CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219083Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	219083
PDUFA Goal Date	December 26, 2025
TTT #	2024-11044
Reviewer Names	Christopher Booze, PharmD, DRM
	Derrick D. Beasley, MS, MPH, DRM
Team Leaders	Yasmeen Abou-Sayed, PharmD, DRM
	Kathryn Marwitz, PharmD, MPH, DMAMES[1]
Associate Directors	Page Crew, PharmD, MPH, BCPS, DMAMES[1]
	Suzanne Robottom, PharmD, DRM
Review Completion Date	December 18, 2025
Subject	Evaluation of Need for a REMS and Evaluation of Proposed REMS
Established Name	aficamten
Trade Name	MyQorzo
Name of Applicant	Cytokinetics
Therapeutic Class	Cardiac myosin inhibitor
Dosage Form(s)	5, 10, 15 and 20 mg oral tablets
Dosing Regimen	Starting dose 5 mg daily, titrated upward every 2-8 weeks based on ECHO monitoring results (max dose 20 mg daily)

[1] The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed and approved the following sections: Section 8.5.3 Compliance, Section 8.6 REMS Assessment Timetable, Section 8.7.1. Key Performance Indicators, Section 8.7.2 REMS Assessment Plan. We acknowledge the contributions of Bethany Ford, PharmD, BCPS to this review.

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EXECUTIVE SUMMARY

This review provides the Division of Risk Management's (DRM) determination that a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) MyQorzo (aficamten) is necessary to ensure the benefits outweigh its risks, and DRM's evaluation of the proposed REMS. This review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan.

Cytokinetics submitted a New Drug Application (NDA) 219083 for aficamten with the proposed indication for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). This application is under review in the Division of Cardiology and Nephrology (DCN). The efficacy of aficamten was demonstrated in the Phase 3 trial, SEQUOIA-HCM, in which subjects with oHCM randomized to treatment with aficamten experienced a statistically and clinically significant improvement in functional capacity, as measured by change in pVO2, compared to placebo. Secondary endpoints such as NYHA functional class and Valsalva left ventricular outflow tract gradient (LVOT-G) saw significant improvements compared to placebo, further supporting the effectiveness of aficamten in treatment of oHCM.

The risks associated with aficamten include the risk of LVEF reduction causing heart failure due to systolic dysfunction. DRM and DCN agree that a REMS is necessary for MyQorzo to ensure the benefits outweigh the risk of heart failure due to systolic dysfunction. Regular monitoring via echocardiogram (ECHO) is required to detect heart failure, and it is critical to ensure this monitoring is performed to mitigate the risk. The symptoms of heart failure overlap with the symptoms of oHCM, which can delay detection of the adverse event if it is not identified by ECHO monitoring. While providers managing oHCM are likely to be specialists who are knowledgeable of the risks and the need for monitoring, the greater concern is whether this monitoring will reliably be performed. Once the patient is established on a maintenance dose, necessary ECHO monitoring is less frequent and may be perceived as less imperative because the patient has completed the titration phase successfully, and monitoring may be missed. Available evidence suggests the risk of LVEF reduction (and therefore the risk of systolic heart failure) persists long term. Further, there is also concern that the risk may be greater in the postmarket setting when the drug may be used in a broader patient population, including in patients who may be more predisposed to LVEF reductions and development of heart failure than patients who met the strict inclusion/exclusion criteria of the clinical trials.

The Applicant's original submission did not include a proposed REMS. Upon notification by the Agency that a REMS would be necessary, the Applicant amended their NDA on March 28, 2025, to include a REMS that consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU include that healthcare providers who prescribe MyQorzo are specially certified (ETASU A), pharmacies, practitioners, and healthcare settings that dispense MyQorzo are specially certified (ETASU B), MyQorzo is dispensed to patients with evidence or other documentation of safe use conditions (ETASU D), and each patient using MyQorzo is subject to certain monitoring (ETASU E). Based on the information available, including the severity of the risk of heart

failure due to systolic dysfunction and identified gaps in care, DRM and DCN agree that ETASU A, B, D, and E in combination are necessary to ensure that the benefits outweigh the risks of MyQorzo.

The goal of the MyQorzo REMS is to mitigate the risk of heart failure due to systolic dysfunction. The objective is that healthcare providers monitor left ventricular ejection fraction (LVEF) by echocardiogram during treatment according to the frequency described in the Prescribing Information to detect heart failure due to systolic dysfunction.

The primary strategy of the REMS is to directly affect the safe use behavior that DRM and DCN determined is necessary to ensure the benefits outweigh the risks. Prior to dispensing, the pharmacy obtains authorization from the REMS to verify that the patient has been monitored with an appropriately recent ECHO and is authorized to continue treatment. The REMS authorizes continuation of treatment based on receipt of a Patient Monitoring Form that the prescriber uses to document that monitoring occurred. Additionally, strategies to directly affect knowledge are included within the REMS to support the primary strategy. Prescriber certification ensures that prescribers are aware of the risk of heart failure and the need to counsel and monitor patients.

To evaluate if the REMS is functioning as designed, meeting its goal and objective, and to determine if modifications to the REMS may be needed, the Applicant developed a REMS Assessment Plan. The timetable for submission of assessments is at 12 months and annually thereafter from the date of the initial approval of the REMS. DMAMES found the REMS Assessment Plan as submitted on December 5th, 2025, to be acceptable.

DRM finds the proposed REMS submitted on December 5th, 2025 acceptable.

1. Introduction

This review provides the Division of Risk Management's (DRM) determination that a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) MyQorzo (aficamten) is necessary to ensure the benefits outweigh its risks, and DRM's evaluation of the proposed REMS. This review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan. Cytokinetics submitted a New Drug Application (NDA) 219083 for MyQorzo with the proposed indication for the treatment of obstructive hypertrophic cardiomyopathy (oHCM). This application is under review in the Division of Cardiology and Nephrology. The Applicant did not originally propose a REMS with their application. The Agency notified the Applicant on March 4, 2025 that a REMS would be necessary to ensure the benefits of MyQorzo outweigh the risk of heart failure due to systolic dysfunction. The Applicant submitted a proposed REMS, last amended on December 5th, 2025, that consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2. Background

2.1. Product Information

MyQorzo (aficamten), a new molecular entity (NME)[a], a cardiac myosin inhibitor, is proposed for the treatment of obstructive hypertrophic cardiomyopathy (oHCM). MyQorzo is proposed as an oral tablet to be available in 5, 10, 15, and 20 mg strengths.

As an allosteric and reversible inhibitor of cardiac myosin, aficamten reduces the force generated by myosin at the cardiac sarcomere, in turn reducing the hypercontractility that characterizes the condition of oHCM.

Aficamten would primarily be prescribed in the outpatient setting and taken by patients at home. Patients taking aficamten would be expected to be on the drug indefinitely[b], as oHCM is a chronic, progressive condition.

The proposed starting dose for aficamten is 5 mg daily, titrated every 2-8 weeks to a maximum of 20 mg daily based on echocardiogram (ECHO) results, specifically left ventricular ejection fraction (LVEF) and left ventricular outflow tract gradient (LVOT-G). Once a maintenance dose has been established, proposed labeling recommends monitoring with ECHOs every 3 months if LVEF is 50 to <55%, or every 6 months if LVEF is at or above 55%.

Aficamten is not currently approved in any jurisdiction. If approved, aficamten would be the second cardiac myosin inhibitor brought to market in the United States. Camzyos (mavacamten), NDA 214998, was approved in 2022 with a REMS (discussed in further detail in section 3.2 of this review).[c]

2.2. Regulatory History

The following is a summary of the regulatory history for 219083 relevant to this review:

- 02/08/2024: At a type B meeting, Cytokinetics informed the agency of its intent to propose to (b) (4). The agency stated in response that it did not object to submission of the NDA without a REMS, but that the need for a REMS would ultimately be a review issue and the Applicant should submit adequate rationale to support their proposal.[d]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Childers, A. Division of Cardiology and Nephrology (DCN). Approval of Camzyos (mavacamten), NDA 214998. April 28, 2022.

[d] Changi, M. Division of Cardiology and Nephrology (DCN). FDA meeting minutes from the aficamten (IND 128814) pre-NDA meeting on February 8, 2024. DARRTS ID# 5337646

- 09/26/2024: Cytokinetics submitted NDA 219083 for aficamten, with a non-REMS risk management plan and rationale in lieu of a REMS.[e]

- 03/04/2025: Applicant was notified at midcycle meeting of the need for a REMS with ETASU including ETASU A, B, D, and E.[f]

- 03/28/2025: Applicant submitted an amendment to NDA 219083 that included a proposed REMS with the required ETASU.

- 04/29/2025: Applicant was notified that the REMS submission constitutes a major amendment and the PDUFA date would be extended by 90 days to 12/26/2025.[g]

- 05/28/2025: Interim comments issued to applicant by DRM and DMAMES. Comments included feedback and edits to REMS materials, instructions to convert the Education Program for Healthcare Providers and Pharmacies to a slide deck format, and a request for additional information related to assessment plan data collection. Applicant was instructed to add Key Risk Messages (KRMs) and additional post-login website screenshots to demonstrate website functionality to the REMS Supporting Document. Applicant was also instructed to adjust Patient Monitoring Form frequency to every 3 months for patients with LVEF 50-55% who are on an every 3 month monitoring schedule, and to require the Patient Enrollment Form to be no older than 3 months at the time of the first dispense.[h]

- 06/18/2025: Applicant submitted a REMS amendment in response to the agency's comments. The amendment included the edits and information requested by DRM and DMAMES in the 5/28/25 communication.

- 09/12/2025: Additional interim comments issued to applicant by DRM and DMAMES. Comments included updates to the REMS goal and objective, revisions to the REMS document, and instructions to add dispensing limits. Comments also included questions about how the REMS will operate in situations such as patients switching providers, monitoring forms being submitted too early, and dose mismatches between the prescription being dispensed and the monitoring form. DMAMES provided comments regarding the REMS Assessment Plan and timetable for submission of assessments.[i]

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[e] Cytokinetics. New drug application (NDA) 219083 for aficamten. September 26, 2024.

[f] Changi, M. Division of Cardiology and Nephrology (DCN). FDA meeting minutes from the aficamten (NDA 219083) mid-cycle meeting on March 4, 2025. DARRTS ID# 5564787

[g] Changi, M. Division of Cardiology and Nephrology (DCN). Notification of review extension (major amendment) for aficamten (NDA 219083). April 29, 2025. DARRTS ID# 5581121

[h] Booze, C. Division of Risk Management (DRM). Interim REMS Review for aficamten (NDA 219083). May 28, 2025. DARRTS ID# 5598249

[i] Booze, C. Division of Risk Management (DRM). Interim REMS Review for aficamten (NDA 219083). September 12, 2025. DARRTS ID# 5657914

- 09/15/2025: Late-cycle meeting with applicant was held. The applicant provided preliminary responses to a number of the questions asked in the September 12 information request (IR).[j]

- 09/26/2025: Applicant submitted REMS amendment in response to the agency's comments. The amendment included the edits and information requested by DRM and DMAMES in the 9/12/25 communication, with the exception of updated post-login REMS website screenshots. The Applicant requested and was granted additional time to update the REMS website and submit the screenshots.

- 10/10/2025: Updated post-login REMS website screenshots sent by applicant as REMS correspondence.

- 11/12/2025: Interim comments issued to applicant by DRM and DMAMES. Comments included feedback and changes to the Applicant's proposed process for additional fills and prescriber overrides to avoid lapses in treatment, as well as questions about how treatment interruptions are processed by the REMS operations. Comments also included addition revisions to REMS materials and assessment plan.[k]

- 11/24/2025: Applicant submitted REMS amendment in response to comments, accepting proposed changes to REMS materials, operations and assessment plan and clarifying the process for treatment interruptions.

- 12/1/2025: Updated post-login REMS website screenshots sent by applicant as REMS correspondence.

- 12/3/2025: Interim comments issued to Applicant by DRM and DMAMES. Comments included a revision to the Key Performance Indicator (KPI) by DMAMES as well as instructions to resubmit the Patient Guide in a more printer-friendly format.[l]

- 12/5/2025: Applicant submitted REMS amendment in response to the Agency's comments. The amendment included the edits requested in the December 3rd communication.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

[j] Changi, M. Division of Cardiology and Nephrology (DCN). FDA meeting minutes from the aficamten (NDA 219083) late-cycle meeting on September 15, 2025. DARRTS ID# 5677333

[k] Booze, C. Division of Risk Management (DRM). Interim REMS Review for aficamten (NDA 219083). November 12, 2025. DARRTS ID# 5694241

[l] Wachter, L. Division of Cardiology and Nephrology (DCN). Information Request (IR) for aficamten (NDA 219083). December 3, 2025.

Hypertrophic cardiomyopathy (HCM) is an inherited, chronic, progressive heart condition characterized by mutations in the cardiac sarcomere that result in thickening of the ventricular wall and ventricular hypercontractility. Approximately 1 in 3000 adults in the United States have symptomatic HCM, but the prevalence is likely much higher due to the high number of asymptomatic cases and is estimated to be closer to 1 in 500[m]. HCM is typically diagnosed via an echocardiogram.

Obstructive HCM (oHCM) is the most common type of HCM, accounting for approximately 70% of HCM cases and involves thickening of the ventricular muscles to the degree that blood flow from the left ventricle to the aorta is obstructed. Obstruction is considered to be present if the left ventricular outflow tract gradient (LVOT-G) is ≥ 30 mmHg.

Many patients with oHCM will be asymptomatic and often may not be diagnosed until late in life, if ever. Other patients may experience symptoms such as angina, dyspnea, or syncope, and symptoms typically worsen with exertion. Patients with oHCM also are at an increased risk of mortality and cardiac comorbidities such as heart failure, stroke, atrial fibrillation, and ventricular arrhythmias. [n]

3.2. Description of Current Treatment Options

Treatment of oHCM is primarily pharmacological, with non-vasodilating beta blockers (titrated to maximally tolerated doses) as the first line option recommended in the 2024 AHA/ACC guidelines.[o] For patients who do not tolerate or respond to beta blockers, non-dihydropyridine calcium channel blockers (i.e. verapamil, diltiazem) are recommended. While both of these classes are generally safe, the ability to titrate to doses effective for oHCM treatment can be limited by their negative inotropic and chronotropic effects resulting in hypotension or bradycardia.

Pharmacologic treatment with mavacamten or disopyramide, as well as septal reduction therapy (SRT), are all recommended for escalation of therapy in patients who have persistent symptoms attributable to left ventricular outflow tract obstruction (LVOTO) after being treated with beta blockers or calcium channel blockers. The AHA guidelines recommend these three options with

[m] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[n] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[o] Ommen, SR, CY Ho, IM Asif, S Balaji, MA Burke, SM Day, JA Dearani, KC Epps, L Evanovich, VA Ferrari, JA Joglar, SS Khan, JJ Kim, MM Kittleson, C Krittanawong, MW Martinez, S Mital, SS Naidu, S Saberi, C Semsarian, S Times, and CB Waldman, 2024, 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines, Circulation, 149(23), doi: 10.1161/CIR.0000000000001250.

equal weight and suggest that personalized discussions regarding the benefits and risks of each should be had with each patient.

Disopyramide can enhance conduction through the atrioventricular (AV) node, which can lead to the onset or worsening of atrial fibrillation (AF); this is of particular concern given oHCM also increases the risk of AF. As a result, disopyramide should be used in combination with another medication that has AV node-blocking properties such as beta blockers or non-dihydropyridine calcium channel blockers, which can be challenging given that some patients who have arrived at disopyramide as a treatment option have done so because of their inability to tolerate those medications.

Mavacamten (Camzyos), also a cardiac myosin inhibitor in the same class as aficamten, is effective at improving LVOT-G and symptoms in oHCM patients and does not have the same potential to impact blood pressure or cardiac rhythm as the previously mentioned treatment options. However, because its mechanism of action reduces cardiac contractility, it can reduce LVEF and cause systolic heart failure. To ensure the benefits of mavacamten outweigh this risk, FDA required a REMS. The REMS requires documentation of ECHO monitoring, specifically monitoring of LVEF, to be submitted prior to dispensing of the drug. In addition, prescribers and pharmacists must review the patient's medication list for potential interactions[p] and counsel the patient with each dispense. The REMS consists of ETASU, an implementation system, and a timetable for submission of assessments. The ETASU consist of prescriber certification (ETASU A), pharmacy certification (ETASU B), documentation of safe use conditions (ETASU D), and patient monitoring (ETASU E).

Septal reduction therapy (SRT), an invasive procedure to reduce the thickness of the heart's septum, is typically performed at comprehensive HCM treatment centers due to the specialized nature of the procedure. SRT may be performed as either a surgical removal of tissue, or as ablation of the septal tissue with an injection of sterile alcohol. SRT is currently only recommended in highly symptomatic patients as there is insufficient data to support its use when reduction in mortality is the only indication.

Finally, if patients remain symptomatic despite optimization of pharmacologic therapy and SRT (or if SRT is not an option), patients with oHCM may be considered for a heart transplant.

4. Benefit Assessment

The Applicant submitted one pivotal phase 3 study, CY 6031 (SEQUOIA-HCM, NCT# 05186818) to support the efficacy of aficamten for the treatment of adult patients with symptomatic oHCM. The Applicant also submitted a supporting phase 2 study, CY 6021 (REDWOOD-HCM) to provide additional dose-finding and safety data.

[p]Mavacamten metabolism is greatly decreased when used concomitantly with CYP2C19 inhibitors or strong CYP3A4 inhibitors – categories that include numerous common prescription drugs as well as some over-the-counter and herbal remedies.

SEQUOIA-HCM was a multicenter, randomized, double-blind, placebo-controlled study that included a 24-week treatment period where subjects were randomized to receive either aficamten or placebo on a 1:1 basis. The study included 282 subjects, 142 of which were randomized to aficamten and 140 of which received placebo. The starting dose of aficamten was 5 mg daily and subjects were assessed via echocardiogram and titrated every 2 weeks up to a maximum dose of 20 mg.

The primary endpoint was change in functional capacity, specifically the change in peak oxygen consumption (pVO2) as measured by cardiopulmonary exercise testing (CPET) from baseline to week 24. Average baseline pVO2 of the two groups was similar (18.38 mL/kg/min for aficamten and 18.59 mL/kg/min for placebo).

The aficamten group had a least squares mean change from baseline of +1.76 mL/kg/min, while the placebo group had a mean change from baseline of +0.02 mL/kg/min. This was a statistically significant treatment effect of +1.74 mL/kg/min (95% CI 1.04-2.44 mL/kg/min) seen in the aficamten group compared to the placebo group. The review team conducted additional analyses using imputed data for subjects who discontinued treatment, which yielded a similar treatment effect (1.69 mL/kg/min, 95% CI 0.99-2.39). The clinical reviewer noted that an increase of 1 mL/kg/min in pVO2 is predictive of reduced risk of death from heart failure and reduced need for heart transplantation in patients with HCM[q], thus, the degree of improvement seen in the aficamten group compared to placebo is clinically significant.[r]

Secondary endpoints of the study included Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), NYHA functional class improvement, Valsalva left ventricular outflow tract gradient (LVOT-G), and total workload during CPET. A statistically significant improvement with aficamten, compared to placebo, was seen with all secondary endpoints, further indicating that aficamten is effective for the treatment of oHCM.

REDWOOD-HCM was a phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-finding trial in which 42 total subjects were split into two dosing cohorts and treated with aficamten or placebo for 10 weeks each. Subjects receiving aficamten in dosing cohort 1 started with a 5 mg dose which was escalated to 10 mg and 15 mg over the course of the 10 week period. Cohort 2 subjects receiving aficamten began at 10 mg and were escalated to 20 mg and 30 mg.

The study demonstrated statistically significant reductions in LVOT-G from baseline compared to placebo. Additionally, a composite endpoint combining pVO2 improvement and NYHA function class improvement was evaluated, and a greater number of subjects in the aficamten cohorts achieved the composite endpoint compared to placebo (42.3% vs 13.6%), supporting the findings from the phase 3 SEQUOIA-HCM study.

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[q] Division of Cardiology and Nephrology. Clinical and Statistical Integrated Review of Aficamten (NDA 219083), Draft accessed December 11, 2025.

[r] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

For the dose-finding component, the 5 mg dose was shown to be pharmacodynamically effective which led to the selection of 5 mg as the recommended starting dose. Only two participants in cohort 2 were escalated to the 30 mg dose; one did not achieve an adequate response on the 30 mg dose, and the other had to be stepped down to 20 mg due to a LVEF reduction. Thus, the Applicant determined that the 30 mg dose did not demonstrate sufficient benefit over risk and 20 mg was selected as the maximum recommended dose for phase 3 trials, and in proposed labeling.

5. Risk Assessment & Safe-Use Conditions

The Agency's safety evaluation of aficamten focused primarily on the population of CY 6031 (SEQUOIA-HCM). The applicant provided a summary of clinical safety that included safety data from CY 6031, CY6021 (REDWOOD-HCM, the phase 2 dose-finding study) and CY 6022, which is an ongoing open-label extension study. The Agency did not pool data from CY6031 and CY6021 because the dosing strategies between the two studies differed.

In total, 142 subjects were exposed to aficamten for a mean duration of 24 weeks in CY6031, and 296 patients with oHCM were exposed for a mean duration of 62 weeks in CY6022. An additional 34 patients with non-obstructive HCM (nHCM) were exposed to aficamten in CY6022 as well.

There were no deaths in CY 6031, nor have any deaths been reported in CY 6022, which is ongoing. There was a single death in CY 6021, which involved a subject with nHCM who experienced a sudden cardiac arrest. The subject had a history of sudden cardiac arrest prior to the study, their LVEF remained > 70% throughout the study, and their NT-proBNP, global longitudinal strain, and troponin I all improved during the study. These factors led the investigator to conclude that the cardiac arrest was unrelated to the study drug.

The overall incidence of adverse events (AEs) and serious adverse events (SAEs) was generally similar between the aficamten and placebo groups in CY 6031. Only one subject in the aficamten group discontinued treatment due to an AE. The AE that led to discontinuation in this participant was psychiatric in nature (paranoia) and deemed unrelated to aficamten.

The Agency's safety review focused on the potential on-target effects of aficamten decreasing ejection fraction and increasing the risk of systolic heart failure. Therefore, clinical events of special interest were cardiac in nature, including major adverse cardiac events, new-onset atrial fibrillation (AF), and ventricular arrhythmias. The incidence of these events was low and was similar between the aficamten and placebo groups.

Hypertension was the most common AE reported in CY6031, and the only AE in which the frequency was at least 5% higher in the aficamten group compared to placebo (8% vs 2%). Most hypertension events in the aficamten group were minor, and most subjects had a medical history of hypertension at baseline. There was also a consistent small mean increase in systolic and diastolic BP with aficamten compared to placebo. For systolic blood pressure, the mean increase ranged from 4-7 mmHg at all timepoints from week 6 to week 24, and was statistically significant at all but one of these timepoints (week 16). One subject with hypertension at baseline was hospitalized with hypertensive urgency

(214/99 mmHg), resulting in interruption of aficamten while the subject was on the 5 mg dose. The event resolved after 2 days and aficamten was subsequently resumed and up-titrated to 15 mg without any further hypertensive events. Ultimately the review team concluded that aficamten likely does increase the risk of hypertension, as a consequence of improved cardiac output that results from relief of LVOT obstruction. The risk of hypertension will be described in section 6 (Adverse Reactions) of labeling.

Lastly, the impact of drug-drug interactions on the safety profile of aficamten was discussed. Aficamten is metabolized by several CYP enzymes, reducing the impact of inhibiting one of these enzymes. CYP2C9 provides the largest contribution to aficamten's metabolism, but pharmacokinetic modeling of a strong CYP2C9 inhibitor result in only a 2-fold change in plasma concentrations. Importantly, there are currently no strong CYP2C9 inhibitors approved for use in the United States.[s]

5.1. LVEF Reduction and Systolic Heart Failure

Based on the mechanism of action of aficamten that reduces cardiac contractility, the risk of greatest concern throughout the review was LVEF reduction and systolic heart failure.[t] A mean decrease in LVEF compared to placebo was seen throughout the 24 weeks of treatment in CY 6031. This decrease grew steadily over the first 8-12 weeks of the trial period, then remained 4-5% lower than baseline through the end of the 24-week treatment period, and mean LVEF returned to baseline at week 28.

Five subjects in the aficamten group experienced LVEF values less than 50% as assessed by the core laboratory, compared to one subject in the placebo group. Of the 5 subjects in the aficamten group, none had associated signs or symptoms of heart failure, and the lowest LVEF recorded was 34%. Only one of the five subjects had LVEF <50% as assessed by *both* core laboratory and site-assessed LVEF, which led to dose reduction. The other four subjects had core laboratory-assessed LVEF <50% but the site-assessed LVEF was >50%, so dose adjustments were not made.

Site-assessed LVEF <50% was observed in seven subjects in the aficamten group compared to one subject in the placebo group. All seven subjects in the aficamten group had a subsequent dose reduction. All subjects who underwent dose reduction had an LVEF ≥ 50% at the next visit. No subjects required treatment interruptions.

There was one aficamten-treated subject with reported signs or symptoms of heart failure at week 12. The site-assessed LVEF at that visit was 55%, down from 65% at the previous visit. Aficamten dosing was not modified at week 12, and the subject had a site-assessed LVEF of 47% at week 16, resulting in dose

[s] U.S. Food and Drug Administration, 2023, Drug Development and Drug Interactions - Table of Substrates, Inhibitors and Inducers, available at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

[t] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

reduction from 20 mg to 15 mg. The subject's LVEF returned to ≥ 50% ten days later. This AE was deemed related to aficamten by the investigator.

There was no clear temporal pattern with the subjects who experienced LVEF <50%; the onset times range from 15 days to 169 days.

In addition to the aforementioned trials studying aficamten in oHCM, there have been clinical trials completed by the applicant evaluating aficamten in nHCM. A total of 376 subjects received aficamten in the clinical program evaluating nHCM, and three subjects experienced HF / ventricular dysfunction. The Applicant was also asked to report cases of HF or LVEF <30% in all ongoing clinical trials. There were six SAEs of HF in the ongoing phase 3 trial CY 6033 in subjects with nHCM; treatment assignments remain blinded in this trial so it is unknown how many of the six were in subjects treated with aficamten. There were also 2 cases of HF in subjects with oHCM in another phase 3 trial comparing the effect of aficamten vs an active control (metoprolol) – one was in a subject on aficamten and the other was on metoprolol.

Overall, the review team concluded that while the risk of HF or severe systolic dysfunction appears low in aficamten-treated oHCM patients, there is uncertainty about the true extent of the risk given the mechanism of action, the relatively low total exposure to date in patients with oHCM (approximately 300 patients), the fact that patients in the clinical program with nHCM have experienced HF, and the lack of a compelling rationale for why the risk of aficamten-associated HF would be lower in oHCM compared to nHCM. Furthermore, there is concern that the risk may be higher in the post-market setting where aficamten is used in a wider range of patients with more comorbidities. For example, CY 6031 excluded patients with *any* history of LVEF <45%, but patients with this history may be prescribed aficamten in the postmarket setting.

Based on the clinical trial experience; to minimize the risk of developing heart failure, it is important that healthcare providers avoid starting treatment in patients with an LVEF <55% and titrate the dose based on echocardiogram results. Other risk management measures have not been identified to mitigate LVEF reduction. Patient report of signs and symptoms of heart failure is not a reliable or timely indicator of this risk, especially since these symptoms can mimic the symptoms of oHCM itself. However, periodic screening and ECHO monitoring for change in LVEF in conjunction with aficamten dose reduction and/or treatment interruption appears to mitigate further serious adverse LVEF sequelae. The echocardiogram monitoring requirements and dose adjustments are described in labeling, including in the Boxed Warning, Warnings and Precautions (section 5), and Dosage and Administration (section 2). The Boxed Warning is as follows:

WARNING: RISK OF HEART FAILURE

MYQORZO reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction *[see Warnings and Precautions (5.1)].*

Echocardiogram assessments are required prior to and during treatment with MYQORZO to monitor for systolic dysfunction. Initiation of MYQORZO in patients with LVEF <55% is not recommended. Decrease the dose of MYQORZO if LVEF is <50% and ≥40% *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Interrupt the dose of MYQORZO if LVEF <40% or if the patient experiences heart failure symptoms or worsening clinical status due to systolic dysfunction *[see Dosage and Administration (2.2)]*.

Because of the risk of heart failure due to systolic dysfunction, MYQORZO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MYQORZO REMS Program *[see Warnings and Precautions (5.2)].*

Additionally, proposed labeling requires monitoring LVEF via echocardiogram (ECHO) every 2-8 weeks during initiation or dose titration, followed by ECHO monitoring every 3 or 6 months once a maintenance dose has been established, depending on whether the patient's LVEF is ≥55% (every 6 months) or 50 to <55% (every 3 months). LVEF less than 50% will result in dose reduction or interruption depending on the severity of the decreased LVEF as well as the current dose. The monitoring and dosing algorithm are captured in the following table from draft labeling. The review team agrees with the proposed dose adjustment table and overall dosing strategy.

Table 1: Dose adjustment of MYQORZO

LVEF	Valsalva LVOT-G	Dose Adjustment
≥55%	≥ 30 mmHg	Increase dose by 5 mg (up to the maximum dose of 20 mg once daily)
≥55%	< 30 mmHg	Maintain Dose
<55% and ≥50%	Any	Maintain Dose
<50% and ≥40%	Any	Decrease dose by 5 mg* Interrupt treatment for 7 days for 5 mg dose
<40%	Any	Interrupt treatment for at least 7 days.

*Dose decrease as follows: 20 mg -> 15 mg; 15 mg -> 10 mg; 10 mg -> 5mg

6. Expected Postmarket Use

(b) (4) is not sufficient to ensure the safe-use conditions described in Section 5 for mitigating the risk of heart failure are followed in the expected postmarket setting.

If approved, the review team expects aficamten to be prescribed primarily by cardiology specialists who are familiar with the diagnosis and treatment of both HCM and HF. While primary care providers (PCPs) may manage this condition, especially in geographic areas where access to specialists is limited, the majority of patients with HCM are often managed at specialized HCM treatment centers, or by cardiologists. Further, cardiac myosin inhibitors are currently recommended as a third-line agent in the

AHA guidelines, meaning patients prescribed aficamten will have likely already failed treatment with other agents such as beta blockers and calcium channel blockers. This increases the likelihood that, by the time aficamten is being considered, patients will be under the care of a cardiology specialist.

Camzyos REMS assessment data from NDA 214998[u], covering a one-year period from February 2024 to February 2025, indicated that (b) (4)% of registered prescribers reported a cardiology specialty. Usage of Camzyos has steadily increased, with the number of active patients (b) (4) from (b) (4) to (b) (4) since the previous assessment reporting period. Over the same period, the proportion of newly certified prescribers reporting a cardiology specialty was slightly higher at (b) (4)% than the (b) (4)% reported in the previous 2-year assessment.[v]

It does not appear based on the assessment data that the increase in usage is the result of any broadening of the prescriber population to non-cardiology providers. Accordingly, we expect the prescribing population of both cardiac myosin inhibitors to continue to consist primarily of cardiologists, even as utilization of cardiac myosin inhibitors increases.

Thus, the expected prescriber population for aficamten will largely be providers who are experienced in the diagnosis and management of oHCM. Many of these prescribers will be current prescribers of mavacamten, some of whom may begin to preferentially prescribe aficamten due to its comparatively low DDI risk and the reduced administrative burden resulting from the lack of a DDI monitoring component in the MyQorzo REMS. These prescribers will be familiar with the need for ECHO monitoring in patients who are on cardiac myosin inhibitors.

This reviewer identified the following care gaps that may not be adequately addressed through labeling:

- Symptoms of systolic heart failure may initially go unnoticed due to their overlap with the symptoms of oHCM making ECHO monitoring to detect change in LVEF imperative.
- Prescribers may not order the periodic echocardiograms as described in labeling particularly once a maintenance dose is established.
- Patients may be unaware of the importance of ECHO monitoring and may miss scheduled ECHOs.

Based on the anticipated medication use process, the review team is specifically concerned about echocardiogram monitoring once patients are established on a maintenance dose. Aficamten is initially titrated from the starting dose of 5 mg daily, every 2-8 weeks in 5 mg increments up to a maximum of 20 mg daily. As seen in Table 1 above, titration is performed based on echocardiogram results. The primary measure of efficacy used to titrate the drug is LVOT-G, and an echocardiogram is needed to measure LVOT-G. Because of this, it seems unlikely that patients will undergo the initial titration without regular

[u] Ford, B. Division of Mitigation Assessment and Medication Error Surveillance (DMAMES). REMS Assessment Review for Camzyos (mavacamten), NDA 214998. November 4, 2025. DARRTS ID# 5689221

[v] Ford, B. Division of Mitigation Assessment and Medication Error Surveillance (DMAMES). REMS Assessment Review for Camzyos (mavacamten), NDA 214998. September 24, 2024. DARRTS ID# 5451194

ECHO monitoring, since it is required in order to follow the dosing algorithm in labeling. It is also unlikely that this expected prescribing population would be unaware that ECHOs are a necessary aspect of this drug treatment.

We have greater concerns about whether the required ECHO monitoring will be performed every 3-6 months once the patient is established on a maintenance dose and the more frequent monitoring for dose titration has ended. It is possible that adherence to the maintenance phase ECHO monitoring could decrease once the prescriber is no longer titrating the dose, and has less frequent contact with the patient. The patient themselves may also be nonadherent with monitoring. The clinical program demonstrated that there is not a clear temporal trend for when LVEF reductions happen, and it is possible that patients could experience an LVEF reduction well into the maintenance phase once an initially well-tolerated maintenance dose has been established.

7. Discussion of the Need for a REMS

FDA determined a REMS is necessary to ensure the benefits outweigh the risk of heart failure due to systolic dysfunction. When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for aficamten, this reviewer considered the expected benefit of the drug in conjunction with the expected patient population, seriousness of the disease, expected duration of treatment, seriousness of known or potential adverse events, and the likely prescribing population. More specifically, DRM and DCN recommended monitoring of LVEF via echocardiograms to address the care gap that patients may not receive regular ECHO monitoring particularly once a maintenance dose is established with aficamten.

The aficamten clinical program demonstrated that aficamten is effective for the treatment of oHCM. Subjects receiving aficamten experienced significant improvements in symptoms and functional capacity compared to placebo. Additionally, while the clinical program was not able to directly assess the impact of aficamten on long-term cardiac mortality, the drug was shown to improve pVO2 to a degree that has been associated with lower cardiac mortality and reduced need for heart transplant in HCM patients. Additionally, aficamten will meet the need for additional treatment options for oHCM in patients who have failed or been unable to tolerate first- and second-line treatment with beta blockers and/or calcium channel blockers.

Aficamten is associated with a risk of LVEF reduction, by approximately 4-5% in the clinical program. While there were no patients with oHCM in the clinical trials who developed severe LVEF reductions or heart failure, this adverse event has been seen with aficamten in the clinical development program for nHCM patients, as well as in oHCM patients with other cardiac myosin inhibitors that have the same mechanism as aficamten. The overall exposure to the drug in oHCM patients was relatively small, approximately 300 patients, and the expected postmarket use will likely involve a broader patient population, some of whom may be more predisposed to LVEF reductions than patients who met the strict inclusion/exclusion criteria of the clinical trials.

Thus, the review team believes that, in absence of more evidence establishing a low risk, it is necessary to assume more severe LVEF reductions and/or systolic heart failure will occur in the postmarket setting with aficamten exposure to a larger population with more comorbidities, despite the fact that there were no cases in the clinical trials for the proposed indication.

The most effective way to mitigate the risk of heart failure in patients taking aficamten is to follow the echocardiogram monitoring schedule and dose titration schedule recommended in labeling, specifically monitoring LVEF every 2-8 weeks during initial dose titration and every 3 or 6 months thereafter (depending on whether LVEF is ≥55% or 50 to <55%). The patients in the aficamten clinical program who developed LVEF reductions below 50% developed them at various times throughout the trial without any clear temporal pattern, demonstrating that monitoring must continue throughout treatment. Furthermore, symptoms of HF may present similarly to the symptoms of oHCM itself, meaning symptoms alone are insufficient to ensure timely detection of HF in the absence of regular echocardiogram monitoring.

During dose titration, it would be difficult for prescribers to not monitor LVEF via ECHO at the recommended frequency of every 2-8 weeks, because the ECHO provides the LVOT-G results needed to titrate the drug to effectiveness. Of greater concern is whether echocardiograms will continue to be performed once the patient is on a maintenance dose. DCN and DRM agree that a REMS requiring documentation of this monitoring is necessary in order for the benefit-risk profile of aficamten to be favorable.

7.1. Collaborative Discussions on the Need for a REMS

REMS Oversight Committee Meeting[w]

On February 26, 2025, a meeting of the REMS Oversight Committee (ROC) was convened to discuss the need for a REMS for aficamten to mitigate the risk of heart failure due to systolic dysfunction.

DCN explained that aficamten's safety profile appears favorable due to the lack of severe drug interactions and a low incidence of LVEF reduction in clinical trials with no cases of heart failure. DCN proposed a REMS with a strategy to directly affect knowledge featuring ETASU A (prescriber certification) and ETASU B (pharmacy certification). The focus of the proposed REMS would be to ensure that aficamten is only prescribed by healthcare providers who have been educated on the risk of systolic heart failure and the need for LVEF monitoring.

DRM explained the most effective risk management strategy to minimize the risk of systolic heart failure associated with aficamten is detecting changes in LVEF with ECHO monitoring. The expected prescribing population would generally be knowledgeable of the need to perform this safe use

[w] As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

behavior, ECHO monitoring is necessary for titrating for optimal treatment effect, and that if patients were not monitored properly, it would rarely be a result of the prescriber not knowing there was a need to monitor the patient. Rather, a gap in care may occur from other factors such as nonadherence, burden/cost associated with ECHOs, patient demonstrating treatment tolerance with no sequelae in the titration phase, less frequent patient-prescriber interaction in the maintenance phase, and/or communication failures between the health care system and the patient. Thus, a REMS focused on knowledge alone would have minimal impact mitigating the risk. DRM recommended that if the team determined that the risk/benefit profile of aficamten was favorable, aficamten should be approved without a REMS and the risk should be managed via labeling. DRM recommended that if the team determined a REMS was necessary for the product to be approvable, the REMS should be focused on affecting and reinforcing the necessary safe use behavior directly rather than knowledge and include ETASU E (patient monitoring) and ETASU D (documentation of the safe use condition) in addition to ETASU A and B.

Ultimately the ROC unanimously recommended that a REMS requiring documentation of monitoring was necessary for aficamten. DCN and DRM agreed to proceed by adopting the ROC's recommendation that a REMS with ETASU A, B, D, and E was necessary to ensure the benefits of aficamten outweigh the risk of systolic heart failure.[x]

8. Risk Management Activities Proposed by the Applicant

With the original submission, the Applicant proposed (b) (4) The Applicant also proposed a Boxed Warning to address the risk of LVEF reduction and heart failure in labeling. However, the review team determined a REMS is necessary to ensure the benefits outweigh the risk of heart failure due to systolic dysfunction as described in Section 7 above. The Applicant was informed on March 28, 2025 that a REMS with ETASU is necessary for MyQorzo.

The Applicant submitted an updated REMS proposal consisting of ETASU, an implementation system, and a timetable for submission of assessments on March 28, 2025 and the REMS was last amended on December 5, 2025.

[x] Guan, N. Office of the Center Director (OCD). Minutes from the February 27, 2025 REMS Oversight Committee (ROC) meeting.

[y] Cytokinetics. New drug application (NDA) 219083 for aficamten. Section 1.16.1: Risk Management (Non-REMS). September 26, 2024.

We note that the enhanced pharmacovigilance plan and registry study proposed by the Applicant are outside the scope of a REMS and defer to the Division of Pharmacovigilance and Division of Epidemiology, respectively, for review and input.

8.1. REMS Goal

The REMS goal and objective statements, which the Applicant included in the September 26th amendment and subsequent submissions, are as follows:

The goal of the MyQorzo REMS is to mitigate the risk of heart failure due to systolic dysfunction.

- **Objective 1: Prescribers monitor LVEF by echocardiogram during treatment according to the frequency described in the Prescribing Information, to detect heart failure due to systolic dysfunction.**

Reviewer's Comments: The REMS goal and objective are acceptable. The goal accurately captures the purpose of the REMS, and the objective is relevant given what is necessary to mitigate the risk, as well as, measurable and specific.

8.2. Strategies

The primary strategy of the MyQorzo REMS is to directly affect safe use behaviors with the following sub-strategies as elements of the REMS, which we have determined are necessary to ensure the benefits outweigh the risks.

Table 2. Strategies and Sub-strategies

Strategy	Sub-strategy
To affect safe-use behaviors	• Monitoring the patient (assessing results of echocardiogram) • Documentation of safe-use behaviors (verify completion of echocardiogram)
To affect knowledge	• Training (pharmacy, prescriber) • Certification (pharmacy, prescriber) • Counseling (patient)

This corresponds to the following elements under Section 505-1 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355-1):

- Elements to Assure Safe Use (ETASU)
    - Healthcare providers who prescribe aficamten are specially certified (ETASU A)
    - Pharmacies and healthcare settings that dispense aficamten are specially certified (ETASU B)
    - Aficamten is dispensed to patients with evidence or other documentation of safe use conditions (ETASU D)

    - Each patient using aficamten is subject to certain monitoring (ETASU E)
- Implementation System
- Timetable for Submission of Assessments

Reviewer's Comments: These strategies and elements were selected to ensure ECHO monitoring is performed prior to initiating treatment and at the required intervals (ETASU E), and that the prescriber assesses and documents the results to determine the appropriateness of initiating or continuing MyQorzo treatment (ETASU D). Prescriber certification (ETASU A) ensures that prescribers are aware of the risk of heart failure due to systolic dysfunction, and the need to monitor patents and submit documentation of the safe use conditions to the REMS. Prior to dispensing, pharmacies must be certified in the REMS (ETASU B) and obtain authorization from the REMS to verify the prescriber is certified, and that the patient is enrolled and authorized to receive treatment. The REMS authorizes continuation of treatment based on receipt of a Patient Monitoring Form that the prescriber uses to document that ECHO monitoring has occurred and it is appropriate to continue treatment at the authorized dose.

8.3. Key Risk Messages

The Applicant included the following key risk messages (KRMs) in the REMS Supporting Document in response to Agency comments. The KRMs are based on the REMS goal and objectives and guide the messaging to participants in the REMS materials.

Key risk messages for prescribers:

- MYQORZO can cause heart failure due to systolic dysfunction (LVEF < 50%).
- Dosing should be modified or discontinued if LVEF <50% as described in the Prescribing Information.
- Healthcare providers must perform echocardiogram (ECHO) monitoring before treatment and routinely during treatment as described in the Prescribing Information.

Key risk messages for patients:

- MYQORZO can cause heart failure due to systolic dysfunction (where your heart cannot pump without enough force)
- You will need to have regular echocardiograms (ECHOs) to check your heart while taking MYQORZO
- You must inform your healthcare provider of any new or worsening symptoms of heart failure.

Key risk messages for pharmacies:

- MYQORZO can cause heart failure due to systolic dysfunction (LVEF < 50%).

- Healthcare providers must perform ECHO monitoring at baseline and routinely during treatment, and patients must be authorized to receive MYQORZO as documented on Patient Monitoring Forms.
- Prior to each dispense, the pharmacy must obtain authorization to dispense each prescription from the MYQORZO REMS to verify that the healthcare provider is certified, the patient is enrolled, the healthcare provider has authorized the patient to receive MYQORZO, and the requested dose is an allowable dose.

Reviewer's Comments: The proposed KRMs are acceptable. The KRMs adequately capture the most important risk messaging of the REMS and support the overall goal and objective of the REMS to support the safe use of aficamten.

8.4. REMS Participant Requirements and Materials

8.4.1. Healthcare Providers Who Prescribe

To become certified to prescribe MyQorzo, prescribers must review the drug's prescribing information, the REMS Overview, and the Education Program for Healthcare Providers and Pharmacies, and subsequently complete and pass the Healthcare Provider Knowledge Assessment and complete the Healthcare Provider Enrollment form.

When enrolling patients, certified prescribers must first counsel the patient on the risk of heart failure using the Patient Guide. The prescriber is required to submit a Patient Enrollment Form for each patient, which includes confirmation that the patient's baseline echocardiogram has been performed and reviewed.

Once a patient has been initiated on MyQorzo, the prescriber must periodically submit Patient Monitoring Forms. The timing of the forms correlates with the frequency that echocardiograms are recommended in labeling. During initial dose titration and after any dose adjustment, the prescriber must submit a Patient Monitoring Form 2-8 weeks after the previous form. Once a patient is established on a maintenance dose, Patient Monitoring Forms are required every 3 or 6 months depending on whether the patient is on an every 3- or 6-month monitoring schedule (which is dependent on whether the patient's LVEF is >55% or 50-55%).

The prescriber is also required to report any adverse events of heart failure to the REMS.

Prescriber REMS Materials

- **Healthcare Provider Enrollment Form:** Serves to enroll the provider in the REMS as an authorized prescriber. The form gathers the provider's credentials and contact information and documents their agreement to follow the REMS requirements. The enrollment form also allows prescribers to name and grant administrative rights to up to four support staff from their healthcare setting. Support staff may fill out Patient

Enrollment Forms and Patient Monitoring Forms on the provider's behalf, for review and final signature by the enrolled prescriber.

- **Education Program for Healthcare Providers and Pharmacies:** An educational slide deck aimed at prescribers and pharmacies that provides information about the risk of heart failure associated with MyQorzo, the recommended dosing and monitoring schedule, and the REMS requirements for each stakeholder.
- **Healthcare Provider Knowledge Assessment:** Measures the prescribers' understanding of the risk being mitigated by the REMS and the requirements of the REMS. The knowledge assessment includes ten multiple choice questions and must be completed with a 100% passing score in order for a prescriber to successfully enroll. The prescriber will be allowed three attempts to pass the knowledge assessment. After three unsuccessful attempts, the prescriber will be contacted by the REMS to assess knowledge deficiencies and provide education, before being given three additional attempts.
- **REMS Overview:** Describes the REMS, the REMS materials, and the requirements for participants.
- **Patient Monitoring Form:** Serves as the documentation that the prescriber has assessed the patient's LVEF via echocardiogram and that the patient is appropriate to continue treatment. The form collects information on the LVEF result (<40%, 40-<50%, 50-<55%, ≥55%) as well as the dose that the patient should be on going forward.

Reviewer's Comments: We agree with the proposed REMS requirements for prescribers. The REMS requirements for prescribers are likely to be effective in ensuring prescribers are aware of the need to monitor patients' LVEF with echocardiograms, and furthermore to ensure that the echocardiograms are performed and reviewed at the frequency recommended in labeling.

The Agency proposed several edits and revisions to the prescriber REMS materials in our comments on May 28, September 12, and November 12, 2025. These included minor revisions for clarity, but also a format change for the Education Program for Healthcare Providers and Pharmacies from a document format to a slide deck format, in order to improve the user experience and comprehension.

The Applicant's initial REMS proposal required Patient Monitoring Forms be submitted every 6 months during the maintenance phase for all patients. This would have created a gap for patients with LVEF 50-55% who should be monitored every 3 months to only be monitored every 6 months. Furthermore, these patients would potentially be more likely to experience the adverse event of LVEF reduction and systolic heart failure since their LVEF is on the lower end of the acceptable range for continued treatment. The Applicant was instructed to align the monitoring form frequency with the monitoring frequency in labeling on May 28, 2025, and this update was submitted on June 18, 2025.

In the September 12, 2025 REMS amendment, the applicant proposed changes to the Patient Monitoring Form. The question "Has the patient's dose changed since the last submitted form? If

yes, what is the new prescribed dose" was removed, and was replaced by question 2: (b) (4) " This change would have resulted in the form not always collecting sufficient information to determine the appropriate dose and monitoring schedule after echocardiogram assessment. For example, if a patient was on a 10 mg daily dose and had an LVEF >55%, they could fall into one of two categories based on the Dose Adjustment Table in draft labeling. Depending on whether the LVOT-G (which is not collected by the form) was <30 mmHg or not, the patient would either remain on 10 mg as their maintenance dose (and need a follow up ECHO in 6 months) or be titrated up to 15 mg (and need a follow up ECHO within 8 weeks). Because of this ambiguity the Applicant was instructed to reinstate the previous version of the question asking what the dose will be going forward, and the Applicant revised the Form in the November 24, 2025 REMS amendment.

8.4.2. Patient

Before treatment initiation and periodically throughout treatment, patients must receive counseling from the healthcare provider on the risk of heart failure due to systolic dysfunction using the Patient Guide.

Patients must undergo a baseline echocardiogram, as well as repeat echocardiograms every 2-8 weeks during initial dose titration or after any dose adjustment, and every 3 or 6 months once a maintenance dose has been established. Patients must also inform the prescriber or seek other medical attention if there are any new or worsening symptoms of heart failure.

Patient REMS Materials

- **Patient Enrollment Form:** Serves to enroll the patient in the REMS and is completed collaboratively by the prescriber and patient. Includes demographic/contact information for the patient as well as documentation that the patient has agreed to follow the REMS requirements. Also contains a section for the prescriber to document the patient's starting dose.
- **Patient Guide:** An educational document describing the risk of heart failure associated with MyQorzo, the symptoms of heart failure, and what is required of patients in the REMS. The Patient Guide is provided to the patient by the prescriber during the initial patient counseling and is utilized during the required patient counseling throughout treatment, as described in the REMS requirements.

Reviewer's Comments: We agree with the proposed REMS requirements for patients. The REMS requirements for patients are likely to be effective in educating patients about the risk of heart failure and the signs and symptoms of heart failure, as well as the importance of monitoring via ECHOs. Patient enrollment in the REMS documents that the patient was counseled and is aware of the requirement to undergo scheduled ECHO monitoring.

The originally proposed version of the Patient Enrollment Form included an attestation by the prescriber that (b) (4),

(b) (4)

.

(b) (4)

, which is stricter than proposed labeling. The Applicant was instructed to modify this section of the enrollment form, which now includes the attestation that "I have assessed the patient's cardiovascular status and the appropriateness of initiating treatment by obtaining an echocardiogram."

8.4.3. Pharmacies That Dispense

To become certified to dispense, pharmacies must designate an Authorized Representative (AR) to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy. The AR must review the prescribing information, REMS Overview, and Education Program for Healthcare Providers and Pharmacies.

The AR must complete and submit the Pharmacy Enrollment Form and train all relevant staff involved in dispensing MyQorzo using the REMS Overview and Education Program for Healthcare Providers and Pharmacies.

Before dispensing, pharmacies must obtain authorization to dispense each prescription from the REMS to verify that the healthcare provider is certified, the patient is enrolled, the healthcare provider has authorized the patient to receive MyQorzo, and the prescribed dose is correct per the valid Patient Monitoring Form. Pharmacies may dispense no more than a 30 days' supply at a time during initial dose titration or after a dose adjustment. Once a patient is established on a maintenance dose, pharmacies may dispense a 90 days' supply.

Pharmacies must maintain records of the completion of REMS training by relevant staff, records that all processes and procedures are in place and are being followed, and dispensing records, all of which must be available during REMS audits. The pharmacy may not distribute MyQorzo to any other pharmacy unless that pharmacy is also certified in the REMS.

Pharmacy REMS Materials

- **Pharmacy Enrollment Form:** Serves to enroll a pharmacy in the REMS. Collects contact and license information for the pharmacy as well as contact information for the AR and, optionally, for a secondary pharmacy contact. Documents the AR's attestation to comply with the requirements of the REMS on behalf of the pharmacy.
- **Education Program for Healthcare Providers and Pharmacies:** as above
- **REMS Overview:** as above

Reviewer's Comments: We agree with the proposed REMS requirements for pharmacies that dispense MyQorzo. The REMS requirements are likely to effectively limit dispensing of MyQorzo to patients who are enrolled in the REMS, under the care of a prescriber who is certified in the REMS, and who has authorized the patient for treatment. Requiring pharmacy certification

(ETASU B) ensures that pharmacy staff will be aware of the need to obtain a dispense authorization from the REMS prior to dispensing the drug.

The REMS is designed so the pharmacy obtains authorization from the REMS for each dispense, rather than requiring the pharmacy to directly verify prescriber certification status and the patient monitoring and safe use conditions (for example, requiring the pharmacist to obtain and assess LVEF results). This design will streamline the process at the pharmacy level, minimize pharmacy staff burden, and reduce the potential for dispensing delays in patients who are otherwise authorized to receive the drug.

8.4.4. Wholesalers-Distributors That Distribute

To be able to distribute, wholesalers-distributors must establish processes and procedures to ensure that the drug is distributed only to certified pharmacies and train all relevant staff on the REMS requirements. Wholesalers-distributors must distribute MyQorzo only to certified pharmacies, maintain records of drug distribution for all MyQorzo shipments, and comply with REMS audits.

Reviewer's Comments: We agree with the proposed REMS requirements for wholesalers-distributors that distribute MyQorzo. The requirements are likely to be effective in ensuring restricted distribution of MyQorzo to certified pharmacies.

8.5. REMS Applicant Requirements and Materials

8.5.1. Training

The Applicant must provide training to healthcare providers who prescribe MyQorzo, which includes the REMS Overview, Education Program for Healthcare Providers and Pharmacies, and the Healthcare Provider Knowledge Assessment.

The Applicant must also provide training to pharmacies that dispense MyQorzo, which includes the REMS Overview and the Education Program for Healthcare Providers and Pharmacies.

The educational materials must be available online and by hard copy via fax and mail for both prescribers and pharmacies.

Reviewer's Comments: We agree with the proposed training for healthcare providers who prescribe MyQorzo and pharmacies that dispense MyQorzo. The training ensures that the REMS participants are educated on the risk of heart failure associated with the drug, and the requirements of the REMS.

Notably, the Applicant has proposed that while both participants must review the Education Program, only prescribers are required to take the Knowledge Assessment. For pharmacies, the Authorized Representative only needs to review the Education Program for Healthcare Providers and Pharmacies and attest that the material has been reviewed.

We agree with this approach, because the pharmacist is not expected to participate in the documentation of echocardiograms or LVEF results directly, nor are there other extensive requirements such as documenting the review of potential drug interactions. Instead, the pharmacist's participation in the process is limited to contacting the REMS to ensure all required monitoring and documentation is complete and receiving authorization from the REMS to dispense the drug. Because of this limited role for the certified pharmacy, knowledge assessment for pharmacists is not necessary.

8.5.2. Operations

The Applicant's requirements to support REMS operations include but are not limited to establishing and maintaining the REMS website, establishing and maintaining a REMS Call Center, establishing and maintaining a validated, secure database of certified participants and patient-specific information, and ensuring that pharmacies are able to obtain authorization to dispense MyQorzo. These aspects of the REMS implementation system are further described in the REMS Supporting Document and are summarized in the sections below.

REMS Website

The Applicant is required to establish and maintain a REMS website available at www.MYQORZOREMS.com. The REMS website must include the capability for healthcare providers and pharmacies to certify online, and for certified prescribers to manage and enroll patients, including completion of the Patient Monitoring Form. The website must also include the capability for participants to review patient and prescriber enrollment status, and for pharmacies to obtain authorization to dispense. The website also contains printable versions of the Prescribing Information, Medication Guide, and REMS materials.

REMS Database

The Applicant is required to establish and maintain a validated and secure database of all enrolled/certified REMS participants. Certified healthcare providers must be provided access to the database of enrolled patients and certified pharmacies. Likewise, certified pharmacies must be provided access to the database of enrolled patients and certified prescribers. Authorized wholesalers-distributors must also be provided access to the database of certified pharmacies.

REMS Call Center

The Applicant must establish and maintain a REMS call center for REMS participants at 1-844-285-7367.

Pharmacy Authorization to Dispense

The Applicant must determine whether a dispense is authorized based on verifying the healthcare provider is certified, the pharmacy is certified, the patient is enrolled, and the patient is authorized to receive MyQorzo at the prescribed dose.

At treatment initiation, the REMS will authorize the initial dispense for up to 3 months from the date the completed Patient Enrollment Form is received. After treatment initiation or a dose adjustment, the Patient Monitoring Form indicating the patient is authorized to continue receiving MyQorzo must be received within 60 days, which reflects the maximum ECHO monitoring frequency of every 8 weeks, plus 4-day grace period.

Once the patient is established on a maintenance dose, the Patient Monitoring Form indicating the patient is authorized to continue MyQorzo must be received every 6 months (for LVEF ≥ 55%) or every 3 months (for LVEF 50% to <55%). In the former scenario, the Patient Monitoring Form will allow a patient to receive up to two 90 day supplies, in the latter, the patient may receive up to one 90 day supply before another form is required.

Pharmacies will submit a request to the REMS for authorization prior to each dispense, and the REMS will provide authorization or denial (including the reason for denial) to the pharmacy.

Reviewer's Comments: The proposed operation and implementation requirements for the MyQorzo REMS are acceptable and support the participant requirements. The authorization to dispense requires Patient Monitoring Forms to be submitted at a frequency consistent with the frequency at which echocardiograms are required by labeling. This authorization process will ensure ECHO monitoring is performed at the required frequency.

The Applicant added a mechanism for the prescriber to initiate a once-yearly override, allowing the patient to access drug beyond the validity of their monitoring form, in the September 26, 2025 REMS amendment. This mechanism would allow for patients to continue to fill prescriptions for MyQorzo if their ECHO was delayed by extenuating circumstances, and requiring the prescriber to initiate the override ensures that this would only be permitted when the benefits outweigh the risks per the healthcare provider's clinical judgement. We agree with the addition of this mechanism.

Additionally, the Applicant was instructed in the September 12, 2025 IR to propose a mechanism by which patients can maintain access to drug if their every 3 or 6 month ECHOs are scheduled slightly more than 90 or 180 days apart, respectively. The Applicant proposed in its September 26, 2025 response to make an additional 30-day supply available to the patient during a 7-day "administrative processing period" to allow for uninterrupted supply of medication in situations such as when a patient may be short on medication due to administrative delays or intervals between ECHOs that slightly exceed 90 or 180 days.

We agreed with this proposal for the maintenance period, but the REMS Supporting Document did not specify whether this additional 30-day supply would also be available while the patient is in the dose titration phase and on an every 2-8 week monitoring schedule. During the titration period, the patient is allowed up to 60 days of drug per Patient Enrollment Form or Patient Monitoring Form, and the required monitoring should be done at minimum every 8 weeks (56 days). Thus, there is already a built-in grace period of four days. An additional 30-day supply could potentially allow a patient to receive 90 days of medication without a documented follow-

up ECHO. The applicant was asked in the November 12, 2025 IR to clarify in the REMS Supporting Document that this extra 30-day supply would be available only once the patient is on a maintenance dose. The Applicant made the requested changes in its November 24th REMS amendment.

8.5.3. Compliance

To ensure REMS participants' compliance with the REMS, the Applicant must maintain adequate records to demonstrate that the REMS requirements have been met, establish and maintain a plan for addressing noncompliance with REMS requirements, monitor participants on an ongoing basis to ensure the REMS requirements are being met, and take reasonable steps to improve operations and compliance with the REMS requirements based on monitoring and evaluation of the REMS. The Applicant must also verify annually that each certified pharmacy Authorized Representative's name and contact information corresponds with a current Authorized Representative (AR) for the certified pharmacy, and require the pharmacy to certify a new AR if it does not.

REMS Participant Audits

To ensure REMS participants' compliance with the REMS, the Applicant must conduct audits. The final proposed REMS participant audit requirements of certified pharmacies and wholesaler-distributors are as follows:

1. Audit all pharmacies no later than 180 calendar days after they become certified, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and support the REMS requirements.
2. Audit all wholesalers-distributors no later than 180 calendar days after they place their first order of MYQORZO, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and support the REMS requirements.

Reviewer's Comments: The proposed compliance requirements for the MyQorzo REMS are acceptable, and will serve to ensure that participants are complying with the requirements of the REMS.

In the Agency's September 12, 2025, interim comments, DMAMES requested revisions to the Applicant's proposed audit requirements for pharmacies and wholesalers-distributors located in the proposed REMS Document. See the September 5, 2025, review[z] for additional details regarding DMAMES' requested edits and rationale. The Applicant implemented our requested

[z] Ford, B. Proposed MyQorzo (aficamten) risk evaluation and mitigation strategy (REMS) Timetable for Submission of Assessments, Audit Requirements in the REMS Document, and REMS Assessment Plan for aficamten (NDA 219083). Silver Spring (MD): FDA, CDER, OSE, DMAMES (US); 2025 Sept 5. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807d82aa

revisions in their September 26, 2025, REMS amendment. DMAMES finds that the proposed REMS participant audit requirements located in the REMS Document, last submitted on November 24, 2025, to be adequate to inform REMS assessment.

8.6. REMS Assessment Timetable

Cytokinetics, Inc. must submit REMS assessments at 12 months and annually thereafter from the date of the initial approval of the REMS (12/19/2025). To facilitate the inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Cytokinetics, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

Reviewer's Comments: DMAMES find the proposed timetable for submission of assessments acceptable.

Cytokinetics, Inc originally proposed a timetable of (b) (4) *from the date of the initial approval of the REMS in their March 28, 2025, initial REMS submission. The Applicant amended their proposed timetable to* (b) (4) *from the date of the initial approval of the REMS, and then* (b) (4) *thereafter in their June 18, 2025, submission. The Agency did not agree with either of the Applicant's timetable proposals. The Agency communicated these findings in our September 12, 2025, interim comments. We requested revisions to the timetable for submission of assessments such that assessments would be submitted at 12 months and annually thereafter from the date of initial approval of the REMS. We determined that more frequent REMS assessments were needed to evaluate if the REMS is functioning as intended and meeting its goal of mitigating the risk of heart failure due to systolic dysfunction. See the September 5, 2025, review*[aa] *for additional details regarding DMAMES' requested edits and rationale.*

The Applicant implemented our requested revisions in their September 26, 2025, REMS amendment. The Applicant revised their REMS Document and REMS Supporting Document to reflect this change. The Applicant did not propose any changes to the REMS Assessment Timetable in their November 24, 2025, amendment.

8.7. REMS Supporting Document

The REMS Supporting Document includes the background on the drug and the risk as well as the Applicant's rationale for the REMS design, implementation, and evaluation. The REMS Supporting

[aa] Ford, B. Proposed MyQorzo (aficamten) risk evaluation and mitigation strategy (REMS) Timetable for Submission of Assessments, Audit Requirements in the REMS Document, and REMS Assessment Plan for aficamten (NDA 219083). Silver Spring (MD): FDA, CDER, OSE, DMAMES (US); 2025 Sept 5. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807d82aa

Document also contains information on participants' responsibilities in the REMS, how they carry out those responsibilities, and how the REMS will be operationalized.

The Applicant did not include a proposed audit plan or non-compliance plan.

Reviewer's Comments: DMAMES recommends the Approval Letter communicate that the Applicant should submit their full audit plan and non-compliance plan as a REMS Assessment Methodology within 30 days of approval for review.

Post-Login REMS Website Screenshots

The Applicant submitted comprehensive post-login screenshots for prescribers, prescriber support staff, and pharmacies.

For prescribers, the Supporting Document included screenshots of the enrollment process including the browser-based version of the Education Program and the Knowledge Assessment, and the results of successful and unsuccessful attempts at taking the assessment.

Screenshots were also included to reflect the process of managing patients, including the process of enrolling a patient, completing a Patient Monitoring Form, looking up patients in the database, reassigning patients to another provider, and adding and removing delegates and support staff.

The website includes a dashboard for healthcare providers that includes a list of active patients and navigation buttons that allow for the prescriber to initiate Patient Monitoring Forms and edit patient information directly from the dashboard. The dashboard also contains a section for patient alerts including Patient Monitoring Forms due within the next 14 days, overdue forms, and forms completed by support staff that require review and signature.

Prescriber support staff have access to similar post-login screens, but with more limited functionality – for example, a support staff member may fill out a Patient Monitoring Form but the ability to sign and submit the form is replaced by the ability to send the form to the prescriber for review and signature.

For pharmacies, the Supporting Document included screenshots of the enrollment process and the ability to add/edit pharmacy staff. Pharmacy staff have the ability to verify a patient's eligibility with the REMS, and request a dispense authorization by inputting prescriber and patient information, and the prescribed dose and quantity. Screenshots were included of both successful and unsuccessful authorizations; when unsuccessful, the website provides the pharmacy staff with the reason(s) the dispense is not authorized.

Reviewer's Comments: The proposed prescriber and pharmacy website portals will support implementation of the REMS. The provided screenshots show that the website will have extensive functionality for prescribers (including support staff) and pharmacies to perform the tasks required of them to participate in the REMS. Having the option to perform these tasks electronically as well as via manual forms and/or phone calls will reduce burden for REMS stakeholders. Additionally, the

ability for support staff to complete administrative tasks for certified healthcare providers will also reduce burden.

8.7.1. Key Performance Indicators

Key performance indicators (KPIs) are quantifiable measures aligned with the REMS objectives used to track progress toward achieving the REMS goal.

Primary KPI: The proportion of prescriptions dispensed with an authorization from the REMS (i.e., an RDA) when the prescription:

1. Is dispensed from a certified pharmacy
2. Is associated with a certified healthcare provider
3. Is for an enrolled patient
4. Has a complete **Patient Enrollment Form** and/or **Patient Monitoring Form** that documents appropriateness to initiate or continue treatment

Numerator: Number of MYQORZO dispenses with an RDA

Denominator: Number of total MYQORZO dispenses (including dispenses with and without an RDA)

Minimum target threshold: 99.9% of dispenses are associated with an RDA

During the audit process, the Applicant will collect all MYQORZO pharmacy dispensing data from pharmacies during annual audits and assess the data for compliance with REMS requirements.

***Reviewer's Comments**: DMAMES finds the proposed key performance indicator (KPI) acceptable.*

The Applicant first proposed a KPI in their March 28, 2025, REMS submission. To obtain the data to inform their proposed KPI, the Applicant proposed collecting and assessing dispensing data during the annual audit process. We note that all pharmacies are to be audited annually as a REMS requirement and the Applicant confirmed in a September 26, 2025, REMS amendment that "all pharmacy data will be obtained during annual audit." Therefore, collection and evaluation of dispensing data to inform the KPI is expected to be robust and encompass data from all pharmacies that dispense MyQorzo. The Applicant's chosen KPI threshold is 99.9%. This high threshold is necessary to evaluate compliance with the REMS requirement of ensuring MyQorzo is dispensed with a REMS Dispense Authorization (RDA). The RDA ensures dispenses are made by a certified pharmacy, based on a prescription written by a certified prescriber, to an enrolled patient, with a completed form (e.g., Patient Enrollment Form and/or Patient Monitoring Form) documenting treatment is appropriate.

During our review, DMAMES determined the proposed KPI required clarification on the scope of the denominator to include the total number of MyQorzo dispenses (dispenses with and without an RDA). These findings were communicated to the Applicant in the Agency's December 3, 2025, interim comments. The Applicant accepted and incorporated DMAMES' requested revisions in their December 5, 2025, REMS amendment.

DMAMES' assessment of the REMS and whether the REMS is meeting its goal will consider the totality of the data reported, including measures related to REMS certification and enrollment, REMS compliance, safe use behaviors, as well as the KPI. A description of the other evidence that

will be used to evaluate whether the REMS is meeting its goal is described in the Assessment Plan (see Section 8.7.2).

8.7.2. REMS Assessment Plan

A proposed REMS Assessment Plan was included in the REMS Supporting Document submitted on March 28, 2025, and amended submissions on June 18, 2025, September 26, 2025, November 24, 2025, December 1, 2025, and December 5, 2025. The proposed REMS Assessment Plan includes metrics on Program Implementation and Operations, REMS Infrastructure and Performance, Safe Use Behaviors, and Overall Assessment of REMS Effectiveness. The REMS Assessment Plan also includes metrics to inform on the KPI (see Section 8.7.1). Collectively, these metrics are necessary to evaluate if the REMS is meeting its goal and objective and operating as intended.

Reviewer's Comments: *The REMS Assessment Plan located within the REMS Supporting Document, includes all revisions proposed by the Agency and adopted by Cytokinetics, Inc. DMAMES finds the Assessment Plan, last submitted on December 5, 2025, acceptable and have no further comments. A copy of the Assessment Plan will be included in the Approval Letter when action is taken on the Application. The Assessment Plan is also included in Section 11.2 of this review.*

DMAMES reviewed the REMS from a REMS assessment and evaluation perspective. DMAMES reviewed the Assessment Plan submissions and comments were provided to the Applicant on September 12, 2025. Refer to the September 5, 2025, DMAMES review for more details.[bb] *The Applicant agreed and accepted the revisions in their September 26, 2025, REMS amendment. Also, the Applicant included additional Assessment Plan metrics to inform on dose mismatches between the RDA request, and Patient Enrollment Form or Patient Monitoring Form.*

In the November 24, 2025, REMS amendment, the Applicant proposed new metrics regarding treatment overrides, aligning with an inquiry from the Agency's November 12, 2025, interim comments. Lastly, the Applicant proposed minor editorial revisions for clarity.

The metrics to inform the KPI (See Section 8.7.1) include 3d, 3e, 3f.

The Division of Epidemiology II (DEPI II) Drug Utilization was consulted to review the proposed MyQorzo REMS Assessment Plan to determine if the drug utilization metrics were adequate to assess the MyQorzo REMS from a drug utilization perspective. Based on their review, DEPI II Drug Utilization noted the metrics proposed by the Applicant provide data to assess REMS effectiveness across the prescribing, dispensing, and monitoring process. They determined the drug utilization metrics within the Assessment Plan submitted by the Applicant on September 26,

[bb] Ford, B. Proposed MyQorzo risk evaluation and mitigation strategy Timetable for Submission of Assessments, Audit Requirements in the REMS Document, and REMS Assessment Plan for aficamten. Silver Spring (MD): FDA, CDER, OSE (US); 2025 Sept 5. NDA 219083. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807d82aa

2025, were acceptable from a drug utilization perspective.[cc] *The same drug utilization metrics were retained within the Assessment Plan with subsequent REMS amendments.*

Additionally, the MyQorzo REMS, similar to the Camzyos REMS, does not require the Applicant to collect adverse event data directly through the REMS. However, the Applicant must comply with postmarketing safety reporting requirements that provides a source of adverse event data (e.g., postmarketing adverse event reports, periodic safety reports, etc.) to the Agency for evaluation.

8.8. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on September 16, 2025, to provide feedback on the content of the REMS Materials. The OPDP review was completed by Melissa Khashei on October 3, 2025.

OPDP recommended to align the language in the REMS materials with the final approved Prescribing Information (PI) and Medication Guide (MG) to accurately reflect the risk information and minimize promotional content. DRM incorporated these recommendations into the REMS materials. To note, the OPDP reviewer highlighted that the MyQorzo risk information slide in the presentation minimized the non-REMS risks. The slide title was revised to focus on REMS risks to more accurately communicate that the risk information was focused on the REMS risks and not all risks associated with the drug. Additionally, at the time of OPDP's review the PI was still under review and the REMS educational materials would need to be later revised to ensure alignment with the revised PI.

Feedback on the REMS materials was first communicated by DRM on September 12, 2025, and additional feedback including confirmation of the incorporation of OPDP's recommendations that DRM agreed with were provided on November 12, 2025. The Applicant incorporated the changes in the November 24, 2025, amendment.

Reviewer's Comments: *The proposed REMS materials are acceptable and align with the changes in the REMS and proposed labeling.*

8.9. Analysis of the MyQorzo REMS Design and Anticipated Health Impact

The REMS design focuses on the safe use behavior, periodic echocardiogram monitoring, as the key risk mitigation measure to minimize systolic heart failure.

The REMS design is informed by key evidence and uncertainties in the risk assessment and medication use process. Clinical trial data demonstrated that LVEF reductions occur with aficamten, LVEF reduction occurs at various timepoints throughout treatment without a clear temporal pattern, detecting changes in LVEF and interrupting treatment can mitigate (and reverse) HF progression, and patients with LVEF changes may be asymptomatic or are unable to distinguish HF symptoms from oHCM progression. No patients in the oHCM clinical trials developed heart failure however a

[cc] Mistry, K. Drug Utilization Review for aficamten. Silver Spring (MD): FDA, CDER, OSE (US); 2025 Nov 13. NDA 219083. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807ec5fb

safety signal is still a concern given the mechanism of action and limited exposure and patient population.

Further, while prescribers are expected to be cardiologists and knowledgeable of the risk and necessary safe use behavior, a care gap was revealed concerning the potential for lack of monitoring particularly in the maintenance phase when a patient has demonstrated treatment tolerance coupled with a decreased frequency of prescriber-patient contact - despite continued risk. The REMS design incorporates systematic documentation to ensure consistent adherence to monitoring requirements to support dose adjustment or treatment intervention sooner to mitigate the risk of progression to heart failure. Implementation of the MyQorzo REMS is expected to support adherence to the ECHO monitoring schedule in labeling. The Patient Monitoring Form requires prescribers to attest that the monitoring has occurred and indicate patient's LVEF range (<40%, 40-<50%, 50-<55%, ≥55%).

Given that patients in clinical trials who experienced LVEF reductions had improvement following dose adjustments, we anticipate this REMS will help ensure that a larger and more heterogeneous postmarket patient population will experience a similar favorable benefit-risk profile that was seen in the clinical program. While the risk is not preventable, the program will prevent patients from continuing therapy without appropriate monitoring during the maintenance phase, when the more frequent titration phase monitoring has ended.

While aficamten is an NME, it is not the first cardiac myosin inhibitor approved. Given the similarities of aficamten and mavacamten, the intention and design of the MyQorzo REMS is similar to the Camzyos REMS and includes the same ETASUs. The Camzyos REMS is currently meeting its goals and has been determined to be meeting goals for all three assessments.[dd] Therefore, we expect that this REMS will be successful in ensuring patients are appropriately monitored for changes in LVEF who are treated with aficamten, given the post-marketing experience with a highly similar REMS, designed to mitigate a similar risk for patients with the same health condition and the same anticipated prescribing population. With respect to burden, we note that the number of active certified prescribers and active enrolled patients has steadily increased over time for Camzyos. Due to its similar design, we expect the degree of burden imposed by the MyQorzo REMS to be comparable and likely lower since prescribers and pharmacies have no requirement to document their review of the patient's medication list for drug interactions, as they are required to do with Camzyos.

REMS programs may be modified in the post-market setting based on REMS assessment data demonstrating the program's effectiveness, or lack thereof, and real-world safety experience. Assuming high compliance with program requirements, potential modifications could include adjustment of the monitoring frequency if post-market data demonstrates patterns of LVEF reduction that result in changes to the monitoring schedule in labeling. Additional restrictions or design changes to the REMS might be warranted if safety signals emerge that suggest higher rates of heart failure than predicted. Conversely, ETASU could be relaxed or removed, or the REMS could be

[dd] Division of Mitigation Assessment and Medication Error Surveillance (DMAMES). REMS Assessment Reviews for Camzyos (mavacamten), NDA 214998. January 12, 2024, September 24, 2024, and November 4, 2025.

eliminated, if additional data and/or post-market surveillance suggests that the risk of severe LVEF reductions is indeed lower with aficamten.

These REMS elements are necessary in combination to form a program that will mitigate the risk of systolic heart failure and provide data to assist in determining if the goals of the REMS are being met.

9. Conclusion & Recommendations

The risk of systolic heart failure associated with aficamten is serious and it is necessary for prescribers to monitor patients according to the frequency described in labeling in order to mitigate the risk. Based on the magnitude and severity of the risk, DRM and DCN agree that requiring a REMS consisting of elements to assure safe use, an implementation system, and a timetable for submission of assessments is necessary to ensure that the benefits of aficamten outweigh the risk of systolic heart failure. The proposed REMS will ensure that patients are being appropriately monitored via echocardiogram in comparison to labeling alone.

Collectively these elements in conjunction with the assessment metrics form a REMS program that is intended to mitigate the risk of systolic heart failure and assess if the REMS is meeting its intended goal. The timetable for submission of assessments is at 12 months, and annually thereafter, from the date of approval of the REMS. DMAMES found the REMS Assessment Plan submitted on December 5, 2025 to be acceptable. DRM finds the Applicant's MyQorzo REMS last amended on December 5, 2025 to be acceptable and it is appended to this review.

10. Appendix

10.1. REMS Materials

Enrollment Forms

Prescriber:

1) Healthcare Provider Enrollment Form

Patient:

2) Patient Enrollment Form

Pharmacy:

3) Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

4) Education Program for Healthcare Providers and Pharmacies
5) REMS Overview
6) Healthcare Provider Knowledge Assessment

Patient:

7) Patient Guide

Pharmacy:

8) Education Program for Healthcare Providers and Pharmacies
9) REMS Overview

Patient Care Form(s)

10) Patient Monitoring Form

Other Material(s)

11) REMS Website

10.2. REMS Assessment Plan

The REMS Assessment Plan includes, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Implementation and Operations

1. REMS Implementation (for the first REMS assessment only)
    a. Date of first commercial availability of MYQORZO
    b. For each participant (healthcare providers, pharmacies, patients), the date they could become certified or enrolled
    c. Date when the MYQORZO Call Center was established and fully operational
    d. Date when the MYQORZO REMS website became live and fully operational
2. REMS Certification and Enrollment Statistics
    a. Healthcare providers
        i. Number of newly certified healthcare providers and number of active healthcare providers (i.e., who have prescribed MYQORZO at least once during the reporting period) stratified by specialty (e.g., Cardiology, Internal/General Medicine, Other).
        ii. Total number of REMS support staff
            1. Number of certified healthcare providers with more than four linked REMS support staff
        iii. Number of newly designated REMS healthcare provider delegates and total number of designated REMS healthcare provider delegates, stratified by credentials (e.g., medical doctor, physician assistant, nurse practitioner), and clinical specialty
    b. Pharmacies
        i. Number of newly certified pharmacies

ii. Number of active pharmacies (i.e., that have dispensed MYQORZO at least once during the reporting period)

c. Patients

i. Number of newly enrolled patients and number of active patients (i.e., who have received at least one dispense of MYQORZO during the reporting period) stratified by age ranges of less than 18, 18-40, 41-60, 61 years and older. Provide the minimum and maximum age of enrolled patients.

d. Wholesalers-distributors

i. Number of newly contracted wholesalers-distributors and number of active wholesalers-distributors (i.e., that have shipped MYQORZO at least once during the reporting period)

3. Drug Utilization

a. The total number of REMS Dispense Authorization (RDA) requests received

b. The number of RDA requests received and authorized, stratified by:

i. Healthcare provider specialty

ii. Patient age

c. The number of RDA requests received and denied (not authorized), stratified by:

i. Reasons and number of denials (numerator) divided by all denials (denominator)

1) Healthcare provider not certified

2) Pharmacy not certified

3) Patient not enrolled

4) No valid documentation of authorization to receive MYQORZO

a. No **Patient Enrollment Form**

b. No **Patient Monitoring Form**

c. Dose mismatch between RDA request and **Patient Enrollment Form**

i. RDA dose exceeds authorized dose on form

ii. RDA dose is lower than authorized dose on form

d. Dose mismatch between RDA request and allowable doses based on **Patient Monitoring Form**

i. RDA dose exceeds allowable dose based on form

ii. RDA dose is lower than allowable dose based on form

d. Number of MYQORZO dispenses with an RDA

e. Total number of MYQORZO dispenses (including those with an RDA and those without an RDA); provide the data source

f. Number of MYQORZO dispenses with an RDA (numerator) divided by total number of MYQORZO dispenses (denominator)

g. Number of prescriptions for unique healthcare providers for which an RDA was requested in the reporting period

h. Number of unique patients who received at least one RDA during the reporting period, stratified by age

4. Treatment Overrides

    a. Total number of treatment overrides requested during the reporting period

        i. Number of treatment overrides granted

        ii. Number of treatment overrides denied

    b. Reasons and number of treatment overrides granted during the reporting period

    c. Number of patients with more than one treatment override granted within a 12-month period

5. REMS Compliance

    a. Noncompliance

        i. A copy of the noncompliance plan, including the criteria for noncompliance for healthcare providers, pharmacies, and wholesalers-distributors, actions taken to address noncompliance for each case, and which events lead to de-certification from the MYQORZO REMS

    b. Audits

        i. A copy of the audit plan for pharmacies and wholesalers-distributors

        ii. Report of audit findings for each participant (i.e., pharmacies and wholesalers-distributors)

        iii. Number of audits expected, and the number of audits performed

        iv. Documentation of REMS participant compliance with REMS requirements, including but not limited to:

            1. Documentation of completion of training for relevant staff

            2. Documentation of processes and procedures in place for complying with the MYQORZO REMS

                a. Pharmacies must agree to maintain records of dispensing information to become certified in the REMS

                b. Auditors will evaluate a representative sample of the MYQORZO pharmacy dispensing data to confirm that an RDA was obtained prior to dispensing, in alignment with REMS compliance requirements

v. Verification for each audited certified pharmacy that each designated Authorized Representative remains the same. If different, and there is no other certified Authorized Representative, document that the pharmacy has certified with the name and contact information for the new Authorized Representative

vi. Number and types of deficiencies noted for each group of audited participants as a percentage of audited participants

vii. For participants with deficiencies noted, the number that successfully completed a Corrective and Preventative Action (CAPA) plan as a percentage of those for which a CAPA plan was requested

viii. For any participants who did not complete the CAPA Plan, a description of actions taken

c. Healthcare provider noncompliance (for each noncompliance event, the source of the report, a description of the event, the root cause analysis of the event, and corrective actions taken)

i. Number of healthcare providers who were noncompliant with the MYQORZO REMS requirements. Provide as a percentage of active healthcare providers

ii. Number of healthcare providers who were decertified and reasons for de-certification, also provided as a percentage of active healthcare providers. Include if any healthcare providers were recertified

d. Pharmacies (for each noncompliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)

i. Number of pharmacies for which noncompliance with the MYQORZO REMS is detected

ii. Number of noncertified pharmacies that dispensed MYQORZO

iii. Number of MYQORZO prescriptions dispensed by noncertified pharmacies

iv. Number of MYQORZO prescriptions dispensed that were written by non-certified healthcare providers

v. Number of MYQORZO prescriptions dispensed to unenrolled patients

vi. Number of MYQORZO prescriptions dispensed to patients based on a prescription from a noncertified healthcare provider

vii. Number of times a MYQORZO prescription was dispensed because a certified pharmacy bypassed the MYQORZO REMS RDA processes

viii. Number of pharmacies decertified, reasons for decertification, and actions to address noncompliance

ix. Number of MYQORZO dispenses without an RDA

e. Wholesalers-distributors (for each noncompliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)

i. Number of contracted wholesalers-distributors for which noncompliance with the MYQORZO REMS is detected

ii. Number of wholesalers-distributors suspended from distributing, reasons for the suspension, and actions to address noncompliance

iii. Number of times MYQORZO was distributed to a noncertified pharmacy

REMS Infrastructure and Performance

6. REMS Website

    a. Number of total visits and unique visits to the REMS website

    b. Number and type of REMS materials downloaded for each material

7. REMS Call Center Reports

    a. Number of contacts by participant type (patient, healthcare provider, REMS support staff, REMS healthcare provider delegate, pharmacy, wholesaler-distributor, other)

    b. Summary of reasons for calls (e.g., enrollment question) and participant type (patient, healthcare provider, REMS support staff, pharmacy, other). Limit the summary to the top five reasons for calls by each participant group

    c. If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues

Safe Use Behaviors

8. Patient Monitoring Forms

    a. Number of **Patient Monitoring Forms** expected, received, and outstanding

    b. Number of unique patients who had a **Patient Monitoring Form** submitted for whom the healthcare provider confirmed reviewing the echocardiogram results

    c. Number of unique patients who had a **Patient Monitoring Form** submitted for whom the healthcare provider authorized treatment

    d. Number of **Patient Monitoring Forms** on which the healthcare provider indicated that the patient experienced a clinical heart failure event requiring clinical intervention or hospitalization since the last submitted form

    e. Number of **Patient Monitoring Forms** on which the healthcare provider indicated the patient's LVEF in the following ranges:

        i. ≥55%

        ii. <55% and ≥50%

        iii. <50% and ≥40%

        iv. <40%

    f. Number of patients who were not authorized to continue treatment as indicated on the **Patient Monitoring Form**

g. Number of **Patient Monitoring Forms** on which the allowable dose matches the dose listed in the corresponding RDA request

h. Number of **Patient Monitoring Forms** on which the allowable dose does *not* match the dose listed in the corresponding RDA request

9. Healthcare Provider Knowledge Assessments

a. Number of completed **Healthcare Provider Knowledge Assessments**, including the method of completion and number of attempts to complete

b. A summary of the most frequently missed **Healthcare Provider Knowledge Assessment** questions

c. A summary of potential comprehension or perception issues identified with the **Healthcare Provider Knowledge Assessment**

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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/

CHRISTOPHER D BOOZE
12/18/2025 02:27:38 PM

DERRICK D BEASLEY
12/18/2025 02:38:23 PM

SUZANNE B ROBOTTOM on behalf of YASMEEN I ABOU-SAYED
12/18/2025 02:46:17 PM

KATHRYN K MARWITZ
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SUZANNE B ROBOTTOM
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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 Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Drug Utilization Memorandum

Date:	November 13, 2025
Reviewer:	Kusum Mistry, PharmD Drug Utilization Analyst Division of Epidemiology II (DEPI-II)
Team Leaders:	Sheheryar Muhammad, PharmD, BCCCP, BCCP, BCPS, CACP Drug Utilization Team Leader, DEPI-II
Deputy Division Director:	Rajdeep Gill, PharmD Deputy Director for Drug Utilization, DEPI-II
Subject:	Review of Applicant's drug utilization metrics in the proposed Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan for Myqorzo™ (aficamten)
Drug Names:	Myqorzo™ (aficamten)
Application Type/Number:	NDA 219083
Applicant/Sponsor:	Cytokinetics, Incorporated
TTT Record ID:	2025-15250

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1 INTRODUCTION

This memorandum from the Division of Epidemiology-II (DEPI-II) evaluates the drug utilization metrics for the proposed Myqorzo (aficamten) Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan, submitted by Cytokinetics, Inc. on September 26, 2025, for New Drug Application (NDA) 219083. The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) consulted DEPI-II to determine whether the drug utilization metrics are adequate to assess the proposed Myqorzo REMS.

2 BACKGROUND

Myqorzo (aficamten), is a new molecular entity and a cardiac myosin inhibitor proposed for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM).[1,2] The U.S. Food and Drug Administration (FDA) approved Camzyos (mavacamten), the first cardiac myosin inhibitor, on April 28, 2022, for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III oHCM to improve functional capacity and symptoms.[3,4] FDA required a Camzyos REMS at the time of approval to ensure that the benefits outweigh the risk of heart failure due to systolic dysfunction.[3]

Given the potential safety risk associated with this drug class, the Applicant (Cytokinetics) submitted a proposed REMS Assessment Plan on March 28, 2025, as part of the Myqorzo REMS Supporting Document in response to a Mid-Cycle Communication meeting with the Agency.[2,5] Subsequently, on June 18, 2025, and September 26, 2025, the Applicant submitted amended REMS Supporting Documents with revisions and responses to comments received by the Agency.[6-11] The proposed REMS includes elements to assure safe use (ETASU) consisting of prescriber certification (A), pharmacy certification (B), documentation of safe-use conditions (D), and patient monitoring (E), along with an implementation system, and a timetable for REMS assessment submissions.[5,11]

DMAMES is reviewing the Applicant's proposed REMS and consulted DEPI-II's Drug Utilization Team to evaluate whether the drug utilization metrics adequately assess the Myqorzo REMS. In response this request, DEPI-II reviewed the drug utilization metrics in the September 26, 2025, proposed REMS Assessment Plan, which is the focus of this memorandum.

2.1 REMS GOAL AND OBJECTIVE

The proposed goal of the Myqorzo REMS is to mitigate the risk of heart failure due to systolic dysfunction.[10,11]

> Objective: Healthcare providers monitor left ventricular ejection fraction (LVEF) by echocardiogram during treatment according to the frequency described in the Prescribing Information, to detect heart failure due to systolic dysfunction.

2.2 REMS ELEMENTS

The proposed Myqorzo REMS consists of the following elements:[10,11]

1. Elements to Assure Safe Use (ETASU):
    - ETASU A: Healthcare providers who prescribe Myqorzo are specially certified
    - ETASU B: Pharmacies that dispense Myqorzo are specially certified

- ETASU D: Myqorzo is dispensed to patients with evidence or other documentation of safe-use conditions
- ETASU E: Each patient using Myqorzo is subject to certain monitoring

2. Implementation System
3. Timetable for Submission of Assessments

2.3 REMS Assessment Plan History

Table 1 summarizes the history of the proposed Myqorzo REMS Assessment Plan, focusing on comments and revisions to the drug utilization metrics.

Table 1. Myqorzo (aficamten) proposed REMS Assessment Plan History

Date	Description
September 26, 2024	Cytokinetics submitted NDA 219083 for Myqorzo, with a non-REMS risk management plan and rationale in lieu of a REMS.[12,13]
March 04, 2025	The Agency informed the Applicant at a Mid-Cycle meeting that a REMS with ETASU A, B, D, and E is necessary to ensure the benefits of Myqorzo outweigh the potential risk of heart failure due to systolic dysfunction.[5]
March 28, 2025	The Applicant submitted a proposed REMS Assessment Plan with the required ETASU as part of the Myqorzo REMS Supporting Document in response to the Agency's request at the Mid-Cycle Communication meeting held on March 04, 2025.[1,5]
May 28, 2025	The Division of Risk Management (DRM) reviewed the proposed REMS Assessment Plan, provided initial comments to the Applicant, and requested additional information on the drug utilization metrics.[14] • DRM Comment: Add details on how pharmacy dispensed data will be obtained to your REMS Supporting Document.
June 18, 2025	The Applicant submitted an amended REMS Supporting Document with revisions and responses to the comments received by the Agency on May 28, 2025.[7,8] • Applicant Response: Myqorzo dispensing data will be obtained as part of the audit process. This information is included in the REMS Supporting Document Section 3.4 and Section 4.2 b Audits.
September 05, 2025	DMAMES reviewed the proposed and amended REMS Assessment Plans submitted on March 28, 2025, and June 18, 2025, and provided revisions and comments to the Applicant. DMAMES proposed revisions to the drug utilization metrics to capture REMS Dispense Authorization (RDA).[15] • DMAMES Comment: Addition of individual metrics needed to inform calculation of the proposed Key Performance Indicator under Drug Utilization. o "Number of Myqorzo dispenses with an RDA" o "Total number of Myqorzo dispenses (including those with an RDA and those without an RDA.) Provide the data source" o "Number of Myqorzo dispenses with an RDA (numerator) divided by total number of Myqorzo dispenses (denominator)"

Table 1 Continued. Myqorzo (aficamten) proposed REMS Assessment Plan History

Date	Description
September 12, 2025	DRM reviewed the amended REMS Assessment Plan submitted on June 18, 2025, and provided additional comments to the Applicant.[16]
September 15, 2025	A Late-Cycle meeting was held where the Applicant discussed the comments and revisions received by the Agency on September 12, 2025.[17]
September 26, 2025	The Applicant submitted an amended REMS Supporting Document with revisions and responses to the comments received by the Agency on September 12, 2025.[10,11]

2.4 PRODUCT INFORMATION

Table 2 provides an overview of the Applicant's proposed product information for Myqorzo.[18,19]

Table 2. Myqorzo (aficamten) proposed U.S. product information

Proposed Product Information	Description
Molecule Name	aficamten
Trade Name	Myqorzo
New Drug Application (NDA)	219083
Applicant	Cytokinetics, Incorporated
Therapeutic Drug Class	Cardiac myosin inhibitor
Indication	Treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM).
Strength and Dosage Formulation	5 mg, 10 mg, 15 mg, and 20 mg oral tablets
Recommended Dosing	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 echocardiographic assessments and clinical status.
Risk Evaluation and Mitigation Strategy (REMS)	Mitigate the risk of heart failure due to systolic dysfunction by monitoring for detection of heart failure due to systolic dysfunction.

3 MATERIAL REVIEWED

DEPI-II reviewed the Drug Utilization metrics in Section 3 of the proposed REMS Assessment Plan submitted by Cytokinetics on September 26, 2025. The REMS Assessment Plan is included in **Appendix 8.1**.

- Risk Evaluation and Mitigation Strategy (REMS) Supporting Document, NDA 219083, Myqorzo (aficamten), Cytokinetics, Incorporated. Submitted on September 26, 2025.

4 APPLICANT'S PROPOSED REMS ASSESSMENT PLAN

4.1 PROPOSED REMS DRUG UTILIZATION METRICS

Below is the Applicant's Drug Utilization metrics in Section 3 of the proposed REMS Assessment Plan as submitted on September 26, 2025.[11]

Drug Utilization

a. The total number of REMS Dispense Authorization (RDA) requests received
b. The number of RDA requests received and authorized, stratified by:
    i. Healthcare provider specialty
    ii. Patient age
c. The number of RDA requests received and denied (not authorized), stratified by:
    i. Reasons and number of denials (numerator) divided by all denials (denominator)
        1) Healthcare provider not certified
        2) Pharmacy not certified
        3) Patient not enrolled
        4) No valid documentation of authorization to receive MYQORZO
            a. No **Patient Enrollment Form**
            b. No **Patient Monitoring Form**
            c. Dose mismatch between RDA request and **Patient Enrollment Form**
                i. RDA dose exceeds authorized dose on form
                ii. RDA dose is lower than authorized dose on form
            d. Dose mismatch between RDA request and allowable doses based on **Patient Monitoring Form**
                i. RDA dose exceeds allowable dose based on form
                ii. RDA dose is lower than allowable dose based on form
d. Number of MYQORZO dispenses with an RDA
e. Total number of MYQORZO dispenses (including those with an RDA and those without an RDA); provide the data source
f. Number of MYQORZO dispenses with an RDA (numerator) divided by total number of MYQORZO dispenses (denominator)
g. Number of prescriptions for unique healthcare providers for which an RDA was requested in the reporting period
h. Number of unique patients who received at least one RDA during the reporting period, stratified by age

4.2 REVIEW OF PROPOSED REMS DRUG UTILIZATION METRICS

The proposed drug utilization metrics evaluate the effectiveness of the Myqorzo REMS through monitoring of REMS Dispense Authorization (RDA) requests. The metrics track the complete RDA request process (received, authorized, and denied), as well as dispensing and prescribing patterns.

Authorization Metrics
Tracking the number of RDA requests received and authorized with stratification by healthcare provider specialty and patient age will help identify potential access issues or inappropriate prescribing patterns.

Denial Metrics
Detailed tracking of the number of RDA requests received and denied provides insight into REMS compliance, system effectiveness, or inappropriate dosing. The metrics stratify denials by specific reasons, including:

- Certification: Healthcare providers or pharmacies not certified
- Patient enrollment: Patients not enrolled in the REMS program
- Documentation: Missing or invalid Patient Enrollment Forms and Patient Monitoring Forms
- Dosing: Mismatches between requested doses and authorized amounts in Patient Enrollment or Monitoring Forms

Dispensing Metrics
Tracking the number of Myqorzo dispenses with an RDA (numerator), as well the total dispenses with and without an RDA (denominator) will allow the Agency to calculate the proportion of dispenses associated with an RDA to determine whether the REMS compliance rate is 99.9%.

Prescription and Patient Metrics
Tracking the number of prescription and patients with an RDA request will help assess prescribing and utilization patterns across age groups.

DEPI-II's Comments: *The Applicant's drug utilization metrics in the proposed Myqorzo REMS Assessment Plan submitted on September 26, 2025, includes revisions based on the edits and comments received from the Agency on May 28, 2025, and June 18, 2025. The Applicant amended the proposed Assessment Plan to include drug utilization metrics that monitor Myqorzo REMS effectiveness through four metric categories: authorizations, denials, dispensing, and prescriptions/patients.*

The authorization metrics ensure that healthcare providers who prescribe Myqorzo are certified, pharmacies that dispense Myqorzo are certified, and patients are enrolled and authorized to receive treatment. The denial metrics provide insight into authorization denials associated with certification failures, patient enrollment gaps, documentation deficiencies, and dosing discrepancies. These potential denial reasons ensure patient safety and support healthcare providers with appropriate patient dosing and monitoring.

The dispensing metric provides authorized and unauthorized dispenses (numerator and denominator data), enabling the Agency to calculate the REMS compliance rate as a

quantifiable measure to determine the effectiveness of REMS program. The prescription and patient metrics provide context on Myqorzo prescribing and utilization, and additional information on patient demographics (age).

Collectively, these four metric categories will provide data to evaluate whether the Myqorzo REMS ensures safe use while maintaining appropriate patient access. They will also allow the Agency to assess for evidence of unanticipated burden and access problems.

DEPI-II agrees that the updated drug utilization metrics submitted by the Applicant on September 26, 2025, are acceptable and will adequately capture the necessary metrics to evaluate the proposed Myqorzo REMS Assessment Plan.

5 DISCUSSION

Cytokinetics initially submitted a proposed REMS Assessment Plan on March 28, 2025, as part of the Myqorzo REMS Supporting Document. However, this initial Assessment Plan did not capture all the metrics necessary to ensure the Myqorzo REMS goal and objectives were met. Subsequently, the Agency provided revisions, and the Applicant submitted amended Assessment Plans on June 18, 2025, and September 26, 2025. The drug utilization metrics in the September 26, 2025, proposed REMS Assessment Plan were the focus of this memorandum.

The proposed Myqorzo REMS consists of ETASU (prescriber certification, pharmacy certification, documentation of safe use conditions, and patient monitoring), an implementation system, and a timetable for REMS assessment submissions. Data used to support these elements include drug utilization metrics in four categories: authorizations, denials, dispensing, and prescriptions/patients. Specifically, these metrics directly support the REMS elements by ensuring certified healthcare providers prescribe the drug, certified pharmacies dispense it, and enrolled patients receive authorized treatment and monitoring by certified healthcare providers.

Authorization metrics ensure certified healthcare providers prescribe Myqorzo, and enrolled patients receive treatment. Additionally, denial metrics identify failures in certification, enrollment, documentation, and dosing to support patient safety and healthcare providers with monitoring. Dispensing metrics measure authorized versus unauthorized dispenses to calculate REMS compliance rates. Lastly, prescription and patient metrics track utilization patterns and demographics across age groups.

These drug utilization metrics collectively evaluate whether the Myqorzo REMS ensures safe use while maintaining appropriate access. Furthermore, the metrics provide data to assess REMS effectiveness across the prescribing, dispensing, and monitoring process. Therefore, the updated drug utilization metrics will capture the necessary information to evaluate the proposed Myqorzo REMS Assessment Plan and identify potential safety concerns or access barriers.

6 CONCLUSION

Based on DEPI-II's review, the drug utilization metrics outlined in the Applicant’s proposed Myqorzo REMS Assessment Plan submitted on September 26, 2025, are acceptable from a drug utilization perspective.

7 REFERENCES

1) Cytokinetics, Inc. Cover Letter: Response to FDA Request for Information – REMS. Aficamten. NDA 219083 – Sequence 0025. Dated 28 March 2025.
2) Cytokinetics, Inc. Myqorzo (aficamten) Risk Evaluation and Mitigation Strategy (REMS) Supporting Document. Aficamten. NDA 219083 – Sequence 0025. Submitted 28 March 2025.
3) Camzyos (mavacamten). NDA 214998. Approval Letter. Dated 28 April 2022. U.S. Food and Drug Administration Drugs@FDA: FDA-Approved Drugs. Accessed October 2025. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
4) Camzyos (mavacamten) Prescribing Information. MyoKardia, Inc.; Princeton, New Jersey; April 2025.
5) Changi M. U.S. Food and Drug Administration: Mid-Cycle Communication Meeting. Aficamten. NDA 219083. Dated 04 March 2025. DARRTS Reference ID: 5564787.
6) Cytokinetics, Inc. Cover Letter: Response to FDA Request for Information – REMS. Aficamten. NDA 219083 – Sequence 0036. Dated 18 June 2025.
7) Cytokinetics, Inc. Response to FDA Request for Information – REMS. Aficamten. NDA 219083 – Sequence 0036. Submitted 18 June 2025.
8) Cytokinetics, Inc. Myqorzo (aficamten) Risk Evaluation and Mitigation Strategy (REMS) Supporting Document. Aficamten. NDA 219083 – Sequence 0036. Submitted 18 June 2025.
9) Cytokinetics, Inc. Cover Letter: Response to FDA Request for Information – REMS. Aficamten. NDA 219083 – Sequence 0046. Dated 26 September 2025.
10) Cytokinetics, Inc. Response to FDA Request for Information – REMS. Aficamten. NDA 219083 – Sequence 0046. Submitted 26 September 2025.
11) Cytokinetics, Inc. Myqorzo (aficamten) Risk Evaluation and Mitigation Strategy (REMS) Supporting Document. Aficamten. NDA 219083 – Sequence 0046. Submitted 26 September 2025.
12) Cytokinetics, Inc. Cover Letter: Request for Priority Review Designation. Aficamten. Original NDA 219083 – Sequence 0004. Dated 26 September 2024.
13) Cytokinetics, Inc. Risk Management (Non-REMS). Aficamten. Original NDA 219083 – Sequence 0004. Submitted 26 September 2024.
14) Booze C, Beasley D, Abou-Sayed Y, Robottom S. Division of Risk Management (DRM): Interim Review of Proposed REMS. Myqorzo (aficamten). NDA 219083. Dated 28 May 2025. DARRTS Reference ID: 5598249.
15) Ford B, Marwitz K, Crew P. Division of Mitigation Assessment and Medication Error Surveillance (DMAMES): Proposed Myqorzo (aficamten) risk evaluation and mitigation strategy (REMS) Timetable for Submission of Assessments, Audit Requirements in the REMS Document, and REMS Assessment Plan. Myqorzo (aficamten). NDA 219083. Dated 05 September 2025. DARRTS Reference ID: 5654554.

16) Booze C, Beasley D, Abou-Sayed Y, Robottom S. Division of Risk Management: Interim Review of Proposed REMS. Myqorzo (aficamten). NDA 219083. Dated 12 September 2025. DARRTS Reference ID: 5657914.

17) Changi M. U.S. Food and Drug Administration: Late-Cycle Meeting Minutes. Aficamten. NDA 219083. Dated 15 September 2025. DARRTS Reference ID: 5677333.

18) Cytokinetics, Inc. Cover Letter: Draft Labeling. Aficamten. NDA 219083 – Sequence 0045. Dated 17 September 2025.

19) Cytokinetics, Inc. Draft Labeling. Aficamten. NDA 219083 – Sequence 0045. Submitted 17 September 2025.

8 APPENDIX

8.1 PROPOSED MYQORZO REMS ASSESSMENT PLAN

(b) (4)

4 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

KUSUM S MISTRY
11/13/2025 10:39:36 AM

SHEHERYAR MUHAMMAD
11/13/2025 11:02:04 AM

RAJDEEP K GILL
11/13/2025 11:37:42 AM

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

Application Type	NDA
Application Number	219083
PDUFA Goal Date	December 26, 2025
Nexus TTT#	2024-11042
Reviewer Name(s)	Christopher Booze, PharmD
	Derrick D. Beasley, MS, MPH
Team Leader(s)	Yasmeen Abou-Sayed, PharmD
Associate Division Director(s)	Suzanne Robottom, PharmD
Review Completion Date	November 12, 2025
Subject	Interim review of proposed REMS
Established/Proper Name	Aficamten
Trade Name	MyQorzo
Name of Applicant	Cytokinetics
Therapeutic Class	Cardiac myosin inhibitor
Dosage Form(s)	5, 10, 15, and 20 mg oral tablets
Dosing Regimen	Starting dose 5 mg daily, titrated upward every 2-8 weeks based on ECHO monitoring results (max dose 20 mg daily)

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1. Introduction

This interim review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for MyQorzo (aficamten), NDA 219083, submitted by Cytokinetics on March 28, 2025, and amended on June 18 and September 26, 2025.

MyQorzo is a cardiac myosin inhibitor proposed for the treatment of obstructive hypertrophic cardiomyopathy (oHCM). This application is under review in the Division of Cardiology and Nephrology (DCN).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of MyQorzo outweigh the risk of heart failure due to systolic dysfunction.

This interim review discusses DRM's comments on the most recent REMS submission.

2. Regulatory History

- 02/08/2024: At a type B meeting, Cytokinetics informed the agency of its intent to propose to manage the risks of aficamten through labeling rather than a REMS. The agency stated in response that it did not object to submission of the NDA without a REMS, but that the need for a REMS would ultimately be a review issue and the Applicant should submit adequate rationale to support their proposal.[i]
- 09/26/2024: Cytokinetics submitted NDA 219083 for aficamten, with a non-REMS risk management plan and rationale in lieu of a REMS.[ii]
- 03/04/2025: Applicant was notified at midcycle meeting of the need for a REMS with ETASU including ETASU A, B, D and E.[iii]
- 03/28/2025: Applicant submitted an amendment to NDA 219083 that included a proposed REMS with the required ETASU.[iv]
- 04/29/2025: Applicant was notified that the REMS submission constitutes a major amendment and the PDUFA date would be extended by 90 days to 12/26/2025.[v]
- 05/28/2025: Interim comments issued to applicant by DRM and DMAMES [vi]
- 06/18/2025: Applicant submitted a REMS amendment in response to the agency's comments[vii]
- 09/12/2025: Additional interim comments issued to applicant by DRM and DMAMES[viii]
- 09/15/2025: Late-cycle meeting with applicant[ix]
- 09/26/2025: Applicant submitted REMS amendment in response to comments[x]
- 10/10/2025: Updated post-login REMS website screenshots sent by applicant as REMS correspondence[xi]

3. Review of Applicant's Proposed REMS

3.1. REMS Requirements

3.1.1. REMS Participant Requirements

3.1.1.1. Healthcare Provider

The applicant proposed changes to the Patient Monitoring Form. The question "**Has the patient's dose changed since the last submitted form? If yes, what is the new prescribed dose**" was removed, and was replaced by question 2: (b) (4)

Reviewer Comment: We do not agree with the changes to the Patient Monitoring Form. The proposed form would not always collect sufficient information to determine the appropriate dose and monitoring schedule after echocardiogram assessment. For example, if a patient was on a 10 mg daily dose and had an LVEF >55%, they could fall into one of two categories based on the Dose Adjustment Table in draft labeling.

1. *The patient would remain on 10 mg as their maintenance dose (and need a follow up ECHO in 6 months) if the LVOT-G was <30 mmHg, or*
2. *The patient would be titrated up to 15 mg (and need a follow up ECHO within 8 weeks) if the LVOT-G was ≥30 mmHg.*

We do not intend for the Patient Monitoring Form to collect the LVOT-G, and the doctor should notate the appropriate dose based on the dosing algorithm.

The Applicant should reinstate the question that was removed or otherwise modify the form so that it collects sufficient information to be able to determine definitively what the dose and monitoring schedule should be in all situations.

3.1.2. REMS Applicant Requirements

3.1.2.1. Operations

In response to Agency comments requesting a proposed mechanism to ensure patients have access to drug when ECHOs may be scheduled in excess of the 90 or 180 day window in the maintenance period, the Applicant proposed two methods for the patient to maintain access to the medication. The first is a prescriber-initiated override process by which a prescriber can contact the REMS to approve access to additional drug beyond the validity of the Patient Monitoring Form, not to exceed one override per year.

The second is an additional 30-day supply available to the patient during a 7-day "administrative processing period" to allow for uninterrupted supply of medication in situations such as when a patient may be short on medication due to administrative delays or intervals between ECHOs that slightly exceed 90/180 days.

Reviewer Comment: The sponsor's proposal for allowing a prescriber-initiated override once per year is acceptable to ensure continued patient access to medication when extenuating circumstances may result in a delay in scheduling the follow-up ECHO, and the prescriber has determined the benefits of preventing a treatment interruption outweigh the risks of delayed monitoring, or other circumstances arise, which should be documented.

The Sponsor's proposal for an additional 30-day supply to be dispensed by the pharmacy to ensure uninterrupted supply is acceptable for the maintenance period (i.e. when the patient is established on a maintenance dose and is being monitored every 3 or 6 months). The REMS supporting document does not specify whether this additional 30-day supply would be available while the patient is in the dose titration phase and on an every 2-8 week monitoring schedule.

During the titration period, the patient is allowed up to 60 days of drug per Patient Monitoring Form, and the required monitoring should be done at maximum by 8 weeks (56 days). Thus, there is a built-in grace period of four days between expected monitoring and amount of drug provided to the patient. If the additional 30-day supply were available to patients during dose titration, a patient new to MyQorzo could potentially obtain a total of 90 days of medication without having a documented follow-up ECHO. This is not acceptable. The additional 30-day supply should only be available to patients who are in the maintenance phase. The prescriber override method would still be available to patients during the titration phase if an ECHO is delayed.

Additionally, the Applicant has not provided detail on how the REMS will operate when a patient is, according to labeling, required to interrupt treatment for at least 7 days and re-titrate from 5 mg due to a low LVEF (<50% if on the 5 mg dose, or <40% on all other doses). The Applicant should include additional information in the REMS Supporting Document on how the REMS will handle this situation, including which dose(s) will be authorized for the patient to fill at the pharmacy and when the next Patient Monitoring Form will be due.

4. Discussion

The sponsor's September 26, 2025 REMS amendment included multiple changes to REMS materials and operations of the REMS, including edits to align with comments provided by the Agency on September 12, 2025.

Changes made to the Patient Monitoring Form, specifically the removal of a question about what the patient's dose will be going forward, are not acceptable as the form no longer collects sufficient information for the REMS to determine what the patient's new dose and monitoring schedule should be. These changes should be reversed, or the form should be otherwise modified to collect sufficient information.

Additionally, the sponsor proposed two methods for patients to avoid interruption in their supply of MyQorzo. The first is a one-time prescriber-initiated override (available annually) for extenuating circumstances, which is acceptable. The other is an extra 30-day supply available to patients within 7 days of when the next Patient Monitoring Form is due. This proposal is acceptable in some but not all situations, and its use should be restricted beyond what the sponsor has proposed in the REMS supporting document.

5. Conclusions and Recommendations

DRM does not find the proposed REMS for MyQorzo (aficamten) as submitted on March 28, 2025, and last amended on October 10, 2025, to be acceptable, as described in the comments to the applicant in Section 4 of this review. Send the comments in Section 4 to Cytokinetics in an Information Request and instruct the Applicant to submit a REMS amendment within 10 business days.

6. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on March 28, 2025, and last amended on September 26, 2025. Review of the REMS proposal is ongoing; these comments should not be considered final.

Submit revised REMS materials (as outlined in the table below), and responses to the information requested below. Responses that clarify REMS operations and implementation of REMS requirements should also be detailed in the REMS supporting document, where appropriate. Accept the tracked changes with which you agree and only indicate any new changes you propose as redlined changes in each Word document in your next submission. Ensure that all Word versions include the author of the

comments so revisions can be identified (not anonymous). The next submission to the Gateway should include clean Word, tracked Word, and PDF formatted versions of REMS materials, and a clean PPT and tracked PPT for the Education Program.

REMS Requirements and Operations

1) We acknowledge your proposed mechanism for patients to receive an additional 30-day supply during the 7-day administrative processing period. This process appears acceptable to minimize gaps in therapy during the maintenance period for patients whose every 3 or 6 month ECHOs may be scheduled more than every 90 or 180 days apart.

   Regarding the dose titration phase before a maintenance dose has been established, the patient can receive up to a 60-day total supply after each Patient Monitoring Form, and the maximum time between ECHOs should be 8 weeks (56 days). It would not be appropriate to dispense an additional 30-day supply during the titration period without submission of an updated Patient Monitoring Form. Doing so could result in patients receiving 90 days' worth of drug without a follow-up ECHO.

   Additionally, the proposed prescriber-initiated treatment override process would still be available for patients during the titration phase if an ECHO is delayed by extenuating circumstances and the provider feels it is appropriate to continue the drug.

   Update the REMS supporting document to indicate that the additional 30-day supply during the administrative processing period is only available once the patient is on a maintenance dose with an every 3 or 6 months monitoring frequency. Additionally, provide detail in the REMS supporting document on when the one-time prescriber-initiated override is permitted, and how the REMS will capture the reason for override.

2) According to labeling, treatment should be interrupted when LVEF is <40% and re-initiated at the starting dose of 5 mg, followed by re-titration. Clarify how the REMS will operate if the LVEF <40% option is selected on the Patient Monitoring Form for a patient that was previously established on a maintenance dose >5 mg, including what dose will subsequently be authorized for the patient to fill at the pharmacy and when the next Patient Monitoring Form would be required. Include as much detail as possible in the REMS Supporting Document.

REMS Materials

REMS Document

An edit is being provided to the punctuation of the REMS goal and objective, and this edit should be carried over anywhere else in the REMS materials where the goal and objective appear.

Patient Monitoring Form

In your proposed form, the question **"Has the patient's dose changed since the last submitted form? If yes, what is the new prescribed dose"** was removed, and was replaced by question 2: (b) (4)

The revised form does not gather sufficient information to determine what the patient's dose and monitoring schedule in all potential situations.

Example:

Patient A has been on MyQorzo 10 mg daily, and has an LVEF > 55% and LVOT-G < 30 mmHg. Based on the Dose Adjustment table (Table 1) in proposed labeling, patient should remain on 10 mg daily as their maintenance dose, and the next ECHO would be due in 6 months.

Patient B has been on MyQorzo 10 mg daily, and has an LVEF > 55% and LVOT-G > 30 mmHg. According to labeling this patient should be titrated up to 15 mg daily, and the next ECHO would be due in 2-8 weeks.

As proposed, the monitoring form would now be filled out the same way for both patients A and B, and without a field to document the prescribed dose going forward, the REMS would not be able to differentiate between the two situations based on the information the form collects.

Revise the Patient Monitoring Form by either 1) reverting back to the original question about what the prescribed dose will be *after* submission of the form, or 2) otherwise adding / modifying questions so that the form collects sufficient information to always be able to determine what the patient's dose should be after submission of the form.

Healthcare Provider Knowledge Assessment

Revisions made to option "c" response option for question 7 to strengthen clarity. Minor revisions made to the instructions section. See redlined Healthcare Provider Knowledge Assessment for revisions.

Pharmacy Enrollment Form

Revisions made to allow space for the pharmacy address to be provided. See redlined Pharmacy Enrollment Form for revisions.

Education Program for Healthcare Providers and Pharmacies

Revisions made to enhance the ordering of how content are presented in the training. Additionally, Mechanism of Action added to slide that provides the indication. Formatting and editorial edits made to several slides to help strengthen readability. See redlined Education Program for Healthcare Providers and Pharmacies for revisions.

REMS Supporting Document (RSD)

We reviewed the proposed REMS Assessment Plan and found the changes acceptable. We made minor editorial revisions to change "ie," back to "i.e.," throughout the REMS Assessment Plan.

The Agency requests that you submit the REMS documents as shown below:

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, PDF
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF
3	Healthcare Provider Enrollment Form	Tracked MS Word, Clean MS Word, PDF
4	Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF
5	Patient Enrollment Form	Tracked MS Word, Clean MS Word, PDF
6	Healthcare Provider Knowledge Assessment	Tracked MS Word, Clean MS Word, PDF
7	Patient Monitoring Form	Tracked MS Word, Clean MS Word, PDF
8	Patient Guide	Tracked MS Word, Clean MS Word, PDF
9	REMS Overview	Tracked MS Word, Clean MS Word, PDF
10	Education Program for HCPs and Pharmacies	Tracked PPT, Clean PPT, PDF
11	REMS Website Screenshots- Public	Tracked PDF, PDF

12	Compiled PDF file that **includes the REMS Document and all REMS materials** in their final format	**PDF Version**

Submit a REMS amendment within 7 business days that addresses these comments.

7. Appendix

1. REMS Document
2. Pharmacy Enrollment Form
3. Education Program for Healthcare Providers and Pharmacies
4. Healthcare Provider Knowledge Assessment

8. References

[i] Changyi, M. Minutes from the February 8, 2024 Type B Meeting for aficamten (IND 138814). February 29, 2024.

[ii] Cytokinetics. Aficamten NDA 219083, September 26, 2024 initial NDA submission

[iii] Changyi, M. Minutes from the March 8, 2025 Mid-cycle Meeting for aficamten (NDA 219083). April 3, 2025.

[iv] Cytokinetics. Aficamten NDA 219083, March 28, 2025 REMS submission

[v] Changyi, M. Notification of review extension for aficamten NDA 219083. April 29, 2025.

[vi] Booze, C. Interim REMS Review for aficamten (NDA 219083). May 28, 2025.

[vii] Cytokinetics. Aficamten NDA 219083, June 18, 2025 REMS submission

[viii] Booze, C. Interim REMS Review for aficamten (NDA 219083). September 12, 2025.

[ix] Changyi, M. Minutes from the September 15, 2025 Late-cycle Meeting for aficamten (NDA 219083). October 15, 2025.

[x] Cytokinetics. Aficamten NDA 219083, September 26, 2025 REMS submission

[xi] Cytokinetics. Aficamten NDA 219083, October 10, 2025 REMS correspondence

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/s/

CHRISTOPHER D BOOZE
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YASMEEN I ABOU-SAYED
11/12/2025 04:38:07 PM

SUZANNE B ROBOTTOM
11/12/2025 04:41:34 PM

Office of Prescription Drug Promotion

Internal Consult

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

To: Derrick Beasley, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Melissa Khashei, Regulatory Review Officer, OPDP

CC: Sapna Shah, Team Leader, OPDP
Monique Killen, Safety Regulatory Project Manager, OSE
Yasmeen Abou-Sayed, Team Leader, DRM
Jina Kwak, OPDP
CDER-OPDP-RPM

Date: October 3, 2025

Re: NDA 219083
MYQORZO™ (aficamten) tablets, for oral use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

---

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for MYQORZO™ (aficamten) tablets, for oral use (Myqorzo):

- Healthcare Provider (HCP) REMS Materials:
  - Healthcare Provider Enrollment Form
  - Pharmacy Enrollment Form
  - Patient Monitoring Form
  - Program Overview (i.e., REMS Overview)
  - Education Program for Healthcare Providers and Pharmacies
  - Healthcare Provider Knowledge Assessment

- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Enrollment Form
  - Patient Brochure

- HCP and DTC (Patient) REMS Materials:
  - MyQorzo REMS Website

The version of the draft REMS materials used in this review were sent from DRM (Derrick Beasley) via email on September 19, 2025. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Myqorzo.

General Comment

Please remind Cytokinetics, Inc. that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.MyQorzoREMS.com and toll-free number 1-844-285-7367. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone.

Comments are provided using the draft Prescribing Information (PI) and Medication Guide (MG) for Myqorzo sent from DRM (Derrick Beasley) via email on September 22, 2025.

OPDP notes that the Myqorzo PI and MG are still being reviewed by DCN. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved labeling for Myqorzo.

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS piece:

- **Education Program for Healthcare Providers and Pharmacies**
  - Slide three of the proposed Education Program for Healthcare Providers and Pharmacies is titled "MyQorzo Risk Information."
    - **Risk**
      - This presentation minimizes the non-REMS risks of Myqorzo by suggesting this REMS piece presents all the risks associated with the drug, when it includes only REMS-related risk information. Therefore, OPDP recommends that this title be revised to more accurately communicate that it is the REMS risk information that is being conveyed in the REMS piece and not all of risks associated with the drug.
      - OPDP also recommends slide five titled "MyQorzo Indication" precede slide three since it does not present risk information.

  - Slide six of the proposed Education Program for Healthcare Providers and Pharmacies, titled "MyQorzo Boxed Warning," includes the following claim boxed under the header "WARNING: RISK OF HEART FAILURE" (in pertinent part):

    > "Heart failure due to systolic dysfunction can occur in patients receiving cardiac myosin inhibitors. MyQorzo can reduce left ventricular ejection fraction (LVEF)."

    - **Risk**
      - This presentation minimizes the REMS risks of Myqorzo by distancing the potentially life-threatening risks associated with Myqorzo from the use of the drug. According to the Boxed Warning for Myqorzo in the draft PI, "MYQORZO reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction." By associating the risk with the drug class rather than the drug, and by using a less certain statement about Myqorzo's effect on LVEF than stated in the PI, this presentation minimizes the REMS risk. Therefore, OPDP recommends revising this presentation.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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

Application Type	NDA
Application Number	219083
PDUFA Goal Date	December 26, 2025
Nexus TTT#	2024-11042
Reviewer Name(s)	Christopher Booze, PharmD Derrick D. Beasley, MS, MPH
Team Leader(s)	Yasmeen Abou-Sayed, PharmD
Associate Division Director(s)	Suzanne Robottom, PharmD
Review Completion Date	September 12, 2025
Subject	Interim review of proposed REMS
Established/Proper Name	Aficamten
Trade Name	MyQorzo
Name of Applicant	Cytokinetics
Therapeutic Class	Cardiac myosin inhibitor
Dosage Form(s)	5, 10, 15, and 20 mg oral tablets
Dosing Regimen	Starting dose 5 mg daily, titrated upward every 2-8 weeks based on ECHO monitoring results (max dose 20 mg daily)

TABLE OF CONTENTS

1. Introduction

This interim review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for MyQorzo (aficamten), NDA 219083, submitted by Cytokinetics on March 28, 2025 and amended on June 18, 2025.

MyQorzo is a cardiac myosin inhibitor proposed for the treatment of obstructive hypertrophic cardiomyopathy (oHCM). This application is under review in the Division of Cardiology and Nephrology (DCN).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of MyQorzo outweigh the risk of heart failure due to systolic dysfunction.

This interim review discusses DRM's comments on the most recent REMS submission.

2. Regulatory History

- 02/08/2024: At a type B meeting, Cytokinetics informed the agency of its intent to propose to manage the risks of aficamten through labeling rather than a REMS. The agency stated in response that it did not object to submission of the NDA without a REMS, but that the need for a REMS would ultimately be a review issue and the Applicant should submit adequate rationale to support their proposal.[i]
- 09/26/2024: Cytokinetics submitted NDA 219083 for aficamten, with a non-REMS risk management plan and rationale in lieu of a REMS.[ii]
- 03/04/2025: Applicant was notified at midcycle meeting of the need for a REMS with ETASU including ETASU A, B, D and E.[iii]
- 03/28/2025: Applicant submitted an amendment to NDA 219083 that included a proposed REMS with the required ETASU.[iv]
- 04/29/2025: Applicant was notified that the REMS submission constitutes a major amendment and the PDUFA date would be extended by 90 days to 12/26/2025.[v]
- 05/28/2025: Interim comments issued to applicant[vi]
- 06/18/2025: Applicant submitted a REMS amendment in response to the agency's comments[vii]

3. Conclusions and Recommendations

DRM does not find the proposed REMS for MyQorzo (aficamten) as submitted on March 28, 2025, and last amended on June 18, 2025, to be acceptable, as described in the comments to the applicant in Section 4 of this review. Send the comments in Section 4 to Cytokinetics in an Information Request, along with the comments from the September 5, 2025 review by DMAMES[viii], and instruct the Applicant to submit a REMS amendment within 10 business days.

4. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on March 28, 2025, and amended on June 18, 2025. Review of the REMS proposal is ongoing; these comments should not be considered final.

Submit revised REMS materials (as outlined in the table below), and responses to the information requested below. Responses that clarify REMS operations and implementation of REMS requirements should also be detailed in the REMS supporting document, where appropriate. Accept the tracked changes with which you agree and only indicate any new changes you propose as redlined changes in each Word document in your next submission. Ensure that all Word versions include the author of the comments so revisions can be identified (not anonymous). The next submission to the Gateway should include clean Word, tracked Word, and PDF formatted versions of REMS materials, and a clean PPT and tracked PPT for the Education Program.

General Comments and Questions

We propose a REMS goal and objective to describe one specific, measurable objective that, if achieved, indicates that the REMS is meeting its goal:

> **The goal of the MyQorzo REMS is to mitigate the risk of heart failure due to systolic dysfunction.**
>
> **Objective 1: Prescribers monitor LVEF by echocardiogram during treatment according to the frequency described in the Prescribing Information, to detect heart failure due to systolic dysfunction.**

Use this goal and objective throughout the REMS, including in the REMS document.

REMS Requirements and Operations

1. We are providing a redlined REMS Document which we believe reflects the REMS requirements and operations as currently proposed, including some of the revisions included in this round of the Agency's comments. This REMS Document should not be considered final and further edits are possible as the review progresses.

2. The REMS should incorporate dispensing limits of up to a 60 days' supply during the initiation / dose titration phase, and up to a 90 days' supply per fill once the patient is on a maintenance dose, to align the quantity of drug dispensed with the monitoring frequency. Update the REMS Document and REMS materials to incorporate this limit.

   For the titration phase, the limit should be a cumulative 60 days' supply. For example, if a pharmacy attempts to fill a third 30-day supply of the starting dose within the 60 day window after the initial dispense, the dispense should not be authorized.

   For the maintenance phase, we recommend a cumulative limit of 90 or 180 days' supply per valid Patient Monitoring Form (based on the every 3 month or 6 month monitoring frequency).We acknowledge that this could occasionally present a barrier to patient access to drug in the post-market setting, for example, in a patient whose every 6 month echocardiograms are scheduled on July 1st and January 1st (184 days apart). Propose a mechanism to ensure treatment is not interrupted in such patients.

3. REMS materials that discuss the cadence for performing ECHO monitoring and/or submitting a Patient Monitoring Form when initiating or changing the dose of aficamten should be modified

from within "2 months" after initiation or a dose change, to (b) (4) in order to align with the recommended monitoring frequency in labeling. However, to reduce burden and align with pharmacy dispensing, the patient monitoring form should be submitted by 2 months (60 days). This also allows for a grace period for the submission of the monitoring form.

4. Clarify how the REMS will handle patients switching prescribers. If a patient is no longer under the care of their original provider and will need to be managed by a new provider, what is the process to transfer a patient to a different certified provider within the REMS?

5. Will patients become inactive in the REMS and/or need to be re-enrolled after being off of MyQorzo for a certain period of time? If so, how long?

6. How will the REMS handle if a prescriber attempts to submit a Patient Monitoring Form and increase the dose faster than the recommended monitoring schedule, for example 1 week after a previous dose change?

7. Is there a proposed mechanism in the REMS for a prescriber to request an override to allow a patient to receive drug beyond the validity of their Patient Monitoring Form, for example, if there is a delay in scheduling an echocardiogram, or other extenuating circumstance? If yes, provide detail on the scenarios in which an override would be permitted and include this detail in the supporting document.

8. The prescriber is required to select a dose on the Patient Monitoring Form, and the pharmacy is required to select a dose when requesting an RDA. Please clarify how these doses factor into determining whether a dispense is authorized.

   Example: A Patient Monitoring Form is submitted with a 10 mg dose and the patient fills a 30 day supply of 10 mg tablets the next day. If the patient returns for an additional fill of 10 mg in one month, the dispense would presumably be authorized - if the patient returns with a prescription for 15 mg instead, would the dispense be authorized or would a new form be required indicating that the dose is now 15 mg?

9. Your REMS proposal indicates the Patient Enrollment Form is valid for the initial dispense and up to 2 months at the starting dose. If a patient is being titrated faster than every 8 weeks, for example every 4 weeks, and returns to the pharmacy to fill an increased dose (10 mg) within the initial 2 month period, clarify whether the dispense will be authorized or whether a new Patient Monitoring Form be required first.

REMS Website

1. The electronic Patient Monitoring Form on the REMS Website has fields for the healthcare provider information (first/last name, NPI number, phone number, fax number, email address). When a provider is signed into the REMS website and begins a patient monitoring form, this information should automatically populate into the form, to reduce burden and the potential for data entry errors. Clarify whether this will be the case or whether the provider will need to

manually input this information into each form. If the information does populate, include a screenshot in the Supporting Document of a form to demonstrate this feature.

2. If the provider initiates a Patient Monitoring Form using the button in a patient-specific row on the dashboard (such as using the "Start New Monitoring Form" button next to a listed patient, in the screenshot on REMS supporting document page 39), the patient information should automatically populate into the form, to reduce burden and the potential for data entry errors. Clarify whether this will be the case or whether the provider will need to manually input this information into each form. If the information does populate, include a screenshot in the Supporting Document of a form to demonstrate the feature.

3. Is the electronic Patient Monitoring Form identical for support staff? Clarify the steps involved for support staff to enter patient monitoring information and send to the provider for final signature. Add screenshots demonstrating all REMS support staff options and workflows to the REMS supporting document.

REMS Materials

1. Names of REMS materials should be bolded throughout each of the REMS materials, including mentions on the REMS website (e.g., "**Patient Enrollment Form**" should be used instead of "Patient Enrollment Form"). 'Prescribing Information' should not be bolded.
2. The attached redlined enrollment forms (i.e., **Healthcare Provider Enrollment Form**, **Patient Enrollment Form**, and **Pharmacy Enrollment Form**) include additional comments and edits to improve clarity and consistency across enrollment forms. We recommend ensuring that the font, size of text, and layout is consistent across enrollment forms. Additionally, the listed agreements on enrollment forms should be revised to align with the agreements document that is included with this communication.
3. The attached redlined **Program Overview**, **Patient Brochure**, **Healthcare Provider Knowledge Assessment,** and **Patient Monitoring Form** include comments and edits to strengthen usability and readability of the documents. We note that the **Program Overview** should be retitled **REMS Overview** to align with wording used in the REMS Document Technical Conformance Guide. Additionally, the **Patient Brochure** should be retitled **Patient Guide** to also align with the REMS Document Technical Conformance Guide.
4. The answers to the **Healthcare Provider Knowledge Assessment** questions should be included in the **REMS Supporting Document** but be omitted from the standalone REMS material. The clean form should not have answers highlighted.
5. The attached **Education Program for Healthcare Providers and Pharmacies** PPT file includes comments on the training program. Confirm that the listed agreements for each of the stakeholders (i.e., healthcare providers, pharmacies) align with the agreements document provided by the Agency. Make additional revisions as necessary throughout the education program to ensure alignment with the agreements document.
6. Revisions made to paper-based REMS materials, including enrollment forms, should be incorporated into the REMS website. Update the REMS website to ensure alignment with the agreements document. Provide updated website screenshots with your resubmission. Website screenshots should demonstrate full functionality of the website both public and behind the log-in. Updated website screen shots for behind the log-in should be included within the updated **REMS Supporting Document**.

REMS Supporting Document (RSD):

1. Align the RSD with the information in the REMS Document and REMS materials.
2. Add a screenshot(s) to the REMS supporting document showing the end of the provider enrollment form. The screenshot on page 33 does not include the bottom of the form.

The Agency requests that you submit the REMS documents as shown below:

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, PDF
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF
3	Healthcare Provider Enrollment Form	Tracked MS Word, Clean MS Word, PDF
4	Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF
5	Patient Enrollment Form	Tracked MS Word, Clean MS Word, PDF
6	Healthcare Provider Knowledge Assessment	Tracked MS Word, Clean MS Word, PDF
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10	Education Program for HCPs and Pharmacies	Tracked PPT, Clean PPT, PDF
11	REMS Website Screenshots- Public	Tracked PDF, PDF
12	Compiled PDF file that **includes the REMS Document and all REMS materials** in their final format	**PDF Version**

Submit a REMS amendment within 10 business days that addresses these comments.

5. Appendix

1. REMS Document
2. Healthcare Provider Enrollment Form
3. Patient Enrollment Form
4. Pharmacy Enrollment Form
5. Education Program for Healthcare Providers and Pharmacies
6. REMS Overview
7. Healthcare Provider Knowledge Assessment
8. Patient Guide
9. Patient Monitoring Form

6. References

[i] Changyi, M. Minutes from the February 8, 2024 Type B Meeting for aficamten (IND 138814). February 29, 2024.

[ii] Cytokinetics. Aficamten NDA 219083, September 26, 2024 initial NDA submission

[iii] Changyi, M. Minutes from the March 8, 2025 Mid-cycle Meeting for aficamten (NDA 219083). April 3, 2025.

[iv] Cytokinetics. Aficamten NDA 219083, March 28, 2025 REMS submission

[v] Changyi, M. Notification of review extension for aficamten NDA 219083. April 29, 2025.

[vi] Booze, C. Interim REMS Review for aficamten (NDA 219083). May 28, 2025.

[vii] Cytokinetics. Aficamten NDA 219083, June 18, 2025 REMS submission

[viii] Ford, B. REMS Assessment Plan Review for aficamten (NDA 219083). September 5, 2025.

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09/12/2025 09:16:09 AM

YASMEEN I ABOU-SAYED on behalf of SUZANNE B ROBOTTOM
09/12/2025 09:19:07 AM

fREMS Assessment Plan Review

Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
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 information that cannot be released to the public*****

Application Type	NDA
Application Number	219083
Task Tracking Tool Number	2024-11044
Submission Type/Number	Original-1/25, Original-1/36
Submission Date	March 28, 2025, and June 18, 2025
Reviewer	Bethany Ford, PharmD, BCPS
Team Lead	Kathryn Marwitz, PharmD, MPH
Associate Director Designee	Page Crew, PharmD, MPH, BCPS
Review Completion Date	September 5, 2025
Non-Proprietary Name	Aficamten
Proprietary Name	MyQorzo
Subject	Proposed MyQorzo (aficamten) risk evaluation and mitigation strategy (REMS) Timetable for Submission of Assessments, Audit Requirements in the REMS Document, and REMS Assessment Plan
Applicant	Cytokinetics, Inc.
Therapeutic Class	Cardiac myosin inhibitor

1. Introduction

This review evaluates the timetable for submission of assessments, audit requirements in the REMS Document, and REMS assessment plan for the proposed MyQorzo (aficamten) risk evaluation and mitigation strategy (REMS), referred to hereafter as the MyQorzo REMS.

2. Background

The Applicant submitted a proposed REMS on March 28, 2025, and an amended submission on June 18, 2025.[a,b] This review includes an evaluation to determine if the proposed timetable for submission of assessments, audit requirements in the REMS Document, and REMS assessment plan are adequate to assess and evaluate the REMS.

2.1. REMS Goal and Statutory Elements, and Timetable for Submission of Assessments

The proposed REMS goal and proposed statutory elements are still under review by the Division of Risk Management.

Goal

The proposed goal of the MyQorzo REMS is to mitigate the risk of heart failure due to systolic dysfunction.

Objective 1: Prescribers monitor LVEF by echocardiogram during treatment according to the frequency described in labeling, to detect heart failure due to systolic dysfunction.

Statutory Elements

The proposed MyQorzo REMS consists of the following elements:

1. Elements to Assure Safe Use:
    - Healthcare providers who prescribe MyQorzo are specially certified under 505-1(f)(3)(A).
    - Pharmacies that dispense MyQorzo are specially certified under 505-1(f)(3)(B).
    - MyQorzo is dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D).
    - Each patient using MyQorzo is subject to certain monitoring under 505-1(f)(3)(E).
2. Implementation System
3. Timetable for Submission of Assessments

[a] Draft REMS for NDA 219083. San Francisco (CA): Cytokinetics, Inc.; 2025 MAR 18. Available from: \\CDSESUB1\EVSPROD\nda219083\0025\m1\us\116-risk-management-plan\rems-supporting-doc.pdf
[b] Draft REMS for NDA 219083. San Francisco (CA): Cytokinetics, Inc.; 2025 JUN 28. Available from: \\CDSESUB1\EVSPROD\nda219083\0036\m1\us\116-risk-management-plan\rems-supporting-doc.pdf

3. Review of the REMS Document

3.1. Timetable for Submission of REMS Assessments

The Applicant proposed the following timetable for submission of REMS assessments for the MyQorzo REMS: Cytokinetics, Inc. must submit REMS assessments (b) (4) months and (b) (4) months from the date of the initial approval of the REMS (MM/DD/YYY), and then every (b) (4) years thereafter. To facilitate the inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for the assessment. Cytokinetics, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

Reviewer's Comments:

- *The Agency does not agree with the Applicant's proposed timetable. To adequately evaluate if the REMS is functioning as intended and meeting its goal of mitigating the risk of heart failure due to systolic dysfunction, more frequent REMS assessments are needed. We also note that limited data for REMS assessment is expected to be available at (b) (4) months, so we propose annual REMS assessments beginning at 12 months from the date of the initial approval of the REMS. An assessment beginning at 12 months will also provide additional time for the Applicant to conduct initial compliance activities to evaluate REMS participant compliance with REMS requirements related to the proposed objective.*
- *The timetable for submission of assessments we will propose to the Applicant is: Cytokinetics must submit REMS assessments at 12 months and annually thereafter from the date of the initial approval of the REMS (MM/DD/YYYY). To facilitate the inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for the assessment. Cytokinetics, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.*

3.2. Audit Requirements for Pharmacies and Wholesalers-distributors

The Applicant proposed the following audit requirement in their REMS Document submission dated March 28, 2025:

1. Audit pharmacies no later than 180 calendar days after they become certified, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and support the REMS requirements.
2. Audit wholesalers-distributors no later than 180 calendar days after they place their first order of MyQorzo, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and support the REMS requirements.

Reviewer's Comments:

- *We request revision to the Applicant's proposed initial and annual pharmacy audits and initial and annual wholesaler-distributor audits (in the REMS Document) by adding the word "all" to clarify how many pharmacies and wholesalers-distributors must be audited.*

- *We recommend providing the following comment to the Applicant: For each REMS participant, the audits must be completed no later than 180 calendar days after the timeframe described in the REMS Document. Audits are considered complete when all the planned audit activities have been completed: 1) initiating the audit, 2) preparing audit activities, 3) conducting the audit, 4) preparing and distributing the report, and 5) completing audit.*
- *The Applicant did not include their REMS Assessment Audit and Noncompliance Plan methodologies in their REMS submission. In order to ensure the data assessing REMS compliance is high-quality and reliable, we recommend the Applicant start developing their audit and noncompliance plan methodologies and plan for submission to the Agency after an action is taken on the application. When developing audit and noncompliance methodologies, we recommend the Applicant consider the following items.*
    - *We recommend the REMS Audit Plan:*
        - *Be tailored specifically to the REMS requirements and objectives.*
        - *Align audit plan procedures with audit requirements in the REMS Document (e.g., audit frequencies).*
        - *Describe data collection methods for audits (e.g., onsite, telephone, questionnaire), frequency of audits, corrective action, and reporting of audit findings. Audit instruments and audit questionnaire(s) used to collect data should be included.*
        - *Describe how audit data will be maintained and analyzed.*
        - *Include timeframes for participant response to audit requests and subsequent actions taken if no response is received.*
        - *Include processes and procedures to ensure corrective and preventive actions for deviations are taken by REMS participants and indicate when follow-up audits will be required.*
        - *Include audit finding classifications (e.g., critical, major, minor) with specific examples and descriptions.*

    - *We recommend the REMS Noncompliance Plan:*
        - *Be tailored specifically to the REMS requirements and objectives.*
        - *Describe how noncompliance events are identified and evaluated, the responsible personnel (e.g., the composition of a Compliance Committee), the frequency of noncompliance review, the data sources/scope of noncompliance data review, and actions proposed for REMS participant noncompliance such as retraining, warning, suspension, and/or decertification.*
        - *Include noncompliance event classifications (e.g., critical, major, minor) with specific examples and descriptions.*
        - *Describe your corrective and preventive action (CAPA) processes and when a CAPA is required (e.g., all noncompliance events, all major noncompliance events, all critical noncompliance events etc.) and include procedures for evaluating the effectiveness of implemented CAPA measures.*
        - *Describe action taken for noncompliance (e.g., written notice, warnings, suspension) and resulting actions required of participants.*

- *Include process for handling repeat noncompliance (e.g., root cause analysis) and how these will be tracked over time to monitor for reoccurring noncompliance. Include consequences of not resolving noncompliance (e.g., decertification, re-education, limitations on patient enrollment, temporary hold on receiving shipments, etc.)*

4. Review of the REMS Supporting Document

4.1. Key Performance Indicator

The Applicant proposed the following Key Performance Indicator (KPI):

Primary KPI: The proportion of prescriptions dispensed with an authorization from the REMS (i.e., a REMS Dispense Authorization [RDA]) when the prescription:

1. Is dispensed from a certified pharmacy
2. Is associated with a certified healthcare provider
3. Is for an enrolled patient
4. Has a complete **Patient Enrollment Form** and/or **Patient Monitoring Form** that documents appropriateness to initiate or continue treatment

The target threshold is 99.9% of dispenses are associated with an RDA. The Applicant plans to calculate the KPI by using a numerator of number of MyQorzo dispenses with an RDA divided by the denominator of number of MyQorzo dispenses.

Reviewer's Comments:
The KPI proposed by the Applicant will support REMS evaluation and help to assess if the REMS is functioning as intended. An RDA will capture if each piece of the program is being completed in order to assess compliance with the REMS strategy. However, the calculation the Applicant proposed requires revision to clarify the scope of the denominator. The KPI should be calculated using the number of MyQorzo dispenses with an RDA as the numerator divided by total number of MyQorzo dispenses in the denominator (including dispenses with and without an RDA). The Applicant will be asked to add the word total to the proposed KPI calculation.

See below for a description of the metrics that will be used to inform KPI calculation.

4.2. REMS Assessment Plan

The Applicant submitted a proposed REMS Assessment Plan with the materials submitted on March 28, 2025, and an amended submission on June 18, 2025. The amended submission contained revision to the REMS Assessment Plan including two pharmacy audit sub-metrics evaluating pharmacy dispensing data for REMS compliance and revisions to a metric capturing left ventricular ejection fraction (LVEF) on the Patient Monitoring Form to align with revisions made to the form in the REMS materials. The proposed REMS Assessment Plan included metrics under the following categories: Program Implementation and Operations, REMS Infrastructure and Performance, Safe Use Behaviors, Knowledge, and Overall Assessment of REMS Effectiveness.

Reviewer's Comments:

DMAMES reviewed the REMS Assessment Plan, as amended on June 18, 2025. We accept the Applicant's proposed revisions to the pharmacy audit sub-metrics and Patient Monitoring Form LVEF data metrics. We also determined the REMS Assessment Plan requires additional revisions. We proposed the following:

- *Addition of metrics to capture data on REMS participants including REMS support staff and REMS Healthcare Provider Delegates*
- *Addition of individual metrics needed to inform calculation of the proposed Key Performance Indicator under Drug Utilization*
    - *"Number of MyQorzo dispenses with an RDA"*
    - *"Total number of MyQorzo dispenses (including those with an RDA and those without an RDA.) Provide the data source"*
    - *"Number of MyQorzo dispenses with an RDA (numerator) divided by total number of MyQorzo dispenses (denominator)"*
    - *Addition of "Number of MyQorzo dispenses without an RDA" under REMS Compliance – Pharmacies*
- *Removal of* (b) (4) *are not necessary to inform assessment of the proposed goal and objective:*
    - *"Evaluation of Knowledge of the MyQorzo REMS and Risks of MyQorzo*
        - *An evaluation of certified healthcare providers' and enrolled patients' knowledge, attitudes, and behaviors (KAB) related to:*
            - *The risk of heart failure due to systolic dysfunction"*

The REMS support staff and REMS Healthcare Provider Delegate metrics will inform assessment of participation and adherence to REMS requirements by REMS participants.

REMS evaluation will be based on the totality of REMS assessment plan data, with a focus on compliance with the safe use condition described in the objective. In addition, the numerator and denominator of the Key Performance Indicator were added as metrics to the REMS Assessment Plan to ensure compliance with REMS requirements. The addition of a metric to measure MyQorzo dispenses without an RDA to the compliance section will assist with our evaluation of noncompliance within the REMS. The patient must have a completed Patient Enrollment Form to initiate treatment, and a Patient Monitoring Form submitted thereafter to document the appropriateness of continued treatment with MyQorzo.

The knowledge section of the assessment plan was removed because this program does not have an education-based goal. We determined that knowledge surveys will not provide additional information to support evaluating the goal of this REMS. REMS evaluation will consider the Key Performance Indicator and compliance data to determine whether the REMS is functioning as intended.

A copy of the MyQorzo REMS Assessment Plan with our proposed revisions will be provided to the Applicant and is included at the end of this review. Review of the Assessment Plan is ongoing and additional revisions may be proposed in the future.

To assess how the Applicant plans to verify if the submitted Patient Monitoring Forms are complete and appropriate, we have a general comment for the Applicant and will request the information be added to their REMS Supporting Document.

5. Conclusions and Recommendations

The proposed audit requirements in the REMS Document require the addition of the word "all" to be acceptable. The proposed timetable for submission of REMS assessments requires revision to be acceptable.

The proposed REMS Assessment Plan for MyQorzo requires further revision. A tracked changed version of REMS Assessment Plan with additions underlined and deletions in strikethrough text will be provided to share with the Applicant. We provided additional explanatory comments to the Applicant in **Section 6**.

We recommend sending the comments in **Section 6** and the revised Assessment Plan to the Applicant.

6. Comments to the Applicant

We have the following comments regarding the proposed timetable for submission of assessments, audit requirements in the REMS Document, and REMS assessment plan within the REMS Supporting Document of the March 28, 2025, submission and amended submission on June 18, 2025.

Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comments

- Two data sources for the MyQorzo REMS assessment are the Patient Monitoring Form and the Patient Enrollment Form. To assist the Agency in evaluating the validity of these data for REMS assessment, explain your process for verifying that when a form is received by the REMS, it is complete and appropriate for the patient. Provide the details of this process in your REMS Supporting Document.
- Confirm all pharmacy dispensing data (not just a representative sample of dispenses) will be collected from pharmacies during annual audits to accurately calculate the key performance indicator. If not, explain how you plan to obtain all pharmacy dispensing data.

Timetable for Submission of Assessments

- The proposed timetable for submission of assessments requires revisions. To adequately evaluate if the REMS is functioning as intended and meeting its goal of mitigating the risk of heart failure due to systolic dysfunction, more frequent REMS assessments are needed. Revise your REMS Document and REMS Supporting Document to align with the following timetable: Cytokinetics must submit REMS assessments at 12 months and annually thereafter from the date of the initial approval of the REMS (MM/DD/YYYY). To facilitate the inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for the assessment. Cytokinetics, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

Audit Requirements in REMS Document

- The proposed pharmacy and wholesaler-distributor audits require revision for clarification that all participants must be audited. Revise your REMS Document to align with the audit requirements described below.
    - Audit all pharmacies no later than 180 calendar days after they become certified, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and support the REMS requirements.
    - Audit all wholesalers-distributors no later than 180 calendar days after they place their

first order of MyQorzo, and annually thereafter, to ensure all REMS processes and procedures are in place, functioning, and support the REMS requirements.

- For each REMS participant being audited, the audits must be completed no later than 180 calendar days after the timeframe described in the REMS Document. Audits are considered complete when all the planned audit activities have been completed: 1) initiating the audit, 2) preparing audit activities, 3) conducting the audit, 4) preparing and distributing the report, and 5) completing audit.

Audit Plan and Noncompliance Plan Methodologies

We recommend you begin developing your REMS audit plan and noncompliance plan methodologies for submission to the Agency following approval of your NDA. To inform REMS assessment and to ensure monitoring of the REMS activities, your REMS audit plan and noncompliance plan should incorporate the following:

Audit Plan

- Be tailored specifically to the REMS requirements and objectives.
- Align audit plan procedures with audit requirements in the REMS Document (e.g., audit frequencies).
- Describe data collection methods for audits (e.g., onsite, telephone, questionnaire), frequency of audits, corrective action, and reporting of audit findings. Audit instruments and audit questionnaire(s) used to collect data should be included.
- Describe how audit data will be maintained and analyzed.
- Include timeframes for participant response to audit requests and subsequent actions taken if no response is received.
- Include processes and procedures to ensure corrective and preventive actions for deviations are taken by REMS participants and indicate when follow-up audits will be required.
- Include audit finding classifications (e.g., critical, major, minor) with specific examples and descriptions.

Noncompliance Plan

- Be tailored specifically to the REMS requirements and objectives.
- Describe how noncompliance events are identified and evaluated, the responsible personnel (e.g., the composition of a Compliance Committee), the frequency of noncompliance review, the data sources/scope of noncompliance data review, and actions proposed for REMS participant noncompliance such as retraining, warning, suspension, and/or decertification.
- Include noncompliance event classifications (e.g., critical, major, minor) with specific examples and descriptions.
- Describe your corrective and preventive action (CAPA) processes and when a CAPA is required (e.g., all noncompliance events, all major noncompliance events, all critical noncompliance events etc.) and include procedures for evaluating the effectiveness of implemented CAPA measures.
- Describe action taken for noncompliance (e.g., written notice, warnings, suspension) and resulting actions required of participants.

- Include process for handling repeat noncompliance (e.g., root cause analysis) and how these will be tracked over time to monitor for reoccurring noncompliance. Include consequences of not resolving noncompliance (e.g., decertification, re-education, limitations on patient enrollment, temporary hold on receiving shipments, etc.)

REMS Assessment Plan

The Agency requires revisions to the REMS Assessment Plan within the Supporting Document of the March 28, 2025, submission and amended submission on June 18, 2025. Revisions are needed to ensure that the REMS Assessment Plan adequately informs REMS assessment by capturing additional information on REMS support staff and REMS Healthcare Provider Delegates, adding in metrics to measure components of your proposed key performance indicator, removing knowledge surveys for healthcare providers because knowledge surveys are not needed to inform assessment of the proposed goal and objective, and adding a metric for noncompliance with the REMS dispense authorization. A tracked changes version is attached that includes our revisions. Review of the REMS Assessment Plan is ongoing; these comments should not be considered final.

Revised MyQorzo REMS Assessment Plan:

The REMS Assessment Plan includes, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Implementation and Operations

1. REMS Implementation (for the first REMS assessment only)
    a. Date of first commercial availability of MyQorzo
    b. For each participant (b) (4) (healthcare providers, pharmacies, patients), the date they could become certified or enrolled
    c. Date when the MyQorzo Call Center was established and fully operational
    d. Date when the MyQorzo REMS website became live and fully operational
2. REMS Certification and Enrollment Statistics
    a. Healthcare providers
        i. Number of newly certified healthcare providers and number of active healthcare providers (i.e., who have prescribed MyQorzo at least once during the reporting period) stratified by specialty (e.g., Cardiology, Internal/General Medicine, Other).
        ii. Total number of REMS support staff
            1) Number of certified healthcare providers with more than four linked REMS support staff
        ~~i.~~iii. Number of newly designated -REMS Healthcare Provider Delegates and total number of designated REMS Healthcare Provider Delegates, stratified by credentials (e.g., medical doctor, physician assistant, nurse practitioner etc.), and clinical specialty
    b. Pharmacies

i. Number of newly certified pharmacies

ii. Number of active pharmacies (i.e., that have dispensed MyQorzo at least once during the reporting period)

c. Patients

i. Number of newly enrolled patients and number of active patients (i.e., who have received at least one dispense of MyQorzo during the reporting period) stratified by age ranges of less than 18, 18-40, 41-60, 61 years and older. Provide the minimum and maximum age of enrolled patients.

d. Wholesalers-distributors

i. Number of newly contracted wholesalers-distributors and number of active wholesalers-distributors (i.e., that have shipped MyQorzo at least once during the reporting period)

3. Drug Utilization

a. The total number of REMS Dispense Authorization (RDA) requests received

b. The number of RDA requests received and authorized, stratified by:

i. Healthcare provider specialty

ii. Patient age

c. The number of RDA requests received and denied (not authorized), stratified by:

i. Reasons and number of denials (numerator) divided by all denials (denominator)

1) Healthcare provider not certified

2) Pharmacy not certified

3) Patient not enrolled

4) No valid documentation of authorization to receive MyQorzo

a. No **Patient Enrollment Form**

b. No **Patient Monitoring Form**

d. Number of MyQorzo dispenses with an RDA

e. Total number of MyQorzo dispenses (including those with an RDA and those without an RDA). Provide the data source.

f. Number of MyQorzo dispenses with an RDA (numerator) divided by total number of MyQorzo dispenses (denominator)

g. Number of prescriptions for unique healthcare providers for which an RDA was requested in the reporting period

h. Number of unique patients who received at least one RDA during the reporting period, stratified by age

4. REMS Compliance

   a. Noncompliance

      i. A copy of the noncompliance plan, including the criteria for noncompliance for healthcare providers, pharmacies, and wholesalers-distributors, actions taken to address noncompliance for each case, and which events lead to de-certification from the MyQorzo REMS

   b. Audits

      i. A copy of the audit plan for pharmacies and wholesalers-distributors

      ii. Report of audit findings for each participant (b) (4) -(i.e., pharmacies and wholesalers-distributors)

      iii. Number of audits expected, and the number of audits performed

      ~~iii.~~iv. Documentation of REMS participant compliance with REMS requirements, including but not limited to:

         1) Documentation of completion of training for relevant staff

         2) Documentation of processes and procedures in place for complying with the MyQorzo REMS

            a) Pharmacies must agree to maintain records of dispensing information to become certified in the REMS

            b) Auditors will evaluate a representative sample of the MyQorzo pharmacy dispensing data to confirm that an RDA was obtained prior to dispensing, in alignment with REMS compliance requirements

      ~~iv.~~v. Verification for each audited certified pharmacy that each designated authorized representative remains the same. If different, and there is no other certified authorized representative, document that the pharmacy has certified with the name and contact information for the new authorized representative

      ~~v.~~vi. Number and types of deficiencies noted for each group of audited (b) (4) participants as a percentage of audited (b) (4)

      ~~vi.~~vii. For (b) (4) -participants with deficiencies noted, the number that successfully completed a Corrective and Preventative Action (CAPA) plan as a percentage of those for which a CAPA plan was requested

      ~~vii.~~viii. For any (b) (4) -participants who did not complete the CAPA Plan, a description of actions taken

   c. Healthcare provider noncompliance (for each noncompliance event, the source of the report, a description of the event, the root cause analysis of the event, and corrective actions taken)

      i. Number of healthcare providers who were noncompliant with the MyQorzo REMS requirements. Provide as a percentage of active healthcare providers

ii. Number of healthcare providers who were decertified and reasons for de-certification, also provided as a percentage of active healthcare providers. Include if any healthcare providers were recertified

d. Pharmacies (for each noncompliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)

i. Number of pharmacies for which noncompliance with the MyQorzo REMS is detected

ii. Number of noncertified pharmacies that dispensed MyQorzo

iii. Number of MyQorzo prescriptions dispensed by noncertified pharmacies

iv. Number of MyQorzo prescriptions dispensed that were written by non-certified healthcare providers

v. Number of MyQorzo prescriptions dispensed to unenrolled patients

vi. Number of MyQorzo prescriptions dispensed to (b) (4) -patients based on a prescription from a noncertified healthcare provider

vii. Number of times a MyQorzo prescription was dispensed because a certified pharmacy bypassed the MyQorzo REMS RDA processes

viii. Number of pharmacies decertified, reasons for decertification, and actions to address noncompliance

~~viii.~~ix. Number of MyQorzo dispenses without an RDA

e. Wholesalers-distributors (for each noncompliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)

i. Number of contracted wholesalers-distributors for which noncompliance with the MyQorzo REMS is detected

ii. Number of wholesalers-distributors suspended from distributing, reasons for the suspension, and actions to address noncompliance

iii. Number of times MyQorzo was distributed to a noncertified pharmacy

REMS Infrastructure and Performance

5. REMS Website

a. Number of total visits and unique visits to the REMS website

b. Number and type of REMS materials downloaded for each material

6. REMS Call Center Reports

a. Number of contacts by (b) (4) -participant type (patient, healthcare provider, REMS support staff, REMS healthcare provider delegates, pharmacy, wholesalers-distributors, other)

b. Summary of reasons for calls (e.g., enrollment question) and (b) (4) -participant type (patient, healthcare provider, REMS support staff, pharmacy, other). Limit the summary to the top five reasons for calls by each (b) (4) -participant group

c. If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues

Safe Use Behaviors

7. **Patient Monitoring Forms**

   a. Number of **Patient Monitoring Forms** expected, received, and outstanding

   b. Number of unique patients who had a **Patient Monitoring Form** submitted for whom the healthcare provider confirmed reviewing the echocardiogram results

   c. Number of unique patients who had a **Patient Monitoring Form** submitted for whom the healthcare provider authorized treatment

   d. Number of **Patient Monitoring Forms** on which the healthcare provider indicated that the patient experienced a clinical heart failure event requiring clinical intervention or hospitalization since the last submitted form

   e. Number of **Patient Monitoring Forms** on which the healthcare provider indicated the patient's LVEF in the following ranges:

      i. ≥55%

      ii. <55% and ≥50%

      iii. <50% and ≥40%

   f. Number of patients who were not authorized to continue treatment as indicated on the **Patient Monitoring Form**

8. **Healthcare Provider Knowledge Assessments**

   a. Number of completed **Healthcare Provider Knowledge Assessments**, including the method of completion and number of attempts to complete

   b. A summary of the most frequently missed **Healthcare Provider Knowledge Assessment** questions

   c. A summary of potential comprehension or perception issues identified with the **Healthcare Provider Knowledge Assessment**

(b) (4)

Overall Assessment of REMS Effectiveness

~~10.~~9. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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.

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

Application Type	NDA
Application Number	219083
PDUFA Goal Date	December 26, 2025
Nexus TTT #	2024-11042
Reviewer Names	Christopher Booze, PharmD (DRM) Derrick D. Beasley, MS, MPH (DRM)
Team Leader	Yasmeen Abou-Sayed, PharmD (DRM)
Associate Director	Suzanne Robottom, PharmD (DRM)
Review Completion Date	May 28, 2025
Subject	Interim Review of proposed REMS
Established Name	Aficamten
Trade Name	Myqorzo
Name of Applicant	Cytokinetics
Therapeutic Class	Cardiac myosin inhibitor
Dosage Form(s)	5, 10, 15, and 20 mg oral tablets
Dosing Regimen	Starting dose 5 mg daily, titrated upward every 2-8 weeks based on ECHO monitoring results (max dose 20 mg daily)

Table of Contents

1. Introduction

This interim review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Myqorzo (aficamten). Cytokinetics submitted a New Drug Application/Biologic Licensing Application (NDA 219083) for aficamten with the proposed indication for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). This application is under review in the Division of Cardiology and Nephrology (DCN). The applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of aficamten outweigh the risk of heart failure due to systolic dysfunction.

This interim review discusses DRM's initial comments on the REMS proposal.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for aficamten (NDA 219083) relevant to this review:

- 02/08/2024: At a type B meeting, Cytokinetics informed the agency of its intent to propose to manage the risks of aficamten through labeling rather than a REMS. The agency stated in response that it did not object to submission of the NDA without a REMS, but that the need for a REMS would ultimately be a review issue and the Applicant should submit adequate rationale to support their proposal.[1]
- 09/26/2024: Cytokinetics submitted NDA 219083 for aficamten, with a non-REMS risk management plan and rationale in lieu of a REMS.[2]
- 03/04/2025: Applicant was notified at midcycle meeting of the need for a REMS with ETASU including ETASU A, B, D and E.[3]
- 03/28/2025: Applicant submitted an amendment to NDA 219083 that included a proposed REMS with the required ETASU.[4]
- 04/29/2025: Applicant was notified that the REMS submission constitutes a major amendment and the PDUFA date would be extended by 90 days to 12/26/2025.[5]

3. Conclusions and Recommendations

DRM does not find the proposed REMS for Myqorzo (aficamten) as submitted on March 28, 2025, to be acceptable. Send the comments in Section 4 to Cytokinetics in an Information Request and instruct the Applicant to submit a REMS amendment within 15 business days.

4. Comments for the Applicant

We have the following comments on the proposed REMS, submitted on March 28, 2025. Review of the REMS proposal is ongoing; these comments should not be considered final.

Submit revised REMS materials (as outlined in the table below) within 15 business days. Accept the track changes with which you agree and only indicate any new changes you propose as redlined changes in each Word document in your next submission. Ensure that all Word versions include the author of the comments so revisions can be identified (not anonymous). The next submission to the Gateway should include clean Word, tracked Word, and pdf formatted versions of the REMS materials, including a clean PPT and tracked PPT for the Education Program.

General Comments

1. All changes described in these comments should be updated throughout the REMS Document, REMS Supporting Document, and REMS materials.

2. The first dispense of aficamten must be within 3 months of the Patient Enrollment Form submission, to ensure the initiation of therapy is based on an appropriately recent ECHO showing a baseline LVEF ≥ 55%. Update REMS materials to reflect that the first prescription must be dispensed within 3 months (rather than 6 months) of the enrollment form submission.

3. For patients with LVEF 50-55%, adjust the frequency that patient monitoring forms are required to every 3 months once in the maintenance phase, rather than every 6 months, to align with the monitoring frequency in draft labeling. Change Question 2 on the Patient Monitoring Form to ask whether the patient's recent LVEF is <50%, 50-55%, or >55%. When selecting the 50-55% category, this will require completion of Patient Monitoring Form in 3 months. See the attached redlined form for suggested edits. Update other REMS materials to align with this change.

REMS Materials

Healthcare Provider/Pharmacy/Patient Enrollment Forms

Formatting changes were made throughout the enrollment forms to improve usability of the forms. These changes include but not limited to the following: revisions to the instruction section, increasing font size, moving the data fields up on the form, and other suggestions related to wording and content.

Patient Brochure

a. Include graphics and logo on Patient Brochure along with finalized formatting.

Patient Monitoring Form

a. Several recommendations are provided on the patient monitoring questions included on the form. Some of the questions warrant follow up guidance (e.g., if a healthcare provider answers "yes" versus "no"). Additionally, consider including a visual diagram or table to display when the Patient Monitoring Form must be submitted.

Program Overview

a. Include graphics and logo on Program Overview along with finalized formatting.

Education Program for Healthcare Providers and Pharmacies

a. Create a slide deck/PowerPoint-based format for the Education Program for Healthcare Providers and Pharmacies for Agency review. The slide deck/PPT-based format will allow participants to easily advance to sections of the slide deck that cover specific requirements associated with the REMS, particularly when completing enrollment online. The PowerPoint-based format should include all necessary content including graphics and be properly formatted.

Healthcare Provider Knowledge Assessment

a. Revise Question 1 to assess HCP understanding of the risk being mitigated by the Myqorzo REMS.
b. Include an additional question that assesses healthcare providers' understanding of the time points for when echocardiograms are needed.

REMS Website

a. Website screenshots are needed to assess functionality of the REMS. Submit all screenshots and actual layout for the Myqorzo REMS website for Agency review, including screenshots of post-login functionality for participants.
    i. We understand that there may be proprietary information related to REMS operations that may not be appropriate for public access in the REMS website. Non-public facing REMS website screenshots (such as the operational processes involved post-login for stakeholders to the REMS website and verification processes) may be submitted as an appendix to the REMS Supporting Document.
    ii. Describe and show through the website screenshots how a prescriber would complete the certification process, including reviewing the **Education Program for Healthcare Providers and Pharmacies**, completing, and submitting both the **Healthcare Provider Knowledge Assessment** and **Healthcare Provider Enrollment Form** online. Explain how the website ensures that the prescriber reviews the required materials before submitting the **Healthcare Provider Knowledge Assessment** and **Healthcare Provider Enrollment Form**.
    iii. Describe and show through the website screenshots how a prescriber would manage a patient including initial enrollment, documentation of monitoring via the **Patient Monitoring Form,** and other patient management activities.
    iv. Describe and show through the website screenshots how a pharmacy would interact with the REMS Website to obtain a REMS Dispense Authorization for a patient, including what happens if a patient is not authorized to receive the drug.
b. We remind you to use bullets, moderate white space, shorter line lengths, and fewer lines of text, when possible, when developing your REMS website. The following is a link to helpful guidelines developed by the U.S. Department of Health and Human Services (HHS) that you may consider in developing your website: http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes
c. The Agency requires that the REMS website be independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website page back to the product website. Any non-REMS materials and services can be located on the product website but not be included on the REMS website.
d. We recommend that you include a prominent link on the product website's homepage for REMS materials. This link should direct users to a separate webpage that describes the REMS and lists only approved REMS materials. The link should state: "Risk Evaluation and Mitigation Strategy (REMS) or just REMS.

Assessment Plan

The submitted assessment plan is under review.

To understand how some data will be collected, provide details on how pharmacy dispensing data will be obtained. For example, will pharmacies submit this information to the REMS electronically? If so, how often will submissions be required? Will submitting dispensing data be required or will it be voluntary? Will the REMS obtain dispensing information through sources outside of or indirectly from certified

pharmacies? Will you be able to obtain record of every Myqorzo (aficamten) dispense, and verify the patient has a patient enrollment form submitted, and up-to-date patient monitoring forms submitted?

Add details of how pharmacy dispensing data will be obtained to your REMS supporting document.

Key Risk Messages (KRMs)

The KRMs are developed to align with the REMS goal. The REMS materials will provide education and support the risk messaging of the REMS. The KRMs should be included in the REMS Supporting Document (RSD) and be incorporated into relevant REMS materials.

- KRMs for Healthcare Providers
  - Myqorzo (aficamten) can cause heart failure due to systolic dysfunction (LVEF < 50%)
  - Dosing should be modified or discontinued if LVEF <50% as described in the Prescribing Information
  - Healthcare Providers must perform echocardiogram (ECHO) monitoring before treatment and routinely during treatment as described in the Prescribing Information
- KRMs for Patients
  - Myqorzo (aficamten) can cause heart failure when your heart is unable to pump enough blood to the body)
  - You will need to have regular echocardiograms (ECHOs) to check your heart while taking Myqorzo (aficamten)
  - You must inform your healthcare prescriber of any new or worsening symptoms of heart failure
- KRMs for Pharmacies
  - Myqorzo (aficamten) can cause heart failure due to systolic dysfunction (LVEF <50%)
  - Healthcare providers must perform ECHO monitoring at baseline and routinely during treatment, and patients must be authorized to receive Myqorzo (aficamten) as documented on Patient Monitoring Forms.
  - Prior to dispensing, the pharmacist must ensure the prescriber is certified, the patient is enrolled, and the healthcare provider has authorized the patient to receive Myqorzo (aficamten).

The Agency requests that you submit the REMS documents as shown below:

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, PDF
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF
3	Healthcare Provider Enrollment Form	Tracked MS Word, Clean MS Word, PDF
4	Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF
5	Patient Enrollment Form	Tracked MS Word, Clean MS Word, PDF
6	Patient Brochure	Tracked MS Word, Clean MS Word, PDF
7	Patient Monitoring Form	Tracked MS Word, Clean MS Word, PDF
8	Program Overview	Tracked MS Word, Clean MS Word, PDF

9	Education Program for HCPs and Pharmacies	Tracked MS Word, Clean MS Word, Tracked PPT, Clean PPT (For New Slide-Based Format)
10	Healthcare Provider Knowledge Assessment	Tracked MS Word, Clean MS Word, PDF
11	REMS Website Screenshots	PDF annotated version, PDF

5. Appendix

1. Healthcare Provider Enrollment Form
2. Patient Enrollment Form
3. Pharmacy Enrollment Form
4. Education Program for Healthcare Providers and Pharmacies
5. Program Overview
6. Healthcare Provider Knowledge Assessment
7. Patient Brochure
8. Patient Monitoring Form

6. References

[1] Changyi, M. Minutes from the February 8, 2024 Type B Meeting for aficamten (IND 138814). February 29, 2024.

[2] Cytokinetics. Aficamten NDA 219083, September 26, 2024 initial NDA submission

[3] Changyi, M. Minutes from the March 8, 2025 Mid-cycle Meeting for aficamten (NDA 219083). April 3, 2025.

[4] Cytokinetics. Aficamten NDA 219083, March 28, 2025 REMS submission

[5] Changyi, M. Notification of review extension for aficamten NDA 219083. April 29, 2025.

28 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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SUZANNE B ROBOTTOM
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