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Bristol Myers Squibb™

PASS INFORMATION

Title	Meta analysis to assess CV safety protocol
Protocol Version Identifier	0.2
Date of Last Version of Protocol	Not applicable
EU PAS Register Number	Study not yet registered
Active Substance	mavacamten
Medicinal Product	CAMZYOS
Product Reference	EU/1/23/1716/001-012
Procedure Number	EMEA/H/C/005457
Marketing Authorisation Holder(s)	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867, Ireland
Joint PASS	No
Research Question and Objectives	**Research Question** What is the risk of major cardiovascular (CV) outcomes associated with mavacamten in adult patients with symptomatic hypertrophic cardiomyopathy (HCM) in placebo-controlled, double-blind, randomized Phase 3 and 3b/4 studies? **Research Objectives** The objective of this study is to assess whether a detrimental CV risk observed under mavacamten treatment is non-inferior to the risk presented under placebo treatment. ***Primary Objective*** The primary objective of this study is to assess whether the risk of major CV events defined herein as expanded MACE (e-MACE) in the mavacamten group is non-inferior to risk in placebo group. ***Secondary Objectives*** The secondary objective of this study is to assess the effect of mavacamten treatment on other CV safety

	outcomes, including the individual components of e-MACE, and all-cause mortality.
Country(ies) of Study	Defined in secondary data sources
Author	

MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867, Ireland
24-hr Emergency Telephone Number	Not applicable

This protocol has been reviewed and approved by the marketing authorization holder's Qualified Person for Pharmacovigilance. The electronic signature is available on file.

Bristol-Myers Squibb Company

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2 LIST OF ABBREVIATIONS

Term	Definition
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AE	Adverse event
BMS	Bristol Myers Squibb
CHMP	Committee for Medicinal Products for Human Use
CMR	Cardiac Magnetic Resonance
CSR	Clinical study report
CV	Cardiovascular
eCTD	Electronic common technical document
e-MACE	Expanded MACE
EC	European Commission
EOS	End of Study
EOT	End of treatment
EU	European Union
EURD list	List of EU reference dates and frequency of submission of periodic safety update reports (PSURs)
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HR	Hazard ratio
ICD	Implanted cardiac device
ICMJE	International Committee of Medical Journal Editors
FFPM	Fellow of Faculty of Pharmaceutical Medicine
LTE	Long-term extension (study)
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MAA	Marketing Authorisation Application
MACE	Major adverse cardiovascular events
MD	Medical doctor
MI	Myocardial infarction
nHCM	Non-obstructive HCM
NYHA	New York Heart Association
oHCM	Obstructive HCM

Term	Definition
PD	Pharmacodynamic(s)
PICOS	Population, intervention, comparators, outcomes, and study design
PBRER	Periodic benefit-risk evaluation report
PK	Pharmacokinetic(s)
PO	Per oral
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
QD	Once daily
RCT	Randomized controlled trials
RMP	Risk management plan
SAP	Statistical analysis plan
SRT	Septal reduction therapy

3 RESPONSIBLE PARTIES

Responsible Parties	Contact Details
Principal Investigator	N/A
Marketing Authorisation Holder	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland

4 ABSTRACT

4.1 Title

Meta-analysis to assess cardiovascular safety of mavacamten.

4.2 Rationale and Background

Mavacamten is a novel small molecule, allosteric inhibitor of cardiac muscle myosin that selectively targets cardiac myosin and reversibly inhibits its binding to actin.

---------- -A meta-analysis approach including all available and planned placebo-controlled trials of mavacamten in hypertrophic cardiomyopathy (HCM) was accepted by the CHMP: patient-level data from the data sources will be utilized to evaluate the risk of clinically significant CV safety-related outcomes in patients with symptomatic HCM treated with mavacamten versus placebo, applying an expanded definition of major adverse cardiovascular events (MACE), defined for this study as expanded MACE (e-MACE; see Sections 4.6 and 9.3.1). In addition to e-MACE, the other variables utilized to characterize CV risk of mavacamten are MACE, MACE-plus and all-cause mortality.

In Europe, this study constitutes a Post Authorization Measure (PAM) referenced as MEA 002, an additional pharmacovigilance activity in the risk management plan (RMP).

4.3 Research Question and Objectives

Research Question

What is the risk of major CV outcomes associated with mavacamten in adult patients with symptomatic HCM in placebo-controlled, double-blind, randomized Phase 3 and 3b/4 studies?

Research Objectives

The objective of this study is to assess whether a detrimental CV risk observed under mavacamten treatment is non-inferior to the risk presented under placebo treatment.

Primary Objective

The primary objective of this study is to assess whether the risk of major CV events, herein defined as e-MACE, in the mavacamten group is non-inferior to risk in placebo group.

Secondary Objectives

The secondary objective of this study is to assess the effect of mavacamten treatment on other major CV safety outcomes, including the individual components of e-MACE, and all-cause mortality.

4.4 Study Design

This is a meta-analysis utilizing patient-level data from all Phase 3 and 3b/4, placebo-controlled, double-blind, randomized studies of mavacamten in adult patients with symptomatic HCM that have been completed or are ongoing prior to the end of 2023 as secondary data sources.

4.5 Population

To make use of the totality of available data in a controlled setting for CV risk assessment, all available randomized, placebo-controlled, double-blind Phase 3 and 3b/4 studies with mavacamten in adults with symptomatic HCM, i.e., 5 studies overall, are utilized as data sources contributing to the meta-analysis (see Table 4.5-1). The dose strengths of the obstructive hypertrophic cardiomyopathy (oHCM) and non-obstructive hypertrophic cardiomyopathy (nHCM) studies include those used in the approved label and all studies include clinically-guided titration schemes. Based on the mechanism of action of the drug and the similarities in the nature of the disease, co-morbidities and expected safety profile, this broader symptomatic HCM patient population is considered appropriate for the purpose of CV risk evaluation.

Table 4.5-1: Overview of studies contributing to meta-analysis

Study Name	Current Status	Study Population
EXPLORER-HCM (MYK-461-005) Phase 3	Completed	Symptomatic obstructive HCM; LVOT gradients at rest or with provocation (ie, Valsalva or exercise) ≥ 50 mmHg
VALOR-HCM (CV027-006) Phase 3	Placebo-controlled, double-blind period completed	
EXPLORER-CN (LB2001-301) Phase 3	Placebo-controlled, double-blind period completed	
MEMENTO (CV027-1088) Phase 3b/4	Open to enrolment and ongoing	
ODYSSEY-HCM (CV027-031) Phase 3	Ongoing	Symptomatic non-obstructive HCM; LVOT gradient at rest < 30 mmHg and with provocation < 50 mmHg

4.6 Variables

The primary outcome variable is defined as time from first dose to the first occurrence of an e-MACE event within the placebo-controlled double-blind treatment period, with

expanded-MACE defined for this study as a composite of adjudicated events of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for heart failure (HF), hospitalization for arrhythmia, other CV hospitalization (for events other than HF or arrhythmia), or appropriate shock therapy from implanted cardiac device (ICD).

The primary analysis will include the treatment group (mavacamten versus placebo) as an independent variable.

The secondary outcome variables are defined as time from first dose to:

- The first occurrence of (4-point) MACE event within the placebo-controlled double-blind treatment period, with MACE defined as a composite of adjudicated event of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF.
- The first occurrence of MACE-plus event within the placebo-controlled double-blind treatment period, where MACE-plus is defined for this study as a composite of adjudicated event of CV death, non-fatal MI, non-fatal stroke, hospitalization for HF, or hospitalization for arrhythmia, or appropriate shock therapy from ICD.
- All-cause mortality within the placebo-controlled double-blind treatment period.
- CV death within the placebo-controlled double-blind treatment period.
- The first occurrence of each of the following events within the placebo-controlled double-blind treatment period:
  - non-fatal MI
  - non-fatal stroke
  - hospitalization for HF
  - hospitalization for arrhythmia
  - other CV hospitalization (for events other than HF or arrhythmia)
  - appropriate shock therapy from ICD

The analyses will include first events that occur on-treatment during the placebo-controlled double-blind period for each study, based on internal or external adjudication of the secondary data sources.

4.7 Data Sources

The study will use pre-existing secondary data sources being the five studies identified in a BMS clinical trial repository of Company (or partner) sponsored Phase 3-4 trials.

4.8 Study Size

The primary goal of this meta-analysis is to assess whether a detrimental CV risk observed with mavacamten treatment is non-inferior to the risk presented with placebo treatment, by evaluating the primary endpoint with a non-inferiority margin of 2.2.

4.9 Study Analysis

A meta-analytical approach will be utilized to combine evidence using patient-level data from the five relevant studies to allow inference to be made to the population of symptomatic hypertrophic cardiomyopathy (HCM) patients.

The time to the first occurrence of e-MACE events will be analyzed using a stratified Cox proportional hazards model, with study as a stratification factor and treatment as a fixed effect, to provide the overall hazard ratio (HR) between mavacamten and placebo along with its associated 2-sided 95% confidence interval. Noninferiority will be concluded if the upper limit of the 95% confidence interval (CI) of hazard ratio (HR) is less than 2.2.

4.10 Milestones

Table 4.10-1: Meta-analysis Study Milestones

Milestone	Planned Date
Protocol submission	within 90 days after EC decision
Submission of study progress reports [a]	Submitted in accordance with EURD list [a]
Submission of final study report	Completed within 1 year after all studies have been unblinded

[a] first progress report planned within 1 year after receipt of PRAC endorsement of the protocol.

5 AMENDMENTS AND UPDATES

None.

6 MILESTONES

The study milestones are presented in Table 6-1 below.

Table 6-1: Meta-analysis Study Milestones

Milestone	Planned Date
Protocol submission	within 90 days after EC decision
Submission of study progress reports	Submitted in accordance with EURD list [a]
Submission of final study report	Completed within 1 year after all studies have been unblinded

[a] first progress report planned within 1 year after receipt of PRAC endorsement of the protocol.

7 RATIONALE AND BACKGROUND

Two hypertrophic cardiomyopathy (HCM) phenotypes are recognized based on the presence or absence of obstruction of the left ventricular outflow tract (LVOT), obstructive hypertrophic cardiomyopathy (oHCM) and non-obstructive hypertrophic cardiomyopathy (nHCM), where obstruction is defined as a peak LVOT gradient ≥ 30 mmHg at rest or with provocation.[2] Patients with both obstructive and non-obstructive forms of HCM often experience symptoms that include

shortness of breath at rest or with exertion, fatigue, chest pain, and limited exercise capacity that worsen over time in the absence of effective treatment. The presence of progressive outflow tract obstruction in oHCM may further exacerbate the disease burden. Patients with hypertrophic cardiomyopathy (HCM) also experience co-morbidities that can lead to a variety of major adverse events over the course of their disease, such as atrial fibrillation, ventricular arrhythmias, stroke, myocardial infarction, heart failure and sudden death. The overall rates of major cardiovascular events in HCM population reported in the literature are relatively low.[3]

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

Clinical safety data from the completed EXPLORER-HCM study and ongoing VALOR-HCM and MAVA-LTE studies were included in the initial Marketing Authorisation Application (MAA) fore valuation by the Committee for Medicinal Products for Human Use (CHMP) and based on these d ata CHMP considered mavacamten to have an acceptable cardiovascular (CV) safety profile.

The low event rate for 4-point MACE (a composite of events of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF) makes it difficult to precisely estimate any differential risk for mavacamten-treated patients compared to those treated with placebo. Similarly, the large sample size that would be required to conduct a sufficiently powered, prospective, randomized trial of these rare outcomes in a reasonable period of time is not feasible. In accordance with the EMA Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015), an alternative to a prospective CV outcome study is to continue to characterize the mavacamten CV safety profile with a meta-analytic approach. CHMP accepted conducting a meta-analysis as an additional pharmacovigilance (PV) activity, referenced as MEA 002 in the risk management plan (RMP), to address the missing information on “long-term safety, including detrimental CV effects”.[4]

To further increase the ability of the trial to characterize the risk of major CV outcomes in light of the low expected rate of 4-point MACE, an expanded definition of MACE (e-MACE, as defined in Sections 4.6 and 9.1.1) was proposed and accepted by the CHMP. This composite primary endpoint, including the components of 4-point MACE plus hospitalization for heart failure (HF), hospitalization for arrhythmia, other CV hospitalization (for events other than heart failure or arrhythmia), and appropriate shock therapy from ICD, reflects the most significant events of CV risk. HF and arrhythmia (eg, atrial fibrillation) are the two most common events that may occur over time with chronic progression of HCM.[5]

Individual patient-level adjudicated events from all existing (completed and ongoing) and planned placebo-controlled, double-blind BMS (or partner)-sponsored mavacamten studies initiated before the end of 2023, are used as secondary data sources for the meta-analysis that will be performed after the last study is unblinded. The meta-analysis aims to assess the effect of mavacamten on CV safety concluding noninferiority for mavacamten if the upper limit of the 95% CI of HR of mavacamten relative to placebo is below 2.2. The safety endpoint of expanded MACE (e-MACE) will be evaluated based on patient-level events derived from the secondary data sources.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

What is the risk of major CV outcomes associated with mavacamten in adult patients with symptomatic HCM in placebo-controlled, double-blind, randomized Phase 3 and 3b/4 studies?

8.2 Research Objectives

The objective of this study is to assess whether a detrimental CV risk observed under mavacamten treatment is non-inferior to the risk presented under placebo treatment.

8.2.1 Primary Objective

The primary objective of this study is to assess whether the risk of major CV events defined herein as e-MACE in the mavacamten group is non-inferior to risk in placebo group.

8.2.2 Secondary Objectives

The secondary objective of this study is to assess the effect of mavacamten treatment on other CV safety outcomes, including the individual components of e-MACE, and all-cause mortality.

8.2.3 Exploratory Objectives

Not applicable.

9 RESEARCH METHODS

9.1 Study Design

This is a patient-level meta-analysis with all available placebo-controlled, double-blind, randomized Phase 3 and Phase 3b/4 studies with mavacamten (completed or ongoing before the end of 2023) contributing as secondary data sources for the assessment of CV safety in the symptomatic adult HCM population. The analysis will be performed after the placebo-controlled double-blind period of the last study is unblinded (see Section 9.7). Each clinical trial utilizes the same intervention (mavacamten with similar dose strengths and clinically-guided titration) and comparator (placebo), while allowing standard-of-care treatment. This representation of the broad HCM patient population is considered appropriate for the purpose of CV risk evaluation based on the mechanism of action of the drug and similarities in the nature of the disease and expected adverse event (AE) profile in the different study populations.

9.1.1 Primary Endpoint

The primary endpoint is defined as:

Time from first dose to the first occurrence of an e-MACE event, where an e-MACE event is defined as a composite of adjudicated events of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for heart failure (HF), hospitalization for arrhythmia, other CV hospitalization (for events other than heart failure or arrhythmia), or appropriate shock therapy from ICD.

9.1.2 Secondary Endpoints

The secondary endpoints are defined as time from first dose to:

1) The first occurrence of MACE (4-point), where MACE is defined as a composite of adjudicated event of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF.
2) The first occurrence of MACE-plus, where MACE-plus is defined as a composite of adjudicated event of CV death, non-fatal MI, non-fatal stroke, hospitalization for HF, or hospitalization for arrhythmia, or appropriate shock therapy from ICD.
3) All-cause mortality.
4) CV death.
5) The first occurrence of each of the following events:
    a) non-fatal MI
    b) non-fatal stroke
    c) hospitalization for HF
    d) hospitalization for arrhythmia
    e) other CV hospitalization (for events other than HF or arrhythmia)
    f) appropriate shock therapy from ICD

9.1.3 Exploratory Endpoints

Not Applicable.

9.2 Setting

Four randomized placebo-controlled double-blind clinical trials were accepted by the Pharmacovigilance Risk Assessment Committee (PRAC) to be included in the meta-analysis (Table 9.2.1-1). A fifth study (MEMENTO) has been added for completeness. The addition of MEMENTO may also mitigate any loss of sensitivity resulting from modifications to the ODYSSEY-HCM protocol that may lead to the collection of fewer events than initially expected (e.g., reduction of the placebo-controlled period).

9.2.1 Study Population

The source population is defined by the parent study protocols, ie, adults 18 years of age or older with symptomatic HCM (oHCM and/or nHCM) in existing Phase 3 and 3b/4 studies.

The populations of EXPLORER-HCM, VALOR-HCM, EXPLORER-CN and MEMENTO trials include symptomatic (primarily New York Heart Association (NYHA) functional classes II-III with some IV) adult oHCM patients with LVOT peak gradients > 50 mmHg with a majority of patients being on standard of care HCM background therapy. The phase 3 nHCM trial ODYSSEY-HCM allows inclusion of patients with provoked gradients < 50 mmHg and utilizes

the dose strengths of mavacamten similar to those used in the oHCM program. Based on the mechanism of action of the drug and similarities in the nature of the disease, co-morbidities and expected safety events, this representation of the broader HCM patient population is considered appropriate to answer the research question regarding the risk of the CV outcomes.

An overview of the study design, dosing regimen, study population, sample size, duration and status for each study that contributes to the meta-analysis is shown in Table 9.2.1-1 below.

Table 9.2.1-1: Overview of BMS (or partner)-sponsored Placebo-controlled Clinical Trials Included in the Meta-analysis

Study	Study Design	Dosing Regimen	Study Population	Sample Size & Study Duration – Current Status
EXPLORER-HCM (MYK-461-005) (placebo-controlled, double-blind period: 2018-2020; completed)[6] [refer to CSR in eCTD sequence number 0000]	Phase 3, double-blind, randomized 1:1, placebo-controlled, multicenter, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo in adults ≥ 18 years with symptomatic oHCM	The starting dose of mavacamten was 5 mg once daily. At Week 8 and Week 14, mavacamten dose was up-titrated for individual subjects based on their mavacamten plasma concentration and pharmacodynamic (PD) responses at Week 6 and Week 12, respectively, and according to dose titration protocol. The permissible doses were 2.5 mg, 5 mg, 10 mg, and 15 mg.	• LVOT peak gradient ≥ 50 mmHg during screening as assessed by echocardiography at rest, after Valsalva maneuver or post-exercise and VLVOT gradient ≥ 30 mmHg (confirmed by echocardiography core laboratory interpretation). • NYHA Class II or III symptoms at screening • Background HCM therapy (e.g., beta-blocker, verapamil, or diltiazem) is allowed.	A total of 251 subjects were randomized 1:1 into the study, including 123 subjects in the mavacamten group and 128 subjects in the placebo group. Subjects remained in the double-blind period for 30 weeks followed by 8 weeks of double-blind study drug washout
VALOR-HCM (CV-027-006)[7] (placebo-controlled, double-blind period: 2020—2022; completed) [refer to primary CSR in eCTD sequence number 0005]	Phase 3, randomized, double-blind, placebo-controlled, multicenter study of adults ≥ 18 years with oHCM who meet 2011 ACCF/AHA criteria for SRT and have been referred for an SRT procedure.	The starting dose of mavacamten in this study was 5 mg once daily and subjects were evaluated for possible down-titration at Week 4 based on Valsalva LVOT < 30mmHg and up-titration at Weeks 8 and 12 to a maximum dose of mavacamten 15 mg based on the LVEF ≥ 50% and Valsalva LVOT gradient ≥30 mmHg dose titration protocol. The permissible doses were 2.5 mg, 5 mg, 10 mg, and 15 mg.	• Dynamic LVOT gradient at rest or with provocation (ie, Valsalva or exercise) ≥ 50 mmHg • NYHA Class III or IV or subjects who are NYHA Class II with exertion-induced syncope or near syncope • Mono- or combination therapy with beta-blockers, non-dihydropyridine calcium channel blockers, and/or disopyramide was allowed	A total of 112 subjects were randomized 1:1 to mavacamten and placebo group, including 56 subjects in the mavacamten group and 56 subjects in the placebo group. Subjects remained in the double-blind period for 16 weeks followed by active-controlled (Week 16 – Week 32) and long-term extension period (up to Week 128) where all subjects receive mavacamten.

Table 9.2.1-1: Overview of BMS (or partner)-sponsored Placebo-controlled Clinical Trials Included in the Meta-analysis

Study	Study Design	Dosing Regimen	Study Population	Sample Size & Study Duration – Current Status
EXPLORER-CN (LB2001-301) (placebo-controlled, double-blind period: 2020-2023; completed) [refer to protocol]	Phase 3, randomized, double-blinded, placebo-controlled, multicenter, parallel-group clinical study with a long-term extension to evaluate the efficacy, safety, and PK of mavacamten in Chinese adults with symptomatic oHCM	The starting dose of mavacamten in this study is 2.5 mg once daily (QD).: At Week 8, Week 14 and Week 20, mavacamten dose will be adjusted (increase, decrease, remain unchanged) for individual subjects based on their mavacamten plasma concentration and pharmacodynamic (PD) responses at Week 6, Week 12, and Week 18, respectively, and according to dose titration protocol. The permissible doses were 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg.	• LVOT peak gradient ≥ 50 mmHg during screening as assessed by echocardiography at rest or after Valsalva maneuver (confirmed by echocardiography core laboratory interpretation). • NYHA Class II or III symptoms at screening • Background HCM therapy (e.g., beta-blocker, verapamil, or diltiazem) is allowed.	Approximately 81 eligible participants were enrolled and randomized (2:1) to mavacamten and placebo group. Participants received mavacamten or matching placebo for 30 weeks in double blinded manner. After 30-week double-blinded placebo-controlled treatment, eligible participants receive mavacamten for additional 48 weeks (placebo group: switch from placebo to mavacamten, mavacamten group: maintain on mavacamten).
MEMENTO (CV020-1088) (placebo-controlled, double-blind period: 2023-2026; ongoing) [refer to protocol]	Phase 3b/4, Randomized, Double-blind, Placebo-controlled Clinical Study to evaluate mavacamten in adults with symptomatic oHCM to assess the impact on myocardial structure with cardiac magnetic resonance imaging (CMR)	The recommended starting dose of mavacamten is 5 mg once daily (QD) per oral (PO). The labelled dose will subsequently be up-titrated, down-titrated, or maintained based on the echocardiographic assessment of the Valsalva LVOT gradient and left ventricular ejection fraction (LVEF) status, as determined by the unblinded local echocardiography team. Participant response to treatment with mavacamten will be assessed at Week 4,	LVOT peak gradient ≥ 30 mmHg during the screening period, as assessed by echocardiography at rest, and ≥ 50 mmHg after Valsalva or after exercise, as determined by echocardiography site interpretation. Documented LVEF ≥ 55% at rest, as determined by site interpretation of screening TTE. NYHA Functional Class II or III symptoms at screening. Documented oxygen saturation ≥ 90% at rest at screening and baseline.	Enrollment target: 100 participants (n = 50 in each treatment arm) will be randomized and treated. The study will involve a total treatment length of up to 96 weeks, of which the first 48 weeks will be the double-blind treatment period, and then the open-label, active mavacamten treatment period for up to Week 96

Table 9.2.1-1: Overview of BMS (or partner)-sponsored Placebo-controlled Clinical Trials Included in the Meta-analysis

Study	Study Design	Dosing Regimen	Study Population	Sample Size & Study Duration – Current Status
		Week 8, Week 12, and every 12 weeks thereafter. The permissible doses are 2.5 mg, 5 mg, 10 mg, and 15 mg.	Patients with ICD are not permitted to enroll as ICD is contraindicated for CMR imaging.	
ODYSSEY-HCM (CV027-031) (Jan. 2023 – 2025; ongoing) [refer to protocol in eCTD sequence number 0005]	Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo (1:1) in adult participants ≥ 18 years with symptomatic nHCM	The starting dose of mavacamten in this study is 5 mg once daily. Subsequently, dosing will be up-titrated, down-titrated or maintained based on evaluation of LVEF by the core echocardiography laboratory. The permissible doses are 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg.	Peak LVOT gradient < 30 mmHg at rest and < 50 mmHg with provocation (Valsalva maneuver and stress echocardiography) NYHA Class II or III At the time of enrollment, participants may be on background therapy for HCM recommended by local contemporary guidelines.	Approximately 420 participants will be randomized in a 1:1 ratio to mavacamten and placebo in a blinded fashion. Participants will receive mavacamten or matching placebo for 48-weeks in double-blinded manner. After 48-week double-blinded placebo-controlled treatment, eligible participants will receive mavacamten for up to 5 years (placebo group: switch from placebo to mavacamten, mavacamten group: maintain on mavacamten).

CMR: Cardiac Magnetic Resonance; CSR: Clinical study report; eCTD: Electronic common technical document; EOS: End of Study; EOT: End of treatment; HCM: Hypertrophic cardiomyopathy; oHCM: Obstructive HCM; nHCM: Non-obstructive HCM; LVEF: left ventricular ejection fraction; LVOT: Left ventricular outflow tract; NYHA: New York Heart Association; PD: Pharmacodynamic(s); PK: Pharmacokinetic(s); PO: Per oral, QD: Once daily; SRT: Septal reduction therapy; TTE: transthoracic echocardiography .

9.2.2 Inclusion Criteria

The following inclusion criteria were used to select studies contributing to the meta-analysis:

- Phase 3 and 3b/4 studies conducted by BMS or its licensed partners for mavacamten that were initiated or planned to initiate prior to the end of 2023.
- Placebo-controlled, double-blind, randomized studies of mavacamten
- Studies including adult (age ≥ 18 years) patients with symptomatic HCM.

Studies are included if they meet all three conditions.

9.2.3 Exclusion Criteria

Not Applicable.

9.3 Variables

9.3.1 Outcomes/Endpoint Variables

The variables in this study are the same as the primary and secondary endpoints defined in Section 9.1.1. The analyses will include first events that occur on-treatment during the placebo-controlled double-blind period for each study, based on internal or external adjudication in the secondary data sources. Please refer to Appendix 1 for the list of Medical Dictionary for Regulatory Activities (MedDRA) terms (Version 26.1) used to define the major CV events included as primary and secondary endpoints.

9.3.2 Exposure/Independent Variables of Interest

The primary analysis will include the treatment group (mavacamten versus placebo) as an independent variable.

9.4 Data Sources

The study will use pre-existing secondary data sources being the five studies identified in a BMS clinical trial repository of Company (or partner) sponsored Phase 3-4 trials.

9.5 Study Size

The primary hypothesis will test the effect of mavacamten against placebo for the primary endpoint. The following hypothesis will be tested:

Null hypothesis (H0): HR ≥ 2.2 vs.
Alternative hypothesis (H1): HR < 2.2
where HR is the hazard ratio of mavacamten relative to placebo.

The study will combine evidence from five clinical trials using patient-level data and test the null hypothesis at 0.025 significance level. The primary endpoint null hypothesis will be rejected if the upper bound of the 95% confidence interval around HR, based on stratified Cox proportional hazards model, is less than 2.2.

A noninferiority margin of 2.2 was proposed for this meta-analysis during MAA, justified based on its consistency with the EMA reflection paper[8] on assessment of CV safety profile of medicinal products that mentions "the absence of signals for increased CV risk" to be a factor of influence in relation to quantification of the CV safety profile in patients. It was acknowledged by CHMP during MAA assessment that the conventionally discussed margin for exclusion of CV harm (e.g. upper confidence limit for relative risk on MACE at 1.8) would not be feasible, and the upper limit of confidence interval (ULCI) for the HR of 2.2 was considered acceptable in the context of its existing acceptable CV safety profile and continued long-term safety monitoring outside of the meta-analysis (EMEA/H/C/005457).

9.6 Data Management/Data Quality Assurance

All aspects of the parent studies will be carefully monitored by the sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures (SOPs).

All statistical analyses (details to be provided in the statistical analysis plan [SAP]) will be conducted using SAS version [9.4] or higher.

All data have been or will be collected under standard clinical trials conditions (ie, GCP maintained), the data have been or will be cleaned and validated, databases with placebo-controlled double-blind periods will have been locked by the time of data collection for the meta-analysis.

The Clinical Operations, Data Management, and Biostatistics departments at the contract research organizations (CRO) will collaborate internally and with the sponsor to ensure that the data collected and analyzed for this meta-analysis are of the highest quality possible and meet the data standards set for the trials. This will be accomplished in part through programmed edit checks which will be reviewed by the statisticians, programmers, and other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified. In addition, periodic reviews of listings of accumulating data, assessment of data query trends and resulting retraining of trial site personnel will be performed to further ensure data quality.

9.7 Data Analysis

The meta-analysis will combine evidence using patient-level data from relevant studies described in Section 9.2 and appropriate statistical methods will be applied, to allow inference to be made to the population of symptomatic HCM patients.

This meta-analysis will be performed within 1 year after the last study is unblinded. At present, EXPLORER-HCM, VALOR-HCM and EXPLORER-CN have completed their double-blind placebo-controlled periods and treatment assignment has been unblinded for this period. ODYSSEY-HCM (ongoing) and MEMENTO (ongoing) are projected to be unblinded by 1Q 2026.

9.7.1 Primary Objective

The primary analysis will include time to the first e-MACE event that occurs on-treatment during the placebo-controlled double-blind period for each study. Patients completing the placebo-controlled double-blind period without any events observed will be censored at the end of the placebo-controlled double-blind treatment period. Patients who prematurely discontinue study or discontinue treatment early without any events observed will be censored at the earliest occurrence of either the last contact date, treatment discontinuation date, or scheduled end of placebo-controlled double-blind treatment period.

The time to the first occurrence of an e-MACE event will be analyzed using a stratified Cox proportional hazards model[9] with study as a stratification factor and treatment as a fixed effect, to provide the overall hazard ratio (HR) between mavacamten and placebo along with its associated 95% confidence interval.[10]

The primary endpoint null hypothesis will be rejected if the upper bound of the two-sided 95% confidence interval around HR, based on stratified Cox proportional hazards model, is less than 2.2. The primary estimand is defined below in Table 9.7.1-1.

Table 9.7.1-1: Estimand definition

Endpoint Category	Estimand			
	Endpoint	**Analysis Population**	**Intercurrent Events**	**Population-level Summary**
Primary objective is to assess the risk of e-MACE in mavacamten group compared to placebo, by evaluating the primary endpoint with a noninferiority margin of 2.2.				
Primary endpoint	Time to first e-MACE event	Safety Analysis Population*	Patients who prematurely discontinue study (including non-CV death) or discontinue treatment, will be censored at the earlier of last contact date or treatment discontinuation date or scheduled end of placebo-controlled double-blind treatment period.	The time to the first occurrence of e-MACE events will be analyzed using a stratified Cox proportional hazards model.

*Safety analysis population is defined as all randomized participants who received at least one dose of study drug with analyses conducted according to the actual treatment received

The number of events and incidence rate for each treatment group will be reported. A forest plot may be used for graphical presentation of the individual treatment effect estimates and confidence interval if appropriate. In addition to the composite endpoints, the number of subjects with an event and the event rate will be tabulated for each type of adjudicated event (i.e., separately for each component: CV death, non-fatal MI, non-fatal stroke, hospitalization for heart failure (HF), hospitalization for arrhythmia, other CV hospitalization (for events other than heart failure or arrhythmia) and appropriate shock therapy from ICD).

9.7.2 Secondary Objectives

The analysis of the secondary endpoints will be descriptive, and no hypothesis testing is planned.

Hazard ratios and corresponding two-sided 95% confidence interval for all secondary endpoints will be estimated using the same meta-analytic approach described for primary endpoint.

9.7.3 Exploratory Objectives

Not Applicable

9.8 Quality Control

Not Applicable, as quality control was performed within the clinical trial protocols of the data sources.

9.8.1 Database Retention and Archiving of Study Documents

Not Applicable. As no investigators are directly involved in this study, database retention and archiving of study documents by investigators is not applicable for this meta-analysis of existing clinical trials.

9.8.2 Registration of Study on Public Website

This study will be registered in the EU PAS Register.

9.9 Limitations of the Research Methods

The following aspects may affect the consistency and robustness of the evaluation of the safety question of interest:

Low prevalence of the disease and low rate of MACE reports: Recent studies in Europe estimate that the prevalence of HCM ranges from 4-7 per 10,000.[11,12,13,14] As the proportion of patients with symptomatic disease is approximately 48-61% in oHCM[15,16,17,18] and 33-35%[17,18] in nHCM, prevalence of symptomatic obstructive HCM in the adult population is < 5 in 10,000. Traditional MACE events (CV-death, non-fatal MI, non-fatal stroke) occur with a low frequency (approximately 1.5-2% per year in registries and cohorts) in HCM population. [3,19,20,21,22,23] Consequently, and to capture a wider range of events that could be considered clinically meaningful, the CV outcome definition was expanded from traditional MACE to e-MACE.

Varied follow-up in randomized, placebo-controlled trials: Mavacamten is intended for chronic use, but due to various constraints in the clinical development (e.g., the expected onset of treatment effect, and ethical considerations regarding the long-term exposure to placebo in symptomatic HCM patients) the available mavacamten RCTs have placebo-controlled periods of various duration. Considering the duration of the placebo-controlled double-blind period and low overall event rate, the number of events is expected to be low in each individual study. Consequently, small changes in the data can cause significant changes in the results. This problem could persist even after pooling data from many studies. Thus, as supplementary analysis, it is proposed to estimate exposure-adjusted incidence rates (from pooled data) for mavacamten and the placebo arm (within placebo-controlled double-blind period) to account for potentially different exposures.

Generalizability: Like all clinical trials, those included in the meta-analysis utilized specific inclusion/exclusion criteria that are more specific than the approved indication. Further, the RCTs included as data sources in the meta-analysis are conducted mostly in academic cardiac centers, some specializing in cardiomyopathy management, with a thorough and close follow up of patients which allows gathering of robust safety data, which may differ from clinical practice. However, the studies selected for the meta-analysis are representative of the broad symptomatic HCM population for which mavacamten is currently approved in the EU (oHCM) or may be approved on the basis of the ODYSSEY-HCM study (nHCM). Consequently, the patient population of this meta-analysis is considered appropriate for the purpose of CV risk evaluation based on the mechanism of action of the drug and similarities in the disease pathophysiology across the different study populations in clinical practice, as was accepted by CHMP (EMEA/H/C/005457).

Limitations of statistical methods: First, as the event rate is low, the study may encounter trial(s) with no events in one or both groups, as was observed for VALOR-HCM. In this situation the problem of monotone likelihood can be encountered, and the standard Cox Proportional Hazards method will have trouble with convergence. Even when the model does converge, the resulting estimates are often imprecise and have large standard errors. Details of statistical method(s) to address this will be provided in the SAP. Second, the model assumes proportional hazards i.e., hazard functions for any two individuals are proportional at any point in time and the hazard ratio does not vary with time. Any departure from proportional hazards will be assessed and additional analysis may be performed to account for non-proportionality. Third, the total number of events in four of five studies is either known or expected to be small (less than 12 events). Therefore, the ability to test for heterogeneity across studies may be limited. [24] The results from the individual studies will be assessed for qualitative consistency to ensure meta-analysis proceeds in a scientific manner and to aid in the interpretation of the results from the meta-analysis.

9.10 Other Aspects

As supplementary analysis, pooled exposure-adjusted incidence rate (EAIR) by treatment group will be presented along with 95% confidence interval of the EAIR as appropriate.

9.10.1 Strengths of Research Methods

The meta-analysis includes all randomized, placebo-controlled studies of mavacamten that have been completed, initiated or planned for initiation prior to the end of 2023, which results in five RCTs that qualify for inclusion (see Section 9.2.2). Utilizing data from RCTs ensures rigorous collection of safety data in a controlled manner in line with the EMA Reflection paper on assessment of cardiovascular safety profile of medicinal products, as these studies were designed and conducted to high standards in respect of assessment of CV outcomes.

Despite some differences in the design and study population in these five studies, each study was or will be adequately controlled and conducted in a well-defined population of adult patients with symptomatic oHCM or nHCM, using thorough inclusion/exclusion criteria in the individual study protocols (e.g., cardiac functional and physiological parameters, as well as permitted background therapy). These study populations were chosen as representative of the broad HCM patient population and considered appropriate for the purpose of CV risk evaluation based on the mechanism of action of the drug and similarities in the disease pathophysiology across the different study populations in clinical practice. Consequently, the trials' results, and the results of the meta-analysis, can be extrapolated to the more broadly defined population of patients with symptomatic HCM.

10 PROTECTION OF HUMAN SUBJECTS

Not Applicable.

10.1 Ethics Committee Review and Informed Consent

Not applicable. This study does utilize previously collected, de-identified data, and does not require review and approval by ethics committees or informed consent.

10.1.1 Ethics Committee Review

Not Applicable.

10.1.2 Informed Consent

Not Applicable. This study does not require that informed consent is obtained from patients.

10.2 Confidentiality of Study Data

The confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). No identifying information will be provided.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The design of this study is characterized by secondary use of data previously collected for other purposes. Therefore, for this study the submission of suspected adverse reactions in the form of Individual Case Safety Reports is not required.

11.1 Adverse Event Collection and Reporting

11.1.1 Adverse Event Collection

All patient-level MACE adverse events have been and will be collected within the individual clinical trials and will be analyzed and reported in aggregate in the final study report of the meta-analysis.

11.1.2 Adverse Event Reporting

Expedited individual case safety reporting is not applicable (secondary use of data).

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study progress reports will be included in the PBRER in accordance with EURD list, starting within 1 year after protocol approval by PRAC (see Section 6). Progress reports will contain status updates of the data sources and any relevant amendments pertaining to the data sources.

The final study report will include all results of this meta-analysis described in the SAP.

12.1 Scientific Publications

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

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

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

Those who make the most significant contributions, as defined above, will be considered for authorship of the publication.

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APPENDIX 1

Major Cardiovascular Events Included as Primary and Secondary Endpoints.

The following list of Medical Dictionary for Regulatory Activities (MedDRA) terms (Version 26.1) is used to define the major cardiovascular events included as primary and secondary endpoints.

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Appropriate Shock Therapy from Implanted Cardiac Device	
Cardiac resynchronisation therapy	10059862
Cardiovascular Death	
Cardiac death	10049993
Sudden cardiac death	10049418
Sudden death	10042434
Non-fatal Myocardial Infarction	
Acute cardiac event	10081099
Acute coronary syndrome	10051592
Acute myocardial infarction	10000891
Angina unstable	10002388
Blood creatine phosphokinase MB abnormal	10005472
Blood creatine phosphokinase MB increased	10005474
Coronary artery embolism	10011084
Coronary artery occlusion	10011086
Coronary artery reocclusion	10053261
Coronary artery thrombosis	10011091
Coronary bypass thrombosis	10059025
Coronary vascular graft occlusion	10075162
Heart-type fatty acid-binding protein increased	10088828
Kounis syndrome	10069167
Myocardial infarction	10028596
Myocardial necrosis	10028602
Myocardial reperfusion injury	10051624
Myocardial stunning	10072186
Papillary muscle infarction	10033697

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Periprocedural myocardial infarction	10079319
Post procedural myocardial infarction	10066592
Postinfarction angina	10058144
Silent myocardial infarction	10049768
Troponin I increased	10058268
Troponin increased	10058267
Troponin T increased	10058269
Non-fatal Stroke	
Amaurosis fugax	10001903
Basal ganglia infarction	10069020
Basal ganglia stroke	10071043
Basilar artery occlusion	10048963
Basilar artery stenosis	10004163
Basilar artery thrombosis	10063093
Benedikt's syndrome	10085451
Brachiocephalic arteriosclerosis	10075449
Brachiocephalic artery occlusion	10069694
Brachiocephalic artery stenosis	10075450
Brain hypoxia	10006127
Brain stem embolism	10074422
Brain stem infarction	10006147
Brain stem ischaemia	10006148
Brain stem stroke	10068644
Brain stem thrombosis	10062573
Brain stent insertion	10080887
CADASIL	10065555
Capsular warning syndrome	10067744
CARASIL syndrome	10081315
Carotid angioplasty	10071260
Carotid arterial embolus	10007684
Carotid arteriosclerosis	10067116
Carotid artery bypass	10053003
Carotid artery disease	10061744
Carotid artery insufficiency	10064949

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Carotid artery occlusion	10048964
Carotid artery restenosis	10072558
Carotid artery stenosis	10007687
Carotid artery stent insertion	10066102
Carotid artery stent removal	10069952
Carotid artery thrombosis	10007688
Carotid endarterectomy	10007692
Carotid revascularisation	10072559
Cerebellar artery occlusion	10053633
Cerebellar artery thrombosis	10008023
Cerebellar atherosclerosis	10084736
Cerebellar embolism	10067167
Cerebellar infarction	10008034
Cerebellar ischaemia	10068621
Cerebellar stroke	10079062
Cerebral angioplasty	10087440
Cerebral arteriosclerosis	10065559
Cerebral artery embolism	10008088
Cerebral artery occlusion	10008089
Cerebral artery restenosis	10075423
Cerebral artery stenosis	10063648
Cerebral artery stent insertion	10081893
Cerebral artery thrombosis	10008092
Cerebral bypass surgery	10089035
Cerebral gas embolism	10070813
Cerebral infarction	10008118
Cerebral infarction foetal	10008119
Cerebral ischaemia	10008120
Cerebral microembolism	10078311
Cerebral microinfarction	10083668
Cerebral revascularisation	10071508
Cerebral septic infarct	10070671
Cerebral small vessel ischaemic disease	10070878
Cerebral thrombosis	10008132
Cerebral vascular occlusion	10076895

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Cerebral vasoconstriction	10059109
Cerebral venous thrombosis	10008138
Cerebrovascular accident	10008190
Cerebrovascular disorder	10008196
Cerebrovascular insufficiency	10058842
Cerebrovascular stenosis	10061751
Claude's syndrome	10085447
Delayed ischaemic neurological deficit	10078388
Embolic cerebellar infarction	10084072
Embolic cerebral infarction	10060839
Embolic stroke	10014498
Foville syndrome	10082594
Hypoxic-ischaemic encephalopathy	10070511
Inner ear infarction	10070754
Internal capsule infarction	10083408
Ischaemic cerebral infarction	10060840
Ischaemic stroke	10061256
Lacunar infarction	10051078
Lacunar stroke	10076994
Lateral medullary syndrome	10024033
Middle cerebral artery stroke	10027580
Migrainous infarction	10056237
Millard-Gubler syndrome	10067462
Moyamoya disease	10028047
Occipital lobe stroke	10089110
Parietal lobe stroke	10089109
Perinatal stroke	10073945
Post cardiac arrest syndrome	10078202
Post procedural stroke	10066591
Precerebral arteriosclerosis	10077033
Precerebral artery embolism	10085250
Precerebral artery occlusion	10036511
Precerebral artery thrombosis	10074717
Pseudo-occlusion of internal carotid artery	10085779
Reversible cerebral vasoconstriction syndrome	10073240

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Reversible ischaemic neurological deficit	10050496
Spinal artery embolism	10049440
Spinal artery thrombosis	10071316
Spinal cord infarction	10058571
Spinal cord ischaemia	10050209
Spinal stroke	10082031
Stroke in evolution	10059613
Subclavian steal syndrome	10042335
Temporal artery stenosis	10089459
Thalamic infarction	10064961
Thalamic stroke	10087626
Thrombotic cerebral infarction	10067347
Thrombotic stroke	10043647
Transient ischaemic attack	10044390
Vascular encephalopathy	10063661
Vascular stent occlusion	10077143
Vascular stent stenosis	10077144
Vertebral artery arteriosclerosis	10084347
Vertebral artery occlusion	10048965
Vertebral artery stenosis	10047330
Vertebral artery thrombosis	10057777
Vertebrobasilar infarction	10089401
Vertebrobasilar insufficiency	10047334
Vertebrobasilar stroke	10082484
Weber's syndrome	10085448
Basal ganglia haematoma	10077031
Basal ganglia haemorrhage	10067057
Basilar artery perforation	10075736
Brain stem haematoma	10073230
Brain stem haemorrhage	10006145
Brain stem microhaemorrhage	10071205
Carotid aneurysm rupture	10051328
Carotid artery perforation	10075728
Central nervous system haemorrhage	10072043
Cerebellar haematoma	10061038

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Cerebellar haemorrhage	10008030
Cerebellar microhaemorrhage	10071206
Cerebral aneurysm perforation	10075394
Cerebral aneurysm ruptured syphilitic	10008076
Cerebral arteriovenous malformation haemorrhagic	10008086
Cerebral artery perforation	10075734
Cerebral cyst haemorrhage	10082099
Cerebral haematoma	10053942
Cerebral haemorrhage	10008111
Cerebral haemorrhage foetal	10050157
Cerebral haemorrhage neonatal	10008112
Cerebral microhaemorrhage	10067277
Epidural haemorrhage	10073681
Extra-axial haemorrhage	10078254
Extradural haematoma	10015769
Extradural haematoma evacuation	10082797
Extraischaemic cerebral haematoma	10080347
Haemorrhage intracranial	10018985
Haemorrhagic cerebellar infarction	10085944
Haemorrhagic cerebral infarction	10019005
Haemorrhagic stroke	10019016
Haemorrhagic transformation stroke	10055677
Intracerebral haematoma evacuation	10062025
Intracranial haematoma	10059491
Intracranial haemorrhage neonatal	10086946
Intracranial tumour haemorrhage	10022775
Intraventricular haemorrhage	10022840
Intraventricular haemorrhage neonatal	10022841
Meningorrhagia	10052593
Periventricular haemorrhage neonatal	10076706
Pituitary apoplexy	10056447
Pituitary haemorrhage	10049760
Putamen haemorrhage	10058940
Ruptured cerebral aneurysm	10039330
Spinal cord haematoma	10076051

e-MACE Component MedDRA PT[a]	MedDRA PT Code
Spinal cord haemorrhage	10048992
Spinal epidural haematoma	10050162
Spinal epidural haemorrhage	10049236
Spinal subarachnoid haemorrhage	10073564
Spinal subdural haematoma	10050164
Spinal subdural haemorrhage	10073563
Subarachnoid haematoma	10076701
Subarachnoid haemorrhage	10042316
Subarachnoid haemorrhage neonatal	10042317
Subdural haematoma	10042361
Subdural haematoma evacuation	10042363
Subdural haemorrhage	10042364
Subdural haemorrhage neonatal	10042365
Thalamus haemorrhage	10058939
Vertebral artery perforation	10075735
Hospitalization for Heart Failure	
Acute left ventricular failure	10063081
Acute pulmonary oedema	10001029
Acute right ventricular failure	10063082
Cardiac asthma	10007522
Cardiac failure	10007554
Cardiac failure acute	10007556
Cardiac failure chronic	10007558
Cardiac failure congestive	10007559
Cardiac failure high output	10007560
Cardiogenic shock	10007625
Cardiohepatic syndrome	10082480
Cardiopulmonary failure	10051093
Cardiorenal syndrome	10068230
Chronic left ventricular failure	10063083
Chronic right ventricular failure	10063084
Congestive hepatopathy	10084058
Cor pulmonale	10010968
Cor pulmonale acute	10010969

e-MACE Component MedDRA PT[a]	MedDRA PT Code
Cor pulmonale chronic	10010970
Ejection fraction decreased	10050528
Hepatojugular reflux	10051448
Left ventricular failure	10024119
Low cardiac output syndrome	10024899
Neonatal cardiac failure	10049780
Obstructive shock	10073708
Pulmonary oedema	10037423
Pulmonary oedema neonatal	10050459
Radiation associated cardiac failure	10076203
Right ventricular ejection fraction decreased	10075337
Right ventricular failure	10039163
Ventricular failure	10060953
Hospitalization for Arrhythmia	
Chronotropic incompetence	10068627
Early repolarisation syndrome	10086230
Electrocardiogram repolarisation abnormality	10052464
Electrocardiogram RR interval abnormal	10088247
Electrocardiogram RR interval prolonged	10067652
Electrocardiogram RR interval shortened	10088248
Electrocardiogram U wave inversion	10062314
Electrocardiogram U wave present	10057913
Electrocardiogram U-wave abnormality	10055032
Bradyarrhythmia	10049765
Ictal bradycardia syndrome	10088979
Ventricular asystole	10047284
Accessory cardiac pathway	10067618
Adams-Stokes syndrome	10001115
Agonal rhythm	10054015
Atrial conduction time prolongation	10064191
Atrial escape rhythm	10085756
Atrial standstill	10087237
Atrioventricular block	10003671
Atrioventricular block complete	10003673

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Atrioventricular block first degree	10003674
Atrioventricular block second degree	10003677
Atrioventricular conduction time shortened	10068180
Atrioventricular dissociation	10069571
Atrioventricular node dysfunction	10084085
Bifascicular block	10057393
BRASH syndrome	10084073
Brugada syndrome	10059027
Bundle branch block	10006578
Bundle branch block bilateral	10006579
Bundle branch block left	10006580
Bundle branch block right	10006582
Conduction disorder	10010276
Defect conduction intraventricular	10012118
Ectopic atrial rhythm	10088339
Electrocardiogram delta waves abnormal	10014372
Electrocardiogram PR prolongation	10053657
Electrocardiogram PR shortened	10014374
Electrocardiogram QRS complex prolonged	10014380
Electrocardiogram QT prolonged	10014387
Fascicular block	10086740
Lenegre's disease	10071710
Long QT syndrome	10024803
Paroxysmal atrioventricular block	10077503
Sinoatrial block	10040736
Trifascicular block	10044644
Ventricular dyssynchrony	10071186
Wolff-Parkinson-White syndrome	10048015
Nodal arrhythmia	10029458
Nodal rhythm	10029470
Sinus arrest	10040738
Sinus arrhythmia	10040739
Sinus bradycardia	10040741
Sinus node dysfunction	10075889
Wandering pacemaker	10047818

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Arrhythmia	10003119
Heart alternation	10058155
Heart rate irregular	10019304
Holiday heart syndrome	10083709
Pacemaker generated arrhythmia	10053486
Pacemaker syndrome	10051994
Paroxysmal arrhythmia	10050106
Pulseless electrical activity	10058151
Reperfusion arrhythmia	10058156
Withdrawal arrhythmia	10047997
Arrhythmia supraventricular	10003130
Atrial fibrillation	10003658
Atrial flutter	10003662
Atrial parasystole	10071666
Atrial tachycardia	10003668
Congenital supraventricular tachycardia	10082343
Familial atrial fibrillation	10088317
Frederick's syndrome	10082089
Junctional ectopic tachycardia	10074640
Sinus tachycardia	10040752
Supraventricular extrasystoles	10042602
Supraventricular tachyarrhythmia	10065342
Supraventricular tachycardia	10042604
Anomalous atrioventricular excitation	10002611
Cardiac fibrillation	10061592
Cardiac flutter	10052840
Extrasystoles	10015856
Tachyarrhythmia	10049447
Accelerated idioventricular rhythm	10049003
Arrhythmic storm	10067339
Parasystole	10033929
Rhythm idioventricular	10039111
Torsade de pointes	10044066
Ventricular arrhythmia	10047281
Ventricular extrasystoles	10047289

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Ventricular fibrillation	10047290
Ventricular flutter	10047294
Ventricular parasystole	10058184
Ventricular pre-excitation	10049761
Ventricular tachyarrhythmia	10065341
Ventricular tachycardia	10047302
Other Cardiovascular Hospitalizations	
Inherited cardiac conduction disorder	10070294
Timothy syndrome	10079205
Baseline foetal heart rate variability disorder	10074638
Bezold-jarisch reflex	10076999
Bradycardia	10006093
Bradycardia foetal	10006094
Bradycardia neonatal	10056471
Central bradycardia	10078310
Foetal heart rate acceleration abnormality	10074642
Foetal heart rate deceleration abnormality	10074636
Marshall-white syndrome	10088084
Neonatal tachycardia	10049775
Nonreassuring foetal heart rate pattern	10074641
Ogden syndrome	10082376
Postural orthostatic tachycardia syndrome	10063080
Rebound tachycardia	10067207
Sinusoidal foetal heart rate pattern	10074643
Tachycardia	10043071
Tachycardia foetal	10043074
Tachycardia paroxysmal	10043079
Neonatal sinus bradycardia	10082188
Neonatal sinus tachycardia	10082191
Cardiac arrest	10007515
Cardiac arrest neonatal	10007516
Cardiac death	10049993
Cardio-respiratory arrest	10007617
Cardio-respiratory arrest neonatal	10007618
Foetal cardiac arrest	10084280

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Sudden death	10042434
Acquired left ventricle outflow tract obstruction	10085294
Acquired right ventricle outflow obstruction	10086308
Acute cardiac event	10081099
Anaesthetic complication cardiac	10002100
Atrial thrombosis	10048632
Cardiac autonomic neuropathy	10066001
Cardiac complication associated with device	10069801
Cardiac contusion	10073356
Cardiac disorder	10061024
Cardiac dysfunction	10079751
Cardiac function disturbance postoperative	10007567
Cardiac herniation	10076751
Cardiac perforation	10058039
Cardiac procedure complication	10057461
Cardiac vein dissection	10064408
Cardiac vein perforation	10064409
Cardiac ventricular disorder	10057455
Cardiac ventricular thrombosis	10053994
Cardiotoxicity	10048610
Cardiovascular deconditioning	10050257
Cardiovascular disorder	10007649
Cardiovascular insufficiency	10065929
Cardiovascular somatic symptom disorder	10078078
Cerebrocardiac syndrome	10086448
Complications of transplanted heart	10010184
Congenital rubella syndrome	10083496
Coronary sinus injury	10084806
Coronary vein stenosis	10078431
Diabetic complication cardiovascular	10086684
Dilatation of sinotubular junction	10070689
Foetal cardiac disorder	10052088
Heart disease congenital	10019273
Heart transplant failure	10087136
Heart transplant rejection	10019315

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Heart-lung transplant failure	10087137
Heart-lung transplant rejection	10019319
Hyperkinetic heart syndrome	10058177
Incomplete atrial appendage closure	10088942
Intracardiac mass	10066087
Intracardiac thrombus	10048620
Larsen syndrome	10073856
Myocardial hypoperfusion	10082580
Oedema due to cardiac disease	10049632
Orthostatic intolerance	10063927
Post procedural cardiac valve avulsion	10086552
Radiation cardiac injury	10087433
Traumatic heart injury	10085907
Hypertensive cardiomegaly	10020801
Hypertensive heart disease	10020823
Malignant hypertensive heart disease	10025603
Cardiac granuloma	10055013
Cardiac infection	10054212
Cardiac tuberculosis	10087547
Cardiovascular syphilis	10007658
Carditis	10062746
Gonococcal heart disease	10078670
Lyme carditis	10078417
Meningococcal carditis	10027270
Abnormal precordial movement	10077162
Athletic heart syndrome	10063428
Cardiac discomfort	10054211
Cardiovascular symptom	10075534
Clubbing	10009691
Cyanosis	10011703
Cyanosis central	10011704
Dizziness	10013573
Dizziness exertional	10013576
Dizziness postural	10013578
Gastrocardiac syndrome	10059360

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Haemoptysis	10018964
Hyperdynamic left ventricle	10068359
Hypoxia intolerance	10080129
Jugular vein distension	10059865
Left ventricular heave	10052348
Mahler sign	10075428
Negative cardiac inotropic effect	10049671
Oculocardiac reflex	10076703
Ortner's syndrome	10063588
Palpitations	10033557
Positive cardiac inotropic effect	10062991
Presyncope	10036653
Right ventricular heave	10070955
Right ventricular hypertension	10074301
Syncope	10042772
Agonal respiration	10085467
Bendopnoea	10077819
Dyspnoea	10013968
Dyspnoea at rest	10013969
Dyspnoea exertional	10013971
Dyspnoea paroxysmal nocturnal	10013974
Fat embolism syndrome	10081148
Laryngeal dyspnoea	10052390
Neonatal dyspnoea	10084238
Nocturnal dyspnoea	10049235
Orthopnoea	10031123
Platypnoea	10035550
Platypnoea-orthodeoxia syndrome	10088118
Sleep-related hypoventilation	10089309
Transfusion-associated dyspnoea	10072266
Trepopnoea	10044590
Benign cardiac neoplasm	10004245
Cardiac fibroma	10055009
Cardiac haemangioma benign	10055011
Cardiac lymphangioma	10055010

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Cardiac myxoma	10061005
Cardiac neoplasm malignant	10061025
Cardiac neoplasm unspecified	10051549
Cardiac neurofibroma	10055012
Cardiac polyp	10085284
Cardiac teratoma	10057456
Cardiac valve fibroelastoma	10068699
Carney complex	10076601
Leukaemic cardiac infiltration	10077563
Metastases to heart	10049717
Pericardial cyst	10051730
Pericardial mesothelioma malignant	10073066
Pericardial mesothelioma malignant recurrent	10034480
Primary cardiac lymphoma	10075993
Aortic annulus rupture	10079586
Aortic valve atresia	10066801
Aortic valve calcification	10050559
Aortic valve disease	10061589
Aortic valve disease mixed	10002912
Aortic valve incompetence	10002915
Aortic valve prolapse	10057454
Aortic valve sclerosis	10002917
Aortic valve stenosis	10002918
Aortic valve thickening	10075851
Bicuspid aortic valve	10004552
Congenital aortic valve incompetence	10010370
Congenital aortic valve stenosis	10010371
Degenerative aortic valve disease	10075846
Heyde's syndrome	10049251
Subvalvular aortic stenosis	10042431
Supravalvular aortic stenosis	10042598
Unicuspid aortic valve	10081548
Williams syndrome	10049644
Carcinoid heart disease	10069010
Cardiac valve abscess	10064267

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Cardiac valve discolouration	10079467
Cardiac valve disease	10061406
Cardiac valve fatty infiltration	10087637
Cardiac valve replacement complication	10053748
Cardiac valve rupture	10068165
Cardiac valve sclerosis	10061082
Cardiac valve thickening	10079587
Cardiac valve vegetation	10057651
Congenital heart valve disorder	10064086
Congenital heart valve incompetence	10077594
Degenerative multivalvular disease	10081779
Heart valve calcification	10058968
Heart valve incompetence	10067660
Heart valve stenosis	10061996
Lambl's excrescences	10083691
Prosthetic cardiac valve regurgitation	10087802
Prosthetic cardiac valve thrombosis	10063176
Shone complex	10066802
Congenital mitral valve incompetence	10010547
Congenital mitral valve stenosis	10010548
Degenerative mitral valve disease	10075847
Ischaemic mitral regurgitation	10077864
Mitral face	10073380
Mitral perforation	10068138
Mitral valve atresia	10066800
Mitral valve calcification	10050558
Mitral valve disease	10061532
Mitral valve disease mixed	10027724
Mitral valve dysplasia	10089005
Mitral valve incompetence	10027727
Mitral valve prolapse	10027730
Mitral valve sclerosis	10051538
Mitral valve stenosis	10027733
Mitral valve thickening	10079336
Myxomatous mitral valve degeneration	10077377

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Parachute mitral valve	10064192
Systolic anterior motion of mitral valve	10076976
Bicuspid pulmonary valve	10063730
Congenital pulmonary valve atresia	10052644
Congenital pulmonary valve disorder	10061075
Pulmonary valve calcification	10057464
Pulmonary valve disease	10061541
Pulmonary valve incompetence	10037448
Pulmonary valve sclerosis	10057465
Pulmonary valve stenosis	10037450
Pulmonary valve stenosis congenital	10037451
Pulmonary valve thickening	10079337
Congenital tricuspid valve atresia	10049767
Congenital tricuspid valve incompetence	10067887
Congenital tricuspid valve stenosis	10010656
Degenerative tricuspid valve disease	10078909
Straddling tricuspid valve	10083223
Tricuspid valve calcification	10057466
Tricuspid valve disease	10061389
Tricuspid valve disease mixed	10086096
Tricuspid valve incompetence	10044640
Tricuspid valve prolapse	10066862
Tricuspid valve sclerosis	10057467
Tricuspid valve stenosis	10044642
Tricuspid valve thickening	10079338
Tricuspid valve thrombosis	10088062
Cardiac malposition	10007585
Congenital great vessel anomaly	10061080
Corrected transposition of great vessels	10011120
Dextrocardia	10012592
Double outlet left ventricle	10080133
Double outlet right ventricle	10013611
Ectopia cordis	10014144
Laevocardia	10071015
Primary ciliary dyskinesia	10069713

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Transposition of the great vessels	10044443
Alagille syndrome	10053870
Cayler cardiofacial syndrome	10085379
Charge syndrome	10064063
Chiari network	10069393
Cor biloculare	10010967
Cor triatriatum	10010972
Double inlet left ventricle	10082665
Ductus arteriosus premature closure	10049996
Ebstein's anomaly	10014075
Fallot's pentalogy	10059205
Fallot's tetralogy	10016193
Fallot's trilogy	10064011
Hypoplastic left heart syndrome	10021076
Hypoplastic right heart syndrome	10064962
Jacobsen syndrome	10089842
Left ventricle outflow tract obstruction	10065930
Patent ductus arteriosus	10034130
Pulmonary artery atresia	10037337
Right ventricle outflow tract obstruction	10064195
Trisomy 14	10071762
Trisomy 17	10053925
Trisomy 18	10053884
Trisomy 9	10071547
Uhl's anomaly	10048951
Velo-cardio-facial syndrome	10066430
Ventricular hypoplasia	10047296
Anomalous pulmonary venous connection	10058079
Congenital cardiovascular anomaly	10061054
Digeorge's syndrome	10012979
Emanuel syndrome	10079203
Kabuki make-up syndrome	10063935
Kleefstra syndrome	10079365
Multiple cardiac defects	10028178
Multiple lentigines syndrome	10062901

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Noonan syndrome	10029748
Persistent foetal circulation	10034708
Rubinstein-taybi syndrome	10039281
Trisomy 11	10044685
Trisomy 13	10044686
Trisomy 21	10044688
Trisomy 22	10044689
Truncus arteriosus persistent	10044703
Twin reversed arterial perfusion sequence malformation	10073455
Vacterl syndrome	10066022
Acquired coronary artery fistula	10086250
Arteriosclerosis coronary artery	10003211
Arteritis coronary	10003232
Congenital coronary artery malformation	10061060
Coronary artery aneurysm	10011071
Coronary artery compression	10079589
Coronary artery dilatation	10065420
Coronary artery disease	10011078
Coronary artery dissection	10048631
Coronary artery embolism	10011084
Coronary artery insufficiency	10052895
Coronary artery occlusion	10011086
Coronary artery perforation	10059611
Coronary artery reocclusion	10053261
Coronary artery restenosis	10056489
Coronary artery stenosis	10011089
Coronary artery thrombosis	10011091
Coronary bypass stenosis	10077824
Coronary bypass thrombosis	10059025
Coronary ostial stenosis	10011105
Coronary sinus dilatation	10082615
Coronary vascular graft occlusion	10075162
Coronary vascular graft stenosis	10077334
Diabetic coronary microangiopathy	10080788
Haemorrhage coronary artery	10055803

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Acute coronary syndrome	10051592
Acute myocardial infarction	10000891
Angina pectoris	10002383
Angina unstable	10002388
Anginal equivalent	10076419
Arteriospasm coronary	10003225
Cardiac perfusion defect	10083602
Chest discomfort	10008469
Chest pain	10008479
Chronic coronary syndrome	10085242
Coronary no-reflow phenomenon	10068534
Coronary steal syndrome	10084081
Kounis syndrome	10069167
Microvascular coronary artery disease	10072685
Myocardial infarction	10028596
Myocardial ischaemia	10028600
Myocardial reperfusion injury	10051624
Myocardial stunning	10072186
Papillary muscle infarction	10033697
Periprocedural myocardial infarction	10079319
Post procedural myocardial infarction	10066592
Postinfarction angina	10058144
Prinzmetal angina	10036759
Silent myocardial infarction	10049768
Subclavian coronary steal syndrome	10064994
Subendocardial ischaemia	10058145
Wellens' syndrome	10080787
Abiotrophia defectiva endocarditis	10085683
Acute endocarditis	10049001
Endocarditis bacterial	10014666
Endocarditis enterococcal	10014671
Endocarditis gonococcal	10014674
Endocarditis haemophilus	10014675
Endocarditis meningococcal	10014679
Endocarditis pseudomonal	10067336

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Endocarditis q fever	10014682
Endocarditis rheumatic	10014683
Endocarditis staphylococcal	10014684
Endocarditis syphilitic	10014685
Janeway lesion	10076949
Osler's nodes	10031131
Rheumatic fever	10039054
Rheumatic heart disease	10062110
Streptococcal endocarditis	10073742
Syphilitic endocarditis of heart valve	10042907
Endocardial disease	10061120
Endocardial fibroelastosis	10014663
Endocardial fibrosis	10014664
Endocardial varices	10070243
Eustachian valve hypertrophy	10081961
Subendocardial haemorrhage	10082459
Endocarditis candida	10014669
Fungal endocarditis	10017529
Fusarium endocarditis	10089359
Coxsackie endocarditis	10011257
Endocarditis viral	10061837
Endocarditis	10014665
Endocarditis fibroplastica	10052837
Endocarditis helminthic	10065327
Endocarditis histoplasma	10014676
Endocarditis noninfective	10062608
Lupus endocarditis	10058225
Prosthetic valve endocarditis	10036984
Septic endocarditis	10085425
Subacute endocarditis	10042276
Ascites	10003445
Gravitational oedema	10018713
Hypervolaemia	10020919
Kidney congestion	10076916
Localised oedema	10048961

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Oedema peripheral	10030124
Peripheral oedema neonatal	10049779
Peripheral swelling	10048959
Pulmonary venous hypertension	10085364
Transfusion-related circulatory overload	10066174
Cardiac cirrhosis	10054936
Cardio-respiratory distress	10049874
Grey syndrome neonatal	10018723
Propofol infusion syndrome	10063181
Pulmonary congestion	10037368
Kyphoscoliotic heart disease	10023508
Pulmonary artery wall hypertrophy	10063561
Shoshin beriberi	10049633
Cardiac amyloidosis	10007509
Cardiac iron overload	10080569
Cardiac steatosis	10077905
Cardiomyopathy	10007636
Cardiomyopathy acute	10048377
Cardiomyopathy alcoholic	10007637
Cardiomyopathy neonatal	10050111
Chagas' cardiomyopathy	10080484
Diabetic cardiomyopathy	10012647
Dilated cardiomyopathy	10056419
Familial dilated cardiomyopathy	10088172
Glycogen storage disease type ii	10053185
Hereditary attr amyloid cardiomyopathy	10089650
Hiv cardiomyopathy	10069658
Hypertensive cardiomyopathy	10058222
Hypertrophic cardiomyopathy	10020871
Ischaemic cardiomyopathy	10048858
Kearns-sayre syndrome	10048804
Metabolic cardiomyopathy	10070909
Mitochondrial cardiomyopathy	10084364
Mybpc3 gene mutation	10089239
Non-compaction cardiomyopathy	10079253

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Non-obstructive cardiomyopathy	10049813
Obesity cardiomyopathy	10081007
Pacing induced cardiomyopathy	10086997
Peripartum cardiomyopathy	10049430
Rbm20 mutation	10087916
Restrictive cardiomyopathy	10038748
Septic cardiomyopathy	10087221
Stress cardiomyopathy	10066286
Tachycardia induced cardiomyopathy	10074269
Thyrotoxic cardiomyopathy	10075043
Toxic cardiomyopathy	10083657
Uraemic cardiomyopathy	10087409
Viral cardiomyopathy	10068767
Coxsackie carditis	10011254
Coxsackie myocarditis	10011258
Cytomegalovirus myocarditis	10056261
Enterovirus myocarditis	10075553
Influenza myocarditis	10089685
Malarial myocarditis	10054123
Myocardiac abscess	10058440
Myocarditis bacterial	10065218
Myocarditis helminthic	10065219
Myocarditis infectious	10066857
Myocarditis meningococcal	10028612
Myocarditis mycotic	10059026
Myocarditis septic	10028615
Myocarditis syphilitic	10028616
Myocarditis toxoplasmal	10028617
Viral myocarditis	10047470
Acquired cardiac septal defect	10000533
Aorto-cardiac fistula	10089896
Atrial enlargement	10079340
Atrial hypertrophy	10048623
Atrial rupture	10048761
Atrial septal defect	10003664

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Atrial septal defect acquired	10003665
Atrio-oesophageal fistula	10075253
Atrioventricular septal defect	10063836
Cardiac aneurysm	10007513
Cardiac contractility decreased	10086706
Cardiac hypertrophy	10007572
Cardiac lipoma	10085049
Cardiac pseudoaneurysm	10048974
Cardiac sarcoidosis	10007604
Cardiac septal defect	10064021
Cardiac septal defect residual shunt	10069121
Cardiac septal hypertrophy	10057576
Cardiac ventricular scarring	10076898
Cardiomegaly	10007632
Chordae tendinae rupture	10008745
Diastolic dysfunction	10052337
Dilatation atrial	10013002
Dilatation ventricular	10013012
Holt-oram syndrome	10050469
Interventricular septum rupture	10022626
Ischaemic contracture of the left ventricle	10070589
Left atrial dilatation	10067286
Left atrial enlargement	10051860
Left atrial hypertrophy	10057500
Left ventricular diastolic collapse	10080987
Left ventricular dilatation	10050043
Left ventricular dysfunction	10049694
Left ventricular enlargement	10050581
Left ventricular false tendon	10079017
Left ventricular hypertrophy	10049773
Left-to-right cardiac shunt	10077834
Myocardial bridging	10052289
Myocardial calcification	10054122
Myocardial depression	10069140
Myocardial fibrosis	10028594

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Myocardial haemorrhage	10048849
Myocardial hypoxia	10078980
Myocardial injury	10085879
Myocardial necrosis	10028602
Myocardial oedema	10064966
Myocardial rupture	10028604
Myoglobinaemia	10058735
Myoglobinuria	10028629
Papillary muscle disorder	10061330
Papillary muscle haemorrhage	10059164
Papillary muscle rupture	10033698
Post cardiac arrest syndrome	10078202
Rhabdomyoma	10039021
Right atrial dilatation	10067282
Right atrial enlargement	10058227
Right atrial hypertrophy	10057501
Right ventricular diastolic collapse	10079613
Right ventricular dilatation	10074222
Right ventricular dysfunction	10058597
Right ventricular enlargement	10050582
Right ventricular false tendon	10080132
Right ventricular hypertrophy	10050326
Sigmoid-shaped ventricular septum	10082038
Single atrium	10083205
Systemic right ventricle	10083204
Systolic dysfunction	10071436
Univentricular heart	10045545
Ventricle rupture	10047279
Ventricular compliance decreased	10080992
Ventricular dysfunction	10059056
Ventricular dyskinesia	10059162
Ventricular enlargement	10079339
Ventricular hyperkinesia	10056472
Ventricular hypertrophy	10047295
Ventricular hypokinesia	10050510

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Ventricular remodelling	10075291
Ventricular septal defect	10047298
Ventricular septal defect acquired	10047299
Autoimmune myocarditis	10064539
Chronic myocarditis	10087106
Eosinophilic myocarditis	10014961
Giant cell myocarditis	10083635
Hypersensitivity myocarditis	10081004
Immune-mediated myocarditis	10082606
Lupus myocarditis	10066391
Myocarditis	10028606
Myocarditis post infection	10064550
Myopericarditis	10028650
Radiation myocarditis	10076389
Atypical mycobacterium pericarditis	10055036
Bacterial pericarditis	10004050
Coxsackie pericarditis	10011259
Cytomegalovirus pericarditis	10056721
Infective pericardial effusion	10077032
Pericarditis amoebic	10058148
Pericarditis fungal	10065220
Pericarditis gonococcal	10034488
Pericarditis helminthic	10065221
Pericarditis histoplasma	10034489
Pericarditis infective	10062491
Pericarditis meningococcal	10034492
Pericarditis mycoplasmal	10034493
Pericarditis rheumatic	10034496
Pericarditis syphilitic	10034497
Pericarditis tuberculous	10055069
Purulent pericarditis	10051071
Viral pericarditis	10047472
Autoimmune pericarditis	10079058
Immune-mediated pericarditis	10087567
Pericarditis	10034484

e-MACE Component MedDRA PT[a]	**MedDRA PT Code**
Pericarditis adhesive	10034486
Pericarditis constrictive	10034487
Pericarditis lupus	10058149
Pericarditis malignant	10034491
Pericarditis uraemic	10034498
Pleuropericarditis	10059361
Postpericardiotomy syndrome	10059483
Benign pericardium neoplasm	10054947
Cardiac tamponade	10007610
Dressler's syndrome	10013637
Intrapericardial thrombosis	10069550
Malignant pericardial neoplasm	10054946
Pericardial calcification	10057614
Pericardial disease	10061338
Pericardial effusion	10034474
Pericardial effusion malignant	10048630
Pericardial fibrosis	10048724
Pericardial haemorrhage	10034476
Pericardial injury	10089819
Pericardial lipoma	10082919
Pericardial mass	10079578
Pericardial neoplasm	10054945
Pericardial rub	10049759
Pericardial rupture	10089820
Pneumopericardium	10048731
Radiation pericarditis	10051308

[a] Preferred terms are coded using MedDRA Version 26.1.
e-MACE, expanded major adverse cardiovascular events; PT, preferred term.