Statistical Analysis Plan: CY 6032

Title: A Phase 3, Multi-center, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

NCT05767346

Approval Date: 20 Mar 2025

# STATISTICAL ANALYSIS PLAN

**VERSION NUMBER: 3.0 FINAL**

**VERSION DATE: 20 March 2025**

## STUDY DRUG:

CK-3773274 (aficamten)

## PROTOCOL NUMBER:

CY 6032

## STUDY TITLE:

A Phase 3, Multi-Center, Randomized, Double-blind, Trial to Evaluate the Efficacy and Safety of Aficamten compared to in Metoprolol in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

## BASED ON:

Protocol Amendment v3.0 dated 14 March 2024

## SPONSOR:

Cytokinetics, Incorporated

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650-624-3000

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

# SIGNATURE PAGE

This plan has been prepared and/or reviewed by*:

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# TECHNICAL SUMMARY REPORT (TSR)

| | | |
|---|---|---|
| **Name of Sponsor/Company**<br>Cytokinetics, Inc. | **Individual Study Table Referring to Part of the Dossier:**<br>**Volume:** | ***(For National Authority Use Only)*:** |
| **Name of Finished Product:**<br>No generic or trade name assigned | **Page:** | |
| **Name of Active Ingredient:**<br>Aficamten (CK-3773274) | | |

**Title of Study:** A Phase 3, Multi-Center, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

**Investigators**:
Study Center(s): Participants will be enrolled from approximately 60 sites worldwide.

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|---|---|
| **Studied period (years):** 2023 to 2025 | **Phase of development:** Phase 3 |

**Objectives and Endpoints:**

| **Objectives** | **Endpoints:** |
|---|---|
| **Primary** | |
| To evaluate the effect of aficamten compared to metoprolol on exercise capacity in participants with obstructive hypertrophic cardiomyopathy (oHCM). | Change in peak oxygen uptake (pVO2) by cardiopulmonary exercise testing (CPET) from baseline to Week 24. |
| Secondary | |
| To evaluate the effect of aficamten compared to metoprolol on New York Heart Association (NYHA) Functional Classification | Proportion of participants with ≥1 class improvement in NYHA Functional Class from baseline to Week 24 |
| To evaluate the effect of aficamten compared to metoprolol on patient health status | Change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) from baseline to Week 24 |
| To evaluate the effect of aficamten compared to metoprolol on structural remodeling | Change in LVMI from baseline to Week 24<br>Change in LAVI from baseline to Week 24 |

| | |
|---|---|
| To evaluate the effect of aficamten compared to metoprolol on NT-proBNP | Change from baseline values in n-terminal prohormone brain natriuretic peptide (NT-proBNP) to Week 24 |
| To evaluate the effect of aficamten compared to metoprolol on post-Valsalva left ventricular outflow tract gradients (LVOT-G) | Change in post-Valsalva LVOT-G from baseline to Week 24 |

**Methodology:**
This is a Phase 3 randomized, double-blind, multi-center trial in participants with symptomatic oHCM. Approximately 170 eligible participants will be randomized in a 1:1 ratio to receive aficamten or metoprolol. Doses of 5, 10, 15, or 20 mg and metoprolol matching placebo or 50, 100, 150 or 200 mg metoprolol and aficamten matching placebo will be administered in an escalating manner using echocardiography and vital signs to guide dose titration.
Randomization will be stratified by cardiopulmonary exercise testing (CPET)exercise modality (treadmill/bicycle), and recently diagnosed vs chronic oHCM. The number of participants using the bicycle CPET exercise modality will be capped at approximately 50%.
All participants on Standard of Care (SOC) therapy will undergo a washout period consisting of up to 14 days of weaning from SOC therapy, followed by an additional 7 days completely off SOC therapy prior to undergoing Screening Visit 2 assessments.
The screening period will begin at the time of informed consent and will include both the pre-(Screening Visit 1) and post-washout (Screening Visit 2) period clinical assessments.
Those not currently on medical therapy for oHCM do not require a washout period and will only participate in Screening Visit 2. The double-blind treatment period will last 24 weeks.
Following the final dose of the investigational product (IP) there will be a 4-week safety follow-up period.
Participants receiving aficamten, dose escalation at the Weeks 2, 4, and 6 visits will occur only if a patient has a post-Valsalva LVOT-G ≥30 mmHg and a biplane LVEF ≥55%.
Participants receiving metoprolol, dose escalation at the Weeks 2, 4, and 6 visits will occur only if a patient has a post-Valsalva LVOT-G ≥30 mmHg, a biplane LVEF ≥55%, SBP ≥90 mmHg and Heart rate ≥55 bpm. An echocardiogram and vital signs will be performed at each subsequent visit during the trial and the dose down titrated if necessary.
The primary endpoint of pVO2 will be measured by CPET at screening and at end of treatment (Week 24).
**Number of Participants (planned and analyzed):** Approximately 170 participants will be randomized to aficamten or metoprolol at 1:1 ratio.

**Diagnosis and main criteria for inclusion:**
The key inclusion criteria are below. A full listing of eligibility criteria can be found in protocol Section 5.

- Males and females between 18 and 85 years of age, inclusive, at signing of informed consent.
- Body mass index <35 kg/m2.
- Diagnosed with oHCM per the following criteria by echocardiography or cardiac magnetic resonance imaging (CMR):

− Has LV hypertrophy and non-dilated LV chamber in the absence of other cardiac disease and

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|---|
| − Has an end-diastolic LV wall thickness as measured by the echocardiography core laboratory of:<br>• ≥15 mm in one or more myocardial segments<br>OR<br>• ≥13 mm in one or more wall segments and a known-disease-causing gene mutation or positive family history of HCM<br>• Has resting LVOT-G ≥30 mmHg and/or post-Valsalva LVOT G ≥50 mmHg during screening as determined by the echocardiography core laboratory.<br>• NYHA Functional Class II or III at screening visit 2.<br>• KCCQ clinical summary score ≤90 at Screening Visit 2<br>• LVEF ≥60% at screening as determined by the echocardiography core laboratory.<br>• Respiratory exchange ratio (RER) ≥1.05 and pVO2 <100% predicted on the screening CPET per the core laboratory.<br>• Hemoglobin ≥10 g/dL at screening. |
| **Test product, dose, and mode of administration:**<br>Aficamten will be administered orally once daily with or without food. Participants receiving aficamten start at a dose of 5 mg once daily and may escalate through doses of 10, 15, and 20 mg once daily during the initial six weeks of treatment if they continue to meet the escalation criteria or will stop at their current dose when escalation criteria are not met. |
| **Duration of treatment:**<br>After signing the informed consent form, participants will complete assessments to determine trial eligibility during a screening period of up to 6 weeks in duration. The double-blind treatment period will last 24 weeks. Following the final dose of IP there will be a 4-week safety follow-up period. |
| **Reference therapy, dose, and mode of administration:**<br>The reference therapy metoprolol will be administered orally once daily with or without food. Participants receiving metoprolol will start at a dose of 50 mg and may escalate to doses of 100, 150, and 200 mg once daily during the initial six weeks of treatment if they continue to meet the escalation criteria or will stop at their current dose when escalation criteria are not met. |
| **Criteria for evaluation (see protocol Section 3):**<br>**Efficacy:**<br>The primary efficacy endpoint is Change in peak oxygen uptake (pVO2) by cardiopulmonary exercise testing (CPET) from baseline to Week 24.<br>The secondary endpoints are as follows:<br>• Proportion of participants with ≥1 class improvement in NYHA Functional Class from baseline to Week 24<br>• Change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) from baseline to Week 24<br>• Change in LVMI from baseline to Week 24<br>• Change in LAVI from baseline to Week 24<br>• Change in NT-proBNP values from baseline to Week 24 |

- Change in post-Valsalva LVOT-G from baseline to Week 24

**Safety:**

- Incidence of reported major adverse cardiac events (cardiovascular [CV] death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization)
- Incidence of treatment emergent adverse events
- Incidence of left ventricular ejection fraction (LVEF) <50%

**Statistical methods:**

Unless specified otherwise, efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized participants. The primary analysis will test the null hypothesis that there is no treatment difference in the primary endpoint between participants randomized to metoprolol and those randomized to aficamten in the FAS. Change from baseline in pVO2 will be analyzed using an ANCOVA model with treatment group, randomization stratification factors (CPET exercise modality and recently diagnosed vs chronic oHCM), baseline pVO2, and baseline weight as covariates in the FAS.

The null hypothesis for the primary and secondary endpoints in the FAS will be tested based on pre-specified closed testing procedure in order to preserve the overall type I error rate at 0.05.

If the primary endpoint achieves statistical significance at two-sided $p<0.05$, then the testing of secondary endpoints at Week 24 will be performed a parallel gatekeeper method with two-sided alpha 0.025 separately allocated to the following groups.

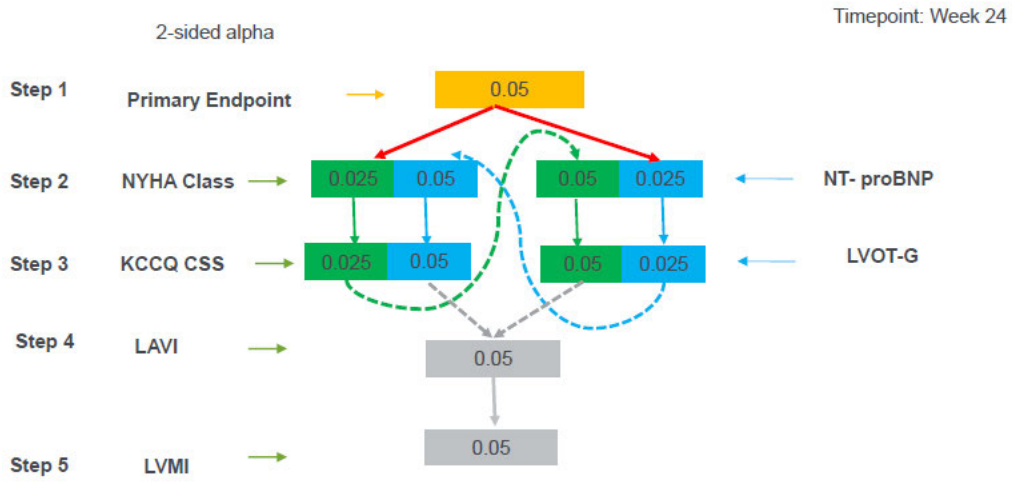
(a) Proportion of participants with >1 NYHA functional class improvement at Week 24 and change from baseline to Week 24 in KCCQ-CSS

(b) change from baseline to Week 24 in NT-proBNP and change from baseline to Week 24 in Valsalva LVOT-G.

The testing of each parallel group will be done in the sequential order as written above. If both endpoints in group (a) have two-sided $p\leq0.025$, then there is recycling of the 0.025 alpha to the endpoints in group (b) so that 0.05 is applicable to the corresponding testing of the two endpoints in group (b). Similarly, if both secondary endpoints listed in group (b) have a two-sided $p\leq0.025$, then there is recycling of the 0.025 alpha to test the two endpoints in group (a), so that sequential testing at 0.05 is applicable to the two endpoints in group (a). If all four secondary endpoints listed in group (a) and group (b) achieve statistical significance then fifth and sixth secondary endpoints, change from baseline to Week 24 in LAVI and change from baseline to Week 24 in LVMI will be tested sequentially at two-sided alpha level of 0.05, if the test for change in LAVI is not statistically significant then test for change in LVMI will be for exploratory purpose only

The multiple testing procedure is illustrated in Figure 1 below.

**Figure 1: Statistical Testing Hierarchy for Primary and Secondary Efficacy Endpoints**




The proportion of participants with ≥ 1 class improvement in NYHA Functional Class from baseline to Week 24 will be analyzed using Cochran–Mantel–Haenszel (CMH) test stratified by randomization factors. The p-value and 95% confidence interval (CI) of the treatment difference will be obtained using the exact method.

Change in KCCQ-CSS, change in post-Valsalva LVOT-G, change in LAVI, and change in LVMI from baseline to Week 24 will be analyzed using a mixed model repeated measures (MMRM) model with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix will be specified. Compound symmetry covariance matrix will be specified if there are computational issues.

For NT-proBNP, the log transformed proportional change (defined as ratio of post randomization NT-proBNP value over baseline) will be analyzed using a MMRM model with log baseline as covariate, treatment group, randomization stratification factors, visit, log baseline by visit and treatment by visit interaction as fixed effects. Median and median difference of NT-proBNP between treatment groups and 95% confidence intervals of the median difference will also be presented. Safety analyses will be performed on the safety analysis set (SAF) which includes all participants who received at least one dose of IP. The pharmacokinetics analysis set (PKS) will consist of participants who have at least one measurable plasma concentration of aficamten.

The number and percentage of participants reporting any treatment-emergent AEs will be coded using the MedDRA dictionary and be tabulated by system organ class and preferred term.

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# LIST OF ABBREVIATIONS

| Abbreviation/Term | Explanation |
|---|---|
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALS | Amyotrophic Lateral Sclerosis |
| ALT | Alanine aminotransferase |
| ANA | Anti-nuclear antibody |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate aminotransferase |
| AUC | Area under the ROC Curve |
| CGI | Clinical Global Impression scale |
| CI | Confidence interval |
| Cmax | Maximum plasma concentration observed |
| CMH | Cochran–Mantel–Haenszel |
| CPET | Cardiopulmonary exercise testing |
| CRF | Case report form |
| CRO | Contract research organization |
| CSR | Clinical Study Report |
| Ctrough | Trough plasma concentration observed |
| CV | Cardiovascular |
| CYP | Cytochrome P450 |
| CYP3A4 | Cytochrome P450 Family 3 Subfamily A Member 4 |
| DILI | Drug induced liver injury |
| DMC | Data monitoring committee |
| EC | Ethics Committee |
| EC | Executive Committee |
| ECG | Electrocardiogra(m/phy) |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EOS | End of study |
| EOT | End of treatment |
| EQ-5D-5L | EuroQol 5-dimension 5-level instrument |
| FAS | Full analysis set |

| Abbreviation/Term | Explanation |
|---|---|
| FU | Follow up |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| HCM | Hypertrophic cardiomyopathy |
| hs-cTnI | High sensitivity cardiac troponin I |
| IB | Investigator's Brochure |
| ICD | Implantable cardioverter defibrillators |
| ICF | Informed consent form |
| ICH | International Council for Harmonization |
| IEC | Independent ethics committee |
| IP | Investigational product |
| IRB | Institutional Review Board |
| IWRS | Interactive web response system |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| LAM | Lactational amenorrhoea method |
| LKM1 | Liver Kidney Microsomal antibody 1 |
| LLN | Lower Limit of Normal |
| LSM | Least Squares Mean |
| LV | Left ventricle(ular) |
| LVEDV | Left ventricular end-diastolic volume |
| LVEF | Left ventricular ejection fraction |
| LVESV | Left ventricular end-systolic volume |
| LVFS | Left ventricular fractional shortening |
| LVOT | Left ventricular outflow tract |
| LVOT-G | Left ventricular outflow tract gradient |
| MAR | Missing At Random |
| MedDRA | Medical Dictionary for Regulatory Activities Terminology |
| MMRM | Mixed Model for Repeated Measures |
| MNAR | Missing Not At Random |
| NIMP | Non-investigational medicinal product |
| NT-proBNP | n-terminal prohormone brain natriuretic peptide |
| NYHA | New York Heart Association |

| Abbreviation/Term | Explanation |
|---|---|
| oHCM | Obstructive hypertrophic cardiomyopathy |
| PD | Pharmacodynamics |
| PDS | Pharmacodynamics analysis set |
| PGI-C | Patient Global Impression of Change scale |
| PK | Pharmacokinetics |
| PKS | Pharmacokinetics analysis set |
| PRO | Patient-reported outcomes |
| PT | Preferred Term |
| pVO2 | Peak oxygen uptake |
| RBC | Red blood cell |
| REB | Research Ethics Board |
| RER | Respiratory exchange ratio |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAQ-7 | Seattle Angina Questionnaire -7 |
| SAS | Statistical Analysis System (SAS®) |
| SC | Steering Committee |
| SD | Standard deviation |
| SoC | Standard of care |
| SOC | System Organ Class |
| TBL | Total bilirubin |
| TEAE | Treatment-Emergent Adverse Event |
| TESAE | Treatment-Emergent Serious Adverse Event |
| ULN | Upper Limit of Normal |
| VAS | Visual Analogue Scale |
| VAT | Ventilatory anaerobic threshold |
| WHO | World Health Organization |

# SAP VERSION HISTORY

| Version Number and Date | Summary of Revision | Rationale |
|---|---|---|
| Final Version 1.0 / 05 June 2023 | Not applicable: original version | Not applicable |
| Final Version 2.0 / 09 October 2024 | Technical Summary: Diagnosis and main criteria for inclusion<br><br>Section 5.5.4: modified FAS definition by removing condition of requiring at least one post baseline efficacy measurement.<br>Section 2.2.3<br>Maximum ST segment depression on resting ECG at Week 12 and 24 is removed.<br>Section 3.5.1.1 Echocardiography Table 2 parameters that will not be available for analysis removed.<br>Section 7.7.1<br>Removed sensitivity analysis exploring the impact of COVID-19<br>Section 7.8.1<br>A sensitivity analysis assigning missing NYHA class at Weeks 24 as non-responders is added.<br>Exploratory endpoints:<br>Proportion of patients with resting LVOT G <30 mmHg, post-Valsalva LVOT G <30 mmHg at Week 12 and Week 24 is added.<br>Proportion of patients with post-Valsalva LVOT G <30 mmHg at Week 12 and Week 24 is added.<br>Proportion of patients with >5, 10, 15 and 20 points improvement in KCCQ overall summary scores at Week 12 and 24 is added.<br>Section 7.9.1<br>Definition of SRT eligibility added. Clarification added that derivation of | The lower limit of KCCQ CSS is removed based on Protocol Amendment 3<br>To incorporate updates made to CY 6031 SAP per FDA comments.<br>Data will not be collected<br>Variables are not available.<br>Deemed unnecessary as the overall COVID-19 impact is waning.<br>Added as worst-case scenario for this endpoint.<br>Deemed supportive for the objective of the study<br>Definition of SRT eligibility was not provided. For clarity of the derivation in the case of intermittent missing values. |

| Version Number and Date | Summary of Revision | Rationale |
|---|---|---|
| | the imputed SRT endpoint with intermittent missing NYHA or LVOT will follow the same imputation method for missing Week 12 or Week 24<br>Section 2.2.5 | Revised to be consistent across clinical program |
| | LVEF<50% with associated signs and symptoms is adjusted to include "symptoms of heart failure" based on customized MedDRA query only. Technical Summary: Objectives and Endpoints section, details of objective of the study and endpoints is added | It was missing even though it was included in the protocol |
| | Section 2.1.3 Safety: Objective is added<br>Exploratory: Objective is added | It was missing even though it was included in the protocol |
| Final Version 3.0 / 03 February 2025 | Section 8.8 Rebound Effect Analysis added | Deemed supportive |
| | Section 4.3 included a section for HCM participant experience to note the analysis will be done by independent vendor | A sub-study specified in the protocol and will be analyzed separately per a separate plan. |
| | Section 2.2.3,<br>SRT analyses to identify the proportion of participants who are SRT eligible at *baseline* was removed. | SRT eligibility at baseline was not well defined because participants Standard of Care (SOC) were washed out at baseline |
| | Section 8.6<br>Analysis of change from baseline in vital signs added<br>Analysis of proportion of participants who meet pre-specified vital signs criteria (e.g. HR<50 BPM vs. HR>=50 BPM) added | Deemed supportive for study objective |
| | Section 7.5<br>Subgroup analysis by race added | Updates made to address FDA comments to the SAP |

| Version Number and Date | Summary of Revision | Rationale |
|---|---|---|
| | Section 7.7.<br>Imputation method for the primary analysis is updated to include a method that takes the types of intercurrent events into account | Updates made to address FDA comments to the SAP |
| | Section 7.8.1<br>Removed the rank-based MMRM approach as an alternative method if the normality assumption not met. | Updates made to address FDA comments to the SAP |
| | Subgroup analyses for LAVI and LVMI endpoints are added | Deemed supportive for study objective |
| | Section 8.2.2<br>Summary of AEs/SAEs that occurred during washout period will be provided | Deemed supportive for study objective |
| | Section 7.9.2<br>Analysis of change from baseline in weight added | Deemed supportive for study objective |
| | Section 8.8.2<br>SMQ search terms that will be used for rebound effect added | For implementation clarity |

# 1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a technical elaboration of the planned analyses and detailed data displays to be included in the Clinical Study Report (CSR) for CY 6032 study.

This SAP was developed in accordance with the International Council for Harmonization (ICH) E9 and ICH E9 (R1) guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to the study database lock. Further study information can be found in the protocol.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Study Objectives

### 2.1.1. Primary Objective

To evaluate the effect of aficamten compared to metoprolol on exercise capacity in participants with obstructive hypertrophic cardiomyopathy (oHCM).

### 2.1.2. Secondary Objective

The secondary objectives of the study are listed as follows:

- To evaluate the effect of aficamten compared to metoprolol on New York Heart Association (NYHA) Functional Classification
- To evaluate the effect of aficamten compared to metoprolol on patient health status
- To evaluate the effect of aficamten compared to metoprolol on structural remodeling
- To evaluate the effect of aficamten compared to metoprolol on NT-proBNP
- To evaluate the effect of aficamten compared to metoprolol on post-Valsalva left ventricular outflow tract gradients (LVOT-G)

### 2.1.3. Safety

To evaluate the safety and tolerability profile of aficamten comparted with metoprolol in participants with oHCM.

### 2.1.4. Exploratory

To evaluate the effect of aficamten comparted with metoprolol on exercise capacity and functional class in symptomatic oHCM participants.

## 2.2. Study Endpoints

### 2.2.1. Primary Endpoints

The primary endpoint of the study is Change in peak oxygen uptake (pVO2) by cardiopulmonary exercise testing (CPET) from baseline to Week 24.

### 2.2.2. Secondary Endpoints

- Proportion of participants with ≥1 class improvement in NYHA Functional Class from baseline to Week 24
- Change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) from baseline to Week 24
- Change in LVMI from baseline to Week 24
- Change in LAVI from baseline to Week 24

- Change from baseline values in n-terminal prohormone brain natriuretic peptide (NT-proBNP) to Week 24
- Change in post-Valsalva LVOT-G from baseline to Week 24

### 2.2.3. Exploratory and Other Endpoints

- Proportion of participants at Week 24 achieving either:

  − Change from baseline of ≥1.5 mL/kg/min in pVO2 AND ≥1 class improvement in NYHA Functional Class

  OR

  − Change from baseline of ≥3.0 mL/kg/min in pVO2 AND no worsening of NYHA Functional Class

- Proportion of participants with resting LVOT<30 mmHg , post-Valsalva LVOT G <50 mmHg at Week 12 and Week 24
- Proportion of participants with post-Valsalva LVOT G <30 mmHg at Week 12 and Week 24
- Proportion of participants with improvement in KCCQ-CSS >5, >10, >15, and >20 points in KCCQ-CSS, KCCQ- Total Symptom Score (TSS) and other KCCQ summary scores at Weeks 12 and 24
- Proportion of participants with resting LVOT G <30 mmHg, post-Valsalva LVOT G <50 mmHg, and NYHA Functional Class I at Week 12 and Week 24
- Proportion of participants with resting LVOT G <30 mmHg, post-Valsalva LVOT G <50 mmHg, and ≥1 class improvement in NYHA Functional Class at Week 12 and Week 24
- Change from baseline to Week 24 on cardiac troponin levels:
  - Change in hs-cTnI from baseline to week 24
- Change from baseline to Week 24 on a measure of diastolic function:
  - Change in E/e` (lateral wall) from baseline to week 24
- Change from baseline to Week 24 on IVST remodeling:
  - Change in IVST from baseline to week 24
- Change from baseline to Week 24 on other CPET parameters:
  - Ventilatory efficiency/carbon dioxide production ($VE/VCO_2$ slope)
  - Circulatory power ($VO_2$ x SBP)
  - Ventilatory anaerobic threshold (VAT)
  - Total workload (watts)
  - Heart rate response

- Proportion of participants who are SRT eligible at Week 24 . Proportion of participants who are SRT eligible will also be evaluated at other scheduled visit weeks
- Change from baseline to Week 24 in echocardiographic measurements of cardiac structure and of systolic function including:
  - Left ventricular ejection fraction (LVEF)
  - Left ventricular global longitudinal strain (LV GLS)
  - Left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV)
  - Maximal wall thickness
- Change from baseline to Week 24 in individual responses to the EQ-5D-5L, EQ-5D-5L VAS and EQ-5D-5L index score
- Change from baseline to Week 24 in CGI
- Change from baseline to Week 24 in PGI-C
- Change from baseline values in all other summary KCCQ scores
  - (Physical Limitation, Symptom Stability, Symptom Frequency, Symptom Burden, Total Symptom Score, Self-efficacy, Quality of Life, Social Limitation, Overall Summary Score) at Weeks 12 and 24.
- Change from baseline to Week 24 in total score and domain scores for the SAQ-7
- Change from baseline to Week 24 in total score and domain scores for the SAQ-7 in participants with baseline SAQ-AF =< 80
- Time to Maximal ST Segment Depression on CPET ECG
- Time to 1 mm ST depression below Baseline on CPET ECG
- Number of participants with new or worsening ST depression during exercise at Weeks 24
- Proportion of participants with LVH with strain pattern (typical+ atypical) on Electrocardiogram (ECG) at Weeks 12 and 24
- Proportion of participants with all LVH (with or without strain) on ECG at Weeks 12 and 24

### 2.2.4. PK Parameters

- PK parameter maximum plasma concentration observed (Cmax) and trough plasma concentration observed (Ctrough)

### 2.2.5. Safety Endpoints

- Incidence of reported major adverse cardiac events (cardiovascular [CV] death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization) based on Standard MedDRA query
- Incidence of treatment emergent adverse events
- Incidence of new onset persistent atrial fibrillation (CMQ)
- Incidence of ventricular arrhythmias requiring treatment (CMQ)Incidence of appropriate implantable cardiac defibrillator (ICD) discharges and aborted sudden cardiac death.

- Incidence of LVEF <50%:

  The incidence of LVEF <50% will be assessed in association with signs and symptoms of heart failure based on customized MedDRA query at the time the LVEF < 50%. Note: signs and symptoms refer to AEs with onset date within ± 7 days relative to the date when LVEF <50%.

- Incidence of LVEF <40%
- Incidence of LVEF <50%

Incidences of LVEF below 40% and 50% will be summarized by site-read, and core laboratory read, and by both.

# 3. STUDY DESIGN

## 3.1. Summary of Study Design

This is a Phase 3, multi-center, randomized, double-blind, active-comparator trial in participants with symptomatic oHCM and elevated LVOT-G. Approximately 170 eligible participants will be randomized in a 1:1 ratio to aficamten or metoprolol. Central randomization will be stratified by cardiopulmonary exercise testing (CPET) exercise modality (treadmill/bicycle), and recently diagnosed vs chronic oHCM and implemented in the Interactive Web Response System (IWRS). The number of participants using the bicycle CPET exercise modality will be capped at approximately 50%.

All participants on SOC therapy will undergo a washout period consisting of approximately 14 days of weaning from SOC therapy, followed by an additional 7 days completely off SOC therapy prior to undergoing Screening Visit 2 assessments.

Each of the study treatments (aficamten and metoprolol) will be administered orally once daily with or without food. During the initial six weeks of the treatment period, doses will be individually titrated at Weeks 2, 4, and 6 using echocardiography and (vital signs for metoprolol group only). Dose escalation at Weeks 2, 4, and 6 will occur only if a patient has a post-Valsalva LVOT-G ≥30 mmHg and a biplane LVEF ≥55% and SBP≥90 mmHg and heat rate ≥55 bpm (for metoprolol group only). Echocardiograms and vital signs will be performed at each subsequent visit during the trial and the dose may down titrated if necessary.

The primary endpoint of pVO2 will be measured by CPET at screening and at end of treatment (Week 24).

## 3.2. Definition of Study Drugs

Table 1 describes any study drug: investigational product (IP) (i.e., aficamten), aficamten matching placebo, metoprolol, and metoprolol matching placebo intended to be administered to a trial patient according to the protocol.

**Table 1: Investigational Products**

| Arm Name | Active (Aficamten) | Placebo (Aficamten) | Active (Metoprolol succinate) | Placebo (Metoprolol) |
|---|---|---|---|---|
| IP/Product Name | Aficamten | Placebo | Metoprolol succinate | Placebo |
| Type | Drug | Drug | Drug | Drug |
| Dose Formulation | Tablet | Tablet | Tablet | Tablet |
| Unit Dose Strength(s) | 5 mg | Matching placebo | 47.5 mg metoprolol succinate tablet | Matching placebo |
| Dosage Level(s) | 5, 10, 15, 20 mg | NA | 50, 100, 150, 200 mg | NA |
| Route of Administration | Oral | Oral | Oral | Oral |

**Table 1: Investigational Products (Continued)**

| Arm Name | Active (Aficamten) | Placebo (Aficamten) | Active (Metoprolol succinate) | Placebo (Metoprolol) |
|---|---|---|---|---|
| Use | Experimental | Placebo | Comparator | Placebo |
| IMP and NIMP | IMP | IMP | IMP | IMP |
| Packaging and Labeling | IP will be provided in bottles which will be labeled as required per country requirement | IP will be provided in bottles which will be labeled as required per country requirement | IP will be provided in blister packages which will be labeled as required per country requirement | IP will be provided in blister packages which will be labeled as required per country requirement |

## 3.3. Sample Size Considerations

### 3.3.1. Sample Size Justifications

Assuming a difference in change from baseline in pVO2 of 2 mL/kg/min for aficamten compared to metoprolol, a standard deviation (SD) of 3 mL/kg/min, and 10% of participants missing change from baseline data of the primary endpoint, a sample size of 170 participants (randomized at 1:1 ratio to aficamten and to metoprolol) provides more than 90% power to detect the difference in pVO2 change from baseline to Week 24 with a 2-sided type I error of 0.05.

## 3.4. Randomization

All eligible participants will be centrally assigned to randomized IP using IWRS. Randomization will be stratified by CPET exercise modality and recently diagnosed vs chronic oHCM and implemented in the IWRS.

## 3.5. Clinical Assessments

### 3.5.1. Efficacy Assessments

Efficacy assessments include CPET, NYHA classification, patient-reported outcomes (KCCQ, EQ-5D-5L, SAQ-7), cardiac biomarkers (NT-proBNP, cTnI), PGI-C and CGI, and echocardiography.

#### 3.5.1.1. Echocardiography

Echocardiography will be done during screening, prior to dosing on Day 1, and 2 hours after dosing in the clinic on Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28.

Site read echocardiographic assessments include LVEF, resting and Valsalva LVOT-G at each visit. Unless otherwise specified, echocardiographic variables will be based on the core echocardiography laboratory assessments. Table 2 below lists the echocardiography parameters from the core laboratory. A full list of echocardiographic parameters is specified in the data transfer agreement from the core laboratory.

**Table 2: Echocardiographic Variables and Names**

| **Endpoint Names** |
|---|
| **Variables Describing LV Structure** |
| Left ventricular end diastolic diameter |
| Left ventricular end diastolic volume Index |
| Left Ventricular End Systolic Volume Index |
| left ventricular end systolic diameter |
| Left Ventricular Posterior Wall Thickness, End-diastole |
| LV Mass indexed |
| Interventricular Septum Thickness, End-Diastole |
| Left ventricular Maximal wall thickness |
| Left ventricular relative wall thickness |
| **Variable Describing LV Systolic Function** |
| Left ventricular ejection fraction |
| Left ventricular fractional shortening |
| Left ventricular stroke volume Index |
| Left ventricular cardiac output Index |
| Left Ventricular Isovolumetric Contraction Time |
| Left Ventricular Isovolumetric Relaxation Time |
| Left Ventricular Ejection Time |
| Left Ventricular Myocardial Performance Index |
| Left Ventricular Outflow Tract Velocity Time Integral |
| Left Ventricular Global Longitudinal Strain |
| Left Ventricular Global Circumferential Strain |
| Variables Describing LV Diastolic Function |
| Peak E Wave Velocity |
| Peak A Wave Velocity |
| Mitral Lateral Annular Early Diastolic Velocity |
| Mitral Septal Annular Early Diastolic Velocity |
| Mitral E/A Wave Velocity Ratio |
| Mitral E Wave to Lateral Annular Early Diastolic Velocity Ratio |
| Mitral E Wave to Septal Annular Early Diastolic Velocity Ratio |

**Table 2: Echocardiographic Variables and Names (Continued)**

| Endpoint Names |
|---|
| **LVOT Dynamic Gradient Assessment Variables** |
| Peak Left Ventricular Outflow Tract Pressure Gradient at Rest |
| Peak Left Ventricular Outflow Tract Pressure Gradient during Valsalva Maneuver |
| Variables Describing LA Size and Function |
| Left Atrial Width |
| Left Atrial Volume Index |
| **Variables Describing RV Size and Function** |
| Right Ventricular Outflow Tract Velocity Time Integral |
| Right Ventricular Myocardial Performance Index |
| Tricuspid annular plane systolic excursion |
| **Valvular Assessment Variables** |
| Presence of Mitral Regurgitation |
| Mitral Regurgitation Jet Area to Left Atrial Area Ratio |
| Presence of Mitral Systolic Anterior Motion |

#### 3.5.1.2. Patient-Reported Outcomes

KCCQ and EQ-5D-5L will be assessed on Day 1, Weeks 2, 4, 6, 8, 12, 16, 20, 24 and 28 (4 weeks after last dose at end of the study). SAQ-7 will be assessed on Day 1, Weeks 4, 8, 12, 16, 20, 24 and 28. PGI-C and CGI will be assessed at Weeks 8 and 24. Algorithms to derive the scores KCCQ, EQ-5D-5L and SAQ-7 are provided in Section 11.1.2.

**EQ-5D-5L**

EQ-5D-5L is the 5-level version of EQ-5D introduced to improve the instrument's sensitivity and to reduce ceiling effects (EuroQol Group 2009). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels indicating no problems, slight problems, moderate problems, severe problems, or extreme problems. Five responses with a response from each of the 5 dimensions form a 5-digit number that defines a patient's health state profile. A health state can potentially be assigned a summary index score based on societal preference weights (societal perspective) for the health state. The health state preferences often represent national or regional values and can therefore differ between countries/regions. The health state index scores will be calculated using the composite time trade-off (cTTO) method based on the United States valuation of EQ-5D-5L (Pickard 2019) for participants from the United States and for the FAS. The health state index score ranges from less than 0 to 1 with higher scores indicating higher health utility; a score 0 represents death, negative values represent worse than death, and 1 represents full health.

#### 3.5.1.3. CPET Assessments

All participants will undergo CPET with gas-exchange analysis and the methodology will be standardized across all sites as specified in the CPET manual. Participants must use the same testing modality for all exercise tests during the trial. CPET are done at baseline and Week 24 post randomization. CPET parameters are listed below. A full list of CPET parameters is specified in the data transfer agreement from core laboratory.

- Workload
- Exercise Duration
- % of Predicted Oxygen Uptake
- Circulatory Power
- Predicted Oxygen Uptake
- Peak Oxygen Uptake per Kilogram
- Peak RER
- Oxygen Uptake Efficiency Slope
- Ventilatory Efficiency
- Anaerobic Threshold
- Aerobic Efficiency

### 3.5.2. Safety Assessments

- Safety assessments include adverse events and serious adverse events (SAEs), ICD discharge
- Electrocardiograms, laboratory assessments, physical examinations, and vital signs.
- Incidence of LVEF <40%
- Incidence of LVEF <50%
- Incidence of LVEF <50% :

  In association with at least one signs and symptoms of heart failure based on customized MedDRA query, at the time of LVEF assessment. Note signs and symptoms referring to AEs with onset date within ± 7 days relative to the date when LVEF <50%.
- Incidence of LVEF below 40% and 50% will be summarized by site read, and by core laboratory read and by both.

### 3.5.3. Pharmacokinetics Assessments

Blood samples will be collected to evaluate plasma concentrations of aficamten at pre-dose and 2 hours post-dose at Day 1, Weeks 2, 4, 6, 8, 16, 24, and Early Discontinuation.

# 4. PLANNED ANALYSES

## 4.1. Interim Analyses

No interim analysis is planned for this study.

## 4.2. Final Analyses

The final analysis will occur after all participants randomized in the study have completed the study including the 4-week safety follow up, all data has been entered into the clinical data base, verified, and locked. Unblinding for the final analysis will occur after the database lock.

## 4.3. HCM Participant Experience Sub-Study Analyses

HCM participant experience data will be collected as sub-study by an independent vendor. The sub-study will include two qualitative interviews (at entry and exit of the study), as well as surveys collected remotely at Day 1, and Weeks 2, 4, 6, 8, 12, 16, 20 and 24. The analyses of the sub study data will be performed separately by the independent vendor per separate analysis plan.

# 5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

## 5.1. General Summary Table and Individual Subject Data Listing Considerations

Descriptive statistics to be presented in a table include number of observations, mean, median, standard deviation, 1st, and 3rd quartiles, minimum and maximum for continuous variables, and count of participants and the percentage for categorical variables. For variables that lognormal distribution assumptions may be appropriate, geometric mean, and geometric coefficient of variation (CV %) will also be displayed. Geometric CV (%) will be derived as $100\% \times \text{sqrt}(\exp(s^2)-1)$, where s is the standard deviation of the natural logarithm (ln) transformed data.

For model-based analysis, least squares mean (LSM), difference of least squares means between treatments, their standard errors and 95% confidence intervals (CI), and two-sided p-values for the statistical inferences will be presented.

Selected listings may be generated to include patient identifier (ID), demographics, randomized treatment group and other relevant items, and sorted by randomized treatment group, patient ID and date of assessment.

## 5.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Post text tables and individual subject data listings are prepared according to ICH Guideline E3. In general, summary and analysis tables will be presented by treatment groups and Week 8 dose levels administered.

## 5.3. Data Management

Data will be entered into the clinical database with programmed edit checks and manual data review to ensure data integrity. The data will be reviewed and cleaned according to a data management plan. Clinical safety laboratory, ECG, Pharmacokinetics (PK) data, CPET and echocardiography will be provided per the pre-specified data transfer agreement from external laboratories.

## 5.4. Data Presentation Conventions

The following conventions will be applied to data presentations:

- For continuous variables, mean and median values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value. For the statistical analyses results that are on the same scale as a measured value (e.g., change from baseline or treatment difference estimates), the LSM estimates and LSM estimate 95% CI boundary values will be formatted to one more decimal place than the measured value; Standard error of the mean SEM estimates will be formatted to two more decimal places

than the measured values. GLSM estimates for the proportional change from baseline, proportional change of treatment ratios, odds ratios, and the corresponding 95% CIs will be presented with two decimal places.

- For categorical variables, the count and percentage of responses are presented in the form XX (XX.X%) where the percentage is in parentheses.
- Date variables are formatted as YYYY-MM-DD for presentation. Time is formatted in military time as HH:MM for presentation.
- P-values, if applicable, will be presented to 3 decimal places. If the p-value is less than 0.0001 then it will be presented as <0.0001. If the rounded result is a value of 1.000, it will be displayed as >0.999.
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 0.05 significance level.

The table and listing shells and table of contents provide the expected layout and titles of the tables, listings, and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP, nor will it be considered a deviation from planned analyses. Only substantial deviation in the analysis methods will require an SAP revision or a change to planned analysis documented in the CSR.

## 5.5. Analysis Populations

### 5.5.1. All Screened Participants

All participants who signed the informed consent form (ICF) are included in the All-Screened Participants Set. Participants who gave informed consent but are not randomized are considered screen failures. Participants are allowed for re-screening, and participants will be considered screen failure if failed on the re-screening as well.

The following reasons for screen failures are collected: inclusion/exclusion criteria (including specific criteria not met), principal investigator decision, subject decision, lost to follow up, and other. For participants who are screen failures, the reasons for failing will be summarized.

### 5.5.2. Safety Analysis Set

Safety analyses will be performed on the safety analysis set (SAF), which includes all randomized participants who receive at least one dose of IP, aficamten or metoprolol. Unless otherwise specified, for safety analyses, participants will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

### 5.5.3. Full Analysis Set

Efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized participants. Participants will be analyzed according to their randomized treatment group assignments.

### 5.5.4. Pharmacokinetics Analysis Set

All randomized participants who have at least one evaluable plasma concentration of aficamten, provided they have no Important protocol deviations that could affect the PK of aficamten.

## 5.6. Baseline Definition

Unless otherwise specified, baseline is defined as the last available measurement taken prior to administration of the first dose of study drug. Baseline for KCCQ, EQ-5D-5L and SAQ-7 assessments are performed on Day 1. The assessments collected on the same date as the first dose of the IP that do not have assessment time are considered to have occurred prior to the first dose. If patient did not take first dose, the latest non-missing assessment prior to or at randomization day will be used as baseline.

## 5.7. Derived and Transformed Data

### 5.7.1. Baseline Age

Age will be calculated as follows:

Age (years) = year of screening date – year of birth, if patient was re-screened, the date of re-screening will be used.

Patient age will be categorized as < 65 years, or ≥ 65 years.

### 5.7.2. Study Day

If the date of interest occurs on or after the first dose date, then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date, then study day will be calculated as (date of interest – date of first dose). There is no study day 0.

### 5.7.3. Body Measurements Variable Derivation

Baseline body surface area (BSA) will be calculated using the weight and height at screening using the DuBois and DuBois formula and rounded to two decimal points for the presentation of results:

BSA ($m^2$) = 0.007184 * (weight (kg) $^{0.425}$ * height (cm) $^{0.725}$).

### 5.7.4. Change from Baseline

Change from baseline is calculated as (post baseline value – baseline value).

Percent change from baseline is calculated as (change from baseline / baseline value) x 100%.

Proportional change from baseline is calculated as (post baseline value-baseline value/baseline value).

If either the baseline or the post-baseline value is missing, the change from baseline, percentage change from baseline, and proportional change from baseline will be set to missing.

### 5.7.5. Summary Scores for Patient Reported Outcomes (PRO)

Calculations of summary scores for KCCQ, SAQ-7, and EQ-5D-5L are specified in Section 11.1.

### 5.7.6. Analysis Windows

Since study visits do not always take place exactly as scheduled per protocol, it is necessary to assign the actual observation dates to analysis windows for analysis purposes.

For data collected at a scheduled post baseline visit, the analysis visit will be assigned based on the scheduled nominal visit as collected on the eCRF.

For unscheduled or early discontinuation post baseline visits, measurements taken on or after the first dose of study drug will be assigned to an analysis window using defined lower and upper bounds for each analysis window. Measurements assigned in an analysis window will have study day greater than or equal to the lower bound but no greater than the upper bound of the analysis window. The lower bound and the upper bound for the analysis windows are defined as the midpoints of the scheduled visits for all assessments (see Section 11.4).

Visits are identified as nominal visits according to the eCRFs. Each visit will be identified with the visit descriptor (e.g., "Week 24").

### 5.7.7. Multiple Assessments

Once analysis windows are assigned, a patient's individual analysis window could potentially contain more than one visit. Records from all visits, including scheduled, unscheduled, and early discontinuation visits could be flagged as the "analyzed record" within the analysis window, although the records from scheduled visit will take priority.

In the event of multiple visits falling within an analysis window, the following rules will be used in sequence to determine the "analyzed record" for the analysis window:

- If a scheduled visit occurred during the analysis window, then the measurement taken from the scheduled visit will be used.
- If no scheduled visit occurred during the analysis window, the measurement taken closest to the scheduled day will be used as the "analyzed record."
- If no scheduled visit occurred during the analysis window and there is a tie between unscheduled visits in the number of days before and after the scheduled day, measurements from the later visit will be used as the "analyzed record."

For all analyses, only the "analyzed record" within each analysis window and the visit will be summarized in a table. Only protocol specified visits will be presented in the summary table. If there are other visit records within the analysis window, they will only be included in data listings.

### 5.7.8. Other Study Related Definitions

Dose Achieved at Week 8Participants in the aficamten actual treatment group will be identified as 5 mg, 10 mg, 15 mg, 20 mg or discontinuing IP prior to dose adjustment based on the dose assigned at Week 8.

Participants in the metoprolol actual treatment group will be identified as 50 mg, 100 mg, 150 mg, 200 mg or discontinuing IP prior to dose adjustment based on the dose assigned at Week 8.

If a patient discontinues IP prior to the start of Week 8 (IWRS Week 8 dispensation), then the subject will be identified as discontinued IP prior to achieving stable dose. The actual dose group may be used in selected displays.

Last IP dose is defined as the last aficamten or placebo for aficamten dose (does not include metoprolol down titration doses done post treatment discontinuation).

End of Treatment (EOT)

End of treatment is defined as the date of the last IP dose as defined above.

Investigational Product Exposure Period
For participants dosed with IP:
[(Last IP administration date – date of first dose) + 1]/7 (in weeks)

Treatment-emergent Adverse Event

For the purpose of reporting, an investigator-reported event starting on or after first dose of IP and up to and including 28 days after the last dose date of IP will be labeled as a treatment-emergent AE.

Last Titrated Dose

Last titrated dose is defined as the last titrated dose assigned to the patient.

### 5.7.9. Derived Echocardiographic Parameters

The following BSA-indexed variables will be derived using the baseline BSA defined in Section 5.7.3:

- LVEDV-I (mL/$m^2$) = LVEDV/BSA
- LVESV-I (mL/$m^2$) = LVESV/BSA
- LVSV-I (mL/$m^2$) = LVSV/BSA
- LAV-I (mL/$m^2$) = LAV/BSA
- LVCO-I (mL/min/$m^2$) = LVCO/BSA
- LVmass-I(g/$m^2$)=LVmas/BSA

For the presentation of results, the BSA-indexed variables will be rounded to the same number of decimal places as the corresponding non-indexed variables provided by the echocardiography core laboratory.

## 5.8. Handling of Missing Data

### 5.8.1. Missing Efficacy Endpoints

For the primary endpoint, missing data will be imputed using multiple imputation method based on the reasons for missing data. The distribution of missing CPET data at Week 24 and the reasons for the missing data will be tabulated in the FAS

The missing data will be imputed as detailed in Section 7.7.1and all observed and imputed missing $pVO_2$ assessments will be included in the analysis. Sensitivity analyses will be

performed by repeating the primary analysis using different imputation strategies for selected causes of missing data . Details are described in Section 7.7.1.

Missing other CPET endpoints will be handled the same way as for the primary endpoint. Missing response for patient reported outcomes will be handled as described in Section 11.1.

### 5.8.2. Missing Start and Stop Dates for Prior and Concomitant Medication

To classify medications as baseline medications and/or , concomitant medications, missing start and stop dates of medications will be imputed as follows:

- If the medication start date day is missing, it will be imputed with the first day of the month,
- If the medication start date day and month are missing, they will be imputed with 01 January,
- If the medication stop date day is missing, it will be imputed with the last day of the month or the date of the last contact with the patient, whichever is the later,
- If the medication stop date day and month are missing, they will be imputed with 31 December or the date of the last contact with the patient, whichever is the later,
- For the ongoing medications, the stop date will not be imputed.

### 5.8.3. Missing Start and Stop Dates for Adverse Events

For AEs with incomplete date information recorded in the eCRF, the imputation will follow the following algorithm:

For missing AE onset Date

- If an AE onset Day is missing and the Month of AE onset is known, then the first day of the month of AE onset will be imputed as the AE onset date. If the month and year of AE onset are the same as month and year of the first dosing, the missing day will be imputed as the first dosing date.
- If AE onset information is not available, then the first dosing date will be imputed as the AE onset date.
- If AE onset day and month are both missing, the missing month and day will be imputed as 01 January. If the year of AE onset is the same as the first dosing date, the AE onset will be imputed as the first dosing date.

For missing AE end Date and Time:

- If the AE end Day is missing and it will be imputed with the last day of the month or the date of the last contact with the patient, with the imputed date doesn’t exceed the date of last contact.
- If the AE end date day and month are missing, they will be imputed with 31 December or the date of the last contact with the patient, with the imputed date doesn’t exceed the date of last contact.
- For the ongoing AEs, the stop date will not be imputed.

# 6. STUDY POPULATION

## 6.1. Participants Disposition

Patient disposition will be summarized based on all randomized participants. The following will be summarized:

- The number and percentage of participants who completed the study and the number of participants who discontinued from the study early,
- For the participants who discontinued from the study early, reasons for early discontinuation,
- The number and percentage of participants who received at least one dose of the IP,
- For the participants who received at least one dose of the IP, the number and percentage of participants who completed study treatment and the number of participants who discontinued the study treatment early,
- For the participants who discontinued the study treatment early, reasons for early discontinuation.

The number and percentage of randomized participants included in each analysis set will be summarized. Reasons for exclusion from analysis sets will be listed.

## 6.2. Screen Failures

Screen failures will be listed and summarized by reasons of screening failure.

## 6.3. Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Examples of Important protocol deviations are

- those who entered the study even though they did not satisfy the entry criteria;
- those who developed withdrawal criteria during the study but were not withdrawn;
- those who received the wrong treatment or incorrect dose;
- those who received an excluded concomitant treatment.

Number of participants who reported Important protocol deviation will be summarized by treatment group for all randomized participants. A summary of protocol deviations due to COVID-19 will be provided separately.

## 6.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, age group [$< 65$, $\geq 65$], sex, race, ethnicity, height, weight, BMI, BSA, randomization stratification variables and baseline disease characteristics will be summarized by randomized treatment group for the FAS using descriptive statistics. All randomized participants will be included in the listing of demographic and baseline characteristics.

## 6.5. Listing of Subject Inclusion and Exclusion Criteria

A listing of randomized participants who did not meet the inclusion and exclusion criteria will be provided.

## 6.6. Medical History and Medical Conditions Present at Entry

Medical history will be summarized by treatment received for the Safety Analysis Set. HCM-related medical history will be summarized, including time since initial diagnosis and number and percentage of participants meeting the oHCM criteria.

Time since oHCM diagnosis will be calculated: screening date – oHCM diagnosis, if patient was re-screened, the date of re-screening will be used.

Selected cardiovascular medical history and other medical history will be summarized by the MedDRA SOC and preferred term (MedDRA version 26.0).

## 6.7. Baseline Medications Use

Medications will be coded using World Health Organization (WHO) Drug Dictionary. Baseline medication use is defined as a medication that starts before the first dose of IP and ends after the first dose of IP or ongoing. The count and percentage of participants with each medication history item will be presented by therapeutic class (ATC Class 3) and preferred name. If ATC Class 3 is not available, ATC Class 2 will be used in the summary.

# 7. EFFICACY

## 7.1. General Considerations

Efficacy analyses will be performed in the FAS by the randomized treatment group. Unless otherwise specified, all hypothesis tests will be reported as 2-sided p-values. Exploratory endpoints and subgroup analyses will be assessed using a nominal alpha level of 0.05 and will not have multiplicity adjustments. In order to preserve an overall type I error rate for the primary and secondary endpoints testing of the primary and secondary endpoints will follow testing procedure specified in in Section 7.6.

## 7.2. Testing Statistical Assumptions Including Comparability at Baseline

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model. Model assumption will be assessed by graphical examination of residuals. If assumptions are substantially violated, rank based analysis will be performed as sensitivity analysis. See Section 7.7.4 for more details.

## 7.3. Statement of the Null and Alternate Hypotheses

The null hypothesis for the primary endpoint is that the treatment difference (aficamten – metoprolol) of mean change from baseline of $pVO_2$ at Week 24 is 0 and the alternative hypothesis is that the treatment difference is > 0 (favors aficamten). The tests will be reported with two-sided p-values, but only the direction favoring aficamten direction will be considered success.

## 7.4. Planned Covariates

Baseline covariates include but are not limited to the stratification factors and baseline measurements. For CPET related endpoints, covariates of age, sex, baseline hemoglobin level, and baseline weight will also be included.

## 7.5. Subgroup Analyses

Subgroup analyses with relatively moderate sample size will be performed to examine the consistency of the observed treatment effect and to gain insight into the effectiveness of aficamten in subpopulations. Analyses of the primary endpoint will be conducted for the following subgroups:

- Sex (male, female)
- Age group (< 65, ≥ 65 years )
- Baseline body mass index (≤ 30 and > 30 $kg/m^2$)
- Baseline NYHA Class (II, and III)
- Baseline KCCQ CSS (≤ median and > median)
- Baseline LVEF (≤ median and > median)

- Baseline N-terminal prohormone brain natriuretic (NT-proBNP) (≤ median and > median)
- CPET modality (treadmill, bicycle)
- Recently diagnosed vs chronic oHCM
- $pVO_2$ on baseline CPET (≤ median, > median)
- Baseline resting LVOT (≤ median and > median)
- Sarcomeric gene mutation status (positive or negative/inconclusive)

Subgroup analysis will be performed by including the subgroup effect and subgroup by treatment interaction to the model. The subgroup analysis will be performed based on the imputed dataset generated for the primary analysis of the endpoint if the primary analysis is based on multiple imputation.

Subgroup analysis by race will be performed with race categorized as White, Asian and Other. Due to the small sample size, only descriptive statistics will be provided for the primary endpoint only.

In addition, subgroup of IND site status (IND sites vs. non-IND sites) analysis will be performed for the primary. endpoint.

## 7.6. Multiple Comparisons and Multiplicity Control

To preserve the overall type I error rate at two-sided 0.05 for the primary and set of secondary endpoints, the null hypotheses for the primary and secondary efficacy variables in the FAS will be tested in a hierarchical order using a closed testing procedure that employs a Bonferroni adjustment and a Holms procedure.

Secondary endpoints are organized and ranked into three groups as follows:

<table>
<tr><th>Group A</th><th>Group B</th></tr>
<tr><td>• Proportion of participants with >1 NYHA functional class improvement at Week 24<br>• Change from baseline to Week 24 in KCCQ-CSS</td><td>• Change from baseline to Week 24 in NT-proBNP<br>• Change from baseline to Week 24 in Valsalva LVOT-G</td></tr>
<tr><td colspan="2">Group C</td></tr>
<tr><td colspan="2">• Change from baseline to Week 24 in LAVI<br>• Change from baseline to Week 24 in LVMI</td></tr>
</table>

The primary endpoint is tested first at two-sided 0.05.

If the primary endpoint achieves statistical significance, then a parallel gatekeeper method will be performed with the two-sided alpha 0.05 split via Bonferroni method, allocating 0.025 to each of the secondary endpoint groups A and B.

These two endpoint groups will be tested in parallel in two steps. Unadjusted p-values will be generated for all four endpoints.

Step 1: The two endpoints within each group A and B will be tested sequentially. In this step, testing within a group will cease at the first instance where statistical significance is not reached at the 2-sided 0.025 level.

Step 2: If the null hypotheses are rejected for both endpoints within one of these endpoint groups but not in the other, per the Holms method the p-values for the endpoints in the latter will be reassessed, again sequentially, at the 2-sided 0.05 level, stopping at the first instance where statistical significance is not reached.

After these steps, if statistical significance was reached for all four endpoints in groups A and B, sequential testing of the two endpoints in group C will proceed at the 2-sided 0.05 level. Testing in group C will cease at the first instance where statistical significance is not reached at the 2-sided 0.05 level.

## 7.7. Analysis of the Primary Efficacy Endpoint

### 7.7.1. Primary Efficacy Analysis

The primary endpoint is change in $pVO_2$ from baseline to Week 24. The primary analysis will be performed using an ANCOVA model that includes terms of treatment, randomization stratification factors (recently diagnosed vs chronic oHCM and CPET modality), baseline $pVO_2$ and baseline body weight as covariates in the FAS. Table 3 below displays details of the two estimands for the primary endpoint.

**Table 3: Estimand for Primary Endpoint**

| Attributes | Primary Estimand | Secondary Estimand |
|---|---|---|
| Population | Treatment policy, target population of potentially treatable aficamten participants. | Hypothetical target population of potentially treatable aficamten participants continue with treatment and are capable of completing the Week 24 assessment. Participants with missing Week 24 $pVO_2$ due to intercurrent events or discontinuing treatment prior to Week 24 will be considered as missing. |

**Table 3: Estimand for Primary Endpoint (Continued)**

| Attributes | Primary Estimand | Secondary Estimand |
|---|---|---|
| Patient level Variable | Change from baseline to Week 24 in $pVO_2$. Data to be analyzed include all observed Week 24 $pVO_2$ values from participants who complete 24 weeks of treatment, or from participants who early terminate from the treatment but remain in the study and have Week 24 $pVO_2$ and imputed $pVO_2$ for participants who don't have Week 24 $pVO_2$. Imputation details are provided below. | Change from baseline to Week 24 in $pVO_2$. Data to be analyzed include observed $pVO_2$ values from participants who complete at least 24 weeks of treatment, and all missing data will be imputed assuming MAR. |
| Population level summary | Mean treatment difference regardless of completing 24 weeks of treatment and experiencing intercurrent events. | Mean treatment difference among all participants who remained on their randomized treatment for 24 weeks. |

Participants will be followed according to the schedule of activities in the protocol from randomization through the date of final visit irrespective of whether the subject is continuing to receive IP unless the subject has discontinued prematurely from the study or withdrawn consent. The protocol allows up to 4 weeks extension of Week 24 in the event that the subject is temporarily unable to exercise due to an AE, eg, ankle sprain, upper respiratory infection etc. or due to equipment malfunction to ensure post randomization CPET data collection.

Reasons for not completing Week 24 CPET will be recorded on eCRF; categories of reasons include adverse events, early termination, equipment failure, investigator decision, subject decision and others. The percentage of missing CPET data at Week 24 and the reasons for the missing data will be tabulated in the FAS.

The CPET core laboratory flags the CPET results as invalid when there are:

- Technical - technical equipment failure during CPET (i.e., air leak/lack of proper equipment utilization with missing nose clip or malfunction of the ergometer or metabolic cart leading to inability to adequately capture gas exchange data)
- Transient non-cardiac issues that precluded conduct of the exercise study (as defined by inability to turn the pedals during the warm-up period for at least 3 min)
- CPET MOP - major CPET process deviation, can impact one or more CPET variables.

$PVO_2$ values arising from CPET results flagged as invalid by the core laboratory will be set to missing in the analysis data sets.

Data handling conventions and imputation methods for intercurrent events and missing $PVO_2$ values at Week 24 are shown in the table below.

**Data handling for estimands for the primary endpoint**

| **Intercurrent event / cause of missing data** | **Primary estimand: Treatment Policy** | **Sensitivity estimand: Treatment Policy** | **Supportive estimand: Hypothetical** |
|---|---|---|---|
| *Intercurrent events (ICE), observations present after ICE* | | | |
| Discontinued treatment early because of AEs | Observed data included | Observed data included | Observed data after ICE ignored and imputed as MAR |
| *Missing data reasons and imputation methods:* | | | |
| Death | Use worst 25% of pVO2 values to construct imputation model | Use worst 25% of pVO2 values to construct imputation model | MAR |
| Discontinued treatment early because of AEs | Control-based method | Control-based method | MAR |
| Completed treatment but participant was not able to perform CPET exercise due to Non-CV AEs (e.g. orthopedic injury) | MAR | Control-based method | MAR |
| Completed treatment but participant was not able to perform CPET exercise due to CV AEs, HCM symptom, or other severe illness | Control-based method | Control-based method | MAR |
| Lost to follow-up prior to Week 24 | MAR | MAR | MAR |
| Discontinued treatment due to lack of efficacy prior to Week 24 assessment | MAR | Control-based method | MAR |
| The CPET core laboratory flags the CPET results as | Invalid results ignored and imputed as MAR | Invalid results ignored and imputed as MAR | Invalid results ignored and imputed as MAR |

| Intercurrent event / cause of missing data | Primary estimand: Treatment Policy | Sensitivity estimand: Treatment Policy | Supportive estimand: Hypothetical |
|---|---|---|---|
| invalid or malfunction of the machine | | | |

Note:

- The control-based method is imputing missing pVO2 based on a model that is constructed using observed $pVO_2$ data from the metoprolol arm.
- In the MAR method the imputation model is constructed using all observed $pVO_2$ data (from both treatment arms).
- The worst 25% of the non-missing $pVO_2$ refers to imputing from among the smallest non-missing 25% of $pVO_2$ values at Week 24 (from both treatment arms).

**The imputation model** will use regression multiple imputation which includes treatment group, randomization stratification factors, baseline $pVO_2$, sex, age, baseline hemoglobin, baseline body weight, baseline KCCQ CSS, and baseline NYHA class and the last available post randomization NYHA, resting and Valsalva LVOT. Categorical variables, i.e., treatment group, baseline NYHA, and sex will be specified in the CLASS statement.

One hundred (100) imputed datasets will be generated. Change from baseline in $pVO_2$ will be calculated based on the observed and imputed data. Each of the imputed dataset will be analyzed using the primary analysis ANCOVA model. LSM estimate of treatment difference and the standard error will be combined using Rubin's rules (Rubin 1987) to produce a LSM estimate of the treatment difference, its 95% confidence interval, and p-value for the test of null hypothesis of no treatment effect. LSM, LSM difference and the corresponding standard error, 95% CIs and pvalue will be presented.

### 7.7.2. Sensitivity Analyses of the Primary Efficacy Endpoint

To evaluate the robustness of the primary analysis sensitivity analysis, using alternative imputation methods for selected intercurrent events will be performed as shown in the table above.

As additional sensitivity analyses:

1. The primary end point will be analyzed without imputing the missing data. The model will include the same covariates as the primary analysis.
2. A repeated measures mixed model will be fit to $pVO_2$ baseline and Week 24 data. The model includes stratification factors, visit, stratification by visit, and a numeric covariate which equals 0 for both treatment groups at baseline and equals 0 for metoprolol at Week 24 and equals 1 for aficamten group at Week 24. The primary treatment comparison is for the numeric covariate for treatments which

corresponds to the treatment difference at week 24 in a specification for which there is no treatment difference at baseline.

### 7.7.3. Subgroup Analyses for the Primary Endpoint

Subgroup analyses will be performed by including the subgroup effect and subgroup by treatment interaction terms to the primary ANCOVA model for the primary endpoint. For subgroup analysis for the primary estimand, missing data imputed in the primary analysis will be used in the subgroup analyses. Only summary statistics will be presented for the subgroup level when the number of participants in either treatment arm is ≤ 15 at this level. LSM estimate of the treatment difference, 95% confidence intervals for the mean treatment difference and nominal p-values will be provided for each subgroup level.

### 7.7.4. Additional Sensitivity Analyses for the Primary Endpoint

To explain heterogeneity or identify treatment effect modifiers from the baseline characteristics, covariates used to define pre-specified subgroups and these covariates by treatment interaction terms will be included in the ANCOVA model as sensitivity analysis. Global test of covariates by treatment interactions will be performed. Stepwise model selection method will be used based on the default stay or entry level of 0.05 to evaluate significant baseline covariates impact on the primary endpoint. ANCOVA model will be repeated by adjusting for the significant baseline covariates. Covariates measured as continuous will be introduced to the model as continuous variable. These analyses will be based on observed data.

The normality assumptions of the ANCOVA model will be investigated graphically. The scaled residuals will be examined. Additional sensitivity analysis will be performed repeated after transforming $pVO_2$ data into ranks if greater than 5% of participants have an extreme change from baseline value at Week 24. Extreme values in the pooled data are defined as observations outside of Tukey's outer fences, i.e. observations that are less than the 25% quartile – 3 times the inter quartile range or greater than 75% quartile + 3 times the inter quartile range. Ranks will be applied to all changes from baseline data after the imputation step. Baseline data will be ranked separately.

### 7.7.5. Supportive Estimand of the Primary Efficacy Endpoint

The supportive estimand will be analyzed using the same primary analysis ANCOVA model for the primary estimand $pVO_2$, assessment performed after discontinuation of IP or intercurrent events will be considered as missing. Missing data will be imputed using a model constructed with MAR assumption.

Subgroup analysis for the supportive estimand will be performed using the same ANCOVA model for the subgroup analysis for the primary estimand.

## 7.8. Analysis of the Secondary Efficacy Endpoints

The secondary endpoint(s) of the trial are:

- Change Proportion of participants with ≥1 class improvement in NYHA Functional Class from baseline to Week 24
- Change in KCCQ-CSS from baseline to Week 24

- Change in LVMI from baseline to Week 24
- Change in LAVI from baseline to Week 24
- Change from baseline values in NT-proBNP from baseline to Week 24
- Change in post-Valsalva LVOT-G from baseline to Week 24

### 7.8.1. Analysis of the Secondary Efficacy Endpoints

**1. Change in proportion of participants with ≥1 class improvement in NYHA Functional Class from baseline to Week 24**

For the proportion of participants with ≥1 class improvement in NYHA class, Week 20 NYHA class data will be used if Week 24 NYHA data are not available. Participants will be considered as not achieving ≥1 improvement in NYHA class at Week 24 if Week 20 and Week 24 NYHA class is not available. Proportion of responders will be analyzed using Cochran– Mantel–Haenszel (CMH) test stratified by randomization factors. The p-value and 95% CI will be obtained using the exact method. A sensitivity analysis will be performed by repeating CMH test by assigning missing NYHA class at Weeks 24 as non-responders.

Subgroup analysis for proportion of participants with ≥1 class improvement in NYHA class will be done by repeating the CMH test for each subgroup level without specifying stratifying by randomization stratification factors.

**2. Change in KCCQ-CSS from baseline to Week 24**

The primary analysis of change from baseline in KCCQ-CSS will be performed using a MMRM model with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix will be specified. Compound symmetry covariance matrix will be specified if there are computational issues. All data observed up to Week 24 post randomization will be included in the model. Estimates for endpoints at Week 24 will be obtained from the LS Means estimate at visit of Week 24 from the model. If there are >10% difference in baseline KCCQ CSS across regions, treatment by visit and region, baseline by visit and region will be included in the model. Treatment effect at each visit week will be estimated from the interaction terms of treatment by visit by region, with coefficients for each region determined by proportion of participants evaluated in each region.

Sensitivity analysis based on multiple imputation with one hundred invocations will be performed. First the intermittent missing data will be imputed using the Markov Chain Monte Carlo (MCMC) method under MAR assumption. The imputation will be performed separately for each randomized treatment group and will include the following terms in the imputation model: endpoint observations from baseline up to Week 24. The monotone missing data will be imputed using the imputation model built from the metoprolol group. 100 complete data sets will be generated and analyzed using the same model for the primary analysis of the change from baseline endpoint. The same model for the primary analysis of the change from baseline endpoint. The results from the 100 complete data sets will be combined using Rubin's combination rule for the inference.

Subgroup analysis will be performed using the primary analysis method, MMRM model including additional effects of subgroup, subgroup by treatment and subgroup by treatment by visit interaction in the model.

The assumptions of the MMRM model will be assessed graphically based upon pooled blinded data before unblinding. The scaled residuals will be examined. Analysis using an alternate method will be provided as supportive analysis if severe deviations from assumptions are observed based on blinded data evaluation.

**3. Change in LAVI from baseline to Week 24**

The primary analysis of change from baseline LAVI will follow the same model as specified above for change in KCCQ-CSS from baseline to Week 24.

Subgroup analysis will be performed for the following subgroups

Subgroup analyses will be performed by (LAVI >=baseline median vs LAVI <baseline median)

Sensitivity analysis for this endpoint will follow the same approach as to change in KCCQ-CSS.

**4. Change in LVMI from baseline to Week 24**

The primary analysis of change from baseline LVMI will follow the same model as specified above for change in KCCQ-CSS from baseline to Week 24.

Subgroup analysis will be performed for the following subgroups

Subgroup analyses will be performed by (LVMI >=baseline median vs LVMI < baseline median)

Sensitivity analysis for this endpoint will follow the same approach as to change in KCCQ-CSS.

**5. Change in NT-proBNP from baseline to Week 24**

For **NT-proBNP** the log transformed proportional change will be analyzed using a MMRM model similar to change in KCCQ-CSS, with log baseline as covariate, treatment group, randomization stratification factors, visit, log baseline by visit and treatment by visit interaction as fixed effects.

Geometric LS Means estimate and ratio of proportional change in NT-proBNP between aficamten vs. metoprolol, 95% CIs of ratio and p-value will be presented. Median and median difference of NT-pro-BNP between treatment group and 95% confidence of the median difference will be presented at 24.

Sensitivity analysis for this endpoint will follow the same approach as to change in KCCQ-CSS.

**6. Change in LVOT-G from baseline to Week 24**

The primary analysis of change from baseline LVOT-G will follow the same model as specified above for change in KCCQ-CSS from baseline to Week 24.

Sensitivity analysis for this endpoint will follow the same approach as to change in KCCQ-CSS.

Table 4 below summarizes the primary and secondary efficacy endpoints and planned analysis method.

**Table 4: Endpoints Summary Table**

| Endpoint | Primary Analysis Method | Sensitivity/Subgroup Analysis |
|---|---|---|
| **Primary Endpoint: Change in pVO2 on CPET from baseline to Week 24** | | |
| **Primary estimand**[a] | Missing data will be imputed using multiple imputation method (Section 7.7.1). Complete dataset will be analyzed using an ANCOVA model with fixed effects of treatment, randomization stratification factors baseline $pVO_2$ value and baseline body weight. | **Sensitivity analysis**<br>• ANCOVA model will be repeated with missing data f imputed as described in section 7.7.1<br>**Additional Sensitivity analysis**<br>• Mixed model with numeric covariate as 0 for baseline and metoprolol group at Week 24 and 1 for aficamten group at Week 24, visit, stratification factors and stratification factors by visit as fixed term. unscheduled covariance structure will be specified.<br>• Multivariate ANCOVA model to evaluate treatment by covariates interaction; ANCOVA model with significant covariates per model selection.<br>**Subgroup analyses** for variables in Section 7.5 |

**Table 4: Endpoints Summary Table (Continued)**

| Endpoint | Primary Analysis Method | Sensitivity/Subgroup Analysis |
|---|---|---|
| **Supportive estimand**[a] | Missing data will be imputed using multiple imputation method under MAR assumption. ANCOVA model with fixed effects of treatment, randomization stratification factors baseline $pVO_2$ value and baseline body weight. | **Subgroup analyses** for variables in Section 7.5 |
| **Secondary Endpoints** | | |
| **Change in KCCQ-CSS from baseline to Week 24** | MMRM model with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix will be specified. | **Sensitivity analysis:**<br>• Intermittent missing data be imputed using multiple imputation MCMC first, and the monotone missing values will be imputed using the imputation model built from the metoprolol group. Complete data will be analyzed using the same MMRM model.<br>**Subgroup analyses** for variables in Section 7.5 |
| **Change in post-Valsalva LVOT-G from baseline to Week 24** | MMRM model with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix will be specified. | **Sensitivity analysis:**<br>• Intermittent missing data be imputed using multiple imputation MCMC first and the monotone missing values will be imputed using the imputation model built from the metoprolol group. Complete data will be analyzed using the same MMRM model.<br>**Subgroup analyses** for variables in Section 7.5 |

**Table 4: Endpoints Summary Table (Continued)**

| Endpoint | Primary Analysis Method | Sensitivity/Subgroup Analysis |
|---|---|---|
| Change in **LAVI** from baseline to Week 24 | MMRM model with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix will be specified. | **Sensitivity analysis:**<br>• Intermittent missing data be imputed using multiple imputation MCMC first and the monotone missing values will be imputed using the imputation model built from the metoprolol group. Complete data will be analyzed using the same MMRM model. |
| Change in **LVMI** from baseline to Week 24 | MMRM model with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix will be specified. | **Sensitivity analysis:**<br>• Intermittent missing data be imputed using multiple imputation MCMC first and the monotone missing values will be imputed using the imputation model built from the metoprolol group. Complete data will be analyzed using the same MMRM model. |
| Log transformed of the ratio of Week 24 value and baseline value of **NT-proBNP** | MMRM model with log transformed of baseline value as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and log transformed of baseline value by visit. An unstructured covariance matrix will be specified. | **Sensitivity analysis:**<br>• Intermittent missing data be imputed using multiple imputation MCMC first and the monotone missing values will be imputed using the imputation model built from the metoprolol group. Complete data will be analyzed using the same MMRM model. |
| Proportion of participants with ≥1 class improvement in **NYHA** Functional Class from baseline to Week 24 | CMH test stratified by randomization factors | **Subgroup analyses** for variables in Section 7.5 |

## 7.9. Analysis of the Exploratory Efficacy Endpoints

Exploratory endpoints are specified in Section 2.2.3. Proportion of participants who meet: PVO2 and NYHA improvement criteria at Week 24 will be analyzed. Proportion of participants who meet: Improvement in Resting and post-Valsalva LVOT-G and NYHA at Week 12 and 24 will be analyzed.

of the proportion of participants who were SRT eligibility during the 24-Week treatment period will be analyzed as exploratory analysis. Other echocardiography parameters and CPET parameters not listed as secondary endpoints or in Section 2.2.3 may also be analyzed as exploratory endpoints.

All 10 summary scores will be derived for KCCQ. Change from baseline in each summary scores (except CSS) to Weeks 12 and 24 will be analyzed as exploratory endpoints. Participants with >5, 10 and 20 points improvement in KCCQ summary scores at Weeks 12 and 24 will also be summarized and analyzed. Domain scores and summary score of SAQ-7 will be derived. Health state for EQ-5D-5L and index value using US value set will be calculated.

### 7.9.1. Analysis of the Exploratory Efficacy Endpoints

For change from baseline to Week 24 endpoints (such as CPET parameters), the same ANCOVA model specified for the primary endpoint will be used to analyze the endpoints.

For continuous exploratory endpoints measured at multiple post randomization visits, for change from baseline endpoints MMRM model similar to the one used for KCCQ-CSS will be used to analyze.

For proportion of responders or binary outcomes, CMH test stratified by randomization factors will be used to analyze.

For change from baseline in hs-cardiac-TnI , the same MMRM model specified for log transformed NT-proBNP will be used. Geometric LS Means estimate and ratio of proportional change in hs-cardiac-TnI between aficamten vs. metoprolol, 95% CI of ratio and p-value will be presented. Median and median difference of hs-cardiac- Tnl between treatment group and 95% confidence of the median difference will be presented at 24.

**Proportion of participants who meet: PVO2 and NYHA improvement criteria at Week 24**

- Change from baseline of ≥1.5 mL/kg/min in pVO2 AND ≥1 class improvement in NYHA Functional Class

  OR

- Change from baseline of ≥3.0 mL/kg/min in pVO2 AND no worsening of NYHA Functional Class

Week 20 NYHA class data will be used if Week 24 NYHA data are not available. Participants will be considered as not responding at Week 24 if Week 20 , Week 24 NYHA class, or pVO2 at Week 24 is not available. This endpoint will be derived at Week 24 and will be analyzed using CMH method stratified by randomization factors. The p-value and 95% CI of treatment difference will be obtained using the exact method.

**Proportion of participants who meet: Improvement in KCCQ CSS score at Week 12 and 24**

- Proportion of participants with >5, 10, 15 and 20 points improvement in KCCQ clinical summary scores at Week 12 and 24

For the proportion of participants with improvement in KCCQ CSS at Week 12, Week 16 KCCQ CSS will be used if Week 12 visit is performed but KCCQ CSS is not available. Week 8 KCCQ

CSS will be used if Week 16 is not available. Similarly, Week 20 KCCQ CSS will be used if Week 24 is performed but KCCQ CSS is not available.

This endpoint will be derived at Week 12 and 24 and will be analyzed using CMH method stratified by randomization factors. The p-value and 95% CI of treatment difference will be obtained using the exact method.

**Proportion of participants who meet: Improvement in KCCQ OSS score at Week 12 and 24**

- Proportion of participants with >5, 10, 15 and 20 points improvement in KCCQ overall summary scores at Week 12 and 24

For the proportion of participants with improvement in KCCQ OSS at Week 12, Week 16 KCCQ OSS will be used if Week 12 visit is performed but KCCQ OSS is not available. Week 8 KCCQ OSS will be used if Week 16 is not available. Similarly, Week 20 KCCQ OSS will be used if Week 24 is performed but KCCQ OSS is not available.

This endpoint will be derived at Week 12 and 24 and will be analyzed using CMH method stratified by randomization factors. The p-value and 95% CI of treatment difference will be obtained using the exact method.

Similarly, proportion of participants with >5, 10, 15 and 20 points improvement in KCCQ social limitations scores at Week 12 and 24 will be analyzed.

**Proportion of participants who meet: Improvement in Resting and post-Valsalva LVOT-G and NYHA at Week 12 and 24**

- Proportion of participants with resting LVOT-G <30 mmHg, post-Valsalva LVOT-G <50 mmHg, and NYHA Functional Class I at Week 12 and Week 24
- Proportion of participants with resting LVOT G <30 mmHg, post-Valsalva LVOT G <50 mmHg, and ≥1 class improvement in NYHA Functional Class at Week 12 and Week 24
- Proportion of participants with post-Valsalva LVOT G <30 mmHg at Week 12 and Week 24
- Proportion of participants with resting LVOT G <30 mmHg, post-Valsalva LVOT G <50 mmHg,

For both resting and post-Valsalva endpoints, for LVOT-G at Week 12, Week 16 LVOT-G will be used if Week 12 visit is performed but LVOT-G is not available. Week 8 LVOT-G will be used if Week 16 is not available. Similarly, Week 20 LVOT-G will be used if Week 24 is performed but LVOT-G is not available. Week 16 NYHA class data will be used if Week 12 NYHA data are not available, if Week 16 is missing Week 8 NYHA class data will be used. Similarly, Week 20 NYHA class data will be used if Week 24 NYHA data are not available.

These endpoints will be derived at Week 12 and 24 and will be analyzed using CMH method stratified by randomization factors. The p-value and 95% CI of treatment difference will be obtained using the exact method.

**Proportion of participants with SRT eligibility during the 24-Week treatment**

SRT eligibility is defined as resting or post-Valsalva LVOT-G ≥ 50 mmHg and NYHA Functional Class ≥ 3. Patient SRT eligibility will be assigned after data handling in case there are missing NYHA class or LVOT assessments. Intermittent missing NYHA or LVOT assessments. Intermittent missing NYHA or LVOT will be imputed follow the same imputing method for missing Week 12 or Week 24; e.g., impute Week 16 NYHA if Week 20 NYHA is available or use Week 12 NYHA if Week 20 NYHA is not available. Patient will be treated as SRT eligible if SRT eligibility can't be determined due to the missing NYHA class or LVOT assessments or clinical visits not performed after patient early terminates from the study.

Proportion of patients who are SRT eligible at Week 24 will be analyzed using CMH stratified by randomization factor diagnosis period (Recently diagnosed vs/ Chronic oHCM) will be performed.
Analysis of proportion of participants SRT eligible at each visit will be provided.

**Time to 1 mm ST depression**
Time to 1 mm ST depression at Week 24 will be analyzed using Cox regression model with treatment, randomization stratification factors as fixed effect. Participants didn't experience 1mm ST depression will be censored at the end of CPET exercise.

**LVH strain pattern on ECG for Week 12 and 24**
Logistic regression model will be fit to LVH strain pattern on ECG for Week 12 and 24, separately. The model will include baseline LVH pattern, stratification factors and treatment. Difference in proportion of participants with no LVH will be estimated and 95% CI for odds ratio (aficamten vs. metoprolol) and its corresponding p value will be obtained.

**Cardiac troponin levels, diastolic function, IVST remodeling and other CPET parameters:**

These endpoints will be analyzed using MMRM

- Change in hs-cTnI from baseline to week 24
- Change in E/e` (lateral wall) from baseline to week 24
- Change in IVST remodeling from baseline to Week 24
- These endpoints will be analyzed same analysis approach for the primary estimand of the primary endpoint. Change from baseline to Week 24 on other CPET parameters
    - Ventilatory efficiency/carbon dioxide production ($VE/VCO_2$ slope)
    - Circulatory power ($VO_2$ x SBP)
    - VAT
    - Total workload (watts)
    - Heart rate response (change in HR, from resting to peak HR)

Change from baseline to Week 24 in echocardiographic measurements of cardiac structure and of systolic function including:

- LVEF

- LVESV and LVEDV
- Left atrial volume

### 7.9.2. Analysis of Other Exploratory Efficacy Endpoint

Other echocardiography parameters and CPET parameters not listed as secondary endpoints or as exploratory endpoints in Section 2.2.3 may also be analyzed as exploratory endpoints.

**Health status and health-related quality of life endpoints**

All 10 summary scores will be derived for KCCQ. Change from baseline in each summary scores (except CSS) to Week 12 and 24 will be analyzed as exploratory endpoints.

Health state for EQ-5D-5L and index value using US value set will be calculated. Change from baseline to Week 24 in individual responses to the EQ-5D-5L will be performed.

Similarly, change from baseline to Week 24 in CGI, change from baseline to Week 24 in PGI-C, change from baseline to Week 24 in total score and domain scores for the SAQ-7 will be derived and analyzed.

Additionally, SAQ-7 total score and domain scores will be analyzed for participants with baseline SAQ-7 AF =<80.

**Weight**

The change from baseline to week 24 in weight of patients will be analyzed using ANCOVA with baseline weight, treatment group, randomization stratification factor (diagnosis period), age at baseline, and sex will be included in the model. Weight collected at the time CPET assessment will be used for this analysis.

Subgroup analysis of this endpoint will be performed by diagnosis period (Chronic oHCM vs Diagnosed recently) . The model will include those specified above and subgroup by treatment interaction as well.

# 8. SAFETY AND TOLERABILITY

Safety and tolerability analyses will be based on the Safety Analysis Set. Safety data will be analyzed descriptively and tabulated by treatment groups.

## 8.1. Overall Summary of Tolerability

Overall summary of tolerability will include the following:

- Number of participants treated
- Number and percentages of participants with TEAEs
- Number and percentages of participants with treatment-emergent serious adverse events (TESAEs)
- Number and percentages of participants with TEAEs leading to premature treatment discontinuation
- Number and percentages of participants with at least one TEAE related to the study drug
- Participants with at least one moderate or severe TEAE,
- Participants with at least one severe TEAE,
- Number of Deaths

Summary of number and percent of participants with each AE category will be provided by treatment group and dose level at AE onset. Summaries of the number of events will also be provided.

## 8.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

### 8.2.1. Summaries of Adverse Event Incidence Rates for All Participants

All AE terms will be coded using MedDRA. TEAEs and TESAEs will be summarized by primary SOC and PT, and also by severity (mild, moderate, and severe) and relationship to study drug (related and not related). For a TEAE reported more than once from a patient, the TEAE will be counted only once in the SOC or PT category using the most severe occurrence or closer relationship to the study drug.

All AEs will be listed.

The following subsets of TEAEs will be summarized by SOC and PT:

- All TEAEs
- TEAEs related to study drug
- TEAEs leading to early discontinuation of study drug
- TESAEs

A summary of all TEAEs by PT will be provided. AE summaries will be sorted by descending order of SOC in aficamten group and descending order of preferred term within the SOC. TEAE

and TESAE summary of ≥5% and ≥2%, respectively will be provided based on incidence rate in either aficamten or metoprolol group.

Summary of TEAEs by maximum severity will display number and percentage of AEs with maximum severity being mild, moderate, or severe within each SOC and PT. All TEAE summary will also be provided by dose level. A summary of number of events will be provided for all TEAE summary.

### 8.2.2. Summaries of Adverse Event Incidence that occur during the washout period

Separate summaries of AEs that started during the pre-treatment washout period (between screening visit 1 and day 1), as well as those started during post treatment (between last dose of Aficamten or placebo for aficamten and Week 28) will be provided.

### 8.2.3. Summaries of Adverse Events of Special Interest

The following events are considered adverse events of special interest:

- Incidence of reported major adverse cardiac events (cardiovascular [CV] death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization)
- Incidence of new onset persistent atrial fibrillation
- Incidence of ventricular arrhythmias requiring treatment
- Incidence of appropriate implantable cardiac defibrillator (ICD) discharges and aborted sudden cardiac death
- Incidence of LVEF <50%

  In association with signs and symptoms of heart failure based on customized MedDRA query at the time of LVEF assessment. Signs and symptoms referring to AEs with onset date within ± 7 days relative to the date when LVEF <50%.
- Incidence of LVEF <40%
- Incidence of LVEF <50%

Incidence of LVEF below 40% and 50% will be summarized by site read, and by core laboratory read and by both.

Summary of participants counts and percentage by each event type will be provided by treatment group.

## 8.3. Total Duration of Therapy, Final Daily Dose of Study Medication, and Compliance

### 8.3.1. Summary of IP Exposure and Overall Compliance

Total duration of treatment and total exposure of study drug will be summarized. Aficamten as well as metoprolol group compliance will be derived as:

Compliance =100% * (number of tablets dispensed – number of tablets returned)/expected number of tablets administered.

Number of tablets dispensed and returned will be collected on the study drug accountability eCRF. For the kits not returned, the number of tablets returned will be set to 0 in this derivation, assuming all tablets were taken. Expected number of tablets administered will be derived as the number of daily tablets times the days in the study drug dosing period, summed over all dosing periods. Days of dosing interruption will be excluded from the expected number of tablets calculation. Note total duration of treatment will be calculated based starting on first dose of the respective IP to the last treatment dose during the 24-week period (does not include the metoprolol down titration doses after treatment period completion or discontinuation).

### 8.3.2. Summary of Dose Titration

IWRS-guided dose titration will be summarized showing the number and percentage of participants at each dose level by visit. Number and percentage of participants by last titrated dose will be provided.

## 8.4. Concomitant and Other Medications

Concomitant medications reported on the eCRF will be summarized. Medications with a start date that is 28 days after the last dose of the study drug will be excluded from the summary. The WHO Drug Dictionary will be used to classify medications by therapeutic class (ATC Class 3) and preferred name. If ATC Class 3 is not available, ATC Class 2 will be used in the summary. Coding will be performed using WHO Drug Dictionary.

## 8.5. Routine Laboratory Data

Clinical chemistry, hematology and urinalysis laboratory measurements and value changes from baseline at each laboratory blood sample collection time point will be summarized. Values below or above the quantifiable limits will be treated as equal to the limits in the summary. The count and percentage of participants who had normal or missing laboratory values at baseline and abnormal laboratory values post baseline will be presented. The lower limit of normal (LLN) and upper limit of normal (ULN) provided by the laboratories will be used as the criteria to determine abnormality. For each parameter, the denominator of the percentage will include participants with normal or missing assessments at baseline, and with at least one assessment post baseline. The numerator of the percentage will include participants who had at least one abnormal assessment post baseline among the participants that were counted in the denominator. Assessment collected at unscheduled visits, or the Follow-up Visit will be included in the summary.

Shift of clinical laboratory results from baseline severity to the maximum post baseline severity will be presented for selected laboratory parameters.

Liver function test results will be summarized as count and percentage of participants with normal baseline and abnormal post-baseline values in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) and bilirubin, with the following categories:

- ALT > 3xULN, > 5xULN, > 8xULN
- AST > 3xULN, > 5xULN, > 8xULN

- ALT and/or AST > 3xULN, > 5xULN, > 8xULN
- ALT and/or AST > 3xULN and total bilirubin > 2xULN and ALP < 2xULN
- ALT and/or AST > 3xULN and total bilirubin > 2xULN
- Bilirubin (total) > 2xULN, >3xULN

ALT or AST > 3 x ULN with symptoms including using "drug related hepatic disorders" SMQ started within +/- 14 days of the ALT/AST abnormalities.

## 8.6. Vital Signs

Vital signs observed value and changes from baseline will be summarized descriptively by treatment group over time. The changes from baseline at each post-baseline on-treatment visit will be additionally summarized by dose level at visit.

The change from baseline in systolic blood pressure, diastolic blood pressure, heart rate and mean arterial blood pressure will be analyzed using MMRM model similar to the change in KCCQ-CSS endpoint. Mean arterial blood pressure is defined as MAP = DP + 1/3(SP – DP).

Additionally, the proportion of participants who meet the following criteria will be analyzed using CMH method stratified by randomization stratification factors.

Heart rate < 50 BPM at all clinical visits during the study,

Systolic blood pressure <90 mmHg at all clinical visits during the study

Participants will also be categorized into the following groups for each of the vital sign parameters if a post baseline value falls into a specific group. Unscheduled assessments will be included in the determination. The number of participants in each group will be summarized for each dosing group.

**Diastolic Blood Pressure**

- ≤ 50 mmHg
- ≥ 100 mmHg

**Systolic Blood Pressure**

- ≤ 80 mmHg
- ≥ 160 mmHg

**Heart Rate**

- ≤ 50 beats/min
- ≥ 120 beats/min

**Respiratory Rate**

- > 18 breaths/min

## 8.7. Electrocardiogram

The baseline ECG is defined as the mean of all pre-dose assessments. PR, RR, QRS, QT, and Fridericia corrected QT (QTcF) intervals and their change from baseline will be summarized by treatment group and scheduled assessment. Participants will be categorized into the following groups per their maximum change from baseline in QTcF. Unscheduled assessments will be included in the determination of the maximum change. The number and percentage of participants in each group will be summarized.

- ≤30 msec
- >30 – 60 msec
- >60 msec

Participants will also be categorized into the following groups per their maximum post baseline QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value. The number of participants in each group will be summarized for each dosing group.

- ≤450 msec
- >450 – 480 msec
- >480 – 500 msec
- >500 msec

## 8.8. Rebound Effect Analysis

The rebound effect is described as the emergence of new disease related symptoms, or worsening of prior symptoms relative to those present at the start of a treatment. This is distinguished from recurrence of the underlying disease in the absence of pharmacological drug actions.

The rebound effect exhibits some particular features:

- it is independent of the individual's disease (symptoms);
- it appears following partial or complete drug discontinuation according to the individual's idiosyncrasy;
- occurs at variable time intervals (usually several half-lives after the last dose) following the partial/complete drug discontinuation;
- duration of action varies - dissipates a number of half-lives later;
- it promotes a clinical state opposite to the drug's primary action;
- the induced symptoms are more intense than those before treatment;
- the effect magnitude is disproportional to the primary effect of the drug.

### 8.8.1. Systematic Approach for Rebound Effect Assessment

A systematic approach to identify cases that experienced a potential rebound effect will be utilized. The customized standard queries are used to identify treatment emergent AEs with onset

between EOT and EOS. A listing of these qualifying events will be generated, including detailed parameters on patient, drug administration, event and relevant assessment/investigations.

### 8.8.2. Rebound Effect Listings

The following criteria will be used to identify adverse events (AEs) to include in the listing.

- Onset date between EOT and EOS (EOT<=AE start date<=EOS)

AND

- AEs that had a preferred term (PT) contained in the cardiovascular events customized standard query (CSQ)

The customized standard query used for the analysis of the rebound effect are using the following terms

- Myocardial infarction SMQ (Broad)
- Cardiac failure customized MedDRA query
- Cardiovascular events customized MedDRA query
- Stroke customized MedDRA query [Ischaemic central nervous system vascular conditions SMQ (Narrow) and Haemorrhagic central nervous system vascular conditions SMQ (Narrow)
- Ventricular tachyarrhythmia customized MedDRA query
- Permanent/persistent atrial fibrillation (lowest level terms ‘Permanent atrial fibrillation and “Persistent atrial fibrillation”)

The parameters listed below will be included for each AE in the listing.

- Patient ID
- Demographics: country, gender, age
- Study drug
- Treatment assignment (for unblinded studies)
- Study drug start date and end date
- Last study drug dosage prior to event
- AE PT and system organ class (SOC)
- AE onset date
- Onset latency to last study drug dosage
- AE severity, seriousness and reported causality
- Outcome, resolution date, and other action
- Concomitant medication (betablocker, non-dihydropyridine CCB and disopyramide) with indication, start date, and end date

- Cardiac biomarker parameters: NT- proBNP, troponin
- Echo parameters: Resting and Valsalva Left Ventricular Outflow Tract Gradient (LVOT-G), Left Ventricular Ejection Fraction (LVEF)ae at baseline, W24, W28, time of event onset
- New York Heart Association (NYHA) functional class at baseline, W24, W28, time of event onset
- Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score and clinical summary score (CSS) at baseline, W24, W28, time of event onset

### 8.8.3. Rebound Effect Assessment Criteria

Programmed analysis for classification of potential rebound requires meeting all of the following criteria (1 and 2 and 3).

3. NT-proBNP 30% increase from baseline
4. Gradients
    a. Resting LVOT-G increase from baseline, AND/OR
    b. Valsalva LVOT-G increase from baseline
5. Symptomatic endpoints
    a. NYHA >1 class increase from baseline, AND/OR
    b. KCCQ-CSS >15 point decrease from baseline

Parameters should be contemporaneous with event. If data are not available at time of event, Week 28 data will be utilized. If any individual category of criteria is missing, default to “meets criterion - yes”.

# 9. PHARMACOKINETICS

Plasma concentrations of aficamten and its measured metabolites and PK parameter maximum plasma concentration observed (Cmax) and trough plasma concentration observed (Ctrough) will be summarized using descriptive statistics including mean, SD, geometric mean, geometric coefficient of variation, median, and range. Geometric mean concentrations over time will be graphically displayed.

# 10. REFERENCES

EuroQol Group. (2009). "Eq-5d-5l." EuroQol Research Foundation, from https://euroqol.org/publications/user-guides, Updated Date Accessed Date.

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Raghunathan, T., & Dong, Q. (2011). Analysis of variance from multiply imputed data sets. Ann Arbor: University of Michigan.

Rubin, D. B. (1987). Multiple imputation for nonresponse in surveys. New York, John Wiley & Sons, Inc.

# 11. APPENDIX

## 11.1. Patient-reported Outcome Scoring Algorithm

### 11.1.1. KCCQ

There are 10 summary scores within the KCCQ, which are calculated as follows:

**1. Physical Limitation**

- Code responses to each of Questions 1a-f as follows:

  Extremely limited = 1
  Quite a bit limited = 2
  Moderately limited = 3
  Slightly limited = 4
  Not at all limited = 5
  Limited for other reasons or did not do = <missing value>

- If at least three of Questions 1a-f are not missing, then compute
  Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) - 1]/4
  (see footnote at end of this appendix for explanation of meaning of "actually answered")

**2. Symptom Stability**

- Code the response to Question 2 as follows:

  Much worse = 1
  Slightly worse = 2
  Not changed = 3
  Slightly better = 4
  Much better = 5
  I've had no symptoms over the last 2 weeks = 3

- If Question 2 is not missing, then compute

  Symptom Stability Score = 100*[(Question 2) – 1]/4

**3. Symptom Frequency**

- Code responses to Questions 3, 5, 7 and 9 as follows:

  <u>Question 3</u>
  Every morning = 1
  3 or more times a week but not every day = 2
  1-2 times a week = 3
  Less than once a week = 4
  Never over the past 2 weeks = 5

  <u>Questions 5 and 7</u>
  All of the time = 1
  Several times a day = 2
  At least once a day = 3

3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4
Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

**4. Symptom Burden**

- Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1
Quite a bit bothersome = 2
Moderately bothersome = 3
Slightly bothersome = 4
Not at all bothersome = 5
I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

**5. Total Symptom Score**

= mean of the following available summary scores:
Symptom Frequency Score
Symptom Burden Score

**6. Self-efficacy**

- Code responses to Questions 10 and 11 as follows:

Question 10
Not at all sure = 1
Not very sure = 2
Somewhat sure = 3
Mostly sure = 4
Completely sure = 5

Question 11
Do not understand at all = 1
Do not understand very well = 2
Somewhat understand = 3
Mostly understand = 4
Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

**7. Quality of Life**

- Code responses to Questions 12, 13 and 14 as follows:

Question 12
It has extremely limited my enjoyment of life = 1
It has limited my enjoyment of life quite a bit = 2
It has moderately limited my enjoyment of life = 3
It has slightly limited my enjoyment of life = 4
It has not limited my enjoyment of life at all = 5

Question 13
Not at all satisfied = 1
Mostly dissatisfied = 2
Somewhat satisfied = 3
Mostly satisfied = 4
Completely satisfied = 5

Question 14
I felt that way all of the time = 1
I felt that way most of the time = 2
I occasionally felt that way = 3
I rarely felt that way = 4
I never felt that way = 5

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

**8. Social Limitation**

- Code responses to each of Questions 15a-d as follows:

Severely limited = 1
Limited quite a bit = 2
Moderately limited = 3
Slightly limited = 4
Did not limit at all = 5
Does not apply or did not do for other reasons = <missing value>

- If at least two of Questions 15a-d are not missing, then compute

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

**9. Overall Summary Score**

= mean of the following available summary scores:
Physical Limitation Score
Total Symptom Score
Quality of Life Score
Social Limitation Score

**10. Clinical Summary Score**

= mean of the following available summary scores:
Physical Limitation Score
Total Symptom Score

Note: references to **"means of questions actually answered"** imply the following.

- If there are n questions in a scale, and the subject must answer m to score the scale, but the subject answers only n-i, where n-i >= m, calculate the **mean of those questions** as

  (sum of the responses to those n-i questions) / (n-i)
  **not**

(sum of the responses to those n-i questions) / n

### 11.1.2. SAQ-7

Three domain scores and one summary score are generated from the SAQ-7:

Physical Limitation Score (SAQ7-PL)

Angina Frequency Score (SAQ7-AF)

Quality of Life Score (SAQ7-QL)

Summary Score (SAQ7)

Scores are scaled 0-100, where 0 denotes the lowest reportable health status and 100 the highest.

Physical limitation Score

The physical Limitation score corresponds to Questions 1a, 1b and 1c. Responses are coded as follows:

| | |
|---|---|
| Extremely limited | 1 |
| Quite a bit limited | 2 |
| Moderately limited | 3 |
| Slightly limited | 4 |
| Not at all limited | 5 |
| Limited for other reasons or did not do the activity | 6 |

A response of 6 is treated as missing value for the purpose of scoring. If responses to two or more questions are missing, no score is computed. If the response to Question 1a or Question 1c is missing, it is assigned the responses from Question 1b. If the response to Question 1b is missing, it is assigned the average of responses to Questions 1a and 1c. The score is then calculated by taking the average of the three responses and rescaling to 0 – 100, as follows:

SA7-PL = 100*[(average of Questions 1a, 1b and 1c)-1]/4

Angina Frequency Score

The Angina Frequency score corresponds to Questions 2 and 3. Responses are coded as follows:

| | |
|---|---|
| 4 or more times per day | 1 |
| 1 – 3 times per day | 2 |
| 3 or more times per week but not every day | 3 |
| 1 -2 times per week | 4 |
| Less than once a week | 5 |
| None over the past 4 weeks | 6 |

If responses to both questions are missing, no score is computed. Otherwise, the score is calculated by taking the average of non-missing responses and rescale to 0-100 as follows:

SAQ7-AF = 100 *[(average of Questions 2 and 3) -1]/5

Quality of Life Score

The quality-of-life score corresponds to Questions 4 and 5. Responses are coded as follows:

| | |
|---|---|
| Question 4 | |
| It has extremely limited my enjoyment of life | 1 |
| It has limited my enjoyment of life quite a bit | 2 |
| It has moderately limited my enjoyment of life | 3 |
| It has slightly limited my enjoyment of life | 4 |
| It has not limited my enjoyment of life at all | 5 |
| Question 5 | |
| Not satisfied at all | 1 |
| Mostly dissatisfied | 2 |
| Somewhat satisfied | 3 |

| | |
|---|---|
| Mostly satisfied | 4 |
| Completely satisfied | 5 |

If responses to both questions are missing, no score is computed. Otherwise, the score is calculated by taking the average of the non-missing response and rescaling to 0 -100, as follows:

SAQ7-QL= 100*[(average of Question 4 and 5)-1]/4

Summary Score

The summary score represents an integration of the participants' physical limitation, angina symptom and quality of life. If all three domain scores are missing, no summary score is computed. Otherwise, the score is calculated as the average of the non-missing domain scores:

SAQ7 = average of SAQ-PL, SAQ-AF, and SAQ-QL

### 11.1.3. EQ-5D-5L

Five dimensions of the EQ-5D-5L include 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. The US Pickard value set will be used to compute the EQ-5D-5L index values. The value set will be denoted as disut_mo for 'mobility', disut_sc for 'selfcare', disut_ua for 'activity', disut_pd for 'pain', and disut_ad for 'anxiety' in Table 5 below:

**Table 5: EQ-5D-5L Value Set**

| | | US value set |
|---|---|---|
| MOBILITY | | disut_mo |
| I have no problems in walking about | 1 | 0 |
| I have slight problems in walking about | 2 | 0.096 |
| I have moderate problems in walking about | 3 | 0.122 |
| I have severe problems in walking about | 4 | 0.237 |
| I am unable to walk about | 5 | 0.322 |
| | | |
| SELF-CARE | | disut_sc |
| I have no problems washing or dressing myself | 1 | 0 |
| I have slight problems washing or dressing myself | 2 | 0.089 |
| I have moderate problems washing or dressing myself | 3 | 0.107 |
| I have severe problems washing or dressing myself | 4 | 0.220 |
| I am unable to wash or dress myself | 5 | 0.261 |
| | | |
| USUAL ACTIVITIES | | disut_ua |
| I have no problems doing my usual activities | 1 | 0 |
| I have slight problems doing my usual activities | 2 | 0.068 |
| I have moderate problems doing my usual activities | 3 | 0.101 |
| I have severe problems doing my usual activities | 4 | 0.255 |
| I am unable to do my usual activities | 5 | 0.255 |
| | | |
| PAIN / DISCOMFORT | | disut_pd |

**Table 5: EQ-5D-5L Value Set (Continued)**

| | | US value set |
|---|---|---|
| I have no pain or discomfort | 1 | 0 |
| I have slight pain or discomfort | 2 | 0.060 |
| I have moderate pain or discomfort | 3 | 0.098 |
| I have severe pain or discomfort | 4 | 0.318 |
| I have extreme pain or discomfort | 5 | 0.414 |
| | | |
| ANXIETY / DEPRESSION | | disut_ad |
| I am not anxious or depressed | 1 | 0 |
| I am slightly anxious or depressed | 2 | 0.057 |
| I am moderately anxious or depressed | 3 | 0.123 |
| I am severely anxious or depressed | 4 | 0.299 |
| I am extremely anxious or depressed | 5 | 0.321 |
| | | |
| We would like to know how good or bad your health is TODAY | 0 to 100 | |

disut_total=disut_mo+disut_sc+disut_ua+disut_pd+disut_ad;
The EQ-5D-5L index value (EQindex) =1-disut_total

The SAS code will be provided in Appendix Section 11.5.

## 11.2. Table of Contents for Data Display Specifications

Table of contents for data display specifications will be provided in a separate document.

## 11.3. Data Display Specifications

Data display specifications will be provided in a separate document.

## 11.4. Analysis Windows

Measurements collected during the 24-week double-blind period will be included only in the analysis windows up to Week 24. For data collected at a scheduled visit post randomization, the analysis visit will be the nominal visit as collected and visit window will not be applied.

For unscheduled or early discontinuation post randomization, analysis visit will be used according to Table 6 below when the scheduled visit is not available.

**Table 6: Analysis Windows for Measurements**

| Visit | Scheduled Day | Lower Bound | Upper Bound |
|---|---|---|---|
| Screening | <1 | <1 | <1 |
| Day 1 | 1 | 1 | 1 |
| Week 2 | 15 | 2 | 21 |
| Week 4 | 29 | 22 | 35 |
| Week 6 | 43 | 36 | 49 |
| Week 8 | 57 | 50 | 70 |
| Week 12 | 85 | 71 | 98 |
| Week 16 | 113 | 99 | 126 |
| Week 20 | 141 | 127 | 154 |
| Week 24 | 169 | 155 | 196 |
| Week 28/Follow-up | last dose + 28 days | - | - |

## 11.5. Sample SAS Codes

**ANCOVA model for primary endpoint**

```
proc mixed data=work;
        class <treatment arm (ref='0')> <Diagnosis Period> <Exercise Modality>;
        model chg=<base pvo2 > <base weight> <treatment arm> < Diagnosis Period >
        <Exercise Modality> /solution s Influence(EFFECT=usubjid) outp=out vciry;
        lsmeans <treatment arm>/pdiff cl;
run;
```

This code assumes that the analysis involves 2 levels in treatment arm (e.g., Metoprolol group is coded as 0 and aficamten is coded as 1).

**MMRM model**

```
proc mixed data=work;
    class <Subject> <treatment arm (ref='0')> < Diagnosis Period > <Exercise Modality> <visit>;
model <chg> = <base> <treatment arm> <visit> <visit>*<treatment arm> < Diagnosis Period >
<Exercise Modality> <visit>*<base>/ddfm=kenwardroger;
repeated <visit> / type=un subject=<Subject>;
lsmeans <visit>*<treatment arm>/cl pdiff;
run;
```

This code assumes 2 level in treatment arm with metoprolol group is coded as 0. visit has level of nominal visit week where continuous measurements are assessed up to Week 24.

Primary analysis imputation algorithm

The data will divided in to three parts;

(a) Data set#1 includes all patients with the worst 25% pvo2 at Week 24 , patients who have missing data due to death will be included with this set

(b) Data set 2 includes all metoprolol patients with non-missing pVO2 data at Week 24, and patients who discontinued treatment due to AEs or patients who completed but not able to exercise due to CV AEs, HCM symptoms, or severe illness.

(c) Data set 3 includes all patients with non-missing pVO2 data at Week 24, and patients who completed treatment but have missing pVO2 due to invalid CPET results , malfunction of equipment, patients who completed but not able to exercise due to non-CV AEs, or COVID-19 related illness .

Using each data set the missing data will be imputed using the SAS procedure provided below. If a data set includes patients from one treatment arm only , then treatment can be dropped from the imputation model.

**Imputation model for primary endpoint**

```
proc mi data=work seed=&seed out=miout NIMPUTE=100 ;
        class <treatment arm> < Diagnosis Period > <Exercise Modality> <base NYHA> <sex>;
        var <treatment arm> <sex> <age> <base pVO2> <base hemoglobin> <base KCCQ
        CSS> <baseline NYHA> <last available post rand NYHA> <last available post rand
        resting LVOT> <last available post rand Valsalva LVOT> <W24 pVO2> ;
        monotone reg(W24 pVO2);
 run;
```

Imputed data from each data set will be combined, for patients with non-missing data the combined data will remove duplicated data that come from each dataset.

Sensitivity analysis imputation algorithm

The data will divided in to three parts;

(a) Data set#1 includes all patients with the worst 25% pvo2 at Week 24 , patients who have missing data due to death will be included with this set

(b) Data set 2 includes all metoprolol patients with non-missing pVO2 data at Week 24, and patients who discontinued treatment due to AEs , patients who completed but not able to exercise due to CV AEs, HCM symptoms, severe illness, or not able to exercise due to non-CV AEs.

(c) Data set 3 includes all patients with non-missing pVO2 data at Week 24, and patients who completed treatment but have missing pVO2 due to invalid CPET results , malfunction of equipment, patients who completed but not able to exercise COVID-19 related illness .

Using each data set the missing data will be imputed using the SAS procedure provided above. If a data set includes patients from one treatment arm only , then treatment can be dropped from the imputation model.

Supportive estimand analysis imputation algorithm

The imputation model will include all patients who meet the supportive estimand population definition, and set the missing data will be imputed using the SAS procedure provided above.

**Multiple Imputation for sensitivity analysis for repeated measures endpoint**

```
Step1:
proc mi data=work1 seed=&seed1 out=miout1 NIMPUTE=100;
        by <treatment arm>;
        mcmc IMPUTE=monotone ;
        var <base> <var week 2> <var week4> <var week6> <var week8> <var week12> <var
week16> <var week20> <var week24>;

run;

Step 2:

proc mi data=miout1 seed=&seed NIMPUTE=1 OUT=miout2;
 class <treatment arm>;
 by _IMPUTATION_;
 var <base> <var week 2> <var week4> <var week6> <var week8> <var week12> <var
week16> <var week20> <var week24>;
 monotone reg /details);
 mnar model <var week 2> <var week4> <var week6> <var week8> <var week12> <var
week16> <var week20> / modelobs = (trt01pn = '0'));
run;
```

**SAS codes using proc minalyze to combine results from imputed datasets**

The pooled estimates from the 100 imputed datasets are obtained from the following codes.

```
Ods output parameterEstimates=zzz
proc mianalyze data=est edf=&df;
  modeleffects estimate;
  stderr stderr;
run;
```

**Multiple Imputation for categorical endpoint**

```
proc mi data=work seed=&seed out=outwork NIMPUTE=100;
 class <var at week8> < var at week 12> < var at week 16> < var at week 20> < var at week 24>
        <treatment arm>;
   var  <treatment arm> <var at week8> < var at week 12> < var at week 16> < var at week 20> < var at
         week 24> ;
fcs logistic (<var at week8> < var at week 12> < var at week 16> < var at week 20> < var at week 24> =
<treatment arm> /link=glogit);
run;
```

**Mixed model for CPET data [page 41 repeated measure analysis]**

```
proc mixed data=work;
    class <subject ID> <trtid> <visit> <stratification factors> ;
    model <chg in CPET>=<trtid> <stratification factors> <stratification factors>*<visit> /s;
    estimate 'active at Week 24' int 1 <trtid> 1 <stratification factors> &c1 &c2 stratification
    factors>*<visit> 0 0 &c1 & / e;
    estimate 'placebo at Week 24' int 1 <trtid> 0 <stratification factors> &c1 &c2 stratification
    factors>*<visit> 0 0 &c1 & / e;
    estimate 'active vs PBO at Week 24' trtid 1 -1 /e cl;
    repeated <visit>/subject=<subject id> type=un;
run;
```

where trtid is assigned as 0 at baseline, 0 for metoprolol group at Week 24 and 1 for active group at Week 24. &c1 and &c2 are the proportion of participants evaluated in each stratification level among all the participants.

**Subgroup analysis for the primary endpoint**

```
proc mianalyze parms=mixparms covb(effectvar=rowcol)=mixcovb;
    class <treatment arm> < Diagnosis Period > <exercise modality> <subgroup> ;
    modeleffects Intercept <base pvo2 > <base weight> <treatment arm> < Diagnosis Period >
    <Exercise Modality> <subgroup>*<treatment arm>;
    run;
```

**SAS codes to evaluate normality assumption for the primary endpoint**

The normality assumptions for the ANCOVA analysis will be assessed by residual illustration. The outpred option in the above code stores residuals which are used to test the assumption of normality. Examination of residuals can be done using the following codes.

```
proc univariate data=work normal;
var ScaledResid; QQPLOT ScaledResid;
ods output QQPlot=qqplot;
run;
```

**SAS codes to perform CMH test**

```
proc freq data=work;
tables < Diagnosis Period >*<CPET modality>*<treatment arm>*<response Y/N>/CMH
COMMONRISKDIFF (cl=mh COLUMN=2) ;
EXACT RISKDIFF (column=2) relrisk (column=2) COMOR ;
run;
```

**SAS code for EQ-5D-5L Index Value**

```
**************************************************************
*SAS syntax code for the computation of index*
*values with the US TTO value set*
**************************************************************

data WORK.CAT;
set WORK.CAT;

if mobility eq 1 then disut_mo=0;
```

```
else if mobility eq 2 then disut_mo=0.096;
else if mobility eq 3 then disut_mo=0.122;
else if mobility eq 4 then disut_mo=0.237;
else if mobility eq 5 then disut_mo=0.322;

if selfcare eq 1 then disut_sc=0;
else if selfcare eq 2 then disut_sc=0.089;
else if selfcare eq 3 then disut_sc=0.107;
else if selfcare eq 4 then disut_sc=0.220;
else if selfcare eq 5 then disut_sc=0.261;

if activity eq 1 then disut_ua=0;
else if activity eq 2 then disut_ua=0.068;
else if activity eq 3 then disut_ua=0.101;
else if activity eq 4 then disut_ua=0.255;
else if activity eq 5 then disut_ua=0.255;

if pain eq 1 then disut_pd=0;
else if pain eq 2 then disut_pd=0.060;
else if pain eq 3 then disut_pd=0.098;
else if pain eq 4 then disut_pd=0.318;
else if pain eq 5 then disut_pd=0.414;

if anxiety eq 1 then disut_ad=0;
else if anxiety eq 2 then disut_ad=0.057;
else if anxiety eq 3 then disut_ad=0.123;
else if anxiety eq 4 then disut_ad=0.299;
else if anxiety eq 5 then disut_ad=0.321;

disut_total=disut_mo+disut_sc+disut_ua+disut_pd+disut_ad;
EQindex=1-disut_total;
run;
```

Signature Manifest

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1: Electronic Approvals

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