Report on the Deliberation Results

March 7, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Camzyos Capsules 1 mg Camzyos Capsules 2.5 mg Camzyos Capsules 5 mg
Non-proprietary Name	Mavacamten (JAN*)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	July 17, 2024

Results of Deliberation

In its meeting held on March 6, 2025, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product, and the re-examination period is 10 years. The drug substance is classified as a poisonous drug, and the drug product is classified as a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of patients have been accrued.

**Japanese Accepted Name (modified INN)*

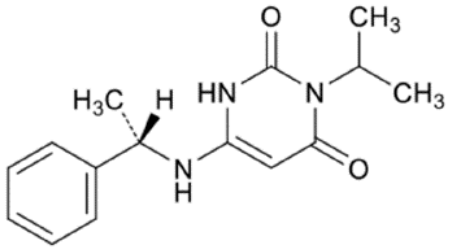
Review Report

February 19, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Camzyos Capsules 1 mg Camzyos Capsules 2.5 mg Camzyos Capsules 5 mg
Non-proprietary Name	Mavacamten
Applicant	Bristol-Myers Squibb K.K.
Date of Application	July 17, 2024
Dosage Form/Strength	Each capsule contains 1 mg, 2.5 mg, or 5 mg of mavacamten
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula:	$C_{15}H_{19}N_3O_2$
Molecular weight:	273.33
Chemical name:	6-{[(1*S*)-1-Phenylethyl]amino}-3-(propan-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 575 of 2023 [*R5 yaku*]; PSEHB/PED Notification No. 0622-1 dated June 22, 2023, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of obstructive hypertrophic cardiomyopathy and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The product is not classified as a biological product or a specified biological product. The drug substance is classified as a poisonous drug, and the drug product is classified as a powerful drug.

Indication

Obstructive hypertrophic cardiomyopathy

Dosage and Administration

The usual adult starting dosage is 2.5 mg of mavacamten orally once daily. The dosage can be increased or decreased according to the patient's condition. The maximum dose is 15 mg once daily.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of patients have been accrued.

Attachment

Review Report (1)

December 27, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Camzyos Capsules 1 mg Camzyos Capsules 2.5 mg Camzyos Capsules 5 mg
Non-proprietary Name	Mavacamten
Applicant	Bristol-Myers Squibb K.K.
Date of Application	July 17, 2024
Dosage Form/Strength	Each capsule contains 1 mg, 2.5 mg, or 5 mg of mavacamten
Proposed Indication	Obstructive hypertrophic cardiomyopathy
Proposed Dosage and Administration	The usual adult starting dosage is 5 mg of mavacamten orally once daily. The dosage can be increased or decreased according to the patient's condition. The maximum dose is 15 mg once daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Hypertrophic cardiomyopathy (HCM) is a condition in which the formation of excess cardiac myosin-actin cross-bridges leads to myocardial hypercontractility and left ventricular hypertrophy. HCM with left ventricular outflow tract (LVOT) obstruction is classified as obstructive hypertrophic cardiomyopathy (oHCM). LVOT obstruction is considered to be caused by various patterns of abnormal ventricular morphology resulting from ventricular septal hypertrophy, reduced ventricular cavity size, and pathological enlargement of the mitral valve (*J Am Coll Cardiol*. 2000;36:1344-54). In patients with oHCM, disease progression and deterioration of cardiac function will increase the risk of developing cardiac failure resulting from atrial fibrillation, which also increases the risk of thromboembolic stroke.

Mavacamten, a small molecule compound developed by MyoKardia, Inc. in the United States (US), is a selective reversible inhibitor of cardiac myosin. Binding of mavacamten to cardiac myosin is considered to inhibit myosin-actin cross-bridge formation, reducing myocardial hypercontractility, thereby improving diastolic dysfunction and reducing LVOT obstruction in patients with oHCM.

The clinical development of mavacamten was started by MyoKardia in 2014 and then was taken over by the applicant in 2020. As of November 2024, mavacamten has been approved in a total of 51 countries and regions, including the US and Europe, for the treatment of oHCM.

The applicant has recently filed an application for marketing approval of mavacamten for the indication of obstructive hypertrophic cardiomyopathy, based on data including those from the phase III studies conducted in and outside Japan.

Mavacamten was granted orphan drug designation in June 2023 (Orphan Drug Designation No. 575 of 2023 [*R5 yaku*]; PSEHB/PED Notification No. 0622-1 dated June 22, 2023, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) for the intended indication of “hypertrophic cardiomyopathy.”

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to off-white solid. Its description, solubility, hygroscopicity, thermal analysis, dissociation constant, partition coefficient, optical rotation, and membrane permeability have been determined. A total of 10 crystalline forms have been identified in the drug substance: 6 [redacted] (Form A, B, C, E, F, and J), 3 [redacted], and 1 metastable form. However, only Form A ([redacted]) is produced in the commercial manufacturing process, and its stability at room temperature has been confirmed.

The chemical structure of the drug substance was elucidated by ultraviolet-visible spectrophotometry (UV/VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR [^{1}H-, ^{13}C-NMR]), mass spectrometry (MS), elemental analysis, and single crystal X-ray structure analysis. The drug substance has a chiral center and an absolute configuration of *S*.

2.1.2 Manufacturing process

The drug substance is synthesized by [redacted], [redacted], and [redacted] as starting materials.

Quality control strategies have been established based on the following evaluations (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on the process risk assessment, design of experiments, one-factor-at-a-time method, failure mode and effects analysis, etc. and evaluation of the acceptable ranges for manufacturing process parameters and in process control (IPC).

Table 1. Outline of the control strategy for the drug substance

CQA	Control method
Content	Manufacturing process, specifications
Description	Manufacturing process, specifications
Identification	Manufacturing process, specifications
Related substances	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
Residual solvents	Manufacturing process, specifications
Elemental impurities	Manufacturing process
[redacted]	Manufacturing process, specifications
Crystalline form	Manufacturing process, specifications
Ignition residue	Manufacturing process, specifications
Water content	Manufacturing process, specifications
Microbial limits	Manufacturing process, specifications

The [redacted] synthesis, [redacted] synthesis, [redacted], and [redacted] steps are defined as critical steps. Process control items and values have been established for the critical steps and reaction steps (manufacturing of [redacted]).

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (high performance liquid chromatography [HPLC], IR, powder X-ray diffraction), purity test (related substances [HPLC], [redacted] [HPLC], residual solvents [gas chromatography (GC)]), water content, ignition residue, [redacted], microbial limits, and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 summarizes the main stability studies for the drug substance. The results of the studies confirmed the stability of the drug substance. A photostability study was conducted and its results showed that the drug substance was photostable.

Table 2. Stability studies for the drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot-scale batches 1 commercial-scale batch	25°C	60% RH	Double-layered polyethylene bag + HDPE drum	60 months
Accelerated		40°C	75% RH		6 months

Based on the above, a retest period of 60 months was proposed for the drug substance when packed in a double-layered polyethylene bag and stored in a high-density polyethylene (HDPE) drum at room temperature.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release hard capsule containing 1, 2.5, or 5 mg of the drug substance. Excipients contained in the drug product are hydrated silicon dioxide, D-mannitol, hypromellose, croscarmellose sodium, and magnesium stearate.

2.2.2 Manufacturing process

The manufacturing process for the 1 mg capsule formulation consists of preliminary mixing, [redacted], [redacted], [redacted], mixing 1, [redacted], [redacted], [redacted], mixing 2, [redacted], capsule filling, and packaging/labeling/testing/storage. The manufacturing process for the 2.5 mg and 5 mg capsule formulations consists of preliminary mixing, [redacted], [redacted], [redacted], mixing, [redacted], capsule filling, and packaging/labeling/testing/storage.

For all strengths of the drug product, [redacted], [redacted], and [redacted] steps are defined as critical steps, and process control items and values have been established for [redacted] and [redacted] steps.

Quality control strategies have been established based on the following evaluations (Table 3):

- Identification of CQAs
- Identification of CPPs based on the quality risk assessment and design of experiments

Table 3. Outline of the control strategy for the drug product

CQA	Control method
Strength	Manufacturing process, specifications
Description	Manufacturing process, specifications
Identification	Manufacturing process, specifications
Related substances	Manufacturing process, specifications
Uniformity of dosage units	Manufacturing process, specifications
Dissolution	Manufacturing process, specifications
Microbial limits	Manufacturing process, specifications
Residual solvents	Manufacturing process
Elemental impurities	Manufacturing process

2.2.3 Control of drug product

The proposed specification for the drug product consists of strength, description, identification (HPLC, UV/VIS), purity test (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), water content, microbial limits, dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 4 summarizes the main stability studies for the drug product. The results of the studies confirmed the stability of the drug product. A photostability study was conducted and its results showed that the drug product was photostable.

Table 4. Main stability studies for the drug product

Strength	Study	Primary batch	Temperature	Humidity	Storage form	Storage period
1 mg	Long-term	4 commercial-scale batches	25°C	60% RH	Blister pack[a]	24 months
	Accelerated		40°C	75% RH		6 months
2.5 mg 5 mg	Long-term	3 pilot-scale batches	30°C	75% RH		[redacted] months
	Accelerated		40°C	75% RH		6 months

a, [redacted] film and aluminum foil

Based on the above results, a shelf life of 24 months for the 1 mg capsule formulation and a shelf life of 36 months for the 2.5 mg and 5 mg capsule formulations were proposed for the drug product when packed in a blister pack ([redacted] film and aluminum foil) and in a paper box at room temperature. The long-term testing on a commercial scale will be continued for up to [redacted] months for all the strengths of the drug product.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Effects on the progression of ATP hydrolysis cycle (CTD 4.2.1.1-1 [reference data])

The inhibitory effects of mavacamten on the progression of adenosine triphosphate (ATP) hydrolysis cycles in myosin were investigated based on the adenosine diphosphate (ADP) production rate, as shown in (1) through (5) below.

(1) Inhibition was evaluated using recombinant human cardiac myosin subfragment-1 (S1) and purified myosin S1 from bovine heart muscles, rabbit fast muscles, and chicken smooth muscles. The IC_{50} values (mean ± standard deviation) were 0.52 ± 0.09 μmol/L (human), 0.27 ± 0.02 μmol/L (bovine), 4.71 ± 0.20 μmol/L (rabbit), and >50 μmol/L (chicken).

(2) Inhibition was evaluated using actomyosin from recombinant human cardiac muscles, bovine cardiac muscles, rabbit fast muscles, and chicken smooth muscles. The IC_{50} values (mean ± standard deviation) were 0.73 ± 0.05 μmol/L (human), 0.47 ± 0.01 μmol/L (bovine), 5.85 ± 0.15 μmol/L (rabbit), and >50 μmol/L (chicken).

(3) Inhibition was evaluated using filaments consisting of actomyosin, troponin, and tropomyosin from recombinant human cardiac muscle, bovine cardiac muscles, and rabbit fast muscles. The IC_{50} values (mean ± standard deviation) were 0.53 ± 0.08 μmol/L (human), 0.53 ± 0.02 μmol/L (bovine), and 5.09 ± 1.22 μmol/L (rabbit).

(4) Inhibition was evaluated using skinned myofibrils from human cardiac muscles, bovine cardiac muscles, bovine slow muscles, rabbit cardiac muscles, rabbit fast muscles, mouse cardiac muscles, rat cardiac muscles, dog cardiac muscles, and porcine cardiac muscles. The IC_{50} values (mean ± standard deviation) were 0.71 ± 0.06 μmol/L (human cardiac), 0.49 ± 0.03 μmol/L (bovine cardiac), 0.43 ± 0.04 μmol/L (bovine slow), 0.76 ± 0.04 μmol/L (rabbit cardiac), 2.14 ± 0.31 μmol/L (rabbit fast), 0.29 ± 0.03 μmol/L (mouse cardiac), 0.32 ± 0.02 μmol/L (rat cardiac), 0.45 ± 0.07 μmol/L (dog cardiac), and 0.49 ± 0.05 μmol/L (porcine cardiac).

(5) Inhibition was evaluated using actomyosin containing wild-type or HCM-pathogenic mutant (R403Q, R453C, R719W, R723G, and G741R) human β myosin heavy chain. The IC_{50} values (mean ± standard deviation) were 0.91 ± 0.05 μmol/L (wild), 0.71 ± 0.01 μmol/L (R403Q), 1.02 ± 0.02 μmol/L (R453C), 1.31 ± 0.51 μmol/L (R719W), 1.04 ± 0.06 μmol/L (R723G), and 0.65 ± 0.03 μmol/L (G741R). Mavacamten inhibited the progression of ATP hydrolysis cycles in mutant human β myosin heavy chains as well as the wild type.

The inhibitory effects of mavacamten on the progression of ATP hydrolysis cycles in myosin were evaluated using porcine cardiac myofibrils in the presence of varying concentrations of Ca^{2+} based on ADP production rate. Mavacamten inhibited the progression of ATP hydrolysis cycles at both systolic and diastolic Ca^{2+} concentrations (−log[Ca^{2+}] [pCa] 6.0 and pCa 7.5, respectively).

3.1.1.2 Effects on the Pi release in ATP hydrolysis cycle (CTD 4.2.1.1-2 [reference data])

In the ATP hydrolysis cycle, the myosin head binds to ADP and inorganic phosphate (Pi) formed by ATP hydrolysis and releases Pi to form strong binding (cross-bridging) with actin, resulting in the power stroke, a step in which myosin pulls actin filaments. The effects of mavacamten on inhibiting the release of Pi from the myosin head were evaluated with the fluorescence intensity of fluorescent-labeled Pi-binding protein as a measure using bovine cardiac actomyosin. The IC_{50} value (mean ± standard error) was 0.46 ± 0.15 μmol/L, demonstrating that mavacamten inhibits Pi release from the myosin head, an important process to initiate the power stroke step.

3.1.1.3 Effects on the myosin heads in DRX state[1)] (CTD 4.2.1.1-3 [reference data], 4.2.1.1-4 [reference data])

The effects of mavacamten (0.05-50 μmol/L) on the rate of detachment of ATP and its hydrolyzed product (ADP) from myosin were evaluated with the fluorescence intensity of fluorescent-labeled ATP as a measure using full-length bovine cardiac myosin. The results showed that the detachment rates of fluorescent-labeled ATP and its hydrolyzed product myosin decreased in a mavacamten concentration-dependent manner,

suggesting that mavacamten decreases myosin heads in the disordered relaxed (DRX) state [1)] and increases myosin heads in the super relaxed (SRX) state.[1)] The progression of ATP hydrolysis cycles for myosin heads in the DRX state was inhibited in a mavacamten concentration-dependent manner, with an IC_{50} value (mean ± standard deviation) of 0.4 ± 0.1 μmol/L.

The effects of mavacamten (at concentrations of up to 50 μmol/L) on the rate of detachment of ATP and its hydrolyzed product from myosin were evaluated using skinned porcine myocardial fibers expressing β myosin heavy chain gene mutation (R403Q). The rate of detachment of fluorescent-labeled ATP and its hydrolyzed product from myosin decreased in a mavacamten concentration-dependent manner.

3.1.1.4 Effects on the sliding velocity of actin filaments (CTD 4.2.1.1-5 [reference data])

The effects of mavacamten on the sliding velocity of actin filaments driven by myosin were evaluated using full-length bovine cardiac myosin and fluorescent-labeled actin filaments by fluorescence microscopy. The IC_{50} value (mean ± standard error) was 0.24 ± 0.05 μmol/L, indicating that the velocity of myosin-driven actin filament sliding can be reduced by mavacamten.

3.1.1.5 Effects on isometric tension of myocardial fibers (CTD 4.2.1.1-4 [reference data], 4.2.1.1-6 [reference data])

Using skinned rat myocardial fibers, the effects of mavacamten (0.3 and 1.0 μmol/L) on isometric tension were evaluated. The tension of myocardial fibers at systolic and diastolic Ca^{2+} concentrations decreased in a mavacamten concentration-dependent manner.

Using skinned porcine myocardial fibers carrying mutation (R403Q) in β myosin heavy chain, mutation (E330X) in myosin-binding protein C, or mutation (R192H) in troponin I, the effects of mavacamten (1 μmol/L) on isometric tension were evaluated in a similar manner. Mavacamten decreased the tension of myocardial fibers with any of the mutant sarcomere protein myocardial fibers studied at systolic and diastolic Ca^{2+} concentrations.

One study suggested the possibility that localized mechanical stress in the sarcomere generates a contractile imbalance between cardiomyocytes, causing cardiomyocyte disarray and fibrosis in patients with HCM (*Pflugers Arch.* 2019;471:719-33). Based on the above, the effect of mavacamten (1.0 μmol/L) on isometric tension was evaluated using skinned porcine myocardial fibers to which stretching stress was applied.[2)] Mavacamten decreased the increasing tension and stiffness of myocardial fibers caused by stretching stress at diastolic Ca^{2+} concentration (pCa 6.4).

[1)] A state in which ATPase activity is high and power stroke is readily initiated. Some myosin heads in the DRX state undergo conformational changes and a transition to the SRX state, in which ATPase activity is low and a power stroke cannot be readily initiated (*J Biol Chem.* 2021;297:101297).

[2)] The fixed myocardial fiber was stretched to induce sarcomere lengthening by 0.3 μm.

3.1.1.6 Effects on contraction and relaxation of cardiomyocytes and intracellular Ca^{2+} concentration (CTD 4.2.1.1-7 [reference data], 4.2.1.1-8 [reference data])

The effects of mavacamten (0.03-1 µmol/L) on the shortening fraction (SF), diastolic (resting) cell length, and intracellular Ca^{2+} concentration in primary cultured rat cardiomyocytes were evaluated. Mavacamten concentration-dependently decreased SF. The resting cell length significantly increased after being treated with mavacamten 0.3 or 1 µmol/L compared to pre-treatment. Conversely, no effects of mavacamten on diastolic or systolic intracellular Ca^{2+} concentration were noted.

An action potential was evoked by electric stimuli in primary cultured rat cardiomyocytes, and SF after treatment with mavacamten (0.25 µmol/L) and then treatment with isoproterenol (2 nmol/L) was evaluated. Although SF decreased after being treated with mavacamten compared with no mavacamten treatment, the decrease in SF was suppressed by addition of isoproterenol even after administration of mavacamten, suggesting that the recruitment of cardiac reserve is possible despite mavacamten-induced contractile depression of cardiomyocytes.

3.1.2 *In vivo* studies

3.1.2.1 Effects on cardiac function and left ventricular hemodynamics in rats (CTD 4.2.1.1-11 [reference data])

A single oral dose of mavacamten (low, intermediate, or high dose level[3)]) or vehicle[4)] was administered to male rats (N = 7 to 13 rats/group) under anesthesia, and cardiac function at 3 hours post-dose was evaluated by echocardiography. Left ventricular fractional shortening (FS) decreased in a mavacamten dose-dependent manner while left ventricular end diastolic volume (EDV) increased significantly at all dose levels compared to the vehicle group. Heart rate (HR) was significantly higher in the mavacamten group than in the vehicle group only at the intermediate dose level.

A single oral dose of mavacamten (1 or 2 mg/kg [N = 8/group]) or vehicle[4)] was administered to male rats (N = 7 to 16/group) under anesthesia, and catheterization was performed to assess left ventricular hemodynamics at 3 hours post-dose. Peak rate of left ventricular pressure increase during systole (dP/dt_{max}) was significantly lower in the mavacamten group than in the vehicle group, while left ventricular end diastolic pressure (EDP) was similar between the groups.

The above results suggest that mavacamten causes depression in cardiac contractile function and increase in EDV while preserving EDP.

3.1.2.2 Effects on hemodynamics in dogs (CTD 4.2.1.1-12 [reference data])

A single oral dose of mavacamten (1.5 mg/kg) or metoprolol (2 mg/kg) (positive control) was administered to conscious male dogs (N = 6 to 8/group), and systemic/left ventricular hemodynamics at 3 hours post-dose was

[3)] Low dose level: 1 or 2 mg/kg (7 or 5 subjects each); intermediate dose level: 4 mg/kg (7 subject); high dose level: 8 or 10 mg/kg (6 or 7 subjects each)

[4)] An aqueous solution of DMA, polyethylene glycol (PEG) 400, and 30% β cyclodextrin (mixing ratio of 5:25:70)

evaluated by telemetry. In the mavacamten group, compared to pre-dosing levels, pulse pressure (PP), peak rate of left ventricular pressure increase during systole (dP/dt_{max}), peak rate of left ventricular pressure decrease during diastole (dP/dt_{min}), V_{max}, left ventricular ejection fraction (LVEF), end systolic elastance (Ees), and preload recruitable stroke work (PRSW) significantly decreased while tau1/2, defined as the time constant of left ventricular pressure decay (half maximal), EDV, left ventricular end systolic volume (ESV), and arterial elastance (Ea) significantly increased. Conversely, there were no significant changes in mean systemic pressure (MBP), EDP, left ventricular end systolic pressure (ESP), cardiac output (CO), or end diastolic elastance (Eed). In the metoprolol group, compared to pre-dosing levels, MBP, dP/dt_{max}, dP/dt_{min}, V_{max}, LVEF, CO, Ees, and PRSW significantly decreased, while EDP, tau1/2, EDV, ESV, Ea, and Eed significantly increased. Conversely, no significant changes were noted in PP or ESP.

The above results suggest that unlike traditional negative inotropes, mavacamten decreased cardiac contractility and increased left ventricular volume, while preserving systemic hemodynamics and left ventricular pressure.

3.1.2.3 Study in feline models for oHCM (CTD 4.3-50, *PLoS One.* 2016;11:e0168407 [reference data])

Atropine (0.04 mg/kg) was intravenously administered to male cats (N = 3 to 5/group) under anesthesia, followed by continuous intravenous administration of isoproterenol (0.04 µg/kg/min) to induce LVOT obstruction, and then intravenous administration of mavacamten (infusion continued at infusion rates in the order of 0.3, 0.12, 0.36, and 0.15 mg/kg/h) or vehicle[5)] was started. Cardiac functions were evaluated by echocardiography. The results showed that compared to the vehicle group, the LVOT pressure gradient in the mavacamten group was significantly lower.

3.1.2.4 Effects of mavacamten on the actions of cardiotonic agents (CTD 4.2.1.1-12 [reference data], 4.2.1.1-14)

In conscious male dogs (N = 12/group), left ventricular hemodynamics was evaluated by telemetry in the group receiving intravenous dobutamine (10 µg/kg/min) 3 hours after administration of a single oral dose of mavacamten (1.5 mg/kg) and in the group receiving intravenous dobutamine (10 µg/kg/min) only. Compared to pre-dobutamine treatment level, the increase in CO in the mavacamten-dobutamine co-administered group was similar to that in the dobutamine monotherapy group. In the co-administered group, however, compared to the dobutamine monotherapy group, there was an insignificant increase in dP/dt_{max} while there was a significant decrease in tau.

A single oral dose of mavacamten (4 mg/kg) was administered to male rats (N = 6 to 7/group) under anesthesia. Three hours later, dobutamine (10 µg/kg/min for 10 minutes) or levosimendan (0.3 µmol/kg for 20 minutes) was administered intravenously and cardiac function was evaluated by echocardiography. Compared

5) The cats treated with mavacamten in the mavacamten group were used in the vehicle group after a washout period of 6 weeks following the completion of treatment with mavacamten. A solution of PEG 400 and physiological saline (mixing ratio of 1:1) was used as the vehicle.

to mavacamten alone, FS and SV were significantly elevated after co-administration of dobutamine or levosimendan with mavacamten.

The above results suggest that the recruitment of cardiac reserve is possible despite mavacamten-induced depression of cardiac contractility.

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors and other proteins (CTD 4.2.1.2-1 [reference data])

The inhibitory and activating effects of mavacamten (10 μmol/L) on a total of 143 types of proteins, namely, enzymes, receptors, kinases, ion channels, and transporters, were evaluated. No inhibitory or activating effects (>50%) were noted on any of the compounds.

3.2.2 Effects on skeletal muscle function (CTD 4.2.1.3-3 [reference data])

A single oral dose of mavacamten (1, 3, or 10 mg/kg) or vehicle (0.5% methylcellulose solution) was administered to conscious male rats (N = 8/group) and the impact of mavacamten on forelimb/hindlimb grip strength and locomotor activity at 2 and 24 hours post-dose were evaluated. No significant differences between the mavacamten group and the vehicle group were noted.

3.3 Safety pharmacology

Table 5 summarizes the results of safety pharmacology studies.

Table 5. Summary of safety pharmacology studies

Item	Test system	Test parameter/method	Dose	Route of administration	Finding	CTD
Central nervous system	Rat (SD) (N = 8 males/group)	FOB	Single dose 0,[a] 1, 3, 10 mg/kg	Oral	No effect	4.2.1.3-3
Cardiovascular system	HEK293 cells stably expressing hERG channels	hERG current	0,[b] 10, 60 µmol/L	*in vitro*	Inhibited hERG current by 1.0% (0 µmol/L), 5.0% (10 µmol/L), and 9.6% (60 µmol/L) compared to pre-dosing level	4.2.1.3-1
	Dog (Beagle) (N = 4 males/group)	Blood pressure, heart rate, electrocardiogram (ECG) (telemetry)	Single dose 0,[a] 1, 3, 10 mg/kg	Oral	3 mg/kg, decrease in SBP and PP, increase in HR, shortened PR interval, shortened QTcR interval 10 mg/kg, decrease in SBP and PP, increase in HR, shortened PR interval, prolonged QTcR interval	4.2.1.3-2
	Dog (Beagle) (7 males)	Left ventricular function, ECG (telemetry)	Single dose 0,[c] 1.5 mg/kg	Oral	At 3 hours post-dose, increase in HR, decrease in dP/d_{max}, shortened QT interval, shortened QT1000 interval, prolonged EMw At 24 hours post-dose, increase in HR, prolonged EMw	4.2.1.1-12 (reference data)
	Dog (Beagle) (N = 4/sex/group)	ECG (6-lead)	3-month repeated dose 0,[a] 0.06, 0.18, 0.30, 0.45 mg/kg/day	Oral	Increase in HR, increase in R-wave and T-wave amplitude	4.2.3.2-8
	Dog (Beagle) (N = 2 to 4/sex/group)	ECG (8 lead)	39-week repeated dose of 0,[a] 0.06, 0.18, 0.30 mg/kg/day (males only), 0.45 mg/kg/day (females only)	Oral	≥0.18 mg/kg/day, prolonged QTcF interval, increase in HR 0.45 mg/kg/day, prolonged QRS duration	4.2.3.2-9
	Dog (Beagle) (4 males)	ECG (telemetry)	Animals received empty gelatin capsule on Day 1, mavacamten 1.5 mg/kg twice daily on Day 2, and mavacamten 0.3 mg/kg once daily on Days 3-15.	Oral	prolonged QTcF interval	4.2.1.3-4 (reference data)
	Rabbit (New Zealand) isolated Purkinje fibers	APD50, APD90	0,[c] 0.3, 3, 10, 30 µmol/L	*in vitro*	30 µmol/L, shortened APD50	4.2.1.3-5 (reference data)

Item	Test system	Test parameter/method	Dose	Route of administration	Finding	CTD
	HEK293 cells[d] stably expressing hVM, hHVM, and human cardiac ion channels	APD30, APD90, ion channel current (physiological temperature)	0,[c] 0.3, 3, 10, 30 µmol/L	*in vitro*	<u>hVM, hHVM</u> ≥3 µmol/L, shortened APD30, shortened APD90, inhibited Nav1.5 (I_{NaL}) by 14.5% (hVM), 22.8% (hHVM) <u>HEK293 cells</u> 30 µmol/L, inhibited hKv4.3/KChiP2.2 (I_{to}) by12.4%, inhibited Cav1.2 (I_{CaL}) by 14.7%, inhibited Nav1.5 (I_{NaL}) by 40.4%	4.2.1.3-7 (reference data)
	HEK293 cells and CHO cells[e] stably expressing human cardiac ion channels	Ion channel current (room temperature)	0,[b] 1, 10 µmol/L	*in vitro*	No ≥10% inhibition	4.2.1.3-8 (reference data)
Cardiovascular system	HEK293 cells and CHO cells[f] stably expressing human cardiac ion channels	Ion channel current (room temperature)	0,[b] 30 µmol/L	*in vitro*	30 µmol/L, inhibited hKv4.3/KChiP2.2 (I_{to}) by 12.6%	4.2.1.3-9 (reference data)
	HEK293 cells stably expressing hERG channels	hERG cell membrane expression	0,[g] 0.1, 0.3, 1, 3, 10, 30 µmol/L	*in vitro*	No effect	4.2.1.3-10 (reference data)
	HEK293 cells stably expressing hERG channels	hKv4.3 cell membrane expression	0,[g] 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 µmol/L	*in vitro*	No effect	4.2.1.3-12 (reference data)
	iPSC-CM	Field potential, impedance	0,[c] 0.03, 0.1, 0.3, 1 µmol/L	*in vitro*	1 µmol/L, impedance decreased by 98.7%	4.2.1.3-13 (reference data)
	Rat (SD) (N = 5 or 12 males/group[h])	<u>Cohort A</u> echocardiography, ECG (unipolar lead) <u>Cohort B</u> echocardiography, ion channel gene expression	7-day repeated dose 0,[i] 2, 4 mg/kg/day	Oral	<u>Cohorts A and B</u> EDV increased, FS decreased, HR increased <u>Cohort A</u> prolonged QT interval, prolonged QTcF interval <u>Cohort B</u> downregulation of KCND3, KCND2, KCNJ12, ABCC8, and KCNJ8	4.2.1.3-14 (reference data)
Respiratory system	Dog (Beagle) (N = 4 males/group)	Respiratory rate, tidal volume, minute volume	Single dose 0,[a] 1, 3, 10 mg/kg	Oral	10 mg/kg, increased respiratory rate, decreased tidal volume	4.2.1.3-2

a, 0.5% methylcellulose solution
b, HEPES-buffered saline solution containing 0.3% (v/v) DMSO
c, Pre-dosing values were used for control.
d, HEK293 cells expressing Nav1.5, Cav1.2, or Kir6.2/SUR2A were used only for the evaluation of the effect on ion channel current.
e, HEK293 cells expressing hCav3.2, hHCN4, hERG, hKir2.1, hKir3.1/hKir3.4, Kir6.2/SUR2A, or hKv4.3, or CHO cells expressing hCav1.2, hHCN2, hKv1.5, hKvLQT1/hminK, or hNav1.5 were used.
f, HEK293 cells expressing hCav3.2, hHCN4, hERG, hKir2.1, hKir3.1/hKir3.4, Kir6.2/SUR2A, or hKv4.3/KChiP2.2, or CHO cells expressing hCav1.2, hHCN2, hKv1.5, hKvLQT1/hminK, or hNav1.5 were used.
g, DMEM/F12 containing 0.3%DMSO
h, In Cohort A, 5 animals received mavacamten 4 mg/kg, in Cohort B, 12 animals received mavacamten (1 received 2 mg/kg and 11 received 4 mg/kg), and 10 animals were in the control group.
i, Pre-dosing values were used for control in Cohort A. In Cohort B, pre-dosing values were used for control (for echocardiography), and rats treated with a 0.5% methylcellulose solution were used for the ion-channel gene expression analysis.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects of mavacamten on oHCM

The applicant's explanation about the pharmacological effects of mavacamten on oHCM:

The cardiac sarcomere consists of 2 types of filaments each containing a myosin complex and actin as major components. A myosin complex, a hexamer composed of myosin heavy chain and light chain, can be divided into functionally and structurally different regions. Sub-fragment 1, also called myosin head, contains binding sites for actin and possesses ATPase activity. Transitions between the steps, i.e., myosin head-actin binding, strongly binding state (cross-bridge) of myosin head and actin, power stroke driving actin filaments, and detachment of myosin head from actin, require ATP binding to the myosin head and detachment of ATP hydrolysis products, Pi and ADP, from the myosin head, in the order given. This ATP hydrolysis cycle in myosin heads plays an important role in the processes of cardiac contractility and ventricular dilation. It is known that there are 2 states of myosin heads: a state characterized by high ATPase activity, readily initiating the power stroke step (DRX state) and a state characterized by low ATPase activity, not readily initiating the power stroke step (SRX state). It has been suggested that myocardial hypercontractility and left ventricular diastolic dysfunction associated with HCM are caused by excess cross-bridge formation of myosin with actin primarily due to mutations of sarcomere proteins, which decrease myosin heads in the SRX state and increase myosin heads in the DRX state (*Pflugers Arch.* 2019;471:701-17).

In vitro studies demonstrated that mavacamten selectively and reversibly binds to cardiac myosin, inhibiting the ATP hydrolysis cycle by decreasing Pi release from myosin heads and increasing myosin heads in the SRX state, thereby lowering myocardial contractility in sarcomere and diastolic tension. *In vivo* studies in normal animals and HCM pathogenic models demonstrated that mavacamten decreased dP/dt_{max} and the LVOT pressure gradient and increased EDV. Based on the above results, mavacamten is expected to be effective in the treatment of diastolic dysfunction and LVOT obstruction in patients with oHCM.

Based on the applicant's explanation, PMDA concluded that mavacamten can be expected to be an effective treatment for patients with oHCM.

3.R.2 Effects of mavacamten on QTc interval

The applicant's explanation about the effects of mavacamten on rate corrected QT interval (QTc interval):
In 3-month and 39-week repeated dose toxicity studies in dogs (CTD 4.2.3.2-8, 4.2.3.2-9), clinical studies in healthy subjects (CTD 5.3.3.1-2), and other studies, QTc interval prolongation was noted. The findings shown below suggest that the underlying mechanism of QTc interval prolongation associated with mavacamten could be a compensatory response (electrical remodeling) to sustained mavacamten-induced depression of cardiac contractility rather than a direct action on hERG channels.

- In the *in vitro* hERG study, mavacamten did not have a significant impact on hERG potassium current up to the maximum concentration studied (60 μmol/L).
- In the *in vitro* studies (CTD 4.2.1.3-5, 4.2.1.3-7, 4.2.1.3-8, 4.2.1.3-9, 4.2.1.3-10, 4.2.1.3-12, and 4.2.1.3-13), mavacamten did not tend to induce reentrant arrhythmia, etc.
- A mechanistic investigation of QTc interval prolongation caused by mavacamten using normal rats (CTD 4.2.1.3-14) suggested that it could be an intrinsic adaptive response involving downregulation of early

repolarization, namely, transient outward potassium current (I_{to}) and adenosine triphosphate dependent potassium current (I_{KATP}).

In addition, given the points below, it is unlikely that QTc interval prolongation associated with mavacamten will pose clinical problems in patients with oHCM.

- Impairment or reduction of I_{to} and I_{KATP} is reported associated with the pathophysiology of HCM (*Mol Med Rep.* 2016;13:1447-54). It is unlikely that QTc interval prolongation occurs as a compensatory response to mavacamten-induced depression of cardiac contractility.
- While prolonged action potential duration accompanying increased late sodium current (I_{NaL}) has been reported to be associated with the pathophysiology of HCM (*Circulation.* 2013;127:575-84), mavacamten inhibits I_{NaL} (CTD 4.2.1.3-7).

PMDA considers that while the applicant's explanation about QTc interval prolongation caused by mavacamten is reasonable to some extent; the risk for QTc interval prolongation in patients with oHCM will be further discussed in Section 7.R.4.4.

3.R.3 Effects of mavacamten on the respiratory system

The applicant's explanation about the findings (increased respiratory rate and decreased tidal volume) related to the respiratory system obtained in the study that evaluated the effects on the respiratory system in dogs (CTD 4.2.1.3-2):

It has been reported that in patients with cardiac failure, an increase in respiratory rate and other findings are observed. These are a result of sympathetic nervous system overactivation to compensate for reduced cardiac contractile function (*J Appl Physiol.* (1985) 2020;128:214-24). Therefore, the increased respiratory rate and decreased tidal volume that occurred in dogs following administration of mavacamten are considered to be secondary effects associated with depressed cardiac contractility induced by mavacamten. It is anticipated that because of the pharmacological action of mavacamten, although an excessive decrease in LVEF is expected in animals and healthy adults with normal cardiac function, normalization of the pathological condition in patients with oHCM presenting with cardiac hypercontractility and elevated LVEF levels can be expected, and it is unlikely that a compensatory response will occur associated with mavacamten-induced depression of cardiac contractility. Taken together, it is unlikely that an increase in respiratory rate and a decrease in tidal volume will become clinical problems associated with mavacamten treatment in patients with oHCM.

PMDA considers that the applicant's explanation about the increase in respiratory rate and decrease in tidal volume reported in dogs is reasonable, and given that mavacamten is to be administered to patients with oHCM, while monitoring their cardiac function, PMDA concluded that an increase in respiratory rate and a decrease in tidal volume are unlikely to become clinical problems associated with mavacamten treatment.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The plasma concentrations of mavacamten were determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 1.00 ng/mL for all animals studied, i.e., mice, rats, dogs, monkeys, and rabbits. Radioactivity levels after administration of ^{14}C-lalbeled mavacamten (^{14}C-mavacamten) were measured by liquid scintillation counter or HPLC with a radioactivity detector.

Unless otherwise specified, pharmacokinetic (PK) parameters are expressed as the mean or the mean ± standard deviation.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1 [reference data], 4.2.2.2-3 [reference data], 4.2.2.2-5 [reference data], 4.2.2.2-6 [reference data])

Table 6 shows PK parameters following administration of a single intravenous or oral dose of mavacamten to male mice, male rats, male dogs, and male monkeys.

Table 6. PK parameters after single intravenous or oral dose of mavacamten

Animal species	Route of administration	Dose (mg/kg)	N	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	BA[b] (%)	V_{ss} (L/kg)	CL (mL/min/kg)
Mouse	IV	1	3/timepoint	853	—	2180	7.02	—	3.81	7.65
	Oral	1	3/timepoint	564	0.5	3170	4.18	145	—	—
Rat	IV	0.2	3	—	—	314 ± 48.2	8.9 ± 1.2	—	6.82 ± 0.637	10.8 ± 1.67
		1	3	—	—	2880 ± 261	11.2 ± 1	—	5.01 ± 0.729	5.82 ± 0.504
	Oral	2	3	522 ± 93.6	0.5[a]	4310 ± 1100	8.2 ± 1	74.8 ± 19.1	—	—
		10	3	1300 ± 107	0.5[a]	34000 ± 13600	21.8 ± 7.5	—	—	—
Dog	IV	0.25	3	—	—	7330 ± 1440	130 ± 20.5	—	7.01 ± 2.68	0.584 ± 0.117
	Oral	0.5	3	186 ± 20	0.3[a]	13500 ± 2760	161.2 ± 74.1	87.1 ± 9.01	—	—
Monkey	IV	0.25	3	—	—	1520 ± 494	44.5 ± 7.8	—	10.6 ± 2.15	2.98 ± 1.07
	Oral	0.5	3	63 ± 23.4	0.5[a]	1410 ± 465	42.7 ± 6.12	46.5 ± 15.3	—	—

—, not calculated; a, median; b, calculated as the percentage of dose-normalized $AUC_{0-\infty}$ relative to that after intravenous administration of mavacamten

4.1.2 Repeated-dose studies

4.1.2.1 Study in rats (CTD 4.2.3.2-2 [reference data], 4.2.3.2-3)

Table 7 shows PK parameters after oral administration of mavacamten once daily for 2 weeks or 6 weeks to male and female rats.

Table 7. PK parameters after administration of repeated oral doses of mavacamten to rats

Treatment duration	Dose (mg/kg/day)	Evaluation timepoint (Day)	N	C_{max} (ng/mL)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
				Male	Female	Male	Female
2 weeks	1	1	3	98.9	184	1600	1720
		14	3	204	384	2760	6950
	3	1	3	331	531	5100	6520
		14	3	696	953	11400	16400
6 weeks	0.3	1	6	28.0	33.9	442	553
		41	6	60.5	62.3	1030	1000
	1	1	6	108	124	1780	2270
		41	6	307	283	4940	4810
	3	1	6	323	475	5790	8740
		41	6	726	919	12400	15200

4.1.2.2 Study in dogs (CTD 4.2.3.2-7)

Table 8 shows the PK parameters after oral administration of mavacamten once daily for 6 weeks to male and female dogs.

Table 8. PK parameters after administration of repeated oral doses of mavacamten to dogs

Dose (mg/kg/day)	Evaluation timepoint (Day)	N	C_{max} (ng/mL)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
			Male	Female	Male	Female
0.1	1	4	33.4 ± 5.4	33.6 ± 16.1	220 ± 38	239 ± 93
	38	4	88.9 ± 19.4	110 ± 30	1690 ± 370	1480 ± 500
0.3	1	4	60.1 ± 13.8	56.1 ± 20.0	621 ± 120	553 ± 43
	38	4	303 ± 82	220 ± 35	5900 ± 1700	3700 ± 780

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3-1 [reference data])

A single oral dose of ^{14}C-mavacamten 1 mg/kg to male pigmented rats, and radioactivity levels in each tissue at 0.5, 1, 4, 8, 24, 72, 168, 336, and 720 hours post-dose (N = 1/timepoint) were investigated. While the radioactivity levels reached their maximum at 0.5 hours post-dose in the majority of the tissues, the highest radioactivity levels were detected in the diaphragm, esophagus, and testis at 1 hour post-dose, skeletal muscles and crystalline lens at 4 hours post-dose, salivary glands at 8 hours post-dose, brain at 24 hours post-dose, and spinal cord at 72 hours post-dose. Compared with the maximum radioactivity level in blood (313 ng eq./g), the maximum radioactivity levels were particularly high in the following tissues: cardiac muscle (4380 ng eq./g), diaphragm (2510 ng eq./g), salivary gland (1710 ng eq./g), muscle (1320 ng eq./g), esophagus (1280 ng eq./g), renal cortex (1080 ng eq./g), kidney (1020 ng eq./g), small intestine (749 ng eq./g), renal medulla (726 ng eq./g), Harderian gland (681 ng eq./g), gastric mucosa (666 ng eq./g), and adrenal gland (648 ng eq./g). The maximum radioactivity levels in melanin-containing tissues, namely, pigmented skin and eyeball, were 229 and 54.9 ng eq./g, respectively, which were lower than the radioactivity levels in blood. The radioactivity levels decreased after reaching their maximum up to 720 hours post-dose over time in all tissues.

A single oral dose of ^{14}C-mavacamten 1 mg/kg was administered to male albino rats, and radioactivity levels in each tissue at 1, 4, 24, 48, and 168 hours post-dose were measured (N = 1/timepoint). The radioactivity

distribution in the tissues at each timepoint was generally similar to the results from male pigmented rats except that radioactivity was not detected in melanin-containing tissues.

4.2.2 Plasma protein binding (CTD 4.2.2.3-3 [reference data])

When ^{14}C-mavacamten 0.2 to 10 μmol/L was added to mouse, rat, dog, or monkey plasma, the plasma protein binding was 83.6% to 84.2% (mouse), 88.5% to 89.4% (rat), 88.8% to 92.6% (dog), and 91.9% to 96.9% (monkey).

4.2.3 Distribution in blood cells (CTD 4.2.2.3-3 [reference data])

When mavacamten 200 μmol/L was added to mouse, rat, dog, or monkey blood, the blood/plasma concentration ratio was 0.72 (mouse), 0.82 (rat), 0.78 (dog), and 0.82 (monkey).

4.2.4 Placental transfer (CTD 4.2.3.5.2-5)

Mavacamten 0.6, 1.2, or 2 mg/kg/day was orally administered to pregnant rabbits (N = 3/group) once daily for 7 days from gestational days 6 to 12. The embryo-to-maternal plasma mavacamten concentration ratio at 24 hours post-dose on gestational day 12 ranged from 0.11 to 0.13. The applicant explained that mavacamten may transfer across the placenta to the fetus.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4-5 [reference data])

When ^{14}C-mavacamten 5 μmol/L was added to mouse, rat, dog, and monkey liver microsomes, the following metabolites of mavacamten were detected in liver microsomes from all animals studied: M1 (product of hydroxylation of the phenyl moiety of mavacamten), M2 (product of hydroxylation of the isopropyl moiety of mavacamten), M6 (N-dealkylation product of mavacamten), and M12 (peroxidation product of mavacamten).

When ^{14}C-mavacamten 10 μmol/L was added to mouse, rat, dog, and monkey hepatocytes, no mavacamten metabolites were detected in mouse hepatocytes, while in hepatocytes from other animals the following metabolites were detected: M1, M2, M4 (glucuronide conjugate of M1), M6, and M10 (compound formed following binding of $C_4H_6O_2$ to the uracil moiety of mavacamten) in rat hepatocytes; M6 in dog hepatocytes; M1, M2, M6, M11 (compound formed by hydroxylation of the phenylethyl moiety and hydrolysis of the aminouracil moiety of mavacamten), and M13 (product of hydroxylation of the aminouracil moiety of mavacamten, followed by glucuronidation) in monkey hepatocytes.

4.3.2 *In vivo* metabolism

4.3.2.1 Metabolites in plasma (CTD 4.2.2.4-1 [reference data])

A single oral or intravenous dose of ^{14}C-mavacamten 1 mg/kg was administered to male rats (N = 4). The unchanged mavacamten accounted for 45.3% (oral) and 66.9% (intravenous) of the total plasma radioactivity

based on $AUC_{0\text{-}72h}$. Following intravenous administration, in addition to the unchanged mavacamten, M1 was also detected, which accounted for <10% of the unchanged mavacamten.

4.3.2.2 Metabolites in urine and bile (CTD 4.2.2.4-1 [reference data])

A single oral or intravenous dose of ^{14}C-mavacamten 1 mg/kg was administered to male rats (N = 3 or 4). Following oral administration, the unchanged mavacamten (7.07%; the percentage of the $AUC_{0\text{-}120h}$ of metabolite to that of the total radioactivity in urine; the same applies hereinafter), M1 (44.2%), M2 (14.1%), and M4 (0.76%) were detected in urine. Following intravenous administration, the unchanged mavacamten (6.17%; the percentage of the $AUC_{0\text{-}96h}$ of metabolite to that of the total radioactivity in urine; the same applies hereinafter), M1 (19.2%), M2 (8.14%), M4 (24.1%), and M8 (enantiomer of M2; 2.00%) were detected in urine; the unchanged mavacamten (3.90%; the percentage of the $AUC_{0\text{-}96h}$ of metabolite to that of the total radioactivity in bile; the same applies hereinafter), M1 (10.3%), M2 (3.90%), M4 (56.3%), and M8 (11.4%) were detected in bile.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion (CTD 4.2.2.3-1 [reference data])

A single oral dose of ^{14}C-mavacamten 1 mg/kg was administered to male rats (N = 3). Up to 120 hours post-dose, 22.6% and 58.0% of administered radioactivity was excreted in urine and feces, respectively.

A single oral dose of ^{14}C-mavacamten 1 mg/kg was administered to bile duct-cannulated male rats (N = 4). Up to 96 hours post-dose, 31.0%, 7.59%, and 41.1% of administered radioactivity was excreted in urine, feces, and bile, respectively.

4.4.2 Secretion into breast milk

Whether or not mavacamten is secreted into the breast milk has not been studied. The applicant explained that given that mavacamten is a small molecule compound (molecular weight, 277.33) with a high lipid solubility (1-octanol/water partition coefficient, 2.8), it is likely that mavacamten is secreted into breast milk.

4.R Outline of the review conducted by PMDA

Based on the submitted non-clinical pharmacokinetic study data, PMDA concluded that the applicant's non-clinical pharmacokinetic evaluation is adequate.

5. Toxicology and Outline of the Review Conducted by PMDA

The following toxicology studies of mavacamten were conducted: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and development toxicity studies, and other toxicity studies (toxicity studies of impurities and degradants). Unless otherwise specified, 0.5% (w/v) methylcellulose aqueous solution was used as a vehicle.

5.1 Single-dose toxicity

The acute toxicity of mavacamten was evaluated based on the results from a single-dose toxicity study in dogs, as well as results obtained following administration of the initial dose in repeated-dose toxicity studies in mice and rats (Table 9).

Table 9. Single-dose toxicity study and repeated-dose toxicity studies (findings obtained following the initial dose)

Test system	Route	Dose (mg/kg)	Key findings	Approximate lethal dose (mg/kg)	CTD
Male/female dog (Beagle)	Oral	0, 1.5, 4.5, 7.0, 30	Animals that died: at 30[a] (1 of 1 male, 1 of 1 female) Decrease in locomotor activity, nausea (females); shortened capillary refilling time (males)	30	4.2.3.1-1 (reference data)
Male/female mouse (CByB6F1)	Oral	0, 5, 6.1, 7	Animals that died: at 6.1 (1 of 35 males), at 7 (11 of 35 males, 1 of 35 females) Irregular respiration, piloerection, decrease in locomotor activity, cold to the touch, emaciation, hunchback position, lateral position, incomplete eyelid opening	6.1 (males) 7 (females)	4.2.3.2-1 (reference data)
Male/female rat (SD)	Oral	0, 1.0, 3.0, 10.0	Animals that died: at 10[b] (14 of 14 males, 14 of 14 females) Increase in respiratory rate, piloerection, cold to the touch, decrease in the amount of stool, inanimation, hunchback position	10	4.2.3.2-2 (reference data)

a, The animals were euthanized in moribund condition due to worsened clinical signs.
b, Two animals died, and those that survived, the majority of which were in moribund condition, were euthanized on Days 3, 4, and 6.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in mice (1 week), rats (26 weeks), and dogs (39 weeks) (Table 10). Key study findings were cardiac failure caused by the excessive pharmacological effects of mavacamten, and those caused by secondary effects. In the repeated-dose toxicity studies in rats and dogs, the exposures ($AUC_{0\text{-}24h}$) at the no-observed adverse effect level (NOAEL) (0.3 mg/kg/day for rats, 0.18 mg/kg/day for dogs) were 1470 ng·h/mL (male rats), 1870 ng·h/mL (female rats), 4570 ng·h/mL (male dogs), and 4790 ng·h/mL (female dogs), corresponding to 0.09-fold (male rats), 0.11-fold (female rats), 0.27-fold (male dogs), and 0.29-fold (female dogs) the maximum daily exposure ($AUC_{0\text{-}24h}$, 16800 ng·h/mL)[6)] in the foreign phase III study (Study MYK-461-005).

6) Study MYK-461-005 was designed to target a mavacamten plasma trough concentration <700 ng/mL and the dose was adjusted accordingly; therefore, the exposure was calculated based on this concentration.

Table 10. Repeated-dose toxicity studies

Test system	Route	Treatment period	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD
Male/female mouse (CByB6F1)	Oral	1 week (once daily)	0, 5, 6.1, 7	Mortality: at 6.1 (1 of 35 males), at 7 (11 of 35 males, 1 of 35 females) At ≥5, increased heart weight, findings in the left atrium (minor to mild myocardial degeneration/necrosis, mixed cell inflammation, thrombus, hemorrhage, endocardial hyperplasia) (males); in the lung, mild to moderate vessel inflammation (males), extramedullary hematopoiesis (females) At ≥6.1, decrease in locomotor activity, hunchback position, piloerection, extramedullary hematopoiesis (males) At 7, decrease in body weight/food consumption, ataxia, emaciation (females), incomplete eyelid opening, irregular respiration, lateral position, cold to the touch, findings in the left atrium (minor to mild myocardial degeneration/necrosis, mixed cell inflammation, thrombus, hemorrhage, endocardial hyperplasia) (females); in the lung, mild to moderate vessel inflammation (females); in the liver, degeneration/necrosis of hepatocytes, thrombosis in hepatic sinusoids, centrilobular hepatocellular vacuolation	<5	4.2.3.2-1 (reference data)
Male/female rat (SD)	Oral	14 days (once daily)	0, 1.0, 3.0, 10.0	Mortality: at 10[a] (14 of 14 males, 14 of 14 females) At ≥1.0, minor decrease in weight gain At 3.0, increased heart weight (females) At ≥3.0, in the heart, atrioventricular dilation, acute or subacute inflammation of cardiac tissues (primarily subendothelial, perivascular, or epicardial tissue of the atrium); in the liver, centrilobular hepatocellular vacuolation (males), centrilobular necrosis (males), centrilobular congestion (males) At 10, decreased body weight, piloerection, dehydration, decrease in the amount of stool, increase in respiratory rate, decrease in red cell mass (red blood cell count, hemoglobin, and hematocrit), increase in neutrophil count, decrease in lymphocyte count, decrease in platelet count, increase in prothrombin time, increase in activated partial thromboplastin time, increase in heart size (males); in the liver, discoloration, centrilobular hepatocellular vacuolation (females), centrilobular necrosis (females), centrilobular congestion (females)	1.0	4.2.3.2-2 (reference data)

Test system	Route	Treatment period	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD
Male/female rat (SD)	Oral	6 weeks (once daily) + 4-week recovery period	0, 0.3, 1.0, 3.0	Mortality: at 3.0 (2 of 15 males, 2 of 15 females) Respiratory distress, labored breathing, decrease in locomotor activity, piloerection, paleness, emaciation, abnormal contents (thin red or yellow fluid) in the thoracic cavity, pancreatic edema; in the heart, cardiac hypertrophy with myocardial degeneration and inflammation, endocardial degeneration/necrosis, atrial thrombosis, ventricular dilatation; in the liver, centrilobular hepatocellular necrosis, centrilobular congestion, diffuse hepatocellular vacuolation, lung congestion, edema (mainly perivascular), increased alveolar macrophages; pancreatic edema At ≥1.0, increase in parathyroid weight At 3.0, increase in heart weight (females), increase in thyroid weight, increase in heart size (females), cardiac hypertrophy, myocardial degeneration, cartilaginous/osseous metaplasia of the chorda tendineae, endocardial degeneration/inflammation, valvular inflammatory cell infiltrate/inflammation Reversibility: partially reversible	1.0	4.2.3.2-3
Male/female rat (SD)	Oral	3 months (once daily) + 4-week recovery period	0, 0.3, 1.0/0.6,[b] 2.0/1.2[b]	Mortality: at 2.0/1.2 (1 of 21 males, 3 of 21 females) Cold to the touch, paleness, decrease in locomotor activity, hunchback position, unkempt fur, incomplete eyelid opening, irregular respiration, labored breathing, decrease in body weight/food consumption, marked left and right ventricular and atrial dilatation of the heart, moderate to marked atrial/auricular dilation associated with mild to marked edema and congestion in the lungs (with macrophagic/neutrophilic infiltration, necrosis and hemorrhage), centrilobular necrosis of the liver At ≥0.3, increase in heart weight, non dose-dependent minor to moderate ventricular dilation At ≥1.0/0.6, increased NT-proANP ratio (females) At 2.0/1.2, increased NT-proANP ratio (males), increase in heart size associated with ventricular dilation (males), atrial/auricular dilation (males) Reversibility: not reversible	<0.3	4.2.3.2-4
Male/female rat (SD)	Oral	6 months (once daily) + 3-month recovery period	0, 0.3, 0.6, 1.2	Mortality: at 1.2 (1 of 21 males, 1 of 21 females) Increase in heart size, dark red abdominal fluid, moderate left ventricular dilation and minor right ventricular dilation, moderate centrilobular degeneration and congestion of the liver, moderate diffuse pulmonary alveolar macrophage infiltrates; in the adrenal cortex, moderate congestion, hemorrhage, necrosis; in the thymus, moderate lymphocyte depletion/necrosis At ≥0.3, increase in red cell mass (red blood cell count, hemoglobin, and hematocrit) (females) At ≥0.6, osseous/cartilaginous metaplasia of the cardiac muscle (females)	0.3[c]	4.2.3.2-5

Test system	Route	Treatment period	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD
				At 1.2, in the echocardiogram examination, increase in end diastolic and end systolic ventricle size (ventricular volume, diameter), left ventricular systolic function (reduction in left ventricular ejection fraction, left ventricular fractional shortening), increase in platelet count (males), increase in heart weight, osseous/cartilaginous metaplasia of the cardiac muscle (males) Reversibility: partially reversible (excluding cardiac osseous metaplasia, etc.)		
Male/female dog (Beagle)	Oral	28 days (once daily)	0, 0.4, 1.3, 4.0	Mortality: at 4.0[d] (2 of 2 males, 2 of 2 females) At 4.0, vomiting, decrease in the amount of stool, decrease in locomotor activity, decrease in food consumption, minor decrease in body weight (males), increase in white blood cell count (neutrophil count, lymphocyte count, eosinophil count), decreased sodium and chloride levels in blood, pulmonary edema (high protein edema fluid within the alveoli, congestion, hemorrhage, fibrin thrombi along the alveolar septa, and inflammatory infiltrate [neutrophils and macrophages]), neutrophilic infiltration in the adrenal cortex	1.3	4.2.3.2-6 (reference data)
Male/female dog (Beagle)	Oral	6 weeks (once daily) + 4-week recovery period	0, 0.1, 0.3, 1.0,[e] 3.0[e]	Mortality: at 1.0 (3 of 6 males), at 3.0 (4 of 6 males, 3 of 6 females) Pale gums, prolonged capillary refilling time, decrease in locomotor activity, labored breathing, tachypnea, paleness, decrease in body weight/food consumption At ≥1.0, increase in reticulocyte count, change in red cell mass, increases in neutrophil count, monocyte count, increases in blood AST, ALT, urea nitrogen, creatinine, potassium, inorganic phosphorus, edema in the gallbladder associated with thickened pale gallbladder walls, edema present in and around the lung, thymus, pancreas, pericardium, mesenteric lymph node, congestion in the liver/gastrointestinal tract; in the heart, minor hemorrhage, inflammatory cell infiltrates, myxomatous change and edema in the atrioventricular valve, minor inflammatory cell infiltrates in the epicardium, minor degenerative changes in coronary vessels; in the lung, alveolar inflammation, increased alveolar macrophages, minor lymphocyte apoptosis in the perivascular inflammatory cell infiltrates; in the thymus and lymph nodes, decrease in lymphocyte cellularity At 3.0, decrease in blood chloride, edema in the brain, thin red fluid in the abdominal cavity (males), foamy red fluid in the trachea (males), apoptosis in the spleen, acinar atrophy of the prostate Reversibility: reversible	0.3	4.2.3.2-7
Male/female dog (Beagle)	Oral	3 months (once daily) +	0, 0.06, 0.18, 0.30,	Mortality: at 0.45 (2 of 6 males)	0.30	4.2.3.2-8

Test system	Route	Treatment period	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD
		8- or 11-week recovery period[f]	0.45[g]	Decrease in locomotor activity, labored breathing, decrease in body weight, decrease in food consumption, red discoloration of the lung, foamy material in the trachea, severe left and right ventricular dilation accompanied by pericardial effusion, mononuclear cell infiltration of cardiac mitral valve and tricuspid valve, congestion and edema in the lung, liver, gallbladder, thymus, pericardium, multifocal reactive hypertrophy/hyperplasia in the pleural mesothelium of the lung, thymic cortex lymphocyte apoptosis, increase in NT-proBNP, decrease in blood total protein and albumin At 0.45, increase in heart rate, increase in R and T amplitudes, bilateral ventricular dilation, mononuclear cell subendothelial infiltration of the cardiac mitral valve Reversibility: reversible		
Male/female dog (Beagle)	Oral	9 months (once daily) + 17-week recovery period	0, 0.06, 0.18, 0.30 (males); 0.45 (females)	At ≥0.18, prolonged QTcF, increase in heart rate (females) At 0.30, increase in heart rate; in the echocardiogram examination, marked increases in left-ventricular end-diastolic and left-ventricular end-systolic volumes, and marked decrease in left ventricular ejection fraction At 0.45, prolonged QRS duration; in the echocardiogram examination, marked increases in left-ventricular end-diastolic and left-ventricular end-systolic volumes, and marked decrease in left ventricular ejection fraction Reversibility: reversible	0.18[h]	4.2.3.2-9

a, Two animals died, and those that survived, the majority of which were in moribund condition, were euthanized on Days 3, 4, and 6. Organ weights were not measured in the euthanized animals.

b, Because of toxicities observed in the 2.0 mg/kg/day group early, doses were interrupted for 4 days in the2.0 mg/kg/day group, and treatment was resumed at the reduced dose of 1.2 mg/kg/day on Day 15 (main study group) or Day 12 (TK group). In the 1.0 mg/kg/day group, doses were interrupted for 2 days, and treatment was resumed at the reduced dose of 0.6 mg/kg/day on Day 15 (main study group) or Day 12 (TK group).

c, The change in the red cell mass in the 0.3 mg/kg/day group was minimal, and determined to be of low toxicological significance.

d, One male animal was euthanized due to moribund condition on Day 14. Although 1 female animal exhibited no change in clinical signs, because all the other animals in the 4.0 mg/kg/day group died or were euthanized, this female animal was also euthanized on Day 15.

e, Because 1 male animal in the 1.0 mg/kg/day group was euthanized on Day 26, the dosing of all animals in the 1.0 mg/kg/day group on Days 26 and 27 was terminated. In the 3.0 mg/kg/day group, because animals were found dead or were euthanized due to worsened condition on Days 6 to 8, the dosing of surviving animals was terminated. The study continued until the scheduled terminal necropsy. At the end of dosing, 4 males and 4 females in each of the 0, 0.1, and 0.3 mg/kg/day group were necropsied. At the end of the recovery period, 2 males and 2 females in each of the 0 and 1.0 mg/kg/day group were necropsied.

f, The duration of the recovery period was 11 weeks for male animals dosed 0.45 mg/kg/day, and 8 weeks for all the remaining animals.

g, In the 0.45 mg/kg/day group, 2 males either died or were euthanized early, dosing was terminated on Day 73. Male animals dosed 0.45 mg/kg/day not subject to reversibility assessment were necropsied at the end of the dosing period (Day 74).

h, Findings such as prolonged QTcF noted in the 0.18 mg/kg/day group were considered toxicologically insignificant given that they were minor changes.

5.3 Genotoxicity

Genotoxicity studies consisted of *in vitro* bacterial reverse mutation assays using mavacamten and MYK-460,[7] the enantiomer of mavacamten, an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, and an *in vivo* rat bone marrow micronucleus assay (Table 11). All the assays were negative for genotoxicity.

Table 11. Genotoxicity studies

Type of testing		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Result	CTD
In vitro	Bacterial reverse mutation assay	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537 *E. coli*: WP2 *uvrA*	S9−	0,[a] 5, 15, 50, 150, 500, 1500, 5000	Negative	4.2.3.3.1-1
			S9+			
	Bacterial reverse mutation assay	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537 *E. coli*: TA102	S9−	MYK-460: 0,[a] 5, 16, 50, 160, 500, 1600, 5000	Negative	4.2.3.3.1-2
			S9+			
	Chromosomal aberration assay in human peripheral blood lymphocytes	Human peripheral blood lymphocytes	S9+ (3 hours)	0,[a] 100, 190, 230	Negative	4.2.3.3.1-3
			S9− (3 hours)	0,[a] 10, 190, 270		
			S9− (20 hours)	0,[a] 5, 30, 50		
	Chromosomal aberration assay in human peripheral blood lymphocytes	Human peripheral blood lymphocytes	S9+ (3 hours)	MYK-460: 0,[a] 60, 120, 160	Negative	4.2.3.3.1-4
			S9− (3 hours)	MYK-460: 0,[a] 120, 160, 220		
			S9− (20 hours)	MYK-460: 0,[a] 10, 25, 40, 80		
In vivo	Micronucleus assay in rats	Male rats (SD) bone marrow		0, 1, 3, 8 (orally, once daily for 2 days)	Negative	4.2.3.3.2-1

a, DMSO

5.4 Carcinogenicity

A 6-month carcinogenicity study in Tg rasH2 mice and a 2-year carcinogenicity study in rats were conducted (Table 12). No mavacamten-related neoplastic lesions were noted. Based on the results, the applicant determined that the carcinogenic risk of mavacamten is low. In the carcinogenicity studies in Tg rasH2 mice and rats, the exposure ($AUC_{0\text{-}24h}$) at the non-carcinogenic dose (2 mg/kg/day for male mice, 3 mg/kg/day for female mice, and 0.6 mg/kg/day for rats) was 30000 ng·h/mL (male mice), 50400 ng·h/mL (female mice), 3640 ng·h/mL (male rats), and 2810 ng·h/mL (female rats), corresponding to 1.79-fold (male mice), 3.00-fold (female mice), 0.22-fold (male rats), and 0.17-fold (female rats) the maximum daily exposure $AUC_{0\text{-}24h}$ (16800 ng·h/mL)[6] in the foreign phase III study (Study MYK-461-005).

[7] 6-{[(1*R*)-1-Phenylethyl]amino}-3-(propan-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione

Table 12. Carcinogenicity studies

Test system	Route	Duration	Major lesion		Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	CTD
					0	0.5	1	2	3		
				N	25/sex	25/sex	25/sex	25 M	25 F		
Male/female mice (Tg-rasH2)	Oral	26 weeks (once daily)	Neoplastic	None						2 (males) 3 (females)	4.2.3.4.1-2
			Non-neoplastic	None							
Male/female rats (SD)	Oral	2 years (once daily)	Major lesion		Dose (mg/kg/day)					0.6	4.2.3.4.1-3
					0[a]	0	0.1	0.3	0.6		
				N	60/sex	60/sex	60/sex	60/sex	60/sex		
			Neoplastic	None							
			Non-neoplastic	≥0.1, decrease in body weight without dose-response relationship (females)							

a, water

5.5 Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation in rats, embryonic and fetal development studies in rats and rabbits, and a study on prenatal and postnatal development and maternal function in rats were conducted (Table 13). In the embryonic and fetal development studies in rats and rabbits, increase in the percentage of post-implantation loss, and findings such as visceral and skeletal abnormalities, suggestive of teratogenicity of mavacamten, were noted. The exposure ($AUC_{0\text{-}24h}$) at the NOAELs (0.75 mg/kg/day and 0.6 mg/kg/day) for embryonic and fetal development in these studies were 5690 ng·h/mL for rats and 7160 ng·h/mL for rabbits, corresponding to 0.3-fold and 0.4-fold the maximum daily exposure (16800 ng·h/mL)[6)] in the foreign phase III study (Study MYK-461-005), respectively.

Table 13. Reproductive and developmental toxicity studies

Type of testing	Test system	Route	Dosing duration	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development to implantation	Male rats (SD)	Oral	28 days prior to mating to the day before necropsy (once daily)	0, 0.3, 0.6, 1.2	No noteworthy findings	General toxicity, 1.2 Reproductive ability, 1.2	4.2.3.5.1-1
	Female rats (SD)		15 days prior to mating to gestation day 7 (once daily)	0, 0.3, 0.6, 1.2	At ≥0.6, decrease in body weight gain without dose-response relationship	General toxicity, 1.2[a] Reproductive ability, 1.2	
Embryonic and fetal development	Female rats (SD)	Oral	Gestation days 6-17 (once daily)	0, 1.0, 1.5, 2.0	Dams: At ≥1.5, minor decrease in body weight gain Embryos/fetuses: At ≥1.5, increased percentage of post-implantation loss (early and late resorptions), decreased number of live fetuses, decreased total fetal weight		4.2.3.5.2-1 (reference data)
	Female rats (SD)	Oral	Gestation days 6-17 (once daily)	0, 0.3, 0.75, 1.5	Dams: No noteworthy findings Embryos/fetuses: At 1.5, increased percentage of post-implantation loss (early and late resorptions), decreased mean fetal weight, visceral abnormalities (complete visceral inversion, right atrioventricular valve with ventricular septal defect), skeletal abnormalities (fused sternebrae, absence of lumbar vertebrae), delayed ossification (incomplete ossification of cervical vertebrae, thoracic vertebrae, phalanges, metatarsal bones)	Dam (general toxicity), 1.5 Embryo-fetal development, 0.75	4.2.3.5.2-2
	Female rabbits (NZW)	Oral	Gestation days 6-19 (once daily)	0, 0.7, 1.5, 2.0	Dams: At ≥1.5, decrease in body weight, decrease in body weight gain Embryos/fetuses: No noteworthy findings		4.2.3.5.2-4 (reference data)
	Female rabbits (NZW)	Oral	Gestation days 6-19 (once daily)	0, 0.6, 1.2, 2.0	Dams: Animals that died: at 2.0 (2 of 22 animals) Decreased/cessation of food consumption, decrease in body weight, bilateral ventricular dilation At ≥1.2, decrease in food consumption, decreased body weight, decrease in body weight gain Embryos/fetuses: At ≥1.2, external malformation (cleft palate) At 2.0, visceral abnormalities (large vessel malformation [pulmonary trunk and aortic arch dilation]), skeletal abnormalities (fused sternebrae)	Dam (general toxicity), 0.6 Embryo-fetal development, 0.6	4.2.3.5.2-5

Type of testing	Test system	Route	Dosing duration	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD
Prenatal and postnatal development and maternal function	Female rats (SD)	Oral	Gestation days 6 to lactation day 20 (once daily)	0, 0.3, 0.75, 1.5	Dams: No noteworthy findings F1 pups: No noteworthy findings	Dam (general toxicity), 1.5 F1 pups, 1.5	4.2.3.5.3-1

a, Decreases in body weight gain noted at ≥0.6 mg/kg/day, which were not dose-dependent, were determined to be of low toxicological significance.

5.6 Other studies

5.6.1 Toxicity studies for impurities and degradants

A repeated-dose toxicity study of impurities (MYK-460[7)] and Related Substance A[8)]) or degradants (Related Substance B[9)] and Related Substance C[10)]) was conducted in rats (Table 14). No enhanced or new toxicity due to spiking of impurities or degradants was noted.

Table 14. Toxicity studies for impurities and degradants

Test system	Route	Duration	Dose (mg/kg/day)	Key findings	CTD
Male/female rats (SD)	Oral	3 months (once daily)	0, 0.3, 0.3[a]	Impurity not-spiked/impurity-spiked At 0.3, increased body weight, increase in body weight gain (females), increase in adrenal, heart, and spleen organ weights (females)	4.2.3.7.6-1
Male/female rats (SD)	Oral	13 weeks (once daily)	0, 0.3, 0.3[b]	No noteworthy findings	4.2.3.7.6-2

a, mavacamten spiked with impurity (MYK-460 [[redacted]% (w/w)] and Related Substance A [[redacted]% (w/w)])
b, mavacamten spiked with impurity (MYK-460 [[redacted]%]) and degradant (Related Substance B [[redacted]%] and Related Substance C [[redacted]%])

5.R Outline of the review conducted by PMDA

5.R.1 Toxicological findings related to excessive pharmacologic effects of mavacamten noted in repeated-dose toxicity studies

In the repeated-dose toxicity studies in rats and dogs, adverse effects related to excessive pharmacologic effects of mavacamten occurred at exposures lower than the maximum daily exposure level in the foreign phase III study (Study MYK-461-005). The applicant's explanation:

The inhibitory activity levels of mavacamten against cardiac myosin for the animal species used in the toxicity studies (e.g., rats and dogs) were similar to those seen in humans. Therefore, the pharmacological activity of mavacamten in the animal species used in the toxicity studies is expected to be comparable to that in humans. However, based on the following factors, it is considered that in healthy animals used in the toxicity studies, toxicities related to excessive pharmacologic effects can occur at lower dose levels compared to patients with oHCM.

- The pharmacologic effect of mavacamten involves decrease in myocardial contractility through inhibition of cardiac myosin. In patients with oHCM, in whom cardiac hypercontractility and increased LVEF occur, mavacamten is expected to normalize these pathological conditions; conversely, in healthy animals

8) [redacted]
9) [redacted]
10) [redacted]

and humans with normal cardiac function and contractility, it is expected that mavacamten will lead to an excessive decrease in myocardial contractility.

- A decrease in LVEF has also been reported in the phase I study in healthy adults (Study MYK-461-003).

PMDA accepted the applicant's explanation. Appropriate cautionary statements regarding cardiac failure to be included in the package insert will be discussed in Section 7.R.4.2 taking into account the results of clinical studies.

5.R.2 Treatment of pregnant women, lactating mothers, etc.

The applicant's explanation as to whether the reproductive and developmental toxicity study findings can become problems in clinical use:

In the clinical studies of mavacamten, women who are or may be pregnant and lactating mothers were excluded, and provisions mandating contraception were established for women of childbearing potential. For this reason, no safety-related data on pregnant women, human fetuses, and newborns have been received. In the embryonic and fetal development studies in rats and rabbits, the percentage of post-implantation loss increased, and other findings such as visceral and skeletal abnormalities, were noted. These findings are suggestive that mavacamten is teratogenic. Because a safety margin is not sufficient for the maximum daily exposure in clinical use, women of childbearing potential should use appropriate methods of contraception during mavacamten treatment and for 4 months after the last dose,[11)] and mavacamten should not be used in women who are or may be pregnant. Cautionary statements to the above effect will be included in the package insert. Mavacamten will be contraindicated in women who are or may be pregnant. Furthermore, given that data have suggested that mavacamten can be secreted in breast milk [see Section 4.4.2], and that in the repeated-toxicity studies of mavacamten, cardiac failure-related adverse effects were noted associated with excessive, depressed cardiac contractility in healthy animals at exposures lower than the maximum daily exposure in clinical use, the possibility that mavacamten could have an impact on infants cannot be ruled out. Therefore, a cautionary statement to the effect that the use of mavacamten in lactating mothers is not recommended will be included int he package insert.

PMDA considers that the actions that the applicant plans to implement regarding treatment of mavacamten for women who are or may be pregnant, lactating mothers, and women of childbearing potential are reasonable.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Unless otherwise specified, PK parameters are expressed as the mean or the mean ± standard deviation.

11) The elimination half-life ($t_{1/2}$) of mavacamten in a CYP2C19 poor metabolizer (PM) is approximately 23 days, a period of 4 months, 5 times the $t_{1/2}$, was selected.

6.1 Summary of biopharmaceutic studies and associated analytical methods

The phase III studies in and outside Japan used 2 types of capsule formulations: Capsule 1 formulation (as a capsule in strengths of 2.5, 5, 10, and 15 mg) and Capsule 2 formulation (as a capsule in strengths of 1, 2.5, 5, 10, and 15 mg). In the foreign phase III study (Study MYK-461-005), both Capsule 1 and Capsule 2 formulations were used while in the Japanese phase III study (Study CV027004), only the Capsule 2 formulation was used. The food effect was evaluated using the 15 mg Capsule 2 formulation in Study MYK-461-014. The to-be-marketed formulation (as a capsule in strengths of 1, 2.5, and 5 mg) is identical to the Capsule 2 formulation for the corresponding strength, except [redacted] and [redacted].

The 2.5 mg Capsule 1 formulation is identical to the 2.5 mg Capsule 2 formulation. Bioequivalence (BE) between the Capsule 1 and Capsule 2 formulations has been demonstrated in the BE studies for the 5 and 15 mg capsules [see Sections 6.1.2 and 6.1.3]. Although the BE between the formulations for the 10 mg capsule has not been directly evaluated, the 10 mg and 15 mg capsules are presented in [redacted] for both formulations. A dissolution study showed that the dissolution behavior of the 10 mg capsule does not differ from that of the 15 mg capsule. The BE between the 15 mg Capsule 2 formulation and the to-be-marketed 5 mg capsule formulation was demonstrated in the BE study [see Section 6.1.3].

As for the BE between strengths for the Capsule 2 formulation, the 2.5 mg and 5 mg capsules are presented in [redacted], and a dissolution study showed no differences in dissolution behavior. However, the BE between the 1 mg and 5 mg capsules was not demonstrated in the BE study [see Section 6.1.2].

Mavacamten concentrations in plasma were determined by LC-MS/MS. The lower limit of quantitation was 0.200 or 20 ng/mL. Radioactivity levels after administration of ^{14}C-mavacamten were measured by liquid scintillation counter or HPLC with a radioactivity detector.

6.1.1 Study on relative bioavailability and food effect (Study MYK-461-014, CTD 5.3.1.2-1 [reference data] [[redacted] to [redacted] 20[redacted]])

A 3-treatment, 3-period crossover study was conducted in 24 healthy non-Japanese adults. Subjects received a single oral dose of the 15 mg capsule (Capsule 1 formulation) in the fasting state, the 15 mg capsule (Capsule 2 formulation) in the fasting state, or the 15 mg capsule (Capsule 2 formulation) after a high-fat meal (with a washout period of ≥35 days).

The geometric least squares mean ratios [90% CI] (15 mg Capsule 2 to 15 mg Capsule 1) for mavacamten C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ were 1.0084 [0.836, 1.2163], 1.0575 [1.0110, 1.1061], and 1.0567 [1.0074, 1.1084], respectively.

The geometric least squares mean ratios [90% CI] (fed to fasting [15 mg Capsule 2 formulation]) for mavacamten C_{max} and $AUC_{0\text{-}\infty}$ were 0.4475 [0.3704, 0.5408] and 0.8773 [0.8364, 0.9203], respectively.

6.1.2 Bioequivalence study (1) (Study CV0271052, CTD 5.3.1.2-2 [reference data] [January to July 2023])

A 6-treatment, 3-period crossover study was conducted in 96 healthy non-Japanese adults. Subjects received a single oral dose of the 5 mg capsule (Capsule 1 formulation), 5 mg capsule (Capsule 2 formulation), or five 1 mg capsules (Capsule 2 formulation) (with a washout period of ≥35 days).

The geometric mean ratios [90% CI] (5 mg Capsule 1 formulation to 5 mg Capsule 2 formulation) for mavacamten C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$ were 1.076 [0.957, 1.211], 1.052 [0.929, 1.192], and 0.981 [0.955, 1.008], respectively. The geometric mean ratios [90% CI] (five 1 mg capsules to one 5 mg capsule [Capsule 2 formulation]) for mavacamten C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$ were 1.109 [0.986, 1.246], 1.130 [0.998, 1.280], and 1.020 [0.992, 1.048], respectively.

6.1.3 Bioequivalence study (2) (Study CV0271090, CTD 5.3.1.2-3 [reference data] [February to August 2023])

A 2-treatment, 2-period crossover study was conducted in 84 non-Japanese healthy adults. Subjects received a single oral dose of three 5 mg capsules or a 15 mg capsule (Capsule 2 formulation) (with a washout period of ≥40 days).

The geometric mean ratios [90% CI] (one 15 mg capsule to three 5 mg capsules) for mavacamten C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$ were 1.023 [0.949, 1.104], 1.005 [0.979, 1.031], and 1.007 [0.981, 1.034], respectively.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biological samples

6.2.1.1 Plasma protein binding (CTD 4.2.2.3-3 [reference data])

When ^{14}C-mavacamten 0.2 to 10 μmol/L was added to human plasma, the protein binding was 92.9% to 93.3%.

6.2.1.2 Distribution in blood cells (CTD 4.2.2.3-3 [reference data])

When mavacamten 200 μmol/L was added to human blood, the blood-to-plasma mavacamten concentration ratio was 0.79.

6.2.1.3 *In vitro* metabolism

6.2.1.3.1 Metabolism of mavacamten (CTD 4.2.2.4-5 [reference data])

When ^{14}C-mavacamten 5 μmol/L was added to human liver microsomes, mavacamten metabolites M1, M2, M6, and M12 were detected.

When ^{14}C-mavacamten 10 μmol/L was added to human hepatocytes, mavacamten metabolites M1, M2, and M6 were detected.

6.2.1.3.2 Identification of CYP isoforms involved in mavacamten metabolism (CTD 4.2.2.4-6 [reference data])

Mavacamten 1 μmol/L was added to the expression systems of human cytochrome P450 (CYP) isoforms (CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11, and CYP4F2). The percentage of mavacamten unmetabolized was 81.8% (CYP2C8), 83.5% (CYP2C9), 28.6% (CYP2C19), 80.6% (CYP2D6), 83.3% (CYP2J2), 56.4% (CYP3A4), 42.8% (CYP3A5), and ≥90% for the other CYP isoform expression systems.

Mavacamten 10 μmol/L was added to human liver microsomes, and the effect of CYP inhibitors on mavacamten metabolism was investigated in the presence and absence of the inhibitor[12)] of each of the CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5). Metabolism into M1 was inhibited in the presence of CYP1A2, CYP2C8, CYP2C9, or CYP2E1 inhibitor, but was not inhibited in the presence of CYP2B6, CYP2C19, CYP2D6, or CYP3A4/5 inhibitor. Metabolism into M2 was inhibited in the presence of CYP2C19 or CYP2E1 inhibitor, but was not inhibited in the presence of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A4/5 inhibitor.

Mavacamten 1 μmol/L was added to the expression systems of human CYP isoforms (CYP2C9, CYP2C19, CYP2J2, or CYP3A4). The relative contribution of the CYP isoforms to mavacamten metabolism was 7.55% (CYP2C9), 74.3% (CYP2C19), 0.21% (CYP2J2), and 18.0% (CYP3A4).

6.2.1.4 Enzyme inhibition (CTD 4.2.2.6-2 [reference data], 4.2.2.6-4 [reference data])

Using human liver microsomes and the substrates[13)] for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5), the inhibitory effects of mavacamten at 3 to 200 μmol/L on the metabolism of the CYP isoform substrates were investigated. Mavacamten inhibited CYP2C9 (IC_{50} = 82.2 μmol/L), CYP2C19 (IC_{50} = 89.7 μmol/L), and CYP3A4/5 (IC_{50} = 175 μmol/L). Mavacamten did not inhibit other CYP isoform substrates (IC_{50} >200 μmol/L).

After preincubation of human liver microsomes with mavacamten at 3 to 200 μmol/L in the presence or absence of nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) for 30 minutes, the microsomes were incubated with the CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5) substrates[13)] to investigate time-dependent inhibition of mavacamten on each of the CYP isoforms. Mavacamten time-dependently inhibited CYP2C19 and CYP2D6. After preincubation of human liver microsomes with mavacamten at 15 to 200 μmol/L in the presence or absence of NADPH for 0 to

12) The following compounds were used as the CYP isoform inhibitors: α-naphthoflavone 1 μmol/L (CYP1A2); thiotepa 50 μmol/L (CYP2B6); montelukast 1 μmol/L (CYP2C8); sulfaphenazole 10 μmol/L (CYP2C9); (+)-*N*-3-benzylnirvanol 1 μmol/L (CYP2C19); quinidine 2 μmol/L (CYP2D6); tranylcypromine 50 μmol/L (CYP2E1); ketoconazole 1 μmol/L and azamulin 1 μmol/L (CYP3A4/5).

13) The following compounds were used as the CYP isoform substrates: phenacetin 80 μmol/L (CYP1A2); bupropion 100 μmol/L (CYP2B6); amodiaquine 3 μmol/L (CYP2C8); diclofenac 8 μmol/L (CYP2C9); S-mephenytoin 45 μmol/L (CYP2C19); dextromethorphan 7 μmol/L (CYP2D6); midazolam 3 μmol/L and testosterone 70 μmol/L (CYP3A4/5).

40 minutes, the microsomes were incubated with the substrates[14)] of CYP2C19 of CYP2D6 to investigate the time-dependent inhibition of CYP2C19 and CYP2D6. The inhibitor concentration producing half-maximal inactivation (K_I) and maximum inactivation rate constant (k_{inact}) of CYP2C19 by mavacamten were 57.2 μmol/L and 0.011 min^{-1}, respectively, and the K_I and k_{inact} of CYP2D6 were 260 μmol/L and 0.031 min^{-1}, respectively.

6.2.1.5 Enzyme induction (CTD 4.2.2.6-5 [reference data], 4.2.2.6-6 [reference data])

Mavacamten at 0.05 to 15 μmol/L was incubated with human hepatocytes at 37°C for 3 days to investigate the induction of CYP1A2, CYP2B6, and CYP3A4 by mavacamten. The messenger ribonucleic acid (mRNA) expression levels of CYP1A2, CYP2B6, and CYP3A4 when mavacamten at 15 μmol/L was added were 0.96- to 1.2-fold, 5.7- to 8.6-fold, and 5.1- to 15-fold, respectively, of the mRNA expression levels when vehicle was added, and <1%, 35% to 74%, and 63% to 107%, respectively, of the mRNA expression levels when the positive control (omeprazole 50 μmol/L for CYP1A2; phenobarbital 1000 μmol/L for CYP2B6, rifampicin 10 μmol/L for CYP3A4) was added. When mavacamten at 15 μmol/L was added, phenacetin *O*-deethylation (CYP1A2) activity, bupropion hydroxylation (CYP2B6) activity, and testosterone 6β-hydroxylation (CYP3A4) activity were respectively 0.74- to 0.88-fold, 3.6- to 7.8-fold, and 2.5- to 9.3-fold the activity when vehicle was added.

Mavacamten at 0.015 to 20 μmol/L was incubated with human hepatocytes at 37°C for 2 days to investigate the induction of CYP2C8, CYP2C9, CYP2C19, and CYP3A4 by mavacamten. The maximum mRNA expression levels of CYP2C8, CYP2C9, CYP2C19, and CYP3A4 when mavacamten 20 μmol/L was added were 93%, 51%, 52%, and 80%, respectively, of the mRNA expression levels when the positive control (sulfinpyrazone 66 μmol/L for CYP2C8, CYP2C9, and CYP2C19; rifampicin 10 μmol/L for CYP3A4) was added.

6.2.1.6 Transporters

6.2.1.6.1 Transporter-mediated transport of mavacamten (CTD 4.2.2.2-12 [reference data], 4.2.2.6-7 [reference data], 4.2.2.6-10)

When mavacamten at 1 to 200 μmol/L was added to Caco-2 cells, the apparent permeability coefficient (P_{app}) in the apical to the basolateral direction ($P_{app\ A\rightarrow B}$) of mavacamten was 99.4 to 156 nm/s, P_{app} in the basolateral to the apical direction ($P_{app\ B\rightarrow A}$) was 130 to 175 nm/s, and the efflux ratio for mavacamten ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) was 0.977 to 1.55.

Mavacamten at 0.5 to 100 μmol/L was added to human hepatocytes, and the effect of transporter inhibitor[15)] on the uptake of mavacamten into cells was investigated in the presence and absence of each transporter

[14)] The following compounds were used as the CYP isoform substrates: S-mephenytoin 200 μmol/L (CYP2C19); dextromethorphan 50 μmol/L (CYP2D6).

[15)] The following compounds were used as inhibitors for the transporters: ciclosporin (20 μmol/L) and rifampicin (20 μmol/L) for OATPs and sodium taurocholate co-transporting polypeptide (NTCP); quinidine (100 μmol/L) for OCTs.

inhibitor. The cellular uptake of mavacamten in the presence of transporter inhibitors was 1.05- to 1.70-fold the cellular uptake in the absence of transporter inhibitors.

When mavacamten at 0.4 or 4 µmol/L was added to HEK293 cells expressing OAT1, OAT3, or OCT2, the cellular uptake of mavacamten was similar to that of control cells. The cellular uptake of mavacamten did not differ in the presence or absence of probenecid (organic anion transporter [OAT]1/OAT3 inhibitor, 1000 µmol/L) or pyrimethamine (organic cation transporter [OCT]2 inhibitor, 100 µmol/L).

6.2.1.6.2 Inhibition of transporters (CTD 4.2.2.6-8 [reference data], 4.2.2.6-9 [reference data])

Transporter substrates [16)] and mavacamten at 0.03 to 400 µmol/L were added to membrane vesicles prepared from Sf9 cells expressing P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or bile salt export pump (BSEP), or to HEK293 cells expressing organic anion transporting polypeptide (OATP)1B1, OATP1B3, OCT1, or OCT2 to evaluate the inhibitory effect of mavacamten on these transporters. Mavacamten did not show any inhibitory effect on P-gp. Mavacamten inhibited BCRP (IC_{50} = 130 µmol/L), BSEP (IC_{50} = 70.7 µmol/L), OATP1B1 (IC_{50} = 425 µmol/L), OATP1B3 (IC_{50} = 484 µmol/L), OCT1 (IC_{50} = 171 µmol/L), and OCT2 (IC_{50} = 91.3 µmol/L).

Transporter substrates [17)] and mavacamten at 0.03 to 300 µmol/L were added to HEK293 cells expressing MATE1, MATE2-K, OAT1, or OAT3 to evaluate the inhibitory effect of mavacamten on these transporters. Mavacamten inhibited MATE1 (IC_{50} = 22.6 µmol/L), MATE2-K (IC_{50} = 72.3 µmol/L), OAT1 (IC_{50} = 227 µmol/L), and OAT3 (IC_{50} = 70.2 µmol/L).

6.2.2 Studies in healthy adults

6.2.2.1 Single dose study in healthy non-Japanese adults (Study MYK-461-002, CTD 5.3.3.1-1 [reference data] [January to July 2015])

A single oral dose of mavacamten (suspension) 1, 2, 6, 12, 24, or 48 mg was administered to healthy non-Japanese adults. Table 15 shows the PK parameters of mavacamten.

16) The following compounds were used as substrates for the transporters: ^{3}H-labeled *N*-methylquinidine (2 µmol/L) for P-gp; ^{3}H-labeled sulfate conjugate of estrone (1 µmol/L) for BCRP; ^{3}H-labeled taurocholic acid (2 µmol/L) for BSEP; ^{3}H-labeled estradiol-17β-glucuronide (1 µmol/L) for OATP1B1; ^{3}H-labeled cholecystokinin (0.5 µmol/L) for OATP1B3; ^{14}C-labeled triethylamine (25 µmol/L) for OCT1; ^{14}C-labeled metformin (25 µmol/L) for OCT2.

17) The following compounds were used as substrates for the transporters: ^{14}C-labeled triethylamine (5 and 3 µmol/L) for MATE1 and MATE2-K; ^{3}H-labeled para-aminohippuric acid (5 µmol/L) for OAT1; ^{3}H-labeled estrone-3-sulfate (1 µmol/L) for OAT3.

Table 15. PK parameters after single oral administration of mavacamten

Dose (mg)	N	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
1	6	23.78 ± 14.558	0.5000	357.47 ± 171.261	141.5 ± 75.736
2	6	66.42 ± 22.507	0.6250	1770.9 ± 1281.37	177.2 ± 53.943
6	6	109.9 ± 44.717	2.250	5110.1 ± 5088.80	221.3 ± 104.70
12	6	219.7 ± 80.899	2.000	6412.1 ± 3437.71	153.5 ± 78.463
24	5	508.4 ± 143.99	2.000	15695 ± 4604.25	141.4 ± 40.273
48	6	939.2 ± 308.54	2.125	43844 ± 19811.9	186.6 ± 56.048

a, median

6.2.2.2 Multiple-dose study in healthy non-Japanese adults (Study MYK-461-003, CTD 5.3.3.1-2 [reference data] [July 2015 to July 2016])

Table 16 shows the PK parameters of mavacamten following oral administration of mavacamten 1 or 3 mg twice daily, or mavacamten 12.5, 18.5, or 25 mg once daily to healthy non-Japanese adults for 28 days.

Table 16. PK parameters after administration of multiple oral doses of mavacamten

Dose (mg)	Dosing frequency	N	Timepoint (Day)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-tau} (ng·h/mL)	$t_{1/2}$ (h)
1	Twice daily	10	1	32.54 ± 15.04	1.00	84.41 ± 24.39	10.37 ± 3.96
		10	28	79.50 ± 26.45	0.50	620.45 ± 266.00	26.59 ± 34.59
3		10	1	61.16 ± 33.75	1.00	190.88 ± 80.95	8.17 ± 4.57
		10	28	175.60 ± 80.04	1.75	1577.61 ± 846.22	105.63 ± 173.34[c]
12.5	Once daily	10	1	214.90 ± 59.06	1.54	1241.31 ± 341.39	25.96 ± 7.22
		10	28	439.11 ± 164.54[b]	2.00[b]	6711.23 ± 2901.98[b]	49.21 ± 19.52[c]
18.5		10	1	376.30 ± 100.89	1.50	2284.81 ± 565.86	20.43 ± 15.69
		10	28	974.10 ± 247.18	2.00	16890.97 ± 5816.85	91.78 ± 54.82[b]
25		10	1	459.00 ± 89.08	1.75	2795.85 ± 525.98	26.43 ± 19.10
		10	28	—	—	—	—

—, not calculated; a, median; b, N = 9; c, N = 7

6.2.2.3 Single-dose study in healthy Japanese and non-Japanese adults (Study MYK-461-011, CTD 5.3.3.3-3 [[redacted] to [redacted] 20[redacted]])

Table 17 shows the PK parameters of mavacamten following single oral administration of mavacamten 5, 15, or 25 mg to healthy Japanese adults or mavacamten 25 mg to healthy non-Japanese adults.

Table 17. PK parameters after single oral administration of mavacamten

Subjects	Dose (mg)	N	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
Japanese	5	4	142.5 ± 21.30	1.500	6458 ± 1716	222.2 ± 54.69
	15	8	293.9 ± 57.37	1.000	15880 ± 3853	221.5 ± 50.93
	25	8	511.4 ± 94.37	1.500	18270 ± 6634	153.8 ± 77.66
Non-Japanese	25	8	534.6 ± 160.8	1.500	21760 ± 12640	155.7 ± 75.00

a, median

6.2.2.4 Mass balance study (Study MYK-461-013, CTD 5.3.3.1-3 [reference data] [[redacted] to [redacted] 20[redacted]])

A single oral dose of ^{14}C-mavacamten 25 mg was administered to 6 healthy non-Japanese adults. Up to 47 days post-dose, 85.2% (2.57% as mavacamten) and 7.02% of administered radioactivity was excreted in urine and

in feces, respectively. Up to 648 hours post-dose, M2 and M13 (50.6% total) were mainly excreted in urine, and up to 528 hours post-dose, M2 (1.15%) was mainly excreted in feces.

6.2.3 Studies in patients

6.2.3.1 Foreign phase I study (Study MYK-461-001, CTD 5.3.3.2-1 [reference data], [[redacted] 20[redacted] to March 2016])

Table 18 shows the PK parameters of mavacamten following single oral administration of mavacamten (suspension) 48, 96, or 144 mg to non-Japanese patients with HCM.

Table 18. PK parameters after single odal administration of mavacamten

Dose (mg)	N	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
48	3	695.7 ± 281.26	2.500	21140 ± 14011	88.15 ± 17.514
96	6	1572 ± 599.71	2.125	80440 ± 12012	157.2 ± 32.408
144	4	1458 ± 478.36	2.125	155800 ± 59089[b]	252.6 ± 19.428[b]

a, median; b, N = 3

6.2.3.2 Foreign phase III study (Study MYK-461-005, CTD 5.3.5.1-1 [May 2018 to May 2020])

Mavacamten was orally administered for 30 weeks to 251 non-Japanese patients with oHCM. The starting dose was 5 mg once daily, and the dose was adjusted in the range of 2.5 to 15 mg [see Section 7.3.1]. Table 19 shows plasma mavacamten concentrations.

Table 19. Plasma mavacamten concentration after administration of multiple oral doses of mavacamten

Timepoint (after the start of treatment)	N	Plasma mavacamten concentration (ng/mL)
Week 4	109	208.261 ± 112.9355
Week 6	121	244.131 ± 141.3190
Week 8	115	260.890 ± 151.4947
Week 12	115	340.566 ± 166.3807
Week 18	117	387.887 ± 176.0088
Week 22	120	373.720 ± 172.2651
Week 26	119	361.218 ± 153.5366
Week 30 (pre-treatment)	119	366.532 ± 153.5525
Week 30 (post-treatment)	119	468.379 ± 173.6499

6.2.3.3 Japanese phase III study (Study CV027004, CTD 5.3.5.2-1 [ongoing since August 2022])

Mavacamten was orally administered for 138 weeks to 38 Japanese patients with oHCM. The starting dose was 2.5 mg once daily, and the dose was adjusted in the range of 1 to 15 mg [see Section 7.3.2]. Table 20 shows plasma mavacamten concentrations.

Table 20. Plasma mavacamten concentration after administration of multiple oral doses of mavacamten

Timepoint (after the start of treatment)	N	Plasma mavacamten concentration (ng/mL)
Week 4	32	156.8 ± 79.77
Week 6	37	196.4 ± 106.19
Week 8	37	271.9 ± 153.87
Week 12	35	288.4 ± 196.54
Week 14	36	424.9 ± 308.50
Week 18	34	443.9 ± 291.31
Week 20	33	576.6 ± 321.25
Week 24	35	514.6 ± 285.89
Week 26	32	488.5 ± 248.98
Week 30	34	537.4 ± 302.90

6.2.4 Investigation of intrinsic factors

6.2.4.1 Effects on hepatic function (Study MYK-461-015, CTD 5.3.3.3-1 [reference data] [[redacted] 20[redacted] to [redacted] 20[redacted]])

A single oral dose of mavacamten 25 mg was administered to non-Japanese patients with mild hepatic impairment (Child-Pugh A), moderate hepatic impairment (Child-Pugh B), or subjects with normal hepatic function. Table 21 shows the PK parameters of mavacamten. In patients with mild and moderate hepatic impairment, the $AUC_{0\text{-last}}$ of mavacamten was 3.24-fold and 1.87-fold, respectively, that in subjects with normal hepatic function; and the C_{max} of mavacamten was 1.12-fold and 1.10-fold, respectively, that in subjects with normal hepatic function.

Table 21. PK parameters of mavacamten after single oral administration of mavacamten

Study population	N	C_{max} (ng/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)	$t_{1/2}$ (h)
Subjects with normal hepatic function[a]	8	534 (35.6)	18200 (67.0)	17500 (60.2)	171 (45.7)
Patients with mild hepatic impairment	8	596 (23.1)	71000 (11.8)[c]	56600 (19.5)	634 (28.5)
Subjects with normal hepatic function[b]	8	426 (46.5)	19700 (85.4)	18700 (77.3)	189 (48.6)
Patients with moderate hepatic impairment	8	468 (30.7)	32800 (104.4)[c]	35000 (66.3)[d]	420 (80.5)[d]

Geometric mean (geometric coefficient of variation, %); a, matched controls for patients with mild hepatic impairment; b, matched controls for patients with moderate hepatic impairment; c, N = 4; d, N = 7

6.2.4.2 Effects of CYP2C19 phenotypes (Study MYK-461-012, CTD 5.3.3.3-2 [reference data] [[redacted] 20[redacted] to [redacted] 20[redacted]])

Table 22 shows mavacamten PK parameters after single oral administration of mavacamten 15 mg to healthy non-Japanese adults who were CYP2C19 normal metabolizers (NMs) or CYP2C19 poor metabolizers (PMs).[18)] The $AUC_{0\text{-}\infty}$ and C_{max} of mavacamten in CYP2C19 PMs were 3.41-fold and 1.47-fold, respectively, those in CYP2C19 NMs.

18) Poor metabolizer (PM): CYP2C19 (*2/*2, *2/*3, or *3/*3); intermediate metabolizer (IM): CYP2C19 (*1/*2, *1/*3, *2/*17, or *3/*17); normal metabolizer (NM): CYP2C19*1/*1; rapid metabolizer RM: CYP2C19*1/*17; ultrarapid metabolizer (UM): CYP2C19*17/*17.

Table 22. PK parameters of mavacamten after single oral administration of mavacamten

CYP2C19 phenotype	N	C_{max}[a] (ng/mL)	t_{max}[b] (h)	$AUC_{0-\infty}$[a] (ng·h/mL)	$t_{1/2}$ (h)
CYP2C19 NM	8	333.21 [224.45, 494.67]	1.000	12534.60 [9368.93, 16769.92]	220.5 ± 130.6
CYP2C19 PM	8	489.89 [329.99, 727.28]	0.750	42801.44 [31991.75, 57263.63]	571.6 ± 139.9

a, geometric least squares mean [95% CI]; b, median

6.2.5 Drug interactions

6.2.5.1 Drug interaction with verapamil (Study MYK-461-009, CTD 5.3.3.4-1 [reference data] [to 20])

Twenty-six healthy non-Japanese adults received a single oral dose of mavacamten 25 mg, or a single oral dose of mavacamten 25 mg in combination with verapamil 240 mg orally once daily for 28 days.[19)] The geometric mean ratio [90% CI] (mavacamten co-administered with verapamil/mavacamten alone) was 1.518 [1.160, 1.985] for mavacamten C_{max} and 1.155 [0.844, 1.582] for mavacamten $AUC_{0-\infty}$.

6.2.5.2 Drug interaction with omeprazole (Study MYK-461-018, CTD 5.3.3.4-2 [reference data] [to 20])

Twenty-nine healthy non-Japanese adults received a single oral dose of mavacamten 15 mg, or a single oral dose of mavacamten 15 mg in combination with omeprazole 20 mg orally once daily for 31 days.[20)] The geometric mean ratio [90% CI] (mavacamten co-administered with omeprazole/mavacamten alone) was 0.99 [0.75, 1.30] for mavacamten C_{max} and 1.48 [1.16, 1.88] for mavacamten $AUC_{0-\infty}$.

6.2.5.3 Drug interaction with midazolam (Study MYK-461-016, CTD 5.3.3.4-3 [reference data] [to 20])

Thirteen healthy non-Japanese adults received the following doses once daily orally: midazolam 5 mg on Day 1, mavacamten 25 mg on Days 2 and 3, mavacamten 15 mg on Days 4 through 16, and midazolam 5 mg and mavacamten 15 mg on Day 17. The geometric mean ratio [90% CI] (midazolam co-administered with mavacamten/midazolam alone) was 0.93 [0.77, 1.13] for midazolam C_{max} and 0.87 [0.68, 1.10] for midazolam $AUC_{0-\infty}$.

6.2.5.4 Drug interaction with norethisterone/ethinyl estradiol combination drug (Study MYK-461-010 [reference data], CTD 5.3.3.4-4 [to 20])

This was a 2-period study conducted in 13 healthy non-Japanese adult women. In Period 1, subjects received a single oral dose of norethisterone (1 mg)-ethinyl estradiol (35 µg) fixed-dose combination drug. In Period 2, while subjects received a single oral dose of norethisterone-ethinyl estradiol fixed-dose combination drug, the subjects also received mavacamten 25 mg[21)] once daily for 2 days, followed by mavacamten 15 mg once daily orally for 15 days (washout period of ≥6 days). The geometric mean ratio [90% CI] (norethisterone-ethinyl

19) Treatment with verapamil started on the day mavacamten was administered.
20) Treatment with omeprazole started 3 days before mavacamten was administered.
21) Treatment with mavacamten started 14 days before the administration of norethisterone/ethinyl estradiol combination drug.

estradiol fixed-dose combination drug co-administered with mavacamten/norethisterone-ethinyl estradiol fixed-dose combination drug alone) was 1.14 [0.979, 1.33] for norethisterone C_{max} and 1.12 [1.01, 1.24] for norethisterone $AUC_{0-\infty}$, and the geometric mean ratio [90% CI] was 1.05 [0.945, 1.16] for ethinyl estradiol C_{max} and 1.20 [1.08, 1.33] for ethinyl estradiol $AUC_{0-\infty}$.

6.2.5.5 Drug interaction with activated charcoal containing sorbitol (Study CV027043, CTD 5.3.3.4-5 [reference data] [April to September 2022])

Forty-five healthy non-Japanese adults were assigned to one of the following 3 treatments: oral mavacamten 15 mg; oral mavacamten 15 mg plus oral activated charcoal 50 g containing sorbitol administered 2 hours after mavacamten; and oral mavacamten 15 mg plus oral activated charcoal 50 g containing sorbitol administered 6 hours after mavacamten. The geometric mean ratio [90% CI] (mavacamten plus activated charcoal with sorbitol/mavacamten alone) was 0.893 [0.670, 1.190] for mavacamten C_{max} and 0.658 [0.458, 0.945] for mavacamten $AUC_{0-\infty}$ when administered 2 hours after mavacamten, and 1.032 [0.778, 1.369] for mavacamten C_{max} and 1.137 [0.802, 1.611] for mavacamten $AUC_{0-\infty}$ when administered 6 hours after mavacamten.

6.2.6 Population pharmacokinetic analysis (CTD 5.3.3.5-3)

A population pharmacokinetic (PPK) analysis ([redacted] Version 2.5.1) was performed using plasma mavacamten concentration data (N = 636, at 10223 timepoints) from 14 clinical studies conducted in and outside Japan in healthy adults, patients with oHCM, and patients with non-obstructive hypertrophic cardiomyopathy (nHCM): Studies MYK-461-002,[22)] MYK-461-003,[22)] MYK-461-004,[23)] MYK-461-005, MYK-461-006,[24)] MYK-461-007,[25)] MYK-461-008,[23)] MYK-461-009,[22)] MYK-461-010,[22)] MYK-461-011,[22)] MYK-461-012,[22)] MYK-461-014,[22)] MYK-461-017,[26)] and CV027004.

The demographics and baseline characteristics of the analysis population included the following: sex (278 females and 358 males); ethnic group (58 Japanese and 578 non-Japanese); CYP2C19 phenotype[18)] (26 PMs, 150 intermediate metabolizers [IMs], 242 NMs, 123 rapid metabolizers [RMs], 17 ultrarapid metabolizers [UMs], and 78 subjects [unknown]); HCM status (192 healthy adults [no HCM] and 444 patients with HCM); concomitant omeprazole use (630 subjects [not used] and 6 subjects [used]); concomitant esomeprazole use (630 subjects [not used] and 6 subjects [used]); concomitant disopyramide use (615 subjects [not used] and 21 subjects [used]); dosage form (463 subjects [capsule], 36 subjects [solution], 137 subjects [tablet]); fasting or fed state (149 subjects [fasting state] and 43 subjects [fed state]); mean body weight [Min, Max] (79.8 kg [40.0, 160]); and mean estimated glomerular filtration rate (eGFR) [Min, Max] (92.2 mL/min/1.73 m^2 [29.5, 148]). These demographics and baseline characteristics and dose level were selected as candidate covariates.

[22)] A foreign phase I study in healthy adults
[23)] A foreign phase II study in patients with oHCM
[24)] A foreign phase II study in patients with nHCM
[25)] A foreign phase III study in patients with oHCM or nHCM
[26)] A foreign phase III study in patients with oHCM

The PK of mavacamten was described by a 2-compartment model including a first-order absorption with absorption lag time, linear clearance (CL) from the central compartment (V2), and a peripheral compartment (V3). The effects of the following covariates were included in the final model: the effect of body weight on apparent total body clearance (CL/F), apparent inter-compartment clearance (Q/F), apparent central volume of distribution (V2/F), and apparent peripheral volume of distribution (V3/F); the effect of sex, CYP2C19 phenotype, HCM status, eGFR, concomitant omeprazole use, concomitant esomeprazole use, concomitant disopyramide use on CL/F; dose level on first-order absorption rate constant (K_a), bioavailability (F), and absorption lag time; dosage form (capsule or solution) and fasting or fed state on K_a and F.

6.2.7 Relationship between the exposure and QT/QTc interval variation (CTD 5.3.3.5-11)

The relationship between plasma mavacamten concentrations and ΔΔ Fridericia-corrected QT Interval (QTcF) was investigated using linear mixed-effect modeling based on data from foreign clinical studies conducted in healthy adults, patients with oHCM, and patients with nHCM (Studies MYK-461-002,[22)] MYK-461-003,[22)] MYK-461-004,[23)] MYK-461-005, MYK-461-006,[24)] MYK-461-007,[25)] MYK-461-008,[23)] MYK-461-010,[22)] and MYK-461-014[22)]). The results suggested that the upper bound of the 90% confidence interval (CI) of ΔΔQTcF in patients with HCM would be lower than 10 ms within the range of plasma mavacamten concentrations studied.

According to the applicant, mavacamten is unlikely to cause prolongation of the QT/QTc interval following administration of mavacamten to patients with HCM at the proposed dosage regimen [see Section 7.R.4.4].

6.R Outline of the review conducted by PMDA

Since the starting dose of mavacamten was changed to 2.5 mg from 5 mg after the applicant filed the application [see Section 7.R.6.1], discussions in this and subsequent sections will be based on a starting dose of 2.5 mg.

6.R.1 Differences in PK between Japanese and non-Japanese populations

The applicant's explanation about the differences in PK of mavacamten between Japanese and non-Japanese populations:

In the phase I study (Study MYK-461-011), no marked differences in PK were noted between the Japanese and non-Japanese populations following single oral administration of mavacamten 25 mg [see Section 6.2.2.3]. In a PPK analysis that used data from clinical studies in healthy adults and patients with HCM [see Section 6.2.6], "ethnic group" (Japanese or non-Japanese) did not affect the CL/F of mavacamten. However, given a higher percentage of CYP2C19 PMs in the Japanese population than in the non-Japanese population, there may be a difference in the PK of mavacamten between the Japanese and non-Japanese populations.

PMDA accepted the applicant's explanation that even though the clinical studies and the PPK analysis indicated no effects of ethnic difference on PK, there may be a difference in the PK of mavacamten between

Japanese and non-Japanese populations due to a difference in the percentage of CYP2C19 PMs between these populations.

6.R.2 Use of mavacamten in patients with hepatic impairment

The exposure to mavacamten increases in patients with mild or moderate hepatic impairment, and the starting dose of mavacamten is to be maintained for at least the first 4 weeks of treatment. Given these facts, PMDA asked the applicant to explain whether mavacamten should be contraindicated or its dose should be reduced in patients with hepatic impairment.

The applicant's explanation:

Based on simulation with the PPK model,[27)] the median $C_{trough,ss}$ (5th and 95th percentile) following administration of mavacamten 5 mg once daily orally to a representative patient with HCM[28)] was calculated as 214 ng/mL (80 and 511, respectively). In the foreign phase I study (Study MYK-461-015), the $AUC_{0\text{-last}}$ after administration of mavacamten to patients with mild or moderate hepatic impairment was 3.24-fold and 1.87-fold, respectively, that after administration of mavacamten to subjects with normal hepatic function. Given these findings, the median $C_{trough,ss}$ (5th and 95th percentile) following administration of mavacamten 2.5 mg is estimated to be 107 ng/mL (40 and 256, respectively) in subjects with normal hepatic function, 346.7 ng/mL (130 and 828, respectively) in patients with mild hepatic impairment, and 200.1 ng/mL (74.8 and 478, respectively) in patients with moderate hepatic impairment. In the Japanese and foreign phase III studies in patients with oHCM (Studies MYK-461-005, MYK-461-017, and CV027004), the maximum C_{trough} at the visit immediately before the first dose adjustment (after 4 or 6 weeks of treatment with mavacamten at the starting dose) was 739.00 ng/mL. The expected $C_{trough,ss}$ following administration of mavacamten 2.5 mg to patients with mild or moderate hepatic impairment will not markedly exceed the exposure range which has been demonstrated to be safe in the clinical studies; therefore, no adjustment to the starting dose is needed for patients with mild or moderate hepatic impairment.

No clinical studies in patients with severe hepatic impairment were conducted. The exposure to and safety of mavacamten in patients with severe hepatic impairment after mavacamten treatment are unknown. However, given the limited treatment options for oHCM, mavacamten should not be contraindicated in such patient population. Additional LVEF monitoring will be required for patients with severe hepatic impairment on mavacamten treatment to ensure safety. The package insert should include a cautionary statement to the effect that additional LVEF monitoring and other measures should be considered during mavacamten treatment, while stating that no clinical study data have been obtained in patients with severe hepatic impairment.

PMDA's view:

The applicant explained that reduction of the starting dose of mavacamten is not necessary for patients with mild or moderate hepatic impairment, and this decision is reasonable.

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27) A final PPK model developed using plasma mavacamten concentration data from 14 clinical studies conducted in and outside Japan in healthy adults, patients with oHCM or nHCM

28) Male, body weight of 84 kg, CYP2C19 NM, eGFR of 95 mL/min/1.73 m^2, no HCM treatment drug

The exposure to mavacamten in patients with severe hepatic impairment is unknown because mavacamten has never been used in this patient population. However, given that mavacamten is predominantly cleared by hepatic metabolism and $t_{1/2}$ in patients with mild or moderate hepatic impairment ranges from 420 to 634 hours, longer than the $t_{1/2}$ in subjects with normal hepatic function, the possibility of a major increase in mavacamten exposure and prolongation of $t_{1/2}$ could occur in patients with severe hepatic impairment cannot be ruled out. In that instance, it is not known whether mavacamten exposure would decrease sufficiently in a short period of time after interrupting mavacamten administration. In addition, there is no established method for eliminating mavacamten from the body. Therefore, even if additional monitoring is implemented, failure to effectively treat an excessive decrease in LVEF may potentially lead to serious outcomes.

Based on the above, mavacamten should be contraindicated in patients with severe hepatic impairment.

6.R.3 Co-administration of mavacamten with CYP2C19 inhibitors

Mavacamten is primarily metabolized by CYP2C19 and CYP3A4. Co-administration of mavacamten with a CYP2C19 inhibitor may result in increased mavacamten exposure. Given these facts, PMDA asked the applicant to explain whether a cautionary statement is necessary regarding dose adjustment of mavacamten when co-administered with a CYP2C19 inhibitor.

The applicant's explanation:
Because patients who are CYP2C19 PMs have no CYP2C19 enzymatic activity, co-administration with a CYP2C19 inhibitor is unlikely to have an impact on exposure. Accordingly, the effect of co-administration of mavacamten with a CYP2C19 inhibitor in patients who are not CYP2C19 PMs was evaluated as described below.

In a drug interaction study in healthy non-Japanese adults, mavacamten was co-administered with omeprazole, a weak CYP2C19 inhibitor. The $AUC_{0\text{-last}}$ of mavacamten in combination with omeprazole was 1.58-fold the $AUC_{0\text{-last}}$ of mavacamten alone. Although no drug interaction studies have been conducted to evaluate co-administration of mavacamten with a strong or moderate CYP2C19 inhibitor, it is inferred that co-administration of mavacomten with a strong or moderate CYP2C19 inhibitor in patients who are not CYP2C19 PMs would result in increased mavacamten exposure to a degree similar to or less than the increase observed in CYP2C19 PMs compared to CYP2C19 NMs (3.41-fold).

In addition to the above, based on the discussions in the following subsections, dose adjustment when mavacamten is co-administered with CYP2C19 inhibitors should be as shown in Table 23.

Table 23. Proposed dose adjustment of mavacamten with concomitant CYP2C19 inhibitors

	A) When initiating mavacamten treatment while receiving an inhibitor	B) When initiating or increasing the dose of an inhibitor while on mavacamten treatment
Strong CYP2C19 inhibitors	No cautionary statements necessary	If the patient is receiving mavacamten 2.5 to 15 mg, decrease the dose by 1 level. If the patient is receiving mavacamten 1 mg, interrupt administration and perform LVEF assessment 4 weeks later.
Moderate CYP2C19 inhibitors		Consider dose reduction of mavacamten and closely monitor the patient's condition.
Weak CYP2C19 inhibitors		

A) When initiating mavacamten treatment while receiving a CYP2C19 inhibitor

Based on simulation with the PPK model,[27] the median $C_{trough,ss}$ following administration of mavacamten 5 mg once daily orally to a representative patient with HCM[28] was calculated as 214 ng/mL. Therefore, based on the degree of predicted increase in mavacamten exposure (3.41-fold) when mavacamten is co-administered with a strong or moderate CYP2C19 inhibitor, the median $C_{trough,ss}$ following administration of mavacamten 2.5 mg while receiving a CYP2C19 inhibitor is estimated to be ≤365 ng/mL. Conversely, in the Japanese and foreign phase III studies (Studies MYK-461-005, MYK-461-017, and CV027004), the maximum C_{trough} at the visit immediately before the first dose adjustment ranged from 478 to 739.00 ng/mL, demonstrating that exposures >365 ng/mL are safe. Therefore, cautionary statements regarding the initiation of mavacamten treatment while on any CYP2C19 inhibitor are unnecessary.

B) When initiating or increasing the dose of a CYP2C19 inhibitor while on mavacamten treatment

In Study CV027004, the C_{trough} of mavacamten at Week 30 in patients receiving mavacamten 1, 2.5, 5, 10, or 15 mg was 138.2, 460.5, 558.1, 715.3, and 660.0 ng/mL, respectively. Given the degree of predicted increase in exposure (3.41-fold), it is inferred that co-administration of mavacamten with a strong CYP2C19 inhibitor will increase the C_{trough} of mavacamten to between 471.3 and 2439.2 ng/mL. Conversely, when the dose of mavacamten is decreased by 1 level, the maximum $C_{trough,ss}$ during treatment with mavacamten 2.5, 5, 10, or 15 mg is predicted to be 1500 ng/mL, which is not substantially greater than the maximum C_{trough} (1359 ng/mL) shown to be safe in Study CV027004. Therefore, as shown in Table 23, the mavacamten dose should be decreased by 1 level or interrupted and LVEF assessment should be performed 4 weeks after the start of co-administration to ensure safety. When a moderate or weak CYP2C19 inhibitor is used, the degree of increase in mavacamten exposure is expected to be smaller than that after the initiation or dose increase of a strong CYP2C19 inhibitor. For this reason, specifying dose reduction criteria is not mandatory, but the patient's condition should be closely monitored.

PMDA's view:

Based on the applicant's explanation, no adjustment of the starting dose or specific cautionary statements are necessary when initiating mavacamten treatment while the patient is receiving a CYP2C19 inhibitor.

The applicant's proposal on dose adjustment is reasonable when initiating or increasing the dose of a strong CYP2C19 inhibitor or a weak CYP2C19 inhibitor during treatment with mavacamten. However, the same dose adjustment criteria as that for initiating or increasing the dose of a strong CYP2C19 inhibitor should be

specified for a moderate CYP2C19 inhibitor, because the increase in exposure to mavacamten co-administered with a moderate CYP2C19 inhibitor is predicted to be comparable to that with a strong CYP2C19 inhibitor.

6.R.4 Co-administration of mavacamten with CYP3A4 inhibitors

Mavacamten is primarily metabolized by CYP2C19 and CYP3A4. Co-administration with a CYP3A4 inhibitor may result in increased mavacamten exposure. Given these facts, PMDA asked the applicant to explain whether a cautionary statement regarding dose adjustment of mavacamten when co-administered with a CYP3A4 inhibitor is necessary.

The applicant's explanation:
Assuming that the increase in the exposure to mavacamten when co-administered with a CYP3A4 inhibitor in patients who are CYP2C19 PMs is comparable to that in patients who are not CYP2C19 PMs, the necessity of cautionary statements was investigated as shown below.

In a drug interaction study in healthy non-Japanese adults, mavacamten was co-administered with verapamil, a moderate CYP3A4 inhibitor. The $AUC_{0-\infty}$ of mavacamten in combination with verapamil was 1.16-fold that of mavacamten alone. No studies on interaction of mavacamten with a strong CYP3A4 inhibitor have been conducted. However, given that strong and moderate inhibitors are defined as agents that increase the AUC of a typical substrate (sensitive index substrate) to ≥5-fold (strong) and ≥2-fold but <5-fold (moderate) (Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information; hereinafter referred to as "DDI Guidelines"), the mavacamten exposure when co-administered with a strong CYP3A4 inhibitor was assumed to be 2.5-fold the mavacamten exposure when co-administered with a moderate CYP3A4 inhibitor (2.9-fold that of mavacamten alone).

In addition to the above, based on the discussions in the following subsections, dose adjustments when mavacamten is co-administered with CYP3A4 inhibitors should be as shown in Table 24.

Table 24. Proposed dose adjustment of mavacamten with concomitant CYP3A4 inhibitors

	A) When initiating mavacamten treatment while receiving an inhibitor	B) When initiating or increasing the dose of an inhibitor while on mavacamten treatment
Strong CYP3A4 inhibitors	No cautionary statements necessary	The package insert should include cautionary statements to the effect that dose reduction of mavacamten should be considered and the patient's condition should be closely monitored.
Moderate CYP3A4 inhibitors		
Weak CYP3A4 inhibitors		No cautionary statements necessary

A) When initiating mavacamten treatment while receiving a CYP3A4 inhibitor
Based on simulation with the PPK model,[27)] the median $C_{trough,ss}$ following administration of mavacamten 5 mg once daily orally to a representative patient with HCM[29)] was calculated as 639 ng/mL for patients who are CYP2C19 PMs and 214 ng/mL for patients who are not CYP2C19 PMs. Therefore, given that the C_{trough} at Week 4 is estimated to be approximately a half of $C_{trough,ss}$ based on the $t_{1/2}$ of mavacamten in patients who are

[29)] Male, body weight 84 kg, CYP2C19 PM or NM, eGFR of 95 mL/min/1.73 m^2, no HCM treatment drug

CYP2C19 PMs (571.6 ± 139.9 hours), and that the predicted increase in mavacamten exposure when co-administered with a strong CYP3A4 inhibitor is 2.9-fold, it is inferred that the median C_{trough} at Week 4 when mavacamten 2.5 mg is administered while receiving a CYP3A4 inhibitor will not exceed 463.5 ng/mL regardless of the phenotype of CYP2C19. Conversely, in Studies MYK-461-005, MYK-461-017, and CV027004, the maximum C_{trough} at the visit immediately before the first dose adjustment was 739.00 ng/mL, demonstrating that exposures >463.5 ng/mL are safe. Therefore, cautionary statements regarding the initiation of mavacamten treatment while on any CYP3A4 inhibitor are unnecessary.

B) When initiating or increasing the dose of a CYP3A4 inhibitor while on mavacamten treatment
Based on the results of Study CV027004, namely, the C_{trough} of mavacamten at Week 30 in patients receiving mavacamten 1 to 15 mg and the degree of predicted increase in exposure when co-administered with a strong or moderate CYP3A4 inhibitor (2.9-fold or 1.16-fold, respectively), the following prediction was made: Concomitant use of mavacamten with a strong or moderate CYP3A4 inhibitor will increase the C_{trough} of mavacamten to between 400.8 and 2074.4 ng/mL (strong) and to between 160.3 and 829.7 ng/mL (moderate), suggesting that the C_{trough} may exceed 1359 ng/mL, the maximum C_{trough} confirmed to be safe in Study CV027004. Nevertheless, even when initiating or increasing the dose of a strong or a moderate CYP3A4 inhibitor while on mavacamten treatment, the safety can be ensured by implementing echocardiography, as necessary, and dose interruption or other measures. Therefore, specifying dose reduction criteria is not mandatory, but the patient's condition should be close monitored. When initiating or increasing the dose of a weak CYP3A4 inhibitor, the degree of increase in mavacamten exposure is expected to be lower than that when co-administered with a moderate CYP3A4 inhibitor (1.16-fold); therefore, no particular cautionary statements are necessary.

PMDA's view:
The applicant assumed that the degree of increase in mavacamten exposure when mavacamten is co-administered with a CYP3A4 inhibitor is comparable between patients who are CYP2C19 PMs and those who are not. In patients who are CYP2C19 PMs lacking CYP2C19 enzymatic activity, the contribution of CYP3A4 in the clearance of mavacamten is greater than that in patients who are not CYP2C19 PMs; therefore, the degree of increase in mavacamten exposure when co-administered with a CYP3A4 inhibitor may be potentially greater. Furthermore, the applicant assumed that based on the definition of the DDI Guidelines, the increase in the mavacamten exposure when co-administered with a strong CYP3A4 inhibitor would be 2.9-fold the exposure to mavacamten alone. However, strong CYP3A4 inhibitors, which increase the exposure of a sensitive index substrate by 5-fold or more, are not taken into consideration, and therefore, the above assumption is not appropriate.

When initiating mavacamten treatment while the patient is receiving a strong CYP3A4 inhibitor, a safety problem may possibly occur in patients who are CYP2C19 PMs as a result of a marked increase in mavacamten exposure. Therefore, mavacamten must be contraindicated in patients receiving a strong CYP3A4 inhibitor. Conversely, when initiating mavacamten treatment while the patient is receiving a weak or moderate CYP3A4

inhibitor, given that the estimated $C_{trough,ss}$ following administration of mavacamten 5 mg once daily orally to a representative patient with HCM who is a CYP2C19 PM is 639 ng/mL, and that the C_{trough} at Week 4 is estimated to be approximately a half of $C_{trough,ss}$ in patients who are CYP2C19 PMs, the exposure is not expected to significantly exceed the range that has been confirmed to be safe in clinical studies conducted in and outside Japan. Therefore, no specific cautionary statements are necessary.

The initiation or dose escalation of a strong CYP3A4 inhibitor during mavacamten treatment must be contraindicated as with the case where the initiation of mavacamten is contraindicated in the patient receiving a strong CYP3A4 inhibitor. When initiating or increasing the dose of a moderate or weak CYP3A4 inhibitor while the patient is receiving mavacamten, the increase in exposure in patients who are CYP2C19 PMs may be possibly greater than the increase in exposure (1.16-fold) when co-administered with a moderate CYP3A4 inhibitor in patients who are not CYP2C19 PMs. Therefore, the package insert should include a cautionary statement to the effect that the dose should be decreased by 1 level or interrupted depending on the mavacamten dose level, and LVEF assessment should be performed 4 weeks after the start of co-administration.

Based on the above discussions, dose adjustments when co-administered with CYP3A4 inhibitors should be as shown in Table 25.

Table 25. Dose adjustment of mavacamten with concomitant CYP3A4 inhibitors

	A) When initiating mavacamten treatment while receiving an inhibitor	B) When initiating or increasing the dose of an inhibitor while on mavacamten treatment
Strong CYP3A4 inhibitors	Co-administration is contraindicated	Co-administration is contraindicated
Moderate CYP3A4 inhibitors	No cautionary statements necessary	If the patient is receiving mavacamten 2.5 to 15 mg, decrease the dose by 1 level. If the patient is receiving mavacamten 1 mg, interrupt administration and perform LVEF assessment 4 weeks later.
Weak CYP3A4 inhibitors		

6.R.5 Co-administration of mavacamten with CYP2C19 or CYP3A4 inducers

Mavacamten is primarily metabolized by CYP2C19 and CYP3A4 [see Section 6.2.1.3.2]. PMDA asked the applicant to explain whether the dose of mavacamten should be discontinued or reduced when discontinuing or reducing the dose of a CYP2C19 or CYP3A4 inducer while on mavacamten treatment.

The applicant's explanation:

When discontinuing or decreasing the dose of a CYP2C19 or CYP3A4 inducer while on mavacamten treatment, the increase in mavacamten exposure is predicted to be comparable to the increase in mavacamten exposure when initiating or increasing the dose of a CYP2C19 or CYP3A4 inhibitor (≤3.41-fold). On the other hand, based on the reported first-order degradation rate constant of CYP3A4, 0.0138/h (*Drug Metab Pharmacokinet.* 2018;33:179-87), the $t_{1/2}$ of CYP3A4 is estimated to be approximately 50 hours. In addition, given that the $t_{1/2}$ of CYP2C19 was reported to be 26 hours (*Curr Drug Metab.* 2008;9:384-94) and that it takes ≥7 days for the CYP3A4 activity of the liver induced by rifampicin (a strong CYP3A4 inducer) to return to baseline levels (*AAPS J*. 2019;21:78), mavacamten exposure is expected to increase gradually until steady state is re-achieved after discontinuation of the CYP inducer. Therefore, the patient's condition should be closely monitored during that period.

Based on the above, a cautionary statement should be included in the package insert to the effect that when discontinuing a strong or moderate CYP2C19 inducer, or a strong CYP3A4 inducer, while on mavacamten treatment, the patient's condition should be closely monitored. Conversely, when discontinuing a moderate CYP3A4 inducer, no cautionary statements are necessary based on the degree of predicted increase in exposure (1.16-fold).

In addition, the effect of dose reduction of CYP inducers on mavacamten exposure is expected to be small compared to the effect of its discontinuation; therefore, no cautionary statements are necessary for dose reduction of CYP inducers.

PMDA's view:
When discontinuing or decreasing the dose of a CYP2C19 or CYP3A4 inducer while on mavacamten treatment, mavacamten exposure may increase to a level that is comparable to the increase in exposure when initiating or increasing the dose of the CYP inhibitors. The applicant explained that after discontinuing the CYP inducer, the patient's condition should be closely monitored until the exposure reaches steady state. However, given that exposure at steady state is predicted to increase compared to mavacamten exposure when co-administered with the CYP inducers, and that it is difficult to clearly estimate the time required to return the steady-state exposure, measures such as decreasing the mavacamten dose should be taken at the time of discontinuing or decreasing the dose of the CYP inducer. When decreasing the dose of these inducers, the degree of increase in mavacamten exposure is expected to be small compared to that when discontinuing the CYP inducers; however, since it is difficult to predict mavacamten exposure for a specific level of dose reduction, the criteria for dose reduction of a CYP inducer should be similar to those for discontinuation of a CYP inducer.

Taken together, cautionary statements to the following effect should be included in the package insert: When discontinuing or decreasing the dose of a strong or a moderate CYP2C19 inducer, or a strong, moderate, or weak CYP3A4 inducer while on mavacamten treatment, the dose of mavacamten should be reduced by 1 level or interrupted depending on the mavacamten dose level, and LVEF assessment should be performed 4 weeks after discontinuation or dose reduction, in the same way as when initiating or increasing the dose of the CYP inhibitors while on mavacamten treatment. When discontinuing or decreasing the dose of a weak CYP2C19 inducer while on mavacamten treatment, dose reduction of mavacamten should be considered and at the same time, the patient's condition should be closely monitored.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of clinical result data from the 7 studies listed in Table 26 [see Section 6 for the data on PK].

Table 26. Outline of main clinical studies

Data	Location	Study ID	Phase	Study population	Number of subjects	Summary of dosage regimen	Main endpoint
Evaluation	Overseas	MYK-461-011	I	Healthy adults	28	Single oral administration of mavacamten 5, 15, or 25 mg	Safety PK
	Overseas	MYK-461-004	II	Patients with oHCM	Part A: 13 Part B: 12	Part A: mavacamten 10, 15, or 20 mg (starting dose, 15 mg[a]) once daily orally for 12 weeks Part B: mavacamten 2 or 5 mg (starting dose, 2 mg) once daily orally for 12 weeks	Safety Efficacy PK PD
	Overseas	MYK-461-008	II	Patients with oHCM	13	Mavacamten 5, 10, or 15 mg (starting dose, 5 mg) once daily orally for 156 weeks	Safety
	Overseas	MYK-461-005	III	Patients with oHCM	251	Placebo or mavacamten 2.5, 5, 10, or 15 mg (starting dose, 5 mg) once daily orally for 30 weeks	Efficacy Safety PK
	Japan	CV027004	III	Patients with oHCM	43	Mavacamten 1, 2.5, 5, 10, or 15 mg (starting dose, 2.5 mg) once daily orally for 138 weeks	Efficacy Safety PK
	Overseas	MYK-461-017	III	SRT-eligible patients with oHCM	112	Placebo,[b] mavacamten 2.5, 5, 10, or 15 mg (starting dose, 5 mg) once daily orally for 128 weeks	Efficacy Safety
	Overseas	MYK-461-007	II/III	Patients with oHCM or nHCM	231[c]	Mavacamten 2.5, 5, 10, or 15 mg (starting dose, 5 mg[d]) once daily orally for 252 weeks	Safety

a, 10 mg for those weighing ≤60 kg
b, After administration of placebo once daily orally for 16 weeks, mavacamten 2.5, 5, 10, or 15 mg (starting dose, 5 mg) was administered once daily orally for 112 weeks.
c, Although the parent studies of this study were Studies MYK-461-005 and MYK-461-006,[30)] data from the patients with oHCM participating in Study MYK-461-005 only are shown.
d, The starting dose was to be 2.5 mg for patients who had been treated with mavacamten 5 mg in the parent study and had mavacamten plasma trough concentrations of >700 ng/mL at the time of discontinuing or completing study drug treatment.

7.1 Phase I studies

7.1.1 Foreign phase I study (Study MYK-461-011, CTD 5.3.3.3-3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in a study center in the US to evaluate the safety and PK of mavacamten administered as a single dose to healthy Japanese and non-Japanese adults (target sample size, approximately 28 subjects [20 Japanese and 8 Caucasian subjects]).

Japanese subjects were to receive a single oral dose of mavacamten 5, 15, or 25 mg and Caucasian subjects were to receive a single oral dose of mavacamten 25 mg.

All 28 enrolled subjects (20 Japanese subjects [4 subjects in the 5 mg group and 8 subjects each in the 15 and 25 mg groups] and 8 Caucasian subjects [25 mg]) received the study drug, and were included in the safety analysis set.

The incidence of adverse events was 25.0% (2 of 8 subjects) in the 15 mg group in Japanese subjects, 0% (0 of 8 subjects) in the 25 mg group in Japanese subjects, and 12.5% (1 of 8 subjects) in Caucasian subjects.

There were no adverse events leading to death or treatment discontinuation. No serious adverse events occurred.

30) A phase II study in patients with nHCM

7.2 Phase II studies

7.2.1 Foreign phase II study (Study MYK-461-004, CTD 5.3.5.2-2 [[redacted] 2016 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 7 study centers in the US to evaluate the safety, efficacy, PK, and PD of mavacamten in non-Japanese patients with oHCM (target sample size, approximately 20 subjects [10 subjects each in Part A and Part B]).

This study consisted of a 12-week study drug treatment period and a 4-week washout period.

Key inclusion criteria were patients with oHCM[31)] aged 18 to 70 years (at screening) who met the following criteria with New York Heart Association (NYHA) class II or higher:

- Resting LVOT gradient at screening ≥30 mmHg and post-exercise LVOT gradient at screening ≥50 mmHg
- Resting LVEF at screening ≥55%

In Part A, the starting dose was mavacamten 10 mg once daily orally for subjects weighing ≤60 kg and 15 mg for those weighing >60 kg. The dose was adjusted in accordance with the criteria for dose adjustment presented in Table 27.

Table 27. Dose adjustment criteria in Study MYK-461-004

Percent decrease from baseline in LVEF at Week 4	Dose level from Week 5 onward
<10%	Increase by 10 mg[a,b]
≥10% and <15%	Increase by 5 mg[b]
≥15% and <20%	Maintain the same dose level
≥20%	Decrease by 5 mg

a, If the starting dose is 15 mg, the dose can be increased up to 20 mg.
b, The dose cannot be increased for a plasma mavacamten concentration of >750 ng/mL at Week 2.

In Part B, the starting dose was mavacamten 2 mg once daily orally. At Week 4, the dose was to be increased to 5 mg if the percent decrease from baseline in resting LVOT gradient was <50%, and the dose was to be maintained at 2 mg if ≥50%. Dose increase was not allowed in subjects whose plasma mavacamten concentrations were >300 ng/mL at Week 2.

Of 25 enrolled subjects (13 subjects in Part A and 12 subjects in Part B), 21 subjects who received the study drug (11 subjects in Part A and 10 subjects in Part B) were included in the safety analysis set and efficacy analysis set. Two subjects (Part A) discontinued the study due to “withdrawal of consent.”

Table 28 shows the change from baseline in post-exercise LVOT gradient at Week 12 in Part A and Part B.

31) Patients meeting the following criteria in accordance with the latest diagnostic criteria such as the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guidelines (*Circulation.* 2011;124:e783-831).
- Patients have unexplained left ventricular hypertrophy without dilation, and no other cardiovascular diseases or systemic diseases are noted
- Patients with a left ventricular wall thickness of ≥15 mm at the initial medical examination, or ≥13 mm for those with family history of HCM

Table 28. Change from baseline in post-exercise LVOT gradient (mmHg) at Week 12 (efficacy analysis set)

	Part A (N = 11)	Part B (N = 10)
Baseline	102.78 ± 50.08 (9)	85.86 ± 43.10 (9)
Week 12	18.91 ± 12.90 (10)	63.46 ± 25.88 (10)
Change from baseline	−89.51 ± 58.39 (8)	−25.03 ± 28.72 (9)

Mean ± standard deviation (N)

In Part A, the incidence of adverse events was 90.9% (10 of 11 subjects). Adverse events occurring in ≥2 subjects were atrial fibrillation, ejection fraction decreased, headache (3 subjects each); nausea, dyspnoea exertional, fatigue, upper respiratory tract infection, urinary tract infection, and rash (2 subjects each). No adverse events led to death. A serious adverse event occurred in 1 subject (atrial fibrillation), for which a causal relationship to the study drug could not be ruled out. Adverse events led to treatment discontinuation of the study drug in 1 subject (oedema peripheral/cardiac failure/dyspnoea), for which a causal relationship to the study drug could not be ruled out.

In Part B, the incidence of adverse events was 100% (10 of 10 subjects). Adverse events occurring in ≥2 subjects were ventricular tachycardia (4 subjects); dizziness (3 subjects); angina pectoris, headache, application site rash,[32)] fatigue, and upper respiratory tract infection (2 subjects each). There were no adverse events leading to death, or study drug treatment discontinuation. No serious adverse events occurred.

7.2.2 Foreign phase II study (Study MYK-461-008, CTD 5.3.5.2-4 [ongoing since [redacted] 20[redacted], data cut-off on [redacted] 20[redacted]])

An open-label uncontrolled study was conducted at 4 study centers in the US to evaluate the long-term safety of mavacamten in non-Japanese patients with oHCM who had completed Study MYK-461-004 (target sample size, up to 20 subjects).

This study consisted of a screening period lasting up to 28 days, a 156-week study drug treatment period, and a 12-week follow-up period.

The key inclusion criteria were to be similar to those of Study MYK-461-004.

Subjects were to receive mavacamten 5 mg once daily orally as the starting dose. The dose was to be adjusted in accordance with the dose adjustment criteria in Table 29. Dose increase after Week 6 was allowed following consultation with the investigator and medical monitor.[33)]

32) The area which came in contact with the electrocardiography device

33) If the investigator and the medical monitor agreed, dose increase exceeding the target dose level for the individual subject was allowed.

Table 29. Dose adjustment criteria in Study MYK-461-008

Criteria at Week 4	Dose level at Week 6
If any of the following criteria is met: ・ LVEF <55% ・ Post-exercise LVOT gradient <30 mmHg ・ Plasma mavacamten trough concentration >350 ng/mL ・ The investigator decided to keep the dose unchanged	No change in dose level
None of the above criteria are met	Dose increased to the target dose level[a,b]

a, Based on the PK results for each subject from the parent study (Study MYK-461-004), the dose level (5, 10, or 15 mg) that would allow the plasma mavacamten concentrations to be maintained in the range from 250 to 500 ng/mL was prespecified as the target dose level for each subject.

b, If the target dose level was 5 mg, the dose level was maintained at 5 mg.

All 13 enrolled subjects received the study drug, and were included in the safety analysis set. One subject discontinued the study due to "adverse events."

The incidence of adverse events was 100.0% (13 of 13 subjects). Adverse events occurring in ≥3 subjects were fatigue, nasopharyngitis and upper respiratory tract infection (4 subjects each); dizziness postural and dyspnoea (3 subjects each).

No adverse events led to death. Serious adverse events occurred in 3 subjects (lumbar vertebral fracture/spinal compression fracture [1 subject], cholangiocarcinoma [1 subject], lumbar radiculopathy [1 subject]). A causal relationship to the study drug was ruled out for all these events. An adverse event (aspartate aminotransferase [AST] increased) led to study drug treatment discontinuation in 1 subject, and its causal relationship to the study drug was ruled out.

7.3 Phase III studies

7.3.1 Foreign phase III study (Study MYK-461-005, CTD 5.3.5.1-1 [May 2018 to May 2020])

A randomized, double-blind, placebo-controlled study was conducted at 68 study centers outside Japan to evaluate the efficacy and safety of mavacamten in non-Japanese patients with oHCM (target sample size, 220 subjects[34)] [110 subjects each per group]).

This study consisted of a screening period lasting up to 35 days, a 30-week double-blind treatment period, and an 8-week follow-up period.

Key inclusion criteria were patients with oHCM[31)] aged ≥18 years (at screening) who met the following criteria with NYHA class II or III.

34) In the study planning stage, for the initial primary endpoint, the change from baseline in peak oxygen consumption (pVO_2) at Week 24, the mean of difference between the mavacamten group and placebo group was assumed to be 3 mL/kg/min, with a standard deviation of 5 mL/kg/min. A power of 88.1% was to be required to detect a statistically significant difference between the groups assuming a dropout rate of 15%, level of significance of 1% (two-sided), and a target sample size of 220 subjects (110 subjects in each group).
In the Protocol Amendment 2 (dated January 25, 2018) and the Protocol Amendment 4 (dated November 13, 2018), the primary endpoint was changed to the proportion of subjects achieving clinical response at Week 30. Accordingly, the clinical response (primary endpoint after amendment) was assumed to be 50% in the mavacamten group and 25% in the placebo group. With a level of significance (two-sided) of 5%, a target sample size of 220 subjects would provide a power of 96% to detect a statistically significant difference between the groups; therefore, the target sample size was not changed.

- Resting or post-exercise LVOT gradient or Valsalva LVOT (VLVOT) gradient at screening ≥50 mmHg
- VLVOT gradient at screening ≥30 mmHg
- Resting LVEF at screening ≥55%

Subjects were randomized to receive placebo or mavacamten at a ratio of 1:1, with stratification factors of NYHA functional classification (Class II or III) at screening, β-blocker use status, exercise type (treadmill or bicycle ergometer), and consent for the cardiac magnetic resonance imaging (CMR) substudy (yes or no).[35)]

Subjects were to receive placebo or mavacamten 5 mg once daily orally as the starting dose. The dose was to be adjusted in accordance with the dose adjustment level in Table 30 and dose adjustment criteria in Table 31.

Table 30. Dose adjustment levels in Study MYK-461-005

Level	1	2	3	4	5
Mavacamten dose	0 mg[a]	2.5 mg	5 mg	10 mg	15 mg

a, changed to placebo under the blinded condition

Table 31. Dose adjustment criteria in Study MYK-461-005

Measurement timepoint	Criteria[a]	Dose adjustment timing and dose level
Week 4	Plasma trough concentration >700 ng/mL and <1000 ng/mL and resting LVEF ≥50%	Decrease the dose by 1 level at Week 6
Weeks 6 and 12	Plasma trough concentration >700 ng/mL and <1000 ng/mL, and resting LVEF ≥50%	Decrease the dose by 1 level at Week 8 and Week 14
	Plasma trough concentration <350 ng/mL and VLVOT gradient ≥30 mmHg	Increase the dose by 1 level at Week 8 and Week 14
	Plasma trough concentration <350 ng/mL and VLVOT gradient <30 mmHg	Maintain the same dose level
	Plasma trough concentration ≥350 ng/mL and ≤700 ng/mL (regardless of VLVOT gradient)	
Week 8	Plasma trough concentration >700 ng/mL and <1000 ng/mL	Decrease the dose by 1 level at Week 10
Weeks 18, 22, and 26	Plasma trough concentration >700 ng/mL and <1000 ng/mL, and resting LVEF ≥50%	Decrease the dose by 1 level at Week 20, 24, and 28

a, determined by central review

Table 32 summarizes the criteria for treatment interruption, treatment discontinuation, and resumption.

35) In the specified trial sites, up to 80 subjects from whom additional consent was obtained were to be enrolled in the CMR substudy. Subjects who participated in the CMR substudy underwent CMR assessment on Day 1 and Week 30 in addition to the usual evaluation.

Table 32. Criteria for treatment interruption, treatment discontinuation, and resumption in Study MYK-461-005

	Criteria
Treatment interruption	Temporarily discontinue study drug treatment if any of the following criteria is met: · Resting LVEF dropped <50% · Plasma mavacamten trough concentration increased to ≥1000 ng/mL · If the QRS width <120 ms, either the percent change from baseline in QTcF interval increased by 15%, or QTcF interval is ≥520 ms, whichever is applicable · If the QRS width ≥120 ms, either the percent change from baseline in QTcF interval increased by 15%, or QTcF interval is ≥550 ms, whichever is applicable
Dose resumption	At a follow-up visit at 2 to 4 weeks after treatment interruption, perform ECG, plasma drug concentration assessment, and echocardiography. At a scheduled or unscheduled visit 2 weeks later (4 to 6 weeks after treatment interruption), if the laboratory values did not meet the treatment interruption criteria, resume treatment 6 weeks after treatment interruption at a dose reduced by 1 level from the pre-interruption dose level.
Treatment discontinuation	If LVEF as determined by trial site dropped ≤30%, permanently discontinue study drug treatment.

All 251 randomized subjects (128 subjects in the placebo group and 123 subjects in the mavacamten group) received the study drug, and were included in the safety analysis set and the intention to treat (ITT) population, which was the primary analysis population. Seven subjects discontinued the study (3 and 4 subjects in the placebo and mavacamten groups, respectively; same applies hereinafter) due to “adverse events” (0 and 2 subjects), “withdrawal of consent” (1 and 1 subject), “death” (1 and 0 subjects), and “other” (1 and 1 subject).

At Week 26, the dose levels in the mavacamten group were 2.5 mg (6 subjects, 4.9%), 5 mg (60 subjects, 48.8%), 10 mg (40 subjects, 32.5%), and 15 mg (13 subjects, 10.6%).[36)]

In the study planning stage, the primary efficacy endpoint was defined as “change from baseline in pVO_2 at Week 24.” However, taking into consideration the discussion with the Food and Drug Administration (FDA), the primary efficacy endpoint was changed to the proportion of subjects achieving clinical response at Week 30, where the clinical response is defined as “an increase in pVO_2 by ≥1.5 mL/kg/min and improvement of ≥1 NYHA class” (Protocol Amendment 2, dated January 25, 2018). Subsequently, to the definition of clinical response, “an increase in pVO_2 by ≥3.0 mL/kg/min and no worsening in NYHA functional class” were added (Protocol Amendment 4, dated November 13, 2018) [see Section 7.R.3.1].

Table 33 shows the proportion of subjects achieving clinical response at Week 30, the primary endpoint after amendment. The results demonstrated the superiority of mavacamten to placebo.

36) Other dose levels were 0 mg (1 subject, 0.8%), and no study drug treatment at Week 30 (3 subjects, 2.4%).

Table 33. Results for the primary endpoint (ITT population)

	Placebo (N = 128)	Mavacamten (N = 123)
Proportion of subjects achieving clinical response[a]	17.2 (22)	36.6 (45)
Proportion of subjects achieving "an increase in pVO_2 by ≥1.5 mL/kg/min and improvement of ≥1 NYHA class"	14.1 (18)	33.3 (41)
Proportion of subjects achieving "an increase in pVO_2 by ≥3.0 mL/kg/min and no worsening in NYHA class"	10.9 (14)	23.6 (29)
Difference from the placebo group in the proportion of subjects achieving clinical response [95% CI][b] (%)	19.4 [8.67, 30.13]	
P-value[c]	*P* = 0.0005	

Percentage, % (n)

a, If pVO_2 data at Week 30 were missing, the subject was considered non-responder. If pVO_2 data were available but NYHA was missing at Week 30, the NYHA class at Week 30 was imputed with the NYHA class at Week 26. After imputation, subjects whose response status was still missing were classified as non-responders.

b, The 95% CI was calculated by the Wald method.

c, Based on a Cochran-Mantel-Haenszel test with NYHA functional classification (Class II/III), β-blocker use status, and exercise type (treadmill or bicycle ergometer) as stratification factors (consent to participate in the CMR substudy was not included because there were 35 participants), significance level 5% (two-sided)

Table 34 shows the changes from baseline in post-exercise LVOT gradient and pVO_2, the secondary endpoints, at Week 30.

Table 34. Changes from baseline in post-exercise LVOT gradient and pVO_2 at Week 30 (ITT population)

		Placebo (N = 128)	Mavacamten (N = 123)
Post-exercise LVOT gradient (mmHg)	Baseline	84.3 ± 35.73 (127)	85.7 ± 34.27 (122)
	Week 30	73.4 ± 34.87 (123)	38.1 ± 32.09 (118)
	Change from baseline	−10.4 ± 29.59 (122)	−47.2 ± 40.31 (117)
	Between-group difference in change from baseline[a]	—	−35.6 [−43.15, −28.06]
pVO_2 (mL/kg/min)	Baseline	19.90 ± 4.909 (128)	18.93 ± 4.858 (123)
	Week 30	19.85 ± 5.403 (125)	20.35 ± 5.358 (120)
	Change from baseline	−0.05 ± 3.017 (125)	1.40 ± 3.115 (120)
	Between-group difference in change from baseline[a]	—	1.35 [0.580, 2.116]

Mean ± standard deviation (N)

a, least squares mean [95% CI] (analysis of covariance with treatment, baseline, NYHA functional classification [class II/III], β-blocker use status, exercise type [treadmill/bicycle ergometer] as covariates)

Table 35 shows the overall incidence of adverse events and the incidence of adverse events occurring in ≥5% of subjects in either group.

Table 35. Incidence of adverse events (safety analysis set)

MedDRA PT	Placebo (N = 128)	Mavacamten (N = 123)
All adverse events	81.3 (104)	87.8 (108)
Dizziness	13.3 (17)	21.1 (26)
Dyspnoea	13.3 (17)	14.6 (18)
Nasopharyngitis	14.8 (19)	12.2 (15)
Headache	7.8 (10)	12.2 (15)
Atrial fibrillation	7.8 (10)	8.1 (10)
Back pain	6.3 (8)	8.1 (10)
Upper respiratory tract infection	4.7 (6)	8.1 (10)
Cough	3.1 (4)	8.1 (10)
Palpitations	7.8 (10)	5.7 (7)
Fatigue	5.5 (7)	5.7 (7)
Gastrooesophageal reflux disease	2.3 (3)	5.7 (7)
Arthralgia	1.6 (2)	5.7 (7)
Syncope	1.6 (2)	5.7 (7)
Diarrhoea	5.5 (7)	4.1 (5)
Angina pectoris	5.5 (7)	2.4 (3)

Incidence, % (n)

An adverse event led to death in 1 subject in the placebo group (sudden death), and its causal relationship to the study drug could not be ruled out. The incidence of serious adverse events was 9.4% in the placebo group and 11.4% in the mavacamten group. Serious adverse events occurring in ≥2% of subjects in either group were atrial fibrillation (3.9% in the placebo group and 2.4% in the mavacamten group) and syncope (0.8% in the placebo group and 2.4% in the mavacamten group). Of the serious adverse events, a causal relationship to the study drug could not be ruled out for sudden death in 1 subject in the placebo group. Adverse events leading to study drug treatment discontinuation occurred in 2 subjects (1.6%) in the mavacamten group (syncope and atrial fibrillation [1 subject each]), and a causal relationship to the study drug could not be ruled out for atrial fibrillation (1 subject).

7.3.2 Japanese phase III study (Study CV027004, CTD 5.3.5.2-1 [ongoing since August 2022, data cut-off in [redacted] 20[redacted]])

An open-label uncontrolled study was conducted at 19 study centers in Japan to evaluate the efficacy and safety of mavacamten in Japanese patients with oHCM (target sample size, 30 subjects[37]).

This study consisted of a screening period lasting up to 35 days, a 30-week treatment period, a 108-week long-term extension period, and an 8-week[38] follow-up period.

Key inclusion criteria were patients with oHCM[31] aged ≥18 years (at the time of obtaining consent) with NYHA class II or III who met the following criteria:

[37] The target sample size was determined based on the feasibility. Using the data from the foreign phase III study (Study MYK-461-005) as a reference, the primary endpoint, the change from baseline in post-exercise LVOT gradient at Week 30 (mean ± standard deviation) was predicted to be −40 ± 45 mmHg. With a sample size of 30 subjects, there was approximately 94% of chance that the mean change from baseline in the post-exercise LVOT gradient (primary endpoint) would be ≤−27 mmHg, which is one of the criteria for assessing similarity to the results of Study MYK-461-005.

[38] Twenty weeks for CYP2C9 PMs

- Resting or post-exercise LVOT gradient or VLVOT gradient at screening ≥50 mmHg
- VLVOT gradient at screening ≥30 mmHg
- Resting LVEF at screening ≥60%

Subjects were to receive mavacamten 2.5 mg once daily orally as the starting dose. The dose was to be adjusted in accordance with the dose adjustment level in Table 36 and dose adjustment criteria in Table 37.

Table 36. Dose adjustment levels in Study CV027004

Level	1	2	3	4	5
Mavacamten dose	1 mg	2.5 mg	5 mg	10 mg	15 mg

Table 37. Dose adjustment criteria in Study CV027004

Measurement timepoint	Criteria	Dose adjustment time and dose level
Week 4	VLVOT gradient <30 mmHg and LVEF ≥50%[a]	Decrease the dose by 1 level at Week 6
Weeks 6, 12, and 18	VLVOT gradient ≥30 mmHg and LVEF ≥55%[a]	Increase the dose by 1 level at Weeks 8, 14, and 20[a]
	VLVOT gradient <30 mmHg and LVEF ≥50%, or VLVOT gradient ≥30 mmHg and LVEF ≥50% and <55%[a]	Maintain the same dose level
Weeks 20 to 30	No dose adjustment criteria	
Week 30 or later (at one point of the visits conducted at 12-week intervals)	VLVOT gradient ≥30 mmHg and resting LVEF ≥55%[b]	After consultation with the medical monitor, the dose may be increased in 1-level increments up to 15 mg
	VLVOT gradient <30 mmHg and LVEF ≥50%, or VLVOT gradient ≥30 mmHg and LVEF ≥50% and <55%[b]	Maintain the same dose level

a, determined by central review
b, determined by the trial site

Table 38 summarizes the criteria for treatment interruption, treatment discontinuation, and resumption.

Table 38. Criteria for treatment interruption, treatment discontinuation, and resumption in Study CV027004

	Criteria
Treatment interruption	Temporary discontinue study drug treatment if any of the following criteria are met: · Resting LVEF <50% · Plasma mavacamten trough concentration increased to ≥1000 ng/mL · If the QRS width <120 ms, either QTcF interval prolongation from baseline by 15% or QTcF interval ≥520 ms · If the QRS width ≥120 ms, either QTcF interval prolongation from baseline by 15% or QTcF interval ≥550 ms
Dose resumption[a]	At a follow-up visit at 2 to 4 weeks after treatment interruption, perform ECG, plasma drug concentration assessment, and echocardiography. At a scheduled or unscheduled visit 2 weeks later (4 to 6 weeks after treatment interruption), if the laboratory values did not meet the treatment interruption criteria, resume treatment 6 weeks after treatment interruption at a dose reduced by 1 level from the pre-interruption dose level. If the pre-interruption dose level was 1 mg, permanently discontinue study drug treatment.
Treatment discontinuation	If LVEF as determined by trial site dropped ≤30%, permanently discontinue study drug treatment.

Echocardiographic measurements were assessed by central review during the primary evaluation period (up to Week 30), and by trial site during the long-term extension period (from Week >30 to Week 138).
a, criteria for the primary evaluation period (up to Week 30)

A total of 38 subjects received the study drug, and all these subjects were included in the safety analysis set and the ITT population. The ITT population was the primary efficacy analysis set. Two subjects discontinued the study due to "withdrawal of consent" and "other" (the treatment interruption criterion "Fridericia-corrected QT Interval [QTcF] prolongation" was met) in 1 subject each.

At Week 30, the dose levels in the mavacamten group were 1 mg (5 subjects, 13.2%), 2.5 mg (6 subjects, 15.8%), 5 mg (10 subjects, 26.3%), 10 mg (10 subjects, 26.3%), and 15 mg (4 subjects, 10.5%).[39)]

Table 39 shows the change from baseline in post-exercise LVOT gradient at Week 30, the primary endpoint. The results met the following criteria, which were established to assess the similarity of the results of this study to those of Study MYK-461-005.

1) The mean change from baseline in post-exercise LVOT gradient at Week 30 ≤−27 mmHg.[40)]
2) The 95% CI of the mean of change from baseline in post-exercise LVOT gradient at Week 30 in this study does not include the mean of value in the placebo group in Study MYK-461-005 (the upper bound of the 95% CI of the mean in this study is lower than −10 mmHg).

Table 39. Change from baseline in post-exercise LVOT gradient at Week 30 (mmHg) (ITT population)

	Overall ITT population (N = 38)
Baseline	85.14 ± 29.24 (38)
At Week 30	28.36 ± 26.46 (35)
Change from baseline	−60.70 ± 31.56 (35) [−71.54, −49.86][a]

Mean ± standard deviation (N)
a, 95% CI of mean

The change from baseline in pVO_2 at Week 30 (mean ± standard deviation) was 0.83 ± 2.540 mL/kg/min.[41)]

The incidence of adverse events that occurred by Week 54 was 73.7% (28 of 38 subjects). Adverse events occurring in ≥2 subjects were COVID-19 (23.7%); nasopharyngitis (15.8%); atrial fibrillation, hypertension, and pyrexia (7.9% each); bronchitis, dermatitis contact, malaise, arthralgia, cataract, decreased appetite, abdominal pain, and palpitations (5.3% each).

No adverse events led to death. Serious adverse events occurred in 15.8% of subjects (6 subjects in total; COVID-19, colonic abscess, arial fibrillation/cerebral haemorrhage, cholangitis/cholecystitis acute, rotator cuff syndrome, macular oedema [1 subject each]). A causal relationship to the study drug was ruled out for all these events. There were no adverse events leading to study drug treatment discontinuation.

39) Other 3 subjects (7.9%) were not receiving the study drug as of Week 30.

40) This criterion was established in view of the following: Based on the preliminary prediction for the primary endpoint (change from baseline in post-exercise LVOT gradient at Week 30), −40 ± 45 mmHg (mean ± standard deviation), it was determined that with a sample size of 30 subjects, a mean change from baseline of at least −27 mmHg was necessary for the upper bound of the 95% CI for the mean of the primary endpoint to be lower than the mean change from baseline in the placebo group in Study MYK-461-005 (−10.4 mmHg).

41) Among the 17 subjects in the cardiopulmonary exercise testing-evaluable population (subjects who received at least 1 dose of the study drug and had evaluable cardiopulmonary exercise test data), the change from baseline was based on data obtained from 15 subjects.

7.3.3 Foreign phase III study (Study MYK-461-017, CTD 5.3.5.1-2 [ongoing since July 2020 data cut-off in [redacted] 20[redacted]])

A randomized, double-blind, placebo-controlled study was conducted at 19 study centers in the US to evaluate the efficacy and safety of mavacamten in patients with oHCM eligible for septal reduction therapy (SRT) (surgical myectomy or percutaneous transluminal septal myocardial ablation [PTSMA]) (target sample size, 100 subjects[42)] [50 subjects per group]).

This study consisted of a 16-week double-blind period, a 16-week active-controlled period, and a 96-week long-term extension period. In the following paragraphs, the double-blind period results, which were used as the primary evaluation data for the present application, will be presented.

Key inclusion criteria were patients with oHCM[31)] aged ≥18 years (at screening) with NYHA function class II to IV, who were referred or under active consideration for SRT within the past 12 months prior to screening, and who met the following criteria:

- The invasive SRT criteria[43)] in accordance with the ACCF/AHA 2011 Guidelines (*Circulation.* 2011;124:e783-831) diagnostic criteria were met.
- LVEF ≥60% at screening

Subjects were randomly assigned to placebo or mavacamten at a ratio of 1:1, with stratification by the type of SRT (myectomy or PTSMA) and NYHA functional class (Class II or Class III/IV) at screening.

Up to Week 16, subjects were to receive placebo or mavacamten 5 mg once daily orally as the starting dose in accordance with the dose adjustment level in Table 40 and dose adjustment criteria in Table 41. In the placebo group, from Week 16 onwards, dose adjustments were implemented in the same manner as in the mavacamten group.

Table 40. Dose adjustment levels in Study MYK-461-017

Level	1	2	3	4
Mavacamten dose	2.5 mg	5 mg	10 mg	15 mg

42) Assuming that 35% of subjects receiving mavacamten and 70% of subjects receiving placebo would meet the primary endpoint criteria, the target sample size of 100 subjects (50 subjects per group) would provide 95% power to detect a statistically significant difference at a two-sided 5% significance level.

43) Clinical criteria: subjects experiencing severe dyspnoea or chest pain despite drug therapy at the maximum dose (generally NYHA Class III or IV) or those who are NYHA Class II with exertion-induced syncope or near syncope.
Hemodynamic criteria: LVOT gradient at rest or with provocation (post-Valsalva or exercise) ≥50 mmHg
Anatomic criteria: target anterior septal thickness sufficient to perform SRT procedure safely and effectively as determined by the investigator

Table 41. Dose adjustment criteria in Study MYK-461-017

Measurement timepoint	Criteria	Dose
Week 4	LVEF ≥50% and VLVOT gradient <30 mmHg	Decrease the dose by 1 level
Weeks 8 and 12	LVEF ≥50% and VLVOT gradient ≥30 mmHg	Increase the dose by 1 level

A total of 112 randomized subjects (56 subjects in the placebo group and 56 subjects in the mavacamten group) were included in the ITT population, which was used as the efficacy analysis set. Among these subjects, 111 subjects (55 subjects in the placebo group and 56 subjects in the mavacamten group) who received the study drug were included in the safety analysis set. Two subjects in the placebo group discontinued the study due to "withdrawal of consent" (1 subject) and "other" (1 subject, who was found to have met the exclusion criteria). At Week 16, the dose levels in the mavacamten group were 2.5 mg (12 subjects, 21.4%), 5 mg (12 subjects, 21.4%), 10 mg (17 subjects, 30.4%), and 15 mg (10 subjects, 17.9%).[44)]

The primary endpoint for this study was the proportion of subjects meeting either of the following criteria: "decision to proceed with SRT prior to or at Week 16" or "eligible for SRT at Week 16 per the 2011 ACCF/AHA Guidelines." The results (Table 42) demonstrated the superiority of mavacamten over placebo.

Table 42. Results for primary endpoint (ITT population)

	Placebo (N = 56)	Mavacamten (N = 56)	Between group difference (placebo-mavacamten) [95% CI] (%)[b] *P*-value[c]
Primary endpoint[a]	76.8 (43)	17.9 (10)	58.9 [43.99, 73.87] *P* <0.0001
Proportion of subjects for whom the decision was made to proceed with SRT prior to or at Week 16	3.6 (2)	3.6 (2)	
Proportion of subjects who were eligible for SRT at Week 16 per ACCF/AHA Guidelines	69.6 (39)	14.3 (8)	

Percentage, % (n)

a, Subjects with missing primary endpoint assessments due to discontinuation prior to Week 16 or lost to follow-up, etc. were classified as meeting the primary endpoint requirement, "eligible for SRT at Week 16 per ACCF/AHA Guidelines."

b, The Mantel-Haenszel method stratified by SRT type (myectomy vs. PTSMA). (NYHA class was not included in the stratification because only 1 subject in NYHA Class II had the SRT type of PTSMA, which followed the pre-specified protocol provision.)

c, a Cochran-Mantel-Haenszel test stratified by SRT type (myectomy vs. PTSMA) at a two-sided 5% significance level

The incidence of adverse events was 61.8% (34 of 55 subjects) in the placebo group and 73.2% (41 of 56 subjects) in the mavacamten group. Adverse events occurring in ≥5% of subjects in either group were fatigue (3.6% and 8.9% in the placebo and mavacamten groups, respectively; the same applies hereinafter), dizziness (5.5% and 7.1%), dyspnoea (5.5% and 7.1%), nausea (1.8% and 7.1%), atrial fibrillation (0% and 7.1%), hypertension (3.6% and 5.4%), urinary tract infection (1.8% and 5.4%), headache (9.1% and 3.6%), and ventricular tachycardia (9.1% and 0%).

There were no adverse events leading to death or study drug treatment discontinuation. The incidence of serious adverse events was 1.8% in the placebo group (1 subject; alcohol poisoning) and 5.4% in

44) For 5 subjects (8.9%), their dose levels were either unknown or were not receiving the study drug as of Week 16.

the mavacamten group (3 subjects total; atrial fibrillation [2 subjects], COVID-19 [1 subject]). A causal relationship to the study drug could not be ruled out for atrial fibrillation (1 subject) in the mavacamten group.

7.3.4 Foreign phase III study (Study MYK-461-007, CTD 5.3.5.2-3 [ongoing since [redacted] 2018, data cut-off in [redacted] 20[redacted]])

An open-label study was conducted at 66 study centers outside Japan to evaluate the long-term safety and other aspects of mavacamten (target sample size, approximately 250 subjects). This was an extension study of Study MYK-461-005 in patients with oHCM and Study MYK-461-006 (foreign phase II study) in patients with nHCM.

This study consisted of a screening period lasting up to 28 days, a 252-week[45)] treatment period, and an 8-week follow-up period. In the following paragraphs, the results of the oHCM patient population, the proposed study population for the present application, will be presented.

Key inclusion criteria were patients with HCM with resting LVEF of ≥50% at screening.[31)]

Subjects were to receive mavacamten 5 mg once daily orally as the starting dose regardless of the treatment group in Study MYK-461-005, unless the plasma mavacamten trough concentration was >700 ng/mL at discontinuation or at the end of study drug treatment in the parent study, in which case, subjects who had received mavacamten 5 mg previously were to start this study at 2.5 mg. The dose was to be adjusted in accordance with the dose adjustment levels outlined in Table 40 and the dose adjustment criteria presented in Table 43.

Table 43. Dose adjustment criteria in Study MYK-461-007

Dose adjustment time	Criteria[a]	Dose
Week 4	VLVOT gradient ≤30 mmHg	Decrease the dose by 1 level
	VLVOT gradient >30 mmHg	Maintain the same dose level
Weeks 8 and 12	VLVOT gradient ≤30 mmHg	Maintain the same dose level
	VLVOT gradient >30 mmHg and LVEF ≥50%	Increase the dose by 1 level
Week 24	Post-exercise LVOT gradient <50 mmHg	Maintain the same dose level
	Post-exercise LVOT gradient ≥50 mmHg and LVEF ≥50%	After consultation with the medical monitor, the dose may be increased in 1-level increments up to 15 mg[c]
Week 24 or later (any timepoint of every 24-week[b] visit)	VLVOT gradient >30 mmHg and LVEF ≥50%	

a, determined by the trial site
b, In Protocol Amendment [redacted] (dated [redacted], 20[redacted]), the interval between evaluation visits after Week 156 was changed to every 24 weeks from every 12 weeks.
c, When the dose was adjusted, echocardiography after Valsalva and at rest including LVEF was to be performed to ensure safety at the follow-up visit 28 days (± 7 days) after the adjustment. Subsequently, post-exercise LVOT gradient was re-evaluated at the discretion of the investigator.

45) In Protocol Amendment [redacted] (dated [redacted], 20[redacted]), the treatment period was extended from 104 weeks to 252 weeks.

All 231 enrolled subjects[46)] received the study drug (116 subjects on placebo and 115 subjects on mavacamten in the parent study) were included in the safety analysis set and the ITT population. Nineteen subjects discontinued the study due to "adverse events" (5 subjects), "death" (5 subjects), "withdrawal of consent" (4 subjects), "treatment interruption criterion was met" (3 subjects), "lost to follow-up" (1 subject), and "other" (1 subject).

The incidence of adverse events was 98.7% (228 of 231 subjects). Adverse events occurring in ≥10% of subjects were COVID-19 (39.8%); dizziness (17.7%); nasopharyngitis and hypertension (15.6% each); atrial fibrillation (14.3%); fatigue (12.6%); back pain and arthralgia (10.4% each); headache and dyspnoea (10.0% each). Adverse events led to death in 2.2% of subjects (5 subjects in total; cholecystitis acute/biliary dilatation/cholangitis/metastases to liver, acute myocardial infarction, cardiac arrest, endocarditis bacterial, cerebral haemorrhage [1 subject each]); and a causal relationship to the study drug was ruled out for all these events. Serious adverse events occurred in 27.3% of subjects, and events occurring in ≥2% of subjects were atrial fibrillation (6.1%); cardiac failure and ejection fraction decreased (2.2% each). Of the serious adverse events, a causal relationship to the study drug could not be ruled out for ejection fraction decreased (5 subjects), cardiac failure (3 subjects), atrial fibrillation (1 subject), and atrial flutter (1 subject). Adverse events leading to study drug treatment discontinuation occurred in 5.6% of subjects (13 subjects in total; ejection fraction decreased [3 subjects]; acute myocardial infarction [2 subjects]; atrial fibrillation, cardiac arrest, cardiac failure, electrocardiogram QT prolonged, muscular weakness, systemic lupus erythematosus, fatigue, biliary tract dilatation, cholangitis, metastases to liver, endocarditis bacterial, and cerebral haemorrhage [1 subject each]). Of the adverse events leading to study drug treatment discontinuation, a causal relationship to the study drug could not be ruled out for ejection fraction decreased (2 subjects); fatigue, atrial fibrillation, electrocardiogram QT prolonged, muscular weakness, cardiac failure, and dyspnoea paroxysmal nocturnal (1 subject each).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of mavacamten

The applicant's explanation about the clinical positioning of mavacamten:

Cardiac hypercontractility and left ventricular hypertrophy are observed in patients with HCM regardless of cardiac disease or systemic disease that causes myocardial hypertrophy. Hypertrophic cardiomyopathy characterized by obstruction in the LVOT caused by myocardial hypertrophy of the ventricular septum and the presence of a certain level of LVOT gradient is classified as oHCM. In patients with oHCM, obstruction in the LVOT increases the left ventricular pressure, which leads to shortness of breath at rest or on exertion, fatigue, syncope, and other symptoms, increasing the risk of cardiac failure and sudden death as a result of progression of disease. Patients with symptomatic oHCM have subjective symptoms such as shortness of breath due to increased left ventricular pressure caused by obstruction in the LVOT and are at the risk of sudden death; therefore, improvement in hemodynamics is needed through treatment intervention (The Japanese Circulation Society [JCS] 2018 Guideline on Diagnosis and Treatment of Cardiomyopathies).

[46)] In accordance with the protocol, re-enrollment of subjects who could not complete evaluation and discontinued the study due to COVID-19, etc. was allowed. For 24 re-enrolled subjects, demographic characteristics data from the initial enrollment and baseline data for efficacy endpoint from re-enrollment were used.

Treatment approaches to oHCM include pharmacotherapy and non-pharmacotherapy. The JCS 2018 Guideline on Diagnosis and Treatment of Cardiomyopathies recommends the use of β-blockers or calcium channel blockers (if β-blockers are difficult to use) as pharmacotherapy to improve subjective symptoms and increase exercise capacity. If the response to these drugs is inadequate, sodium channel blockers, such as disopyramide and cibenzoline, are used in combination with the above drugs; however, the treatment effect of these drugs is rather limited. As a non-pharmacotherapy approach, SRT (myectomy or PTSMA) may be considered for patients with severe LVOT obstruction who have an inadequate response to pharmacotherapy and have symptoms affecting their activities of daily living. However, there are certain risks associated with SRT such as complications.

Selective binding of mavacamten to cardiac myosin is considered to inhibit the formation of myosin-actin cross-bridges to reduce cardiac hypercontractility, thereby improving diastolic dysfunction and reducing LVOT obstruction in patients with oHCM. The foreign phase III study (Study MYK-461-005) and Japanese phase III study (Study CV027004), both of which were conducted in patients with symptomatic oHCM, demonstrated the efficacy of mavacamten and its acceptable safety in the patient population. Therefore, mavacamten can serve as a new treatment option for patients with oHCM, for whom effective therapeutic options are currently limited.

PMDA's view:
Conventional pharmacotherapies are used for the treatment of patients with symptomatic oHCM with the aim that drugs will improve subjective symptoms through negative chronotropic effects; however, the drugs do not directly act on the pathophysiology to improve hemodynamics. The results of Studies MYK-461-005 and CV027004 in patients with symptomatic oHCM demonstrated the efficacy of mavacamten and its clinically acceptable safety [see Sections 7.R.3 and 7.R.4]. In addition, most of patients enrolled in these studies had previously received conventional pharmacotherapies. Given these findings, mavacamten is expected to be effective in patients with symptomatic oHCM that responded inadequately to conventional pharmacotherapies, and therefore, it is meaningful to make mavacamten available to patients and healthcare professionals in Japan as a new option for the treatment of oHCM. However, mavacamten carries a risk of systolic dysfunction that may result in serious outcomes; therefore, whether to initiate treatment and dose adjustment should be carefully considered for each individual patient [see Sections 7.R.5 and 7.R.6].

7.R.2 Developmental strategy of mavacamten

The applicant's explanation about the developmental strategy of mavacamten in Japan:
In the development of mavacamten in Japan, participation of Japanese patients in Study MYK-461-005, which was underway at that time, was also considered. However, compared to non-Japanese patients, many Japanese patients have lower body weight and a higher prevalence of CYP2C19 PMs, raising the concern of increased mavacamten exposure in Japanese patients. Therefore, The applicant considered it appropriate to conduct a separate clinical study in Japanese patients, using a lower starting dose and implementing additional

safety assurance measures, to evaluate the efficacy and safety of mavacamten in Japanese patients with oHCM while also assessing if the results of this study are similar to those of Study MYK-461-005. Accordingly, Study CV027004 was conducted. Based on the following considerations, the applicant considered it reasonable to use data from Study MYK-461-005 to demonstrate the efficacy of mavacamten in Japanese patients with oHCM.

The intrinsic and extrinsic ethnic factors of mavacamten were assessed. In terms of intrinsic ethnic factors, no clear differences have been reported in the pathophysiology and etiology of oHCM between Japanese and non-Japanese populations. Except for the higher proportion of CYP2C19 PMs in the Japanese population, ethnic differences between Japanese and non-Japanese populations are unlikely to have a significant impact on the PK of mavacamten. As for extrinsic ethnic factors, diagnosis of HCM requires confirmation of left ventricular hypertrophy based on radiographic findings; in addition, secondary cardiomyopathy needs to be ruled out. This is consistent both in Japan and internationally. Furthermore, oHCM is diagnosed when the resting or physiologically induced (e.g., during exercise) LVOT gradient is 30 mmHg or higher— again, a shared diagnostic criterion worldwide. Thus, there are no clear differences in the diagnosis between Japan and other countries in terms of how oHCM is diagnosed. In addition, there are no marked differences between Japan and other countries in terms of the following factors: pharmacotherapy includes β-blockers, calcium channel blockers, and sodium channel blockers, while available non-pharmacotherapy is SRT (myectomy or PTSMA). These therapies are chosen depending on the patient's condition. Taken together, ethnic factors are unlikely to have an impact on the efficacy and safety evaluation of mavacamten.

Table 44 shows the distribution of demographics and baseline characteristics of subjects enrolled in Studies MYK-461-005 and CV027004. Subjects enrolled in Study CV027004 tended to be lower in weight, with higher resting LVOT gradient and VLVOT gradient at baseline, compared to those in Study MYK-461-005. The percentages of women, CYP2C19 PMs, and subjects with concomitant use of β-blockers were higher in Study CV027004.

Table 44. Distribution of demographics and baseline characteristics of subjects in Studies MYK-461-005 (ITT population) and CV027004 (ITT population)

		MYK-461-005		CV027004 (N = 38)
		Placebo (N = 128)	Mavacamten (N = 123)	
≥65 years		31.3 (40)	36.6 (45)	55.3 (21)
Body weight (kg)[a]		84.40 [46.0, 156.1]	83.50 [52.0, 148.2]	68.25 [40.0, 101.7]
Sex	Male	64.8 (83)	53.7 (66)	34.2 (13)
	Female	35.2 (45)	46.3 (57)	65.8 (25)
CYP2C19 PM		2.3 (3)	1.6 (2)	21.1 (8)
Baseline LVOT gradient (mmHg)[b]	Resting LVOT gradient	51.08 ± 31.95 (128)	51.71 ± 29.44 (123)	73.64 ± 34.23 (38)
	VLVOT gradient	73.92 ± 32.02 (128)	72.35 ± 31.72 (123)	91.45 ± 32.11 (38)
	Post-exercise LVOT gradient	84.35 ± 35.73 (127)	85.67 ± 34.27 (122)	85.14 ± 29.24 (38)
Baseline NYHA functional class	I	0 (0)	0 (0)	0 (0)
	II	74.2 (95)	71.5 (88)	86.8 (33)
	III	25.8 (33)	28.5 (35)	13.2 (5)
Concomitant drugs	β-blockers	74.2 (95)	76.4 (94)	89.5 (34)
	Calcium channel blockers	13.3 (17)	20.3 (25)	7.9 (3)
	No concomitant drugs	12.5 (16)	3.3 (4)	7.9 (3)

Percentage, % (n)
a, median [Min, Max]
b, mean ± standard deviation (N)

A subgroup analysis by demographics and baseline characteristics, for which differences were observed between the studies, was conducted for the change from baseline in pVO_2 and post-exercise LVOT gradient. The results showed no clear differences among the subgroups. Therefore, although the limited number of subjects in Study CV027004 precludes a stringent interpretation of results, the differences in the demographics and baseline characteristics identified between the studies are unlikely to affect the efficacy evaluation of mavacamten.

To compare the results from different studies, in the early stage of planning, Study CV027004 was to be conducted as a placebo-controlled study, similar to Study MYK-461-005. However, the results of Study MYK-461-005 had already been released at that point, and the risk of a decrease in cardiac contractile function associated with mavacamten had been made clear. If echocardiographic results were not disclosed to trial sites, a smaller number of sites would be willing to participate in the study due to subjects' safety concerns. On the other hand, if echocardiographic results were disclosed, the blinding of a placebo-controlled study might not be maintained. In addition, given the limited number of patients with oHCM in Japan, the applicant decided to conduct Study CV027004 as an open-label, uncontrolled study. The applicant initially considered the use of change from baseline in pVO_2, a composite primary endpoint of Study MYK-461-005, as the primary endpoint of Study CV027004. However, given the limited availability of cardiopulmonary exercise testing (CPET) in Japan, among other reasons, the change from baseline in post-exercise LVOT gradient was chosen, which is one of important indicators used in the treatment of oHCM and has been reported to be related to the outcome. Change from baseline in post-exercise LVOT gradient is a secondary endpoint in Study MYK-461-005, and is an objective indicator based on echocardiogram. In addition, the difference in the inclusion criteria related to

resting LVEF and concomitant therapies (i.e., placement of an implantable cardioverter-defibrillator [ICD]) between the two studies are unlikely to affect efficacy and safety. In view of these considerations, the applicant determined that comparison of the results between the two studies was feasible.

PMDA's view:
Based on the applicant's explanation, it is reasonable that the applicant decided to conduct Study CV027004 as an open-label uncontrolled study and that the developmental strategy involved evaluating the efficacy and safety of mavacamten in Japanese patients with oHCM based on the results of both studies, MYK-461-005 and CV027004 after confirming the similarity between them. In addition, there are no marked differences in intrinsic and extrinsic ethnic factors between Japanese and non-Japanese populations. The differences in demographics and baseline characteristics identified between the studies are unlikely to have a marked impact on the efficacy evaluation of mavacamten.

Although the primary endpoint of Study CV027004 differs from that for Study MYK-461-005, the similarity of the results between the studies can be evaluated based on the comparison of changes from baseline in post-exercise LVOT gradient following administration of mavacamten, given the following factors: (i) change from baseline in post-exercise LVOT gradient is an objective indicator; (ii) the differences between the studies in the demographics and baseline characteristics are unlikely to affect the change from baseline in post-exercise LVOT gradient following administration of mavacamten; and (iii) as discussed in Section 7.R.3.1, the primary endpoints for both studies are considered appropriate.

Based on the above, the results of Study MYK-461-005 can be used to demonstrate the efficacy of mavacamten in Japanese patients with oHCM.

7.R.3 Efficacy

7.R.3.1 Appropriateness for the selection of primary endpoints

The applicant's explanation about the appropriateness for the selection of the primary endpoints for the foreign phase III study (Study MYK-461-005) and for the Japanese phase III study (Study CV027004) was presented below

(1) Primary endpoint of Study MYK-461-005

In the treatment of oHCM, the true endpoint is the improvement in survival outcomes (*Eur J Heart Fail.*;18:1106-18); however, the limited number of patients with oHCM makes it difficult to conduct a clinical study of sufficient scale to evaluate efficacy using a survival outcome indicator such as mortality as the primary endpoint. Because pVO_2, an objective indicator of exercise capacity, has been reported to be correlated with survival outcome of patients with oHCM (e.g., *JACC.* 2013;61:10 Suppl.E1304, *Circ Heart Fail.* 2020;13:e007230), change from baseline in pVO_2 at Week 24 was selected as the primary endpoint in the early stage of study planning. Subsequently, after discussion with the FDA, the primary endpoint was changed to the proportion of subjects achieving clinical response at Week 30, where clinical response was defined

as meeting one of the criteria shown below (Protocol Amendment 2, dated January 25, 2018 and Protocol Amendment 4, dated November 13, 2018).

- An increase in pVO_2 by ≥1.5 mL/kg/min and improvement of ≥1 NYHA class
- An increase in pVO_2 by ≥3.0 mL/kg/min and no worsening in NYHA class

The rationale for the selection of criteria for clinical response is as follows:
The short-term treatment goals of oHCM are improvement of exercise capacity and subjective symptoms (*Eur J Heart Fail.* 2016;18:1106-18). Clinical response was therefore defined as a composite of pVO_2 and NYHA class, which are generally used as measures for exercise capacity and clinical symptoms. Regarding the first criterion for clinical response, an increase in pVO_2 by ≥1.5 mL/kg/min was selected as a conservative threshold for the improvement of exercise capacity because published articles has reported that an increase in pVO_2 by ≥1.0 mL/kg/min leads to improvement in outcome in patients with HCM (*Circ Heart Fail.* 2015;8:1022-31, *Am Heart J*. 2015;169:684-92 e1); and improvement of at least 1 NYHA class was defined as the threshold for the improvement of clinical symptoms. Based on the reports that improvement of clinical symptoms was associated with an increase in pVO_2 by approximately 3.0 mL/kg/min in patients with oHCM who had undergone SRT (*Eur Heart J*. 2002;23(20):1617-24, *Eur J Heart Fail.* 2008;10:1123-6), an increase in pVO_2 by ≥3.0 mL/kg/min and no worsening in NYHA class was selected as the second criterion.

(2) Primary endpoint of Study CV027004
Because of the limited number of patients with oHCM and insufficient availability of CPET in Japan, it was difficult to conduct the study using pVO_2 as the primary endpoint, which was used as a composite primary endpoint in Study MYK-461-005. Conversely, post-exercise LVOT gradient, one of the secondary endpoints for Study MYK-461-005, is an echocardiography-based, objective indicator. Post-exercise LVOT gradient, which was reported to be associated with survival outcome (*Engl J Med.* 2003;348:295-303, *J Am Coll Cardiol.* 2016;67:1399-409), is one of the important indicators in the treatment of oHCM, even though it does not directly reflect exercise capacity or clinical symptoms.

Based on the above, the applicant decided to select change from baseline in post-exercise LVOT gradient at Week 30 as the primary endpoint, and to evaluate LVOT gradient based on the assessment by central review to reduce bias, taking into consideration that Study CV027004 was to be conducted as an unblinded study.

PMDA's view:
The proportion of subjects achieving clinical response was selected as the primary endpoint of Study MYK-461-005. While improvements in exercise capacity and clinical symptoms are the focus in the pharmacological treatment of oHCM, and it has been assumed that the change in pVO_2 is correlated with the change in clinical symptoms in patients with oHCM (JCS 2018 Guideline on Diagnosis and Treatment of Cardiomyopathies), the proportion of subjects achieving clinical response has not been established as an indicator for evaluating the efficacy of oHCM drugs, thus, the clinical relevance of the difference in the proportion of responders between the groups in Study MYK-461-005 is not clear. Accordingly, the efficacy of mavacamten should be

comprehensively assessed after examining the results for each component included in the criteria for clinical response, and the effect on survival outcome based on the change in pVO_2, incidence of cardiovascular events, and other factors in each group.

The applicant's explanation about the difficulties in adopting pVO_2 as the primary endpoint in Study CV027004 is acceptable, considering the limited number of patients with oHCM and insufficient availability of CPET in Japan. Given that LVOT gradient is one of the objective indicators for the severity of oHCM, and that the indicator has been reported to be associated with survival outcome, efficacy can be evaluated to a certain extent by using the change from baseline in post-exercise LVOT gradient, as assessed by central review, as the primary endpoint.

7.R.3.2 Efficacy evaluation results

The applicant's explanation of the efficacy of mavacamten was as follows:

(1) Results for Study MYK-461-005

The results for the primary endpoint in Study MYK-461-005, the proportion of subjects achieving clinical response (responders) at Week 30, are presented in Table 33. The between-group difference in the proportion of responders was 19.4% (17.2% in the placebo group and 36.6% in the mavacamten group), demonstrating the superiority of mavacamten to placebo. The proportion of subjects meeting the clinical response criteria, (1) an increase in pVO_2 by ≥1.5 mL/kg/min and improvement of ≥1 NYHA class and (2) an increase in pVO_2 by ≥3.0 mL/kg/min and no worsening in NYHA class, was higher in the mavacamten group than in the placebo group for both criteria. The change from baseline in pVO_2 at Week 30 (mean ± standard deviation) was −0.05 ± 3.017 mL/kg/min in the placebo group and 1.40 ± 3.115 mL/kg/min in the mavacamten group. Given that an increase in pVO_2 by 1.0 mL/kg/min is reported to correlate with reduced mortality risk in patients with HCM (*Circ Heart Fail.* 2020;13:e007230), and with reduced risks of death and hospitalization in patients with heart failure (*Circ Heart Fail.* 2015;8:1022-31; *Am Heart J.* 2015;169:684-92 e1), the results of this study are considered to demonstrate the beneficial effect of the drug on pVO_2. According to the JCS 2018 Guideline on Diagnosis and Treatment of Cardiomyopathies, an LVOT gradient of ≥50 mmHg is one of the criteria for considering SRT. Among patients with a post-exercise LVOT gradient of ≥50 mmHg at baseline in Study MYK-461-005, the proportion of those whose post-exercise LVOT pressure gradient dropped below 50 mmHg at Week 30 was 20.8% in the placebo group and 74.3% in the mavacamten group. These findings suggest that mavacamten treatment produced a meaningful improvement in the pathophysiology of oHCM by mavacamten treatment.

Based on the above, the efficacy of mavacamten was demonstrated in the patient population of Study MYK-461-005.

(2) Efficacy of mavacamten in Japanese patients

The change from baseline in post-exercise LVOT gradient at Week 30, the primary endpoint of Study CV027004, met the prespecified criteria for assessment of similarity to Study MYK-461-005. While

change from baseline in post-exercise LVOT gradient in Study CV027004 was greater than that in the mavacamten group in Study MYK-461-005, the difference between the studies was considered attributable to the difference in baseline resting or post-exercise LVOT gradient or VLVOT gradient.

The change from baseline in pVO_2 at Week 30 in Study CV027004 (mean ± standard deviation) was 0.83 ± 2.540 mL/kg/min, smaller than that in the mavacamten group in Study MYK-461-005, 1.40 ± 3.115 mL/kg/min. The higher percentage of subjects using β-blockers at baseline in Study CV027004 than that in Study MYK-461-005 (Table 44) might have resulted in the difference in pVO_2 between the studies; however, the efficacy of mavacamten was demonstrated regardless of concomitant β-blocker use. Thus, the efficacy of mavacamten in Study CV027004 was also demonstrated by the pVO_2 results, in a similar manner as Study MYK-461-005.

Based on the above, the efficacy of mavacamten can also be expected in Japanese patients with oHCM.

PMDA's view:
The results for Study MYK-461-005 demonstrated the superiority of mavacamten over placebo in terms of the proportion of subjects achieving clinical response, the primary endpoint. In addition, based on the results of each component included in the criteria for clinical response, and change from baseline in pVO_2 in each group, mavacamten also improved exercise capacity and clinical symptoms, which is clinically meaningful for patients with oHCM.

In Study CV027004, the pre-specified criterion for determining similarity to Study MYK-461-005 was met with respect to the change from baseline in post-exercise LVOT gradient, the primary endpoint. The applicant explained that differences in demographics and baseline characteristics and concomitant drug use may have contributed to differences in the magnitude of change from baseline in both post-exercise LVOT gradient and pVO_2 that were observed between the studies, and the explanation is generally acceptable. Taken together, given that post-exercise LVOT gradient decreased in Study CV027004, consistent with the results in Study MYK-461-005, and data, albeit limited, suggested improvement in pVO_2, the improvement in exercise capacity and clinical symptoms demonstrated in Study MYK-461-005 can also be expected in Japanese patients with oHCM treated with mavacamten.

7.R.3.3 Demographics and baseline characteristics affecting efficacy

The applicant's explanation about the demographics and baseline characteristics affecting the efficacy of mavacamten:
Subgroup analyses of the primary endpoint of Study MYK-461-005, the proportion of subjects achieving clinical response, were performed based on a range of demographics and baseline characteristics. In all of the subgroups based on age, sex, body weight, baseline LVEF and CYP2C19 genotype, the proportion of subjects achieving clinical response was higher in the mavacamten group than in the placebo group, and the results were generally consistent with those of the overall population. Conversely, subgroup analyses by β-blocker use, calcium channel blocker use, prior SRT history, history of ICD or pacemaker implantation showed

differences in the endpoint, change from baseline in pVO_2, and change from baseline in post-exercise LVOT gradient (Table 45). Therefore, the effects on the efficacy of mavacamten were evaluated by agents that are expected to be co-administered to patients with oHCM, prior SRT history, history of ICD or pacemaker implantation. The results are presented in the following subsections (1) through (4).

Table 45. Results for the primary endpoint and key secondary endpoints by β-blocker use, calcium channel blocker use, prior SRT history, history of ICD or pacemaker implantation in Study MYK-461-005 (ITT population)

β-blocker						
	Yes			No		
	Placebo (N = 95)	Mavacamten (N = 94)	Difference from placebo[c]	Placebo (N = 33)	Mavacamten (N = 29)	Difference from placebo[c]
Proportion of responders[a]	21.1 (95)	29.8 (94)	8.73 [−3.622, 21.091]	6.1 (33)	58.6 (29)	52.56 [32.873, 72.247]
Change from baseline in pVO_2 at Week 30 (mL/kg/min)[b]	0.09 ± 3.205 (94)	1.13 ± 3.107 (91)	1.04 [0.122, 1.954]	−0.46 ± 2.355 (31)	2.23 ± 3.042 (29)	2.69 [1.288, 4.090]
Change from baseline in LVOT gradient at Week 30 (mmHg)[b]	−9.12 ± 30.567 (92)	−47.05 ± 37.910 (89)	−37.94 [−48.021, −27.851]	−14.41 ± 26.436 (30)	−47.86 ± 47.932 (28)	−33.45 [−53.625, −13.266]
Calcium channel blocker						
	Yes			No		
	Placebo (N = 17)	Mavacamten (N = 25)	Difference from placebo[c]	Placebo (N = 111)	Mavacamten (N = 98)	Difference from placebo[c]
Proportion of responders[a]	11.8 (17)	52.0 (25)	40.24 [15.374, 65.097]	18.0 (111)	32.7 (98)	14.64 [2.917, 26.353]
Change from baseline in pVO_2 at Week 30 (mL/kg/min)[b]	−0.09 ± 1.618 (16)	2.19 ± 3.280 (25)	2.28 [0.487, 4.064]	−0.04 ± 3.176 (109)	1.19 ± 3.054 (95)	1.23 [0.362, 2.089]
Change from baseline in LVOT gradient at Week 30 (mmHg)[b]	−17.19 ± 23.562 (16)	−44.51 ± 49.586 (24)	−27.33 [−54.324, −0.329]	−9.40 ± 30.356 (106)	−47.95 ± 37.841 (93)	−38.55 [−48.096, −29.011]
Prior SRT history						
	Yes			No		
	Placebo (N = 8)	Mavacamten (N = 11)	Difference from placebo[c]	Placebo (N = 120)	Mavacamten (N = 112)	Difference from placebo[c]
Proportion of responders[a]	12.5 (8)	36.4 (11)	23.86 [−12.651, 60.378]	17.5 (120)	36.6 (112)	19.11 [7.891, 30.324]
Change from baseline in pVO_2 at Week 30 (mL/kg/min)[b]	1.05 ± 5.164 (8)	1.84 ± 3.342 (11)	0.79 [−3.321, 4.893]	−0.12 ± 2.835 (117)	1.35 ± 3.104 (109)	1.47 [0.693, 2.249]
Change from baseline in post-exercise LVOT gradient at Week 30 (mmHg)[b]	−6.48 ± 9.094 (8)	−50.01 ± 57.552 (11)	−43.53 [−87.179, 0.120]	−10.70 ± 30.514 (114)	−46.96 ± 38.458 (106)	−36.26 [−45.457, −27.071]
ICD or pacemaker implantation history						
	Yes			No		
	Placebo (N = 29)	Mavacamten (N = 27)	Difference from placebo[c]	Placebo (N = 99)	Mavacamten (N = 96)	Difference from placebo[c]
Proportion of responders[a]	34.5 (29)	40.7 (27)	6.26 [−19.095, 31.611]	12.1 (99)	35.4 (96)	23.30 [11.769, 34.822]
Change from baseline in pVO_2 at Week 30 (mL/kg/min)[b]	1.88 ± 3.202 (29)	2.07 ± 3.455 (27)	0.19 [−1.592, 1.975]	−0.63 ± 2.717 (96)	1.20 ± 3.000 (93)	1.83 [1.005, 2.647]
Change from baseline in LVOT gradient at Week 30 (mmHg)[b]	−3.51 ± 22.993 (29)	−45.26 ± 35.398 (26)	−41.75 [−57.727, −25.764]	−12.57 ± 31.157 (93)	−47.82 ± 41.774 (91)	−35.24 [−45.945, −24.537]

a, percentage, % (n); b, mean ± standard deviation (number of subjects with nonmissing data at evaluation timepoint); c, mean [95% CI]

(1) Co-administration with β-blockers or calcium channel blockers

In Study MYK-461-005, 189 patients (75.3%) used β-blockers and 42 patients (16.7%) used calcium channel blockers. Simultaneous use of a β-blocker and a calcium channel blocker was prohibited.

In subjects who were using β-blockers, between-group difference in the proportion of responders and in the change from baseline in pVO_2 tended to be small compared with subjects who were not using β-blockers, while no clear differences in demographics and baseline characteristics, such as age, NYHA class, were noted between subjects who were and were not using β-blockers. There have been reports that pVO_2 tends to decrease in patients who were using β-blockers (*JCPT*. 2019;24:37-45, *JACC Heart Fail*. 2016;4:607-16). In the mavacamten group in this study, baseline pVO_2 was lower in subjects who were using β-blockers than in subjects who were not (20.3 mL/kg/min and 18.5 mL/kg/min, respectively). Therefore, the difference in the results between the groups seems to be attributable to β-blocker use. Given that the changes from baseline in post-exercise LVOT gradient in the mavacamten group are similar regardless of β-blocker use, the efficacy of mavacamten can also be expected in patients who are using β-blockers.

In subjects who were not using calcium channel blockers, between-group difference in the proportion of clinical responders and in the change from baseline in pVO_2 tended to be small compared with subjects who were using calcium channel blockers, while no clear differences were noted in demographics and baseline characteristics between subjects with and without calcium channel blocker use. Most of subjects who were not using calcium channel blockers were using β-blockers; therefore, the results for the primary endpoint and pVO_2 may have been affected by β-blockers. However, given that among subjects who were not using calcium channel blockers, change from baseline in pVO_2 in the mavacamten group tends to be large compared with the placebo group, and that post-exercise LVOT gradient decreased, the efficacy of mavacamten in patients who are using calcium channel blockers can also be expected.

(2) Co-administration with sodium channel blockers

While co-administration of sodium channel blockers was not allowed in Study MYK-461-005, the use of sodium channel blockers was allowed in Study MYK-461-017,[47)] in which 19.6% (22 of 112) of patients were using disopyramide in combination with mavacamten.

In the mavacamten group in Study MYK-461-017, the mean change from baseline in post-exercise LVOT gradient at Week 16 tended to be small in subjects who were using disopyramide compared to those who were not (−28.9 mmHg in disopyramide users, −42.2 mmHg in non-disopyramide users). In a PPK analysis using data including data from Study MYK-461-017, co-administration with disopyramide increased the CL/F of mavacamten by approximately 96%. Because of the small number of subjects who were using disopyramide, it remains unclear why the change from baseline in post-exercise LVOT gradient tended to decrease and the CL/F of mavacamten increased. However, given that the results for the primary endpoint, i.e., the proportion of subjects who met SRT eligibility criteria or who decided to proceed with SRT, did not differ

47) A foreign phase III study in patients with oHCM eligible for SRT [see Section 7.3.3].

significantly regardless of the status of disopyramide use, and that among subjects who were using disopyramide, post-exercise LVOT gradient and VLVOT gradient tended to improve in the mavacamten group compared to the placebo group, the efficacy of mavacamten can also be expected in patients who are using disopyramide.

Although there is no clinical trial data on co-administration with cibenzoline, another sodium channel blocker expected to be used in clinical settings in Japan, given that its mechanism of action is similar to that of disopyramide, the efficacy of mavacamten can also be expected in patients who are using cibenzoline.

(3) Prior SRT history

In Study MYK-461-005, 19 subjects (7.6%) had prior SRT history. In Study MYK-461-005, among subjects with prior SRT, between-group difference in the change from baseline in pVO_2 tended to be small compared to those with no prior SRT (1.47 mL/kg/min for subjects with no prior SRT and 0.79 mL/kg/min for those with prior SRT). No clear differences in demographics and baseline characteristics between subjects with and without prior SRT were noted. One of 8 subjects in the placebo group who had prior SRT had started receiving β-blocker approximately 1 month prior to screening, and pVO_2 improved remarkably, suggesting that the data from this subject may have affected the results of between-group difference in the change from baseline in pVO_2 in subjects with prior SRT. On the other hand, in subjects with prior SRT in Study MYK-461-005, changes from baseline in pVO_2, in post-exercise LVOT gradient, and in VLVOT gradient tended to be greater in the mavacamten group than in the placebo group. Give this findings, mavacamten can be expected to be effective in patients with prior SRT.

(4) History of ICD or pacemaker implantation

In Study MYK-461-005, 56 subjects (22.3%) had had an ICD or pacemaker implanted in the past. In Study MYK-461-005, the results for between-group differences in the primary endpoint and change from baseline in pVO_2 in subjects who had had an ICD/pacemaker implanted in the past tended to be small compared to those in subjects who had no history of ICD/pacemaker implantation. Among subjects who had had an ICD/pacemaker implanted in the past, β-blocker use was higher (83.9% in subjects who had had an ICD/pacemaker implanted, 72.8% in subjects with no history of ICD/pacemaker implantation). Taking into account the effect of β-blocker use on pVO_2 mentioned above, the difference in the percentage of subjects using β-blockers may have been contributed to the difference in the results of subjects with and without history of ICD/pacemaker implantation. One subject in the placebo group who had had an ICD/pacemaker implanted in the past showed a remarkable improvement in pVO_2, which may have skewed the results. When the data from this subject were excluded from those of subjects who had had an ICD/pacemaker implanted, the achievement of the primary endpoint was still higher in the mavacamten group than in the placebo group, with trends towards an increase in pVO_2, post-exercise LVOT gradient, and VLVOT gradient. Therefore, the efficacy of mavacamten can also be expected in patients who had had an ICD/pacemaker implanted in the past.

PMDA's view on discussions presented in (1) through (4):
Regarding the discussion in (1), based on the applicant's explanation, mavacamten can be expected to be effective in patients using β-blockers or calcium channel blockers. Given that the findings suggest that there are no new safety concerns in the β-blocker use subgroup or calcium channel blocker use subgroup, mavacamten can be administered to patients who are receiving a β-blocker or a calcium channel blocker.

Regarding the discussion in (2), cibenzoline is the sodium channel blocker expected to be used in clinical practice in Japan; however, no studies have evaluated the efficacy of mavacamten in combination with cibenzoline. The applicant explained that mavacamten is expected to be effective in patients using cibenzoline because the mechanism of action of cibenzoline is similar to that of disopyramide; however, this explanation cannot be justified. Conversely, no significant concerns about the efficacy or safety of mavacamten were identified when co-administered with disopyramide. Therefore, given that the dose of mavacamten can be adjusted based on monitoring by echocardiography, mavacamten can be co-administered with sodium channel blockers including cibenzoline.

Regarding (3), although the number of patients with prior SRT enrolled in clinical studies was small, given the applicant's explanation, the mechanism by which mavacamten improves LVOT obstruction by acting directly on cardiac myosin to reduce myocardial contractility, and the absence of any new safety concerns in patients with prior SRT, mavacamten can be administered to patients with prior SRT.

Regarding (4), based on the applicant's explanation, mavacamten can be expected to be effective in patients who have had an ICD or pacemaker implanted in the past. Since no new safety concerns were identified in the subgroup with a history of ICD or pacemaker implantation, mavacamten can be administered to patients regardless of history of ICD or pacemaker implantation.

7.R.4 Safety

Based on the results of discussions in the following sections as well as the efficacy of mavacamten presented in Section 7.R.3, PMDA concluded that mavacamten has acceptable safety in patients with oHCM.

7.R.4.1 Safety profile of mavacamten

The applicant's explanation about the incidence of adverse events in the clinical studies of mavacamten:
Table 46 summarizes the incidence of adverse events in the foreign phase III study (Study MYK-461-005), Japanese phase III study (Study CV027004), and All-Mava oHCM integrated analyses.[48)]

In Study MYK-461-005, one of the common adverse events with an incidence higher in the mavacamten group than in the placebo group was dizziness (14.1% in the placebo group and 23.6% in the mavacamten group),

[48)] Integrated analyses involving patients with oHCM who received at least 1 dose of mavacamten in Studies MYK-461-005, MYK-461-004, MYK-461-007, and MYK-461-008.

with all of the events being non-serious. No clear differences were noted in the safety profile of the mavacamten groups in Study CV027004 and Study MYK-461-005. The results of the All-Mava oHCM integrated analyses, integrated analyses from 4 studies including a long-term extension study, showed a trend towards a higher incidence of adverse events compared to the mavacamten group in Study MYK-461-005; however, this was considered attributable to the differences in the duration of mavacamten exposure. Serious adverse events in the All-Mava oHCM group were similar to those in the mavacamten group in Study MYK-461-005 in terms of the type and incidence of events. With the exception of 3 subjects who died due to cardiac disorders, the majority of the events resolved or were resolving during the study period. There were no clear differences in the incidence of adverse events leading to death between the All-Mava oHCM group and the mavacamten group of Study MYK-461-005. Therefore, the long-term safety of mavacamten is acceptable.

Table 46. Incidence of adverse events in Studies MYK-461-005, CV027004, and All-Mava oHCM integrated analyses (safety analysis set)

	MYK-461-005		CV027004 (N = 38)	All-Mava oHCM (N = 260)
	Placebo (N = 128)	Mavacamten (N = 123)		
All adverse events	81.3 (104)	87.8 (108)	63.2 (24)	92.3 (240)
Serious adverse events	9.4 (12)	11.4 (14)	7.9 (3)	19.6 (51)
Adverse events leading to death	0.8 (1)	0 (0)	0 (0)	1.2 (3)
Adverse events leading to study drug treatment discontinuation	0 (0)	1.6 (2)	0 (0)	5.0 (13)
Adverse events for which a causal relationship to the study drug could not be ruled out.	14.1 (18)	15.4 (19)	2.6 (1)	26.2 (68)

Incidence, % (n)

Based on the applicant's explanation, PMDA concluded that there were no safety concerns about mavacamten that could cause clinically significant problems, and there are no differences between Japanese and non-Japanese populations that could cause clinical problems. The following sections discuss issues such as the incidence of adverse events of special interest.

7.R.4.2 Systolic dysfunction and cardiac failure

The applicant's explanation about the incidence of systolic dysfunction and cardiac failure:

Mavacamten, which is a selective inhibitor of cardiac myosin, may cause systolic dysfunction and cardiac failure.

In the double-blind period of Study MYK-461-005, no events of LVEF ≤30% were reported, while LVEF <50% occurred in 7 subjects in the mavacamten group. Among these, treatment with mavacamten was resumed in 2 subjects after a temporary interruption, and no further adverse events occurred. One of the subjects was diagnosed as having ampulla cardiomyopathy, and mavacamten treatment was interrupted. However, treatment was resumed after the condition improved, and a causal relationship to mavacamten was ruled out. Treatment with mavacamten was discontinued in the remaining 4 subjects. The decreased LVEF was mild in all cases and no cases of concomitant cardiac failure were reported.

In the double-blind period of Study MYK-461-017, no events of LVEF ≤30% were reported. Although LVEF <50% occurred in 2 subjects in the mavacamten group, no particular symptoms developed, and treatment with mavacamten resumed following treatment interruption. During the long-term extension period of Study MYK-461-017, 2 subjects experienced an LVEF reduction to ≤30%. One of the subjects developed atrial fibrillation, followed by an LVEF reduction to ≤30%, and developed cardiac failure congestive, which then resolved after hospitalization for treatment. Atrial fibrillation and cardiac failure congestive were considered related to mavacamten. The other subject experienced an LVEF reduction to ≤30% at Week 56, resulting in mavacamten treatment discontinuation. Five days after the last dose, this patient died from sudden cardiac death, which was considered by the investigator to be related to mavacamten.

In Study CV027004, no events of LVEF ≤30% were reported. A mild LVEF reduction of <50% occurred in 1 subject, and administration of mavacamten resumed after interruption. The subject developed no adverse events.

In the All-Mava oHCM integrated analyses,[48)] no events of LVEF ≤30% were reported. Although an LVEF reduction of <50% occurred in 19 subjects, the LVEF reductions were all reversible. LVEF returned to ≥50% in patients whose LVEF was measured after interruption of mavacamten treatment. Eleven subjects experienced cardiac failure, 5 of which were classified as serious events. Of these, 4 subjects improved after discontinuation of mavacamten administration followed by appropriate treatment.[49)] The other subject developed serious atrial fibrillation and cardiac failure, and died due to serious cardiac arrest on Day 520. The investigator considered that the event of cardiac failure was not related to the study drug.

Based on the above discussions, the package insert will include a warning that cardiac failure due to systolic dysfunction is a serious adverse reaction; in addition, cautionary statements will be included in the package insert and other information materials to the following effect: Patients may develop cardiac failure due to systolic dysfunction; if any abnormality in laboratory findings suggestive of cardiac failure or any physical abnormalities are noted, immediately perform cardiac function assessment and consider dose interruption, treatment discontinuation of mavacamten, or other measures; and patients should be monitored by echocardiography on a regular basis. The incidence of cardiac failure will be assessed by post-marketing surveillance.

PMDA's view:

Based on the mechanism of action of mavacamten, as well as the occurrence of systolic dysfunction and cardiac failure observed in the clinical studies, there is a risk of such events occurring during treatment with mavacamten. Therefore, systolic dysfunction and cardiac failure must be included as clinically significant adverse reactions in the package insert to increase vigilance. After initiation of mavacamten, the cardiac function of patients should be assessed by echocardiography on a regular basis, and patients should

[49)] Of the 4 subjects who were recovering, 2 subjects developed serious cardiac failure as a result of unnecessary dose increases due to data input errors that occurred at the trial site.

be monitored closely for any physical findings and laboratory findings suggestive of cardiac failure. Post-marketing data on adverse events related to systolic dysfunction and cardiac failure should be gathered to investigate the incidence of events in clinical practice in Japan.

7.R.4.3 Cardiovascular events

The applicant's explanation about the incidence of cardiovascular events during treatment with mavacamten:
The incidence of cardiovascular events in the past clinical studies was investigated to evaluate the effects of mavacamten on survival outcome. Table 47 summarizes the incidence of cardiovascular-related events reported in Study MYK-461-005 and its extension study, MYK-461-007.[50)]

Table 47. Incidence of cardiovascular-related events in Studies MYK-461-005 and MYK-461-007[50)]
(safety analysis set)

	MYK-461-005		MYK-461-007 (N = 231)
	Placebo (N = 128)	Mavacamten (N = 123)	
MACE-adjudicated	2.3 (3)	4.1 (5)[a]	3.5 (8)
Cardiovascular death	0.8 (1)	0 (0)	1.3 (3)
Stroke	0 (0)	0.8 (1)	0.4 (1)
Acute myocardial infarction	0.8 (1)	2.4 (3)	0 (0)
Heart failure-related hospitalization	0.8 (1)	2.4 (3)	2.2 (5)
Heart failure	0.8 (1)	2.4 (3)	2.2 (5)
Heart failure-related hospitalization	0.8 (1)	2.4 (3)	2.2 (5)
Emergency visit due to heart failure (non-hospitalization)	0 (0)	0 (0)	0 (0)
Atrial fibrillation	3.9 (5)	3.3 (4)	4.8 (11)
ICD therapy	0 (0)	0.8 (1)	0 (0)
Cardiovascular-related hospitalization	3.9 (5)	6.5 (8)	7.4 (17)

Incidence, % (n)
a, The incidence in the double-blind period (30 weeks) was 2.4% (3 subjects)

In Study MYK-461-005, the incidence of major adverse cardiovascular events (MACE)-adjudicated[51)] events and heart failure-related hospitalization[52)] tended to be higher in the mavacamten group than in the placebo group. However, 2 of the 3 subjects who were reported as being hospitalized for heart failure in the mavacamten group developed the events after the completion of mavacamten treatment during the follow-up period. At Week 30, the incidence of heart failure-related hospitalization was the same (0.8%) in both groups.

In Study MYK-461-007, the annual incidence rates (per 100-patient years) of MACE-adjudicated[51)] events and heart failure-related hospitalization[52)] were 2.47 and 5.32, respectively—lower than those in the mavacamten group in Study MYK-461-005 (5.75 and 9.29), and similar to those in the placebo group in Study MYK-461-005 (3.27 and 5.51). These results indicate that extending the duration of exposure to mavacamten showed no trends towards an increase of MACE-adjudicated events.

50) The oHCM patient group
51) Cardiovascular death, stroke, acute myocardial infarction, and heart failure-related hospitalization adjudicated by the Clinical Event Adjudication Committee.
52) Events adjudicated by the Clinical Event Adjudication Committee.

In Study CV027004, there were no events identified as MACE, and no heart failure-related hospitalization occurred.

Based on the above, currently available clinical study results indicate no risks of cardiovascular events associated with mavacamten; therefore, no particular cautionary statements will be necessary.

PMDA's view:
Although the limited number of cardiovascular-related events reported in the clinical studies of mavacamten precludes stringent evaluation of the risk, there is currently no data to suggest that mavacamten poses a clear risk of worsening survival outcomes.

7.R.4.4 Risk of QT prolongation

In non-clinical studies of mavacamten as well as a clinical study in healthy subjects (Study MYK-461-003[22)]), QTc prolongation occurred [see Section 3.R.2]. PMDA asked the applicant to explain the risk of QT prolongation in patients with oHCM based on the results from clinical studies conducted in patients with oHCM:

The applicant's explanation:
The relationship between plasma mavacamten concentrations from the data of foreign clinical studies of mavacamten and ΔΔQTcF was investigated. No QTcF interval prolongation associated with increased plasma mavacamten concentrations occurred [see Section 6.2.7].

In the mavacamten groups in clinical studies conducted in and outside Japan, adverse events of electrocardiogram QT prolonged occurred in 2 subjects in Study MYK-461-007[50)] and 1 subject in Study MYK-461-017, with all events being mild in severity. In Studies MYK-461-005 and CV027004, no electrocardiogram QT prolonged occurred.

Based on the above, no cautionary statements regarding QT prolongation are necessary because no QT prolongation that could cause clinical problems occurred in the clinical studies of mavacamten.

PMDA concluded that current data indicate no risk of QT prolongation associated with mavacamten treatment.

7.R.5 Intended patient population and indication of mavacamten

The applicant's explanation about the intended patient population and indication of mavacamten:
The results of Study MYK-461-005, which was conducted in patients with symptomatic oHCM, demonstrated the clinical usefulness of mavacamten. The results of Study CV027004, which was conducted in Japanese patients with oHCM, demonstrated the efficacy of mavacamten and acceptable safety.

Efficacy and safety by severity of cardiac failure were analyzed. Table 48 shows the proportion of subjects achieving clinical response (for Study MYK-461-005 only) at Week 30 and the change from baseline in both pVO_2 and post-exercise LVOT gradient by baseline NYHA functional class in Studies MYK-461-005 and CV027004. In both baseline NYHA II and III subgroups, the results tended to be more favorable in the mavacamten group than in the placebo group. The incidence of adverse events in the NYHA II or III subgroup of the mavacamten group in Study MYK-461-005 was consistent with that in the corresponding subgroup in Study CV027004.

Patients classified in NYHA class I or IV were not eligible for enrollment in Studies MYK-461-005 and CV027004, and the use of mavacamten in this patient population is considered as follows.

Patients in NYHA class I generally experience no subjective symptoms during ordinary daily activities, and are therefore not considered eligible for treatment with mavacamten. They are not included in the intended patient population of mavacamten. The “Precautions Concerning Indication” section of the package insert will include a cautionary statement to the effect that mavacamten is indicated for use in patients with symptomatic oHCM only.

One patient in NYHA class IV was enrolled in Study MYK-461-017. Resting LVOT gradient and VLVOT gradient decreased in this patient at Week 8. Although there was an improvement in NYHA class at Week 16, mavacamten treatment was interrupted because LVEF decreased to 43%. Treatment resumed approximately 2 weeks later at a dose reduced by 1 level. Following resumption, the VLVOT gradient remained comparable to the baseline level and the improvement in NYHA class was maintained. The subject developed no adverse events, except for decreases in LVEF and therefore mavacamten was considered to have acceptable safety. Of patients who had NYHA class II or III at baseline, NYHA class worsened to class IV during the study in 2 subjects in Study MYK-461-005 and 1 subject in Study MYK-461-017. In the 2 subjects in Study MYK-461-005, neither of these subjects developed serious adverse events for which a causal relationship to the study drug could not be ruled out. It was decided that the subject in Study MYK-461-017 would undergo SRT because of exacerbation of fatigue, breathlessness, and palpitations that developed within 1 week from the start of treatment, and these adverse events were considered attributable to worsening of the underlying disease. Since the pathophysiology of oHCM is the same regardless of NYHA functional class, the effectiveness of mavacamten in patients in NYHA class IV is expected to be comparable to that in patients in NYHA II or III. In addition, although the number of patients evaluated was small, no safety concerns were raised when mavacamten was administered to patients in NYHA class IV in the clinical studies. Therefore, patients in NYHA class IV can also be included in the intended patient population.

Table 48. Proportion of subjects achieving clinical response at Week 30 and the change from baseline in both pVO_2 and post-exercise LVOT gradient by baseline NYHA functional class in Studies MYK-461-005 and CV027004 (ITT population)

	MYK-461-005						CV027004	
	Class II			Class III				
	Placebo (N = 95)	Mavacamten (N = 88)	Difference from placebo [95% CI]	Placebo (N = 33)	Mavacamten (N = 35)	Difference from placebo [95% CI]	Class II (N = 33)	Class III (N = 5)
Proportion of clinical responders[a]	16.8 (95)	33.0 (88)	16.1 [3.74, 28.49]	18.2 (33)	45.7 (35)	27.5 [6.42, 48.64]	—	—
Change from baseline in pVO_2[b] (mL/kg/min)	0.05 ± 3.050 (93)	1.55 ± 3.085 (85)	1.50 [0.596, 2.413]	−0.31 ± 2.951 (32)	1.02 ± 3.200 (35)	1.33 [−0.177, 2.836]	0.72 ± 2.715 (13)	1.60 ± 0.707 (2)
Change from baseline in post-exercise LVOT gradient[b] (mmHg)	−10.25 ± 31.66 (90)	−48.67 ± 39.29 (82)	−38.42 [−49.117, −27.718]	−10.89 ± 23.20 (32)	−43.91 ± 43.02 (35)	−33.02 [−50.115, −15.926]	−62.85 ± 29.67 (30)	−47.75 ± 42.88 (5)

—, not applicable
a, percentage, % (n)
b, mean ± standard deviation (N)

Based on the above, “obstructive hypertrophic cardiomyopathy” was selected as the proposed indication of mavacamten.

PMDA’s view:
Based on the applicant’s explanation, and given that pharmacological therapy for oHCM is administered to patients with symptomatic oHCM (JCS 2018 Guideline on Diagnosis and Treatment of Cardiomyopathies), it is appropriate to include patients in NYHA class II and III in the intended patient population and not to include patients in NYHA class I. The package insert should state that patients in NYHA class II and III were eligible for enrollment in Studies MYK-461-005 and CV027004, and include a cautionary statement to the effect that mavacamten is intended to treat patients with symptomatic oHCM.

Although clinical trial experience with patients in NYHA class IV are extremely limited, given the limited treatment options for oHCM in addition to the factors below, such patients can be included in the intended patient population, while advising caution that the efficacy and safety of mavacamten have not been established in patients in NYHA class IV.

- The pathophysiology of oHCM is fundamentally the same regardless of the NYHA functional class, and based on the mechanism of action of mavacamten, similar efficacy can be expected in patients in NYHA class IV as in patients in NYHA II or III.
- No safety concerns were identified in patients with NYHA class IV in Studies MYK-461-005 and MYK-461-017 within the verifiable range.
- The safety of patients with NYHA class IV can be assured by monitoring by echocardiography.

Based on the above discussions and the applicant’s explanation, “obstructive hypertrophic cardiomyopathy” is acceptable as the indication of mavacamten. However, given that the majority of patients enrolled in clinical studies conducted in and outside Japan had received prior therapy with conventional oHCM drugs (β-blockers,

calcium channel blockers, sodium channel blockers), and that mavacamten carries the risk of systolic dysfunction that can lead to severe outcomes, the following cautionary statements should be made to the effect: whether a patient is eligible for the treatment should be decided only after gaining a thorough understanding of the demographics and baseline characteristics of patients (e.g., prior treatment and left ventricular ejection fraction) enrolled in the clinical studies; and whether treatment is necessary for a patient should be determined using the Guideline on Diagnosis and Treatment of Cardiomyopathies of Japan as a reference.

Based on the above discussion, the "Indication" and "Precautions Concerning Indication" sections should be as shown below.

Indication

Obstructive hypertrophic cardiomyopathy

Precautions Concerning Indication

- Mavacamten should be administered to patients with symptomatic obstructive hypertrophic cardiomyopathy.
- Whether a patient is eligible for the treatment should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the demographics and baseline characteristics of patients (e.g., prior treatment and left ventricular ejection fraction) enrolled in the clinical studies using the latest treatment practice guidelines as a reference.
- The efficacy and safety of mavacamten in patients with NYHA functional class IV have not been established.

7.R.6 Dosage and administration

Based on the discussions in Sections 7.R.6.1 through 7.R.6.4, PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be as shown below.

Dosage and Administration

The usual adult starting dosage is 2.5 mg of mavacamten orally once daily. The dosage can be increased or decreased according to the patient's condition. The maximum dose is 15 mg once daily.

Precautions Concerning Dosage and Administration

- Prior to starting treatment with mavacamten, left ventricular ejection fraction (LVEF) should be assessed by echocardiography. Mavacamten should not be initiated in patients with LVEF <55%.
- The starting dose should be 2.5 mg once daily. Dose adjustment should be performed in accordance with the table below. The dose should be increased or decreased by 1 level at a time. The minimum dosage should be 1 mg once daily and the maximum dosage should be 15 mg once daily.

Level	1	2	3	4	5
Dose	1 mg	2.5 mg	5 mg	10 mg	15 mg

- At Week 4, left ventricular outflow tract (LVOT) gradient after Valsalva maneuver and LVEF should be assessed by echocardiography, and whether to decrease the dose by 1 level or maintain the same dose level should be determined based on the dose adjustment criteria shown below.
- From Week 12 onwards, Valsalva LVOT gradient and LVEF should be assessed by echocardiography at least every 12 weeks, and whether to increase the dose by 1 level or maintain the same dose level should be determined based on the dose adjustment criteria shown below. The dose should be up-titrated at an interval of at least 12 weeks. After any dose increase, LVEF should be assessed by echocardiography 4 weeks later: the increased dose level should be maintained unless the patient has LVEF <50%. If it is determined that the maintenance dose has been achieved (i.e., Valsalva LVOT gradient <30 mmHg and LVEF ≥55% in 2 consecutive assessments by echocardiography every 12 weeks), the interval of echocardiography may be extended by up to 24 weeks.

Dose adjustment criteria

	Echocardiography	Dose adjustment
4 weeks after the start of treatment	Valsalva LVOT gradient <20 mmHg and LVEF ≥50%	Decrease the dose by 1 level
	Valsalva LVOT gradient ≥20 mmHg and LVEF ≥50%	Maintain the same dose level
12 weeks after the start of treatment and later	Valsalva LVOT gradient ≥30 mmHg and LVEF ≥55%	Increase the dose by 1 level
	LVEF ≥50% and <55%, regardless of Valsalva LVOT gradient	Maintain the same dose level
	Valsalva LVOT gradient <30 mmHg and LVEF ≥55%	

- If LVEF <50% after starting treatment, mavacamten should be interrupted or discontinued in accordance with the criteria below.

Criteria for dose interruption or treatment discontinuation

Criteria for dose interruption	If LVEF <50%, interrupt doses for at least 4 weeks until LVEF ≥50%. After LVEF ≥50%, resume treatment at a dose reduced by 1 level from the interrupted dose level. If interrupted while receiving 1 mg, resume treatment at 1 mg. Assess LVEF at 4 weeks and 12 weeks after restarting mavacamten.
Criteria for discontinuation	If the dose was interrupted because LVEF <50% while receiving 1 mg, and if LVEF dropped <50% at 4 weeks after restarting mavacamten at 1 mg, permanently discontinue mavacamten treatment.

- When initiating or increasing the dose of a strong or moderate CYP2C19 inhibitor, or a moderate or weak CYP3A4 inhibitor while on treatment with mavacamten, the dose should be decreased by 1 level (or interrupt the dose if receiving 1 mg), and LVEF should be assessed 4 weeks later.
- When discontinuing or decreasing the dose of a strong or moderate CYP2C19 inducer, or a strong, moderate, or weak CYP3A4 inducer while receiving mavacamten, the dose should be decreased by 1 level (or interrupt the dose if receiving 1 mg), and LVEF should be assessed 4 weeks later.
- If the patient does not respond to treatment with mavacamten at the maximum tolerated dose for 6 months, discontinuation of the treatment should be considered.

7.R.6.1 Rationales for the selection of dosage regimens for Studies MYK-461-005 and CV027004

The applicant's explanation about the rationales for selection of the dosage regimens for the foreign phase III study (Study MYK-461-005) and the Japanese phase III study (Study CV027004):

(1) Dosage regimen of Study MYK-461-005

In Study MYK-461-004 (phase II study), at plasma mavacamten trough concentrations of 350 to 700 ng/mL, LVEF was maintained in the normal range (50% to 70%) and LVOT gradient and other parameters tended to improve. Conversely, at plasma mavacamten trough concentrations ≥1000 ng/mL, LVEF fell below the normal range, and N-terminal pro brain natriuretic peptide (NT-proBNP) tended to increase; therefore, plasma mavacamten trough concentrations should be maintained in the range of 350 to 700 ng/mL.

To determine the dosage regimen for Study MYK-461-005, a PK model, which was constructed using data from clinical studies, was used for the analysis. When mavacamten 5 mg is administered once daily to patients with oHCM for 30 weeks, 2.9% of the patients were predicted to have plasma mavacamten trough concentrations of >700 ng/mL by Week 30, and in 85% of the patients, the plasma mavacamten trough concentration was predicted to be <350 ng/mL by Week 30. Accordingly, the applicant considered that the dose of mavacamten should be increased as necessary depending on the patient's condition. After defining the dose adjustment criteria, plasma mavacamten concentrations following administration of mavacamten to patients with oHCM for 30 weeks were analyzed based on the above model. The model predicted that the plasma mavacamten trough concentrations at Week 30 would be within the range from 350 to 700 ng/mL in 85% of patients; therefore, the applicant decided to use these dose adjustment criteria in Study MYK-461-005.

The applicant decided that dose adjustments were to be made based on not only the plasma mavacamten trough concentrations but also LVEF (from the safety perspective) and VLVOT gradient (from the efficacy perspective). A conservative threshold of LVEF 50% was selected considering the risk of cardiac failure, while 30 mmHg was set as the threshold for VLVOT gradient referencing the diagnostic criteria for oHCM.

(2) Dosage regimen of Study CV027004

To determine the dosage regimen for Study CV027004, simulations were performed using a PPK/E-R model, which had been constructed using data from clinical studies. The effects on LVEF and VLVOT gradient were analyzed for the following cases: when the same dosage regimen as that of Study MYK-461-005 was applied to a virtual non-Japanese population modeled using the demographics and baseline characteristics of patients in Study MYK-461-005 (A in Figure 1); and when mavacamten was administered under 4 different dosage regimens to a virtual Japanese population in which CYP2C19 phenotype, body weight, and other factors were taken into account (B to E of Figure 1).

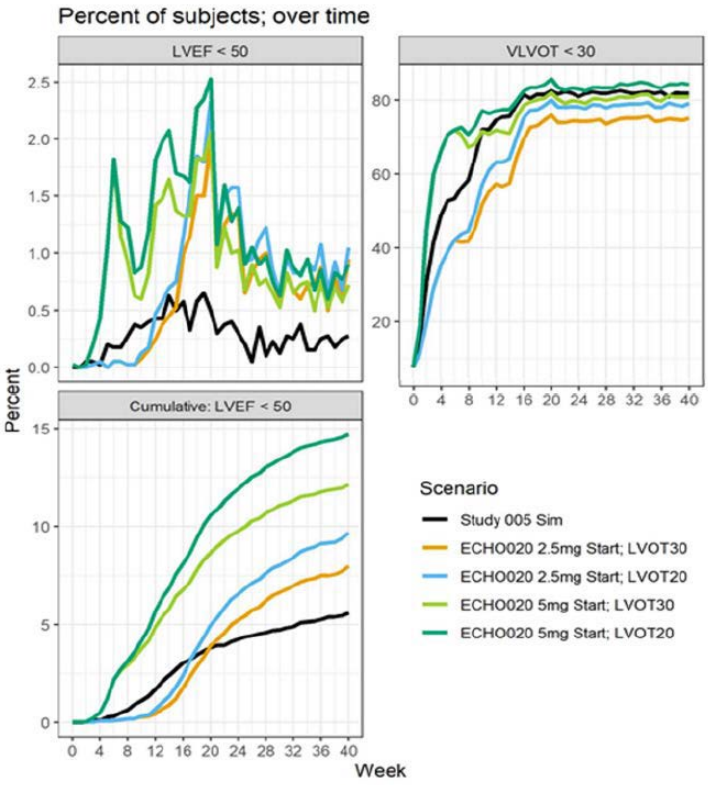

Figure 1. The LVEF and VLVOT gradient over time following administration of mavacamten

Top left, the percentage of patients with LVEF <50%
Bottom left, cumulative percentage of patients with LVEF <50%
Top right, the percentage of patients with VLVOT gradient <30 mmHg

A Black line: in the virtual non-Japanese population, mavacamten was administered under the same dosage regimen as that used in Study MYK-461-005 [see Section 7.3.1]
B Orange line: in the virtual Japanese population, mavacamten was initiated at a starting dose of 2.5 mg, under a dosage regimen in which the dose was to be decreased if VLVOT gradient <30 mmHg at Week 4
C Light blue line: in the virtual Japanese population, mavacamten was initiated at a starting dose of 2.5 mg, under a dosage regimen in which the dose was to be decreased if VLVOT gradient <20 mmHg at Week 4
D Light green line: in the virtual Japanese population, mavacamten was initiated at a starting dose of 5 mg, under a dosage regimen in which the dose was to be decreased if VLVOT gradient <30 mmHg at Week 4
E Green line: in the virtual Japanese population, mavacamten was initiated at a starting dose of 5 mg, under a dosage regimen in which the dose was to be decreased if VLVOT gradient <20 mmHg at Week 4

The above simulations showed that in the virtual Japanese population, the percentage of patients who would have a VLVOT gradient of <30 mmHg was smaller at a starting dose of 2.5 mg, compared to that at a starting dose of 5 mg. Conversely, the cumulative percentage of patients who would have an LVEF of <50% was lower at a starting dose of 2.5 mg, compared to that at a starting dose of 5 mg, which did not differ markedly from the scenario in which mavacamten was administered to the virtual non-Japanese population under the same dosage regimen as that used in Study MYK-461-005. In addition, the higher percentage of CYP2C19 PMs and lower body weight in Japanese patients than in non-Japanese patients may lead to an increase in mavacamten exposure. Accordingly, a starting dose of 2.5 mg was selected for Study CV027004.

In the virtual Japanese population, the percentage of patients whose VLVOT gradient decreased to <30 mmHg was similar regardless of whether the dose was reduced based on VLVOT gradient <20 mmHg or <30 mmHg

at Week 4. Accordingly, the protocol of Study CV027004 specified a dose reduction at Week 4 if the VLVOT gradient <30 mmHg.

Furthermore, to allow the treatment to be resumed in patients who met the criteria for dose interruption after starting mavacamten treatment at 2.5 mg, the minimum dose of 1 mg was selected in Study CV027004. Given that treatment with mavacamten is initiated at a lower dose level and eligibility for dose escalation is determined according to the patient's condition, the dose of 15 mg was selected as the maximum dose level in Study CV027004, the same as the dose level in Study MYK-461-005.

PMDA's view:
The applicant's approach to the dosage regimen used in Study MYK-461-005 was decided with the intention to maintain mavacamten exposure within a specified range. Taking into account the results of Study MYK-461-004, the dose was to be adjusted based on PK, LVEF, and VLVOT gradient. This approach is generally justified because (i) it has been reported that a relationship exists between LVOT gradient and the survival outcome of patients with oHCM, although LVOT gradient is not an indicator that directly reflects the clinical efficacy of mavacamten; and (ii) LVEF is an indicator for systolic dysfunction and cardiac failure. Based on the applicant's explanation and the results of Study MYK-461-004, the dosage regimen of Study MYK-461-005 is acceptable from a safety perspective. However, no dose adjustment was performed in the range from 2.5 to 15 mg in any studies that had been conducted before the start of Study MYK-461-005; therefore, the rationale for the dosage regimen, including the starting dose, maximum dose, minimum dose, and timing of dose adjustment, cannot be fully justified.

The applicant's approach to dosage regimen of Study CV027004 was that based on the dosage regimen of Study MYK-461-005, the dose was to be adjusted based on LVEF and VLVOT gradient, with the maximum dose being 15 mg. This approach is considered reasonable. Although the rationale for selecting the starting dose of 2.5 mg is not adequate, given the lack of sufficient data to evaluate the safety of administering the same starting dose as that of Study MYK-461-005 to Japanese patients, it is reasonable to select a starting dose level lower than that of Study MYK-461-005, taking into account the risk of systolic dysfunction, etc. associated with mavacamten in Japanese patients. However, the efficacy of mavacamten at 1 mg, the minimum dose level set by the applicant, was not evaluated in Study MYK-461-005. In addition, the efficacy and safety of mavacamten after dose adjustments made at different timing from that implemented in Study MYK-461-005 remain unknown. The appropriateness of the recommended dosage regimen, including dose adjustment criteria, should be discussed further, taking into account the efficacy and safety results from these studies.

7.R.6.2 Starting dose

The applicant's explanation about the starting dose of mavacamten:
Study MYK-461-005 was conducted using a starting dose of 5 mg, and the results demonstrated its efficacy and acceptable safety. Study CV027004 was conducted using a starting dose of 2.5 mg, and the results demonstrated its efficacy and safety comparable to those in Study MYK-461-005.

Although mavacamten exposure may increase in Japanese patients, the safety of mavacamten can be ensured even at a starting dose of 5 mg in Japanese patients if the dose is reduced at Weeks 4 and 8, where necessary, for the following reasons, among others: (i) the safety in patients who were CYP2C19 PMs was demonstrated in a foreign clinical study conducted with a starting dose of 5 mg, and (ii) the simulation results indicated that the risk of decreased LVEF in CYP2C19 PMs who initiated mavacamten at 2.5 mg is similar to that in those who started mavacamten at 5 mg. In addition, because a reduction in LVOT gradient needs to be achieved in patients with oHCM as early as possible, a starting dose of 5 mg should be selected for Japanese patients with oHCM.

Considering the reason for a decision to select a starting dose of 2.5 mg in Study CV027004, and the fact that no clinical study data in Japanese patients with oHCM treated with mavacamten at a starting dose of 5 mg are available, PMDA asked the applicant to explain as to whether the starting dose needs to be changed to 2.5 mg, taking also into account the following factors.

- Data, such as results of exposure-response (ER) analyses, suggest that increased mavacamten exposure will increase the risk of a reduction in LVEF.
- The results of clinical pharmacology studies showed an increase in mavacamten exposure in CYP2C19 PMs [see Section 6.2.4.2]. However, only a small number of patients who were CYP2C19 PMs were evaluated in foreign clinical studies. Thus, there is insufficient safety data from patients with CYP2C19 PM phenotype who initiated mavacamten at 5 mg.
- The clinical significance of achieving the target dose early is not clear. It is unknown whether the expected benefits of mavacamten outweigh its risks such as a reduction in LVEF associated with the use of the 5-mg starting dose.

Considering the safety concerns when a starting dose of 5 mg is selected for Japanese patients, the applicant explained its intention to change the starting dose to 2.5 mg. Because the results of Study CV027004 demonstrated the efficacy and safety of mavacamten which were comparable to those in Study MYK-461-005, PMDA accepted the applicant’s explanation.

7.R.6.3 Minimum dose

The applicant’s explanation about the minimum dose of mavacamten:

In Study MYK-461-005, the minimum dose was 2.5 mg. In Study CV027004, however, a minimum dose of 1 mg was established since 2.5 mg was selected as the starting dose. Table 49 shows change from baseline in post-exercise LVOT gradient at Week 30 by dose level in Study CV027004.

Table 49. Change from baseline in post-exercise LVOT gradient at Week 30 by dose level (ITT population)

	1 mg	2.5 mg	5 mg	10 mg	15 mg
Baseline (mmHg)	66.6 ± 17.7 (5)	120.0 ± 23.9 (6)	86.3 ± 26.1 (10)	78.1 ± 25.0 (10)	87.6 ± 18.8 (4)
Week 30 (mmHg)	20.3 ± 6.8 (5)	35.7 ± 32.2 (6)	29.7 ± 34.6 (10)	21.4 ± 18.5 (9)	26.0 ± 15.9 (4)
Change from baseline (mmHg) [95% CI]	−46.3 ± 14.2 [−64.0, −28.7] (5)	−84.3 ± 37.0 [−123.1, −45.5] (6)	−56.6 ± 39.5 [−84.8, −28.4] (10)	−61.2 ± 21.5 [−77.7, −44.7] (9)	−61.6 ± 29.7 [−108.9, −14.3] (4)

mean ± standard deviation (n)

Of the 11 subjects who received 1 mg in the study period, 5 subjects were receiving 1 mg at Week 30. In all 5 subjects, post-exercise LVOT gradient at Week 30 decreased from baseline, and was lower than 50 mmHg. At Week 30, of the 5 subjects, 4 had an improvement in NYHA class. Of the 4 subjects, 2 had an increase in pVO_2 as determined by CPET. The incidence of adverse events in 11 subjects receiving 1 mg did not substantially differ from that in the overall population of Study CV027004, and none of the 11 subjects experienced LVEF <50%. It should be noted that, among the 11 subjects who received the 1 mg dose, 3 subjects received this dose due to unnecessary dose reductions.[53)] However, in the remaining 8 subjects, dose adjustment was appropriately made according to the study design, and the administration of 1 mg was deemed necessary.

Based on the above, the applicant considers it reasonable to establish a minimum dose of 1 mg.

PMDA's view:

In Study MYK-461-005, which evaluated the efficacy of mavacamten, the dose of 1 mg was not used. In addition, only a small number of patients received 1 mg in Study CV027004. Therefore, although stringent evaluation is difficult, there were a certain number of patients who required dose reduction to 1 mg in Study CV027004. Consequently, all of the subjects who were receiving 1 mg at Week 30 had a reduction in post-exercise LVOT gradient, and NYHA class improved in many of the subjects. Given the higher percentage of CYP2C19 PMs and lower body weight in Japanese patients than in non-Japanese patients, a certain percentage of patients initiating mavacamten at 2.5 mg will require dose reduction in clinical practice. The results of Study CV027004 suggest a certain level of efficacy of mavacamten at 1 mg, and no safety concerns were indicated in patients receiving the 1 mg dose. Therefore, it is reasonable to offer the option to continue treatment at a reduced dose of 1 mg while advising that treatment discontinuation should be considered in patients who do not respond to the treatment.

7.R.6.4 Maximum dose and criteria for dose adjustment

The applicant's explanation about the maximum dose and the criteria for dose adjustment:

Table 50 summarizes first and second dose adjustments in Study CV027004, Study MYK-461-005, and for the

[53)] In all subjects enrolled in Study CV027004, from the start of the study up to [redacted], although the dose should have been adjusted according to VLVOT gradient, the dose was erroneously adjusted according to resting LVOT gradient. This was due to a programming error related to data transmission from the site of central review for echocardiography to the system vendor. Consequently, there were protocol deviations in which 4 subjects who required a dose increase did not receive it, and 3 subjects underwent unnecessarily dose reductions.

intended commercial dosage regimen.

Table 50. Dose adjustments in Study CV027004, Study MYK-461-005, and for the intended commercial dosage regimen

	CV027004	MYK-461-005	Intended commercial dosage regimen
Indicators for dose adjustment	LVEF, VLVOT gradient	Plasma mavacamten trough concentration, LVEF, VLVOT gradient	LVEF, VLVOT gradient
First dose adjustment	Week 6[a]	Week 6[a]	Week 4
Action for first adjustment	Decrease or maintain the dose level	Decrease or maintain the dose level	Decrease or maintain the dose level
Second dose adjustment	Week 8[b]	Week 8[b]	Week 12
Action for second adjustment	Increase or maintain the dose level	Increase, decrease, or maintain the dose level	Increase or maintain the dose level

a, LVEF and VLVOT gradient were measured at Week 4.
b, LVEF and VLVOT gradient were measured at Week 6.

(1) Maximum dose and indicators used for dose adjustment

In Study MYK-461-005, the dose of mavacamten was to be adjusted within the range from 2.5 to 15 mg according to the plasma mavacamten trough concentration, LVEF, and VLVOT gradient. At Week 26, the dose levels in the mavacamten group were 2.5 mg (6 subjects, 4.9%), 5 mg (60 subjects, 48.8%), 10 mg (40 subjects, 32.5%), and 15 mg (13 subjects, 10.6%).[36)] In 12 of the 13 subjects receiving 15 mg, the dose was maintained at 15 mg at and after Week 14. Based on the results of Study MYK-461-005, the dose was to be adjusted within the range from 2.5 to 15 mg according to the LVEF and VLVOT gradient in the extension study, MYK-461-007. The results revealed no new safety concerns. In Study CV027004, the dose was adjusted within the range from 1 to 15 mg according to the LVEF and VLVOT gradient. At Week 30, the dose levels were 1 mg (5 subjects, 13.2%), 2.5 mg (6 subjects, 15.8%), 5 mg (10 subjects, 26.3%), 10 mg (10 subjects, 26.3%), and 15 mg (4 subjects, 10.5%).[39)] In the 4 subjects receiving 15 mg, the dose was maintained at 15 mg at and after Week 30. In Study MYK-461-007 [see Section 7.3.4] and Study CV027004, plasma mavacamten trough concentration was not used as an indicator for dose adjustment. Th efficacy and acceptable safety of mavacamten demonstrated in Study CV027004 were not markedly different from those in Study MYK-461-005 and its long-term safety was demonstrated in Study MYK-461-007. Additionally, in the US and Europe, dose adjustments are made based solely on echocardiogram parameters, and no significant safety concerns have been identified in the post-marketing setting. Therefore, the applicant determined that no dose adjustment based on plasma mavacamten trough concentration would be necessary.

Based on the above, the applicant considers it appropriate to adjust the dose of mavacamten according to LVEF and VLVOT gradient with a maximum dose of 15 mg.

(2) Timing of dose adjustment

In Studies MYK-461-005 and CV027004, for the first dose adjustment after the initiation of treatment, whether to decrease or maintain the dose level was determined based on the results of echocardiographic assessment

and/or plasma drug concentration testing performed at Week 4. However, because the assessment/test results were to be reviewed by central laboratory, which required time for communication of the results to the trial site, the dose adjustment was to be implemented at Week 6. Conversely, echocardiography and dose adjustment can be performed at the same time in clinical settings; therefore, the applicant considered that the first dose adjustment after the initiation of treatment should be performed at Week 4.

In Studies MYK-461-005 and CV027004, the second dose adjustment was implemented at Week 8 based on the results of assessment/test performed at Week 6. Since the second and subsequent dose adjustments involve dose escalation or maintenance, dose adjustment should be determined after the steady-state plasma mavacamten concentration has been reached. Given that the elimination half-life is approximately 3 weeks in the CYP2C19 PM group, i.e., slow metabolizers of mavacamten, the steady-state plasma mavacamten concentration may not have been reached in Japanese patients with CYP2C19 PM phenotype at Week 8 (4 weeks after the first dose adjustment). Therefore, although the second dose adjustment was set at Week 8 in the dosage regimen approved in other countries, in Japan, the second dose adjustment should take place at Week 12 to determine whether to increase or maintain the dose level.

In Study MYK-461-007, the third and subsequent dose adjustments were implemented every 12 weeks after Week 12, and every 24 weeks after Week 156. Because the study demonstrated the long-term safety of mavacamten in the study, the applicant considered it appropriate to determine whether to increase or maintain the dose every 12 weeks based on LVEF and VLVOT gradient. If it is determined that the maintenance dose has been achieved, extending the dose adjustment interval up to 24 weeks was considered acceptable.

(3) Criteria for dose reduction, dose increase, interruption, and treatment resumption

In Studies MYK-461-007[50)] and CV027004, the criteria for dose reduction at the first dose adjustment were "LVEF ≥50% and VLVOT gradient ≤30 mmHg" and "LVEF ≥50% and VLVOT gradient <30 mmHg," respectively. In Study MYK-461-007,[50)] 108 subjects (47.0%) met the criteria at Week 4 and the dose was decreased. Of these, 92 subjects had a visit at Week 12, of which, 40 subjects met the criteria for dose increase. In Study CV027004, 8 subjects (21.1%) met the criteria at Week 4 and the dose was decreased. Of these, 3 subjects met the criteria for dose increase at Week 12 (VLVOT gradient ≥30 mmHg). As described above, there were some patients who had undergone dose decrease at Week 4 and required dose increase at Week 12. The results of simulations using PPK analysis and ER analysis on the data from Study MYK-461-005 suggest that if the criterion for dose reduction related to VLVOT gradient is changed to <20 mmHg, the risk of decreasing LVEF would be similar. Accordingly, in the US and Europe, mavacamten was approved with the dose reduction criteria of "LVEF ≥50% and VLVOT gradient <20 mmHg," and no safety concerns have been identified in the post-marketing clinical setting. Based on the above, the dose reduction criteria of "LVEF ≥50% and VLVOT gradient <20 mmHg" were also proposed in Japan.

The applicant considered that the dose increase criteria at and after Week 12 should be "LVEF ≥55% and

VLVOT gradient ≥30 mmHg," as with the criteria in Study CV027004. To address the risk of reduced LVEF, echocardiography will be performed 4 weeks after dose increase to assess if a reduction in LVEF has occurred.

The criterion for treatment interruption guided by echocardiogram was LVEF <50% in Studies MYK-461-005, MYK-461-007, and CV027004, and the results of these studies demonstrated the acceptable safety of mavacamten. Therefore, the applicant considered that LVEF <50% would be justified as the criterion for treatment interruption. After treatment interruption, echocardiography was performed at the visit 2 to 4 weeks after interruption in Studies MYK-461-005 and CV027004, and at the visit 4 to 6 weeks after interruption in Study MYK-461-007. If LVEF increased to ≥50%, treatment was to be resumed at a dose reduced by 1 level at 2 weeks after echocardiography. The results demonstrated acceptable safety. The applicant considered as follows: in clinical settings, if LVEF increased to ≥50% after interruption for at least 4 weeks, treatment should be resumed at a dose reduced by 1 level. When the criterion for interruption is met while on treatment at 1 mg, the minimum dose, if LVEF ≥50% is confirmed 4 weeks after interruption, treatment may be resumed at 1 mg, and if LVEF drops <50% again at 4 weeks after interruption, then mavacamten treatment should be discontinued.

PMDA's view on (1):

(1) In Studies MYK-461-005 and CV027004, dose adjustments were implemented in accordance with the protocols of each study. In both studies, patients received mavacamten at individually determined dose levels, including the maximum dose, and the results demonstrated the efficacy and acceptable safety of mavacamten. Study MYK-461-007 demonstrated the long-term safety of mavacamten. Although data from Japanese subjects who received 15 mg are limited, the maximum dose of 15 mg is justified, considering that the mavacamten dose adjustment is guided by echocardiogram to ensure the safety. From the efficacy and safety perspectives, it is appropriate to implement dose adjustments according to LVEF and VLVOT gradient, instead of implementing dose adjustment based on plasma mavacamten trough concentrations.

PMDA's view on (2):

Based on the timing of assessment/test for dose adjustment in Studies MYK-461-005 and CV027004, the first dose adjustment is set at Week 4 to determine whether to decrease or maintain the dose level. This decision is appropriate. For the second dose adjustment, the risk of reduced LVEF at Week 8 is unlikely to be high because (i) a starting dose of 2.5 mg has been selected in Japan, which is different from that in other countries, and (ii) the necessity of dose reduction may be assessed at Week 4 based on LVEF and VLVOT gradient. Therefore, it is acceptable for the applicant to specify that echocardiography is not mandatory at Week 8 in Japan, and that the second dose adjustment is set at Week 12 to determine whether to increase or maintain the dose level. Furthermore, it is appropriate that based on the results from Study MYK-461-007, the third and subsequent dose adjustments should be implemented every 12 weeks, and if it is determined that the maintenance dose has been achieved, the dose adjustment interval can be extended to 24 weeks.

PMDA's view on (3):
It is inferred that safety profiles do not significantly defer between the VLVOT gradient criteria of <20 mmHg and <30 mmHg; therefore, a VLVOT gradient of <20 mmHg is acceptable as the dose reduction criterion.

It is appropriate that the criterion similar to that for Study CV027004 can be used as the dose increase criterion at and after Week 12, and echocardiography will be performed 4 weeks after dose increase, based on the results from Study CV027004.

As for the treatment interruption criteria, the criteria for QT interval and plasma mavacamten trough concentrations were also specified in Studies MYK-461-005 and CV027004. However, the studies did not suggest no QT prolongation risk [see Section 7.R.4.4], and safety can be ensured with dose adjustment guided by echocardiogram. Therefore, no criteria other than LVEF are necessary. The risk of cardiac failure is not expected to be high at LVEF ≥50%, therefore, safety can be ensured by specifying treatment interruption at LVEF <50%.

7.R.7 Post-marketing investigations

The applicant's explanation about the post-marketing investigations of mavacamten:
The applicant has planned to conduct a specified use-results survey to evaluate the long-term safety and efficacy of mavacamten in clinical use (registration period of 2.5 years; observation period of 1 year; target sample size of 200 patients for safety analysis) by all-case surveillance. In this survey, cardiac failure is included in the safety specification. A planned sample size of 200 patients will allow detection of increase in risk at a 92% probability (at the one-sided significance level of 0.025) assuming that the incidence of cardiac failure in this survey increases by 3-fold (7.2%) compared to the incidence of cardiac failure in Study MYK-461-005 (2.4%, 3 of 123 patients).

PMDA's view:
Given the small number of Japanese patients who received mavacamten, and that the risk of cardiac failure associated with the use of mavacamten in Japanese patients is unclear, the applicant's plan to conduct a specified use-results survey to monitor adverse events in routine clinical practice is appropriate.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that mavacamten has efficacy in the treatment of obstructive hypertrophic cardiomyopathy, and that mavacamten has acceptable safety in view of its benefits. The drug substance is classified as a poisonous drug, and the drug product is classified as a powerful drug. It is clinically meaningful to make this new therapy available in clinical settings as a new treatment option for obstructive hypertrophic cardiomyopathy. PMDA considers that further discussions will be necessary for indication, dosage and administration, and post-marketing investigations.

PMDA has concluded that mavacamten may be approved if mavacamten is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 18, 2025

Product Submitted for Approval

Brand Name	Camzyos Capsules 1 mg Camzyos Capsules 2.5 mg Camzyos Capsules 5 mg
Non-proprietary Name	Mavacamten
Applicant	Bristol-Myers Squibb K.K.
Date of Application	July 17, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the efficacy, safety, dosage and administration, and post-marketing investigations presented in Review Report (1).

1.1 Clinical positioning, intended patient population, and indication of mavacamten

The expert advisors supported PMDA's conclusion: "it is meaningful to make mavacamten available to patients and healthcare professionals as a new option for the treatment of oHCM that responded inadequately to conventional pharmacotherapies" described in Section "7.R.1 Clinical positioning of mavacamten" in Review Report (1). The expert advisors also supported PMDA's conclusion that the indication should be "obstructive hypertrophic cardiomyopathy" based on the discussion in Section "7.R.5 Intended patient population and indication of mavacamten" in Review Report (1).

The expert advisor also made the following comments:

Mavacamten is recommended for the patient population equivalent to the population in which its efficacy was evaluated in Studies MYK-461-005 and CV027004. Mavacamten was co-administered with β-blockers or calcium channel blockers to the majority of patients enrolled in these studies. Therefore, in addition to the

status of prior treatment in the clinical studies, the use of these concomitant drugs should also be included in the package insert.

PMDA concluded that the "Indication" and "Precautions Concerning Indication" sections should be as follows, taking into account the comments from the expert advisors above.

Indication

Obstructive hypertrophic cardiomyopathy

Precautions Concerning Indication

- Mavacamten should be administered to patients with symptomatic obstructive hypertrophic cardiomyopathy.
- Whether a patient is eligible for treatment with mavacamten should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the demographics and baseline characteristics of patients (e.g., prior treatment, concomitant drugs, and left ventricular ejection fraction) enrolled in the clinical studies using the latest treatment practice guidelines as a reference.
- The efficacy and safety of mavacamten in patients in NYHA functional class IV have not been established.

1.2 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in Review Report (1), and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for mavacamten should include the safety specification presented in Table 51, and the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 52 and 53.

Table 51. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cardiac failure	None	• Long-term safety • Administration to patients with NYHA class IV
Efficacy specification		
None		

Table 52. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (long-term)	• Disseminate data gathered through early post-marketing phase vigilance • Organize and disseminate information materials for healthcare professionals (proper use guide) • Organize and disseminate information materials for patients (Camzyos capsules brochure for patients, patient safety card)

Table 53. Outline of specified use-results survey (all-case surveillance) (draft)

Objective	To evaluate the safety and efficacy of mavacamten in clinical settings
Survey method	All-case surveillance
Population	Patients with symptomatic obstructive hypertrophic cardiomyopathy
Observation period	52 weeks
Planned sample size	200 patients (for safety analysis)
Main survey items	Baseline characteristics of patients (e.g., time of diagnosis, prior treatment, medical history, comorbidities), treatment status (date of treatment initiation, daily dose, status of administration [continuing, dose interruption, dose change, discontinuation]), concomitant drugs, combined therapy, clinical laboratory test, incidence of adverse events

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The inspection confirmed that the study was generally conducted in compliance with the GCP. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding requiring corrective action. Although the issues had no significant impact on the overall assessment of the studies, the finding was notified to the Sponsor as a finding requiring correction.

Finding requiring corrective action

Sponsor

• Because of the defect in the study drug assignment system managed by the Sponsor, the correct dose of the study drug was not administered to some patients in accordance with the protocol.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below. Since the product is designated as an orphan drug, the re-examination period is 10 years.

Indication

Obstructive hypertrophic cardiomyopathy

Dosage and Administration

The usual adult starting dosage is 2.5 mg of mavacamten orally once daily. The dosage can be increased or decreased according to the patient's condition. The maximum dose is 15 mg once daily.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of patients have been accrued.

Appendix

List of Abbreviations

ABCC8	Adenosine triphosphate binding cassette subfamily C member 8
ACCF	American College of Cardiology Foundation
ADP	Adenosine diphosphate
AHA	American Heart Association
ALT	Alanine aminotransferase
APDx	Action potential duration at x% of repolarization
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration versus time curve
$AUC_{0\text{-last}}$	AUC from time zero to last quantifiable concentration
$AUC_{0\text{-x}}$	AUC from time zero to time x
$AUC_{0\text{-}\infty}$	AUC from time zero to infinity
BA	Bioavailability
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BSEP	Bile salt export pump
Ca	Calcium
Camzyos	Camzyos Capsules
Cav1.2/3.2	Voltage gated calcium channel alpha subunit 1.2/3.2
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
CL/F	Apparent total body clearance
C_{max}	Maximal drug plasma concentration
CMR	Cardiac magnetic resonance imaging
CO	Cardiac output
COVID-19	Coronavirus disease 2019
CPET	Cardiopulmonary exercise testing
CPP	Critical process parameter
CQA	Critical quality attribute
CTD	Common technical document
C_{trough}	Trough drug plasma concentration
$C_{trough,ss}$	Trough drug plasma concentration at steady state
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI Guidelines	Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information (PSEHB/PED Notification No. 0723-4, dated July 23, 2018)
DMEM/F12	Dulbecco's Modified Eagle Medium/Nutrient Mixture F12
DMSO	Dimethyl sulfoxide
dP/dt_{max}	Peak rate of left ventricular pressure increase during systole
dP/dt_{min}	Peak rate of left ventricular pressure decrease during diastole
DRX	Disordered relaxed
Ea	Arterial elastance
EDP	Left ventricular end diastolic pressure
EDV	Left ventricular end diastolic volume
Eed	End diastolic elastance
Ees	End systolic elastance

eGFR	Estimated glomerular filtration rate
EM	Extensive metabolizer
EMw	Electromechanical window
ESC	European Society of Cardiology
ESP	Left ventricular end systolic pressure
ESV	Left ventricular end systolic volume
F	Bioavailability
FDA	Food and Drug Administration
FOB	Functional observation battery
FS	Left ventricular fractional shortening
GC	Gas chromatography
HCM	Hypertrophic cardiomyopathy
HCN2/4	Hyperpolarization activated cyclic nucleotide gated potassium and sodium channel 2/4
HDPE	High-density polyethylene
HEK293 cells	Human embryonic kidney cells 293
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
hERG	Human ether-à-go-go related gene
hHVM	Human hypertrophied ventricular myocytes
HPLC	High performance liquid chromatography
HR	Heart rate
hVM	Human healthy ventricular myocytes
I_{CaL}	L type calcium channel current
IC_{50}	50% inhibitory concentration
ICD	Implantable cardioverter defibrillator
ICH Q1E Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q1E Guidelines: Evaluation for Stability Data (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
ICR	Institute of Cancer Research
I_{KATP}	Adenosine triphosphate dependent potassium current
IM	Intermediate metabolizer
I_{NaL}	Late sodium current
IPC	In process control
iPSC-CM	Cardiomyocytes derived from induced pluripotent stem cells
IR	Infrared absorption spectroscopy
I_{to}	Transient outward potassium current
ITT	Intention to treat
K_a	First-order absorption rate constant
KCCQ	Kansas City Cardiomyopathy Questionnaire
KChIP2.2	Potassium channel interacting protein 2.2
KCND2/3	Potassium voltage gated channel subfamily D member 2/3
KCNJ8/12	Potassium inwardly rectifying channel subfamily J member 8/12
K_I	Inhibitor concentration producing half-maximal inactivation
k_{inact}	Maximum inactivation rate constant
Kir2.1/3.1/3.4/6.2	Inward rectifier potassium channel 2.1/3.1/3.4/6.2
Kv1.5/4.3	Voltage gated potassium channel subunit 1.5/4.3
KvLQT1/minK	IKs producing slow voltage gated potassium channel subunit alpha/beta
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MACE	Major adverse cardiovascular events
MATE	Multidrug and toxin extrusion

Mavacamten	Mavacamten
MBP	Mean systemic pressure
MedDRA	Medical dictionary for regulatory activities terminology
mRNA	Messenger ribonucleic acid
MS	Mass spectrometry
Na	Sodium
NADPH	Nicotinamide adenine dinucleotide phosphate, reduced form
Nav1.5	Voltage gated sodium channel subunit alpha 5
nHCM	Non-obstructive hypertrophic cardiomyopathy
NM	Normal metabolizer
NMR	Nuclear magnetic resonance spectroscopy
NTCP	Sodium taurocholate co-transporting polypeptide
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
oHCM	Obstructive hypertrophic cardiomyopathy
P_{app}	Apparent permeability coefficient
$P_{app\ A\rightarrow B}$	P_{app} in the apical to the basolateral direction
$P_{app\ B\rightarrow A}$	P_{app} in the basolateral to the apical direction
pCa	$-\log[Ca^{2+}]$
[redacted]	[redacted]
PD	Pharmacodynamics
PEG	Polyethylene glycol
P-gp	P-glycoprotein
Pi	Inorganic phosphate
PK	Pharmacokinetics
PM	Poor metabolizer
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Pulse pressure
PPK	Population pharmacokinetics
PRSW	Preload recruitable stroke work
PT	Preferred term
PTP	Press through pack
PTSMA	Percutaneous Transluminal Septal Myocardial Ablation
[redacted]	[redacted]
pVO_2	Peak oxygen consumption
QD	Quaque die
Q/F	Apparent inter-compartment clearance
QTc	Rate corrected QT interval
QTcF	Fridericia-corrected QT Interval
QTcR	Corrected QT interval using the Ollerstam's formula
QT1000	QT interval duration at an RR interval of 1000 ms
RH	Relative humidity
RM	Rapid metabolizer
SBP	Systolic blood pressure
SD	Sprague-Dawley
SF	Shortening fraction
SRT	Septal reduction therapy

SRX	Super relaxed
SUR2A	Sulfonylurea receptor 2A
SV	Stroke volume
S1	Subfragment-1
tau	Time constant of left ventricular pressure decay
tau1/2	time constant of left ventricular pressure decay (half maximal)
Tg	Transgenic
TK	Toxicokinetics
t_{max}	Time to maximum plasma concentration
$t_{1/2}$	Elimination half-life
UM	Ultrarapid metabolizer
UV/VIS	Ultraviolet-visible spectrophotometry
VLVOT	Valsalva LVOT
V_{max}	Estimated maximal velocity of contractile element shortening
V_{ss}	Volume of distribution at steady state
V2/F	Apparent central volume of distribution
V3/F	Apparent peripheral volume of distribution