CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219083Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	December 12, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 219083
Product Name, Dosage Form, and Strength:	Myqorzo (aficamten) tablet, 5 mg, 10 mg, 15 mg, 20 mg
Applicant Name:	Cytokinetics, Incorporated
FDA Received Date:	December 09, 2025
TTT ID #:	2024-11043-3
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Cytokinetics, Incorporated submitted a response to the FDA's Request for Information regarding revising the container label dosage statement to reference prescribing information and revising temperature storage requirement.[a]

2 CONCLUSION

Cytokinetics has addressed FDA's container label concerns. We have no further recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Changi, M. Information Request for Myqorzo (NDA 219083). Silver Spring (MD): FDA, CDER, OSE (US);2025 Dec 05. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807f1ebf

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NICOLE F IVERSON
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 13, 2025

To: Maryam Changi, Regulatory Project Manager, Division of Cardiology and Nephrology (DCN)

Tzu-Yun McDowell, Clinical Reviewer, DCN

Michael Monteleone, Associate Director for Labeling, DCN

From: Tierra Butler, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for MYQORZOTM (aficamten) tablets, for oral use

NDA: 219083

Background:
In response to DCN's consult request dated November 13, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide for the original NDA submission for MYQORZOTM (aficamten) tablets, for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 29, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on November 6, 2025.

Thank you for your consult. If you have any questions, please contact Tierra Butler at (301) 796-1368 or tierra.butler@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 6, 2025
To:	Maryam Changi, PharmD Regulatory Health Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Tierra Butler, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	MYQORZO (aficamten)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 219083
Applicant:	Cytokinetics, Incorporated

1 INTRODUCTION

On July 30, 2024, and August 14, 2024, Cytokinetics, Incorporated submitted for the Agency's review Parts 1 and 2, respectively, of a Rolling Submission for an original New Drug Application (NDA) 219083 for MYQORZO (aficamten) tablets. On September 26, 2024, the Applicant submitted the final part of the Rolling Submission. The proposed indication for MYQORZO (aficamten) tablets is for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on November 13, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for MYQORZO (aficamten) tablets.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Mitigation Assessment and Medication Errors Surveillance (DMAMES) and will be provided to DCN under separate cover.

2 MATERIAL REVIEWED

- Draft MYQORZO (aficamten) tablets MG received on August 14, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 29, 2025.
- Draft MYQORZO (aficamten) tablets Prescribing Information (PI) received on August 14, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 29, 2025.
- Approved CAMZYOS (mavacamten) capsules comparator labeling dated April 17, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the font size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 21, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 219083
Product Name, Dosage Form, and Strength:	Myqorzo (aficamten) tablet, 5 mg, 10 mg, 15 mg, 20 mg
Applicant Name:	Cytokinetics, Incorporated
FDA Received Date:	October 17, 2025
TTT ID #:	2024-11043-2
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Cytokinetics, Incorporated submitted a response to the FDA's Request for Information regarding container label expiration date formatting for aficamten and concerns about clarity in expiration date presentation.[a]

2 CONCLUSION

Cytokinetics has addressed FDA's container label concerns by confirming implementation of the "YYYY-MM" numerical format for expiration dates on aficamten container labels, consistent with FDA guidance documents. We have no further recommendations at this time.

[a] Changi, M. Information Request for Myqorzo (NDA 219083). Silver Spring (MD): FDA, CDER, OSE (US);2025 Oct 07. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807e09c8

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COA Tracking ID: C2024349
NDA Number: 219083 /Referenced IND for NDA: 138814

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2024349
NDA#/Referenced IND for NDA:	219083 / 138814
Applicant:	Cytokinetics
Established Name/Trade Name:	Aficamten
Indication:	Treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)
Review Division:	Division of Cardiology and Nephrology
Clinical Reviewer:	Tzu-Yun McDowell
Clinical Team Leader (TL)	Fred Senatore
Regulatory Project Manager:	Maryam Changi
COA Reviewer:	Susan Pretko
COA TL:	Onyeka Illoh
Instruments reviewed:	COA Type: ☒ Patient-reported outcome (PRO) • Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) • Patient Global Impression of Change (PGI-C) ☒ Clinician Reported Outcome (ClinRO) • New York Heart Association Functional Classification (NYHA FC) ☒ Performance Outcome (PerfO) • Peak oxygen uptake (pVO_2)

Table of Contents

1. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Cardiology and Nephrology regarding NDA 219083 for aficamten (MYQORZO). The Applicant submitted the initial 505(b)(1) application and is seeking marketing approval for MYQORZO for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM). The Sponsor has submitted data from a single phase 3 study to support this Application.

The Applicant proposes patient-reported (PRO)-related labeling claims describing an improvement in health status with aficamten treatment, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), which was evaluated in the following ranked secondary efficacy endpoints in the phase 3 study CY6031:

- Change from baseline to Week 24 in KCCQ-Clinical Summary Score (CSS)
- Change from baseline to Week 12 in KCCQ-CSS

Data from Study CY6031 demonstrated that MYQORZO treatment resulted in statistically significant improvement in the KCCQ-CSS compared with placebo. Study data also supports that subject receiving aficamten experienced clinically meaningful change in the KCCQ-CSS (proposed by the Applicant as a 10-point improvement) compared to placebo.

The primary objective of this COA review is to evaluate from a measurement perspective if the submitted information supports the PRO-related labeling claims. Following discussion with the review team, the COA review was expanded to also explore meaningful change from Baseline at Week 24 in peak oxygen uptake (pVO_2).

This COA review concludes the following:

- The KCCQ-CSS and its corresponding endpoints adequately support the proposed PRO-related labeling claims. Given not all KCCQ-CSS items demonstrated a score change, consideration is warranted to direct labeling claims to specific KCCQ-CSS items for which a treatment effect was observed.
- Meaningful change in pVO_2 could not be estimated using Study CY6301 data, nor was evidence supporting interpretation of meaningful change found in existing literature. As such, the clinical meaningfulness of the pVO_2 statistical results is uncertain.

2. REVIEW CONCLUSIONS

Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS)

- The KCCQ-CSS was reviewed for meaningful within-patient change.
- While the evidence supports that study subjects experienced a meaningful change in the KCCQ-CSS, the change was driven by < 1/3 of items comprising the KCCQ-CSS. Therefore, consideration is warranted to direct labeling claims to specific KCCQ-CSS items for which a treatment effect was observed, rather than to overall health status.

Peak oxygen uptake (pVO2)

- Based on discussion with the review team, pVO_2 meaningful within-patient change was also reviewed. However, given the limited data, it is uncertain what amount of pVO_2 change is considered meaningful in patients with oHCM.

3. RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we have the following recommendations.

1. It may be helpful to obtain qualitative input from patients and/or explore patient global impression scales that measure functional capacity/physical function limitations to facilitate interpretation of pVO_2 meaningful change.

2. The measurement concept assessed by anchor scale(s) should align with that of the target COA measure for which it is being used to interpret, to provide more confidence for interpretation of target COA change scores that is meaningful from the patient perspective. Likewise, multiple anchors with easily interpretable scores should be explored for the derivation of meaningful change.

4. BACKGROUND, CORRESPONDENCE ON COAS, AND MATERIALS REVIEWED

4.1. Regulatory Background

- FDA agreed a single study with $p < 0.01$ could provide the basis for approval.
- There are no previous COA reviews under the aficamten IND program for the treatment of oHCM. Previous COA reviews for IND 138814 (b) (4) (b) (4)
- Another product in this drug class (CAMZYOS®/mavacamten, NDA 214998) received FDA-approval on April 28, 2022, for the treatment of adults with symptomatic New York Heart Association (NYHA) functional class (FC) II-III oHCM to improve functional capacity and symptoms.

4.2. Materials Reviewed

Materials reviewed to inform this COA review C2024349 are described in **Table 1.**

Table 1. Materials Reviewed

Document	SDN	eCTD#	Date Received
NDA 219083 Response to FDA IR dated 07 April 2025 containing: • Correlation coefficients at Baseline, Week 24, and change from Baseline to Week 24 between pVO_2 and 3 potential anchor scales (i.e., NYHA FC, `PGI-C, and KCCQ-PLS) • Information on what score ranges on the KCCQ-PLS constitutes "Minimally Improved", "Much Improved" and "Very Much Improved"	27	0027	08Apr2025
NDA 219083 Response to FDA IR dated 24 February 2025 containing results of anchor-based analyses for the change from Baseline at Week 12 and Week 24 in pVO2	19	0019	07Mar2025

COA Tracking ID: C2024349
NDA Number: 219083 /Referenced IND for NDA: 138814

Document	SDN	eCTD#	Date Received
NDA 219083 Response to FDA IR dated 19 February 2025 containing results of anchor-based analyses or the change from Baseline at Week 12 and Week 24 in KCCQ-23 CSS	18	0018	03Mar2025
NDA 219083 Response to FDA IR dated 12 February 2025 containing: • Copies of COA measures used in Study CY6031 • CDF curves for KCCQ-CSS change from Baseline at Week 12 and Week 24, by treatment arm • Descriptive statistics for the change from baseline to Week 12 and Week 24 in CY 6031 for each KCCQ item, by treatment arm	16	0016	19Feb2025
NDA 219083 Response to FDA IR dated 18 Dec 2024 regarding the clinical meaningfulness of the KCCQ-CSS instrument	11	0011	03Jan2025
NDA 219083 Rolling Submission – Part 3 of 3 (Complete Submission)	4	0004	25Sep2025
Communications and Reviews	**DARRTS Ref ID**		**Date**
NDA 219083 FDA request for information supporting interpretation of pVO_2 and KCCQ-PLS meaningful score change	5566209		07Apr2025
NDA 219083 ACDA	5536076		25Feb2025
Communications and Reviews	**DARRTS Ref ID**		**Date**
NDA 219083 FDA request for analyses assessing the clinical meaningfulness of the observed improvement in KCCQ-CSS, including detailed methodology and results	5501738		18Dec2024
Previous COA review for mavacamten application: C2021051_NDA 214998_KCCQ-CSS, HCMSQ_DCN	4865437		30Sep2021
IND 138814 Type B End of Phase 2 MPC	4835626		04Aug2021
Publications			
• CAMZYOS® (mavacamten) USPI. 17 April 2025. • Chambers DJ, Wisely NA. Cardiopulmonary exercise testing -- a beginner's guide to the nine-panel plot. BJA Education. 2019; 19(5): pp 158-164. • Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: A New Health Status Measure for Heart Failure. J Am Coll Cardiol 2000; 35:1245–55 • Nassif M., Fine JT, et al. Validation of the Kansas City Cardiomyopathy Questionnaire in Symptomatic Obstructive Hypertrophic Cardiomyopathy. JACC Heart Fail. 2022;10(9):531-539. • Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Nov 17;76(20):2379-2390. • The Voice of the Patient Report for Hypertrophic Cardiomyopathy (HCM). Hypertrophic Cardiomyopathy Association. 09 January 2021.			

ACDA, Advisory Committee Decision Aid; CDF, cumulative distribution function; IR, information request; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; KCCQ-PLS, Kansas City Cardiomyopathy Questionnaire – Physical Limitations Score; MPC, Meeting Preliminary Comments; `PGI-C, Patient Global Impression of Change scale; pVO_2, Peak oxygen uptake; NYHA FC, New York Heart Association Functional Classification; Ref, reference; USPI, U.S. Prescribing Information

5. CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

Eligible subjects in the phase 3 CY6031 study, were males and females aged 18 to 85 years (inclusive) that were diagnosed with HCM, had left ventricular ejection fraction (LVEF) ≥ 60%, and were NYHA Functional Class (FC) II or III. Additionally, subjects on beta-blockers, verapamil, diltiazem, or disopyramide should have been on a stable regimen for > 6 weeks prior to randomization.

A total of 282 subjects were randomized 1:1 in Study CY6031 to receive aficamten (n=142) or placebo (n=140). Over 95% of subjects across both arms completed treatment and are included in the analysis of study results.

5.2 Study CY6031 Design, Efficacy Endpoints, and Results

Study CY6031 (SEQUOIA-HCM) is a completed randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial to evaluate the efficacy and safety of aficamten in adult subjects with symptomatic oHCM.

The primary and patient-reported outcome (PRO)-based secondary endpoint definitions and Study results are in **Table 2.**

Table 2. Study CY6031: Primary and PRO-based secondary endpoints and results

Endpoint definition	Study results
Primary endpoint	
Change in pVO2 by CPET from baseline to Week 24	The LSM change in pVO2 by CPET from baseline to Week 24 was statistically significantly greater in the aficamten group (n=142) than in the placebo group (n=140): 1.76 mL/kg/min vs 0.02 mL/kg/min. The LSM difference between treatment groups was 1.74 mL/kg/min (95% CI: 1.04, 2.44; p < 0.0001).
PRO-based secondary endpoint (numbered by testing hierarchy)	
1. Change from baseline[1] to Week 24 in KCCQ-CSS	The LSM change in KCCQ-CSS from baseline to Week 24 was statistically significantly greater in the aficamten group than in the placebo group: 11.6 vs. 4.3 points. The LSM difference between treatment groups was 7.3 points (95% CI: 4.6, 10.1; p < 0.0001).
6. Change from baseline to Week 12 in KCCQ-CSS	The LSM change in KCCQ-CSS from baseline to Week 12 was statistically significantly greater in the aficamten group than in the placebo group: 11.1 vs. 4.0 points. `The LSM difference between treatment groups was 7.0 points (95% CI: 4.5, 9.5; p < 0.0001).

CI, confidence interval; CPET, cardiopulmonary exercise testing; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LSM, Least squares mean; PRO, Patient-Reported Outcome; pVO2, peak oxygen uptake
[1] The Baseline KCCQ-CSS score was obtained on Day 1 of the study (i.e., the first clinic visit where subjects received their first dose of assigned treatment)

Additional study results (e.g., KCCQ-CSS cumulative distribution function (CDF) curves by treatment arm and item-level change) are in **Appendix 1**.

PRO measures used to support exploratory endpoints include the KCCQ-CSS, EuroQol 5-dimension 5-level instrument (EQ-5D-5L), and Seattle Angina Questionnaire-7 (SAQ-7).

Additional COA-related information for Study CY6031 is in **Appendix 2**.

*[Reviewer's Comment: KCCQ-CSS change from Baseline at Week 24 appears to be driven by the items assessing limitation in climbing a flight of stairs without stopping (Item 1e), limitation in hurrying or jogging (as if to catch a bus) (Item 1f), times shortness of breath (SOB) limited ability to what the patient wanted (Item 7), and SOB bother (Item 8). KCCQ-CSS change from Baseline at Week 12 appears to be driven by items 1e, 1f, and 7 (see Change from Baseline to Weeks 12 and 24 in item scores comprising the KCCQ-CSS in **Appendix 1**.*

At all analysis timepoints in Study CY6031, subjects in the aficamten group showed greater improvement from Baseline in the KCCQ-CSS.]

5.3 Targeted COA-Related Labeling Claims

The Applicant has proposed the following specific targeted COA-related labeling claims (in blue text).

5.3.1. COA-related labeling claim #1: Improvement in health status based on KCCQ-CSS

Secondary Endpoints

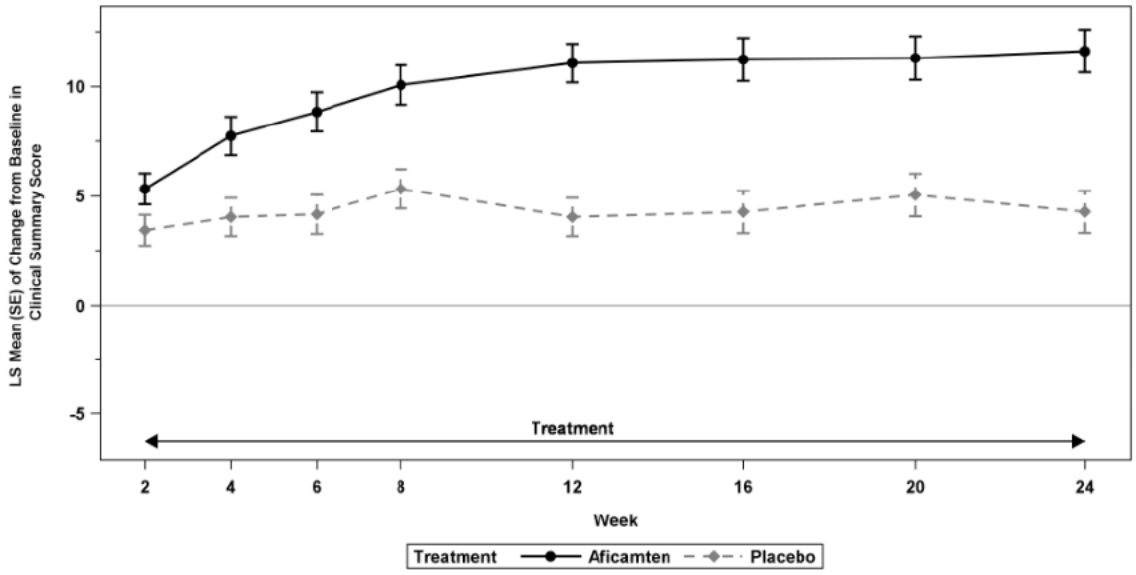
The treatment effects of MYQORZO on health status, functional capacity, and LVOT obstruction were assessed by change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS), proportion of patients with ≥ 1 class improvement in NYHA functional class… and change in total workload during CPET. At Week 24, patients receiving MYQORZO had greater improvement compared to the placebo group across all secondary points (Table 5, Figure 2, Figure 3, (b) (4)).

Table 1: Results of Secondary [redacted] (b) (4) Efficacy Endpoints in SEQUOIA-HCM

Endpoints	Aficamten N=142	Placebo N=140	Difference (95% CI)	p-Value
Change from Baseline in KCCQ-CSS[1]				
Week 12	11.1 (0.9)	4.0 (0.9)	7.0 (4.5, 9.5)	< 0.0001
Week 24	11.6 (1.0)	4.3 (1.0)	7.3 (4.6, 10.1)	< 0.0001
Proportion of Patients with ≥ 1 NYHA Class Improvement[2]				
Week 12	69 (48.6)	25 (17.9)	OR: 4.6 (2.6, 8.4) [redacted] (b) (4)	< 0.0001
Week 24	83 (58.5)	34 (24.3)	OR: 4.4 (2.6, 7.6) [redacted] (b) (4)	< 0.0001

KCCQ CSS: Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; NYHA: New York Heart Association
[1] LS means (SE) and LS mean difference (95% CI) presented for continuous endpoints.
[2] The number (percentage) and rate difference (Diff) and common OR (exact 95% CI of the OR) are presented for binary endpoints

Figure 1: Change from Baseline in KCCQ-CSS through Week 24



[Reviewer's comments: U.S. Prescribing Information (PI) for mavacamten includes the following, proposed by the mavacamten Applicant:

- *A standalone Table 4 showing the baseline, change from Baseline to Week 30, and least squares mean (LSM) difference for the KCCQ-CSS and the baseline and change from*

Baseline to Week 30 in the KCCQ-Total Symptom Score (TSS) and KCCQ-Physical Limitations Score (PLS).

- *Figure 2 showing CDF curves for change from Baseline to Week 30 for the KCCQ-CSS.*

The Applicant for this NDA 219083 did not propose including similar tables/figures in the draft aficamten PI.]

5.4 Clinical Outcome Assessments

5.4.1. COA Descriptions

KCCQ-23
The KCCQ-23 (**Appendix 3**) is a 23-item PRO measure assessing heart failure symptoms and impacts in the past 2-weeks using a verbal rating scale (VRS) across 7 domains (symptom frequency [4 items], symptom burden [3 items], symptom stability [1 item], physical limitations [6 items], social limitations [4 items], quality of life [3 items], and self-efficacy [2 items]).

The KCCQ-CSS is a summary score derived from physical limitation, symptom frequency, and symptom burden domain scores.

[Reviewer's Comments: The Applicant did not provide evidence to support content validity of the KCCQ-CSS in the context of use for this NDA. However, content validity of the KCCQ-CSS in the oHCM population has been established to support KCCQ-CSS labeling claims in other FDA-approved medical products indicated to treat oHCM.

The Applicant did not evaluate KCCQ-CSS measurement properties using Study CY6031 data and instead submitted literature to support KCCQ-CSS performance in patients with heart failure. Ideally, the Applicant should have confirmed the KCCQ-CSS measurement properties in their phase 3 study. However, this does not preclude establishment of the KCCQ-CSS fitness-for-purpose in the proposed context of use.

Two versions of the KCCQ are available, the full 23-item version (i.e., KCCQ-23) and a shorter 12-i1tem version (i.e., KCCQ-12). The scoring algorithms for both versions are similar (i.e., domain and summary scores can be derived for both).]

NYHA FC
The NYHA FC is a clinician-reported outcome (ClinRO) measure that assigns patients to 1 of 4 functional classes based on physical activity limitations and symptoms of heart failure (e.g., fatigue, palpitation or dyspnea). The NYHA FC is in **Appendix 4**.

PGI-C
The PGI-C (**Appendix 5**) is a single-item PRO measure assessing overall status since the start of the study using a 7-point VRS.

EQ-5D-5L
The EQ-5D-5L is a generic (i.e., not disease-specific) preference-based PRO measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit for labeling claims.

Cardiopulmonary Exercise Testing (CPET)/pVO_2
CPET is a non-invasive assessment of the cardiopulmonary system at rest and during exercise. The objective of CPET is to determine functional capacity in an individual. Deficiencies in CPET-derived variables (e.g., pVO_2) are associated with worse morbidity and mortality. CPET is usually conducted using a treadmill or cycle ergometer. Measurements are taken at rest, during exercise, with continuously increasing resistance, and in the recovery phase immediately after exercise. These data are used with the individual's height, weight, age, and gender into a CPET computer software package to measure work rate, metabolic gas exchange, ventilation, and cardiovascular performance.

During progressively increasing exercise intensity, oxygen uptake (VO_2) normally increases linearly in proportion to work. Peak VO_2 is the highest VO_2 achieved during the test.

5.4.2. Interpretation of Meaningful Change

KCCQ-CSS Meaningful Change
The Applicant proposed a 10-point reduction in KCCQ-CSS change from Baseline at Week 24 as a meaningful within-patient score change based on triangulation of literature evidence, and analysis results using distribution-based and anchor-based methods. These data are summarized in **Table 3.**

Table 3. Submitted evidence to support the 10-point meaningful change in KCCQ-CSS

Methodology	Summary of Results
Literature	
• In the study by Nassif et al (N=171), anchor-based analyses were conducted using data from the EXPLORER-HCM study for mavacamten to evaluate KCCQ domain score change from BL to Week 6 using a `PGI-C anchor scale asking patients to compare their current health status with how it was at BL using a 7-point VRS. The mean KCCQ-CSS change from BL to Week 6 corresponding to the `PGI-C response categories "Minimally Improved" (n=55) and "Much Improved" (n=41) was 5.1 ±11.4 and 11.8 ± 15.0, respectively.	
Anchor-based methods	
Anchor-based analyses were conducted to explore meaningful change from BL at Week 12 and at Week 24 in KCCQ-CSS using NYHA FC, EQ-5D-5L VAS, SAQ-7 Summary Score, and `PGI-C as anchor scales.	Change for the KCCQ-CSS was moderately correlated with change in NYHA FC at Week 24 (|r| = 0.35) and PGI-C at Week 24 (|r| = 0.48). Change for the KCCQ-CSS was poorly correlated with change in NYHA FC at Week 12 (|r| = 0.26). The correlation between the KCCQ-CSS and the proposed anchor scales are in **Appendix 7**. For the PGI-C anchor scale: • The CDF curves for `PGI-C response categories "Minimally Improved" and "Much Improved" were clearly separated from the curve for "No Change." • The corresponding mean change from BL to Week 24 in KCCQ-CSS for these `PGI-C response categories was **6.3 – 11.5 points** For the NYHA FC anchor scale: • The CDF curves for NYHA FC change from Baseline to Week 24 for 1- and 2-FC improvement were clearly separated from the curve for "No Change". • The median change from BL to Week 24 in KCCQ-CSS corresponding with a 1- to 2-class improvement in NYHA FC was **8.3 - 20.8 points**

BL, baseline; CDF, cumulative distribution function curve; EQ-5D-5L VAS, EuroQol 5-dimension 5-level instrument visual analog scale; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; NYHA FC, New York Heart Association Functional Class; `PGI-C, Patient Global Impression of Change scale; SAQ-7, Seattle Angina Questionnaire -7

[Reviewer's Comments:

- *Additional literature referenced by the Applicant to support KCCQ-CSS meaningful change are not described* (b) (4) *the generalizability of these data to the target patient population is unclear.*
- *Limitations for the EQ-5D-5L, SAQ-7 and PGI-C anchor scales are as follows:*
  - *The EQ-5D-5L VAS is not an ideal anchor scale given that it is a complex tool that lacks evidence of content validity in the target patient population and because it uses a VAS which is difficult to interpret.*
  - *The SAQ-7 is not an ideal anchor scale given that it is cognitively burdensome (asks patients to average frequency of experiencing symptoms), includes distal concepts (e.g., enjoyment of life, feelings about angina) that may be influenced by factors unrelated to the disease and/or treatment, and is subject to recall bias given its long recall period (i.e., "past 4 weeks").*

  - *The PGI-C is not an ideal anchor scale given that it measures overall status (which is not specific to symptoms and physical limitations assessed by the KCCQ-CSS) and it has a long recall period (i.e., "Since the start of the study" and is subject to recall bias. Ideally, a PGIS scale, which is less prone to recall error, would be used as the primary anchor scale to support interpretation of COA change scores. However, a PGIS was not used to collect Study CY6031 data.*
- *The moderate, rather than strong, correlation coefficient observed for the change from Baseline to Week 24 in KCCQ-CSS and PGI-C at Week 24 may be due to potential recall error for the PGI-C given its long recall period and because the measurement concepts for the PGI-C and KCCQ-CSS do not fully align. Despite these limitations, the eCDF curves by treatment arm for the change from Baseline at Week 24 in KCCQ-CSS show separation between the aficamten and placebo groups across a wide range of improvement change scores.*
- *Also, based on the eCDF curves by treatment arm in Study CY6031, approximately 50% of subjects in the aficamten treatment group experienced a meaningful change from Baseline to Week 24 in KCCQ-CSS compared to approximately 2% of subjects in the placebo treatment group (see eCDF of Change from Baseline to Week 24 in **Appendix 1**).*
- *A 10-point threshold for KCCQ-CSS meaningful change from Baseline was also proposed and supported by anchor-based analyses as described in the previous COA review for the mavacamten NDA, C2021051. Although the mavacamten endpoint analysis timeframe was slightly different than for this aficamten NDA 219083 (i.e., change from Baseline to Week 30 in mavacamten phase 3 clinical trial vs. change from Baseline to Week 24 in the aficamten phase 3 clinical trial), the similar mechanism of action for these drug products appears to support similar estimates for clinically meaningful within-patient change from Baseline in KCCQ-CSS.*

The Applicant's proposed threshold of 10-points as a reflection of KCCQ-CSS within-patient clinically meaningful change from Baseline to Week 24 appears reasonable based on the results of the anchor-based analysis and findings from the mavacamten clinical trials. ***]***

pVO2 Meaningful Change

The Applicant did not propose a range of pVO_2 change that is clinically meaningful to patients.

[*Reviewer's Comments: During the NDA review, DCN asked DCOA for assistance interpreting meaningful change in pVO_2 scores.*

- *The Applicant was asked to explore meaningful change from Baseline at Week 24 in pVO_2 using NYHA FC, KCCQ-PLS, and PGI-C as anchor scales. However, given the low correlation coefficients (i.e., $|r| < 0.3$) between pVO_2 and the anchor scales for the change from Baseline at Week 24 (**Appendix 6**), a suitable anchor scale to estimate pVO_2 meaningful change in Study CY6031 was not identified.*
- *Following an internal literature review, an estimate of pVO_2 meaningful change in existing literature informed by qualitative input from the target patient perspective was not found.*

While the threshold for within-patient clinically meaningful change from Baseline at Week 24 in pVO_2 could not be estimated, there was clear separation between the eCDF curves by treatment

*arm across a wide range of pVO_2 improvement change scores in Study CY6031 (**Appendix 1. Change from Baseline to Week 24 in pVO2**).]*

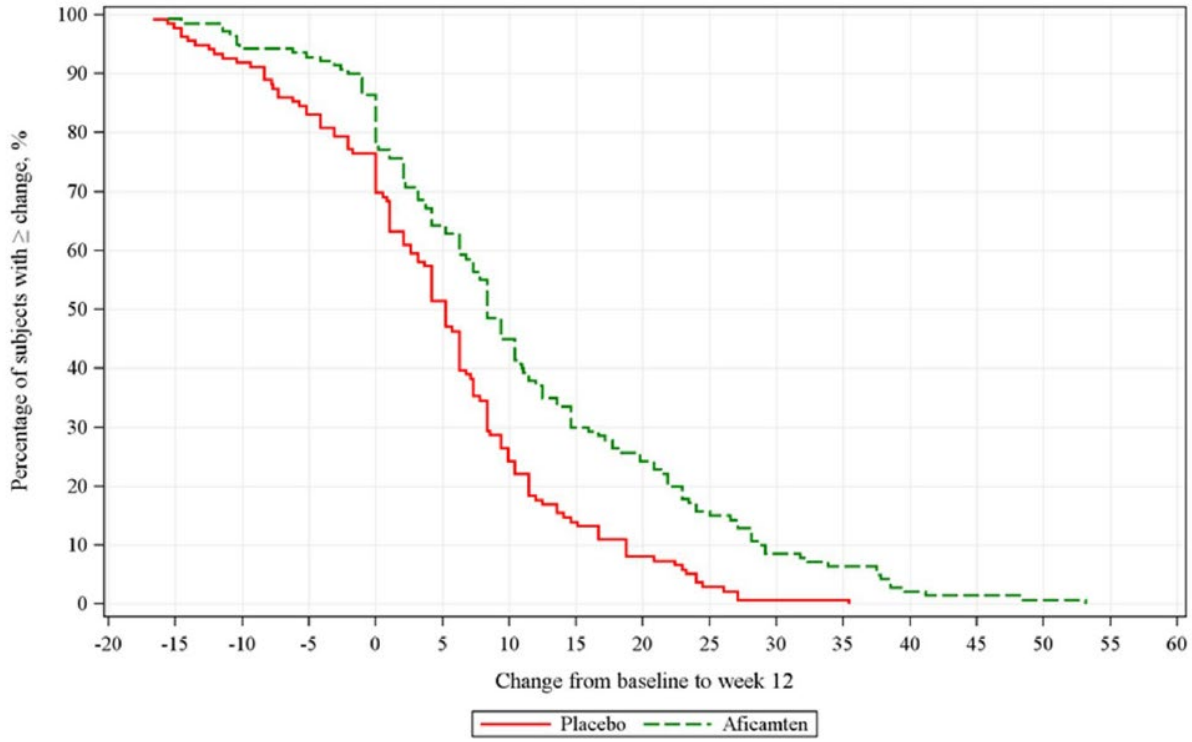
6. APPENDICES

Appendix 1. Study CY 6031 Results

Treatment arm eCDF curves of Change from Baseline to Week 12 in KCCQ-CSS

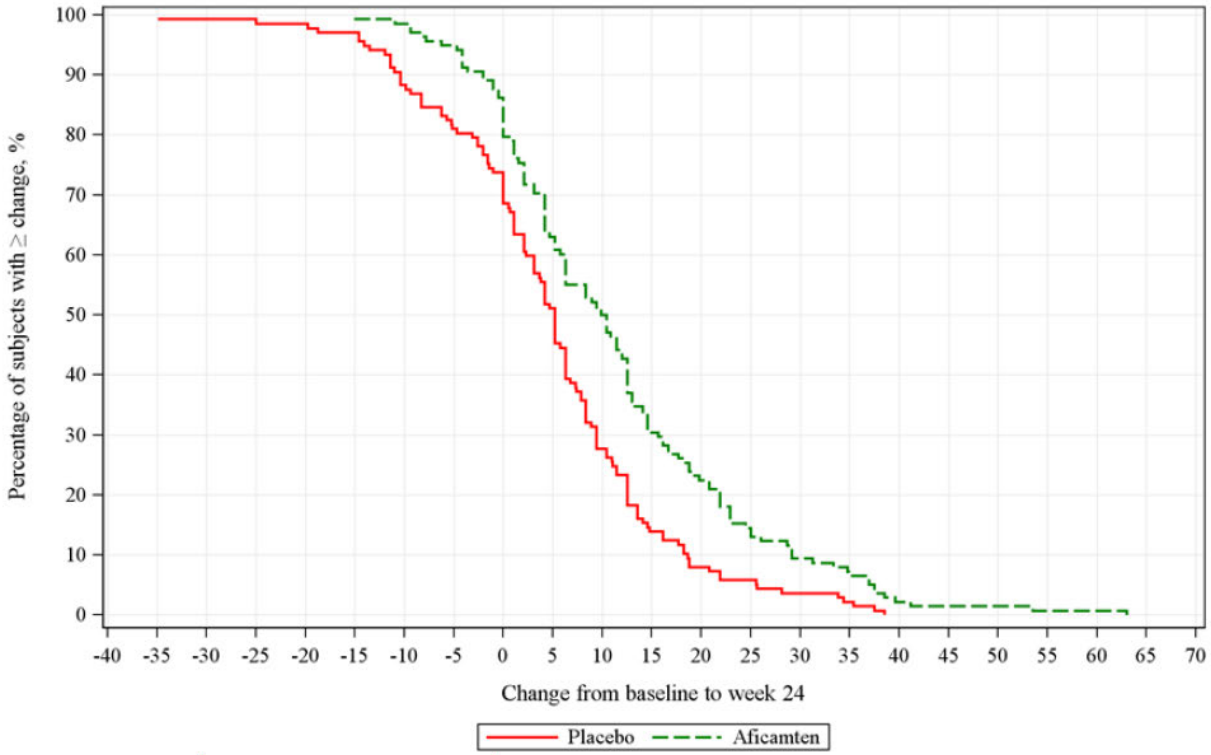
Figure 1: CY 6031: Cumulative Distribution Curve of Change from Baseline for KCCQ-CSS

A. Baseline to Week 12



Treatment arm eCDF curves of Change from Baseline to Week 24 in KCCQ-CSS

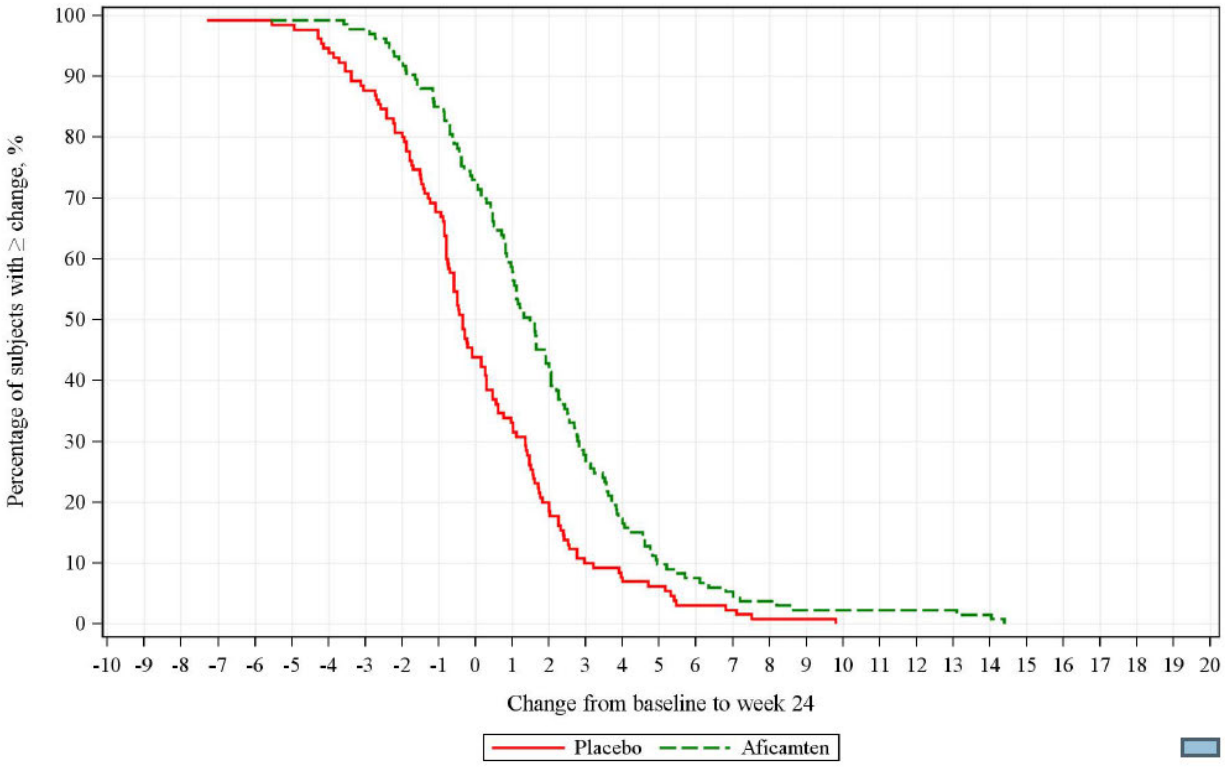
B. Baseline to Week 24



Source: FDA RTQ Figure 1.1; CY 6031 CSR Figure 14.2.3.5

Treatment arm eCDF curves of Change from Baseline to Week 24 in pVO2

Figure 14.2.3
Cumulative Distribution of Change from Baseline to Week 24 in pVO2
Full Analysis Set



Summary Table of Change from Baseline to Weeks 12 and 24 in item scores comprising the KCCQ-CSS

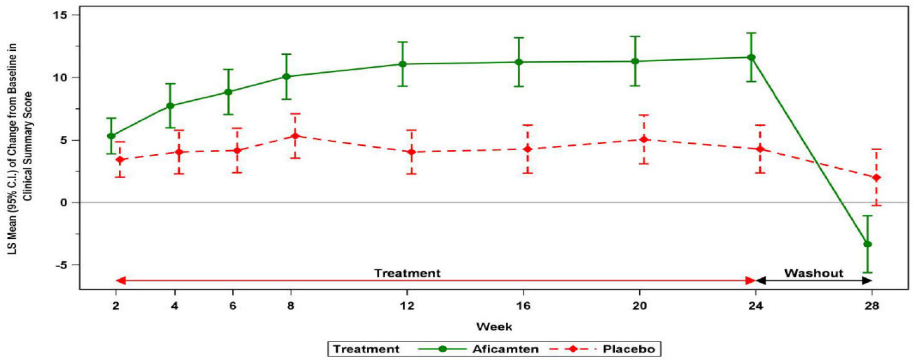
KCCQ-23 Item	Median Change from Baseline to Week 12		Median Change from Baseline to Week 24	
	Aficamten (N=142)	Placebo (N=140)	Aficamten (N=142)	Placebo (N=140)
(1a) Dressing yourself	0.0	0.0	0.0	0.0
(1b) Showering/Bathing	0.0	0.0	0.0	0.0
(1c) Walking 1 block on level ground	0.0	0.0	0.0	0.0
(1d) Yardwork, housework, carrying groceries	0.0	0.0	0.0	0.0
(1e) Climbing stairs without stopping	1.0	0.0	1.0	0.0
(1f) Hurrying or jogging (as if to catch a bus)	1.0	0.0	1.0	0.0
(3) Times morning swelling feet/ ankles/ legs	0.0	0.0	0.0	0.0
(4) How much swelling feet bothered you?	0.0	0.0	0.0	0.0
(5) Times fatigue limited your ability	0.0	0.0	1.0	1.0
(6) How much fatigue bothered you?	0.0	0.0	0.0	0.0
(7) Times short breath limited your ability	1.0	0.0	1.0	0.0
(8) How much short breath bothered you?	0.0	0.0	0.5	0.0
(9) Times forced to sleep sitting up	0.0	0.0	0.0	0.0

Summary Table of Change from Baseline to Week 24 in KCCQ domain scores comprising the KCCQ-CSS

KCCQ Domain	Mean (SD) Week 24 Change from Baseline			
	Aficamten (N=142)	Placebo (N=140)	Overall (N=282)	LS Mean Diff vs. Placebo (95% CI); p-value
Physical Limitation	12.0 (14.04)	4.0 (14.87)	8.0 (14.99)	8.5 (5.3, 11.6); p-value: < 0.0001
Symptom Burden	11.2 (18.22) (n=138)	4.8 (14.98) (n=137)	8.0 (16.96) (n=275)	7.1 (3.7, 10.6); p-value: < 0.0001
Symptom Frequency	10.6 (16.05) (n=138)	6.2 (12.96) (n=137)	8.5 (14.73) (n=275)	5.5 (2.5, 8.5); p-value: <0.001

Plot of Least Squares Mean Change in KCCQ-CSS from Baseline Over Time

Figure 14.2.3.3
Least Squares Mean Change (95% Confidence Interval) in KCCQ Clinical Summary Score from Baseline Over Time
Full Analysis Set



Notes: Data up to Week 24 were analyzed using MMRM model with baseline as covariate, randomization stratification factors, visit, treatment group, region, and interaction terms of treatment by visit, baseline by visit, region by treatment, region by visit, baseline by region, treatment by visit and region, baseline by visit and region as fixed effects. An unstructured covariance matrix was specified. Data at Week 28 were analyzed using an ANCOVA model with baseline as covariate, randomization stratification factors, region, treatment, baseline by region, region by treatment as fixed effects.

Appendix 2. Additional COA-related information for Study CY 6031

Table A1 shows the Schedule of COA data collection in Study CY 6031.

Table A1. Schedule of COA data collection in Study CY 6031

Trial Procedure	Screening[a] (≤ 42 days)	Day 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	EOT[b] (Week 24)	EOS[c] (Week 28)	ED[d]
Visit Window	Up to 42 days prior to Day 1	N/A	+ 3 days	+ 3 days	+ 3 days	+ 3 days	± 3 days	± 7 days	± 7 days	± 7 days	+ 7 days	As soon as possible after withdrawal
PATIENT-REPORTED OUTCOMES AND FUNCTIONING ASSESSMENTS												
NYHA Functional Classification	X	X	X	X	X	X	X	X	X	X	X	X
KCCQ[p]		X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[p]		X	X	X	X	X	X	X	X	X	X	X
CGI										X	X	X
PGI-C[p]										X		X
SAQ-7[p]		X		X		X	X	X	X	X	X	X

CGI = Clinical Global Impression scale; ED = early discontinuation; EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQol 5-dimension 5-level instrument; IP = investigational product; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; SAQ-7 = Seattle Angina Questionnaire-7; PGI-C = Patient Global Impression of Change scale

[a] The cardiopulmonary exercise testing (CPET) must be completed within four weeks but not less than one week prior to randomization.

[b] If a patient is temporarily unable to exercise on the treadmill or bicycle (whichever modality was used at baseline) due to an adverse event (e.g., ankle sprain, upper respiratory infection, migraine), but not due to HCM symptoms, or if the site is unable to perform CPET (e.g., equipment malfunction), then the Week 24 visit may be postponed by up to 4 weeks. The patient should continue to receive IP until the visit. Sites should contact patients shortly before the Week 24 visit and confirm their ability to perform CPET. If necessary, the Week 24 visit may be split across two consecutive days within the visit window. If the visit is split, all assessments, except the CPET, should occur
on the first day of the split visit. The CPET should occur on the second day of the split visit. Dosing will occur on site on both split visit days.

[c] The EOS visit (Week 28) will occur 4 weeks after last dose. It is not required for patients who discontinue IP >4 weeks prior to the Week 24.

[d] Patients who withdraw from the trial IP should complete an early discontinuation visit as soon as possible if they no longer wish to be part of the study. An EOS visit should be performed 4 weeks after their final IP dose if possible

[p] All PROs, KCCQ, ED-5D-5L, SAQ-7, and PGI-C, should be done prior to other assessments.

Subjects were asked to complete the KCCQ, EQ-5D-5L, SAQ-7 and PGI-C questionnaires in a quiet place prior to the medical consultation and prior to undergoing any tests and procedures to avoid biasing their responses. Site staff verified the questionnaires for completeness before the subjects left the clinic or hospital.

The investigator (or qualified designee) recorded the CGI scale assessment.

Appendix 3. Additional information for the KCCQ

KCCQ-23

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

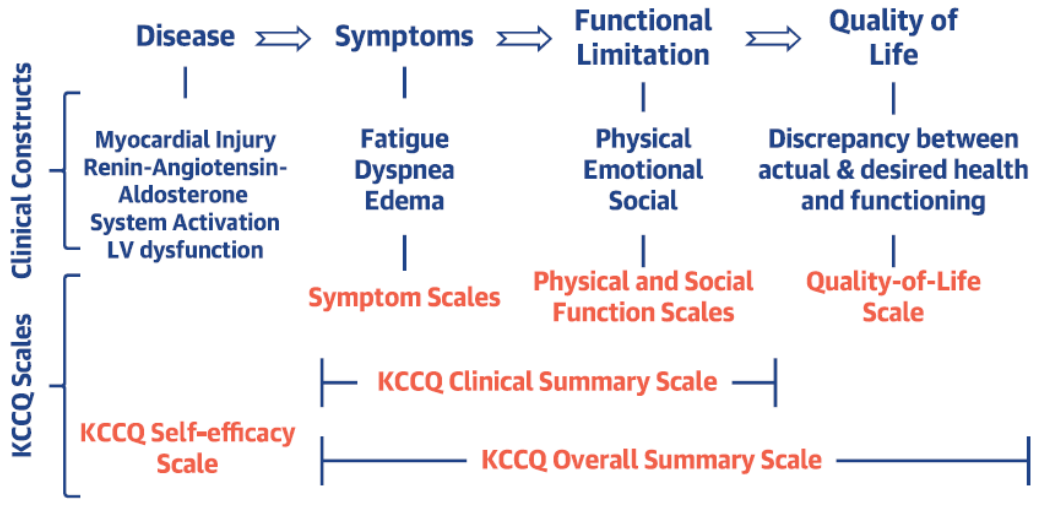
Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

Original US English

KCCQ-23 Conceptual Framework from the public domain

CENTRAL ILLUSTRATION **Conceptual Mapping of the Kansas City Cardiomyopathy Questionnaire to Different Manifestations of Heart Failure**



Spertus, J.A. et al. J Am Coll Cardiol. 2020;76(20):2379–90.

Whereas there is an underlying disease process causing the heart failure syndrome, patients are aware of the symptoms that they experience and how those symptoms affect their ability to function and quality of life. Different scales and summary scores map to different manifestations of heart failure, as demonstrated in the figure. KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular.

KCCQ-23 Scoring Algorithm

There are 10 summary scores within the KCCQ. KCCQ scores comprising the KCCQ-CSS are below.

Physical Limitation Summary Score

Responses for items 1a-f are scored as follows:

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

At least three of items 1a-f are needed to calculate the physical limitations summary score, as shown below.

Physical Limitation Score = 100*[(mean score for items 1a-f - 1]/4

Symptom Frequency Summary Score

Responses for items 3, 5, 7 and 9 are scored as follows:

Question 3

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

Questions 5 and 7

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

Question 9

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

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

S3 = [(Question 3) – 1]/4

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

Symptom Burden Summary Score

Responses for items 4, 6 and 8 are scored as follows:

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

If at least one of Items 4, 6 and 8 is not missing, then compute:

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

Total Symptom Summary Score

The Total Symptom Summary Score is calculated as the mean of the Symptom Frequency and Symptom Burden Summary Scores.

Clinical Summary Score

The Clinical Summary Score is calculated as the mean of the Physical Limitation and Total Symptom Summary Scores.

Appendix 4. NYHA FC

The NYHA classification is as follows:

- Class I - No symptoms and no limitation in ordinary physical activity (eg, shortness of breath when walking, climbing stairs).
- Class II - Mild symptoms (eg, mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms, even during less-than- ordinary activity (eg, walking short distances [20-100 m]). Comfortable only at rest.
- Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Appendix 5. PGI-C

Since the start of the study, my overall status is:

✓*one box only:*

[1] ☐ Very Much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No Change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very Much Worse

(US/English)

Appendix 6. Correlation coefficients between pVO_2 and anchor scales

The correlation coefficients between change from Baseline to Week 24 in pVO_2 (ml/kg/min) and potential anchor scales are in **Table 9.1.**

Table 9.1
Correlation of pVO_2 (mL/kg/min), PGI-C, NYHA and KCCQ-PLS at Baseline and Week 24 in CY 6031
Full Analysis Set

Visit/Variables	Statistics	NYHA Functional Class	KCCQ-PLS	Patient Global Impression of Change (PGI-C)
Baseline	n	282	282	
	Correlation coefficient	-0.25	0.22	
	P value	<0.0001	0.0003	
Week 24	n	263	261	
	Correlation coefficient	-0.24	0.25	
	P value	0.0001	<0.0001	
Change from Baseline	n	263	261	263
	Correlation coefficient	-0.21	0.18	-0.23
	P value	0.0005	0.0032	0.0002

Appendix 7. Anchor-Based Analyses Results for KCCQ-CSS

Correlation between KCCQ-CSS and Potential Anchor Scales

Table 4: CY 6031: Correlation of KCCQ-CSS and Other Efficacy Measures (Full Analysis Set)

Visit Statistics	NYHA Functional Class	EQ-5D-5L VAS	SAQ-7 Summary Score	PGI-C[a]
Baseline				
n	282	282	281	-
Correlation coefficient	-0.39	0.55	0.61	-
p-value	<0.0001	<0.0001	<0.0001	-
Week 12				
n	276	276	273	-
Correlation coefficient	-0.57	0.60	0.66	-
p-value	<0.0001	<0.0001	<0.0001	-
Change from Baseline				
n	276	276	272	-
Correlation coefficient	-0.26	0.42	0.49	-
p-value	<0.0001	<0.0001	<0.0001	-
Week 24				
n	275	274	275	-
Correlation coefficient	-0.55	0.64	0.73	-
p-value	<0.0001	<0.0001	<0.0001	-
Change from Baseline				
n	275	274	274	275
Correlation coefficient	-0.35	0.41	0.58	-0.48
p-value	<0.0001	<0.0001	<0.0001	<0.0001

PGI-C = Patient Global Impression of Change; SAQ = Seattle Angina Questionnaire; VAS = visual analog scale.
Notes: Spearman correlations are provided. PGI-C response categories were coded as 1: very much improved, 2: very much improved, 3: minimally improved, 4: no change, 5: minimally worse, 6: much worse, and the numeric value of the PGI-C response were used in the correlation calculation.
[a] PGI-C only collected at Week 24.

Anchor-based analysis results for the PGI-C anchor scale at Week 24

Figure 1: Cumulative Distribution of Change from Baseline to Week 24 in KCCQ-CSS by Patient Global Impression of Change (PGI-C) Category (Un-collapsed)

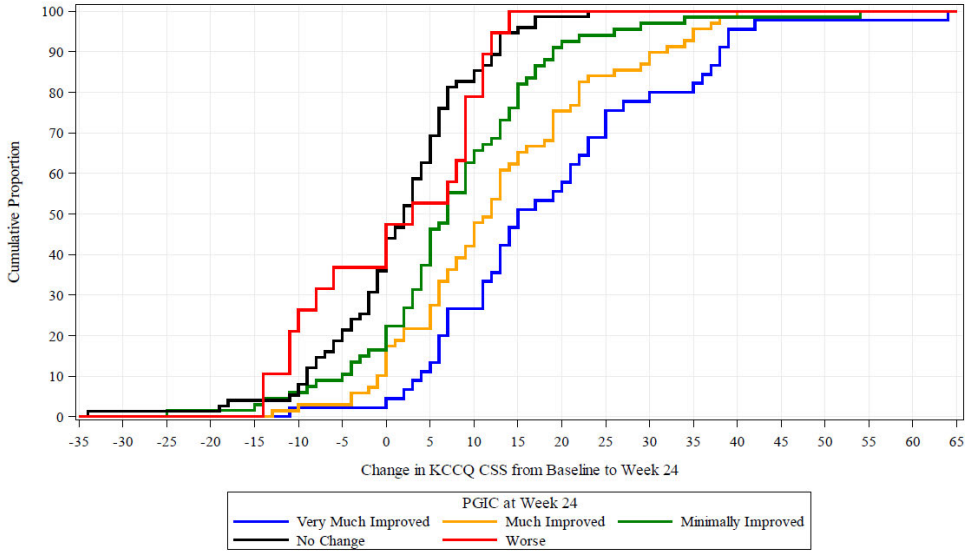


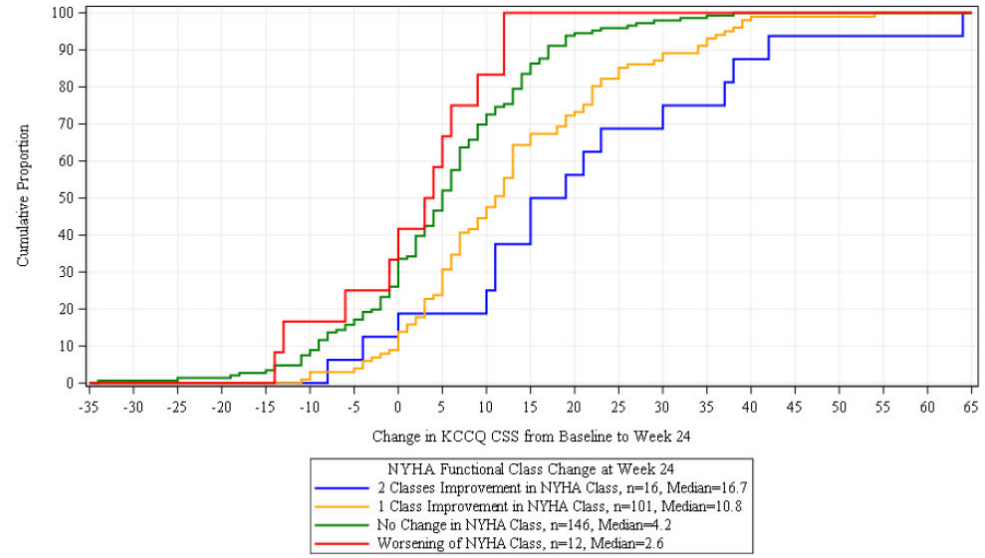
Table 1: CY 6031: Analysis of KCCQ-CSS Change from Baseline to Week 24 by Patient Global Impression of Change (PGI-C) (Full Analysis Set)

Visit Statistics	Patient Global Impression of Change (PGI-C) at Week 24				
	Very Much Improved (n=45)	Much Improved (n=69)	Minimally Improved (n=68)	No Change (n=75)	Worse (n=19)
Baseline					
Mean (SD)	76.4 (15.75)	75.3 (17.75)	72.8 (20.94)	76.7 (17.18)	68.2 (15.46)
Median	79.2	80.2	80.2	78.1	69.8
Q1, Q3	63, 89	64, 90	60, 88	65, 92	50, 79
Min, Max	35, 100	31, 100	11, 100	26, 100	41, 90
Week 24					
Mean (SD)	94.7 (9.84)	87.7 (12.35)	79.5 (19.33)	77.6 (17.07)	68.8 (16.39)
Median	99.0	90.6	85.4	79.2	68.8
Q1, Q3	94, 100	82, 98	73, 93	66, 92	59, 80
Min, Max	44, 100	49, 100	13, 100	27, 100	38, 100
Change from Baseline					
Mean (SD)	18.4 (14.26)	12.4 (11.92)	7.1 (11.73)	0.9 (8.92)	0.6 (9.82)
Median	14.6	11.5	6.3	1.0	2.1
Q1, Q3	6, 25	4, 19	1, 14	-4, 6	-10, 9
Min, Max	-11, 63	-14, 40	-25, 54	-35, 23	-15, 13
LS Mean and 95% CI	18.9 [16.0, 21.8]	12.6 [10.2, 14.9]	6.3 [4.0, 8.7]	1.6 [-0.7, 3.8]	-1.5 [-6.0, 2.9]
LS Mean Diff and 95% CI between adjacent PGI-C Category	6.4 [2.7, 10.1]	6.2 [2.9, 9.6]	4.7 [1.5, 8.0]	NA	-3.1 [-8.1, 1.9]

Notes: LS mean estimates and 95% confidence intervals were obtained from an ANCOVA model with change from baseline in KCCQ-CSS at Week 24 as dependent variable, baseline KCCQ-CSS as covariate and PGI-C category as fixed effect. No patient reported PGI-C of very much worse. PGI-C of minimally worse and much worse were combined as worse category due to few patients reported much worse. LS mean difference between adjacent PGI-C category are provided as very much improved vs. much improved under very much improved column, much improved vs. minimally improved and minimally improved vs. no change are reported under much improved and minimally improved columns, respectively. Difference of worse vs. no change is reported under worse column.
Source: FDA RTQ CY 6031 Table 2.2.1

Anchor-based analysis results for the NYHA FC anchor scale at Week 24

B. Week 24

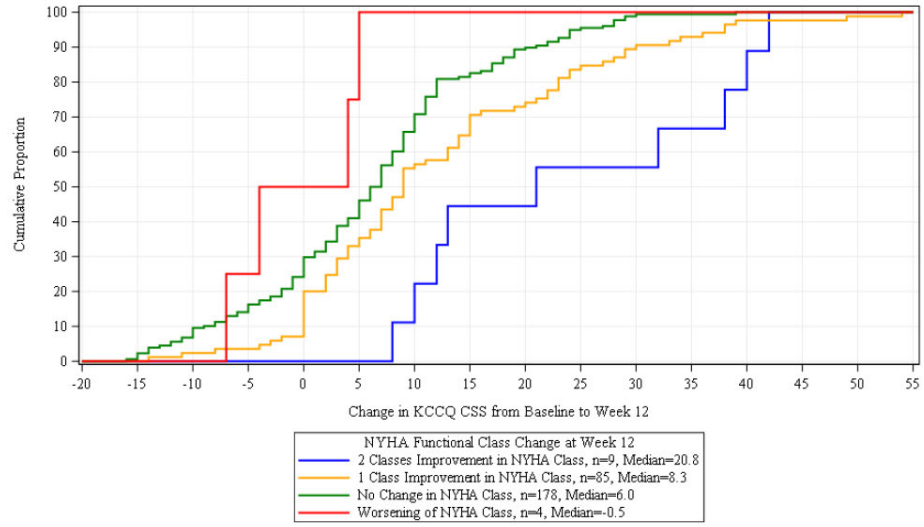


Source: FDA RTQ Figure 5.1.1 and Figure 5.2.1

Anchor-based analysis results using the NYHA FC anchor scale at Week 12

Figure 1: Cumulative Distribution of Change from Baseline in KCCQ-23 CSS by NYHA Functional Class Change

A. Week 12



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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 6, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 219083
Product Name, Dosage Form, and Strength:	Myqorzo (aficamten) tablet, 5 mg, 10 mg, 15 mg, 20 mg
Applicant Name:	Cytokinetics, Incorporated
FDA Received Date:	September 17, 2025
TTT ID #:	2024-11043-1
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Cytokinetics, Incorporated submitted revised container labels received on September 17, 2025 for Myqorzo. We reviewed the revised container labels for Myqorzo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The container labels are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Cytokinetics, Incorporated in Section 3.

3 RECOMMENDATIONS FOR CYTOKINETICS, INCORPORATED

A. Container Labels

1. As currently presented, it is unclear if the month portion, "MM," of the expiration date format will use alphabetical or numerical characters. A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors. Presenting the month as two alphabetical characters does not clearly communicate, for example, whether 'MA' or 'JU' is for the months of March or May and June or July, respectively. Clarify how you intend to express the month portion for the expiration date. FDA recommends using only numerical characters if only the year and 2-digit month is expressed. If using alphabetical characters, we recommend you revise the format for the month portion to three-letters (for example, "MAR" vs. "MA" to represent March) to prevent confusion.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Kattappuram, R. Label and Labeling Review for Myqorzo (NDA 219083). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAR 19. TTT ID: 2024-11043.

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NICOLE F IVERSON
10/06/2025 11:27:12 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns
Version: 2024-09-13

Date:	8/20/2025
Product Name(s):	Aficamten
Application Type/Number(s):	NME NDA 219083
Applicant:	Cytokinetics Inc.
NEXUS Task Tracking Tool ID #:	Milestone mtgs under TTT# 2024-11042 ARIA Sufficiency Memo [TTT# 2025-15611]
Primary Reviewer:	Margie R. Goulding, PhD, Epidemiologist Division of Epidemiology II
Secondary Reviewer:	Natasha Pratt, PhD, Epidemiologist Division of Epidemiology II
Division Director:	Monique Falconer, MD, MS Division of Epidemiology II
Sub-Office Director:	Judith Zander, MD Office of Pharmacovigilance and Epidemiology
Sentinel Program Lead:	Patricia Bright, PhD, MSPH Regulatory Science Staff, Office of Surveillance and Epidemiology

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Aficamten is an allosteric and reversible inhibitor of cardiac myosin motor activity. Aficamten reduces the force generated by myosin at the cardiac sarcomere, which contributes to the pathophysiology of hypertrophic cardiomyopathy (HCM). In HCM patients, myosin inhibition with aficamten may reduce cardiac sarcomere contractility and left ventricular outflow tract (LVOT) obstruction. The proposed indication for this second-in-the-class of cardiac myosin inhibitors is the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). It has an orphan drug designation because of the low incidence of oHCM. Aficamten's predecessor, the first-in-class drug mavacamten (Camzyos) was approved on April 28, 2022 with a PMR to conduct a worldwide descriptive study that collects data in women exposed to mavacamten during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant through at least the first year of life.

1.2. Describe the Safety Concern

In the animal reproduction toxicity studies, malformations were observed in the rats and rabbits at exposures at or higher than the maximum recommended human dose (MRHD). In rats, kinked/bent tail malformations were observed at exposures 3.5-5-times the clinical exposure at the MRHD. Cardiac malformations were observed in rabbits at 1-times the clinical exposure at the MRHD. These cardiac malformations were only observed at the mid-dose tested- not observed at the high dose, so the relationship to exposure to the drug is called into question. Although the aficamten animal studies did not identify a specific safety signal indicating an increased risk for embryo-fetal toxicity at clinical exposures, study findings in another drug in the class for both rat and rabbit have demonstrated major visceral and skeletal malformations at clinically equivalent dose exposures. Hypertrophic cardiomyopathy occurs in females of reproductive age and, because aficamten is systemically absorbed, fetal exposure to aficamten during pregnancy is anticipated. Therefore, there is a need to collect data in humans to assess potential risks of pregnancy and maternal complications, and adverse effects on the developing fetus and neonate related to the use of aficamten.

For labeling, currently no boxed warning, pregnancy contraindication or Section 5 warning is proposed. But Section 8.1 and 8.2 read:

8.1. Pregnancy

Risk Summary

There are no available data on the use of MYQORZO during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The underlying maternal condition during pregnancy poses a risk to the mother and fetus (see Clinical Considerations). In embryo-fetal and pre- and postnatal development studies, when pregnant rats were administered aficamten during the period of organogenesis, aficamten increased the incidence of structural malformations at exposures

>=4-times the maximum recommended human dose (MRHD) of 20 mg based on AUC [redacted] No adverse effects on development were seen at 3-times the MRHD exposure (see Data).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and Embryo-Fetal Risk

Obstructive HCM in pregnancy has been associated with increased risk for preterm birth.

Data

Animal Data

Aficamten given to pregnant rats (2, 6 and 9 mg/kg/day) during the period of organogenesis [redacted] No adverse effects on embryofetal development were observed at 3-times the exposure at the MRHD.

Pregnant rabbits given aficamten (5, 10 and 20/15 mg/kg/day) during the period of embryofetal organogenesis [redacted] a numerical increase in post-implantation loss (late resorptions) and fetuses with cardiac malformations [redacted]

Pregnant rats given aficamten (0.5, 1.5, 6 mg/kg/day) during organogenesis through offspring weaning in a pre- and postnatal development study had reduced offspring viability at the [redacted] in the presence of maternal toxicity, [redacted] An increased number of offspring with bent tails was also observed at the [redacted] no adverse maternal toxicity or developmental effects occurred at [redacted] Aficamten did not affect neurobehavioral parameters, sexual maturation, or reproductive function of the offspring at any dose.

8.2 Lactation

Risk Summary

There are no data on the presence of aficamten in human milk, the effects on the breastfed infant, or the effects on milk production. Aficamten was detected in the plasma of rat pups when dams were dosed with the drug orally during the lactation period. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MYQORZO and any potential adverse effects on the breastfed

infant from MYQORZO or from the underlying maternal condition.

1.3. AAA Purpose (per Section 505(o)(3)(B))

Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.

☐ Assess a known serious risk
☐ Assess signals of serious risk
☒ Identify unexpected serious risk when available data indicate potential for serious risk

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication in pregnant women, but practitioners may use product off-label in pregnant women
☒No approved indication in pregnant women, but there is the potential for inadvertent exposure before a pregnancy is recognized
☐ No approved indication in pregnant women, but use in women of childbearing age is a general concern

2.2. Regulatory Goal[1]

☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest*.
☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome*.
☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a targeted or multiple safety concern(s)/health outcome(s)*.
  ☐ Targeted evaluation of specific safety concern
  ☒ Simultaneous identification of multiple unspecified adverse outcomes

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review ☐ E. database study without chart review
☒ Other: **Descriptive Pregnancy Safety Study:** Conduct a worldwide descriptive study

[1] Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.

that collects prospective and retrospective data in women exposed to Myqorzo (aficamten) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.

2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain	**Explanation on ARIA insufficiency**
☒ Study Population	Only a small number of pregnant women exposed to aficamten is expected since pregnancy in women with symptomatic obstructive hypertrophic cardiomyopathy (oHCM) has been associated with increased risk of pre-term birth. Symptomatic oHCM during pregnancy poses a risk to the mother and fetus. But the 2020 AHA/ACC guidelines for the diagnosis and treatment of patients with HCM[2], say that "For women with clinically stable HCM who wish to become pregnant, it is reasonable to advise that pregnancy is generally safe as part of a shared discussion regarding potential maternal and fetal risks, and initiation of guideline-directed therapy." Beta-blockers, not cardiac myosin inhibitors, are currently recommended for symptoms related to outflow tract obstruction in pregnant women with HCM.
.☐ Exposures (& Comparators)	
☒ Outcomes	ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.
☒ Covariates	Detailed information is needed on any covariates (e.g. family history/genetics, illicit substance use, alcohol use, smoking) that may be associated with adverse outcomes, but may not be available in Sentinel secondary data. Primary data collection is needed.
☐ Analytic Tools	
Overall ARIA sufficiency determination	
☒ Insufficient ☐ Sufficient	

[2] "2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy" in Circulation, vol. 142, no. 25, 12/22/2020. Accessed at https://www.ahajournals.org/toc/circ/142/25 on 7/31/2025.

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Myqorzo (aficamten) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus, the neonate, and the infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

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PATRICIA L BRIGHT
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The Clinical Inspection Summary

Date	July 29, 2025
From	Suyoung Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Tzu-Yun McDowell, M.D., Clinical Reviewer, DCN Fortunato Senatore, M.D., Clinical Team Leader, DCN Charu Gandotra, M.D., MSCTR, FACC, FASE, Acting Associate Director of Therapeutic Review Maryam Changi, PharmD, Regulatory Project Manager Division of Cardiology and Nephrology
NDA #	219083
Applicant	Cytokinetics Inc.
Drug	Myqorzo (aficamten)
NME (Yes/No)	Yes
Proposed Indication(s)	Treatment of symptomatic obstructive hypertrophic cardiomyopathy
Consultation Request Date	November 26, 2024
Summary Goal Date	August 14, 2025
Action Goal Date	September 26, 2025
PDUFA Date	September 26, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Masri, Nassif, and the sponsor Cytokinetics were inspected in support of NDA 219083, covering Study CY 6031. Based on the results of the inspections, the study appears to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the sponsor appear acceptable in support of the respective indication. Of note, there was one unreported adverse event of a dental infection for one subject at Dr. Masri's site, who was randomized to aficamten. Infections does not appear to be included in the sponsor's proposed label. This unreported adverse event is presented here for the review division's consideration.

II. BACKGROUND

According to the sponsor, aficamten is a small molecule cardiac myosin inhibitor. The sponsor submitted NDA 219083 for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM). Two BIMO Review-Based clinical investigator inspections and a sponsor inspection were requested for Study CY 6031.The following describes the study:

Protocol CY 6031: "A Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of CK-3773274 in Adults With Symptomatic

Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction."

The study was a randomized, double-blind, placebo-controlled study to evaluate the effect of aficamten on exercise capacity in participants with symptomatic oHCM.

Sites: Subjects were randomized at 82 sites across China, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Portugal, Spain, the United Kingdom, and the United States.

Subjects: A total of 282 subjects were randomized (i.e., 142 subjects who received aficamtem and 140 subjects received placebo), and 276 subjects completed the Treatment Period (i.e., 139 subjects who received aficamten and 137 subjects who received placebo).

Study initiation and completion dates: (b) (6) (first subject, first screening visit); (b) (6) (last subject, last visit)

Database lock date; study unblinding date: December 21, 2023; December 21, 2023

The study consisted of three periods, including a 6-week screening period, a 24-week treatment period, and a 4-week follow-up period.

During the treatment period, subjects were randomized 1:1 to receive aficamten or placebo once daily for 24 weeks. All subjects started on a dose of 5 mg daily and were titrated individually based on echocardiography results at Weeks 2, 4, and 6 visits. If a subject had a post-Valsalva left ventricular outflow tract gradient (LVOT-G) ≥30 mmHg and a biplane left ventricular ejection fraction ≥55%, then the dose would be escalated, with the maximum dose being 20 mg. Cardiopulmonary exercise testing (CPET) was conducted at screening and at Week 24, where they would exercise on a stationary cycle or treadmill while attached to machines that would measure the peak oxygen uptake (pVO2).

Key inclusion criteria: Male or female subjects aged 18 to 85 years of age, with a body mass index <35 kg/m^2. Subjects were to have a diagnosis of hypertrophic cardiomyopathy (HCM), with left ventricular hypertrophy and non-dilated left ventricular (LV) chamber in the absence of other cardiac disease, and end diastolic LV wall thickness measured by echocardiography core laboratory of ≥15 mm in at least 1 myocardial segment or ≥13 mm in at least 1 wall segment, and a known disease-causing gene mutation or positive family history of HCM; a resting LVOT-G ≥30 mmHg and Valsalva LVOT-G ≥50 mmHg at screening as determined by the echocardiography core laboratory; an LVEF ≥60% per the echocardiography core laboratory; New York Heart Association functional class of II or III at screening; and a respiratory exchange ratio of ≥1.05 and pVO2 ≤90% predicted on the screening CPET per the core laboratory. Subjects on beta-blockers, verapamil, diltiazem, or disopyramide were to have been on a stable regimen for >6 weeks prior to randomization, which was individually optimized according to local practice. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Change in peak oxygen uptake (pVO2) measured by cardiopulmonary exercise testing (CPET) from baseline (screening) to the end of treatment (Week 24).

III. RESULTS (by site):

1. **Dr. Ahmad Masri**
   Site 1001
   3181 Sw Sam Jackson Park Road
   Portland, OR 97239-3011
   PDUFA Inspection Dates: February 10-18, 2025

For Protocol CY 6031, 29 subjects were screened, and 20 subjects were enrolled and randomized. All randomized subjects completed the study.

An audit of the study records was conducted for all 29 screened subjects. Records reviewed included, but were not limited to, protocol and amendments, informed consent forms, case report forms, medical records for office visits, laboratory reports, echocardiography videos and reports, ECG reports, cardiopulmonary exercise testing (CPET) documentation and reports, drug accountability records, site correspondence with sponsor, monitor, and IRB, regulatory records, FDA 1572s, financial disclosure records, Institutional Review Board submission and approvals, concomitant medications, protocol deviations, subject selection criteria, adverse event reporting, and paper source records for verification of primary efficacy endpoint.

The pVO2 (ml/kg/min) at Baseline (Screening Visit) and Week 24 were verified by comparing the data in the sponsor's data line listings with the site's paper source documents. No discrepancies were noted.

There was one unreported adverse event involving Subject (b) (6) who was randomized to aficamten on (b) (6) The electronic medical record documented that this subject experienced a moderate dental infection from (b) (6) which was treated with cephalexin, resolved completely, and was assessed as not related to the study drug.

Reviewer's comment: The cephalexin treatment was properly documented in the sponsor's concomitant medications listings. Site staff acknowledged during the inspection that failing to report the dental infection as an adverse event was an oversight on their part. The proposed label submitted by the sponsor appears not to include any infections. This isolated event is unlikely to impact overall safety results and is provided for the review division's consideration.

2. **Dr. Michael Nassif**
   Site 1009
   4401 Wornall Road
   Kansas City, MO 64111-3220
   PDUFA Inspection Dates: February 20-25, 2025

For Protocol ISIS CY 6031, 18 subjects were screened, and 12 subjects were enrolled and randomized. All randomized subjects completed the study.

An audit of the study records was conducted for all 18 screened subjects. Records reviewed included, but were not limited to, protocol and amendments, informed consent forms, eligibility criteria, protocol deviations, adverse event reporting, Institutional Review Board submission and approvals, 1572s, financial disclosures, drug accountability, monitoring and annual reports, sponsor monitoring activities, and paper source records for verification of the primary efficacy endpoint.

The pVO2 (ml/kg/min) at Baseline (Screening Visit) and Week 24 were verified by comparing the data in the sponsor's data line listings with the site's paper source documents. No discrepancies were noted. There was no evidence of underreporting of adverse events.

3. **Cytokinetics Inc.**
   350 Oyster Point Boulevard
   South San Francisco, CA 94080-1912
   PDUFA Inspection Dates: February 25-March 3, 2025

This inspection covered the sponsor's conduct and oversight of Protocol CY 6301. Records reviewed included, but were not limited to, institutional review board approvals, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, quality assurance, safety/adverse event reporting, data collection and handling, records retention, financial disclosures, and monitoring records in more detail for the two above clinical investigator sites, Sites 1001 and 1009.

The inspection found the site monitoring and general oversight by the sponsor to be adequate. The sponsor did not identify any serious noncompliance at any of the active clinical investigator sites, and none of the sites were terminated. In general, the sponsor appeared to be in compliance with Good Clinical Practice and FDA regulations. No significant concerns regarding the conduct or oversight of study were identified.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
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OSI/ GCP Program Analysts/
OSI/Database PM/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatrics and Maternal Health Review

Date: June 3, 2025 **Date consulted:** February 14, 2025

From: Kerry R. Shaab, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health

To: Division of Cardiology and Nephrology (DCN)

Drug: Myqorzo (aficamten)

NDA: 219083

Applicant: Cytokinetics

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM).

Materials Reviewed:

- DPMH consult request, dated 2/14/2025. DARRTS Reference ID: 5532118.
- Applicant's background package and proposed labeling for NDA 219083, Sequence Number (SN) 0004, dated 9/26/2024.

- Applicant's response to DPMH Information Request (IR) dated 3/11/2025, SN 0023, submitted 3/20/2025.
- DPMH Memorandum regarding Postmarketing Requirement (PMR) for descriptive pregnancy safety study for Camzyos (mavacamten), NDA 214998, by Kristie Basden, DO, dated August 20, 2021. DARRTS Reference ID: 4833004.[1]
- DPMH PLLR Review for Camzyos (mavacamten), NDA 214998, by Tamara Johnson, MD, dated February 16, 2022. Reference ID: 4937638.[1]

Consult Question: "The Division would like DPMH to assist with reviewing the PLLR part of labeling".

I. INTRODUCTION AND BACKGROUND

On September 26, 2024, the Applicant, Cytokinetics, Inc., submitted a 505(b)(1) New Drug Application (NDA) for Myqorzo (aficamten) for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). The Division of Cardiology and Nephrology (DCN) consulted the Division of Pediatrics and Maternal Health (DPMH) on February 14, 2025, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Aficamten received Orphan Drug Designation for the treatment of symptomatic hypertrophic cardiomyopathy on January 5, 2021.
- Aficamten was granted Breakthrough Therapy designation by the FDA for the treatment of oHCM on December 6, 2021.
- Camzyos (mavacamten) was the first-in-class cardiac myosin inhibitor for the treatment of adults with symptomatic oHCM. It was approved by the FDA on April 28, 2022[1].

Drug Characteristics[2]

Drug Class	Cardiac myosin inhibitor
Proposed Mechanism of Action	Aficamten is an allosteric and reversible inhibitor of cardiac myosin motor activity. Aficamten reduces the force generated by myosin at the cardiac sarcomere, which contributes to the pathophysiology of HCM. In HCM patients, myosin inhibition with aficamten (b) (4) reduce cardiac sarcomere contractility and left ventricular outflow tract (LVOT) obstruction.
Proposed dosage form and administration	5 mg, 10 mg, 15 mg, and 20 mg tablets Recommended starting dose is 5 mg orally once daily. Increase the dose every 2 to 8 weeks by 5 mg until a maintenance dose or maximum recommended dose of 20 mg once daily is achieved. Dosage is individualized based on (b) (4) (b) (4)

[1] This review was part of the materials reviewed but DPMH did not rely on data in the Camzyos NDA or the agency's finding of safety and effectiveness for Camzyos to support labeling recommendations provided in this review for NDA 219083.
[2] NDA 219083, draft Annotated Labeling with DCN review team edits, review ongoing.

Molecular weight	337.38 g/mol
Half-life	Median terminal half-life of 80 hours
% protein-bound	Approximately 90%
Bioavailability	Bioavailability after oral administration is unknown.

Hypertrophic cardiomyopathy (HCM) and Pregnancy

HCM is a heterogeneous genetic heart disease inherited in an autosomal dominant pattern with an estimated prevalence of 0.6% in the general population. HCM is characterized by left ventricular (LV) hypertrophy in the absence of other cardiac, systemic, or metabolic diseases capable of explaining the degree of LV hypertrophy.[3] Clinical manifestations of HCM vary considerably, with symptoms ranging from none or mild exercise intolerance to severe lifestyle-limiting symptoms such as chest pain, syncope, and dyspnea on exertion, arrhythmias, advanced heart failure, and sudden cardiac death.[3] Obstructive HCM (oHCM) is characterized by dynamic left ventricular outflow tract (LVOT) obstruction and is present in approximately 75% of patients with HCM.[3] Regardless of the presence of symptoms, LVOT at rest that is ≥ 30 mm Hg is an independent predictor of progressive heart failure (HF) symptoms, HF, and stroke death in patients with HCM.[4] Mortality in HCM patients is significantly higher than the U.S. general population. Mortality in young HCM patients (20-29 years of age) is elevated > 4-fold, and in older patients (50-69 years of age) > 3-fold.[5]

Pregnancy places a significant burden on the cardiovascular system (such as marked increases in circulating blood volume, stroke volume, and heart rate) which may lead to heart failure, arrhythmias, and, rarely, maternal mortality in women with a pre-existent cardiomyopathy.[6] According to the 2020 AHA/ACC Guideline for Hypertrophic Cardiomyopathy, pregnancy is generally safe for women with clinically stable HCM as part of a shared discussion regarding potential maternal and fetal risks, and initiation of guideline-directed therapy. Selected beta-blockers should be administered for symptoms related to outflow tract obstruction or arrythmias, with monitoring of fetal growth.[7] In all women with HCM, pre-pregnancy risk assessment and counseling as well as genetic counseling are indicated. Pre-pregnancy genetic counseling involves identifying genetic mutations associated with HCM, assessing risk of

[3] Erika Hutt, Milind Y. Desai, Medical Treatment Strategies for Hypertrophic Cardiomyopathy, The American Journal of Cardiology, Volume 212, Supplement, 2024, Pages S33-S41, ISSN 0002-9149, https://doi.org/10.1016/j.amjcard.2023.10.074.

[4] Maron, MS. Hypertrophic Cardiomyopathy: Natural history and prognosis. In:UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed 4/22/2025)

[5] Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM, Olivotto I. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation. 2018 Oct 2;138(14):1387-1398. doi: 10.1161/CIRCULATIONAHA.117.033200. Epub 2018 Aug 23. PMID: 30297972; PMCID: PMC6170149.

[6] Schinkel, Arend F.L. MD, PhD. Pregnancy in Women with Hypertrophic Cardiomyopathy. Cardiology in Review. September/October 2014-Volume 22-Issue 5-p 217-222.

[7] Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020 Dec 22;142(25):e558-e631. doi: 10.1161/CIR.0000000000000937. Epub 2020 Nov 20. Erratum in: Circulation. 2020 Dec 22;142(25):e633. doi: 10.1161/CIR.0000000000000945. PMID: 33215931.

inheritance to offspring, and providing information about available prenatal and preimplantation testing options; thus, allowing affected women to make informed choices about family planning and prenatal testing. Most pregnant women with HCM carry moderate risk of morbidity, have clinical evaluations and echocardiography each trimester, and deliver vaginally. Those who are symptomatic or have significant left ventricular outflow obstruction or recurrent arrhythmias prior to pregnancy are at higher risk of morbidity, including worsening symptoms and complications including heart failure.[8] Advising against pregnancy is justified in only a small minority with left ventricular ejection fraction less than 30%, New York Heart Association classes II-IV with restrictive physiology, or severe symptomatic left ventricular outflow obstruction.[8] A systematic review of 18 studies including randomized controlled trials, prospective and retrospective case series, and cohort studies with 1624 pregnancies among a total of 1319 women with HCM demonstrated that maternal and fetal outcomes among women with HCM are favorable. Nevertheless, pregnancy in women with HCM carries maternal and fetal risks. The incidence of maternal death was 0.2%. Across 12 studies and 928 pregnancies reporting fetal outcomes, the overall rate of stillbirth was 1%, preterm birth was 22% (18-25%) and the neonatal mortality rate was 0.22%.[9]

II. REVIEW

PREGNANCY

Nonclinical Experience

The nonclinical team reviewed the Applicant's submission and provided the following information:

In the Embryo-Fetal Development (EFD) study conducted in rats, aficamten given to pregnant rats (2, 6 and 9 mg/kg/day) during the period of organogenesis increased post-implantation loss (early and late resorptions), external fetal malformations (kinked tail), and decreased mean fetal body weight at 9 mg/kg/day (an exposure level 5-times the MRHD clinical exposure based on $AUC_{unbound}$). No adverse effects on embryofetal development were observed at 3.5-times the exposure in humans at the MRHD.

In the rabbit EFD study, pregnant rabbits given aficamten at doses of 5, 10, and 20/15 mg/kg/day during the period of organogenesis had a numerical increase in post-implantation loss (late resorptions) and fetuses with cardiac malformations at the mid-dose only (an exposure level < 1-times the MRHD based on free AUC). These findings were observed with an overall low incidence and an unclear relation to the drug. These effects were not observed at the high dose. The high dose caused maternal toxicity at a clinically relevant exposure level.

In the Pre- and Postnatal Development (PPND) study in rats, aficamten was administered orally to pregnant female rats from implantation through weaning at doses up to 6 mg/kg/day. The pregnant rats showed signs of maternal toxicity, had increased incidence of offspring with bent tails, and reduced viability of the newborn pups after birth during the preweaning period at the highest dose (3.5-times the MRHD exposure). No adverse maternal toxicity or developmental effects occurred at 1-times the exposure in humans at the MRHD. Aficamten did not affect

[8] Sara Saberi, Hypertrophic Cardiomyopathy in Pregnancy, Cardiology Clinics, Volume 39, Issue 1, 2021, Pages 143-150, ISSN 0733-8651, ISBN 9780323809269, https://doi.org/10.1016/j.ccl.2020.09.009.

[9] Moolla M, Mathew A, John K, Yogasundaram H, Alhumaid W, Campbell S, Windram J. Outcomes of pregnancy in women with hypertrophic cardiomyopathy: A systematic review. Int J Cardiol. 2022 Jul 15;359:54-60. doi: 10.1016/j.ijcard.2022.04.034. Epub 2022 Apr 12. PMID: 35427704.

sexual maturation, neurobehavioral or reproductive function parameters of the offspring at any dose.

The reader is referred to the full nonclinical review by Andrew Jacob, Ph.D.

> ***Reviewer Comment:***
> *DPMH discussed the animal reproduction studies with the nonclinical team. With respect to the observed malformations, two different malformations occurred: kinked/bent tail malformation in the rat and cardiac malformations in the rabbit. The kinked/bent tails were observed in both the rat EFD and PPND studies with the malformations occurring in a dose-related manner in the PPND study. It is unclear how the kinked/bent tail malformation relates to humans. The cardiac malformations were observed in rabbits only at the mid-dose tested. These were not observed at the high dose tested, so the relationship to exposure to the drug is called into question. Additionally, according to the nonclinical team, there were no cross-species concordant findings at clinically equivalent exposures to identify a potential safety signal. In the PPND study, the reduced pup viability resulted from feeding issues occurring in the presence of maternal toxicity at the highest doses tested. To clarify the 20/15 mg/kg/day dosing in the rabbit EFD study, the initial high dose tested was 20 mg/kg/day, however, the rabbits did not tolerate this dose. As a result of this intolerance, the high dose was decreased to 15 mg/kg/day.*

Review of Pharmacovigilance Database

The Applicant reported two pregnancy cases during the clinical development program.[10,11]

- A 36-year-old female participant (Study participant CY-6022-(b) (6)) in Study CY 6022 with a past medical history significant for symptomatic oHCM, ovarian cyst (b) (6) and a previous induced abortion (unknown dates) received aficamten 5 mg orally once daily from Day 1 to Day 49, then the aficamten dose was up-titrated to 10 mg from Day 50 to Day 340. The participant "refused" further aficamten administration from Day 341 due to "unspecified personal reasons" and aficamten "remained interrupted". On (b) (6) (b) (6) (Day 362), the participant became pregnant via *in vitro* fertilization, undergoing an embryo transfer 22 days after the last aficamten dose. On (b) (6) (Day 386), the participant's pregnancy test was positive. The last menstrual period was on (b) (6) (Day 340), and the estimated date of conception was on (b) (6) (Day 357), which was 17 days after the last dose of aficamten. The participant's concomitant medications during the pregnancy included colecalciferol, pyridoxine, docosahexaenoic acid/eicosapentaenoic acid, vitamins, calcium carbonate, docusate, magnesium glycinate, macrogol, nadolol, estrogen patches, acetylsalicylic acid, probiotics, famotidine, and omeprazole. On (b) (6) (Day 620), she vaginally delivered a full-term male infant at 39 weeks and 4 days. The infant's Apgar scores were 7 at 1 minute and 9 at 5 minutes. Birth weight was 7 lbs 3 oz (3.26 kg), height was 49.5 cm (19.5 inch), and head circumference was 35 cm, and the examination was reported to be normal. The infant's 12-month "post-delivery check-up" confirmed a healthy infant.

[10] NDA 219083, Module 2.7.4, Summary of Clinical Safety, p. 79 and Interim Clinical Study Report for Study CY6022.
[11] NDA 219083, SN 0023, Applicant's response to DPMH IR, dated 3/11/2025, submitted 3/20/2025.

There were no developmental delays or complications. Aficamten remained interrupted as the participant was breastfeeding.

- The female partner of a male participant (CY-6022-(b) (6)) in Study CY 6022, with a past medical history significant for obesity and a prior pregnancy with gestational diabetes resulting in a live birth with no fetal complications, became pregnant. The male participant received aficamten 5 mg orally once daily from Day 1 to Day 15; dose up-titrated to 10 mg from Day 16 to Day 29; dose up-titrated to 15 mg from Day 30 to Day 43; and to 20 mg from Day 44 to Day 174. On an unknown date, the participant's partner tested positive for pregnancy. It was confirmed as a planned pregnancy. The partner's last menstrual period was on (b) (6) (Day 67), and the estimated date of conception was on (b) (6) (Day 80). The male participant was taking aficamten at the time of conception. The participant's partner had a full-term vaginal delivery at 39 weeks. The infant was female with normal physical status. The infant's Apgar scores were 8 at 1 minute and 9 at 5 minutes. Birth weight was 3.38 kg, height was 20 inches, and head circumference was 33.5 cm. The 12-month follow-up for the infant was planned to occur in (b) (6) No further details provided.

  Reviewer Comment:
  Aficamten has a median terminal half-life ($t_{1/2}$) of approximately 80 hours in patients with oHCM and approximately 95% of patients with oHCM are expected to have a $t_{1/2}$ of less than 155 hours. Using the median terminal half-life of 80 hours, aficamten is mostly cleared from systemic circulation in approximately 17 days. Based on the estimated date of conception for study participant CY-6022-(b) (6) it is possible that early pregnancy aficamten-exposure occurred. This pregnancy resulted in a full-term delivery of a healthy newborn. In the second pregnancy case, although paternal aficamten exposure occurred prior to and at the time of conception, there is no expectation that male exposure to a non-mutagenic drug would lead to any consequences. There are insufficient human pregnancy data from the pregnancy in the aficamten-exposed female participant to inform the safety of aficamten use in pregnancy.

Review of Literature

Applicant's review:

The Applicant did not perform a literature search related to aficamten use during pregnancy.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "aficamten" or "cardiac myosin inhibitor" and "pregnancy", "pregnancy outcomes", "pregnant", "major birth defects", "birth defects", "congenital malformations", "congenital anomalies", "teratogenicity", "miscarriage", "spontaneous abortion", "elective abortion", "pregnancy loss", "stillbirth", "fetal loss", "fetal demise", "fetotoxicity", "safety events", and "adverse events". No relevant publications were found.

In addition, DPMH conducted a search for aficamten in Micromedex[12], Reprotox[13], TERIS[14], Shepard's[15], and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[16]. No entries for aficamten were found.

> ***Reviewer comment:***
> *The Applicant did not perform a literature search. There are no relevant publications or information to inform the safety of aficamten use in pregnancy.*

LACTATION

Nonclinical Experience

The nonclinical team reviewed the Applicant's submission and provided the following information:

In the PPND study, aficamten was associated with reduced viability of the newborn pups after birth during the preweaning period. In addition, aficamten was detected in the plasma of preweaning pups on Postnatal Day (PND) 4. Although direct measurements of aficamten in the rat milk were not obtained, the presence of aficamten in the weaning pups suggests transfer through rat milk. The half-life of aficamten in adult rats is approximately 8 hours, based on the toxicokinetic (TK) data from the 6-month repeat dose study. Therefore, the presence of aficamten in the plasma of rat pups is not likely related to prenatal maternal exposure.

The reader is referred to the full nonclinical review by Andrew Jacob, Ph.D.

Review of Pharmacovigilance Database

According to the Applicant, there were no incidental cases of aficamten exposure in lactating women during the drug development program.[11]

Review of Literature

Applicant's review:

The Applicant did not provide a literature search related to aficamten use in lactating women.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "aficamten" or "cardiac myosin inhibitor" and "lactating", "lactation", "nursing", "breastfeeding", "breastfed", "breast fed", "neonates", and "infants". No relevant publications were found.

[12] Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 3/5/2025.
[13] Reprotox Website: www.Reprotox.org. Accessed 3/5/2025.
[14] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 3/5/2025.
[15] Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 3/5/2025.
[16] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021.

In addition, DPMH conducted a search for aficamten in Micromedex[12], Reprotox[13], Hale's *Medications and Mothers' Milk*[17], the Drugs and Lactation Database (LactMed)[18], and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[16]. No information was found.

> ***Reviewer comment:***
> *The Applicant did not perform a literature search. There are no relevant publications or information to inform the safety of aficamten use during lactation.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

A Fertility and Early Embryonic Development (FEED) study was conducted in rats in which aficamten was administered at doses up to 6 mg/kg/day in females and 3 mg/kg/day in males, with no drug-related effects on fertility.

The nonclinical team agrees with the Applicant's conclusion that aficamten did not impact fertility in male or female rats.

The reader is referred to the full nonclinical review by Andrew Jacob, Ph.D.

Drug-Hormonal Contraceptive Interaction (DDI)

Despite being a weak CYP3A inducer, mavacamten, the first-in-class cardiac myosin inhibitor, may be used concomitantly with combined oral contraceptives containing norethindrone based on results of a study conducted using ethinyl estradiol and norethindrone. However, its potential effect on the exposures of progestins other than norethindrone is unknown. With respect to a potential aficamten-hormonal contraceptive interaction, the Clinical Pharmacology team provided the following information[19]:

Aficamten is not expected to induce CYP3A4 at clinically relevant concentrations based on *in vitro* drug interaction studies. Therefore, the Clinical Pharmacology team concluded there were no specific concerns for potential clinical drug-drug interactions involving combined oral contraceptives.

The reader is referred to the full clinical pharmacology review by Chongwoo Yu, Ph.D.

> ***Reviewer Comment:***
> *Unlike mavacamten, the first-in-class cardiac myosin inhibitor, which has a potential effect on the exposures of progestins other than norethindrone due to its ability to induce CYP34A substrates, aficamten is not expected to have a significant effect on hormonal contraceptives at clinically relevant concentrations.*

[17] Hale, Thomas W. Hale's Medications and Mother's Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com. Accessed 3/5/2025.
[18] Drugs and Lactation Database (LactMed). Accessed 3/5/2025.
[19] Personal communication with Chongwoo Yu, Ph.D., Clinical Pharmacology Review Team, dated 4/2/2025.

Review of Pharmacovigilance Database

According to the Applicant, the potential effects on male or female fertility were assessed based on the data set supporting the 120-day Safety Update (cutoff date of August 31, 2024) The search utilized the Standardized MedDRA Query (SMQ) for Fertility Impairment, which includes preferred terms (PT) for male and female reproductive dysfunctions. The search identified 3 participants with adverse events within the SMQ Fertility Impairment criteria. The events are summarized as follows[11]:

- Study participant CY 6022-(b) (6): 41-year-old Caucasian female with oHCM and medical history of anemia, on concomitant medications including atenolol and progesterone was started on aficamten 5 mg orally once daily on (b) (6) and maintained that dosage throughout the study. In (b) (6) approximately 590 days after starting aficamten treatment, the participant experienced an adverse event of "menstruation irregular (PT)". This event was assessed as non-serious, mild, and not related to aficamten. The event was reported as "not resolved" as of the cut-off date of August 31, 2024. The participant continued in the study. No further details provided.

- Study participant CY 6022(b) (6): 39-year-old Caucasian female with non-obstructive HCM and relevant medical history of ferropenic anemia since 2009, on concomitant medications including bisoprolol, edoxaban, and furosemide was started on aficamten 5 mg orally once daily on (b) (6) and up-titrated to highest dose of 20 mg. On (b) (6) aficamten was down titrated to 15 mg and to 5 mg on (b) (6) (b) (6) On (b) (6) 483 days after starting aficamten treatment, the participant experienced an adverse event of "abnormal uterine bleeding (PT)". This event was assessed as non-serious, moderate, and not related to aficamten. There was no change to aficamten dosage in response to the event. The participant was treated with desogestrel 75 micrograms daily, and the event resolved approximately 11 weeks later ((b) (6) (b) (6)). The participant experienced a concurrent event of "anemia (PT)" starting on Study Day 483. This event was assessed as non-serious, moderate, not resolved, and not related to aficamten. The participant continued in the study. No further details provided.

- Study participant CY 6031-(b) (6): 41-year-old Caucasian male with oHCM on concomitant medications including disopyramide and betaxolol was started on aficamten 5 mg orally once daily on (b) (6) and up-titrated to highest dose of 20 mg. On (b) (6) 158 days after starting the aficamten treatment, the participant experienced an adverse event of "varicocele (PT)". This event was assessed as non-serious, mild, and not related to aficamten. The event resolved on (b) (6) (Study Day 188). The participant completed study CY 6031 on (b) (6) and enrolled in study CY 6022 (Participant ID 6022-(b) (6)). The participant continued in the study. No further details provided.

The Applicant concluded that all three cases have plausible alternative explanations, including "hormonal contraceptive use, age-related changes, or common physiologic conditions". Additionally, there is "no known plausible pharmacological mechanism by which aficamten could cause any of the reported events". Therefore, the available evidence "does not support a causal relationship between aficamten and these events."

Reviewer Comment:
DPMH agrees with the applicant's conclusions that all three cases have plausible alternative explanations and the number of cases is too low to draw any meaningful conclusions. Furthermore, none of the identified cases suggest that aficamten affects fertility.

Review of Literature

Applicant's review:
The Applicant did not provide a literature search related the effects of aficamten use on female and male reproductive potential.

DPMH review:
DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "aficamten" or "cardiac myosin inhibitor" and "fertility", "infertility", "decreased sperm count", "contraception", "oral contraceptives", "effects on fertility", and "reproduction".

In addition, DPMH conducted a search for aficamten in Micromedex[12], Reprotox[13], and TERIS[14]. No relevant publications or additional information on the effects of aficamten on human fertility were found in the literature search.

Reviewer comment:
The Applicant did not perform a literature search. There are no relevant publications or information to inform the safety of aficamten use in females or males of reproductive potential.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

In the animal reproduction studies, malformations were observed in the rats and rabbits at exposures at or higher than the MRHD. In rats, kinked/bent tail malformations were observed at exposures 3.5-5-times the clinical exposure at the MRHD. The clinical significance of this is unclear. Cardiac malformations were observed in rabbits at 1-times the clinical exposure at the MRHD. These malformations were only observed at the mid-dose tested. These were not observed at the high dose tested, so the relationship to exposure to the drug is called into question. Additionally, there were no cross-species findings at low exposures. DPMH concludes that the animal reproduction data do not suggest a serious risk of developmental toxicity during pregnancy.

With respect to the human data available, there were insufficient data on aficamten use in pregnancy to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Hypertrophic cardiomyopathy occurs in females of reproductive age. According to the 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with HCM, for women with

clinically stable HCM, pregnancy is considered generally safe "as part of a shared discussion regarding potential maternal and fetal risks, and initiation of guideline-directed therapy."[7] Currently, in pregnant women with HCM, selected beta-blockers, not cardiac myosin inhibitors, are recommended for symptoms related to outflow tract obstruction. Although the animal reproduction studies did not identify a specific safety signal indicating an increased risk for embryo-fetal toxicity at clinical exposures, animal findings do not always predict findings in humans. Therefore, there is a need to collect pregnancy outcome data in humans exposed via a postmarketing pregnancy safety study. Pregnancy exposures are likely to be rare, so DPMH recommends a descriptive pregnancy safety study (DPSS) rather than a pregnancy exposure registry to capture prospective and retrospectively reported cases of aficamten exposure during pregnancy to assess risk.

Lactation

There are no available data on the presence of aficamten in human breast milk, the effects of aficamten on the breastfed infant or the effects on milk production. In the PPND study, the presence of aficamten in the plasma of newborn pups suggests transfer into rat milk. When a drug is present in animal milk, it is likely the drug will be present in human milk. Additionally, aficamten's physiochemical properties indicate it will likely be transferred into breast milk. Since aficamten use during lactation may occur, DPMH recommends issuing a postmarketing requirement (PMR) for a clinical milk-only lactation study. The data obtained from a clinical milk-only lactation study would be helpful in determining the amount of aficamten in human breastmilk. If a clinical milk-only lactation study demonstrates a clinically important amount of aficamten in breast milk, further study to examine systemic exposure in the breastfed infant may be needed.

Females and Males of Reproductive Potential

There are no available clinical data to inform labeling related to aficamten effects on human fertility. Animal fertility studies do not indicate any adverse effects at clinical exposures and, thus, aficamten is not expected to impair human fertility. Given there is no evidence of embryo-fetal toxicity or genotoxicity, pregnancy testing or contraception in conjunction with aficamten use are not recommended. Therefore, DPMH recommends omitting labeling subsection 8.3 Females and Males of Reproductive Potential.

POSTMARKETING REQUIREMENTS (PMR) SUGGESTED LANGUAGE

- **Descriptive Pregnancy Safety Study**: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Myqorzo (aficamten) during pregnancy to assess risk of pregnancy and maternal complications, adverse effect on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.

- **Lactation Study**: Perform a milk-only lactation study in lactating women who have received aficamten to measure concentrations of aficamten in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 4/8/2025 and 5/15/2025. DPMH recommendations are below and reflect the discussions with DCN. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on the use of MYQORZO during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The underlying maternal condition during pregnancy poses a risk to the mother and fetus *(see Clinical Considerations)*.

In embryo-fetal and pre- and postnatal development studies, when pregnant rats were administered aficamten during the period of organogenesis, aficamten increased the incidence of major structural malformations at exposures >=4-times the maximum recommended human dose (MRHD) of 20 mg based on $AUC_{\mathbf{unbound}}$. No adverse effects on development were seen at 3-times the MRHD exposure (see *Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and Embryo-Fetal Risk
Obstructive HCM in pregnancy has been associated with increased risk for preterm birth.

Data
Animal Data
Aficamten given to pregnant rats (2, 6 and 9 mg/kg/day) during the period of organogenesis lead to increased post-implantation loss (early and late resorptions) and decreased mean fetal body weight in the presence of maternal toxicity at an exposure level 5-times the MRHD clinical exposure based on $AUC_{unbound}$. External fetal malformations (kinked tail) were observed at an aficamten exposure 5-times MRHD with uncertain human relevance. No adverse effects on embryofetal development were observed at 3-times the exposure at the MRHD.

Pregnant rabbits given aficamten (5, 10 and 20/15 mg/kg/day) during the period of embryofetal organogenesis had a numerical increase in post-implantation loss (late resorptions) and fetuses

with cardiac malformations at the mid dose only. The high dose caused maternal toxicity at a clinically relevant exposure level.

Pregnant rats given aficamten (0.5, 1.5, 6 mg/kg/day) during embryofetal organogenesis through offspring weaning in a pre- and postnatal development study had reduced offspring viability at the highest dose in the presence of maternal toxicity (4-times the MRHD exposure). An increased number of offspring with bent tails was also observed at the same dose. No adverse maternal toxicity or developmental effects occurred at the mid dose at clinical exposure level. Aficamten did not affect neurobehavioral parameters, sexual maturation, or reproductive function of the offspring at any dose.

8.2 Lactation

Risk Summary

There are no data on the presence of aficamten in human milk, the effects on the breastfed infant, or the effects on milk production. Aficamten was detected in the plasma of rat pups when dams were dosed with the drug orally during the lactation period *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MYQORZO and any potential adverse effects on the breastfed infant from MYQORZO or from the underlying maternal condition.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KERRY R SHAAB
06/03/2025 11:47:16 AM

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06/03/2025 01:20:49 PM

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06/04/2025 03:07:59 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 19, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 219083
Product Name, Dosage Form, and Strength:	Myqorzo (aficamten) tablet, 5 mg, 10 mg, 15 mg, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Cytokinetics, Incorporated
FDA Received Date:	August 14, 2024 and September 26, 2024
TTT ID #:	2024-11043
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Myqorzo (aficamten) tablet, we reviewed the proposed Myqorzo Prescribing Information (PI), Medication Guide (MG), and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

The proposed Myqorzo Prescribing Information (PI) and container labels may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Cardiology and Nephrology (DCN) in Section 4 and for Cytokinetics, Incorporated in Section 5.

We evaluated the proposed Myqorzo Medication Guide (MG) and determined that it is acceptable from a medication error perspective.

4 RECOMMENDATIONS FOR THE DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. General Issues
    a. As currently presented, the prescribing information contains the symbols "→" with the intended meaning of "to". Error prone symbols may lead to misinterpretation and medication error. We recommend replacing the symbol "→" with "to". For example, revise to "20 mg to 15 mg; 15 mg to 10 mg; and 10 mg to 5 mg".

2. Highlights of Prescribing Information
    a. The route of administration and frequency are missing in the *Dosage and Administration* section. Failure to include the route of administration and frequency may lead to wrong route and dosing errors. We recommend adding "orally once daily" to each recommended dosage, for example "Recommended starting dose is 5 mg orally once daily".
    b. As currently presented, the abbreviation of "LVEF" is undefined. Abbreviations that are not spelled out may lead to wrong indication medication errors. We recommend spelling out the abbreviation "LVEF"

after the first time it is used to state the intended meaning for this abbreviation “left ventricular ejection fraction”.

3. Section 2 Dosage and Administration

    a. The frequency of administration is missing in the *Dosage and Administration* section. Failure to include the frequency of administration may lead to dosing errors. We recommend adding the frequency of administration (once daily) to all doses stated in this section (e.g. 20 mg once daily).

5 RECOMMENDATIONS FOR CYTOKINETICS, INCORPORATED

A. Container Labels

1. As currently presented, the presentation of the proprietary name (b) (4) We recommend revising the presentation of the proprietary name (b) (4) to “Myqorzo”.
2. The storage information on the container label is inconsistent with the Prescribing Information. Providing inconsistent storage statements may lead to deteriorated drug medication errors. We recommend revising the storage statement to be consistent with the PI by replacing the hyphens with its intended meaning to read “Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F) [see USP controlled Room Temperature]”.
3. The net quantity statement is in close proximity to the product strength on the principal display panel (PDP). From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. We recommend relocating the net quantity statement away from the product strength, such as below the medication guide statement. Additionally, we recommend removing the colored box so it does not compete in prominence with the product strength. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
4. As currently presented, the “Rx only” statement competes with the prominence with the strength statement on the principal display panel. The “Rx only” statement should not compete in prominence with critical information on the

principal display panel. We recommend decreasing prominence of the "Rx only" statement by relocating it to a corner of the principal display panel. Additionally, we recommend removing the colored box so it does not compete for prominence with the strength statement.

5. The linear barcode is oriented in a horizontal position on the small container. Barcodes placed in a horizontal position may not scan due to container curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode. We recommend reorienting the linear barcode on the container label to a vertical position to improve the scannability of the barcode.
6. We note the carton labeling includes the Medication Guide (MG) statement (b) (4) However, the carton labeling does not include how the MG is provided (e.g., accompanied, enclosed, or provided separately). Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).
7. As currently presented, the graphic competes with the prominence of the proprietary name on the principal display panel. The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). Furthermore, see 21 CFR 201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Decrease the prominence of your graphic relative to the prominence of the proprietary name needed for proper identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6). For example, this may be accomplished through minimizing the graphic itself or moving it to another panel.
8. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human- readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical

characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Myqorzo received on September 26, 2024 from Cytokinetics, Incorporated.

Table 2. Relevant Product Information for Myqorzo

Initial Approval Date	N/A
Active Ingredient	aficamten
Indication	Treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)
Dosage Form	tablet
Strength	5 mg, 10 mg, 15 mg, 20 mg
Route of Administration	Oral
Dose and Frequency	The recommended starting dose of MYQORZO is 5 mg orally once daily. Increase the dose every 2 to 8 weeks by 5 mg until a maintenance dose or the maximum recommended dose of 20 mg. **Table 1: Dose Adjustment of MYQORZO** LVEF: ≥55% → Valsalva LVOT-G: ≥ 30 mmHg → Dose Adjustment: Increase dose by 5 mg (up to the maximum dose of 20 mg once daily) LVEF: ≥55% → Valsalva LVOT-G: < 30 mmHg → Dose Adjustment: Maintain Dose LVEF: <55% and ≥50% → Valsalva LVOT-G: Any → Dose Adjustment: Maintain Dose LVEF: <50% and ≥40% → Valsalva LVOT-G: Any → Dose Adjustment: Decrease dose by 5 mg* [redacted (b) (4)] LVEF: <40% → Valsalva LVOT-G: Any → Dose Adjustment: Interrupt treatment for at least 7 days. * Dose decrease as follows: 20 mg → 15 mg; 15 mg → 10 mg; 10 mg → 5mg
How Supplied	MYQORZO is supplied as purple, film-coated tablets containing 5 mg, 10 mg, 15 mg, or 20 mg aficamten. The tablets are debossed on one side with "CK" and the other side with "5", "10", "15" and "20" for the 5 mg, 10 mg, 15 mg, and 20 mg strength, respectively.
Storage	Store at 20°C to 25°C (68°F to 77°F) [(b) (4)] excursions permitted between 15°C [(b) (4)] 30°C ([(b) (4)] 59°F [(b) (4)] 86°F) [see USP controlled Room Temperature].
Container Closure	Bottle, 30 cc, HDPE, wide mouth, round 28-mm finish and closure

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Myqorzo labels and labeling submitted by Cytokinetics, Incorporated.

- Prescribing Information received on September 26, 2024, available from \\CDSESUB1\EVSPROD\nda219083\0004\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text.pdf
- Medication Guide received on August 14, 2024, available from \\CDSESUB1\EVSPROD\nda219083\0002\m1\us\114-labeling\draft\labeling\medication-guide.pdf
- Container label(s) received on September 26, 2024

B.2 Container Label Images

Container Label(s):

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On January 17, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘aficamten’, ‘Myqorzo’, ‘219083’. Our search identified no previous reviews.

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/s/

ROBBIE S KATTAPPURAM
03/19/2025 03:29:39 PM

NICOLE F IVERSON
03/20/2025 08:35:30 AM