & Title                                                                                                            | Description of Change | Brief Rationale |
| <a href="#">Table 2-1</a> : Screening Procedural Outline (CV027031)<br><a href="#">Table 9.8-1</a> : Biomarker Sampling Schedule  | [REDACTED]            | [REDACTED]      |
| <a href="#">Table 2-2</a> : Schedule of Activities [REDACTED]<br>[REDACTED] (CV027031)                                            |                       |                 |
| <a href="#">Table 2-2</a> : Schedule of Activities [REDACTED]<br>[REDACTED] (CV027031)<br><a href="#">Section 4.1</a> : Sub-study |                       |                 |
| <a href="#">Table 2-4</a> : Schedule of Activities [REDACTED]<br>[REDACTED] (CV027031)                                            |                       |                 |
| <a href="#">Table 4-1</a> : Objectives and Endpoints<br><a href="#">Table 10.4.3-1</a> : Estimands                                |                       |                 |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                             |
|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Section Number & Title                                | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Brief Rationale                                                             |
|                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                             |
| Section 5.1.1: Screening [REDACTED]                   | Added text specifying “demographics (such as age, gender, ethnicity, and race where local regulatory requirements permit)”.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Updated to align with local laws and regulations regarding data collection. |
| Table 7.1-1 Study Intervention                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                             |
| Section 9.4.4: Clinical Safety Laboratory Assessments |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                             |
| Section 10.2: Sample Size Determination [REDACTED]    | <p>Updated the following paragraph from:</p> <p>A sample size of 420 participants will provide ~95% power to reject the primary null hypothesis of KCCQ-23 CSS, ~ 98% power to reject the primary null hypothesis of pVO<sub>2</sub>, and ~ 99% power to claim study success (power of at least one primary null hypothesis is rejected) while adjusting for multiplicity.</p> <p>To:</p> <p>A sample size of 420 participants will provide at least 94% power to reject the primary null hypothesis of KCCQ-23 CSS, at least 98% power to reject the primary null hypothesis of pVO<sub>2</sub>, and at least 99% power to claim study success (power of at least one primary null hypothesis is rejected) while adjusting for multiplicity.</p> | [REDACTED]                                                                  |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                             |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Section Number & Title                       | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Brief Rationale                                                                                             |
| Section 10.4.2: Primary Endpoint(s)          | Updated the following paragraph:<br>“The primary efficacy endpoint of change from baseline in the KCCQ-23 CSS will be analyzed using Mixed Model with Repeated Measurements (MMRM), including stratification factors, baseline KCCQ-23 CSS score, treatment, visit, visit×treatment (interaction between visit and treatment) as covariates or factors, and participant as a random effect, using an unstructured variance-covariance matrix.”<br><br>To:<br>“Both primary efficacy endpoints will be analyzed using analysis of covariance (ANCOVA), including stratification factors, baseline value, and treatment as covariate or factor in the model, as appropriate.” | <div></div> <div>regarding potentially limited retrieved dropout samples at intermittent timepoints.</div>  |
|                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                             |
| Section 10.4.2.1: Sensitivity Analysis       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                             |
| Section 10.4.2.2: Supportive Analysis        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                             |
|                                              | Added the following paragraph:<br>“Change from baseline in the KCCQ-23 CSS will be analyzed using Mixed Model with Repeated Measurements (MMRM), including treatment, stratification factors, visit and                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | MMRM model without imputation will be conducted to provide summary statistics for intermediate time points. |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                            |
|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Section Number & Title                       | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Brief Rationale                                                                                            |
|                                              | treatment-by-visit interaction as fixed effects, baseline of the dependent variable as a covariate, and participant as a random effect, using an unstructured variance-covariance matrix, if appropriate.”                                                                                                                                                                                                                                                                                           |                                                                                                            |
|                                              | <p>Updated the following bullet for the supportive analysis of the primary endpoint of pVO<sub>2</sub>:</p> <ul style="list-style-type: none"> <li>Percentages of responders with moderate (eg, 1.5) and large improvements from baseline (eg, 3.0) at Week 48 will be summarized by treatment group and nominal p-values will be provided.</li> </ul> <p>To:</p> <p>Percentages of participants with clinical meaningful change from baseline at Week 48 will be summarized by treatment group.</p> | Updated as example thresholds for moderate and large improvements are not supported by current literature. |



| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                               |
|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Section Number & Title                                                                                        | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Brief Rationale                                                                                               |
| <p><a href="#">Section 10.4.3</a>: Secondary Endpoint(s)</p> <p><a href="#">Table 10.4.3-1</a>: Estimands</p> | <p>Updated the following paragraph:</p> <p>“Continuous endpoints of HCMSQ SoB, NT-proBNP, and cTn-T will be analyzed in a similar way as the primary endpoint of KCCQ-23 CSS by using similar MMRM model, treatment policy strategy and missing data scheme. The supportive analyses for these endpoints will also be similar to those specified for the KCCQ-23 CSS.”</p> <p>To:</p> <p>“Continuous endpoints of HCMSQ SoB and NT-proBNP will be analyzed in a similar way as the primary endpoint of KCCQ-23 CSS by using similar ANCOVA model, treatment policy strategy and missing data scheme.”</p> | <p>Changed [REDACTED] regarding potentially limited retrieved dropout samples at intermittent timepoints.</p> |
|                                                                                                               | <p>Updated the following paragraph:</p> <p>[REDACTED]</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>[REDACTED]</p>                                                                                             |
|                                                                                                               | <p>Moved the following paragraph to exploratory endpoints section:</p> <p>“Time to first MACE-plus events will be analyzed by using a stratified Cox proportional hazards model with treatment as a fixed factor if proportional hazard assumption holds. The hazard ratio estimate between mavacamten and placebo along with</p>                                                                                                                                                                                                                                                                         | <p>Time to first MACE-plus event is considered as an exploratory endpoint.</p>                                |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                 |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Section Number & Title                                                         | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Brief Rationale |
|                                                                                | <p>its associated 2-sided 95% CI will be provided. [REDACTED]</p> <p>[REDACTED] All data after study intervention discontinuation will be included in analysis (treatment policy strategy). Missing data will not be imputed. As a supportive analysis for the distribution of time to first MACE-plus events will be compared between mavacamten and placebo using log-rank test (a fully non-parametric test). Details will be provided in the SAP.”</p>                                                                                                                                                              |                 |
|                                                                                | <p>Updated the estimands for the following endpoints:</p> <ul style="list-style-type: none"> <li>• Change from baseline in KCCQ-23 CSS at Week 48</li> <li>• Change from baseline in pVO2 at Week 48</li> <li>• Proportion of participants with at least one class of improvement in NYHA from baseline to Week 48</li> <li>• Change from baseline in VE/VCO2 slope to Week 48</li> <li>• Change from baseline to Week 48 in NT-proBNP</li> <li>• Change from baseline to Week 48 in HCMSQ SoB domain</li> <li>• Deleted the estimand: Time to first major adverse cardiovascular events (MACE) plus events.</li> </ul> | [REDACTED]      |
| <p><a href="#">Section 10.4.3</a>: Secondary Endpoint(s)</p> <p>[REDACTED]</p> | [REDACTED]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                 |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03                            |                                                                                                |                                              |
|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------|
| Section Number & Title                                                  | Description of Change                                                                          | Brief Rationale                              |
|                                                                         |                                                                                                |                                              |
| <a href="#">Appendix 2</a> : Study Governance Considerations            | Deleted European Union Directive from Institutional Review Board/Independent Ethics Committee. | To comply with EU Clinical Trial Regulation. |
| <a href="#">Appendix 6</a> : Country-specific Requirements/ Differences |                                                                                                |                                              |
| All                                                                     | Minor formatting and typographical corrections.                                                | Minor, therefore, have not been summarized.  |

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## 1 PROTOCOL SUMMARY

**Protocol Title:** A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

**Brief Title:** Mavacamten in non-obstructive HCM

### Rationale:

Safer and more effective treatments to reduce symptoms and increase functional capacity for participants with non-obstructive hypertrophic cardiomyopathy (nHCM) have been identified as unmet medical needs by guidelines from the American College of Cardiology/American Heart Association and the European Society of Cardiology. Mavacamten has the potential to meet this unmet need. In contrast to currently available therapies, mavacamten is a first-in-class, selective, and reversible modulator of cardiac myosin that targets the underlying pathophysiology of the disease.

### Objectives and Endpoints:

| Objectives                                                                                                                                                                                                                                                                                                                                                                                                          | Endpoints                                                                                                                                                                                                                                                                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b> <ul style="list-style-type: none"> <li>To assess the efficacy of a 48-week course of mavacamten compared to placebo on patient-reported health status (symptoms and physical limitations)</li> <li>To assess the efficacy of a 48-week course of mavacamten compared to placebo on exercise capacity</li> </ul>                                                                                      | <ul style="list-style-type: none"> <li>Change from baseline in KCCQ-23 CSS at Week 48</li> <li>Change from baseline in pVO<sub>2</sub> at Week 48</li> </ul>                                                                                                                                                                            |
| <b>Secondary</b> <ul style="list-style-type: none"> <li>Evaluate the effects of mavacamten on ventilatory efficiency as measured by the VE/VCO<sub>2</sub> slope</li> <li>Evaluate the effects of mavacamten on NYHA classification</li> <li>Evaluate the effects of mavacamten on cardiac biomarkers of wall stress</li> <li>Evaluate the effects of mavacamten on patient-reported shortness of breath</li> </ul> | <ul style="list-style-type: none"> <li>Change from baseline in VE/VCO<sub>2</sub> slope to Week 48</li> <li>Proportion of participants with at least 1 class of NYHA improvement from baseline to Week 48</li> <li>Change from baseline in NT-proBNP to Week 48</li> <li>Change from baseline in HCMSQ SoB domain to Week 48</li> </ul> |
| <b>Safety</b> <ul style="list-style-type: none"> <li>To assess the safety and tolerability of mavacamten</li> <li>To assess the effects of mavacamten on LVEF determined by echocardiography, ECG, and vital sign parameters over time</li> <li>To assess the incidence of LVEF [REDACTED]</li> </ul>                                                                                                               | <ul style="list-style-type: none"> <li>Incidence of AEs, SAEs, AEs leading to study intervention discontinuation, AEs leading to death.</li> <li>Change in laboratory, LVEF determined by echocardiography, ECG, and vital sign parameters over time</li> <li>Percentage of participants with an LVEF [REDACTED]</li> </ul>             |



Abbreviations: AE, adverse event; CV, cardiovascular; ECG, electrocardiogram; HCMSQ SoB, hypertrophic cardiomyopathy symptom questionnaire-shortness of breath; KCCQ-23 CSS, Kansas City Cardiomyopathy Questionnaire (23-item) Clinical Summary Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; pVO<sub>2</sub>, peak oxygen consumption; nHCM, non-obstructive hypertrophic cardiomyopathy; SAE, serious adverse event; VE/VCO<sub>2</sub>, ventilatory efficiency.

## Overall Design:

CV027031 is a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo in participants with symptomatic nHCM. The study will randomize approximately 420 participants at about [REDACTED] ratio to mavacamten and placebo. Randomization will be stratified by New York Heart Association (NYHA) class (II or III), type of exercise (treadmill or exercise bicycle), and beta blocker use (Yes/No) at baseline. The study consists of a placebo controlled double-blind treatment period (Part A) which will last 48 weeks and a long term extension (LTE) period [REDACTED] for up to approximately [REDACTED]. To participate in the study, participants must have:

- 1) New York Heart Association (NYHA) Functional Classification II or III and Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score (KCCQ-23 CSS) [REDACTED]
- 2) Increased cardiac wall stress [REDACTED]
- 3) Cardiac wall thickness  $\geq 15$  mm (or  $\geq 13$  mm if family history)
- 4) Left ventricular ejection fraction (LVEF) [REDACTED]
- 5) Left ventricular diastolic dysfunction (E/e' [REDACTED] OR left atrial volume index [REDACTED] mL/m<sup>2</sup>) OR myocardial damage as indicated by elevated cardiac troponin [REDACTED] of the upper limit of normal of the assay used by the analyzing laboratory
- 6) Left ventricular outflow tract gradient  $< 30$  mm Hg at rest and  $< 50$  mm Hg after provocation (Valsalva and post exercise).

Cardiac medications cannot be initiated, discontinued, or dose adjusted within [REDACTED]. Background therapy is permitted throughout the duration of the study. At Week 48 after study intervention, the effects of mavacamten compared to placebo on health status (symptoms and physical limitations) will be assessed by change from baseline in KCCQ-23 CSS and the effect on exercise capacity by change from baseline in peak oxygen consumption (pVO<sub>2</sub>). The 2 primary endpoints were selected to assess the symptoms and functional limitation reported most frequently as troublesome by participants with nHCM: exertional dyspnea, fatigue, and limited exercise capacity.

## Number of Participants:

Approximately 420 participants will be randomized.

Assuming a [REDACTED] screen failure rate, approximately [REDACTED] screened participants (signed Informed Consent Form) will be required to achieve approximately 420 randomized.

### Study Population:

Participants must be at least 18 years old, or local age of majority with symptomatic nHCM.

### Intervention Groups and Duration:

- [REDACTED] will be allocated for screening to identify eligible participants.
- The placebo-controlled double-blind treatment period (Part A) with oral mavacamten or placebo will last 48 weeks.
- Primary outcomes for all participants will be assessed at Week 48.
- Participants who complete study intervention at Week 48 [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

### Study Intervention:

| Study Intervention for CV027031      |            |                |
|--------------------------------------|------------|----------------|
| Medication                           | Potency    | IP/Non-IP/AxMP |
| Mavacamten                           | [REDACTED] | IP             |
| PBO matching mavacamten oral capsule | NA         | IP             |

Abbreviations: AxMP, auxiliary medicinal product; IP, investigational product; NA, not applicable; PBO, placebo.

### Statistical Methods:

Study design: randomized, double-blind, and parallel-group study

The study will test the primary hypotheses that mavacamten is superior to placebo on the 2 primary endpoints of change from baseline to Week 48 in the KCCQ-23 CSS and change from baseline to Week 48 in pVO<sub>2</sub>. The study will be claimed successful if at least 1 primary null hypothesis is rejected.

Both primary efficacy endpoints will be analyzed using analysis of covariance (ANCOVA), including stratification factors, baseline value, and treatment as covariate or factor in the model, as appropriate.

The efficacy analysis will be performed in all randomized participants with the intercurrent event of study intervention discontinuation being handled by treatment policy strategy (all data after study intervention discontinuation will be included for analysis) and missing data being imputed by multiple imputation approach, where applicable.

[REDACTED]

[REDACTED] A sample size of 420 participants will provide at least 94% power to reject the primary null hypothesis of KCCQ-23 CSS, at least 98% power to reject the primary null hypothesis of pVO<sub>2</sub>, and at least 99% power to claim study success (power of at least one primary null hypothesis is rejected) while adjusting for multiplicity. No interim analysis is planned for this study.

### **Study Committees:**

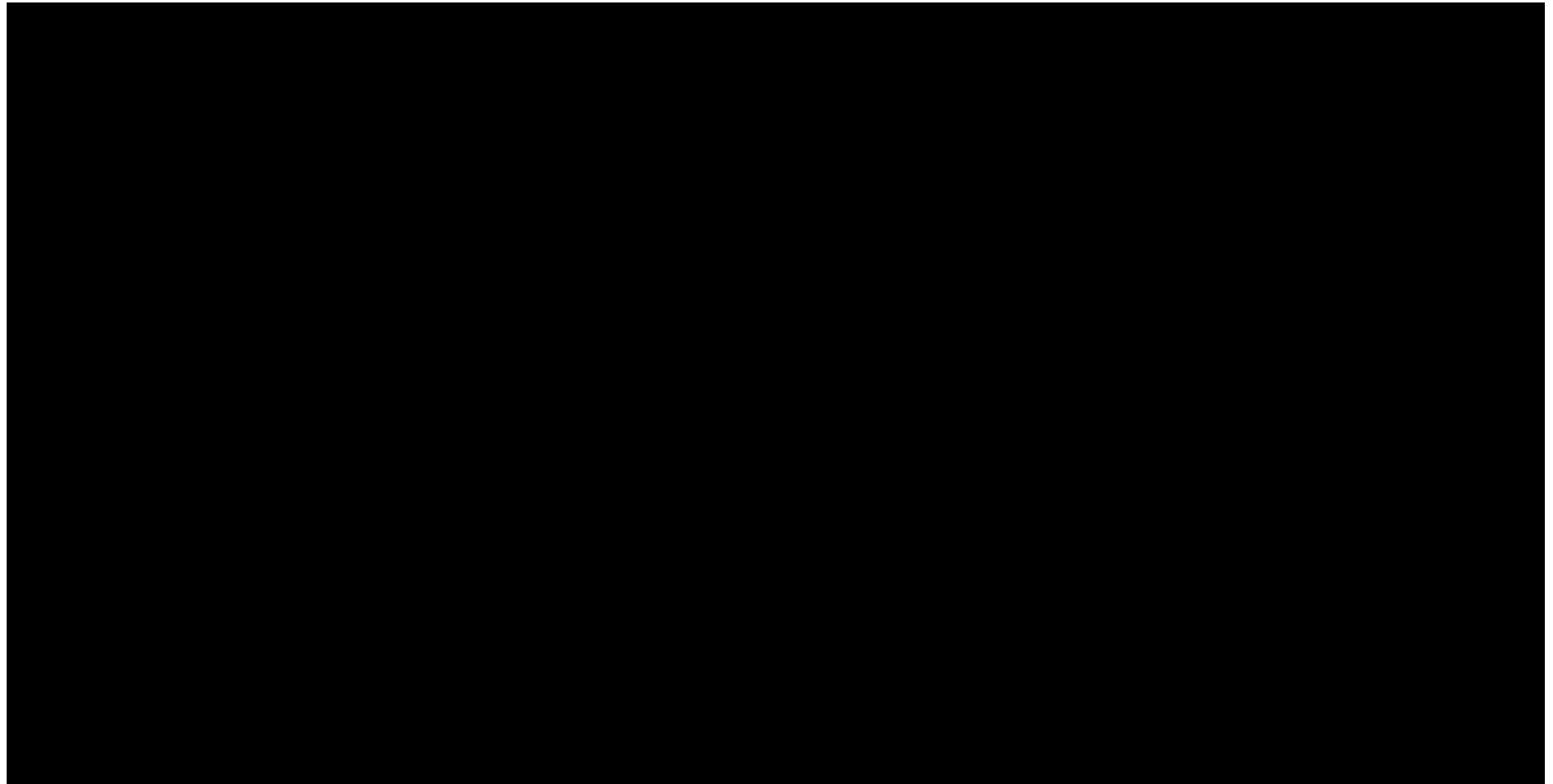
Data Monitoring, Steering, Executive, and Clinical Event Committees will be used in the study.

### **Brief Summary:**

The purpose of this study is to test the hypothesis that treatment with oral mavacamten compared to placebo improves health status (symptoms and physical limitations) and increases exercise capacity in participants with nHCM who are symptomatic and have diminished physical function and exercise capacity. The effects of treatment on health status (symptoms and physical limitations) will be assessed by the KCCQ-23 CSS, and the effects of treatment on exercise capacity will be assessed by pVO<sub>2</sub> measured by cardiopulmonary exercise testing. The placebo-controlled double-blind treatment period with oral mavacamten or placebo will last 48 weeks.

[REDACTED]

Primary outcomes for all participants will be assessed at Week 48.



## 2 SCHEDULE OF ACTIVITIES

**Table 2-1: Screening Procedural Outline (CV027031)**

| Procedure                                       | Screening [REDACTED] | Notes                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Eligibility Assessments</b>                  |                      |                                                                                                                                                                                                                                                                                                |
| Informed Consent                                | X                    | A participant is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures.                                                                                                                                  |
| KCCQ-23                                         | X                    | [REDACTED]                                                                                                                                                                                                                                                                                     |
| NT-proBNP/BNP                                   | X                    | NT-proBNP/BNP are done at the local laboratory for eligibility, and the results sent to ICON (iRIS). If the local laboratory cannot complete these assessments, then the samples should be sent to the [REDACTED] laboratory as part of the Screening [REDACTED] laboratory visit kit.         |
| Cardiac Troponin                                | X                    | Cardiac Troponin (T or I) is done at the local laboratory for eligibility, and the results sent to ICON (iRIS). If the local laboratory cannot complete this assessment, then the sample should be sent to the [REDACTED] laboratory as part of the Screening [REDACTED] laboratory visit kit. |
| Inclusion/Exclusion Criteria                    | X                    | See <a href="#">Section 6.1</a> inclusion criteria/ <a href="#">Section 6.2</a> exclusion criteria                                                                                                                                                                                             |
| Medical History                                 | X                    | All medical history relevant to disease under study as well as any recent medical conditions                                                                                                                                                                                                   |
| ICD information                                 | X                    | Date of implantation, number of appropriate or inappropriate discharges                                                                                                                                                                                                                        |
| Resting & Valsalva Transthoracic Echocardiogram | X                    | Includes LVEF and LVOT gradient [REDACTED] See Echo manual for more details.                                                                                                                                                                                                                   |
| CPET                                            | X                    | CPET parameters, including, but not limited to, RER, pVO <sub>2</sub> , VE/VCO <sub>2</sub> , maximum exercise time, and METs will be obtained. The results of this CPET will be used as baseline values.                                                                                      |
| NYHA Functional Classification                  | X                    | Based on original questions in the functional classification                                                                                                                                                                                                                                   |

**Table 2-1: Screening Procedural Outline (CV027031)**

| Procedure                                                                       | Screening [REDACTED] | Notes                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Post-exercise Stress Echocardiogram                                             | X                    | Required after resting TTE and TTE with Valsalva maneuver to exclude a post-exercise LVOT gradient > 50 mm Hg [REDACTED] See Echo manual for more details.                                                                                                                                                                                                                                                                                                |
| <b>Safety Assessments</b>                                                       |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Physical Examination                                                            | X                    | A complete physical examination including height, weight, and assessment of the following: general appearance, skin, head, neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems.                                                                                                                                                                                                            |
| Vital Signs                                                                     | X                    | Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.                                                                                                                                                                                                                                            |
| Prior/Concomitant Therapy                                                       | X                    | See <a href="#">Section 7.7</a>                                                                                                                                                                                                                                                                                                                                                                                                                           |
| ECG                                                                             | X                    | ECGs should be recorded after the participant has been supine for at least 5 minutes. The ECG obtained during screening will be used for baseline assessment.                                                                                                                                                                                                                                                                                             |
| <b>Laboratory Tests</b>                                                         |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Clinical Laboratory Assessments: Chemistry, Coagulation, Hematology, Urinalysis | X                    | Includes blood and urine samples.                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Pregnancy Test (WOCBP only)                                                     | X                    | A serum $\beta$ -hCG pregnancy test is required at screening and should be done at the local laboratory for eligibility, and the results sent to ICON (iRIS). If the local laboratory cannot complete this assessment, then the sample should be sent to the [REDACTED] laboratory as part of the Screening [REDACTED] laboratory visit kit. A urine $\beta$ -hCG pregnancy test is required at randomization, prior to first dose of study intervention. |
| Follicle-stimulating Hormone (FSH)                                              | X                    | Women only. Refer to <a href="#">Appendix 4</a> .                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>AE Reporting</b>                                                             |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Monitor for SAEs                                                                | X                    | All SAEs must be collected from the date of participant's written consent until EOS as defined in <a href="#">Section 9.2.1</a> . Laboratory results performed locally for assessment of SAEs should be sent to ICON (iRIS).                                                                                                                                                                                                                              |

**Table 2-1: Screening Procedural Outline (CV027031)**

| Procedure                                   | Screening [REDACTED]                                                                   | Notes                                                                                                                                                                                                                                             |
|---------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Patient-reported Outcome Assessments</b> | See <a href="#">Section 9.1.3.9</a> for PRO Administration, Method, Mode, and Training |                                                                                                                                                                                                                                                   |
| HCMSQ                                       | X                                                                                      | Participants will complete the HCMSQ daily from the day of screening visit to [REDACTED] to have at least 14 days' worth of HCMSQ data.                                                                                                           |
| PGI-S (PGIS-KCCQ, PGIS-SoB)                 | X                                                                                      | During screening visit, participants will complete the KCCQ-23 prior to completing the PGIS-KCCQ. Participants will complete the PGIS-SoB on [REDACTED]. Participants will complete the HCMSQ assessment prior to the completion of the PGIS-SoB. |

Abbreviations:  $\beta$ -hCG, beta-human chorionic gonadotropin; AE, adverse event; BMI, body mass index; CPET, cardiopulmonary exercise testing; [REDACTED]; ECG, electrocardiogram; Echo, echocardiogram; EOS, end of study; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; ICD, implantable cardioverter-defibrillator; ICON (iRIS), ICON Results Integration Service; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MET, metabolic equivalent of task; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; pVO<sub>2</sub>, peak oxygen consumption; RER, respiratory exchange ratio; SAE, serious adverse event; SoB, shortness of breath; TTE, transthoracic echocardiogram; VE/VCO<sub>2</sub>, ventilatory efficiency; WOCBP, women of childbearing potential.

**Table 2-2:**                      **Schedule of Activities**  
**(CV027031)**

|                                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
|-----------------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------|
| Procedures                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Visit Number                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Week                                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Day (± 7D Visit Window, except for Day 1)     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Eligibility Assessments                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Randomization <sup>a</sup>                    | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Inclusion/Exclusion Criteria                  | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| ICD Information                               | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Efficacy Assessments                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| CPET                                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| NYHA Functional Classification                | X | X |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X              |
| Resting Transthoracic Echocardiogram          | X | X |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X <sup>†</sup> |
| Safety Assessments                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Physical Examination                          | X |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   | X              |
| Targeted CV Physical Examination <sup>b</sup> |   | X |   | X |   | X |   | X |   | X |   |   |   | X |   | X | X |                |
| Vital Signs                                   | X | X |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X              |
| Assessment of Signs and Symptoms              | X | X |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X              |
| ECG                                           |   | X |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X              |
| Concomitant Medication Use                    | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X              |
| Concomitant Procedures                        | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X              |
| AE Reporting                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                |
| Monitor for AEs/SAEs                          | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X              |



**Table 2-2: Schedule of Activities**  
(CV027031)

|                                                   |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|--|----------------|--|---|---|----------------|--|---|---|----------------|--|---|---|----------------|----------------|------------------|
| Procedures                                        |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Visit Number                                      |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Week                                              |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Day (± 7D Visit Window, except for Day 1)         |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Laboratory Tests                                  |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Clinical Laboratory Assessments                   | X                                                                                                                           | X                                                                                                          |  |                |  | X |   |                |  | X |   |                |  | X |   |                |                | X                |
| Pregnancy Test (WOCBP only) <sup>c,d</sup>        | X                                                                                                                           | X                                                                                                          |  | X              |  |   | X | X              |  |   | X | X              |  |   | X | X              | X              | X                |
| Cardiomyopathy Genotyping                         | X                                                                                                                           | Note: See <a href="#">Section 9.7.2</a> and <a href="#">Table 9.8-1</a> .                                  |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Pharmacogenetics                                  | X                                                                                                                           | Note: DMET, including CYP genes polymorphisms (eg, CYP2C19 genotypes). See <a href="#">Section 9.7.1</a> . |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
|                                                   |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| PK Assessments                                    | Note: See <a href="#">Table 9.5-1</a> .                                                                                     |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Biomarker Assessments                             | Note: Including cTn-T, cTn-I, NT-proBNP, and exploratory biomarkers. See <a href="#">Table 9.8-1</a> for sampling schedule. |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Sub-study Assessments (Separate Consent Required) |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| CMR <sup>e</sup>                                  |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Study Intervention                                |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Dispense Study Medication                         |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| Patient Reported Outcome Assessments <sup>g</sup> |                                                                                                                             |                                                                                                            |  |                |  |   |   |                |  |   |   |                |  |   |   |                |                |                  |
| KCCQ-23                                           | X                                                                                                                           | X                                                                                                          |  | X              |  |   |   | X              |  |   |   | X              |  |   |   | X              | X              | X                |
| HCMSQ                                             | X <sup>h</sup>                                                                                                              | X <sup>h</sup>                                                                                             |  | X <sup>i</sup> |  |   |   | X <sup>i</sup> |  |   |   | X <sup>i</sup> |  |   |   | X <sup>i</sup> | X <sup>i</sup> | X <sup>i,j</sup> |
| EQ-5D-5L                                          | X                                                                                                                           | X                                                                                                          |  | X              |  |   |   | X              |  |   |   | X              |  |   |   | X              | X              | X                |
| PGIS-KCCQ & PGIS-SoB <sup>k</sup>                 | X <sup>l</sup>                                                                                                              | X                                                                                                          |  | X              |  |   |   | X              |  |   |   | X              |  |   |   | X              | X              | X                |
| PGIC-KCCQ & PGIC-SoB <sup>k</sup>                 |                                                                                                                             | X                                                                                                          |  | X              |  |   |   | X              |  |   |   | X              |  |   |   | X              | X              | X                |

Abbreviations: β-hCG, beta human chorionic gonadotropin; AE, adverse event; CMR, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; cTn-I, cardiac troponin I; cTn-T, cardiac troponin T; CV, cardiovascular; CYP, cytochrome P450; D, day(s); DMET, drug metabolism enzymes and drug transporters; ECG, electrocardiogram; EQ-5D-5L, 5-level EuroQol-5 Dimension Version; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; PRO, patient-reported

outcome; SAE, serious adverse event; SoB, shortness of breath; TTE, transthoracic echocardiogram; [REDACTED] WOCBP, women of childbearing potential.

- [REDACTED]
- † [REDACTED]
- a [REDACTED]
- b [REDACTED]
- c If a WOCBP reports any urine  $\beta$ -hCG pregnancy test result as positive or ambiguous post randomization, the Principal Investigator will instruct the participant to suspend further study intervention and schedule a follow-up appointment as soon as possible, where a confirmatory serum  $\beta$ -hCG pregnancy test will be performed.
- d A pregnancy test is required every 4 weeks throughout the entire study. [REDACTED]
- e [REDACTED]
- [REDACTED]
- g The PRO assessments that are completed at visits should be completed prior to any other study procedure taking place, where possible, and prior to any meaningful discussion about the study or study intervention with investigative site staff. See [Section 9.1.3.9](#) for PRO Administration, Method, Mode, and Training.
- h Participants will complete the HCMSQ daily for the first 4 weeks after initiation of study intervention.
- i Participants will complete the HCMSQ daily for a consecutive 7-day (1-week) period prior to the Week 8, 16, 28, 40, 44, and 48 visits.
- j For participants who enter the LTE, HCMSQ will be completed daily for the first 4 weeks after the Week 48 visit.
- k Participants will complete the KCCQ-23 prior to completing the PGIS-KCCQ and PGIC-KCCQ; participants will complete the 7th day of the HCMSQ assessment prior to the completion of the PGIS-SoB and PGIC-SoB. The PGIS-KCCQ and PGIC-KCCQ are collected at the Week 48 visit.
- l At randomization, participants will only complete the PGIS-KCCQ. Participants will not need to complete the PGIC-KCCQ at randomization.

**Table 2-3: Schedule of Activities** [REDACTED] **(CV027031)**

|                                               |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <b>Procedures</b>                             |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>Visit Number</b>                           |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>Week</b>                                   |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>Day (± 7D Visit Window)</b>                |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>Efficacy Assessments</b>                   |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| NYHA Functional Classification                | X                                                                                                                           |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X |
| Resting Transthoracic Echocardiogram          | X                                                                                                                           |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X |
| <b>Safety Assessments</b>                     |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Physical Examination                          |                                                                                                                             |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   | X |
| Targeted CV Physical Examination <sup>a</sup> | X                                                                                                                           |   | X |   | X |   | X |   | X |   |   |   | X |   | X | X |   |
| Vital Signs                                   | X                                                                                                                           |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X |
| Assessment of Signs and Symptoms              | X                                                                                                                           |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X |
| ECG                                           | X                                                                                                                           |   | X |   | X |   | X |   | X |   | X |   | X |   | X | X | X |
| Concomitant Medication Use                    | X                                                                                                                           | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Procedures                        | X                                                                                                                           | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| <b>AE Reporting</b>                           |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Monitor for AEs/SAEs                          | X                                                                                                                           | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| <b>Laboratory Tests</b>                       |                                                                                                                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Clinical Laboratory Assessments               | X                                                                                                                           |   |   |   | X |   |   |   | X |   |   |   | X |   |   |   | X |
| Pregnancy Test (WOCBP only) <sup>b,c</sup>    | X                                                                                                                           |   | X |   |   | X | X |   |   | X | X |   |   | X | X | X | X |
| <b>PK Assessments</b>                         | Note: See <a href="#">Table 9.5-1</a> .                                                                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>Biomarker Assessments</b>                  | Note: Including cTn-T, cTn-I, NT-proBNP, and exploratory biomarkers. See <a href="#">Table 9.8-1</a> for sampling schedule. |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

**Table 2-3: Schedule of Activities [REDACTED] (CV027031)**

|                                                   |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
|---------------------------------------------------|---|---|---|---|--|---|---|---|--|---|---|---|--|---|---|---|---|
| Procedures                                        |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| Visit Number                                      |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| Week                                              |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| Day (± 7D Visit Window)                           |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| Sub-study Assessments (Separate Consent Required) |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| CMR <sup>d</sup>                                  |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| Study Intervention                                |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| Dispense Study Medication                         |   | X |   | X |  | X |   | X |  | X |   | X |  | X |   |   | X |
| Patient Reported Outcome Assessments <sup>c</sup> |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |   |
| KCCQ-23                                           | X |   | X |   |  |   | X |   |  |   | X |   |  |   | X | X | X |
| HCMSQ <sup>f,g</sup>                              | X |   | X |   |  |   | X |   |  |   | X |   |  |   | X | X | X |
| EQ-5D-5L                                          | X |   | X |   |  |   | X |   |  |   | X |   |  |   | X | X | X |
| PGIS-KCCQ & PGIS-SoB <sup>h</sup>                 | X |   | X |   |  |   | X |   |  |   | X |   |  |   | X | X | X |
| PGIC-KCCQ & PGIC-SoB <sup>h</sup>                 | X |   | X |   |  |   | X |   |  |   | X |   |  |   | X | X | X |

Abbreviations: β-hCG, beta human chorionic gonadotropin; AE, adverse event; CMR, cardiac magnetic resonance imaging; cTn-I, cardiac troponin I; cTn-T, cardiac troponin T; CV, cardiovascular; D, day(s); ECG, electrocardiogram; EQ-5D-5L, 5-level EuroQol-5 Dimension Version; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; PRO, patient-reported outcome; SAE, serious adverse event; SoB, shortness of breath; TTE, transthoracic echocardiogram; [REDACTED] WOCBP, women of childbearing potential.

§ [REDACTED]

a [REDACTED]

- <sup>b</sup> If a WOCBP reports any urine  $\beta$ -hCG pregnancy test result as positive or ambiguous post randomization, the Principal Investigator will instruct the participant to suspend further study intervention and schedule a follow-up appointment as soon as possible, where a confirmatory serum  $\beta$ -hCG pregnancy test will be performed.
- <sup>c</sup> A pregnancy test is required every 4 weeks throughout the entire study. [REDACTED]
- <sup>d</sup> [REDACTED]
- <sup>e</sup> The PRO assessments that are completed at visits should be completed prior to any other study procedure taking place, where possible, and prior to any meaningful discussion about the study or study intervention with investigative site staff. See [Section 9.1.3.9](#) for PRO Administration, Method, Mode, and Training.
- <sup>f</sup> For participants who enter the LTE, HCMSQ will be completed daily for the first 4 weeks after the Week 48 visit.
- <sup>g</sup> Participants will complete the HCMSQ daily for a consecutive 7-day (1-week) period prior to the Week 56, 64, 76, 88, 92, and 96 visits.
- <sup>h</sup> Participants will complete the KCCQ-23 prior to completing the PGIS-KCCQ and PGIC-KCCQ; participants will complete the 7th day of the HCMSQ assessment prior to the completion of the PGIS-SoB and PGIC-SoB.

**Table 2-4:**            **Schedule of Activities**  
**(CV027031)**

| Procedure                                     |                                                                                                                             |   |   |   |   |   |   |   |   |   |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|
| Visit Number                                  |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| Week                                          |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| Day                                           |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| Efficacy Assessments                          |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| NYHA                                          | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| Resting Transthoracic Echocardiogram          | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| Safety Assessments                            |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| Targeted CV Physical Examination <sup>a</sup> | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| Vital Signs                                   | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| Assessment of Signs and Symptoms              | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| ECG                                           | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| Concomitant Medication Use                    | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| Concomitant Procedures                        | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| AE Reporting                                  |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| Monitor for AEs/SAEs                          | X                                                                                                                           | X | X | X | X | X | X | X | X | X |
| Laboratory Tests                              |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| Clinical Laboratory Assessments               | X                                                                                                                           |   | X |   | X | X | X | X | X |   |
| Pregnancy Test (WOCBP only) <sup>b,c</sup>    | X                                                                                                                           | X | X | X | X | X | X | X | X |   |
| PK Assessments                                | Note: See <a href="#">Table 9.5-1</a> .                                                                                     |   |   |   |   |   |   |   |   |   |
| Biomarker Assessments                         | Note: Including cTn-T, cTn-I, NT-proBNP, and exploratory biomarkers. See <a href="#">Table 9.8-1</a> for sampling schedule. |   |   |   |   |   |   |   |   |   |
| Study Intervention                            |                                                                                                                             |   |   |   |   |   |   |   |   |   |
| Dispense Study Medication                     | X                                                                                                                           | X | X | X | X | X | X | X |   |   |

**Table 2-4:**                      **Schedule of Activities**  
**(CV027031)**

| Procedure                                         |  |   |  |   |  |   |   |   |   |  |
|---------------------------------------------------|--|---|--|---|--|---|---|---|---|--|
| Visit Number                                      |  |   |  |   |  |   |   |   |   |  |
| Week                                              |  |   |  |   |  |   |   |   |   |  |
| Day                                               |  |   |  |   |  |   |   |   |   |  |
| Patient Reported Outcome Assessments <sup>d</sup> |  |   |  |   |  |   |   |   |   |  |
| KCCQ-23 <sup>e</sup>                              |  | X |  | X |  | X | X | X | X |  |
| HCMSQ <sup>f</sup>                                |  | X |  | X |  | X | X | X | X |  |
| EQ-5D-5L                                          |  | X |  | X |  | X | X | X | X |  |
| PGIS-KCCQ & PGIS-SoB                              |  | X |  | X |  | X | X | X | X |  |
| PGIC-KCCQ & PGIC-SoB                              |  | X |  | X |  | X | X | X | X |  |

Abbreviations:  $\beta$ -hCG, beta human chorionic gonadotropin; AE, adverse event; cTn-I, cardiac troponin I; cTn-T, cardiac troponin T; CV, cardiovascular; D, day(s); ECG, electrocardiogram; EQ-5D-5L, 5-level EuroQol-5 Dimension Version; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; SAE, serious adverse event; SoB, shortness of breath; WOCBP, women of childbearing potential.

<sup>a</sup> [REDACTED]

<sup>b</sup> A pregnancy test is required every 4 weeks throughout the entire study. [REDACTED]

<sup>c</sup> If a WOCBP reports any urine  $\beta$ -hCG pregnancy test result as positive or ambiguous post randomization, the Principal Investigator will instruct the participant to suspend further study intervention and schedule a follow-up appointment as soon as possible, where a confirmatory serum  $\beta$ -hCG pregnancy test will be performed.

<sup>d</sup> The PRO assessments that are completed at visits should be completed prior to any other study procedure taking place, where possible, and prior to any meaningful discussion about the study or study intervention with investigative site staff. See [Section 9.1.3.9](#) for PRO Administration, Method, Mode, and Training.

<sup>e</sup> Participants will complete the KCCQ-23 prior to completing the PGIS-KCCQ and PGIC-KCCQ.

- <sup>f</sup> Participants will complete the HCMSQ daily for a consecutive 7-day (1-week) period prior to the Week 24, 48, 84, 108, 132, and 156 visits.



## 2.1 Definition of Visits

Please see [Table 2.1-1](#) for definitions of participant visits.

**Table 2.1-1: Definitions of Participant Study Visits**

| Name of Visit | Definition                                                           |
|---------------|----------------------------------------------------------------------|
| EOT           | Occurs when a participant stops study intervention                   |
| EOS           | Occurs at least [REDACTED] after the last dose of study intervention |

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

## 3 INTRODUCTION

Mavacamten is a cardiac myosin modulator developed for the treatment of adults with hypertrophic cardiomyopathy (HCM) to reduce symptoms and increase exercise capacity.

### Non-clinical Studies with Mavacamten

Mavacamten targets the underlying pathophysiology of HCM: the formation of an excessive number of crossbridges between actin and myosin. Studies on isolated cells and muscle fibers and in intact animals have shown that mavacamten inhibits sarcomere force production which decreases left ventricular (LV) hypercontractility that can be associated with HCM. Mavacamten modulates cardiac myosin by several mechanisms including decreased release of phosphate from cardiac myosin and decreases in the number of actin-binding heads transitioning from the weakly to the strongly bound state.<sup>1</sup>

Studies in animals with non-obstructive HCM (nHCM) showed that mavacamten alleviates hyperdynamic contraction and normalizes sarcomere dynamics. In HCM models, direct myosin inhibition also improves or restores cardiac filling and function, as well as cardiac reserve. Mavacamten (or an analog) improved survival, reducing the cardiac injury and adverse remodeling characteristic of disease progression in animals carrying pathogenic HCM mutations. Mechanistically, mavacamten corrects the sarcomeric abnormalities and diastolic dysfunction that are hallmarks of nHCM.

A recently published in vitro study in engineered human heart tissue that allowed investigation of length and load dependence showed that mavacamten could improve diastolic function by reducing diastolic stiffness and the duration of isometric relaxation. Mavacamten caused a dose-dependent decrease in the diastolic force elicited by lengthening myocardial tissue suggesting that crossbridge-based force contributes to diastolic stiffness. Mavacamten also caused a concentration-dependent decrease in contractility.<sup>2</sup>

### Clinical Characteristics of HCM

HCM is a genetically determined disease of heart muscle caused most often by mutations in genes encoding the sarcomere or its constituents. Clinically, HCM is characterized by left ventricular hypertrophy that cannot be explained by another cause or systemic disease.<sup>3</sup> Sarcomere mutations are found in ~60% to 70% of patients with a family history of HCM and in ~30% to 40% of

apparently sporadic cases. More than 1000 distinct mutations have been identified, most of which are unique to a specific family. Mutations in myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3) are most common accounting for ~80% of sarcomeric HCM. The natural variation in human genetic sequence is substantial and the clinical manifestations of HCM are diverse. Therefore, it is frequently not clear whether a deoxyribonucleic acid (DNA) variant identified in a patient is causing the disease, modifying the disease, or a clinically insignificant polymorphism.<sup>4</sup>

A defining feature of HCM is reduced LV compliance which causes increased LV filling pressures (LVFP). Elevated LVFP increases left atrial (LA) pressure and pulmonary capillary pressure (PCP). Increasing PCP causes efflux of fluid from the capillaries into the interstitium of the lungs. Accumulation of extravascular fluid in the lungs causes dyspnea, especially during exercise. Other clinical features of HCM are reduced ventricular chamber size and supra-normal left ventricular ejection fraction (LVEF).

HCM is classified clinically into obstructive (oHCM) and nHCM based on the magnitude of LV outflow tract (LVOT) gradient.<sup>3</sup> Those with an LVOT gradient < 30 mm Hg are classified as nHCM. LVOT gradient is dynamic and can vary considerably so classification can be challenging. About 70% of patients with HCM have a resting or exercise-provoked LVOT gradient.<sup>5</sup>

The frequency of symptoms at diagnosis varies considerably according to the population being studied: patients with HCM managed in standard clinical practices versus those managed at specialized HCM management centers. A retrospective cohort study of 277 outpatients from a nonreferral population from Minnesota and adjoining regions found that approximately 90% were asymptomatic at presentation. During 8 years of follow-up, 69% remained asymptomatic or had only mild symptoms, and survival in adults was similar to that in a normal control age-matched population.<sup>6</sup>

In a series of 320 patients from 3 referral centers, transthoracic echocardiography was performed in all patients. Stress echocardiography was done only in those who had an LVOT gradient < 50 mm Hg at rest. One hundred sixty-nine patients (59%) had New York Heart Association (NYHA) Class II or greater at presentation. With exercise, 76 (24%) developed an LVOT gradient  $\geq$  50 mm Hg, and 46 (14%) developed dyspnea with exertion. Ninety-five patients (30%) were asymptomatic with little or no gradient ( $\leq$  30 mm Hg) at rest or with exertion.<sup>7</sup>

About one-third of patients in a referral-based cohort do not have an outflow gradient at rest or with exercise. Most patients with nHCM have a relatively benign or stable clinical course with no or only mild symptoms of heart failure. About 10% progress to severe limitation and disability refractory to maximal medical management. Between 2% and 3% of patients who develop end-stage heart failure in NYHA functional class III/IV have a unique phenotypic transformation from diastolic dysfunction (ie, impaired filling, relaxation and distensibility, or restriction) to LV systolic failure, LV remodeling involving wall thinning and/or ventricular chamber enlargement due to diffuse myocardial scarring. The annual mortality rate of patients with nHCM is low but

rates of non-fatal adverse clinical events can be high and comparable to those in patients with oHCM.<sup>8</sup>

The incidence of supraventricular and ventricular arrhythmias is higher in patients with HCM than in the general population of similar age. Atrial fibrillation (AF) is the most common supraventricular arrhythmia and will develop in about 20% of patients with HCM.<sup>9</sup> Ventricular arrhythmias are common in patients with HCM and range from isolated ventricular premature beats to non-sustained ventricular tachycardia to sustained VT and ventricular fibrillation. The frequency of ventricular arrhythmias is highly variable. Clinically documented sustained VT is relatively rare: the annual incidence of sudden cardiac arrest (SCA) in clinically identified HCM referral populations is about 1%. The reported rate of SCA is lower in patients in the general community.<sup>10</sup>

### Management of Patients with HCM

Current guidelines for the pharmacological management of HCM recommend the use of negative inotropic agents, including beta blockers, non-dihydropyridine calcium channel blockers, and disopyramide.<sup>11, 12</sup> While these pharmacological therapies, originally developed for other cardiovascular (CV) diseases, are partially effective in some but not all patients, there are tolerability issues that can limit the possibility to titrate these drugs up to an optimal dose.<sup>13</sup> Fatigue and significant reductions in heart rate and blood pressure inhibit their effective use,<sup>14</sup> and these agents cannot be used in persons with asthma, sinus bradycardia, greater than first-degree atrioventricular conduction block, cardiogenic shock, right ventricular failure secondary to pulmonary hypertension or overt cardiac failure. Furthermore, by limiting increases in heart rate response to exercise, they limit functional capacity. Patients may also become intolerant when these drugs are used chronically at high doses.

None of the recommendations in the current European Society of Cardiology (ESC) or American College of Cardiology (ACC)/American Heart Association (AHA) treatment guidelines for HCM (both oHCM and nHCM) are supported by Level A Evidence. The evidence for clinical management of symptomatic HCM without LVOT obstruction (nHCM) is based predominantly on observational cohort studies and analyses of registries rather than on randomized controlled trials.<sup>15</sup>

ESC guidelines recommend that most patients with a maximum resting or provoked LV outflow tract gradient <50 mm Hg should be managed in accordance with the recommendations for nHCM. For nHCM patients with preserved ejection fraction (EF) (ie, LVEF  $\geq$  50%), beta blockers, verapamil, diltiazem or low-dose loop and thiazide diuretics should be considered, to improve heart failure symptoms (class IIa, level of evidence C).<sup>11</sup>

Beta blockers, however, have not been consistently shown to improve exercise capacity; particularly, no effect has been shown on peak oxygen consumption ( $\text{pVO}_2$ ), a hallmark of exercise capacity.<sup>16,17</sup> In a recent study in 29 oHCM patients, metoprolol was effective in decreasing peak LVOT gradient compared to placebo, both at rest and during exercise, but failed to show any

meaningful improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ), pVO<sub>2</sub>, E/e' or left atrial volume index (LAVI). The lack of positive effect of beta blockers on exercise capacity has been attributed to the blunted heart rate response to exercise, but other mechanisms have been proposed to play a role such as peripheral vascular and/or skeletal muscle limitation to exercise, since the lack of improvement was also seen on 6-minute walk distance which does not require achievement of a maximum heart rate.<sup>18,19,20</sup>

An implantable cardioverter defibrillator (ICD) may be considered in HCM to prevent sudden cardiac death (SCD). The ESC has developed an SCD risk calculator to inform recommendations for ICD implantation.<sup>21</sup> A small proportion of patients (approximately 3% to 4%) will evolve toward end-stage disease, where orthotopic cardiac transplantation is sometimes the only effective treatment option.<sup>22,23</sup>

There is a substantial unmet medical need for a targeted therapy that addresses the underlying disease pathophysiology of HCM particularly in the non-obstructive form. This is echoed by the Committee for Medicinal Products for Human Use (CHMP) Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure, in which patients with HCM are identified as a population with high unmet medical need.<sup>24</sup>

The recent 2020 ACC/AHA HCM guidelines state that reduction of symptom burden and increase in functional capacity, particularly in nHCM, represent an area of high unmet medical need and a gap in knowledge. More data are needed to identify strategies to improve functional capacity (particularly in symptomatic nHCM) to attenuate disease progression and to reduce adverse outcomes.<sup>3</sup>

### 3.1 Study Rationale

The efficacy of medications commonly used to treat symptomatic patients with nHCM (beta blockers, verapamil, and diltiazem) can be limited by side effects and bradycardia.<sup>25</sup> Accordingly, safer and more effective treatments to reduce symptoms and increase functional capacity for patients with nHCM have been identified as unmet medical needs by guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology.<sup>3</sup>

The Sponsor believes mavacamten has the potential to meet this unmet need (see [Section 3.2](#)). In contrast to currently available therapies, mavacamten is a first-in-class, selective, and reversible modulator of cardiac myosin that targets the underlying pathophysiology of the disease.

Dyspnea and fatigue are the most common symptoms reported by patients with nHCM. Dyspnea associated with nHCM can be attributed to reduced LV compliance characteristic of HCM. The formation of an excessive number of myosin-actin crossbridges that persist during diastole in patients with HCM decreases diastolic compliance. Reduced LV compliance increases left ventricular filling pressure (LVFP) which increases LA pressure causing exudation of fluid into pulmonary tissue. The accumulated pulmonary fluid causes dyspnea, especially with exertion. Mavacamten can reduce dyspnea by increasing LV compliance through reducing the number of

crossbridges that persist during diastole. Increased LV compliance reduces the increased LVFP that causes dyspnea.

Beta blockers and non-dihydropyridine calcium channel blockers are often used to treat patients with symptomatic nHCM but unlike mavacamten, neither targets the abnormal crossbridge formation that underlies the disease. Therapy with these drugs can be limited by adverse reactions.

Data from clinical studies with mavacamten (see [Section 3.2](#)) suggest that mavacamten could provide a safe potential treatment option to reduce symptoms and improve exercise capacity in patients with nHCM.

### **Justification of the Primary Endpoints**

Dyspnea and fatigue are by far the most common symptoms in patients with nHCM.<sup>26</sup> Reducing these symptoms and increasing physical function and exercise capacity are clinically meaningful therapeutic goals for patients with nHCM. To determine the effects of mavacamten on these endpoints, the Sponsor has selected KCCQ-23 CSS to assess symptoms and physical limitations and pVO<sub>2</sub> to assess exercise capacity.

### **pVO<sub>2</sub>**

Determination of pVO<sub>2</sub> during a maximal symptom-limited treadmill or bicycle cardiopulmonary exercise testing (CPET) is an objective and reproducible method to assess exercise capacity in patients with heart failure.<sup>27</sup> pVO<sub>2</sub> has been used in clinical studies to assess the effectiveness of interventions and to assess its relationship to clinical outcomes (death, hospitalization, time to cardiac transplantation).

See [Appendix 5](#) for a summary of the result of studies in populations with heart failure. Excluding the study on septal reduction therapy (SRT), increases in pVO<sub>2</sub> ranged from 0.7-2.7 mL/kg/min depending on the population and the intervention. In the 2 studies in participants with HCM, pVO<sub>2</sub> increased 1.4 mL/kg/min with mavacamten and exercise training (See Appendix 5).

### **Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS)**

Reducing symptoms is a key therapeutic goal for patients with symptomatic nHCM.

The KCCQ-23 is a self-reported assessment of health status in the setting of cardiovascular disease and its treatment. The KCCQ-23 CSS is derived from the Total Symptom Score (TSS) and the Physical Limitation Score (PLS) of the KCCQ-23.<sup>28</sup>

The KCCQ-23 was originally developed for use and validated in the heart failure population. Previous evidence suggested that KCCQ-23 responded to changes in heart failure status over time in patients with chronic heart failure.<sup>28</sup> Low KCCQ scores were consistently associated with poor prognosis. Changes in KCCQ-23 overall summary scores correlate with several clinical outcomes; each 5-point improvement in KCCQ-23 was associated with an 11% reduction in the risks of mortality and hospitalizations.<sup>29</sup>

To further support the use of KCCQ-23 and to substantiate the most important and relevant disease-related symptoms and impacts from the perspective of patients with HCM, MyoKardia, Inc. conducted a series of studies to assess the content validity and psychometric properties of KCCQ-23 in patients with HCM. Qualitative research was conducted in 27 patients with HCM (13 oHCM, 11 nHCM, and 3 unknown/missing obstructive status). The results were consistent with data in the literature and interviews with clinical experts identifying shortness of breath and fatigue as the symptoms reported most and considered most burdensome.<sup>26</sup> MyoKardia, Inc. has also conducted qualitative interviews in patients with HCM and psychometric analyses using data from the EXPLORER-HCM and the MAVERICK-HCM studies in patients with oHCM and nHCM, respectively. The results suggest that the KCCQ-23 CSS measures the concepts most relevant and important to patients with HCM and it generates reliable, valid, and sensitive outcomes.

Exercise capacity and symptomatic limitation represent two modestly correlated aspects of the disease that characterize patients with symptomatic nHCM. A significant percentage of patients with HCM have reduced exercise capacity as measured by cardiopulmonary exercise testing, and symptomatic status alone is not an accurate index of exercise capacity for any single patient.<sup>30</sup> These data suggest that assessment of exercise capacity by pVO<sub>2</sub> and of symptomatic and physical functional improvement by the KCCQ-23 CSS will add complementary information, provide a better characterization through an orthogonal view on patients' journey in nHCM, and provide justification for using 2 primary endpoints in the proposed trial.

## 3.2 Background

### Clinical Studies with Mavacamten

Mavacamten has been well tolerated in the clinical studies in patients with oHCM (LVOT gradient  $\geq 50$  mm Hg). In a Phase 3 study (EXPLORER-HCM), treatment with mavacamten: (1) reduced symptoms and social and physical limitations as measured by the New York Heart Association Functional Classification (NYHA Functional Class) and the Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score (KCCQ-23 CSS); (2) increased exercise capacity (pVO<sub>2</sub>, VE/VCO<sub>2</sub> slope); (3) reduced LVOT gradient, LAVI, and wall thickness measured by echocardiography; and (4) reduced levels of biomarkers of myocardial wall stress (NT-proBNP) and injury cardiac troponin I (cTn-I).

MAVERICK-HCM was a Phase 2 study entitled A Randomized, Double-blind, Placebo-controlled, Concentration Guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy and Preserved Left Ventricular Ejection Fraction. It was a multicenter, exploratory study to evaluate the safety and tolerability of mavacamten in participants with symptomatic nHCM conducted in the United States. Eligible participants had nHCM (LV wall thickness  $\geq 15$  mm or  $\geq 13$  mm with a family history of HCM); LVEF  $\geq 55\%$ ; and LVOT  $< 30$  mm Hg at rest, during Valsalva, and after exercise.

Participants were randomized 1:1:1 to receive mavacamten (2 active treatment groups with target mavacamten trough concentrations of [REDACTED] or placebo once daily (QD)



for 16 weeks. Randomization was stratified by current beta blocker treatment status (yes or no) and type of exercise testing (treadmill or bicycle).

Mavacamten dosing in each active treatment group was based on a concentration-guided approach (ie, mavacamten was up-titrated once at [REDACTED] to one of the 2 pre-specified concentration targets [REDACTED] or placebo).

[REDACTED] The starting dose for both active treatment groups was mavacamten [REDACTED]. At [REDACTED] doses were adjusted based on plasma concentrations at [REDACTED] to achieve target mavacamten concentrations.

Approximately 60 participants were planned; 59 participants were enrolled in the study and 58 participants received at least one dose of study medication (39 received mavacamten and 19 received placebo). The study was designed to assess safety and tolerability as the primary objective.

Mavacamten was well tolerated in this nHCM study population. The majority of treatment-emergent adverse events (TEAEs) were mild or moderate in severity, with few severe TEAEs and no fatal adverse events (AEs). The combined rates of atrial flutter and AF were similar for the mavacamten and placebo groups, and all participants who experienced AF/flutter events had a history of atrial arrhythmias. Protocol-specified stopping criteria of LVEF  $\leq$  45% and/or heart failure with systolic dysfunction were observed [REDACTED] treated with mavacamten. For 2 participants (both in the high dose concentration group), the events that met the protocol-specified stopping criteria were associated with symptoms of heart failure, for one of them in a context of hospitalized AF. The decreases in LVEF, with precipitating causes in some of these participants, were not unexpected given the dose-ranging nature of the study design and the known on-target effect. [REDACTED] In addition to the LVEF decrease, no new CV safety concerns were identified.

The most notable between-group differences in efficacy following 16 weeks of treatment with mavacamten compared with placebo were improvements (ie, decreases from baseline) in the cardiac biomarkers NT-proBNP and cTn-I (in the subset of patients with elevated cTn-I). A post hoc analysis identified a subset of patients that responded better to mavacamten compared to placebo for the efficacy endpoints of change from baseline in KCCQ-23 CSS and pVO<sub>2</sub>.

MYK-461-007/CV027-003 (MAVA-LTE) is an ongoing long-term extension (LTE) study that enrolled participants in the MYK-461-006 (MAVERICK-HCM, nHCM participants) and MYK-461-005 (EXPLORER-HCM, oHCM participants) studies who elected to take open-label mavacamten after completing those studies. Enrollment started after a washout period of 8 weeks from completion of the parent study.

In the nHCM cohort of this long-term open-label extension study, mavacamten demonstrated sustained reduction in NT-proBNP levels through Week 48, consistent with the parent study. Significant reductions in E/e' ratio and LAVI were observed with mavacamten treatment, suggesting improvement in LV relaxation and diastolic function with longer-term mavacamten treatment. Treatment with mavacamten was generally well tolerated, and the observed safety profile in the long-term study is consistent with the safety profile observed in the parent study of

MAVERICK-HCM as well as the known safety profile in patients with oHCM. No new safety findings were observed. The results of an interim analysis of data collected through 30-Oct-2020 for the MAVERICK Cohort are shown in [Table 3.2-1](#) and [Table 3.2-2](#).

**Table 3.2-1: Change from Baseline in NT-proBNP and Echocardiographic Measurement at 48 Weeks**

| Parameter                                                         |                                       |
|-------------------------------------------------------------------|---------------------------------------|
| NT-proBNP<br>Mean (IQR)                                           | -67 % (n = 38)<br>(-77, 32)           |
| E/e'<br>Mean (SD)<br>(IQR)                                        | -2.4 (±3.1) (n = 32)<br>(-3.6, -1.3)  |
| Left atrial volume index, mL/m <sup>2</sup><br>Mean (SD)<br>(IQR) | -4.3 (± 7.2) (n = 37)<br>(-6.7, -1.9) |
| Left ventricular ejection fraction, %<br>Mean (SD)<br>(IQR)       | -5.4 (± 6.0) (n = 36)<br>(-7.4, -3.4) |

Abbreviations: NT-proBNP, N-terminal pro B-type natriuretic peptide; IQR, interquartile range; SD, standard deviation.

**Table 3.2-2: Adverse Events at 48 Weeks**

| AEs                       | N = 43    |
|---------------------------|-----------|
| Any TEAEs, n (%)          | 33 (76.7) |
| Drug-related TEAEs, n (%) | 6 (14.0)  |
| SAEs, n (%)               | 3 (7.0)   |
| Drug-related SAEs, n (%)  | 0 (0)     |

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Taken together, these results support further development of mavacamten in participants with nHCM to improve symptoms and functional capacity in a confirmatory Phase 3 trial. [REDACTED]

### 3.3 Benefit/Risk Assessment

In oHCM participants in a Phase 3 trial, 30 weeks of mavacamten treatment demonstrated a significant benefit across the composite primary endpoint of NYHA and pVO<sub>2</sub>, its components, and clinically meaningful improvements in hemodynamic status, functional capacity, symptoms, and health status. Favorable structural changes from imaging methods at rest, together with results from multiple parameters by CPET, demonstrated an improvement in exercise capacity and cardiac



function with mavacamten treatment. Mavacamten treatment was associated with reductions in biomarkers of cardiac wall stress and myocardial injury.

In another trial enrolling participants with nHCM, those treated with mavacamten showed significant improvements in cardiac biomarkers at 16 weeks in the overall population. Improvements in clinical benefit, as measured by KCCQ-23 CSS, NYHA and pVO<sub>2</sub>, were observed in a subgroup of participants with elevated E/e' or troponin at baseline.

The safety of mavacamten has been evaluated for single and multiple doses in healthy participants and participants with symptomatic HCM. For mavacamten-treated participants in the pivotal study on oHCM, the incidence of AEs leading to permanent treatment discontinuation was low (1.6%, 2 participants), and no participants met protocol-specified criteria for permanent discontinuation of study intervention. Across the integrated analyses with all mavacamten-treated participants and including data from LTE studies with extended exposure to mavacamten, the incidence of AEs leading to permanent treatment discontinuation remained low (3.2%, 10 participants).

In the mavacamten program, systolic dysfunction associated with mavacamten, due to excessive on-target pharmacologic action, was observed as episodes of reversible LVEF reduction below the normal range. Systolic dysfunction with mavacamten has been reversible and has not been suggestive of progressive cardiac failure (recurrent hospitalizations and progressive LVEF reduction) as described in the literature associated with progression of underlying HCM. Based on detailed review of complex cases of heart failure, intercurrent illness including AF or infection may also be precipitating factors. Reversibility is achieved following temporary interruption of therapy and treatment of any intercurrent illness.

In the Phase 2 study in nHCM participants, mavacamten was overall well tolerated. Protocol-specified stopping criteria of LVEF  $\leq 45\%$  and/or heart failure with systolic dysfunction were met by [REDACTED] treated with mavacamten. For 2 participants (both in the high dose concentration group), the events were associated with symptoms of heart failure, for one of them in a context of hospitalized AF. The decreases in LVEF, with precipitating causes in some of these participants, were not unexpected given the dose-ranging nature of the study design and the known on-target effect. [REDACTED] In addition to the LVEF decrease, no new CV safety concerns were identified.

Therefore, heart failure due to systolic dysfunction (defined as symptomatic LVEF [REDACTED] has been identified as an important identified risk. This important risk can be mitigated through baseline and periodic monitoring of LVEF through echocardiograms, education of prescribers on the clinical context in which these events occurred in the mavacamten clinical program, and education of patients on signs and symptoms that may represent these events.

[REDACTED]

Increased mavacamten exposure due to drug interactions (with strong cytochrome P450 [CYP] 2C19 inhibitors and to a lesser extent moderate cytochrome P450 [CYP] 2C19 or strong CYP3A4 inhibitors) and teratogenicity have been identified as potential risks. Dizziness is determined as an adverse drug reaction. Study inclusion/exclusion criteria and monitoring during the study will mitigate these risks.

The current data do not suggest an increased risk for major adverse cardiovascular events (MACE), QTc prolongation, or serious arrhythmias in participants with HCM on treatment with mavacamten.

Overall, mavacamten appears to be generally well tolerated with little evidence for off-target toxicity. The benefit risk profile for mavacamten supports further development in its clinical program.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of mavacamten may be found in the Investigator's Brochure (IB).<sup>31</sup>

### 3.3.1 Risk Assessment

**Table 3.3.1-1: Risk Assessment**

| Potential Risk of Clinical Significance                                                                                                                                                                     | Summary of Data/Rationale for Risk                                                                                                                                                                                                                                                   | Mitigation Strategy                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| The risk of cardiac failure due to systolic dysfunction (symptomatic LVEF [REDACTED]) is an identified risk. Cardiac failure and systolic dysfunction are considered adverse drug reactions for mavacamten. | Mavacamten acts by reducing the number of actin-myosin crossbridges formed during myocardial contraction and relaxation. The reduction in crossbridges during systole can reduce myocardial contractility.<br><br>See Section 7 of the BMS-986427 IB for more details. <sup>31</sup> | Regular monitoring of LVEF by echocardiography. [REDACTED] |

**Table 3.3.1-1: Risk Assessment**

| Potential Risk of Clinical Significance                                                                                                                                                                                                           | Summary of Data/Rationale for Risk                                                                                                                                                                                                                                                                                                 | Mitigation Strategy                                                                                                                                                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                       |
| Increased mavacamten exposure due to drug interactions (with CYP2C19 inhibitors or moderate to strong CYP3A4 inhibitors) has been identified as a potential risk. The greatest exposure increases are expected with strong inhibitors of CYP2C19. | Mavacamten is primarily metabolized by CYP2C19 and to a smaller extent CYP3A4. Thus exposure increases could be expected with inhibitors of these pathways with the greatest increase expected with concomitant administration of strong inhibitors of CYP2C19. See Section 7 of the BMS-986427 IB for more details. <sup>31</sup> | Regular monitoring of concomitant medications, of safety and of LVEF by echocardiography.<br><br>No new concomitant medications (prescription, over-the-counter, or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. |
| Teratogenicity has been identified as an important potential risk.                                                                                                                                                                                | There are no clinical data available for pregnancy with exposure to mavacamten. However, in definitive non-clinical reproductive toxicology studies, mavacamten was found to cause developmental abnormalities at exposure levels that were less than the maximum recommended human exposures.                                     | Contraception requirements are implemented in the study.                                                                                                                                                                                                                              |

Abbreviations: CYP, cytochrome P450; ECG, electrocardiogram; IB, Investigator's Brochure; LVEF, left ventricular ejection fraction.

### 3.3.2 Benefit Assessment

The potential clinical benefit of mavacamten in this study is to provide symptomatic and functional improvement in symptomatic nHCM patients. Clinical studies with mavacamten to date have shown clinical benefits on exercise and functional capacity, hemodynamic status, symptoms, and health status, in participants with oHCM and a subset of participants with nHCM with elevated E/e' or troponin at baseline or with higher symptoms burden. However, the number and duration of exposure of participants with nHCM are limited.

The principal safety concern with mavacamten treatment (ie, systolic dysfunction resulting from excessive pharmacology) is monitorable by echocardiography and clinical assessment and has been shown to be reversible. The current data do not support an increased risk for participants with HCM receiving mavacamten treatment for MACE events, QTc prolongation or serious arrhythmias, or for off-target effects in other organ systems.

### 3.3.3 Overall Benefit/Risk Conclusion

Overall, the benefit/risk profile of mavacamten is positive and warrants further evaluation in the population of nHCM that carries a high unmet medical need. This study has been designed with appropriate measures in place to monitor and minimize any potential health risks to participating patients. Based on prior clinical studies with mavacamten, the Sponsor believes that the favorable benefit/risk will be maintained for the approximately 5-year duration of the study.

Taking into account the clinical experience with mavacamten to date and the extent of monitoring and precautions included in the study protocol, participation in this study should represent an acceptable risk to patients who meet the inclusion/exclusion criteria and consent to participate in the study.

An independent Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of the study participants by reviewing safety data throughout the study. The DMC and Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available data, with particular attention to: (i) AEs or other safety trends in this or any other clinical study of BMS-986427 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new data suggesting unreasonable and significant risk of illness or injury.

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

## 4 OBJECTIVES AND ENDPOINTS

**Table 4-1: Objectives and Endpoints**

| Objectives                                                                                                                                                                                                                                                                                                      | Endpoints                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b>                                                                                                                                                                                                                                                                                                  |                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>To assess the efficacy of a 48-week course of mavacamten compared to placebo on patient-reported health status (symptoms and physical limitations)</li> <li>To assess the efficacy of a 48-week course of mavacamten compared to placebo on exercise capacity</li> </ul> | <ul style="list-style-type: none"> <li>Change from baseline in KCCQ-23 CSS at Week 48</li> <li>Change from baseline in pVO<sub>2</sub> at Week 48</li> </ul> |

**Table 4-1: Objectives and Endpoints**

| Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Secondary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>Evaluate the effects of mavacamten on ventilatory efficiency as measured by the VE/VCO<sub>2</sub> slope</li> <li>Evaluate the effects of mavacamten on NYHA classification</li> <li>Evaluate the effects of mavacamten on cardiac biomarkers of wall stress</li> <li>Evaluate the effects of mavacamten on patient-reported shortness of breath</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>Change from baseline in VE/VCO<sub>2</sub> slope to Week 48</li> <li>Proportion of participants with at least 1 class of NYHA improvement from baseline to Week 48</li> <li>Change from baseline in NT-proBNP to Week 48</li> <li>Change from baseline in HCMSQ SoB domain to Week 48</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Exploratory</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>Evaluate the effects of mavacamten on other parameters of exercise as measured by CPET (eg, exercise duration and intensity)</li> <li>Evaluate the effects of mavacamten on the composite of NYHA and pVO<sub>2</sub></li> <li>Evaluate the effects of mavacamten on diastolic and systolic function and cardiac remodeling as measured by echocardiography</li> <li>Evaluate the effects of mavacamten on quality of life as measured by EQ-5D-5L</li> <li>Evaluate the effects of mavacamten on mortality</li> <li>Explore the effects of mavacamten on parameters of exercise capacity as measured by CPET (eg, exercise duration and intensity)</li> <li>Evaluate the effects of mavacamten on diastolic and systolic function and cardiac remodeling as measured by echocardiography</li> <li>Evaluate the effects of mavacamten on composite of cardiovascular events</li> </ul> | <ul style="list-style-type: none"> <li>Change from baseline in peak exercise time to Week 48</li> <li>Change from baseline to Week 48 in the Borg Perceived Exertion Scale rating at matched work rates during exercise</li> <li>Proportion of participants with (1) pVO<sub>2</sub> ≥ 1.5 mL/kg/min and NYHA improvement ≥ 1; or (2) pVO<sub>2</sub> ≥ 3 mL/kg/min and NYHA no worsening, from baseline to Week 48</li> <li>Change from baseline in echocardiographic measures of diastolic function, including E/A, average medial and lateral E/e', LAVI at Week 48</li> <li>Change from baseline to Week 48 in EQ-5D scores (both Index and VAS)</li> <li>Time to all-cause death</li> <li>Time to CV death</li> <li>Change from baseline in exercise capacity as measured by estimated METs to Week 48</li> <li>Other echocardiographic parameters of cardiac structure and systolic function</li> <li>Time to first MACE-plus event defined as any CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, hospitalization for arrhythmias, or appropriate ICD therapy</li> </ul> |
| <ul style="list-style-type: none"> <li>Evaluate the effects of mavacamten on MACE, MACE-plus, and MACE-expanded</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>MACE events (first as well as total [including first and recurrent]) defined as any CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

**Table 4-1: Objectives and Endpoints**

| Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Evaluate the effects of mavacamten on other CV events</li> <li>Evaluate the effects of mavacamten on cardiac biomarkers of myocardial injury</li> <li>Explore the effects of mavacamten on biomarkers related to disease activities and associated pathophysiology pathways</li> <li>To assess the proportion of patients achieving meaningful within-patient change on the KCCQ-23 CSS</li> <li>To assess the proportion of patients achieving meaningful within-patient change on the HCMSQ SoB</li> <li>To assess the effects of mavacamten on patient-reported symptoms of HCM and health-related quality of life</li> </ul> | <ul style="list-style-type: none"> <li>Total (including first and recurrent) MACE-plus events</li> <li>MACE-expanded events (first as well as total [including first and recurrent]): defined as any CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, hospitalization for arrhythmias, worsening heart failure not requiring hospitalization, new arrhythmia (AF or flutter and/or ventricular arrhythmias), or syncope requiring medical attention</li> <li>Stroke, MI, new AF, recurrent AF requiring cardioversion, ablation, or antiarrhythmic drugs, ventricular arrhythmias lasting &gt; 30 seconds, appropriate ICD discharges, unexplained syncope, heart failure requiring hospitalization or an unscheduled visit, CV hospitalization, all-cause death (excluding sudden cardiac death), and sudden cardiac death</li> <li>Exposure-adjusted event rate of clinical outcome events <ul style="list-style-type: none"> <li>Exposure-adjusted event rate = total number of event/total duration in the study (rate/100*person-year)</li> </ul> </li> <li>Change from baseline in biomarkers such as cTn-T, cTn-I</li> <li></li> <li>Proportion of participants with a meaningful within-patient change on the KCCQ-23 CSS from baseline to Week 48 (meaningful within-patient change definition derived from within the trial using PGIS-KCCQ, PGIC-KCCQ, and distribution-based approaches)</li> <li>Proportion of participants with a meaningful within-patient change on the HCMSQ SoB from baseline to Week 48 (meaningful within-patient change definition derived from within the trial using PGIS-SoB, PGIC-SoB, and distribution-based approaches)</li> <li>Change from baseline to Week 48 in the following patient-reported endpoints: <ul style="list-style-type: none"> <li>Health-related quality of life as assessed by the KCCQ-23 Total Symptom Score (TSS), the Physical Limitation Score (PLS), and the Overall Summary Score (OSS)</li> <li>HCM symptoms as assessed by the HCMSQ total score and the 2 domain scores of tiredness and CV symptoms</li> </ul> </li> </ul> |

**Table 4-1: Objectives and Endpoints**

| Objectives                                                                                                                                                                                                                                                                                               | Endpoints                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pharmacokinetic (PK)/Pharmacodynamic (PD)</b>                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>To assess the PK of mavacamten in participants with nHCM</li> <li>To assess the PK/PD relationship of mavacamten in participants with nHCM</li> <li>To assess the PK/PD relationship between mavacamten PK and cardiac biomarkers in nHCM participants</li> </ul> | <ul style="list-style-type: none"> <li>Trough plasma concentrations of mavacamten by visit</li> <li>Concentration-response relationship between mavacamten PK and echocardiographic parameters of systolic or diastolic function such as LVEF and E/e'</li> <li>Concentration-response relationship between mavacamten PK and cardiac biomarkers (NT-proBNP and cTn-T)</li> </ul> |
| <b>Pharmacokinetic (PK)/Pharmacodynamic (PD) Exploratory</b>                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>To assess the PK/PD relationship of mavacamten in nHCM participants using population PK and E-R modeling</li> </ul>                                                                                                                                               | <ul style="list-style-type: none"> <li>Population PK parameters, exposure-response relationship between select PK measures of exposure and safety (LVEF), and efficacy endpoints/cardiac biomarkers using population PK/PD modeling, if applicable</li> </ul>                                                                                                                     |
| <b>Safety</b>                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>To assess the safety and tolerability of mavacamten</li> <li>To assess the effects of mavacamten on LVEF determined by echocardiography, ECG, and vital sign parameters over time</li> <li>To assess the incidence of LVEF [REDACTED]</li> </ul>                  | <ul style="list-style-type: none"> <li>Incidence of AEs, SAEs, AEs leading to study intervention discontinuation, AEs leading to death.</li> <li>Change in laboratory, LVEF determined by echocardiography, ECG, and vital sign parameters over time</li> <li>Percentage of participants with an LVEF [REDACTED]</li> </ul>                                                       |

Abbreviations: AE, adverse event; AF, atrial fibrillation; CPET, cardiopulmonary exercise testing; cTn-I, cardiac troponin I; cTn-T, cardiac troponin T; Ctrough, trough-observed plasma concentration; CV, cardiovascular; ECG, electrocardiogram; EQ-5D, EuroQol-5 Dimension; E-R, exposure-response; HCM, hypertrophic cardiomyopathy; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; ICD, implantable cardioverter-defibrillator; KCCQ-23 CSS, Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MET, metabolic equivalent of task; MI, myocardial infarction, nHCM, non-obstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamic; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; PRO, patient-reported outcome; pVO<sub>2</sub>, peak oxygen consumption; SAE, serious adverse event; SoB, shortness of breath; VAS, visual analogue scale; VE/VCO<sub>2</sub>, ventilatory efficiency.

## 4.1 Sub-Study

The signing of an additional informed consent will be required at screening for participants who agree to participate in the optional sub-study.

### Cardiac magnetic resonance imaging (CMR) sub-study

- Primary endpoint: change in measures of LV mass index
- Exploratory endpoints: such as changes in myocardial fibrosis, LA structure and function, and LV structure and function.

- [REDACTED]

## **5 STUDY DESIGN**

### **5.1 Overall Design**

CV027031 is a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo [REDACTED] in participants with symptomatic nHCM.

[REDACTED]



### 5.1.1 Screening [REDACTED]

A screening visit will be conducted after participants provide signed informed consent. The following will be obtained: inclusion and exclusion criteria, demographics (such as age, gender, ethnicity, and race where local regulatory requirements permit), weight, height, medical and family history, physical examination, information on implanted cardiac defibrillator (ICD) if applicable, transthoracic echocardiogram (TTE), CPET, stress echocardiogram, NYHA class, KCCQ-23 questionnaire, prior and concomitant therapy, 12-lead ECG, clinical laboratory assessments (chemistry, coagulation, hematology, urinalysis, NT-proBNP or BNP, cardiac troponin), and serum beta-human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test for women of childbearing potential (WOCBP).

[REDACTED]

Mavacamten is being studied as an add-on therapy. Accordingly, at the time of enrollment, participants should be on a therapy for HCM considered appropriate by the investigator and the therapy can be continued for the duration of the study. Participants should be clinically stable and cardiac medications cannot be initiated, discontinued, or dose adjusted within [REDACTED]

[REDACTED]

The following screening assessments may be repeated within the [REDACTED] screening window: blood tests, ECG and/or TTE; CPET and stress echocardiogram can be repeated if either test is stopped before completion for technical reasons (eg, equipment failure). Repeat assessments are allowed if [REDACTED] require a repeat submission due to quality and 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 screen failure and after consultation with the Medical Monitor. One attempt at rescreening will be allowed.

### 5.1.2 ***Placebo-controlled Double-blind Treatment Period (Part A)***

The placebo-controlled double-blind treatment period will begin at [REDACTED] and end when the last participant completes the Week 48 visit.

[REDACTED]

Participants who meet all eligibility criteria at screening will be randomized via an interactive response system (IRT) in a [REDACTED] ratio to receive treatment with a starting dose of mavacamten 5 mg QD or matching placebo QD.

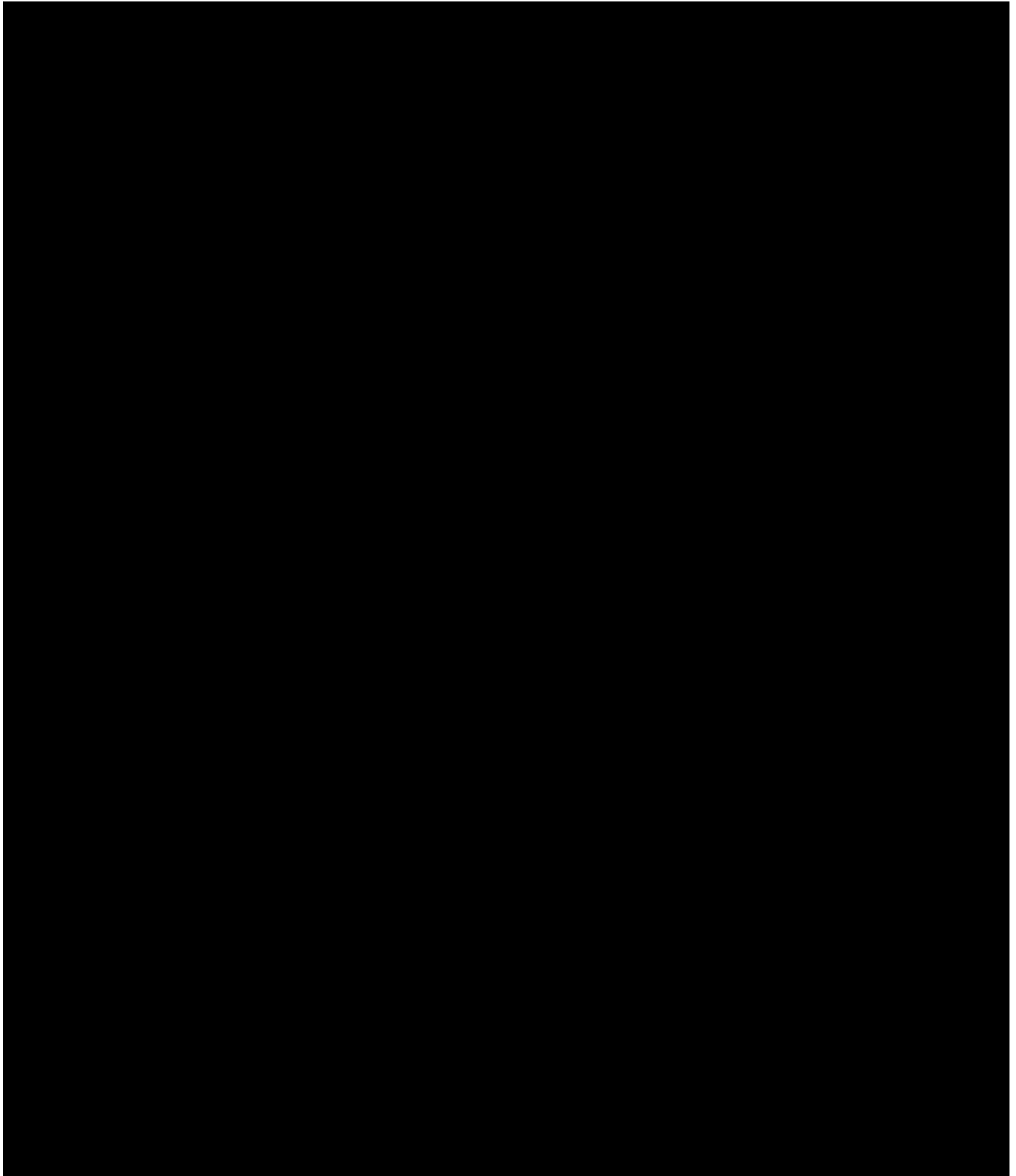
[REDACTED]

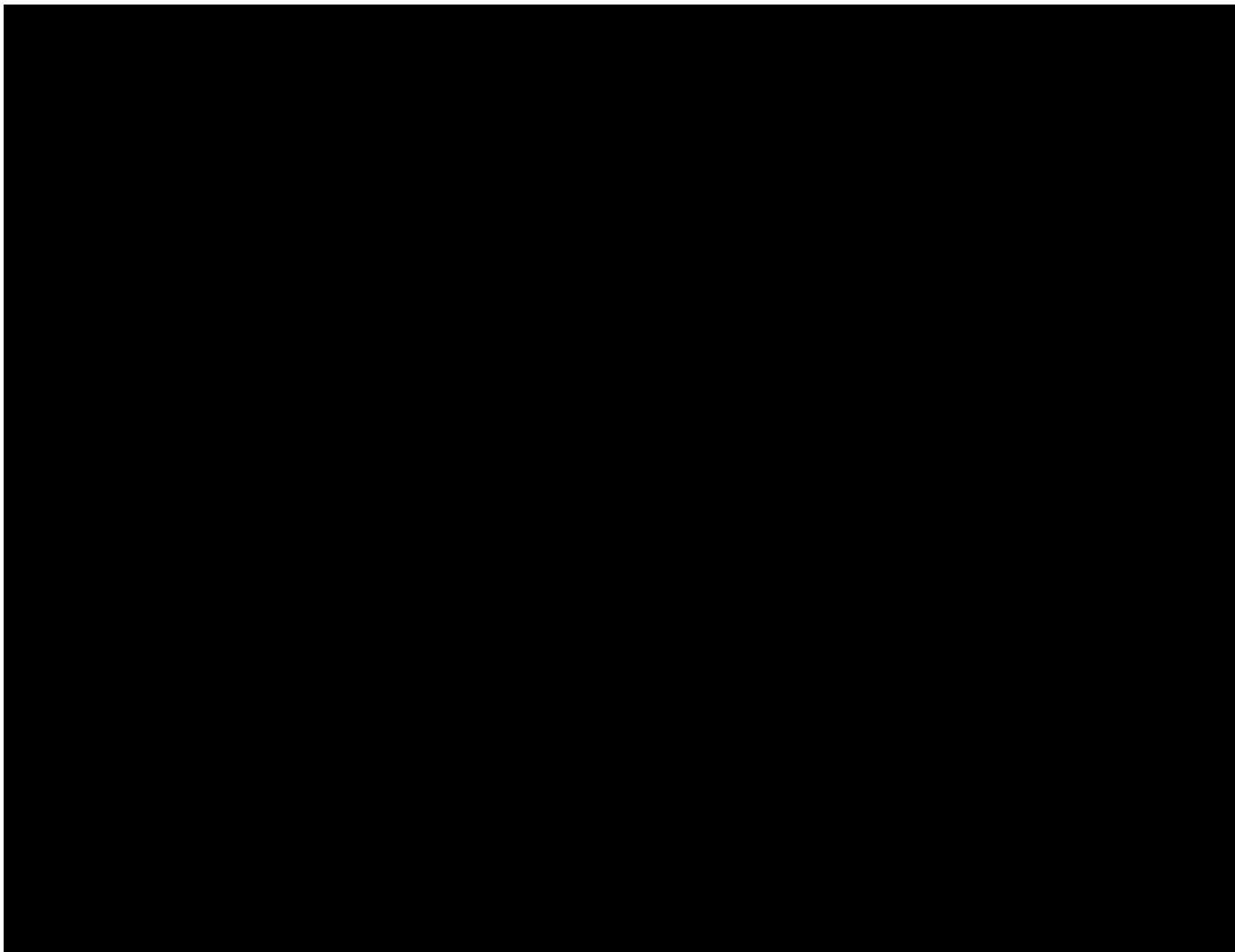
At [REDACTED] participants will complete a CPET and evaluation of symptoms.

[REDACTED]

Every effort should be made to encourage participants to stay in the study and complete the remaining scheduled visits, [REDACTED]

[REDACTED]





#### **5.1.6 Data Monitoring Committee and Other Committees**

Data Monitoring, Steering, Executive, and Clinical Event Committees will be used in the study. The duties of each committee will be described in their respective charters.

Charters will describe the procedures related to operations of the committees in greater detail.

**Data Monitoring Committee (DMC):** An independent committee, whose activities will be described in a charter, will monitor the study. The DMC will be composed of experienced clinicians, trialists, and statistical experts. Recommendations for criteria to stop the clinical trial for safety concerns will be defined in the DMC charter.

**Steering Committee (SC):** The SC will consist of the Lead Investigator(s), who will serve as SC Chair. Other members will include: National Leaders from participating countries, other experts, and Sponsor representatives. The SC will be responsible for scientific aspects of the study and will ensure that the study execution and management are of the highest quality. The SC will convene regularly to discuss and report on ongoing supervision of the study.

**Executive Committee (EC):** The EC will consist of the Chair(s) and selected members of the SC, Academic Research Organization (ARO), and the Sponsor. The EC will review and advise on clinical trial design, study protocols, study amendments, and help select and support potential study sites, review and advise on recruitment updates, participate in meetings with the BMS team and with the other members of the Steering Committee, provide guidance on analysis of study results, and serve as the members of the Publications Committee for the study with oversight of abstracts and manuscripts reporting the trial design and results.

**Clinical Event Committee (CEC):** An independent, central CEC with multidisciplinary representation will evaluate outcome events as specified in the protocol and according to guidelines using standardized criteria. Their decisions will be based on blinded clinical data and will consider the impressions of the investigator. Their decisions will be used for the final statistical analyses.

## 5.2 Number of Participants

Assuming a [REDACTED] screen failure rate, approximately [REDACTED] screened participants (signed Informed Consent Form) will be required to achieve approximately 420 randomized.

These 420 participants will be randomized in a [REDACTED] ratio to mavacamten and placebo in a blinded fashion.

Details regarding sample size determination are provided in [Section 10](#), Statistical Considerations.

## 5.3 End of Study Definition

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

End of trial is defined as last participant last visit.

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

## 5.4 Scientific Rationale for Study Design

The study design is based on the characteristics of the disease and the results of previous studies with mavacamten (EXPLORER-HCM, MAVERICK-HCM, and MAVALTE) described above in [Section 3.2](#). This Phase 3 study is designed to evaluate the effect of treatment with mavacamten for 48 weeks on symptoms assessed by KCCQ-23 CSS and exercise capacity assessed by CPET.

NT-proBNP is a marker of the B-type natriuretic peptide precursor proBNP released predominantly from the ventricles in response to myocyte stretch from increased LV wall stress and pressure. NT-proBNP levels are commonly elevated in participants with HCM, where NT-proBNP has been associated with elevated LV end-diastolic pressures and diastolic dysfunction.<sup>32</sup> NT-proBNP concentration correlates with markers of disease severity and exercise intolerance. Indeed, NT-proBNP has been shown to correlate with pVO<sub>2</sub> in HCM and was more predictive of functional impairment than other conventional markers of disease severity.<sup>33</sup> Natriuretic peptides are closely tied to the cellular basis of disease and hemodynamic burden in HCM and can be adjuncts to the assessment of disease status in HCM.

In participants with HCM, elevated NT-proBNP concentration is a strong predictor of overall prognosis, particularly heart failure-related events, death, and transplantation.<sup>34, 35, 36</sup>

Elevated troponin level is an indicator of subclinical and ongoing myocardial injury and stress. In HCM participants, elevated plasma troponin has been associated with a greater frequency of subsequent adverse cardiac events, including HCM-related death and heart failure hospitalization.<sup>37</sup>

ESC guidelines recommend measurement of NT-proBNP and troponin T in participants with hypertrophic cardiomyopathy (HCM) because high concentrations are associated with cardiovascular events, heart failure, and death.

To assess CV safety in light of the infrequency of these events in the nHCM population (see [Section 6](#)), the study contains secondary and exploratory endpoints that capture these data during Parts A and B.

#### **5.4.1 Participant Input Into Study Design**

Input into study design was obtained from Patient Voice interviews. Patients living with nHCM are uniquely positioned to help in the drug development process.

### **5.5 Justification for Dose**

Mavacamten's mechanism of action is directed toward what is considered the key biological abnormality of HCM, the excessive actin-myosin cross-bridges which cause hypercontractility and diastolic dysfunction. Hypercontractility increases myocardial work, which can cause myocardial ischemia and damage. Mavacamten reduces myocardial oxygen consumption by reducing the number of cross-bridges available to generate ventricular contraction, thereby restoring the balance between oxygen supply and demand. An additional therapeutic benefit of mavacamten is that the reduction in the number of cross-bridges during diastole should improve diastolic function by increasing ventricular compliance and relaxation, an effect that could prove particularly beneficial in patients with nHCM.

The clinical pharmacology of mavacamten has been characterized extensively, including in vitro experiments, physiologically based PK modeling, clinical trials, exposure-response, and population PK analyses. The effect of intrinsic and extrinsic factors on mavacamten exposure are well understood, but they do not fully explain existing interindividual PK and pharmacodynamic (PD) variability. To ensure both safety and efficacy of mavacamten despite this variability in PK and PD, the dosing regimen is individualized. The Phase 2 data of mavacamten in nHCM have shown that the beneficial effects on diastolic function, biomarkers, and functional capacity were correlated to mavacamten exposure. LVEF has shown a correlation with mavacamten exposure.

Consistent with mavacamten's mechanism of action, small decreases in LVEF from the baseline hypercontractile state were observed during treatment with mavacamten. The primary pharmacological effect of mavacamten of decreasing cardiac contractility was beneficial in oHCM as it led to a marked amelioration of LVOT obstruction and potentially beneficial in nHCM as decreases in cross-bridges formation led to enhanced diastolic function. Due to this mechanism of action, corresponding reductions in LVEF are also expected.

The starting dose of mavacamten in this study will be 5 mg QD in all participants followed by [REDACTED]; 5 mg was chosen as the starting dose based on the collective knowledge from clinical studies including EXPLORER, MAVERICK, VALOR, and LTE studies. [REDACTED]

The starting dose is 5 mg QD. There are [REDACTED]

### **5.5.1 Justification for Placebo**

No disease-specific drug therapy is currently approved for treatment of patients with nHCM. Mavacamten is being studied as an add-on therapy. Accordingly, at the time of enrollment, participants should be on a therapy for HCM (eg, beta blockers) considered appropriate by the principal investigator and the therapy can be continued for the duration of the study. In this study, participants randomized to the placebo arm will receive the therapy for nHCM that they would have received if they were participating in the study, ie, participants who receive placebo will not forgo currently recommended treatment for nHCM.

The use of a placebo allows objective assessment of symptoms, physical limitations, and AEs that will be assessed in this study.

## 6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The time frame for establishing eligibility is within [REDACTED] prior to randomization.

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

### 6.1 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 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) Diagnosis of HCM consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines: unexplained left-ventricular hypertrophy with non-dilated ventricular chambers in the absence of other cardiac or systemic disease which can produce the required magnitude of hypertrophy of a maximal LV wall thickness  $\geq 15$  mm (or  $\geq 13$  mm with positive family history of hypertrophic cardiomyopathy [HCM]) as determined by core laboratory interpretation
- b) Peak LVOT pressure gradient  $< 30$  mm Hg at rest and  $< 50$  mm Hg with provocation (Valsalva maneuver and stress echocardiography)
- c) New York Heart Association (NYHA) Class II or III
- d) **Not applicable per Protocol Amendment 02 (see 2[i] below):** KCCQ-23 CSS Score [REDACTED] at screening
- e) LVEF [REDACTED] on screening echocardiography measured by [REDACTED] Echocardiography Laboratory
- f) CPET: Documented oxygen saturation at rest [REDACTED] at screening.

g) [REDACTED]



ii)

h) Any of the following:

i) Evidence of myocardial damage:

(1) Elevated cardiac troponin (T or I) [REDACTED] of the upper limit of normal of the assay used by the analyzing laboratory,  
*OR*

ii) Evidence of LV diastolic dysfunction

(1) Average E/e' [REDACTED] on screening echocardiography measured by [REDACTED] Echocardiography Laboratory  
*OR*

(2) LAVI [REDACTED] mL/m<sup>2</sup> on screening echocardiography measured by [REDACTED] Echocardiography Laboratory

i) KCCQ-23 CSS Score [REDACTED] at screening

### 3) Age of Participant

Participants must be at least 18 years old or local age of majority at the time of signing the informed consent.

### 4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP, defined in [Appendix 4](#)) participants 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.

#### 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 or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study intervention.
- For this trial, a serum  $\beta$ -hCG pregnancy test is required at screening and a urine  $\beta$ -hCG pregnancy test is required at randomization, prior to first dose of study intervention.

- 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 highly effective 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 and included in the ICF).
  - v) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
    - (1) Is not a WOCBP
    - OR
    - (2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year) as described in Appendix 4 and included in the ICF during the intervention period [REDACTED] and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

**b) Male Participants:**

No additional contraceptive measures are required to be used for male participants.

## 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 nHCM such as amyloidosis, Fabry disease, or Noonan syndrome with LV hypertrophy

[REDACTED]

- b) History of unexplained syncope within 6 months prior to screening
- c) History of sustained ventricular tachyarrhythmia (> 30 seconds) within 6 months prior to screening

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**2) Reproductive Status**

- a) Women who are breastfeeding
- b) Women who are pregnant

**3) Prior/Concomitant Therapy**

- a) Inability to comply with restrictions and prohibited treatments as listed in [Section 7.7](#), Concomitant Therapy.
- b) Any adjustments of beta blockers, verapamil, or diltiazem within [REDACTED]

**4) Physical and Laboratory Test Findings**

**5) Allergies and Adverse Drug Reaction**

- a) History of allergy to mavacamten

**6) Other Exclusion Criteria**

- a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- b) Any other serious condition that in the opinion of the investigator could prevent participation in the study and follow-up, including active infection with COVID-19 from 4 weeks prior to screening up to randomization
- c) Completed a study with:
- i) an investigational device [REDACTED] to screening
  - OR
  - ii) an investigational drug [REDACTED] to screening
- d) Participants who have completed a study with mavacamten or aficamten
- e) Enrolled in another study and receiving any investigational treatment (device or drug) other than the study intervention given in this study

**6.3 Lifestyle Restrictions**

**6.3.1 Meals and Dietary Restrictions**

No restrictions.

**6.3.2 Caffeine, Alcohol and Tobacco**

No restrictions.

**6.3.3 Activity**

No activity restrictions.

**6.4 Screen Failures**

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

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities.

Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

#### **6.4.1 Retesting During Screening**

**Participant Re-enrollment:** This study does not permit the re-enrollment of a participant who has discontinued the study as a pretreatment failure.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in [Table 2-1](#), Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

### **7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY**

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

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

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

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

#### **7.1 Study Interventions Administered**

Study intervention is defined as mavacamten or placebo.

Mavacamten capsules and matching placebo have the same appearance. The study intervention presentation is [REDACTED]

[REDACTED] Each capsule contains [REDACTED]

[REDACTED] The active capsules are supplied in [REDACTED]

[REDACTED] Mavacamten active and placebo capsules have been manufactured according to current Good Manufacturing Practice regulations. All study intervention will be labelled according to applicable local regulatory guidelines. Study intervention at the investigational site will be stored in a secure area with access limited to authorized study

personnel. Refer to [Table 7.1-1](#) for the complete schedule of study intervention administration. Participants will take study intervention as directed by the study investigator.

Study intervention should be taken with approximately 8 ounces (~235 mL) of water.

**Table 7.1-1: Study Interventions**

| Product Description/<br>Class and Dosage Form | Potency    | IP/Non-<br>IMP | Blinded or Open<br>Label | Packaging/<br>Appearance | Storage Conditions<br>(per label) |
|-----------------------------------------------|------------|----------------|--------------------------|--------------------------|-----------------------------------|
| Mavacamten oral capsule                       | [REDACTED] | IP             | Blinded <sup>a</sup>     | Bottle                   | Refer to label on container       |
| PBO matching mavacamten oral capsule          | NA         | IP             | Blinded                  | Bottle                   | Refer to label on container       |

Abbreviations: IMP, investigational medicinal product; IP, investigational product; NA, not applicable; PBO, placebo.

<sup>a</sup>

## 7.2 Method of Study Intervention Assignment

All participants will be centrally randomized using IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

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]. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned [REDACTED].

## 7.3 Blinding

Participants will be randomized to receive mavacamten or matching placebo in a double-blind manner such that the principal investigator, site staff including the pharmacist, and the participant will not know which study intervention is being administered. In addition, the Sponsor, the [REDACTED] and clinical site monitors will be blinded to assigned treatment. Mavacamten and matching placebo will be identical in appearance in order to preserve the blind. Study intervention (mavacamten or matching placebo) will be labeled with a unique identifying number assigned to a participant through the IRT. [REDACTED]

The pharmacovigilance team will be unblinded for suspected unexpected serious adverse reaction (SUSAR) reporting. The DMC may also be unblinded to treatment allocation and all safety and efficacy data.

Blinding of study intervention assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

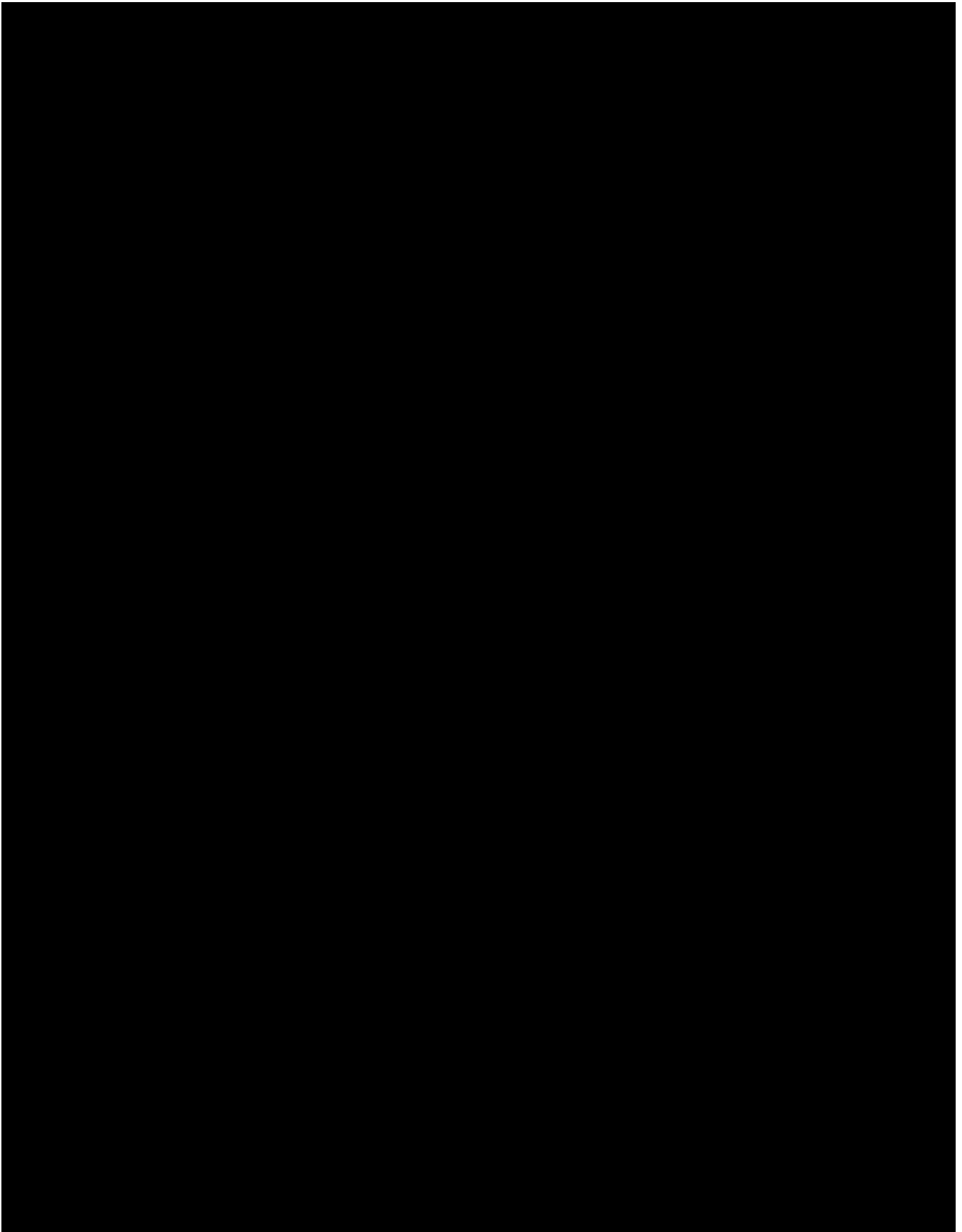
Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding after the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is described below.

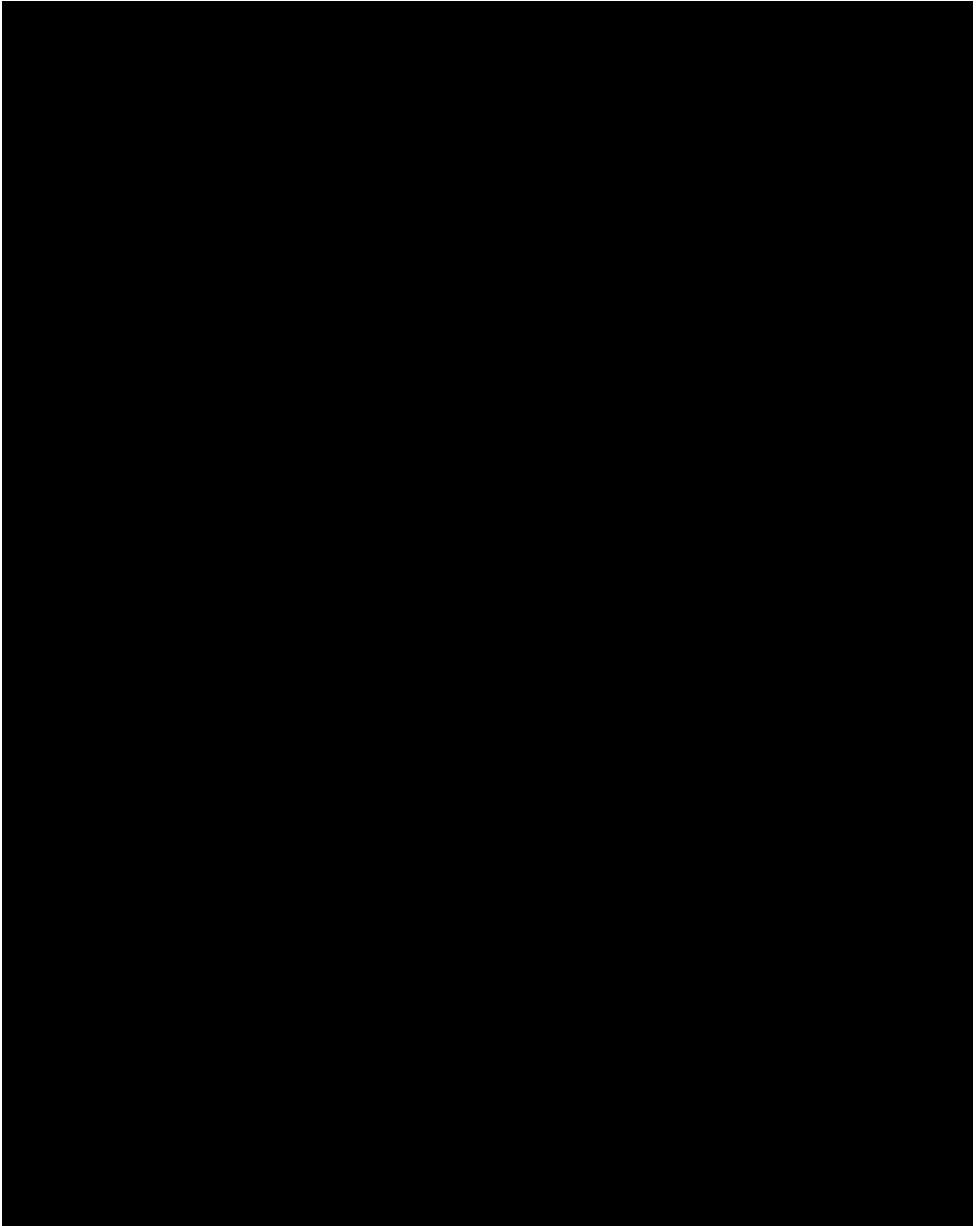
In case of an emergency, the investigator(s) has unrestricted access to randomization information via the IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. Following the unblinding, the investigator shall notify the Medical Monitor or designee that the unblinding took place. The investigator should provide the reason for unblinding.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for nonemergency purposes should be discussed with the Medical Monitor.







## 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.
- 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 and [Appendix 2](#).

### 7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

## 7.6 Treatment Compliance

Each time study intervention is dispensed, compliance will be reinforced. When study intervention is returned, compliance will be assessed based upon the participant's interview and a count of the capsules returned. Compliance should be between [REDACTED]. The Investigator (or designee) will record the amounts of study intervention dispensed and returned at each visit, as well as document reasons for non-compliance in the source document. The dates of all study intervention dosing, including interruptions, missed doses or overdose, must be recorded on the electronic case report form (eCRF). Non-compliant participants should be re-educated regarding treatment compliance.

## 7.7 Concomitant Therapy

### 7.7.1 Prohibited and/or Restricted Treatments

Medications taken within [REDACTED] must be recorded on the CRF. No new concomitant medications (prescription, over-the-counter, or herbal) are to be

administered during study unless they are prescribed for treatment of specific clinical events. Cardiac medications cannot be initiated, discontinued, or dose adjusted [REDACTED]

[REDACTED] Any concomitant therapies must be recorded on the eCRF.

## **7.7.2 Other Restrictions and Precautions**

### **7.7.2.1 Magnetic Resonance Imaging Restriction and Precautions**

For those who agree to participate in the CMR sub-study, it is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to magnetic resonance imaging (MRI), participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m<sup>2</sup>) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. Further details will be outlined in the imaging manual.

Gentle hydration before and after intravenous contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

## **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.

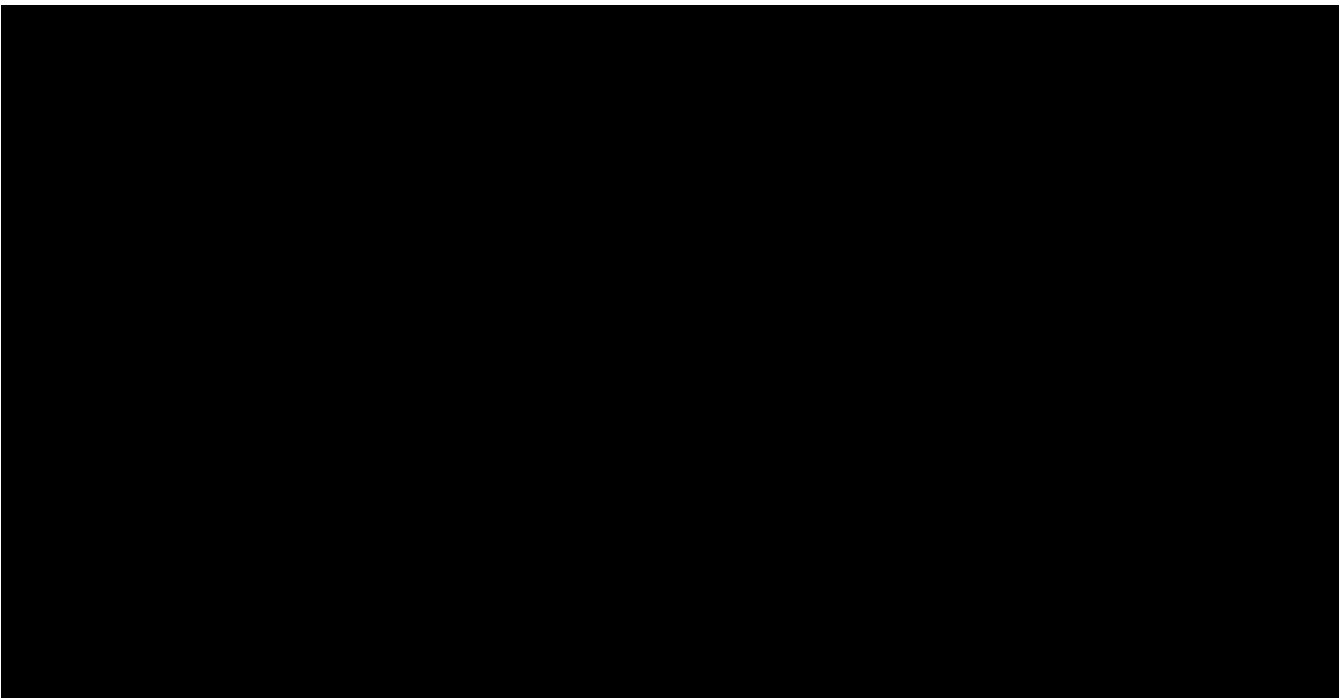
BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of mavacamten is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study 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**

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

[REDACTED]

- 
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued administration of study intervention is not in the best interest of the participant
  - Termination of the study by the Sponsor.
  - Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
  - Pregnancy (refer to [Section 9.2.5](#))
  - Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the Medical Monitor.

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 follow-up procedures as outlined in [Section 2](#) [REDACTED]. 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.

### **8.1.2 Post-study Intervention Study Follow-up**

Participants who discontinue study intervention may continue to be followed. See [REDACTED] for further details.

## **8.2 Discontinuation From the Study**

- 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 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.
- See the [Schedule of Activities](#) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

### 8.3 Lost to Follow-up

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

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

## 9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in [Section 2: Schedule of Activities](#).
- All assessments should be performed [REDACTED] unless otherwise specified.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

## 9.1 Efficacy Assessments

Details are provided in the Study Reference Manual. All echocardiography and CPET data will be sent to [REDACTED] laboratories; echocardiography results will be entered into the IRT.

### 9.1.1 Efficacy Assessment for the Study

The primary efficacy assessments will be change from baseline at 48 weeks [REDACTED] of treatment in KCCQ-23 CSS and pVO<sub>2</sub>.

pVO<sub>2</sub> will be obtained from CPET done at sites with certified expertise in conducting the test. The data acquired from CPET will be analyzed by a blinded independent [REDACTED] with recognized expertise in conducting and analyzing data from the test.

#### 9.1.1.2 Kansas City Cardiomyopathy Questionnaire (23-item Version)

The Kansas City Cardiomyopathy Questionnaire (23-item version) (KCCQ-23) is a patient-reported questionnaire that measures the impact of participants' cardiovascular disease or its treatment on 7 distinct domains using a 2-week recall: symptom stability, symptom frequency, symptom burden, physical limitations, quality of life, social limitation, and self-efficacy. In addition to the individual domains, 3 summary scores can be calculated from the KCCQ-23: the Overall Summary Score (OSS; includes the total symptom, physical limitation, social limitation, and quality of life scores), the CSS (derived from the TSS and PLS), and the TSS. Domain and summary scores all range from 0 to 100, with higher scores reflecting better health status. The CSS

will be one of the 2 primary endpoints (see [Section 4](#)). The other scores from the KCCQ-23 (the TSS, the PLS, and the OSS) will be evaluated as exploratory endpoints. The KCCQ-23 will be administered to participants as indicated in [Table 2-1](#), [Table 2-2](#), [Table 2-3](#), and [Table 2-4](#). See [Section 9.1.3.9](#) for patient-reported outcome (PRO) administration, method, mode, and training.

## **9.1.2 Imaging Assessment for the Study**

### **9.1.2.1 Transthoracic Echocardiography**

Resting transthoracic echocardiography will be assessed [REDACTED] during on-site visits as described in [Section 2](#). Left ventricular ejection fraction (2 dimensional LVEF) will be analyzed along with a variety of other echocardiographic measures (see Echo Instruction Manual).

Prior to enrollment in the study, participants will undergo a resting and Valsalva TTE and a post-exercise stress echocardiogram that will be submitted to the [REDACTED] imaging vendor for review to confirm eligibility. The [REDACTED] imaging vendor will assess the ejection fraction, parameters of diastolic dysfunction, and the quality of echocardiography images and windows.

For on-study resting TTE visits listed in [Section 2](#), [REDACTED]

Contrast echocardiograms may be considered in selected participants to enhance image quality in those participants with poor endocardial definition. For further details, please refer to the Echo Instruction Manual.

At screening and [REDACTED] (Week 48), [REDACTED].

At screening, resting TTE should be performed before post-exercise echocardiography.

### **9.1.2.2 Cardiac Magnetic Resonance Imaging**

Qualified sites and participants will participate in the CMR assessments. [REDACTED]

[REDACTED] Refer to the  
CMR Instruction Manual for additional details.

## **9.1.3 Patient-reported Outcomes**

### **9.1.3.1 Kansas City Cardiomyopathy Questionnaire 23-item Version (KCCQ-23)**

See ([Section 9.1.1](#)).

### **9.1.3.2 Hypertrophic Cardiomyopathy Symptom Questionnaire**

The Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) is a self-administered questionnaire that assesses the core symptoms of HCM. The finalized HCMSQ (v2.0) produces



four domain scores (SoB [4 items], tiredness [1 item], CV symptoms [3 items], syncope [1 item]), which are combined to create a total score (sum of the SoB, tiredness, and CV symptoms domains [8 items]). The HCMSQ SoB domain is the secondary endpoint measured through overall severity of SoB, severity of SoB during light activity, severity of SoB during moderate activity, and frequency of SoB. The HCMSQ tiredness score, the CV symptoms score, as well as the total score are the exploratory outcomes in this Phase 3 trial to measure the severity of other HCM symptoms including fatigue/tiredness, heart palpitation, dizziness, and chest pain. Participants will complete the HCMSQ once per day, according to the schedule described in [Section 2](#) (Schedule of Activities). See [Section 9.1.3.9](#) for PRO administration, method, mode, and training.

#### **9.1.3.3 Patient Global Anchor Items**

Patient global anchor items will be used to generate anchor-based estimates of meaningful within-patient change on the KCCQ-23 CSS and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath Score (HCMSQ SoB). All patient global anchors should be completed after the completion of any other PRO assessment at the associated site visit. See [Section 9.1.3.9](#) for PRO administration, method, mode, and training.

#### **9.1.3.4 Patient Global Impression of Severity (PGIS): PGIS-KCCQ**

The Patient Global Impression of Severity (PGIS): PGIS-KCCQ is a single item patient reported anchor that asks participants to rate the severity of their HCM symptoms and physical limitations over the past 14 days. Responses will be captured on a 5-point categorical rating scale (none, mild, moderate, severe, very severe) per the Schedule of Activities ([Section 2](#)).

#### **9.1.3.5 Patient Global Impression of Severity (PGIS): PGIS-SoB**

The Patient Global Impression of Severity (PGIS): PGIS-SoB is a single item patient reported anchor that asks participants to rate the severity of their shortness of breath over the past 7 days. Responses will be captured on a 5-point categorical rating scale (none, mild, moderate, severe, very severe) per the Schedule of Activities ([Section 2](#)).

#### **9.1.3.6 Patient Global Impression of Change (PGIC): PGIC-KCCQ**

The Patient Global Impression of Change (PGIC): PGIC-KCCQ is a single item patient reported anchor that asks participants to rate the overall change in their HCM symptoms and physical limitations since they started taking the study medication. Responses will be captured on a 7-point categorical rating scale (very much worse, much worse, a little worse, no change, a little better, much better, very much better) per the Schedule of Activities ([Section 2](#)).

#### **9.1.3.7 Patient Global Impression of Change (PGIC): PGIC-SoB**

The Patient Global Impression of Change (PGIC): PGIC-SoB is a single item patient reported anchor that asks participants to rate the overall change in their shortness of breath since they started taking the study medication. Responses will be captured on a 7-point categorical rating scale (very much worse, much worse, a little worse, no change, a little better, much better, very much better) per the Schedule of Activities ([Section 2](#)).

### **9.1.3.8 EQ-5D**

Participants' reports of general health status will be assessed using the EQ-5D-5L, which is composed of 2 components: a descriptive system and a visual analogue scale (VAS). The EQ-5D-5L descriptive system is composed of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels including no, slight, moderate, severe, and extreme or unable to. A dimension for which there are no problems is rated at level 1, while a dimension for which there are extreme problems is rated at level 5. Accordingly, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively. Altogether, the EQ-5D-5L describes 3125 health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index measuring the value to society of his or her current health. In addition, the EQ-5D-5L VAS allows respondents to rate their own current health on a 101-point scale ranging from best imaginable to worst imaginable health. Participants will complete the EQ-5D-5L according to the schedule described in [Section 2](#) (Schedule of Activities). See [Section 9.1.3.9](#) for PRO Administration, Method, Mode, and Training.

### **9.1.3.9 PRO Administration, Method, Mode, and Training**

Participants will be provided with provisioned handheld electronic devices for completion of all the PRO assessments. Participants will complete the HCMSQ, the PGIS-SoB, and the PGIC-SoB on the device outside of clinic site visits. The KCCQ-23, the PGIS-KCCQ, the PGIC-KCCQ, and EQ-5D-5L will be completed on the same device at clinical site visits (ie, they will bring their devices with them to scheduled clinic site visits to complete these PRO assessments).

Participants will be asked to complete the KCCQ-23, the PGIS-KCCQ, the PGIC-KCCQ, and the EQ-5D-5L on provisioned handheld electronic devices at clinical site visits. With the exception of screening, participants will bring their devices with them to the scheduled clinic visits to complete these PRO assessments. Participants and study staff will be advised to complete the PRO assessments prior to any other study procedure taking place during the study visit, where possible, and prior to any meaningful discussion about the study or study intervention with investigative site staff. The backup devices will be provided to clinical sites to prevent data collection issues in circumstances such as device loss or breakage or in case the participant forgets to bring their device to the clinical site visit. The backup devices will be the same as the provisioned handheld electronic devices.

During the coronavirus disease 2019 (COVID-19) public health emergency, trial participants may not be able to come to the investigational site for protocol-specified visits, therefore a backup option will be implemented in the form of remote administration of KCCQ-23, PGIS-KCCQ, PGIC-KCCQ, and EQ-5D-5L outside of the study site (field-based). It is important to note that this backup option will only be deployed in specific circumstances (eg, site unable to perform the participant's visit, participants to be adequately quarantined due to COVID-19 or other public health emergency) and would represent a temporary solution. The timeframe will be limited and will not replace the original administration strategy (ie, site-based completion), in order to minimize potential selection bias based on participant preference. Reminder alarms on the

electronic device and clinic reminders from the site staff will be implemented to encourage completion of the PRO assessment for the backup solution, if needed.

Participants will complete the HCMSQ, the PGIS-SoB, and the PGIC-SoB on the device outside of clinic site visits. Reminder alarms on the electronic device will be implemented to try to ensure completion of these PRO assessments on schedule and limit missing data. The alarm will be defaulted to go off at a certain local time every day if the PRO assessments have not been completed. The site will have the ability to change the time the alarm goes off for each participant and their accommodation.

Trainings will be provided to the study coordinators with hands-on training with the device at the Investigator meeting as well as a study brochure on how to set up the diary and train the participant. The training given to participants by the study site coordinators will be completed during the screening visit. Following training from the study site coordinators, participants will be required to complete a training module on the handheld device to ensure they understand how to navigate through the device. They will be offered a chance to ask any questions to the site coordinator during the training at the screening visit. The coordinator will need to confirm the completion of the training module prior to sending the participant home with the device.

Sites will monitor participant completion of the HCMSQ, the PGIS-SOB, and the PGIC-SoB (between clinical site visits) and the KCCQ-23, the PGIS-KCCQ, the PGIC-KCCQ, and the EQ-5D-5L (during clinical site visits) in an electronic clinical outcome assessment portal. This allows sites to oversee completion of the PRO assessments ahead of study visits (eg, HCMSQ), as well as confirm the visit on the handheld device to trigger the questionnaires tied to the specific visit (eg, KCCQ-23). Guidance will be provided to the site staff to ensure they answer all the questions and complete submission.

Additional training regarding the importance of PRO compliance and monitoring will be provided to the clinical research associates (CRAs) during study status web conferences.

#### **9.1.4 Other Efficacy Assessments for the Study**

Cardiac biomarkers NT-proBNP and high-sensitivity troponin T and troponin I will be assessed to support the efficacy of mavacamten in nHCM. The values for these tests will be masked (except the screening values).

##### **9.1.4.1 New York Heart Association Functional Classification**

The NYHA functional classification of heart failure assigns participants to 1 of 4 categories based on the participant's symptoms as outlined in [Table 9.1.4.1-1](#). Every effort should be made to have the same investigator use the symptoms in [Table 9.1.4.1-1](#) to determine NYHA Classification at each study visit.

**Table 9.1.4.1-1: New York Heart Association Classifications of Cardiovascular Disability**

| Class | Patient Symptoms                                                                                                                                                                                                                                                      |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I     | Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.                                                                                 |
| II    | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.                                                                |
| III   | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.                                                          |
| IV    | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

Source: [https://carepartners.org/wp-content/uploads/2019/08/NYHA-C\\_heart\\_failure-highlighted.pdf](https://carepartners.org/wp-content/uploads/2019/08/NYHA-C_heart_failure-highlighted.pdf). UpToDate® Official report from UpToDate® ©2019 UpToDate, Inc. and/or its affiliates. All Rights Reserved. [www.uptodate.com](http://www.uptodate.com)  
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed, Little, Brown & Co, Boston, 1994. p.253.

## 9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in [Appendix 3](#).

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

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.

The treatment-emergent period is defined as the time from the first dose of study intervention to the last dose of study intervention [REDACTED] AEs with onset during the treatment-emergent period (ie, TEAEs) or with an onset before the first dose of study intervention that increase in severity or become serious during the treatment-emergent period will be considered TEAEs.

**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, [REDACTED]

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 as quickly as possible but within 24 hours, as indicated in [Appendix 3](#).
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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

### **9.2.2 Method of Detecting AEs and SAEs**

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

### **9.2.3 Follow-up of AEs and SAEs**

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

All SAEs 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](#)).

The duration of

all AEs including SAEs will not be included in the final CSR; however, they will be part of later study safety reports.

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**

A serum  $\beta$ -hCG pregnancy test is required for all WOCBP at screening and a urine  $\beta$ -hCG pregnancy test is required at randomization, prior to first dose of study intervention, and at visits designated in the Schedule of Activities for the placebo-controlled double-blind treatment period. In addition, urine  $\beta$ -hCG pregnancy testing is required at all visits during the LTE period as well as at home, occurring every 4 weeks between visits through the EOS visit.

If any urine  $\beta$ -hCG pregnancy test result is positive or ambiguous, the Investigator will instruct the participant to suspend further study intervention and schedule a follow-up appointment as soon as possible, where a confirmatory serum  $\beta$ -hCG pregnancy test will be performed.

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, 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. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant. WOCBP who become pregnant will be discontinued from the study. The WOCBP will be asked to provide information on the outcome of the pregnancy through 1 year after birth or details of premature termination.

### **9.2.6 Laboratory Test Result Abnormalities**

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE



- Any laboratory test result abnormality that required the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

### **9.2.7 Potential Drug-induced Liver Injury**

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

Potential DILI is defined as:

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

### **9.2.8 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**

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 and may reflect enhanced on-target PD effects of mavacamten. 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 ACCF/AHA Guideline for the Management of Heart Failure and in the 2016 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.

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see [Appendix 3](#)).

In the event of an overdose, the investigator should:

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

## 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 and DMC.

### 9.4.1 Physical Examinations

Refer to [Schedule of Activities](#). A complete physical examination should consist of height (only required at the screening visit), weight, and assessment of the following: general appearance, skin, head, neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems.

### 9.4.2 Vital Signs

Refer to Schedule of Activities.

- Systolic Blood Pressure
- Diastolic Blood Pressure
- Pulse or Heart Rate



- Respiratory Rate
- Temperature

### 9.4.3 **Electrocardiograms**

Refer to [Schedule of Activities](#).

### 9.4.4 **Clinical Safety Laboratory Assessments**

- Investigators must document their review of each laboratory safety report.
- Unblinding: The Investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the Investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the participant's study medication has been made.

A [REDACTED] laboratory will perform the analyses and will provide reference ranges for these tests except for urine pregnancy tests.

**Table 9.4.4-1: Clinical Laboratory Assessments**

|                                               |                                       |
|-----------------------------------------------|---------------------------------------|
| <b>Hematology/Coagulation</b>                 |                                       |
| Hemoglobin                                    |                                       |
| Hematocrit                                    |                                       |
| Total leukocyte count, including differential |                                       |
| Platelet count                                |                                       |
| CBC, including differential count             |                                       |
| INR                                           |                                       |
| aPTT                                          |                                       |
| <b>Chemistry</b>                              |                                       |
| Aspartate aminotransferase                    | Total protein                         |
| Alanine aminotransferase                      | Albumin                               |
| Total bilirubin                               | Sodium                                |
| Direct bilirubin                              | Potassium                             |
| Alkaline phosphatase                          | Chloride                              |
| Lactate dehydrogenase                         | Calcium                               |
| Creatinine                                    | Phosphorus                            |
| Blood urea nitrogen                           | Magnesium                             |
| Uric acid                                     | Creatine kinase                       |
| Glucose                                       | Creatinine clearance - screening only |
|                                               | Cholesterol                           |
|                                               | Bicarbonate                           |
| <b>Urinalysis</b>                             |                                       |
| Protein                                       |                                       |
| Glucose                                       |                                       |
| Blood                                         |                                       |

**Table 9.4.4-1: Clinical Laboratory Assessments**

|                                                                                                                |
|----------------------------------------------------------------------------------------------------------------|
| Leukocyte esterase                                                                                             |
| Specific gravity                                                                                               |
| pH                                                                                                             |
| Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick |
| Nitrite                                                                                                        |
| <b>Imaging Assessment:</b><br>LVEF                                                                             |
| <b>Other Assessments:</b><br>FSH<br>Pregnancy test                                                             |

Abbreviations: aPTT, activated partial thromboplastin clotting time; CBC, complete blood count; INR, international normalized ratio; LVEF, left ventricular ejection fraction; FSH, follicle-stimulating hormone.

#### 9.4.5 Imaging/Other Safety Assessment

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

### 9.5 Pharmacokinetics

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK samples.

Concentration analyses for mavacamten will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected immunogenicity related AE, etc).

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, metabolite analyses, etc) and or for additional method purposes (including, but not limited to, cross-validation, PK selectivity, cutpoint, bridging to a therapeutic drug monitoring assay etc).

Pharmacokinetic assessments of mavacamten will be performed using sparse sampling. Sparse samples will be taken in all participants. The date and time of dosing and sample collection will be documented. Further sample and processing instructions will be provided separately.

|         |                                                 |
|---------|-------------------------------------------------|
| Ctrough | Mavacamten plasma trough concentration by visit |
|---------|-------------------------------------------------|

One trough sample to be collected at every visit, and placebo samples will not be analyzed.

Blood samples will be collected for mavacamten plasma concentration assessments at most post Day 1 on-site visits (Table 9.5-1) [REDACTED]. It is expected that every effort be made to collect PK samples at the times indicated in the protocol. [REDACTED]

At visits from [REDACTED] participants should not take study intervention before their visit on days PK samples will be collected. They will be instructed to take their dose after the PK sample is collected (see [Table 9.5-1](#)). The date and time of dosing will be documented. All PK samples will be sent to a [REDACTED] for processing.

**Table 9.5-1: Pharmacokinetic Sampling Schedule**

| Study Day of Sample Collection | Event <sup>a</sup> | Time (Relative to Mavacamten Dose)<br>Hour:Min | Mavacamten PK Plasma Sample |
|--------------------------------|--------------------|------------------------------------------------|-----------------------------|
| [REDACTED]                     | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
| [REDACTED]                     |                    |                                                |                             |
| [REDACTED]                     | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |
|                                | Predose            | 00:00                                          | X                           |

Abbreviations: [REDACTED] PK, pharmacokinetic.

<sup>a</sup> [REDACTED]

PK samples may be collected at additional time points based on an unscheduled event during the study if warranted and agreed upon between the investigator and/or the Sponsor.

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

## **9.6 Immunogenicity Assessments**

Not applicable.

## **9.7 Genetics**

### **9.7.1 Pharmacogenetic Assessments for Drug Metabolism Enzymes and Drug Transporters Genotyping**

Blood will be collected preferably on Day 1 or any visit thereafter for testing of genes encoding for drug metabolism enzymes and drug transporters (DMET) which may include but are not limited to CYP2C19. Genetic variations in DMET have the potential to significantly impact an individual's metabolic capacity for mavacamten. See [Table 9.8-1](#) for sample collection schedule.

### **9.7.2 Cardiomyopathy Genotyping**

A blood sample for cardiomyopathy genotyping will be collected preferably on Day 1 or any visit thereafter for assessment of cardiomyopathy genotypes. See [Table 9.8-1](#) for sample collection schedule.

## **9.8 Biomarkers**

Collection of samples for biomarker research is part of this study. The following samples for biomarker research are required and will be collected from all participants in this study at predose as specified in the Schedule of Activities and in this section:

- **Cardiac Biomarkers:**

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

- **Exploratory Biomarkers:**

Blood samples will be collected for relevant exploratory biomarker analysis

(Table 9.8-1).

Details on processes for collection and shipment of these samples can be found in the laboratory manuals. Results of exploratory biomarker analysis may be reported separately from CSR.

**Table 9.8-1: Biomarker Sampling Schedule**

| Study Day of<br>Sample Collection <sup>a</sup>                                                                                                                          | Blood Sample for<br>Cardiomyopathy<br>Genotyping <sup>b</sup> | Pharmacogenetic<br>Assessments <sup>b</sup> | Cardiac<br>Biomarkers<br>(NT-proBNP) | Cardiac<br>Biomarkers<br>(hsTn-I) | Cardiac<br>Biomarkers<br>(hsTn-T) | Exploratory<br>Biomarkers<br>(Plasma) |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------|--------------------------------------|-----------------------------------|-----------------------------------|---------------------------------------|-------------------------------------------------------------------------------------|
|                                                                                       | X                                                             | X                                           | X                                    | X                                 | X                                 | X                                     | X                                                                                   |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 | X                                     |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 | X                                     |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 | X                                     |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 | X                                     |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 |                                       |                                                                                     |
|                                                                                                                                                                         |                                                               |                                             | X                                    | X                                 | X                                 | X                                     |                                                                                     |
|                                                                                      |                                                               |                                             |                                      |                                   |                                   |                                       |                                                                                     |
|   |                                                               |                                             | X                                    | X                                 | X                                 | X                                     |                                                                                     |

**Table 9.8-1: Biomarker Sampling Schedule**

| Study Day of Sample Collection <sup>a</sup> | Blood Sample for Cardiomyopathy Genotyping <sup>b</sup> | Pharmacogenetic Assessments <sup>b</sup> | Cardiac Biomarkers (NT-proBNP) | Cardiac Biomarkers (hsTn-I) | Cardiac Biomarkers (hsTn-T) | Exploratory Biomarkers (Plasma) |  |
|---------------------------------------------|---------------------------------------------------------|------------------------------------------|--------------------------------|-----------------------------|-----------------------------|---------------------------------|--|
|                                             |                                                         |                                          | X                              | X                           | X                           | X                               |  |
|                                             |                                                         |                                          | X                              | X                           | X                           | X                               |  |
|                                             |                                                         |                                          | X                              | X                           | X                           | X                               |  |
|                                             |                                                         |                                          | X                              | X                           | X                           | X                               |  |
|                                             |                                                         |                                          | X                              | X                           | X                           | X                               |  |
|                                             |                                                         |                                          | X                              | X                           | X                           | X                               |  |

Abbreviations: HCM, hypertrophic cardiomyopathy; hs-Tn-I, high-sensitivity troponin-I; hs-Tn-T, high-sensitivity troponin-T; NT-proBNP, N-terminal pro B-type natriuretic peptide; SAE, serious adverse event; [REDACTED]

<sup>a</sup> Biomarker samples to be taken before exercise.

<sup>b</sup> Will be collected preferably on Day 1 or any visit thereafter.

[REDACTED]

## 9.9 Additional Research

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

### For All Sites

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

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

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

### Sample Collection and Storage

- Residual pharmacokinetic, pharmacogenetic, or CM genotyping, [REDACTED] cardiac biomarker, and exploratory biomarker collections from all 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 Schedule**

| Sample Type                  | Timepoints for Which Residual Samples Will Be Retained |
|------------------------------|--------------------------------------------------------|
| PK                           | All                                                    |
| Pharmacogenetic<br>DMET      | All                                                    |
| Cardiomyopathy<br>Genotyping | All                                                    |
|                              |                                                        |
| Cardiac Biomarkers           | All                                                    |
| Exploratory<br>Biomarkers    | All                                                    |

Abbreviations: DMET, drug metabolism enzymes and drug transporters; PK, pharmacokinetic;

## 9.10 Health Economics or Medical Resource Utilization and Health Economics

Medical resource utilization will be derived based on relevant health events collected throughout the study. The data collected may be used to conduct exploratory economic analyses, given meaningful results are obtained.

## 10 STATISTICAL CONSIDERATIONS

### 10.1 Statistical Hypotheses

The primary hypotheses will test the treatment effect of mavacamten against placebo on the KCCQ-23 CSS and pVO2. The following hypotheses of the primary endpoints will be tested:

#### Primary hypothesis 1:

- Null hypothesis ( $H_{10}$ ):  $\mu_{t.kccq} - \mu_{p.kccq} = 0$  vs
- alternative hypothesis ( $H_{1a}$ ):  $\mu_{t.kccq} - \mu_{p.kccq} \neq 0$ ,

Where  $\mu_{t.kccq}$  is the adjusted mean change from baseline in KCCQ-23 CSS at Week 48 for the mavacamten group and  $\mu_{p.kccq}$  is the adjusted mean change from baseline in KCCQ-23 CSS score at Week 48 for the placebo group.

#### Primary hypothesis 2:

- Null hypothesis ( $H_{20}$ ):  $\mu_{t.pvo2} - \mu_{p.pvo2} = 0$  vs
- alternative hypothesis ( $H_{2a}$ ):  $\mu_{t.pvo2} - \mu_{p.pvo2} \neq 0$ ,

Where  $\mu_{t.pvo2}$  is the adjusted mean change from baseline in pVO<sub>2</sub> at Week 48 for the mavacamten group and  $\mu_{p.pvo2}$  is the adjusted mean change from baseline in pVO<sub>2</sub> at Week 48 for the placebo group.

The study will be claimed successful if at least one primary endpoint is statistically significant after multiplicity adjustment.

## 10.2 Sample Size Determination

The sample size estimation of this study is based on the analysis of the primary endpoints of change from baseline to Week 48 in KCCQ-23 CSS and change from baseline to Week 48 in pVO<sub>2</sub>. Approximately 420 participants will be randomized to achieve at least 95% power to reject the first primary null hypothesis H<sub>10</sub> and at least 99% power to reject the second primary null hypothesis H<sub>20</sub>, both at alpha = 0.05 (2-sided) significance level, respectively.

The sample size calculation is based on the following assumptions informed by the MAVERICK 006 study:

- Treatment effect is assumed to be an increase of [REDACTED] points in mean KCCQ-23 CSS change from baseline to Week 48 between mavacamten and placebo. Common standard deviation of [REDACTED] is assumed for the change from baseline in KCCQ-23 CSS for each treatment group.
- Treatment effect is assumed to be an increase of [REDACTED] mL/kg/min in mean pVO<sub>2</sub> change from baseline to Week 48 between mavacamten and placebo. Common standard deviation of [REDACTED] is assumed for the change from baseline in pVO<sub>2</sub> for each treatment group.

## Randomization:

Approximately 420 participants will be randomized in a 1:1 ratio to mavacamten and placebo. Randomization will be stratified according to NYHA class (II or III), type of exercise (treadmill or exercise bicycle), and beta blocker use (Yes/No) at baseline.

## 10.3 Analysis Sets

The populations defined for the purposes of analysis will include and not limited to the following:

| Population | Description                                                                                                                                                                                                                                                                                                                                                                                                |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Enrolled   | All participants, <i>who have</i> agreed to participate in a clinical study following completion of the informed consent process.                                                                                                                                                                                                                                                                          |
| Randomized | All participants who were randomized using Interactive Response Technology                                                                                                                                                                                                                                                                                                                                 |
| Safety     | All randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group to which they were randomized.<br><br>Data in this dataset will be analyzed based on randomized treatment, except if a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received. |

| Defined Analysis Data Sets | Description                                                                                                                                                                                                                                                                       |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Efficacy Analysis Set      | For all randomized participants, all available efficacy data will be included for efficacy analysis regardless of participant's treatment interruption, study intervention discontinuation, and/or prohibited medication taken.                                                   |
| PK analysis set            | All randomized participants who are exposed to study intervention and have at least 1 evaluable mavacamten concentration. For participants who discontinue study intervention, all post-discontinuation or post-prohibited observations will not be included in the analysis set. |

## 10.4 Statistical Analyses

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

### 10.4.1 General Considerations

All comparisons will be of mavacamten versus placebo. The baseline value is defined generally as the last non-missing value before the first dose of study intervention. For participants randomized but not treated, the last non-missing value before or on the randomization date will be used as baseline value.

The study will be unblinded after the last participant completes the Week 48 visit and the database is locked. With this data cutoff, an intermediate database (locked) will be used to perform the primary analyses at the end of Part A (assessing primary and secondary hypotheses) and assess the study success.

The data collected after the last participant completes the Week 48 visit (end of Part A) until the end of the LTE period [REDACTED] will be summarized descriptively.

#### **10.4.2 Primary Endpoint(s)**

The primary efficacy endpoints are the change from baseline in KCCQ-23 CSS at Week 48 and the change from baseline in pVO<sub>2</sub> at Week 48.

The KCCQ-23 scores are calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. In addition, the KCCQ-23 CSS score is derived as the average of the TSS and the PLS.

Both primary efficacy endpoints will be analyzed using analysis of covariance (ANCOVA), including stratification factors, baseline value, and treatment as covariate or factor in the model, as appropriate.

Participants who discontinue study intervention prematurely/temporarily are encouraged to follow the planned clinical visits. For these participants, missing data may still happen despite all efforts to collect the data after intercurrent events. For participants who discontinue study intervention prematurely, all data collected after study intervention discontinuation will be used in the analysis (treatment policy strategy).

Missing data will be imputed as described (but not limited to) below:

[REDACTED]

All imputed complete datasets will be used to estimate the difference between mavacamten and placebo groups in least squares means, the corresponding 95% confidence intervals (CI) as well as the p-values.

The primary estimand of this trial is defined below in [Table 10.4.3-1](#). Full details of the imputation strategy will be provided in the Statistical Analysis Plan.

#### **10.4.2.1 Sensitivity Analysis**

Tipping point analysis based on the same multiple imputation method as applied to the primary analyses will be performed to examine the robustness of the results from the primary analyses.

#### **10.4.2.2 Supportive Analysis**

In addition to the primary efficacy analysis of the between-group difference, supportive analysis will be provided to demonstrate the clinical relevance (robustness, magnitude, and consistency) of the observed/estimated treatment effect.

For primary endpoint of KCCQ-23 CSS:

- Empirical cumulative distribution function of change from baseline at Week 48 will be plotted by treatment group to compare the proportion of participants who are meeting certain thresholds.
- Change from baseline in the KCCQ-23 CSS will be analyzed using Mixed Model with Repeated Measurements (MMRM), including treatment, stratification factors, visit and treatment-by-visit interaction as fixed effects, baseline of the dependent variable as a covariate, and participant as a random effect, using an unstructured variance-covariance matrix, if appropriate.

For primary endpoint of pVO2:

- Empirical cumulative distribution function of change from baseline at Week 48 will be plotted by treatment group to compare the proportion of participants who are meeting certain thresholds.
- Percentages of participants with clinical meaningful change from baseline at Week 48 will be summarized by treatment group.
- Additional supportive analyses and details will be provided in the SAP.

#### **10.4.2.3 Subgroup Analysis**

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the 2 primary efficacy endpoints with respect to age group, gender, NYHA class at baseline, beta blocker use at baseline, sodium-glucose cotransporter-2 inhibitors as comedication, and other factors that will be specified in the SAP.

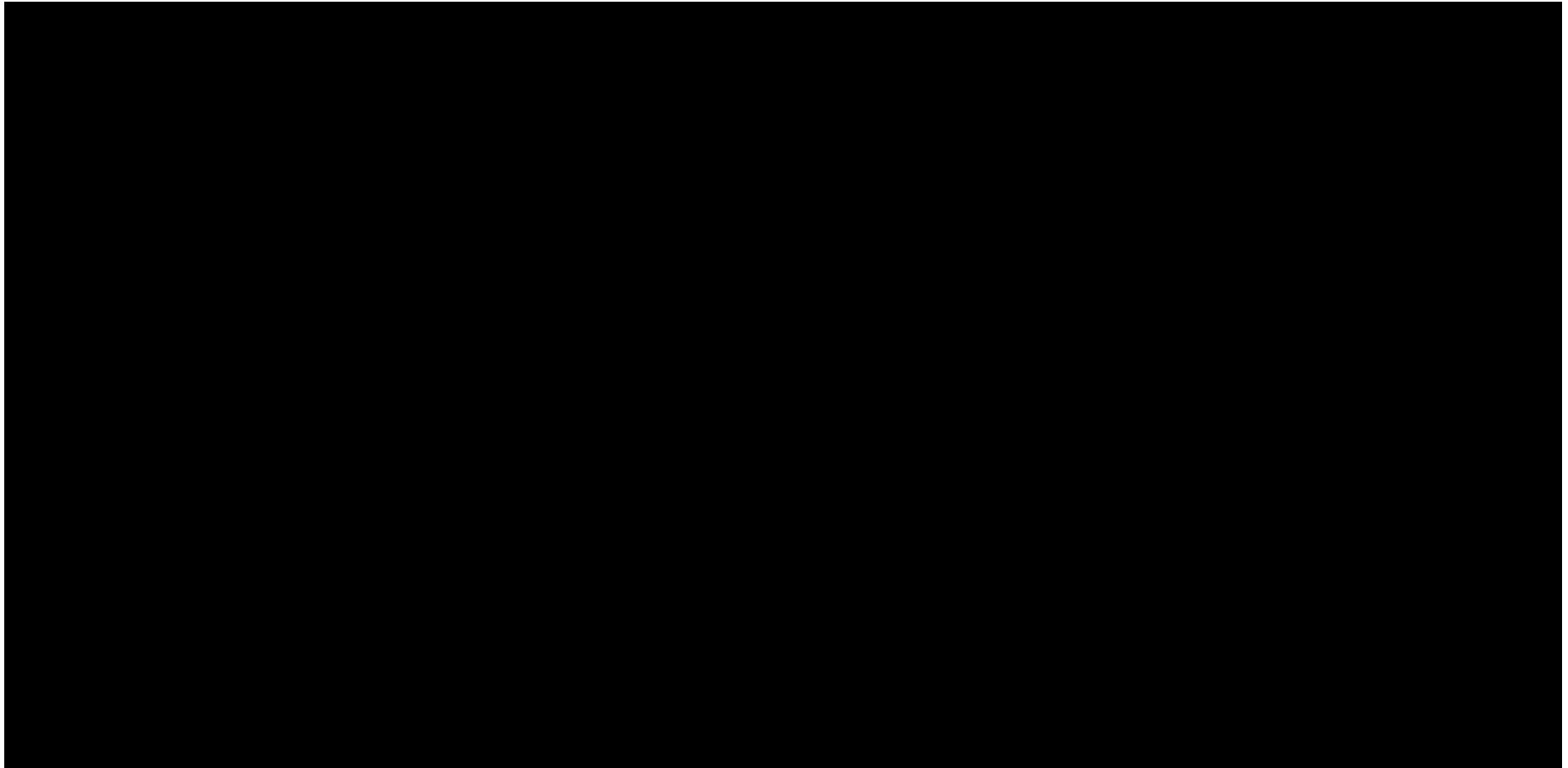
### **10.4.3 Secondary Endpoint(s)**

CPET parameter (VE/VCO<sub>2</sub> slope) will be analyzed in a similar way as the primary endpoint pVO<sub>2</sub> by using the same ANCOVA with treatment policy strategy and the same missing data approach. Further details will be provided in the SAP.

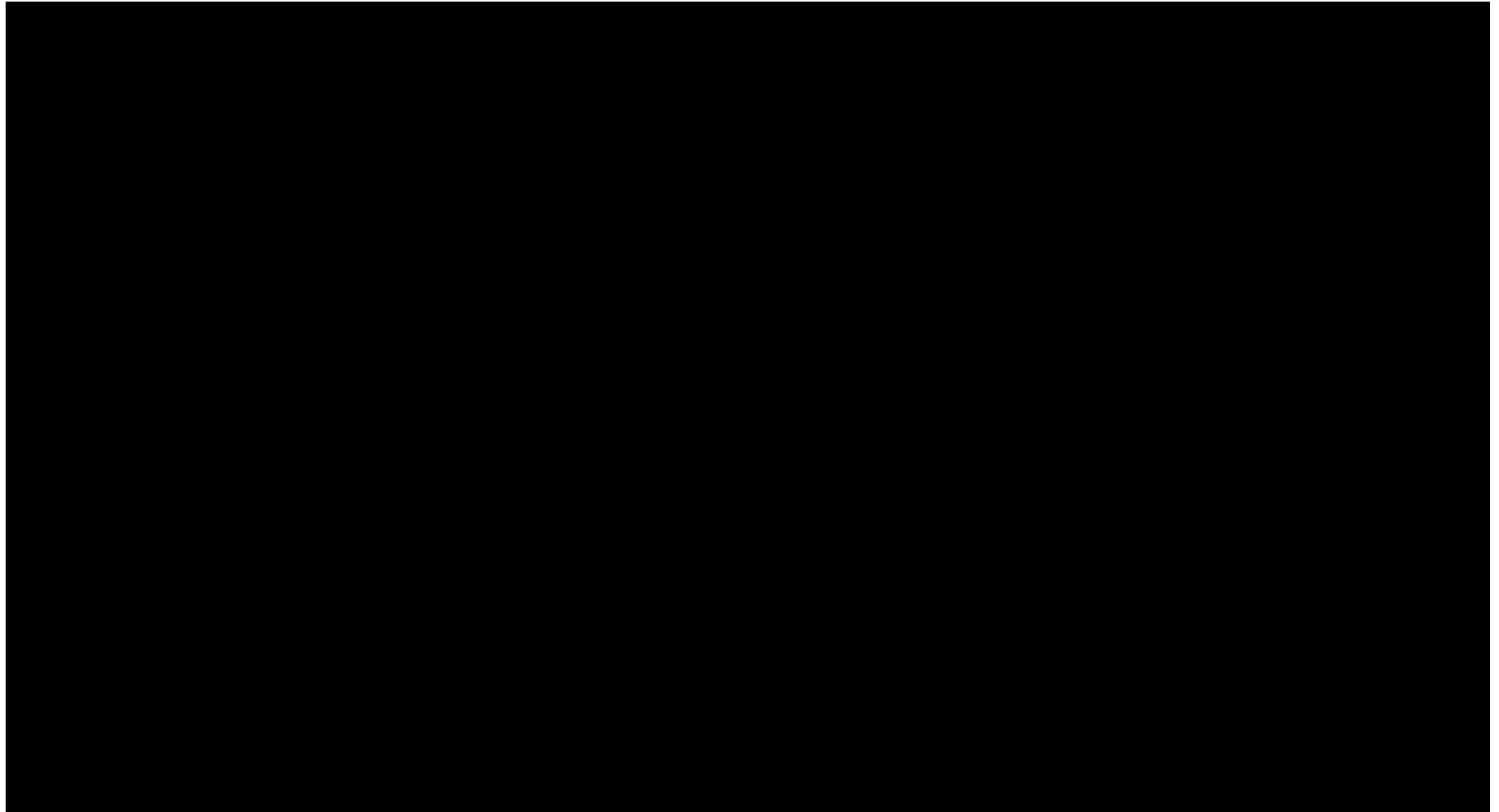
Continuous endpoints of HCMSQ SoB and NT-proBNP will be analyzed in a similar way as the primary endpoint of KCCQ-23 CSS by using ANCOVA model, treatment policy strategy and missing data scheme.



**Table 10.4.3-1:      Estimands**



**Table 10.4.3-1:      Estimands**





**Table 10.4.3-1: Estimands**

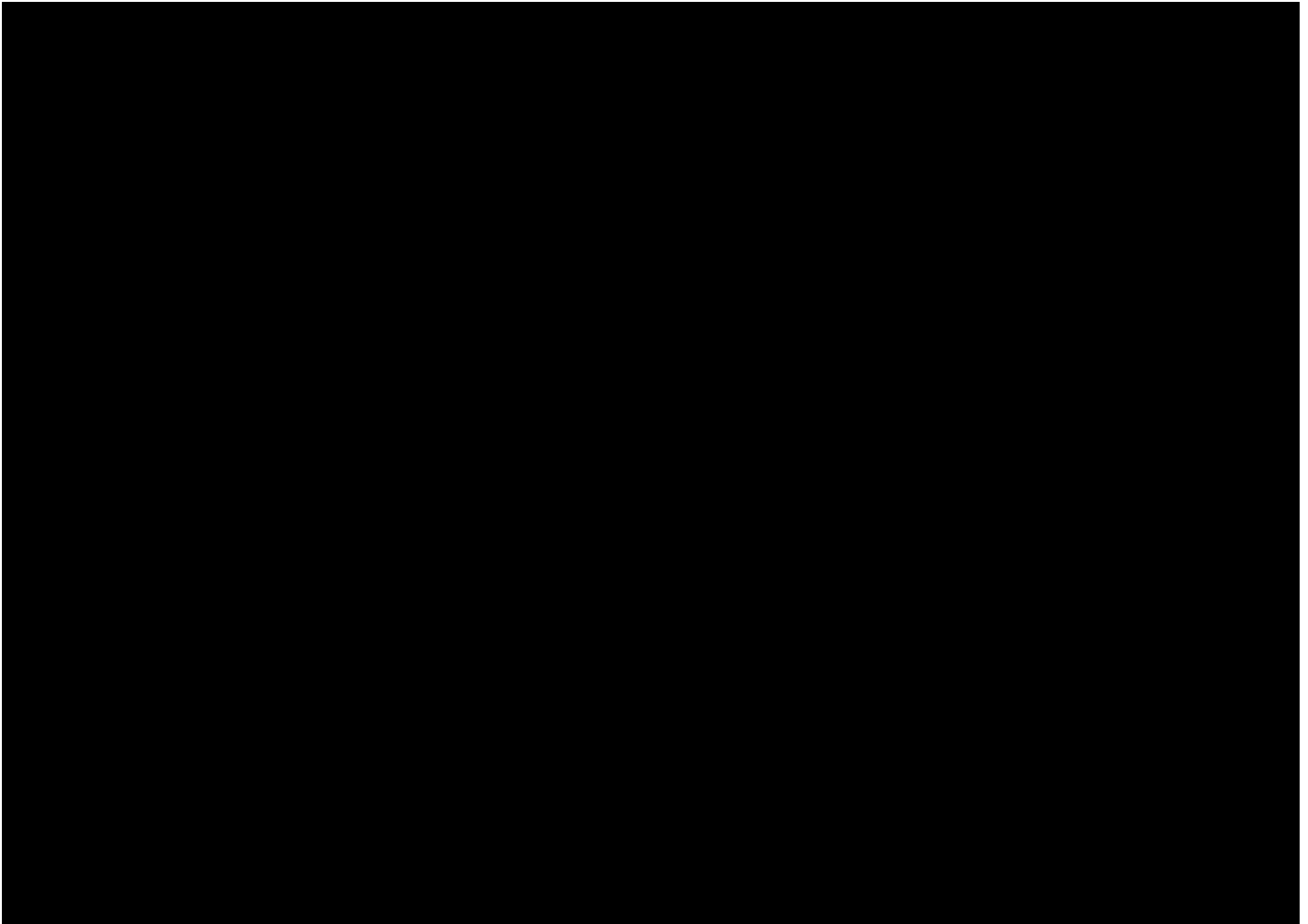
| Endpoint Category                                                                     | Estimands                                                    |                                      |                                                                                                                                                                       |                                                                                                                             |
|---------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
|                                                                                       | Endpoint(s) <sup>a</sup>                                     | Population                           | Intercurrent Event(s) Handling Strategy and Missing Data Handling                                                                                                     | Analysis Method to Provide Population-level Summary                                                                         |
| Secondary objective: To demonstrate the efficacy of mavacamten on secondary endpoints |                                                              |                                      |                                                                                                                                                                       |                                                                                                                             |
| Secondary endpoint – continuous                                                       | Change from baseline in VE/VCO <sub>2</sub> slope to Week 48 | Adult patients with symptomatic nHCM | <ul style="list-style-type: none"> <li>The intercurrent events and missing data will be handled the same as primary continuous endpoint of pVO<sub>2</sub></li> </ul> | ANCOVA with stratification factors, baseline VE/VCO <sub>2</sub> slope, and treatment as covariate and factor in the model. |
| Secondary endpoint – continuous                                                       | Change from baseline to Week 48 in NT-proBNP                 | Adult patients with symptomatic nHCM | <ul style="list-style-type: none"> <li>The intercurrent events and missing data will be handled the same as primary continuous endpoint of KCCQ-23 CSS</li> </ul>     | ANCOVA including stratification factors, baseline NT-proBNP, and treatment as covariate and factor in the model             |
| Secondary endpoint – continuous                                                       | Change from baseline to Week 48 in HCMSQ SoB domain          | Adult patients with symptomatic nHCM | The intercurrent events and missing data will be handled the same as primary continuous endpoint of KCCQ-23 CSS                                                       | ANCOVA including stratification factors, baseline HCMSQ SoB, and treatment as covariate and factor in the model             |

Abbreviations: ANCOVA, analysis of covariance; CPET, cardiopulmonary exercise testing; CMH, Cochran-Mantel-Haenszel; CV, cardiovascular; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ-23 CSS, Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score; LOCF, last

observation carried forward; MMRM, mixed model with repeated measurements; nHCM, non-obstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; pVO<sub>2</sub>, peak oxygen consumption; SoB, shortness of breath; VE/VCO<sub>2</sub>, ventilatory efficiency.

a Note: Additional exploratory objectives/endpoints not included in this table would be handled with a similar strategy as the endpoint type (ie, continuous and proportion) specified in this table with regards to intercurrent events.

**Multiplicity Adjustment:**



#### **10.4.4 Exploratory Endpoint(s)**

Details of all exploratory endpoint analyses will be provided in the SAP.

No multiplicity adjustments will be made for exploratory endpoints or subgroup analyses for which nominal p-values may be provided for descriptive purposes only.

#### **10.4.5 Pharmacokinetic/Pharmacodynamic Analyses**

All PK and PK/PD analyses will be based on the PK analysis set. The PK analysis set will be used for all listings. Plasma concentration ( $C_{\text{trough}}$ ) of mavacamten will be determined and summarized using descriptive statistics. The PK/PD (PD endpoints: LVEF and NT-proBNP) relationships will be represented in scatterplots for all time points. Further details will be provided in the study SAP. The exploratory PK and PK/PD modeling (including population PK and exposure-response modeling) will be reported in separate reports. Data from previously conducted studies might be added for model development for PK and PK/PD.

#### **10.4.6 Other Safety Analyses**

All safety analyses will be performed on the Safety population. Safety summary will be provided for the placebo-controlled double-blind treatment period in addition to the overall study duration (placebo-controlled double-blind treatment period and LTE period).

Treatment-emergent AEs and SAEs, and AEs leading to discontinuation of study intervention, as well as death will be summarized using counts and percentages of participants experiencing the event by System Organ Class, Preferred Term, and treatment group. Vital signs, clinical laboratory test results, echocardiography, and ECG test results will be summarized by treatment group using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions (counts and percentages) for categorical variables. Additionally, the percentage of participants with an LVEF [REDACTED] will be summarized.

All other safety analysis will be further described in the SAP finalized before database lock.

#### **10.4.7 Other Analyses**

PK analyses will be described in the SAP that will be finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main CSR.

In addition, descriptive analyses will be conducted on the data collected after the last participant completes the Week 48 visit (end of Part A) until the end of the LTE period [REDACTED]. The summary descriptive statistics will be provided.

#### **10.5 Interim Analyses**

No interim analysis is planned for this study.

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## **12 APPENDICES**

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term            | Definition                                     |
|-----------------|------------------------------------------------|
| ACC             | American College of Cardiology                 |
| AE              | adverse event                                  |
| AF              | atrial fibrillation                            |
| AHA             | American Heart Association                     |
| ■               | ■                                              |
| ALT             | alanine aminotransferase                       |
| ANCOVA          | analysis of covariance                         |
| AR              | additional research                            |
| ARO             | Academic Research Organization                 |
| AST             | aspartate aminotransferase                     |
| AT              | aminotransaminase                              |
| AxMP            | auxiliary medicinal product                    |
| BMI             | body mass index                                |
| BMS             | Bristol-Myers Squibb Company                   |
| BNP             | B-type natriuretic peptide                     |
| β-hCG           | beta-human chorionic gonadotropin              |
| CBC             | complete blood count                           |
| CEC             | Clinical Event Committee                       |
| CFR             | Code of Federal Regulations                    |
| CHMP            | Committee for Medicinal Products for Human Use |
| CI              | confidence interval                            |
| CMH             | Cochran-Mantel-Haenszel                        |
| CMR             | cardiac magnetic resonance imaging             |
| CO <sub>2</sub> | carbon dioxide                                 |
| COVID-19        | coronavirus disease 2019                       |
| CPET            | cardiopulmonary exercise testing               |
| CRF             | Case Report Form, paper or electronic          |
| CSR             | clinical study report                          |
| CSS             | clinical summary score                         |

| Term     | Definition                                    |
|----------|-----------------------------------------------|
| CTAg     | Clinical Trial Agreement                      |
| cTn-I    | cardiac troponin I                            |
| cTn-T    | cardiac troponin T                            |
| Ctrough  | trough-observed plasma concentration          |
| CV       | cardiovascular                                |
| CYP      | cytochrome P450                               |
| D        | day                                           |
| DB       | double-blind                                  |
| DILI     | drug-induced liver injury                     |
| DMC      | Data Monitoring Committee                     |
| DMET     | drug metabolism enzymes and drug transporters |
| DNA      | deoxyribonucleic acid                         |
| EC       | executive committee                           |
| ECG      | electrocardiogram                             |
| Echo     | echocardiogram                                |
| eCRF     | electronic Case Report Form                   |
| EDC      | electronic data capture                       |
| ██████   | ████████████████████                          |
| EF       | ejection fraction                             |
| eGFR     | estimated glomerular filtration rate          |
| ██████   | ████████████████████                          |
| EOS      | end of study                                  |
| EOT      | end of treatment                              |
| EQ-5D    | EuroQol-5 Dimension                           |
| EQ-5D-5L | 5-level EuroQoL-5 Dimension version           |
| ESC      | European Society of Cardiology                |
| ET       | early termination                             |
| EU       | European Union                                |
| EuroQol  | European Quality of Life                      |
| FSH      | follicle-stimulating hormone                  |

| Term      | Definition                                                                  |
|-----------|-----------------------------------------------------------------------------|
| FU        | follow-up                                                                   |
| GCP       | Good Clinical Practice                                                      |
| HCG       | human chorionic gonadotropin                                                |
| HCM       | hypertrophic cardiomyopathy                                                 |
| HCMSQ     | Hypertrophic Cardiomyopathy Symptom Questionnaire                           |
| HCMSQ-SoB | Hypertrophic Cardiomyopathy Symptom Questionnaire-Shortness of Breath Score |
| HR        | heart rate                                                                  |
| IB        | Investigator's Brochure                                                     |
| ICD       | implantable cardioverter defibrillator                                      |
| ICF       | informed consent form                                                       |
| ICH       | International Council for Harmonisation                                     |
| ICMJE     | International Committee of Medical Journal Editors                          |
| IEC       | Independent Ethics Committee                                                |
| IMP       | Investigational Medicinal Product                                           |
| IND       | Investigational New Drug                                                    |
| IP        | Investigational Product                                                     |
| IQR       | interquartile range                                                         |
| IRB       | Institutional Review Board                                                  |
| IRT       | Interactive Response Technology                                             |
| IU        | international unit                                                          |
| KCCQ      | Kansas City Cardiomyopathy Questionnaire                                    |
| KCCQ CSS  | Kansas City Cardiomyopathy Questionnaire Clinical Summary Score             |
| L         | liter                                                                       |
| LA        | left atrial                                                                 |
| LAVI      | left atrial volume index                                                    |
| LOCF      | last observation carried forward                                            |
| LTE       | Long-term extension                                                         |
| LV        | left ventricular                                                            |
| LVEF      | left ventricular ejection fraction                                          |

| Term           | Definition                                  |
|----------------|---------------------------------------------|
| LVFP           | left ventricular filling pressures          |
| LVOT           | left ventricular outflow tract              |
| MACE           | major adverse cardiovascular events         |
| MET            | metabolic equivalent of task                |
| MI             | myocardial infarction                       |
| min            | minute                                      |
| mm Hg          | millimeters of mercury                      |
| MMRM           | mixed model with repeated measurements      |
| MNAR           | missing not at random                       |
| MRI            | magnetic resonance imaging                  |
| MYBPC3         | myosin binding protein C                    |
| MYH7           | mutations in myosin heavy chain             |
| µg             | microgram                                   |
| N              | number of participants or observations      |
| NA             | not applicable                              |
| ng             | nanogram                                    |
| nHCM           | non-obstructive hypertrophic cardiomyopathy |
| Non-IMP        | Non-investigational Medicinal Product       |
| NT-proBNP      | N-terminal pro B-type natriuretic peptide   |
| NYHA           | New York Heart Association                  |
| O <sub>2</sub> | oxygen                                      |
| oHCM           | obstructive hypertrophic cardiomyopathy     |
| OLE            | open-label extension                        |
| OSS            | Overall Study Score                         |
| PBO            | placebo                                     |
| PCP            | pulmonary capillary pressure                |
| PD             | pharmacodynamic                             |
| pEOS           | premature end of study                      |
| pEOT           | premature end of treatment                  |
| PGIC           | Patient Global Impression of Change         |

| Term                | Definition                                    |
|---------------------|-----------------------------------------------|
| PGIS                | Patient Global Impression of Severity         |
| PID                 | patient identification number                 |
| PK                  | pharmacokinetic                               |
| PLS                 | physical limitation score                     |
| PRO                 | patient-reported outcomes                     |
| PO                  | per os (by mouth route of administration)     |
| pVO <sub>2</sub>    | peak oxygen consumption                       |
| QD, qd              | quaque die, once daily                        |
| QoL                 | quality of life                               |
| QTc                 | QT interval corrected for heart rate          |
| R&D                 | research and development                      |
| RER                 | respiratory exchange ratio                    |
| RNA                 | ribonucleic acid                              |
| SAE                 | serious adverse event                         |
| SAP                 | statistical analysis plan                     |
| SC                  | steering committee                            |
| SCA                 | sudden cardiac arrest                         |
| SD                  | standard deviation                            |
| SoB                 | shortness of breath                           |
| SRT                 | septal reduction therapy                      |
| SUSAR               | suspected unexpected serious adverse reaction |
| TEAE                | treatment emergent adverse event              |
| TSS                 | Total Symptom Score                           |
| TTE                 | transthoracic echocardiogram                  |
| ULN                 | upper limit of normal                         |
| USA                 | United States of America                      |
| VAS                 | visual analogue scale                         |
| VE/VCO <sub>2</sub> | ventilatory efficiency                        |
| visit×treatment     | interaction between visit and treatment       |
|                     |                                               |

| Term  | Definition                      |
|-------|---------------------------------|
| Wk    | week                            |
| WOCBP | women 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 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 and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.

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

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

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

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

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

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

## **BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS**

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

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

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

## **DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY**

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

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

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAs) 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 that may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol-required assessments, drug accountability records, laboratory notes, clinic and office charts, subject's diaries or evaluation checklists, recorded data from automated instruments, x-ray film and reports, ECG results, memoranda, and pharmacy dispensing records.

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):                                                                                                                      | <p>Records or logs must comply with applicable regulations and guidelines and should include:</p> <ul style="list-style-type: none"> <li>• amount received and placed in storage area</li> <li>• amount currently in storage area</li> <li>• label identification number or batch number</li> <li>• amount dispensed to and returned by each participant, including unique participant identifiers</li> <li>• amount transferred to another area/site for dispensing or storage</li> <li>• nonstudy disposition (eg, lost, wasted)</li> <li>• amount destroyed at study site, if applicable</li> <li>• amount returned to BMS</li> <li>• retain samples for bioavailability/bioequivalence/biocomparability, if applicable</li> <li>• dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form</li> </ul> |
| Sourced by site and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply or a specialty pharmacy) | The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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

## CASE REPORT FORMS

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

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

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

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

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

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

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

## **MONITORING**

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

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

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

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

## **RECORDS RETENTION**

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

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

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

## RETURN OF STUDY TREATMENT

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

| If                                                                                                                                                                      | Then                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study treatments supplied by BMS (including its vendors)                                                                                                                | <p>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).</p> <p>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.</p> <p>If study treatments will be returned, the return will be arranged by the responsible Study Monitor.</p> |
| 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
- Unjustifiable risk and/or toxicity in risk-benefit analysis and therefore a medical and/or ethical reason
- If new scientific evidence becomes available during the study that could affect the participant's safety
- Request of regulatory agency as a consequence of inspection
- Favorable opinion withdrawn by ethics committee
- Withdrawal of the license to manufacture and/or of the permission to import

In all cases, all necessary measures will be taken to guarantee appropriate safety follow-up of all participants already included in the trial. The IRB or IEC and the Regulatory Authorities will be informed in writing about any termination of the trial.



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

## **DISSEMINATION OF CLINICAL STUDY DATA**

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

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

## **CLINICAL STUDY REPORT**

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

## **SCIENTIFIC PUBLICATIONS**

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

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

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, [www.icmje.org](http://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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Adverse Event Definition:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Events <u>Meeting</u> the AE Definition</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <ul style="list-style-type: none"> <li>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.</li> <li>Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.</li> <li>New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.</li> <li>Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li> <li>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.</li> </ul> |
| <b>Events <u>NOT</u> Meeting the AE Definition</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <ul style="list-style-type: none"> <li>Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.</li> <li>Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

## 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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 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:<br>The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: <ul style="list-style-type: none"><li>• A visit to the emergency room or other hospital department &lt; 24 hours that does not result in admission (unless considered an important medical or life-threatening event).</li><li>• Elective surgery, planned prior to signing consent.</li><li>• Admissions as per protocol for a planned medical/surgical procedure.</li><li>• Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy).</li><li>• Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.</li><li>• 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).</li><li>• Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).</li></ul> |
| Results in persistent or significant disability/incapacity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Is a congenital anomaly/birth defect.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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

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

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

## EVALUATING AES AND SAES

### Assessment of Causality

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

- **Assessment of Intensity**

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

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

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

**Follow-up of AEs and SAEs**

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

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

All SAEs must be followed to resolution or stabilization.

## REPORTING OF SAEs TO SPONSOR OR DESIGNEE

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

**SAE Email Address:** [worldwide.safety@BMS.com](mailto:worldwide.safety@BMS.com)

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

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

## **APPENDIX 4      WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION**

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

### **DEFINITIONS**

#### **Woman of Childbearing Potential (WOCBP)**

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

#### **Women in the following categories are not considered WOCBP:**

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

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

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

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

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



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

### End of Relevant Systemic Exposure

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

## METHODS OF CONTRACEPTION

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

| <b>Highly Effective Contraceptive Methods That Are <u>User Dependent</u></b><br><i>Failure rate of &lt; 1% per year when used consistently and correctly.<sup>a</sup></i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• 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.)<sup>b</sup> <ul style="list-style-type: none"> <li>– Oral (birth control pills)</li> <li>– Intravaginal (rings)</li> <li>– Transdermal</li> </ul> </li> <li>• Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.</li> </ul> |
| <ul style="list-style-type: none"> <li>• 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.)<sup>b</sup> <ul style="list-style-type: none"> <li>– Oral</li> <li>– Injectable</li> </ul> </li> <li>• Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.</li> </ul>                                                                                                                                         |
| <b>Highly Effective Methods That Are User Independent</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>• 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.)<sup>b</sup></li> <li>• Intrauterine device.</li> </ul>                                                                                                                                                                                                                                                                              |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• 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.)<sup>b,c</sup></li> <li>• Bilateral tubal occlusion.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <ul style="list-style-type: none"> <li>• Vasectomized partner</li> </ul> <p>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.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <ul style="list-style-type: none"> <li>• Sexual abstinence.</li> </ul> <p><i>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.</i></p> <ul style="list-style-type: none"> <li>• Continuous abstinence must begin at least 30 days prior to initiation of study therapy.</li> <li>• It is not necessary to use any other method of contraception when complete abstinence is elected.</li> <li>• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in <a href="#">Section 2</a>.</li> <li>• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence.</li> <li>• 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.</li> </ul>                                                                                                                                                                                                       |
| <p>NOTES:</p> <p><sup>a</sup> 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.</p> <p><sup>b</sup> 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 <a href="#">Sections 6.1 INCLUSION CRITERIA</a> and <a href="#">7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS</a> of the protocol.</p> <p><sup>c</sup> 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 <a href="#">Sections 6.1 INCLUSION CRITERIA</a> and <a href="#">7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS</a> of the protocol.</p> |

### **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 EFFECTS OF INTERVENTIONS ON PV<sub>O</sub><sub>2</sub>

### Effects of Interventions on pV<sub>O</sub><sub>2</sub>

| Study (year)                                        | Primary endpoint?             | Population                                                                  | Intervention                                                                                                              | Mean pV <sub>O</sub> <sub>2</sub> Change from baseline (mL/kg/min)                                       |
|-----------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| HF-ACTION (2009) <sup>1</sup>                       | No                            | Chronic HFrEF<br>Median EF ~ 25%<br>(N = 1442)                              | Exercise training<br>Usual care                                                                                           | + 0.7 (IQR = -1.0 to 2.5)<br>+ 0.1 (IQR = -1.5 to 1.8)<br>Nominal P < 0.001                              |
| RESET-HCM (2017) <sup>2</sup>                       | Yes                           | HCM mean peak LVOT gradient after exercise<br>57 ± 52 mmHg<br>48 ± 43 mmHg  | Exercise training (n = 67)<br>Usual activity (n = 69)                                                                     | 1.35 (95% CI = 0.50-2.21)<br>0.08 (95% CI = -0.62-0.79)<br>P=0.02                                        |
| EXPLORER-HCM (2020) <sup>3</sup>                    | Composite with NYHA Class     | oHCM mean peak LVOT gradient after exercise<br>86 ± 34 mmHg<br>84 ± 36 mmHg | Mavacamten (n = 120)<br>Placebo (125)                                                                                     | 1.4 ± 3.1<br>-0.05 ± 3.02<br>Nominal P = 0.0006                                                          |
| Septal Reduction Therapy (2002) <sup>4</sup>        | No primary endpoint specified | Symptomatic drug-refractory oHCM                                            | Surgical myectomy (n = 24)<br>Alcohol ablation (n = 20)                                                                   | 5.1 (16.4 ± 5.8 to 21.5 ± 4.5)<br>Nominal P = 0.03<br>2.7 (16.2 ± 5.2 to 18.9 ± 6.1)<br>Nominal P = 0.18 |
| OptimEx-Clin (2021) <sup>5</sup>                    | Yes                           | HFpEF NYHA II-III<br>Diastolic dysfunction                                  | High-intensity interval training (HIT) (n = 53)<br>Moderate continuous training (MCT) (54)<br>Guideline control (GC) (52) | 1.1(3.0)<br>1.6 (2.5)<br>-0.6 (3.3)<br>P = 0.002 HIT and MCT vs GC                                       |
| MUSTIC Multisite RV + LV pacing (2002) <sup>6</sup> | No                            | Heart failure NYHA III (N = 38)                                             | Pacing<br>No pacing<br>Difference                                                                                         | 16.2 ± 4.7<br>15 ± 4.9<br>1.2<br>Nominal P = 0.08                                                        |

## Effects of Interventions on pVO<sub>2</sub>

| Study (year)                                    | Primary endpoint?                                         | Population                                                                                   | Intervention                                                                                                                                                                                               | Mean pVO <sub>2</sub> Change from baseline (mL/kg/min)                                                                                                               |
|-------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MUSTIC RV vs RV + LV pacing (2002) <sup>7</sup> | No primary endpoint specified                             | Heart failure NYHA III + Chronic Atrial Fibrillation with slow ventricular response (N = 32) | RV pacing<br>RV + LV pacing<br>Difference                                                                                                                                                                  | 13.4 ± 4.0<br>14.8 ± 4.1<br>1.4                                                                                                                                      |
| MIRACLE CRT (2003) <sup>8</sup>                 | No                                                        | Heart failure NYHA III or IV QRS interval ≥ 180 msec                                         | Control (145)<br>CRT (158)                                                                                                                                                                                 | 0.2 (95% CI -0.2 to + 0.8)<br>1.1 (95% CI -0.6 to + 1.7)<br>Nominal P < 0.009                                                                                        |
| PATH-CHF (2002) <sup>9</sup>                    | Composite with anaerobic threshold and 6-minute walk test | Heart failure NYHA III or IV (N = 29)                                                        | Baseline<br>Pacing for 12 months<br>Difference                                                                                                                                                             | 12.6 ± 0.6<br>15.3 ± 0.9<br>2.7<br>P < 0.001                                                                                                                         |
| CRT-HF (2003) <sup>10</sup>                     | No                                                        | Heart failure NYHA I-IV IVCD, VT/VF                                                          | All participants<br>CRT (n = 216)<br>No CRT (n = 201)<br>Difference<br><br>NYHA III and IV<br>CRT (n = 96)<br>No CRT (n = 80)<br>Difference<br><br>NYHA I or II<br>CRT (120)<br>No CRT (121)<br>Difference | 0.8 ± 0.3<br>0.0 ± 0.3<br>0.8<br>Nominal P = 0.03<br><br>1.8 ± 0.4<br>0.0 ± 0.4<br>1.8<br>Nominal P = 0.003<br><br>0.2 ± 0.3<br>0.0 ± 0.3<br>0.2<br>Nominal P = 0.77 |

Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; EF, ejection fraction; GC, guideline control; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFREF, heart failure with reduced ejection fraction; HIT, high-intensity interval training; HR, heart rate; Ht, height; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT, left ventricular outflow tract; MCT, moderate continuous training NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy.

- <sup>1</sup> O'Connor CM; Whellan DJ; Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure HF-ACTION randomized controlled trial. (Reprinted) JAMA. 2009;301(14):1439-50.
- <sup>2</sup> Saberi S; Wheeler, M; Bragg-Gresham J, et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy. JAMA. 2017;317(13):1349-1357. doi:10.1001/jama.2017.2503.

- <sup>3</sup> Olivotto I; Oreziak A; Barriales-Villa R; et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020; (396): 759–69.
- <sup>4</sup> Firoozi S, Elliott, PM, Sharma S, et al. Septal myotomy–myectomy and transcatheter septal alcohol ablation in hypertrophic obstructive cardiomyopathy. *EUHJ*. 2002;23:1617-24.
- <sup>5</sup> Mueller S; Winzer EB; Duvinage A; et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction a randomized clinical trial. *JAMA*. 2021;325(6):542-551.
- <sup>6</sup> Leclercq C; Walker S; Linde C; et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *EUHJ*. 2002;23:1780-87. doi:10.1053/euhj.2002.3232.
- <sup>7</sup> Cazeu S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344(12).
- <sup>8</sup> Abraham WT; Fisher WG; Smith AL; et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*, 2002;346,(24):1845-53).
- <sup>9</sup> Auricchio A; Stellbrink C; Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *JACC*. 2002;39(12):2026-33.
- <sup>10</sup> Higgins SL; Hummel JD; Niazi IK; et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *JACC*. 2003;42(8):1454–9. doi:10.1016/S0735-1097(03)01042-8.

## APPENDIX 6 COUNTRY-SPECIFIC REQUIREMENTS/DIFFERENCES

| Country/Location Requirement | Original Language                                                                   | Country-specific Language or Differences                                                                                                                                                                                                                              |
|------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Czech Republic               | No additional contraceptive measures are required to be used for male participants. | During heterosexual intercourse with a woman who can become pregnant, heterosexually active men on treatment with study intervention should use a condom during the period of treatment and for at least [REDACTED] after taking the last dose of study intervention. |
| Norway                       | [REDACTED]                                                                          |                                                                                                                                                                                                                                                                       |

## APPENDIX 7      PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

### Overall Rationale for Protocol Amendment 02, 02-Aug-2023

The 3 key changes in this amendment are: 1) removal of the extended double-blind treatment period, 2) addition of a long-term extension (LTE) period, and 3) [REDACTED] the Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) clinical summary score (CSS) threshold at screening from [REDACTED]

[REDACTED]

Based on experience in the trial so far, a KCCQ-23 CSS score of [REDACTED] excluded several patients who the Investigator was confident were sufficiently symptomatic clinically, based on New York Heart Association (NYHA) Functional Classification. This observation suggested that the KCCQ-23 CSS score of [REDACTED] was excluding patients who were symptomatic based on expert clinical assessment. Therefore, the KCCQ-23 CSS score threshold for inclusion was [REDACTED] to [REDACTED] to be more consistent with the clinical non-obstructive hypertrophic cardiomyopathy (nHCM) population but still allows room for improvement.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

This protocol amendment applies to all participants.

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02                                      |                                                           |                 |
|---------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------|
| Section Number & Title                                                                | Description of Change                                     | Brief Rationale |
| Table 2-1: Screening Procedural Outline (CV027031)<br>Section 6.1: Inclusion Criteria | [REDACTED]                                                |                 |
| Table 2-1: Screening Procedural Outline (CV027031)                                    | Updated note for Post-exercise Stress Echocardiogram row. | Clarification.  |
| Table 2-2: Schedule of Activities [REDACTED]<br>[REDACTED]<br>(CV027031)              | [REDACTED]                                                |                 |



| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02                                                       |                       |                 |
|--------------------------------------------------------------------------------------------------------|-----------------------|-----------------|
| Section Number & Title                                                                                 | Description of Change | Brief Rationale |
| Table 2-2: Schedule of Activities [REDACTED]<br>[REDACTED]<br>(CV027031)                               | [REDACTED]            | [REDACTED]      |
| Table 2-3: Schedule of Activities [REDACTED]<br>[REDACTED] (CV027031)                                  |                       |                 |
| Table 2-4: Schedule of Activities [REDACTED]<br>[REDACTED] (CV027031)                                  |                       |                 |
| Table 2.1-1: Definitions of Participant Study Visits                                                   |                       |                 |
| Section 4.1: Sub-studies<br>[REDACTED]                                                                 |                       |                 |
| Section 5.1.2: Placebo-controlled Double-blind Treatment Period [REDACTED]<br>[REDACTED]<br>[REDACTED] |                       |                 |
| [REDACTED]                                                                                             |                       |                 |
| [REDACTED]                                                                                             |                       |                 |
| [REDACTED]                                                                                             |                       |                 |
| [REDACTED]                                                                                             |                       |                 |
| [REDACTED]                                                                                             |                       |                 |
| Section 7.8: Continued Access to Study Intervention After the End of the Study<br>[REDACTED]           |                       |                 |
| Section 9.1.2.1: Transthoracic Echocardiography                                                        |                       |                 |
| Section 9.1.2.2: Cardiac Magnetic Resonance Imaging                                                    |                       |                 |
| Section 9.2.3: Follow-up of AEs and SAEs                                                               |                       |                 |
| Section 9.2.5: Pregnancy                                                                               |                       |                 |
| Section 9.5: Pharmacokinetics                                                                          |                       |                 |
| Table 9.5-1: Pharmacokinetic Sampling Schedule                                                         |                       |                 |
| Table 9.8-1: Biomarker Sampling Schedule                                                               |                       |                 |
| Section 10.4: Statistical Analyses                                                                     |                       |                 |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                  |                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Section Number & Title                                                                                                                                                                                                                                                                                                                                                                  | Description of Change                                                                                                            | Brief Rationale                                                                                          |
| Section 10.4.2: Primary Endpoint(s)<br>Section 10.4.3: Secondary Endpoint(s)<br>Section 10.4.6: Other Safety Analyses<br>Section 10.4.7: Other Analyses<br>Table 2-3: Schedule of Activities<br>(CV027031)<br>Section 4.1: Sub-studies<br>Section 9.1.2.2: Cardiac Magnetic Resonance Imaging<br>Table 3.3.1-1: Risk Assessment<br>Section 8.1: Discontinuation From Study Intervention |                                                                                                                                  |                                                                                                          |
| Table 3.3.1-1: Risk Assessment                                                                                                                                                                                                                                                                                                                                                          | Updated language regarding cytochrome P450 (CYP) inhibitors.                                                                     | Updated to align with the most recent Investigator's Brochure.                                           |
| Section 3.3.3: Overall Benefit/Risk Conclusion                                                                                                                                                                                                                                                                                                                                          | Added statement that the favorable benefit/risk will be maintained for the approximately 5-year duration of the study.           | To update the extension of expected favorable benefit/risk for the longer duration of the amended study. |
| Table 4-1: Objectives and Endpoints                                                                                                                                                                                                                                                                                                                                                     | Moved the exposure-response modeling objective and endpoint to pharmacokinetic (PK)/pharmacodynamic (PD) exploratory objectives. | PK-PD modeling is exploratory and will be reported separately from the clinical study report.            |
| Section 4.1: Sub-studies                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                  |                                                                                                          |
| Section 5.1.1: Screening                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                  |                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                  |                                                                                                          |
| Section 5.5.1: Justification for Placebo                                                                                                                                                                                                                                                                                                                                                | Updated language regarding the use of a placebo.                                                                                 | Clarification.                                                                                           |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02       |                                                                                                                                                              |                                               |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Section Number & Title                                 | Description of Change                                                                                                                                        | Brief Rationale                               |
| Section 6.1: Inclusion Criteria                        | <div></div> <p>Added that participants must be “at least” 18 years old or local age of majority at the time of signing the informed consent.</p> <div></div> | <div></div> <p>Clarification.</p> <div></div> |
|                                                        | <p>Updated criteria 4) a) iv) and v) regarding methods of contraception.</p>                                                                                 | <p>Clarification.</p>                         |
| Section 6.2: Exclusion Criteria                        |                                                                                                                                                              |                                               |
|                                                        |                                                                                                                                                              |                                               |
| Section 7.7.1: Prohibited and/or Restricted Treatments |                                                                                                                                                              |                                               |
| Section 8.1: Discontinuation From Study Intervention   |                                                                                                                                                              |                                               |
|                                                        |                                                                                                                                                              |                                               |
| Section 9.1.2.1: Transthoracic Echocardiography        |                                                                                                                                                              |                                               |
| Section 9.4.1: Physical Examinations                   |                                                                                                                                                              |                                               |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02                   |                                                                                                                                                                                                                                 |                                                                                                                 |
|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Section Number & Title                                             | Description of Change                                                                                                                                                                                                           | Brief Rationale                                                                                                 |
| Table 9.5-1: Pharmacokinetic Sampling Schedule                     |                                                                                                                                                                                                                                 |                                                                                                                 |
| Section 10.4.1: General Considerations                             | Added language regarding unblinding, database lock, and data collected after the last participant completes the Week 48 visit.                                                                                                  | To specify that the data (data cut-off) will be used for the primary analysis.                                  |
| Section 10.4.3: Secondary Endpoint(s)                              | Added language regarding the point estimate of treatment effect.                                                                                                                                                                | To clarify the estimate will be provided for the treatment effect.                                              |
| Section 10.4.3: Secondary Endpoint(s)<br>Table 10.4.3-1: Estimands | Updated language regarding analysis of the binary endpoints and added that Breslow-day test will be used for homogeneity.<br><br>Updated language regarding analysis of time to first major adverse cardiovascular events-plus. | To allow estimation of marginal odds ratio.<br><br>To clarify that the model will be a stratified model.        |
| Section 10.4.5: Pharmacokinetic/Pharmacodynamic Analyses           | Updated PK population to PK analysis set.                                                                                                                                                                                       | Clarification.                                                                                                  |
| Throughout                                                         | Minor formatting, typographical corrections, and edits.                                                                                                                                                                         | Corrections for clarity and consistency within the document were minor, and therefore have not been summarized. |

### Overall Rationale for Protocol Amendment 01, 10-Apr-2023

The rationale for Protocol Amendment 01 is to accommodate revisions [REDACTED] and to clarify sections of the protocol based on input from investigators, the clinical research organization, and the executive committee. The table below provides a summary of key changes in the amendment.

Other secondary endpoints that were not key secondary and were not multiplicity controlled were moved to exploratory endpoints to reduce the number of secondary endpoints.

Exclusion criteria for atrial fibrillation, previous septal reduction therapy, and left ventricular apical aneurysm were clarified.

[REDACTED]

[REDACTED] Section 5.1.1 was revised to clarify that background therapy is permitted throughout the duration of the double-blind treatment period, [REDACTED]

was added to describe the [REDACTED] after the last dose of study intervention, and Section 5.5.1 was added to justify the use of the placebo arm.

The number of applications of wearable electrocardiogram (ECG) monitors in the substudy was [REDACTED] and the limit on the number of participants [REDACTED] was removed to allow collection of data on arrhythmias from a broader population.

The frequency for the measurements of patient-reported outcomes, clinical laboratory, pharmacokinetics (PK), and biomarkers were decreased to further reduce participant and site burden.

The protocol revisions are not expected to significantly impact benefit/risk of the trial participants or impact the integrity of the study.

Updates to the Protocol Summary have also been made to reflect the changes listed below.

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                                      |                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section Number & Title                                                                                | Description of Change                                                                                                                                                                                                                                                                                                                 | Brief Rationale                                                                                                                                                                                                                                                                                                             |
| Table 2-1: Screening Procedural Outline (CV027031)<br>Table 9.4.4-1: Clinical Laboratory Assessments  |                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                             |
| Table 2-1: Screening Procedural Outline (CV027031)                                                    | <ul style="list-style-type: none"> <li>Updated language on where to send N-terminal pro B-type natriuretic peptide (NT-proBNP)/BNP and cardiac troponin samples.</li> <li>Updated Pregnancy Test (Women of Childbearing Potential [WOCBP] only) note.</li> <li>Updated Monitor for Serious Adverse Events (SAEs) footnote.</li> </ul> | <ul style="list-style-type: none"> <li>To ensure NT-proBNP/BNP and cardiac troponin analysis and to clarify guidance for who completes these assessments.</li> <li>Updated to clarify requirements for pregnancy testing.</li> <li>Updated to align with new end of study (EOS)/end of treatment (EOT) language.</li> </ul> |
| Table 2-1: Screening Procedural Outline (CV027031)<br>Section 9.1.2.1: Transthoracic Echocardiography | <ul style="list-style-type: none"> <li>Added Valsalva Transthoracic Echocardiogram (TTE).</li> </ul>                                                                                                                                                                                                                                  | Both Valsalva and post-exercise stress TTE required at screening.                                                                                                                                                                                                                                                           |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                           |                                                                                             |                                                                                                                                 |
|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Section Number & Title                                                                     | Description of Change                                                                       | Brief Rationale                                                                                                                 |
| Table 2-1: Screening Procedural Outline (CV027031)<br>Section 9.4.1: Physical Examinations | <ul style="list-style-type: none"> <li>Updated physical examination description.</li> </ul> | To provide clarification to sites on the differences between physical examination and targeted cardiovascular (CV) examination. |
| Table 2-2: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          | [REDACTED]                                                                                  | [REDACTED]                                                                                                                      |
| Table 2-3: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          |                                                                                             |                                                                                                                                 |
| Table 2-2: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          |                                                                                             |                                                                                                                                 |
| Table 2-2: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          |                                                                                             |                                                                                                                                 |
| Table 2-3: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          |                                                                                             |                                                                                                                                 |
| Table 2-4: Double-blind Treatment [REDACTED]<br>(CV027031)                                 |                                                                                             |                                                                                                                                 |
| Table 2-2: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          |                                                                                             |                                                                                                                                 |
| Table 2-3: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          |                                                                                             |                                                                                                                                 |
| Table 2-4: Double-blind Treatment [REDACTED]<br>(CV027031)                                 |                                                                                             |                                                                                                                                 |
| Table 2-2: Double-blind Treatment Period [REDACTED]<br>(CV027031)                          |                                                                                             |                                                                                                                                 |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                                                                                                                                                                                                                          |                       |                 |
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| Section Number & Title                                                                                                                                                                                                                                                                    | Description of Change | Brief Rationale |
| <p>(CV027031)</p> <p>Table 2-3: Double-blind Treatment Period</p> <p>(CV027031)</p> <p>Table 2-4: Double-blind Treatment</p> <p>(CV027031)</p> <p>Section 4.1: Sub-studies</p>                                                                                                            |                       |                 |
| <p>Table 2-2: Double-blind Treatment Period</p> <p>(CV027031)</p> <p>Table 2-3: Double-blind Treatment Period</p> <p>(CV027031)</p> <p>Table 2-4: Double-blind Treatment</p> <p>(CV027031)</p> <p>Section 9.10: Health Economics OR Medical Resource Utilization and Health Economics</p> |                       |                 |
| <p>Table 2-2: Double-blind Treatment Period</p> <p>(CV027031)</p> <p>Table 2-3: Double-blind Treatment Period</p> <p>(CV027031)</p> <p>Table 2-4: Double-blind Treatment</p> <p>(CV027031)</p> <p>Section 9.2.5: Pregnancy</p>                                                            |                       |                 |
| <p>Table 2-3: Double-blind Treatment Period</p> <p>(CV027031)</p>                                                                                                                                                                                                                         |                       |                 |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |                 |
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| Section Number & Title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Description of Change | Brief Rationale |
| Table 4-1: Objectives and Endpoints<br>Section 4.1: Sub-studies<br>Section 5.1.2: Double-blind Treatment<br>[REDACTED]<br>Section 5.4: Scientific Rationale for Study Design<br>Section 9.1.1: Efficacy Assessment for the Study<br>[REDACTED]<br>Section 9.1.2.1: Transthoracic Echocardiography<br>Section 9.1.2.2: Cardiac Magnetic Resonance Imaging<br>Section 9.2.3: Follow-up of AEs and SAEs<br>Table 9.5-1: Pharmacokinetic Sampling Schedule<br>Table 9.8-1: Biomarker Sampling Schedule<br>Section 10.1: Statistical Hypotheses<br>Section 10.2: Sample Size Determination<br>Section 10.4.2: Primary Endpoint(s)<br>Section 10.4.2.2: Supportive Analysis<br>Section 10.4.3-1: Estimands | [REDACTED]            | [REDACTED]      |
| Table 2-2: Double-blind Treatment Period<br>[REDACTED]<br>(CV027031)<br>Section 9.1.2.2: Cardiac Magnetic Resonance Imaging                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                       |                 |
| Table 2-3: Double-blind Treatment Period<br>[REDACTED]<br>(CV027031)<br>Section 9.1.2.1: Transthoracic Echocardiography                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                       |                 |
| Table 2-3: Double-blind Treatment Period<br>[REDACTED]<br>(CV027031)<br>Section 2.1: Definition of Visits                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                 |



| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                                                                                |                                                                                                                                                               |                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Section Number & Title                                                                                                                          | Description of Change                                                                                                                                         | Brief Rationale                                                                                             |
| Table 2-4: Double-blind Treatment<br>(CV027031)<br>Section 5.1.2: Double-blind Treatment<br>Table 9.8-1: Biomarker Sampling Schedule            |                                                                                                                                                               |                                                                                                             |
| Table 2-4: Double-blind Treatment<br>(CV027031)                                                                                                 |                                                                                                                                                               |                                                                                                             |
| Section 3.1: Study Rationale                                                                                                                    | Updated Joint Committee on Clinical Practice Guidelines to the European Society of Cardiology.                                                                | These guidelines were not included in the original protocol.                                                |
| Section 3.2: Background                                                                                                                         |                                                                                                                                                               |                                                                                                             |
| Table 3.3.1-1: Risk Assessment<br>Section 8.1: Discontinuation From Study Intervention                                                          |                                                                                                                                                               |                                                                                                             |
| Table 3.3.1-1: Risk Assessment<br>Section 6.2: Exclusion Criteria<br>Section 7.7.1: Prohibited and/or Restricted Treatments                     |                                                                                                                                                               |                                                                                                             |
| Table 4-1: Objectives and Endpoints<br>Section 9.1.3.2: Hypertrophic Cardiomyopathy Symptom Questionnaire<br>Section 10.4: Statistical Analyses | <ul style="list-style-type: none"> <li>Renamed key secondary and other secondary objectives to secondary and exploratory categories, respectively.</li> </ul> | To provide clarity and classify efficacy endpoints into 3 categories - primary, secondary, and exploratory. |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                |
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| Section Number & Title                                                           | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                              | Brief Rationale                                                                                                                                                                                |
| Section 10.4.3: Secondary Endpoint(s)<br>Section 10.4.4: Exploratory Endpoint(s) |                                                                                                                                                                                                                                                                                                                                                                                                                                                    | In addition, a section has been added with PK endpoints and other exploratory PK analysis which will be provided in a standalone report.                                                       |
| Table 4-1: Objectives and Endpoints                                              | <ul style="list-style-type: none"> <li>Updated exercise capacity to ventilatory efficiency and exercise intensity to exercise capacity.</li> <li>Updated “first major adverse cardiovascular events (MACE)-plus events” to “time to first MACE-plus events.”</li> <li>Updated Borg Perceived Exertion Scale endpoint from “measured by CPET to Week 48” to “rating at matched work rates during exercise between Baseline and Week 48.”</li> </ul> | <ul style="list-style-type: none"> <li>To clarify CPET endpoints.</li> <li>To clarify the endpoint is “Time to first MACE-plus.”</li> <li>To define the Borg Scale more accurately.</li> </ul> |
|                                                                                  | <ul style="list-style-type: none"> <li>Removed “adverse events (AEs) leading to study discontinuation” from Safety endpoint.</li> </ul>                                                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>These AEs will be captured through AE leading to study intervention discontinuation.</li> </ul>                                                         |
| Table 4-1: Objectives and Endpoints<br>Table 10.4.3-1: Estimands                 | <ul style="list-style-type: none"> <li>Moved composite NYHA and peak oxygen consumption (pVO<sub>2</sub>) objective and respective endpoint from secondary to exploratory.</li> </ul>                                                                                                                                                                                                                                                              | This endpoint was reclassified to exploratory based on advice from the Executive committee.                                                                                                    |
| Table 4-1: Objectives and Endpoints<br>[REDACTED]                                | [REDACTED]                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                |
| Section 4.1: Sub-studies                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                |
| Section 5.1.1: Screening [REDACTED]<br>[REDACTED]                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01 |                                                                  |                                                                                                                                                                                                                                  |
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| Section Number & Title                           | Description of Change                                            | Brief Rationale                                                                                                                                                                                                                  |
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| Section 5.2: Number of Participants              |                                                                  |                                                                                                                                                                                                                                  |
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|                                                  |                                                                  |                                                                                                                                                                                                                                  |
| Section 5.5.1: Justification for Placebo         | <ul style="list-style-type: none"> <li>Added section.</li> </ul> | To explain that use of placebo allows an objective assessment of benefit-risk of treatment of nHCM with mavacamten and to clarify that those in the placebo arm do not forgo background therapy recommended for this population. |
| Section 6.2: Exclusion Criteria                  |                                                                  |                                                                                                                                                                                                                                  |
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| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                              |                                                                                                                                          |                                                                                                                       |
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| Section Number & Title                                                                        | Description of Change                                                                                                                    | Brief Rationale                                                                                                       |
|                                                                                               |                                                                                                                                          |                                                                                                                       |
| Section 6.3.1: Meals and Dietary Restrictions<br>Section 6.3.2: Caffeine, Alcohol and Tobacco |                                                                                                                                          |                                                                                                                       |
| Section 7.2: Method of Study Intervention Assignment                                          | <ul style="list-style-type: none"> <li>Removed language regarding restarting of sequential numbering.</li> </ul>                         | To clarify that the Interactive Response Technology (IRT) has already assigned sequential number independent of site. |
|                                                                                               |                                                                                                                                          |                                                                                                                       |
| Section 7.7.1: Prohibited and/or Restricted Treatments                                        |                                                                                                                                          |                                                                                                                       |
| Section 8.2: Discontinuation From the Study                                                   | <ul style="list-style-type: none"> <li>Removed language regarding participants who request to discontinue study intervention.</li> </ul> | To align with current standards regarding discontinuation.                                                            |
| Section 9.1: Efficacy Assessments                                                             |                                                                                                                                          |                                                                                                                       |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                           |                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                     |
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| Section Number & Title                                                     | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                   | Brief Rationale                                                                                                                     |
| Section 9.1.1.2 Kansas City Cardiomyopathy Questionnaire (23-item Version) | <ul style="list-style-type: none"> <li>Updated the description of the Kansas City Cardiomyopathy Questionnaire 23-item Version (KCCQ).</li> </ul>                                                                                                                                                                                                                                                                       | Updated the total number of the individual domains and the summary scores.                                                          |
| Section 9.1.4: Other Efficacy Assessments for the Study                    | <ul style="list-style-type: none"> <li>Added troponin I.</li> </ul>                                                                                                                                                                                                                                                                                                                                                     | Initially omitted unintentionally.                                                                                                  |
| Section 9.2: Adverse Events                                                | <ul style="list-style-type: none"> <li>Added language regarding treatment-emergent adverse events.</li> </ul>                                                                                                                                                                                                                                                                                                           | To clarify the treatment-emergent period.                                                                                           |
| Section 9.2.3: Follow-up of AEs and SAEs                                   |                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                     |
| Section 9.2.5: Pregnancy                                                   | <ul style="list-style-type: none"> <li>Added that if any urine beta human chorionic gonadotropin (<math>\beta</math>-hCG) pregnancy test result is positive or ambiguous, the investigator will instruct the participant to suspend further study intervention and schedule a follow-up appointment as soon as possible, where a confirmatory serum <math>\beta</math>-hCG pregnancy test will be performed.</li> </ul> | For further instruction/clarification to site teams and to reiterate what was noted in the footnotes of the Schedule of Activities. |
| Table 9.4.4-1: Clinical Laboratory Assessments                             | <ul style="list-style-type: none"> <li>Removed NT-proBNP and troponin.</li> </ul>                                                                                                                                                                                                                                                                                                                                       | These are not part of the Clinical Safety Laboratory Assessments.                                                                   |
| Section 9.5: Pharmacokinetics                                              |                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                     |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01                                 |                                                                                                                             |                                                                                                                                               |
|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Section Number & Title                                                           | Description of Change                                                                                                       | Brief Rationale                                                                                                                               |
| Table 9.5-1: Pharmacokinetic Sampling Schedule                                   |                                                                                                                             |                                                                                                                                               |
| Section 9.8: Biomarkers                                                          | <ul style="list-style-type: none"> <li>Updated exploratory biomarker language.</li> </ul>                                   | To simplify biomarker wording according to recent data from prior mavacamten studies.                                                         |
| Section 9.8: Biomarkers<br>Table 9.8-1: Biomarker Sampling Schedule              |                                                                                                                             |                                                                                                                                               |
| Table 9.8-1: Biomarker Sampling Schedule                                         | <ul style="list-style-type: none"> <li>Added predose to each collection.</li> </ul>                                         | <ul style="list-style-type: none"> <li>To clarify the timepoint for sample collection on each day and to align with PK timepoints.</li> </ul> |
|                                                                                  |                                                                                                                             |                                                                                                                                               |
| Section 9.11: Exposure-response Analysis                                         | <ul style="list-style-type: none"> <li>Removed section.</li> </ul>                                                          | Added new Section 10.4.5 to describe the PK and PK/PD analyses.                                                                               |
| Section 10.2: Sample Size Determination<br>Section 10.4.3: Secondary Endpoint(s) | <ul style="list-style-type: none"> <li>Updated language regarding sample size, multiplicity, power, and control.</li> </ul> | To clarify the language.                                                                                                                      |
| Section 10.2: Sample Size Determination<br>Section 10.4.2.3: Subgroup Analysis   |                                                                                                                             |                                                                                                                                               |
| Section 10.4.2: Primary Endpoint(s)<br>Table 10.4.3-1: Estimands                 | <ul style="list-style-type: none"> <li>Updated instructions for missing data.</li> </ul>                                    | The details of missing data imputation will be provided in the study statistical analysis plan (SAP).                                         |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01         |                                                                                                                                            |                                                                                                                                                                                       |
|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section Number & Title                                   | Description of Change                                                                                                                      | Brief Rationale                                                                                                                                                                       |
|                                                          |                                                                                                                                            |                                                                                                                                                                                       |
| Section 10.4.4: Exploratory Endpoint(s)                  | <ul style="list-style-type: none"> <li>Added statement regarding multiplicity adjustments for exploratory endpoints.</li> </ul>            | <ul style="list-style-type: none"> <li>To clarify that no multiplicity adjustments will be made for exploratory endpoints or subgroup analyses.</li> </ul>                            |
|                                                          |                                                                                                                                            |                                                                                                                                                                                       |
| Section 10.4.5: Pharmacokinetic/Pharmacodynamic Analyses | <ul style="list-style-type: none"> <li>Added section.</li> </ul>                                                                           | Added to describe the PK and PK/PD analyses.                                                                                                                                          |
| Appendix 2: Study Governance Considerations              | <ul style="list-style-type: none"> <li>Added more reasons for the early closure of a study site by the Sponsor or investigator.</li> </ul> | To provide examples for early closure of study site for clarity.                                                                                                                      |
| Appendix 6: Country Specific Requirements/Differences    | <ul style="list-style-type: none"> <li>Added new appendix.</li> </ul>                                                                      | To capture contraceptive differences specific to the Czech Republic.                                                                                                                  |
| Throughout the protocol.                                 | <ul style="list-style-type: none"> <li>Updated EOS/EOT definitions and language.</li> </ul>                                                | <ul style="list-style-type: none"> <li>To provide and/or clarify instructions to sites on how to separately conduct the EOT visit and the EOS visit, especially for WOCBP.</li> </ul> |
|                                                          | <ul style="list-style-type: none"> <li>Minor editorial and format changes that do not affect content.</li> </ul>                           | <ul style="list-style-type: none"> <li>Clarification.</li> </ul>                                                                                                                      |