EU Risk Management Plan
for
MYQORZO

(aficamten)

RMP version to be assessed as part of this application:

RMP Version number:	1.0
Data lock point for this RMP:	31 October 2023
Date of final sign off:	

Rationale for submitting an updated RMP:

Summary of significant changes in this RMP:	Not applicable

Other RMP versions under evaluation:

RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:

Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

QPPV name: Stephen Heaton, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the applicant´s QPPV. The electronic signature is available on file.

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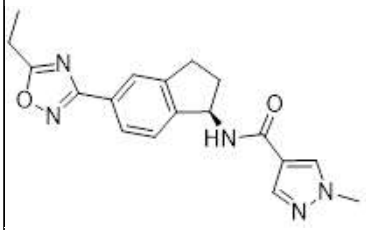
LIST OF ABBREVIATIONS

AF	Atrial fibrillation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CARDIA	Coronary Artery Risk Development in Young Adults
CL/F	Apparent oral clearance
C_{max}	Maximum serum concentration
CPET	Cardiopulmonary exercise testing
CrCL	Creatinine clearance
CYP	Cytochrome P450
EC	European Commission
EFD	Embryo-foetal development
EORP	EURObservational Research Programme
ESC	European Society of Cardiology
EU	European Union
F1	First filial
GLP	Good laboratory practice
HCM	Hypertrophic cardiomyopathy
HCP	Healthcare professional
hERG	Human ether-à-go-go related gene
IC_{50}	Half maximal inhibitory concentration
ICD	Implantable cardioverter defibrillator
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
LVOT-G	Left ventricular outflow tract gradient
MACE	Major adverse cardiovascular events
nHCM	Non-obstructive hypertrophic cardiomyopathy
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NYHA	New York Heart Association
oHCM	Obstructive hypertrophic cardiomyopathy
PASS	Post-authorization safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic

PK	Pharmacokinetics
PK-PD	Pharmacokinetic-pharmacodynamic
PopPK	Population pharmacokinetic
PPND	Pre-Post-Natal Development
PSUR	Periodic safety update report
PBRER	Periodic Benefit Risk Evaluation Report
QTc	Corrected QT Interval
SCD	Sudden cardiac death
SHaRe	Sarcomeric Human Cardiomyopathy Registry
SmPC	Summary of Product Characteristics
SRT	Septal reduction therapies
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US	United States

PART I: PRODUCT(S) OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Aficamten
Pharmacotherapeutic group(s) (ATC Code)	Cardiac therapy, other cardiac preparations (C01EBXX)
Marketing Authorization Applicant	Cytokinetics (Ireland) Limited
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	MYQORZO
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Substituted indane Chemical name: (R)-N-(5-(5-ethyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-inden-1-yl)-1-methyl-1H-pyrazole-4-carboxamide Molecular formula: $C_{18}H_{19}N_5O_2$ Chemical structure: 
	Summary of mode of action: Aficamten is a reversible allosteric cardiac myosin inhibitor that binds directly to the motor domain of cardiac myosin and prevents it from entering the force-producing state. It is selective for the cardiac isoform of myosin by approximately 5-fold compared to fast skeletal myosin. Aficamten is designed to reduce the hypercontractility in the cardiac sarcomere fundamental to the pathophysiology of hypertrophic cardiomyopathy (HCM). The consequent reduction in cardiac contractility is expected to alleviate left ventricular outflow tract (LVOT) obstruction in HCM patients. LVOT obstruction is a primary cause of morbidity in the majority of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) patients.
	Important information about its composition: Not applicable

<table>
<tr><td>Hyperlink to the Product Information</td><td>Proposed SmPC</td></tr>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current (if applicable):
MYQORZOis indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.</td></tr>
<tr><td>Proposed (if applicable):
Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current (if applicable):
The recommended starting dose is 5 mg orally once daily. A starting dose of 10mg should be considered for patients with left ventricular outflow tract-gradient (LVOT-G) >100mmHg. The dose should be increased every 2 to 8 weeks by 5 mg until a maintenance dose or the maximum dose of 20 mg is achieved. The maintenance dose is individualised based on the patient’s LVEF and LVOT-G. Recommendations for dosing based on LVEF and LVOT-G criteria are in the table below.

Dose Adjustments for MYQORZO
<table>
<tr><th>LVEF</th><th>Valsalva LVOT-G</th><th>Dose Adjustment</th></tr>
<tr><td>≥ 55%</td><td>≥ 30 mmHg</td><td>Increase dose by 5 mg
(up to the maximum dose of 20 mg once daily)</td></tr>
<tr><td>≥ 55%</td><td>< 30 mmHg</td><td>Maintain dose</td></tr>
<tr><td>< 55% and ≥ 50%</td><td>Any</td><td>Maintain dose</td></tr>
<tr><td>< 50% and ≥ 40%</td><td>Any</td><td>Decrease dose by 5 mg*
Interrupt treatment for 7 days for 5 mg dose</td></tr>
<tr><td>< 40%</td><td>Any</td><td>Interrupt treatment for at least 7 days</td></tr>
</table>
LVEF=left ventricular ejection fraction; LVOT-G=left ventricular outflow tract gradient
*Dose decrease as follows: 20 mg to 15 mg; 15 mg to 10 mg; 10 mg to 5 mg
** After a treatment interruption when LVEF <40%, treatment should be resumed with a dose reduced by 5 mg when LVEF ≥55%. If at 5 mg and LVEF <50%, treatment should be interrupted for 7 days, and treatment can be resumed at 5 mg when LVEF ≥55%
Proposed (if applicable):
Not applicable</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>Current (if applicable):
Film-coated tablets 5 mg, 10 mg, 15 mg, and 20 mg</td></tr>
<tr><td>Proposed (if applicable):
Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication:

MYQORZO is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease caused by a variety of mutations in sarcomere protein genes which affect heart contractility (Basit 2024). Approximately 1 in 500 people worldwide are carriers of a potential pathogenic genetic variant (Maron 1995; Maron 2018a). In the 2023 European Society of Cardiology (ESC) guidelines on the management of cardiomyopathies, HCM is defined as a hypertrophied, nondilated left ventricle which is identified by means of echocardiography or magnetic resonance imaging (MRI) in the absence of another identifiable cardiac, systemic, metabolic, or syndromic etiology (Arbelo 2023).

HCM is a heterogeneous disorder with marked diversity in clinical expression, natural history, and prognosis. Approximately 70% of patients with phenotypic HCM will demonstrate an element of left ventricular (LV) outflow tract (LVOT) obstruction (Maron 2006). The mechanisms for developing obstruction are well defined and involve a complex interplay between asymmetric septal hypertrophy and the mitral valve leaflets that result in alterations of LV outflow. The result is abnormal systolic contact with the mitral valve leaflets (most commonly the anterior leaflet) and the development of an LVOT gradient (LVOT-G). Approximately two-thirds of adult patients with HCM have oHCM, defined as mechanical impedance to left ventricular outflow at a level below the aortic valve (systolic pressure gradients ≥ 30 mmHg) at rest or with physiologic provocation. Subaortic gradients characteristically are dynamic and subject to change with physiologic loading conditions (eg, decreased preload due to dehydration or a rapid change in position or physical exertion level) (Maron 2018b; Ommen 2024; Arbelo 2023). Such changes are responsible for the variability in daily symptoms. Additional clinical manifestations of HCM include heart failure syndrome due to diastolic dysfunction; chest pain due to microvascular ischemia; palpitations and stroke due to atrial fibrillation (AF); syncope and presyncope due to either ventricular arrhythmias or an abnormal blood pressure response to exercise; sudden cardiac death (SCD) due to ventricular fibrillation, and, in a minority of patients, progression to systolic heart failure (Maron 2022).

Prevalence:

The prevalence of HCM in the general population based on left ventricular hypertrophy detected on imaging is estimated to be 0.2% (1:500); this estimate came from echocardiographic data (1987-1988) from the CARDIA (Coronary Artery Risk Development in Young Adults) cohort study (Maron 1995).

Some population-based studies in Europe have provided lower estimates of prevalence of HCM ranging from 0.04% to 0.07%, with prevalence of oHCM ranging from 0.016% to 0.042% as detailed below.

Prevalence of HCM was estimated to be 4,000 out of 5,490,810 patients (0.07%; 1:1,372) using data from a healthcare claims database (InGef) in Germany for the year 2015 (Husser 2018). The annual prevalence increased from 75.8 (95% CI 75.2–76.4) in 2011 to 84.2 (95% CI 83.5-84.8) in 2015 per 100,000 persons (Husser 2018). In a population-based cohort study using linked primary care, hospital, and mortality records in England (CALIBER) for the period 1997–2010, the prevalence of HCM among 3,290,455 eligible people was 1375/3.3 million or 4 per 10,000 persons (0.04%) (Pujades-Rodriguez 2018). A population-based clinical and genetic

study conducted in Iceland using medical records and imaging studies (1997 to 2010) found a prevalence of HCM of 180/320,000 or 5.6/10,000 (0.06%) (Adalsteinsdottir 2014).

The prevalence of oHCM among 1.6 million inhabitants of West Götaland Region of Sweden was estimated by searching hospital diagnostic databases (Jan 2002 to Dec 2013) and reviewing case notes; 1142 patients had a verified diagnosis of primary HCM, and 22% of these (251 patients [128 male, 123 female]) fulfilled the oHCM criteria (LVOT-G ≥ 30 mmHg at rest). The estimated prevalence of oHCM was 251 per 1.6 million persons or 1.6 per 10,000 persons (0.016%) (Javidgonbadi 2019). A further study utilizing the Swedish National Patient Register to identify patients with HCM for the period from 2006-2016 estimated a HCM prevalence of 74/183,337 or 4.0 diagnosed cases per 10,000 (0.04%) in the adult population aged ≥18 years (Magnusson 2017).

The real-world proportion of oHCM and non-obstructive HCM (nHCM) was estimated in the United Kingdom (UK) (01 Apr 2009 to 30 Oct 2020) and Germany (2011 to 2019) using electronic health records from the Clinical Practice Research Datalink (CPRD) and nationally representative administrative claims data pool (WIG2 Benchmark database), respectively. The proportion of oHCM ranged from 49% in Germany to 68% in the UK. The average annual prevalence rate of oHCM was 2.84/10,000 in the UK and 4.18/10,000 in Germany (Schultze 2022).

Demographics of the population in the proposed indication and risk factors for the disease:

Demographics:

HCM can affect people of all ages, but it develops slowly and is usually diagnosed in mid-life. In the Cardiomyopathy Registry of the EURObservational Research Programme (EORP), the median (Q1, Q3) age of HCM diagnosis was 47 (33.00 to 59.00) years (Charron 2018). In a population-based cohort study, the median age of HCM was 57 years (Pujades-Rodriguez 2018). Husser et al found that the prevalence of HCM increased gradually with age from 7.4/100,000 persons (95% CI 5.2–10.1) in 0–9 years old to 298.7/100,000 persons (95% CI 276.4–322.4) in patients >80 years (Husser 2018).

HCM affects all genders, but some studies report a higher prevalence in males. Husser et al found a higher prevalence in males in all age categories with significant differences between the sexes in patients older than 30 years (Husser 2018). Pujades-Rodriguez et al found that 41% of a population-based sample of HCM patients were female (Pujades-Rodriguez 2018).

HCM can affect all races. Most studies of disease expression and prognosis in HCM reflect the experience of white patients. In a retrospective cohort study using data from the US-based sites of the Sarcomeric Human Cardiomyopathy Registry (SHaRe) from 1989 through 2018, black patients with HCM were diagnosed at younger age, were less likely to have disease caused by sarcomere mutations, had a greater burden of symptomatic heart failure, and were more likely to be obese and hypertensive compared with white patients (Eberly 2020). Out of 1900 patients referred to HCM programs at a US HCM referral center from 2004 to 2017, 90 consecutive black patients were identified and followed for 3±3 years (Wells 2018). Phenotypic expression of HCM was similar among black and white patients, but the black patients had fewer heart failure symptoms and risk factors for sudden death than white patients. However, heart failure progression, and all-cause mortality was similar in the black and white patients (Wells 2018).

Risk factors:

The main risk factor for HCM is a family history of HCM or SCD in a first-degree relative. Most cases of HCM (40-60%) in adults and adolescents are caused by mutations in genes encoding cardiac sarcomere proteins. Mutations in genes that cause metabolic disorders, neuromuscular

disease or inherited genetic syndromes including Noonan syndrome account for a further 5-10% of HCM cases. HCM is passed on as an autosomal dominant trait (Akhtar 2018).

The main existing treatment options:

The ESC has recently published guidelines for the management of cardiomyopathies (Arbelo 2023). The main approaches to treatment of symptomatic oHCM are medical management and septal reduction therapy (SRT). First-line, guideline-directed pharmacologic options include beta-blockers, calcium channel blockers, and disopyramide. Non-vasodilating beta-blockers (Class 1) are the recommended initial treatment for the management of LVOT obstruction in symptomatic patients with HCM. In patients who are intolerant or have a contraindication to beta-blockers, calcium channel antagonists (verapamil or diltiazem) are recommended. If patients are still symptomatic, disopyramide can be added to improve symptoms in patients with resting or provoked LVOT obstruction. The cardiac myosin inhibitor mavacamten should also be considered in addition to beta-blockers or verapamil/diltiazem or as monotherapy in symptomatic patients with resting or provoked LVOT obstruction who are intolerant to beta-blockers or verapamil/diltiazem. Echocardiographic assessment of left ventricular ejection fraction (LVEF) is required in patients taking mavacamten to allow up titration of medication to an optimal dose while avoiding left ventricular dysfunction due to an excessive pharmacological effect.

Despite frequent side effects of fatigue, depression, and impotence, beta-blockers continue to be first-line therapies for patients with symptomatic oHCM. Although non-dihydropyridine calcium channel blockers (verapamil or diltiazem) can be used in patients who do not tolerate beta-blockade, these medications often result in poorly tolerated side effects (eg, constipation, hypotension, dizziness, and edema) (Taha 2023), and their use in high-gradient patients is discouraged by experts in the field (Houston 2015). Disopyramide is effective at reducing the degree of LVOT obstruction and improving symptoms in a subset of patients who are refractory to either beta-blockers and/or non-dihydropyridine calcium channel blockers. However, anticholinergic side effects and tachyphylaxis limit adherence (Adler 2017). A risk evaluation and mitigation strategy (REMS) program is in place in the US for mavacamten to monitor the risk of heart failure due to systolic dysfunction, exacerbated by the presence of strong drug-drug interactions and a long plasma half-life. Additional risks associated with mavacamten include potential teratogenicity and QT prolongation, neither of which have been observed with aficamten.

Septal reduction therapies (septal myectomy) can be considered in patients with a LVOT obstruction ≥ 50 mmHg, severe symptoms (New York Heart Association [NYHA] Class III-IV), and/exertional or unexplained recurrent syncope despite maximum drug therapy. Patients with mild symptoms and LVOT obstruction ≥ 50 mmHg may also be considered for SRT if they have moderate-to-severe systolic anterior motion-related mitral regurgitation, or AF, or moderate-to-severe left atrial dilatation (Arbelo 2023). Septal reduction therapies are associated with the inherent risks of invasive therapies (eg, death, bleeding, nosocomial infection, myocardial infarction, and complete heart block), and their use is limited to centers with adequate experience and expertise (Kim 2016; Elliot 2014; Ommen 2024). Importantly, SRT only addresses obstruction by relieving it mechanically and does not address the underlying etiopathology of HCM, namely hypercontractility of the cardiac sarcomere, such that many patients are left with residual disability.

Natural history of the indicated condition in the population, including mortality and morbidity:

Mortality rates of 1% to 4% have been reported in patients with HCM, but these numbers have greatly improved in the past two decades (Basit 2024).

In adult patients with HCM, cardiovascular death has been reported with an annual incidence of 1-2%. Most causes of the cardiovascular deaths are recorded as SCD, heart failure and thromboembolism. Spontaneous ventricular fibrillation, asystole, atrioventricular block, and pulseless electrical activity have also been recorded (Arbelo 2023).

Most patients with HCM can have a normal life expectancy without limiting symptoms or the need for major treatments. However, among referral-based cohorts of patients with HCM, 30% to 40% will experience adverse events, including: 1) sudden death events; 2) progressive limiting symptoms because of LVOT obstruction or diastolic dysfunction; 3) heart failure symptoms associated with systolic dysfunction; and 4) AF with risk of thromboembolic stroke. Identification of adult patients most at risk of SCD and use of implantable cardioverter-defibrillator (ICD) placement in those patients has led to a reduction in mortality with heart failure becoming the main cause of disease-related death (Ommen 2020).

Data from SHaRe demonstrate that mortality in patients with HCM is significantly higher than in the US general population. Mortality in 20- to 29-year-olds with HCM was 4-fold higher than expected for that age in the general population. SCD accounted for 16% of deaths in SHaRe. Overall deaths due to heart failure and noncardiac death were more frequent than fatal arrhythmias. However, 26% of patients diagnosed with HCM under the age 40 had lethal arrhythmia by 60 years of age (Ho 2018).

Complications of HCM in SHaRe were mostly due to heart failure or AF. The risk of having heart failure or AF by age 60 years was 47% (95% CI, 42–52) and 62% (95% CI, 56–67) in patients diagnosed with HCM before 40 years of age and higher than the risk in 40-year-olds in the general US population (Heart failure 20% to 45%; AF 23% to 26% [women and men, respectively]). HCM-related complications mainly occurred later in life, peaking between 50 and 70 years of age. The cumulative incidence of ventricular arrhythmias and sudden death was low (2%) in those diagnosed with HCM at >60 years of age, but AF, heart failure, and overall mortality were greatest in this age group (Ho 2018).

In an unselected cohort in Sweden, Javidgonbadi et al found that heart failure was the main cause of death in HCM patients; female sex, age and persisting LVOT obstruction were important independent risk factors for disease-related, and specifically heart failure-related deaths (Javidgonbadi 2019).

In a population based cohort study using linked primary care, hospital and mortality records in England (CALIBER), people with HCM were found to have a higher risk compared to general population of the following conditions: ventricular arrhythmia (incidence rate ratio = 23.53, [95% CI 12.67–43.72]), cardiac arrest or SCD (6.33 [3.69–10.85]), heart failure (4.31, [3.30-5.62]), and AF (3.80 [3.04–4.75]). HCM was also associated with a higher incidence of myocardial infarction (1.90 [1.27–2.84]) and coronary revascularization (2.32 [1.46–3.69]). Absolute Kaplan-Meier risks at 3 years were 8.8% for the composite endpoint of cardiovascular death or heart failure, 8.4% for the composite of cardiovascular death, stroke, or myocardial infarction, and 1.5% for major bleeding (Pujades-Rodriguez 2018).

Important co-morbidities

The main complications or comorbidities in patients with HCM are heart failure, AF, ventricular arrhythmia, stroke, and SCD. In a Danish nationwide study, the following co-morbidities were

statistically more frequent in a cohort of HCM patients compared to a matched cohort from the general population: AF (19.2% vs 5.6% p<0.001), heart failure (13.6% vs 3.6% p<0.001), valvular disease (8.2% vs 1.2% p<0.001) and stroke (6.6% vs 4.9% p=0.03) (Jacobsen 2022).

Baseline data for 1,739 patients enrolled in the Cardiomyopathy Registry of the EORP from 2012 -2016 indicated that 49.9% had NYHA Class II heart failure and 16.1% had NYHA Class III heart failure. Among patients with HCM (median age at enrolment: 55.0 years), 26.6% had a history of AF, 7.7% had sustained ventricular tachycardia, 2.8% had resuscitated ventricular fibrillation/cardiac arrest, 3.4% had stroke, and 9.5% had atrioventricular block. (Charron 2018).

A population-based cohort study in patients with HCM found that the most common cardiovascular co-morbidities were stable angina (24.3%), AF (16.1%) and heart failure (12.8%) (Pujades-Rodriguez 2018).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Toxicology

Key safety findings from definitive GLP non-clinical toxicology studies and relevance to human usage are described below.

Repeat-dose toxicity studies

In repeat-dose toxicology studies in Sprague Dawley rats for up to 6 months (and beagle dogs for up to 9 months), the primary adverse findings at supratherapeutic doses were consistent across all studies and were observed in the heart consisting of atrial/ventricular dilatation that correlated with increased heart weights (Rat: Nonclin-0014, Nonclin-0046, Nonclin-0054, Dog: Nonclin-0047, Nonclin-0056). The anatomic and/or functional effects of aficamten in rats and dogs are similar to the adaptive changes that occur when cardiac function is depressed and likely to be related to the primary pharmacodynamic (PD) properties of aficamten. Microscopic changes, considered secondary to the ventricular/atrial dilatation in the heart, included myocardial degeneration with fibrosis in rat and dog repeat-dose toxicology studies. These cardiac effects are related to maximum serum concentration (C_{max}) and are generally reversible over several weeks following cessation of dosing.

In conjunction with the cardiac atrial/ventricular dilatation in the rat 13-week study (Nonclin-0046) was the presence of respiratory pigmented macrophages that correlated with an increase in lung weights. Additionally, the high-dose level of 9 mg/kg/day evaluated in the 4-week rat study (Nonclin-0014) was associated with hepatotoxicity consistent with development of congestive heart failure.

There were no other notable consistent organ weight changes, macroscopic findings, or adverse microscopic changes in the GLP toxicology studies.

Relevance to human usage

Similar effects to those observed in the toxicology studies would be expected in humans if aficamten was administered chronically at excessively high doses. Excessive on-target pharmacology of cardiac myosin inhibitors at supra-pharmacological doses for a sustained period may cause excessive and prolonged reductions in cardiac systolic function that can lead to potential heart failure (Bishev 2023). In addition, studies suggest that congestive heart failure due to prolonged, excessive reduction in cardiac contractility may be a possible underlying cause of acute liver failure and altered lung function that results from either low cardiac output and impaired perfusion or passive congestion from increased filling pressures (Alvarez 2011, Møller 2013, Saner 2009, Verbrugge 2020). Therefore, it is likely that the effects observed in the liver and lungs were secondary to the ventricular/atrial dilatation noted in affected animals.

The no-observed-effect level (NOEL) in the 26-week oral rat study and the no--observed--adverse--effect level (NOAEL) in the 39-week oral dog toxicity studies were 1.5 mg/kg/day and 1.0 mg/kg/day, respectively, corresponding to a mean C_{max} of 3340 ng/mL in the female rat and 537 ng/mL in the male dog, respectively. The safety margin to the human C_{max} at the highest dose of 20 mg QD in oHCM participants is up to 2.9 x in the rat and up to 7.3 x in the dog.

Clinical studies of aficamten in participants with oHCM employed an individualized dose titration strategy based on achievement of target LVOT gradients and maintenance of normal LVEF to optimize treatment benefit and mitigate the potential risk of heart failure due to systolic dysfunction. As a result, toxicity related to adverse remodeling of the heart has not been observed

in humans. However, heart failure due to systolic dysfunction is included as an important potential risk in the RMP. No signals of hepatotoxicity were observed in participants studied in Phase 2 and 3 clinical trials.

Reproductive/developmental toxicity

Aficamten did not have an adverse effect on fertility or on early embryonic development at doses up to 3.0 mg/kg/day in male Sprague Dawley rats and 6.0 mg/kg/day in female Sprague Dawley rats (Nonclin-0161, Nonclin-0264). In the embryo-foetal development (EFD) studies, aficamten demonstrated maternal toxicity at doses ≥ 6.0 mg/kg/day in Sprague Dawley rats and 20/15 mg/kg/day in New Zealand White rabbits (Nonclin-0199). There was no evidence of an adverse effect on fetal growth or of teratogenicity (dysmorphogenesis) in either species. At 9 mg/kg/day, the dose above the NOAEL for maternal toxicity, embryo fetal mortality was evidenced in rats by an increased number of resorptions (total and early resorptions) and the lower number of live fetuses. There was no evidence of an effect on embryo-foetal mortality in rabbits. The NOAELs for fertility were considered to be 3 mg/kg/day and 6 mg/kg/day for male and female rats, respectively, and 6 mg/kg/day for both early embryonic development and EFD in rats. The NOAEL for EFD in rabbits was considered to be 15 mg/kg/day.

In a study examining the effects of aficamten on pre- and postnatal development (PPND), pregnant female Sprague Dawley rats were administered aficamten daily beginning on Gestation Day 6 and continuing until Lactation Day 21 via oral (gavage) administration at 0.5, 1.5 and 6.0 mg/kg/day (Nonclin-0360). At 6.0 mg/kg/day, there were reductions in maternal body weight, increased heart weights and a decrease in viability index of the pups; therefore, the maternal NOAEL for aficamten was 1.5 mg/kg/day.

Maternal administration of aficamten resulted in adverse clinical signs in the pups, reduced pup body weight during the preweaning period and a slight delay in the acoustic startle reflex during the preweaning period at 6.0 mg/kg/day. There were no effects on growth or development of the F1 generation observed during the postweaning period at any dose level. There were no effects on sexual maturation, neurobehavioral or reproductive function in the F1 generation rats. Based on these data, the developmental, growth and reproduction NOAEL for aficamten in rats was 1.5 mg/kg/day.

In summary, rats administered 6 mg/kg/day in the embryo-foetal study had a 100% pregnancy rate and showed no evidence of teratogenicity and no adverse effect on foetal growth. Increases in heart weight in the pregnant females, a compensatory response to chronic reductions in cardiac function, were evident at this dose, confirming a clinically relevant exposure had been surpassed in the pregnant females. Embryo-foetal toxicity was observed at a dose of 9 mg/kg/day, a dose of aficamten not administered in pharmacological studies out of concern for animal welfare. At this dose, substantial adverse effects were evident in the pregnant females, including reduced food consumption, reduced body weight gain, and increased heart weight. At 9 mg/kg/day, fetal viability was compromised most likely due to profoundly reduced cardiac function in the mother and potentially the fetus, although at birth there was no evidence of teratogenicity or adverse effect on cardiac structure or fetal growth suggesting maternal effects had the predominate impact on fetal viability.

Relevance to human usage

There was no evidence of an adverse effect on fetal growth or of teratogenicity in reproductive studies in rats at doses up to 6 mg/kg/day (approximately 9.1-fold the C_{max} and 3.5-fold the AUC_{24} at the maximum recommended human dose of 20 mg) and in rabbits at doses of 15 mg/kg/day (approximately 2.3-fold the C_{max} and 0.17-fold the AUC_{24} at the maximum recommended human dose of 20 mg. There is an estimated >10-fold pharmacodynamic (PD)

margin comparing the effects on cardiac function in rats at 6 mg/kg/day to that in humans at the maximum recommended dose (MRHD) of 20 mg. There are no data available from the use of aficamten in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity or teratogenicity. As the relevant exposure margins that were reached in these animal studies are insufficient with respect to characterizing the reproductive toxicity profile of aficamten, embryo-foetal toxicity is included in the RMP as an important potential risk with risk minimization measures including the recommendation for effective contraception in women of childbearing potential, and enhanced maternal and fetal cardiac monitoring, including fetal echocardiography, if pregnancy occurs.

Genotoxicity

In a bacterial reverse mutation assay, aficamten was demonstrated to be non-mutagenic (Nonclin-0004) in both the absence and presence of exogenous metabolic activation. In a GLP combination genotoxicity study conducted in rats (Nonclin-0036), aficamten was negative for the induction of micronuclei in bone marrow polychromatic erythrocytes and for the induction of DNA strand breakage in liver tissues.

Relevance to human usage

The results of this genotoxicity testing battery indicate that aficamten is neither mutagenic nor clastogenic/aneugenic and does not pose a genotoxic risk to humans.

Carcinogenicity

There was no evidence of carcinogenic potential for aficamten in the 26-week oral rasH2 transgenic mouse carcinogenicity study (Nonclin-0306) or the 2-year rat carcinogenicity study (Nonclin-0248).

Relevance to human usage

Based on the carcinogenicity studies, aficamten does not pose a carcinogenic risk in humans.

Safety Pharmacology

Key safety findings from definitive GLP safety pharmacology studies and relevance to human usage are described below.

Cardiovascular system

In vitro cardiovascular safety assessments were conducted for aficamten and each of its main metabolites, CK-3834282 (M1a) and CK-3834283 (M1b). In cardiovascular safety assessments, the inhibitory effect of aficamten on the human ether-à-go-go related gene (hERG) potassium current at 10 μM was 3.7 ± 0.6% versus 2.8 ± 0.4% in vehicle (Nonclin-0003). Higher concentrations could not be tested due to limitations in solubility, so no IC_{50} was determined. The in-vitro effect of the M1a metabolite on the hERG channel current (IKr) was examined. The hERG potassium currents were inhibited by 9.90 ± 8.07% with 30 μM M1a vs. 1.76 ± 2.87% in vehicle (Nonclin-0292). The effect of the M1b metabolite on the hERG channel current was also examined and the IC_{50} of M1b was estimated to be 51.13 μM (Nonclin-0298).

Aficamten-related hemodynamic effects in telemetered dogs administered 0.5, 1, or 2 mg/kg/day aficamten for 7 consecutive days included transient decreases in the maximum rate of left ventricular contraction at all dose levels on Days 1 and 7, transiently increased heart rate and decreased systolic and pulse pressures at 1 mg/kg/day (Day 1) and 2 mg/kg/day (Days 1 and 7), and increased left ventricular end diastolic pressure and decreased maximum rate of left ventricular relaxation (-dP/dt) at 2 mg/kg on Days 1 and 7 (Nonclin-0013). All transient changes were resolved by 6 hours post-dose. There were no aficamten-related effects on quantitative or

qualitative ECG parameters at any dose level evaluated on either Day 1 or Day 7. These findings were consistent with the expected pharmacology of reduced fractional shortening (FS), ejection fraction and stroke volume. In addition, there was an expected compensatory increase in heart rate, increased left ventricular end diastolic pressure and decreased -dP/dt, mainly at the high dose of 2 mg/kg. These changes were resolved by 6 hours post dose. Slight decreases in PR and QT intervals were noted at 2 mg/kg and were considered normal physiological responses to an increased heart rate over the same time period. After individual rate corrections for heart rate were used, a slight but not significant decrease in the QTc interval was still noted over this time period.

Relevance to human usage

There were no effects on the QTc interval or ECG waveform abnormalities or arrhythmias at any dose level in the cardiovascular safety pharmacology studies, and the estimated IC_{50} for human hERG channel inhibition (> 10 µM) far exceeds (> 180x) the predicted maximal clinical C_{max} (328 ng/mL total = 0.054 µM free) at the 20 mg QD dose in patients with oHCM (CY 6031; population pharmacokinetic (PopPK) analysis (CYT-AFI-PMX-001, Table 5.13)). Therefore, aficamten presents a low risk for QT prolongation and arrhythmias, consistent with clinical observations in participants with symptomatic oHCM (Module 2.5, Section 3.6) and the results of the dedicated thorough QT study (CY 6019) in healthy participants that revealed no increased risk for QT prolongation up to aficamten plasma concentrations of 1660 ng/mL (Phase 3 plasma concentration range at 20 mg QD: 179 to 813 ng/mL) (Module 2.7.2, Section 3.7.2).

Data from the telemetered dogs suggest that non-adverse, transient hemodynamic effects associated with the primary pharmacodynamic properties of aficamten may be expected in humans at C_{max} values up to 888 ng/mL and area under the plasma concentration-time curve (AUC) values up to 7,050 ng·h/mL. The effect on heart rate is likely compensatory, with the reduction in cardiac contractility reducing stroke volume, which may lead to increased heart rate to maintain cardiac output.

Central nervous system

There were only transient non-adverse CNS behavioral effects (decrease in alertness and arena rearing counts, slightly drooping eyelids and decreased body temperature) observed following a single high dose (9 mg/kg) oral administration of aficamten in the rat safety pharmacology study (Nonclin-0011). These effects are resolved by 24 hours post-dose.

Relevance to human usage

No relevance to human use at the recommended doses.

Respiratory system

There were only transient non-adverse respiratory effects (statistically significant increase in respiratory rate at 1- (4/6 animals only) and 4-hours post-dose, slight decrease in tidal volume at 4 hours post-dose) observed following a single high dose (9 mg/kg) oral administration of aficamten in the rat safety pharmacology study (Nonclin-0012). These effects are resolved by 24 hours post-dose.

Relevance to human usage

The respiratory findings are not considered to be of relevance to human use at the recommended doses.

Conclusion

Heart failure due to systolic dysfunction is included as an important potential risk in the RMP. As the relevant exposure margins observed in animal studies are insufficient to characterize the reproductive toxicity profile of aficamten, adverse PD effects on foetal viability, growth, and cardiac development cannot be excluded, and therefore, embryo-foetal toxicity is included as an important potential risk in the RMP.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The clinical development program for aficamten comprises 8 Phase 1 studies (CY 6011, CY 6012, CY 6013, CY 6014, CY 6017, CY 6019, CY 601-10, JX01001), 1 Phase 2 study in participants with HCM (CY 6021), 1 Phase 3 trial (CY 6031) in participants with oHCM, and 1 ongoing open-label extension study (CY 6022) in participants with oHCM or nHCM who completed study CY 6021 or CY 6031.

A total of 610 participants have received aficamten in completed studies and ongoing study CY 6022 sponsored by Cytokinetics through cutoff date 31 October 2023 (Table 2).

Table 2: Cumulative Subject Exposure in the Development Program (Safety Analysis Set)

Study Population	Number of Subjects Exposed to Aficamten
Healthy Participants[a]	286
Patients with oHCM[b]	283
Patients with nHCM[c]	41
Total	**610**

nHCM = non-obstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy
Safety Analysis Set includes the following studies: CY 6011, CY 6012, CY 6013, CY 6014, CY 6017, CY 6019, CY 601-10, CY 6021, CY 6022, CY 6031
[a] The pooled analyses of healthy participants did not include the Phase 1 study JX01001 in which 21 healthy Chinese participants (16 males and 5 females aged 18 to ≤ 45 years) received aficamten.
[b] Subject exposure for oHCM includes patients in CY 6021 Cohorts 1-3 (41 participants), CY 6031 (142 participants), CY 6022 (100 participants who received placebo in either CY 6031 or CY 6021 and initiated aficamten treatment in CY 6022).
[c] Subject exposure for nHCM includes patients in CY 6021 Cohort 4 only.

Exposure by duration and dose is presented in Table 3 for the overall population exposed to aficamten including healthy participants as well as sub-populations of patients with oHCM and nHCM, respectively.

Table 3: Exposure to Aficamten by Duration and Dose (Overall N=610)

	Overall
	Aficamten (N=610)
Duration of Exposure (days)[a]	
Mean (SD)	145.2 (212.76)
Median	28.5
Q1, Q3	2.0, 204.0
Min, Max	1, 959
Duration of Exposure Categories, n (%)[a]	
≤7 days	278 (45.6)
>7 days-1 month	30 (4.9)
>1-3 months	46 (7.5)
>3-6 months	82 (13.4)
>6-9 months	54 (8.9)
>9-12 months	47 (7.7)

Table 3: Exposure to Aficamten by Duration and Dose (Overall N=610) (Continued)

>12-24 months	46 (7.5)
>24-36 months	27 (4.4)
Aficamten Total Dose Administered (mg)[b]	
Mean (SD)	1,977.1 (3,053.36)
Median (Min, Max)	205.0
Q1, Q3	20.0, 2,945.0
Min, Max	1, 16,460

Max = maximum; Min = minimum; N = number of participants; Q1 = 25% quartile; Q3 = 75% quartile; SD = standard deviation
Safety Analysis Set includes the following studies: CY 6011, CY 6012, CY 6013, CY 6014, CY 6017, CY 6019, CY 601-10, CY 6021, CY 6022, CY 6031
[a] For Phase 2/3 studies, duration of exposure is defined as time from the first dose date in the program to the last dose date in the program for patients who completed or discontinued treatment, or to the data cutoff date for ongoing patients. If the patient received aficamten in both parent studies CY 6021/CY 6031 and CY 6022, the gap between CY 6021/CY 6031 last dose date and first dose date in CY 6022 was excluded. For Phase 1 studies, duration of exposure is the number of days receiving treatment.
[b] Aficamten total dose administered is calculated as sum across all dosing records collected in all studies in the pool.
Source: ISS Table 2.7.4.1.8.4

Exposure by duration and dose is presented in Table 4 for the sub-populations of patients with oHCM and nHCM, respectively.

Table 4: Exposure to Aficamten by Duration and Dose (oHCM and nHCM Participants)

	oHCM	**nHCM**
	Aficamten (N=283)	**Aficamten (N=41)**
Duration of Exposure (months)[a]		
Mean (SD)	8.75 (7.791)	10.04 (4.226)
Median	5.88	10.45
Q1, Q3	3.94, 10.64	9.59, 11.93
Min, Max	0.0, 31.5	1.5, 18.0
Duration of Exposure Categories, n (%)[a]		
≤7 days	0	0
>7 days-1 month	0	0
≤ 1 month	22 (7.8)	0
>1-3 months	39 (13.8)	7 (17.1)
>3-6 months	82 (29.0)	0
>6-9 months	53 (18.7)	1 (2.4)
>9-12 months	24 (8.5)	23 (56.1)
>12-24 months	36 (12.7)	10 (24.4)
>24-36 months	27 (9.5)	0

Table 4: Exposure to Aficamten by Duration and Dose (oHCM and nHCM Participants) (Continued)

Aficamten Total Dose Administered (mg)		
Mean (SD)	3,581.6 (3,471.59)	4,462.0 (2,326.58)
Median (Min, Max)	2,788.8 (5, 16,460)	4,875.0 (335, 9,940)
Q1, Q3	1,325.0, 4,360.0	3,060.0, 5,570.0
Aficamten Average Daily Dose (mg/day)[b]		
Mean (SD)	12.6 (3.97)	14.0 (3.54)
Median (Min, Max)	13.3 (5, 23)	15.9 (6, 18)
Q1, Q3	9.5, 15.9	11.7, 16.8
Aficamten Last Daily Dose (mg), n (%)[c]		
5	30 (10.6)	3 (7.3)
10	68 (24.0)	5 (12.2)
15	91 (32.2)	10 (24.4)
20	93 (32.9)	23 (56.1)
30	1 (0.4)	0

Max = maximum; Min = minimum; nHCM = non-obstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy; Q1 = 25% quartile; Q3 = 75% quartile; SD standard deviation
Subject exposure for oHCM includes patients in CY 6021 Cohorts 1-3, CY 6031 and CY 6022
Subject exposure for nHCM includes patients in CY 6021 Cohort 4 only.
[a] Duration of exposure is defined as time from the first aficamten dose date to the last aficamten dose date if patient received aficamten in one study, or to the last dose date of the open-label extension study CY 6022 if patient received aficamten in both parent studies CY 6021/CY6031 and CY 6022, excluding the gap between CY 6021/CY 6031 last dose date and first dose date in CY 6022. Last dose date is as reported for patients who completed or discontinued treatment, or the data cutoff date for ongoing patients.
[b] Aficamten average daily dose is calculated as total dose administered divided by duration of adjusted exposure. Adjusted exposure excludes days of dose interruptions from duration of exposure.
[c] Aficamten last daily dose is from the last study (parent or open-label extension) in which a patient received aficamten.
Source: ISS Tables 2.7.4.1.8.2 and 2.7.4.1.8.3

Cumulative exposure by age/sex is presented separately for healthy participants, patients with oHCM, and patients with nHCM in Table 5, Table 6, and Table 7, respectively.

Table 5: Cumulative Healthy Participant Exposure to Aficamten by Age and Sex for Completed Studies

Age Range (Years)	Number of Healthy Participants Exposed to Aficamten		
	Male	Female	Total
< 18	0	0	0
18 to < 65	172	113	285
65 to < 75	0	1	1
75 and above	0	0	0
Total	172	114	286

Studies: CY 6011, CY 6012, CY 6013, CY 6014, CY 6017, CY 6019, CY 601-10

Table 6: Cumulative Patient (oHCM) Exposure to Aficamten by Age and Sex for Completed and Ongoing Studies

Age Range (Years)	Number of Patients with oHCM Exposed to Aficamten		
	Male	Female	Total
< 18	0	0	0
18 to < 65	120	50	170
65 to < 75	34	52	86
75 and above	11	16	27
Total	**165**	**118**	**283**

oHCM = obstructive hypertrophic cardiomyopathy
Patient exposure for oHCM includes patients in CY 6021 Cohorts 1-3, CY 6031 and CY 6022

Table 7: Cumulative Patient (nHCM) Exposure to Aficamten by Age and Sex for Completed Studies

Age Range (Years)	Number of Patients with nHCM Exposed to Aficamten		
	Male	Female	Total
< 18	0	0	0
18 to < 65	9	19	28
65 to < 75	4	3	7
75 and above	4	2	6
Total	**17**	**24**	**41**

nHCM = non-obstructive hypertrophic cardiomyopathy
Subject exposure for nHCM includes patients in CY 6021 Cohort 4 only.
Source: ISS Table 2.7.4.1.2.3 and CSR 6021 Listing 16.2.1.2

Cumulative exposure by ethnic origin is presented separately for healthy participants, patients with oHCM, and patients with nHCM in Table 8, Table 9, and Table 10, respectively.

Table 8: Cumulative Healthy Participant Exposure by Ethnic Origin for Completed Studies

Ethnic Origin	Healthy Participants Exposed to Aficamten
American Indian or Alaska Native	5
Asian	9
Black or African American	58
Native Hawaiian or Other Pacific Islander	1
White	201
Multiple	11
Other	1
Total	**286**

Studies: CY 6011, CY 6012, CY 6013, CY 6014, CY 6017, CY 6019, CY 601-10

Table 9: Cumulative Patient (oHCM) Exposure by Ethnic Origin for Completed and Ongoing Studies

Ethnic Origin	Patients with oHCM Exposed to Aficamten
Asian	31
Black or African American	5
White	245
Other	2
Total	**283**

oHCM = obstructive hypertrophic cardiomyopathy
Subject exposure for oHCM includes patients in CY 6021 Cohorts 1-3, CY 6031 and CY 6022
Source: ISS Table 2.7.4.1.2.2

Table 10: Cumulative Patient (nHCM) Exposure by Ethnic Origin for Completed Studies

Ethnic Origin	Patients with nHCM Exposed to Aficamten
American Indian or Alaska Native	1
Asian	2
Black or African American	8
White	27
Other	3
Total	**41**

nHCM = non-obstructive hypertrophic cardiomyopathy
Subject exposure for nHCM includes patients in CY 6021 Cohort 4 only.
Source: ISS Table 2.7.4.1.2.3

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

The main exclusion criteria from Study CY 6031, a Phase 3, multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of aficamten (CK-3773274) in adults with symptomatic hypertrophic cardiomyopathy and left ventricular outflow tract obstruction, are presented below:

Exclusion criteria: Patients < 18 years or > 85 years of age

Reason for exclusion:

Safety and efficacy are typically established in adults before studying in children and adolescents. Patients > 85 years would be less likely to be able to undertake the required study procedures such as cardiopulmonary exercise testing (CPET).

Is it considered to be included as missing information? No

Rationale:

The current proposed indication is in adults. A pediatric investigation plan for aficamten (EMEA-002958-PIP01-21) was agreed on 31 January 2022 with a deferral for subjects aged from 6 years to less than 18 years and a waiver for subjects from birth to less than 6 years of age. The pediatric study has been initiated.

No clinically significant differences in the pharmacokinetics (PK) of aficamten were observed using population PK modelling based on age in adults (CYT-AFI-PMX-001). Patients > 85 years were not excluded from the study on safety grounds. Therefore, these patients are not considered to be missing information in the RMP.

Exclusion criteria: LVEF < 60% at screening

Reason for exclusion:

A decrease in LVEF is expected with aficamten due to its mechanism of action. As a precautionary measure and because aficamten had not been extensively evaluated at the time of study initiation, patients with a LVEF < 60% were conservatively excluded from entering the study to reduce the risk of potential systolic dysfunction with the starting dose of 5 mg.

Is it considered to be included as missing information? No

Rationale:

Per the Summary of Product Characteristics (SmPC) treatment initiation or up-titration is not recommended in patients with LVEF < 55%. Patients with LVEF as low as 55% were permitted to enroll in study CY 6022, and there were no occurrences of LVEF < 50% during the dose titration phase. Further, in CY 6031, the starting dose of 5 mg and the next dose of 10 mg reduced LVEF by only -0.7% (−1.8 to 0.4; nominal P=0.20) and -1.4% (−2.5 to −0.2; P=0.023), respectively, and would not reduce LVEF below 50% in patients whose LVEF was 55%.

Exclusion criteria: History of LV systolic dysfunction (LVEF < 45%) or stress cardiomyopathy at any time during their clinical course.

Reason for exclusion:

Patients with a history of LV systolic dysfunction (LVEF < 45%) or stress cardiomyopathy at any time during their clinical course could be at higher risk of LV systolic dysfunction if treated with a cardiac myosin inhibitor.

Is it considered to be included as missing information? No

Rationale:

The SmPC will include a statement that treatment initiation or up-titration is not recommended for patients with LVEF < 55%. The SmPC also recommends dose reduction for patients with LVEF < 50% to 40% and treatment interruption for patients with LVEF < 40%.

Exclusion criteria: NYHA Class IV

Reason for exclusion:

Patients with NYHA Class IV would not be able to adequately perform the CPET required by the study protocol.

Is it considered to be included as missing information? No

Rationale:

Patients who are NYHA Class IV and have documented hypercontractility, based on elevated LVEF and severe LVOT obstruction, likely have functional disability specifically due to this obstruction; therefore, these patients have a high probability of benefit from aficamten treatment and LVOT gradient reduction. This prediction of treatment benefit for NYHA Class IV patients is informed by subgroup analyses in CY 6031 demonstrating that patients who were NYHA Class II or Class III at baseline had similar improvements in pVO_2, Valsalva LVOT gradients, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS), and NYHA Class at the final Week 24 visit. Furthermore, the safety profile of aficamten in patients with NYHA Class IV is not expected to be different from patients who were NYHA Class II or Class III at baseline.

Exclusion criteria: Pregnancy and breastfeeding

Reason for exclusion:

Although an integrative analysis of pharmacodynamic, EFD and PPND studies suggests that foetal toxicity can only occur at exposures that greatly exceed those that are clinically relevant, the exposure margins observed in animal studies are low and therefore insufficient to fully characterize the reproductive effects of aficamten in humans. Therefore, adverse PD effects on foetal viability, growth, and cardiac development cannot be excluded, and embryo-foetal toxicity is included as an important potential risk in the RMP.

It is unknown whether aficamten or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. However breastfeeding exposure is anticipated to be extremely limited due to expected low number of pregnancies and an even lower probability of lactation during treatment. Therefore, breastfeeding is not considered a relevant missing information element, and no additional risk minimization measures are proposed beyond routine pharmacovigilance activities.

Is it considered to be included as missing information? No (breastfeeding)

Embryo-foetal toxicity is included as an important potential risk (Part II: Module SVII).

Exclusion criterion: Documented history of current obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.

Reason for exclusion:

Patients with obstructive coronary artery disease would be more likely to experience ischemia while performing CPET as required by the protocol, thus confounding the primary endpoint analysis. In addition, these patients could be at higher risk of cardiac adverse events confounding the safety assessment for aficamten.

Is it considered to be included as missing information? No

Rationale:

There is no mechanistic rationale or clinical evidence that aficamten increases cardiovascular risk in patients with coronary artery disease; therefore, no additional risk is anticipated with use of aficamten in these patients. This prediction is supported by the similar incidence of major adverse cardiovascular events (MACE) in the aficamten and placebo groups in CY 6031 (CY 6031 CSR, Table 44).

Exclusion criterion: Known or suspected infiltrative, genetic or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis).

Reason for exclusion:

Patients with HCM have underlying cardiac muscle abnormality associated with increased contractility, mainly due to underlying mutations in sarcomere and sarcomere-related genes. Infiltrative and storage disorders are characterized by deposits of matter (depending on the type of metabolic abnormality) within or outside myocytes and can present with LV hypertrophy that mimics the appearance of oHCM on imaging studies. However, due to differences in the underlying pathophysiology of these disorders from oHCM, aficamten is not expected to be efficacious in these patients.

Is it considered to be included as missing information? No

Rationale:

The proposed indication for aficamten is oHCM and it does not include the infiltrative, genetic or storage disorders mentioned above.

Exclusion criteria: Documented paroxysmal AF during the screening period. Paroxysmal or permanent AF if rhythm restoring treatment has been required ≤ 6 months prior to screening or rate control and anticoagulation have not been achieved for at least 6 months prior to Screening.

Reason for exclusion:

Patients with AF who were not adequately anticoagulated or had poorly controlled rhythm were excluded from clinical trials because they are at higher risk of thromboembolic complications and systolic dysfunction unrelated to aficamten treatment. Therefore, inclusion of such patients would potentially confound safety assessments. In addition, episodic and/or poorly rate controlled AF can affect the ability to evaluate the treatment effect over time on study assessments, particularly CPET and echocardiograms.

Is it considered to be included as missing information? No

Rationale:

Patients with adequately controlled AF were permitted in CY 6031, and furthermore, there were occurrences of AF during the study, all of which resolved without aficamten dose modification or discontinuation. The SmPC will provide guidance that patients with arrhythmia (eg, new or uncontrolled AF or other uncontrolled tachyarrhythmia) may be at greater risk of developing systolic dysfunction and heart failure and additional monitoring should be considered.

Exclusion criteria: History of syncope or sustained ventricular tachyarrhythmia with exercise or appropriate ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to screening. ICD placement within 3 months prior to screening or planned ICD placement during the trial.

Reason for exclusion:

Patients with exercise-associated ventricular arrhythmia and/or syncope or ICD discharge within 6 months of screening were excluded from the study for safety reasons due to their increased risk of developing serious, life-threatening arrhythmias that might confound the general safety assessment of aficamten. Patients with recent or planned ICD placement are not appropriate for maximal exercise testing for safety reasons and were therefore excluded.

Is it considered to be included as missing information? No

Rationale:

There is no evidence that aficamten is pro-arrhythmic.

Exclusion criterion: Hepatic impairment defined by a total bilirubin (TBL) ≥ 1.5 × the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × ULN at screening.

Reason for exclusion:

Patients with hepatic impairment were excluded in Phase 2 and 3 clinical trials since the PK of aficamten had not yet been studied in patients with hepatic impairment, and clearance of aficamten after oral administration is primarily through metabolism in the liver.

Is it considered to be included as missing information? No

Rationale:

Since aficamten is anticipated to undergo hepatic metabolism and biliary excretion, a Phase 1 open-label, single-dose study to evaluate the PK of aficamten and its metabolites CK-3834282 and CK-3834283 in participants with moderate hepatic impairment was conducted (CY 6017). Plasma aficamten AUC was similar between participants with moderate hepatic impairment and normal hepatic function, while C_{max} was moderately (38%) higher in participants with moderate hepatic impairment relative to those with normal hepatic function (Module 2.7.2, Section 2.2.3.2). Given no clinically relevant changes in aficamten PK were observed in participants with moderate hepatic impairment versus matched control participants with normal hepatic function, substantial increases in aficamten exposures in patients with severe hepatic impairment are not expected. Individualized echocardiography-based dose titration further minimizes any potential impact of hepatic impairment on aficamten exposure. The SmPC will inform that aficamten has not been studied in severe hepatic impairment, therefore the effects of severe hepatic impairment are unknown.

Exclusion criterion: Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at screening.

Reason for exclusion:

The effect of renal impairment on the PK of aficamten had not been evaluated.

Is it considered to be included as missing information? No

Rationale:

In Study CY 6013 in which 8 healthy male participants received a single 20-mg dose of [^{14}C]-aficamten, the fraction of the dose excreted in the urine as unchanged drug was low with a geometric mean percentage of dose administered of 0.055% being eliminated up to 456 hours postdose. The primary route of elimination of total radioactivity was feces, with an arithmetic mean recovery of 32.0% in urine and 57.7% in feces by 600 hours postdose (Module 2.7.2, Section 2.2.2.2). Importantly, the renal safety and PK profiles of aficamten were not different by grades of renal impairment in patients with oHCM in CY 6031 (Module 2.7.4, Section 5.1.5.3).

In addition, no impact of creatinine clearance (CrCL; Cockcroft-Gault equation) on aficamten PK was identified in PopPK analysis (CYT-AFI-PMX-001) of Phase 2 and 3 data (CY 6021 and CY 6031) that included participants with oHCM with mild (60 to 89 mL/min) or moderate (CrCL of 30 to 59 mL/min) renal impairment (Module 2.7.2 Section 3.4.7).

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table 11: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. Two pregnancies, one in a female study participant after discontinuation of aficamten and one in a female partner of a male study participant, were reported in Study CY 6022[a] (outcome 1 healthy baby 40 weeks gestation, 1 pregnancy ongoing, respectively). The mother with known pregnancy outcome had undergone 5-day fetal embryo transfer 22 days after stopping aficamten 10 mg daily.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities	

Table 11: Exposure of special populations included or not in clinical trial development programs (Continued)

Type of special population	Exposure
• Patients with hepatic impairment	Participants with severe hepatic impairment were not included in the clinical development program. Exposure in study CY 6017[b] conducted in participants with hepatic impairment: Mild hepatic impairment - No participants Moderate hepatic impairment - 8 participants Severe hepatic impairment - No participants Baseline characteristics in oHCM (N=283)[c] 238 (84.1%) participants had normal liver function defined as ALT, AST and total bilirubin all in the normal range (Module 2.7.4 Table 8).
• Patients with renal impairment	Patients with severe renal impairment were not included in the clinical development program. CY 6021 and CY 6031 (participants with oHCM) Mild (CrCL 60 to 89 mL/min) N = 54 Moderate (CrCL of 30 to 59 mL/min) N = 13 (Module 2.7.2 Section 3.4.7)
• Patients with functional limitations due to heart failure	Patients with NYHA Class IV were excluded Baseline characteristics in oHCM (N=283)[c] NYHA Class I - 2 (0.7%) NYHA Class II - 198 (70.0%) NYHA Class III - 83 (29.3%) NYHA Class IV - 0 (Module 2.7.4 Table 8)
• Immunocompromised patients	There were no exclusion criteria limiting immunocompromised patients from inclusion in studies with aficamten, however, immune status at baseline or during the course of clinical trials was not ascertained.
• Population with relevant different ethnic origin	Clinical trials have been conducted in a variety of ethnic groups. The majority of subjects in the aficamten clinical trials were white (78% [473/610]). No ethnicities were excluded – see Table 8, Table 9, and Table 10: In addition, 28 healthy Chinese participants (21 received aficamten and 7 received placebo) were studied in JX01001.[d]

Table 11: Exposure of special populations included or not in clinical trial development programs (Continued)

Type of special population	Exposure
• Subpopulations carrying relevant genetic polymorphisms	In CY 6031, patients who consented were genotyped to identify pathogenic variants; 24/142 (16.9%) and 25/140 (17.9%) who received aficamten and placebo, respectively, had a known HCM-causing gene mutation. Aficamten is metabolized, in part, by CYP2C9. The effect of CYP2C9 genetic polymorphisms on the PK of aficamten was not evaluated clinically, but PK modelling results indicate only a small (47%) increase in aficamten PK in CYP2C9 poor metabolizers relative to normal metabolizers (M 2.7.2 Section 3.5.2).

[a] CY 6022 is an open-label, safety, and tolerability study of chronic dosing of aficamten in patients with symptomatic HCM. Study CY 6022 is open to eligible patients with HCM who have participated in a previous study of aficamten, such as CY 6021 or CY 6031.

[b] A Phase 1, 2-Part, Open label, Single dose Study to Evaluate the Pharmacokinetics of Aficamten and its Metabolites CK-3834282 and CK-3834283 in Participants with Hepatic Impairment

[c] Participants with oHCM who received aficamten in the completed Studies CY 6031 and CY 6021 and/or are in the ongoing open-label extension study CY 6022 as of the data cutoff date of 31 October 2023

[d] A Phase 1, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Aficamten in Healthy Chinese Subjects. Aficamten PK in healthy Chinese participants was similar to that observed in other Phase 1 studies in the Caucasian population as evaluated in the dedicated Phase 1 study in healthy Chinese participants (JX01001; Section 2.2.3.3) and via PopPK analyses of the Phase 2 (CY 6021) and Phase 3 (CY 6031) data. Likewise, no impact of ethnicity on aficamten PK was identified in PopPK analysis (CYT-AFI-PMX-001 Section 5.4) (Module 2.7.2 Section 3.4.6).

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

Not applicable

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

There is no evidence from the available data on aficamten to suggest that aficamten treatment has the potential to cause dependence or be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

There are no identified or potential risks that are not considered important for inclusion in the list of safety concerns in the RMP.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Potential Risk: Heart failure due to systolic dysfunction

Risk-benefit impact:

Aficamten is a small molecule, reversible, allosteric inhibitor of cardiac myosin under development as a chronic, oral treatment for patients with symptomatic oHCM. Aficamten was designed to reduce the hypercontractility that underlies the pathophysiology of HCM by reducing the number of active actin-myosin cross bridges in the cardiac sarcomere. An expected pharmacodynamic effect that has been observed in healthy participants and patients with HCM dosed with aficamten is a reduction in LVEF. Patients with HCM have a supranormal LVEF. However, an exaggerated pharmacological response could potentially lead to systolic dysfunction and potential heart failure.

Heart failure due to systolic dysfunction, alone or in combination with intercurrent illnesses, was observed with another inhibitor of cardiac myosin, mavacamten. Aficamten was designed to have a pharmacokinetic pharmacodynamic (PK-PD) profile that minimizes the risk of heart failure due to systolic dysfunction (Chuang 2021). Aficamten exhibits a favorable clinical pharmacology profile with low inter- and intra-subject PK variability, rapid reversibility of PD effects, and metabolism by multiple Cytochrome P450 (CYP) enzymes, which minimizes clinically significant DDIs (Module 2.5, Section 3.5). The elimination half-life facilitates rapid PD reversibility in case of decreases of LVEF < 50%, enabling management of these cases by dose reduction without the need for treatment interruption unless LVEF < 40%. Aficamten has a consistent and predictable PK-PD relationship, resulting in low within-subject variability for LVEF at steady state (%CV for the PK-PD slope: 7.6%), which further decreases the risk of systolic dysfunction (Module 2.7.2, Section 3.7.3.2).

Cumulatively, there have been no reports of heart failure events in clinical trial participants with oHCM that are considered attributable to aficamten-induced systolic dysfunction (ie, with documented concurrent reduction in LVEF < 50%). For this reason, heart failure due to systolic dysfunction is classified as an important potential risk. The pharmacological properties of aficamten and individualized dose titration strategy have successfully mitigated the risk of heart failure due to systolic dysfunction in the clinical trials of aficamten. Additional risk minimization measures are proposed to alert healthcare professionals (HCPs) and make patients aware of the important potential risk of heart failure due to systolic dysfunction (Part V.2.). With a low starting dose of 5 mg once daily and dose-adjustments (up and down-titration) based on specific echocardiographic criteria (LVEF and LVOT-G), the benefit of aficamten treatment in patients with HCM outweighs the important potential risk of heart failure due to systolic dysfunction.

Important Potential Risk: Embryo-foetal toxicity

Risk-benefit impact:

There are no data available from the use of aficamten in pregnant women. Although an integrative analysis of pharmacodynamic (PD), EFD and PPND studies suggests that foetal toxicity can only occur at exposures that greatly exceed those that are clinically relevant, the exposure margins observed in animal studies are low and therefore insufficient to fully characterize the potential reproductive effects of aficamten in humans. Therefore, adverse PD effects on foetal viability, growth, and cardiac development cannot be excluded, and embryo-foetal toxicity is included as an important potential risk.(Part II: Module SII). Women of childbearing potential should avoid pregnancy and need to use effective contraception. To minimize the risk, a careful benefit/risk evaluation is required before use during pregnancy and aficamten should not be used during pregnancy unless the clinical condition of the woman requires treatment with aficamten. If a woman is treated with aficamten during pregnancy, regular foetal echocardiography (e.g. every 2 weeks) is recommended. Dose reduction or discontinuation of aficamten should be considered if any sign of foetal cardiac dysfunction is observed. Routine pharmacovigilance will monitor all reported pregnancy and infant outcomes, with summary analyses included in the PBRER Additional risk minimization measures, including the Health Care Professional Checklist and Patient Card are proposed to ensure the patients are informed on the risk and continuation of treatment is based on individualized benefit-risk assessment. Considering the therapeutic need and the risk minimization and pharmacovigilance activities proposed above, the overall benefit-risk balance of aficamten remains favorable.

Missing information: Long-term safety, including CV safety

Risk-benefit impact:

Aficamten is intended as a chronic treatment for patients with oHCM. In the Phase 3 trial CY 6031 treatment duration was for 24 weeks. An open-label extension study CY 6022 is ongoing and has enrolled participants with oHCM or nHCM from the Phase 2 study CY 6021 and those with oHCM from the Phase 3 trial CY 6031. Through 31 October 2023, 174/324 (53.7%) participants with oHCM or nHCM received aficamten for > 6 months, and 73/324 (22.5%) participants with oHCM or nHCM received aficamten for > 12 months (Table 4). In placebo-controlled studies, aficamten was safe and well tolerated with a similar profile observed with longer term exposure. However, since long-term data are limited, “long-term safety, including CV safety” is included as missing information in the RMP.

The European post-authorization safety study (PASS) CY 6042 and ongoing open-label extension study CY 6022 will provide further information on long-term safety, including CV safety (see section III.2).

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Heart failure due to systolic dysfunction

Potential mechanisms:

Aficamten is a cardiac myosin inhibitor that reduces cardiac contractility and reduces the pressure gradient between the left ventricle and outflow tract thereby improving symptoms and function in patients with oHCM. These beneficial effects are associated with small reductions in the LVEF. A decrease in LVEF is an expected pharmacodynamic effect that has been observed in healthy participants and patients with HCM dosed with aficamten. A fundamental finding in HCM is cardiac hypercontractility that manifests clinically as a supranormal LVEF. Therefore, a decrease in LVEF in patients with HCM is generally well tolerated. Systolic dysfunction due to an excessive reduction in LVEF (ie, < 50%) can be asymptomatic or may potentially increase the risk of heart failure.

Evidence source(s) and strength of evidence:

Aficamten reduces cardiac contractility by inhibiting cardiac myosin leading to reduction of LVEF (amount of blood ejected from the left ventricle). Consequently, systolic dysfunction related to an exaggerated pharmacologic effect can occur. Systolic dysfunction, defined as LVEF reduction < 50%, has been observed in clinical studies with aficamten. Generally, these occurrences have been asymptomatic and reversible after aficamten dose reduction. Systolic dysfunction can potentially lead to heart failure. During the development program of aficamten, there were no adverse events of clinical heart failure due to systolic dysfunction in participants with oHCM that were attributed to the use of aficamten.

Heart failure due to systolic dysfunction is considered an important potential risk because these adverse effects have been observed with another cardiac myosin inhibitor.

Characterization of the risk:

The key data that establish the clinical safety profile of aficamten in participants with HCM comes from the pivotal Phase 3 trial CY 6031, supported by results from the Phase 2 dose-finding study CY 6021 and the open-label extension study CY 6022. The safety data related to the potential risk of heart failure due to systolic dysfunction from these studies in participants with HCM are summarized below.

Decreases in LVEF/heart failure are summarized in Table 12 for the following safety analysis pools:

- Pool 1 (Placebo controlled group) - 2 cohorts of participants with oHCM (aficamten [170 participants] vs placebo [153 participants]) from the completed placebo-controlled studies CY 6021 (Cohorts 1 and 2) and CY 6031.
- Pool 2 (Total oHCM exposure group) – 283 participants with oHCM who received aficamten in the completed Studies CY 6031 and CY 6021 and/or are in the ongoing open-label extension study CY 6022 as of the data cutoff date of 31 October 2023.
- Pool 3 (Total nHCM exposure group) – 41 participants with nHCM who received aficamten in the completed Study CY 6021 and/or the ongoing open label extension study CY 6022.

Mean (SD) baseline LVEF values, as determined by the core laboratory, were 74.7% (5.6%) in the aficamten group and 74.7% (6.2%) in the placebo group of Pool 1 (ISS Tables 2.7.4.5.8.1.1). Small mean decreases from baseline in the aficamten group compared with placebo were observed during the treatment period, with mean changes of −4.0 vs −0.5%, respectively, at Week 8 (after completion of dose titration) and −6.8 vs 2.1%, respectively, at Week 24 at the end of treatment. There was no significant difference in mean LVEF between the aficamten and placebo groups after the 4-week washout period (-3.5% vs -2.7%, respectively).

Per the core laboratory assessment in Pool 1, 7 participants (4.1%) in the aficamten group (5 participants from CY 6031 [CY 6031 CSR, Section 12.4.3] and 2 participants from CY 6021 [CY 6021 CSR, Section 12.1.4.3]) and 1 participant (0.7%) in the placebo group (from CY 6031) had an LVEF < 50% (Table 12), with exposure-adjusted incidence rates of 8.6 and 1.3 persons per 100 person-years in the 2 treatment groups, respectively (ISS Table 2.7.4.5.8.3.1). One of these participants in the aficamten group (from CY 6031) had core laboratory-assessed LVEF of 39% at Week 8 (concurrent with an AE of COVID-19) and 34% at Week 16, the latter of which was 49% by site read. Based on the site-read assessment of LVEF < 50%, the participant's dose was decreased (from 15 mg QD to 10 mg QD) per protocol, and subsequent core laboratory LVEF values were > 50% (CY 6031 CSR, Section 12.4.3). The remaining aficamten-treated participants with core laboratory-assessed LVEF < 50% did not have dose adjustments since none were observed to have LVEF < 50% by site-read assessments. None of the 7 aficamten-treated participants with core laboratory-assessed LVEF < 50% had associated signs or symptoms of heart failure, and all subsequent LVEF values were ≥ 50% (Table 12, CY 6031 CSR, Section 12.4.3, and CY 6021 CSR, Section 12.1.4.3).

Eight participants in Pool 2 (2.8%) had an LVEF < 50% per the core laboratory evaluation (Table 12), with exposure-adjusted incidence rates of 3.8 per 100 person-years (ISS Table 2.7.4.5.8.3.2). These are the same participants as in Pool 1 except for 1 additional participant in CY 6022. None of these participants had associated clinical heart failure.

In Pool 3 (nHCM), LVEF was determined to be < 50% for 4 (9.8%) participants per the core laboratory with exposure-adjusted incidence rates of 11.3 per 100 person-years (ISS Table 2.7.4.5.8.3.3). For 2 participants, the occurrences of LVEF < 50% were associated with treatment emergent adverse events (TEAEs) (CY 6022 CSR, Section 12.2.4.3). One participant had an LVEF of 35% by site read (34% by core laboratory) that was associated with a TEAE of AF. Another participant had an LVEF of 49% by site read (51% by core laboratory) that was associated with a TEAE of cardiac failure, which occurred 2 weeks after elective pulmonary vein ablation.

Table 12: Summary of Treatment-Emergent LVEF Decreases (Pool 1, Pool 2, and Pool 3 Safety Analysis Set)

	Pool 1		Pool 2	Pool 3
Clinical Outcome	**Aficamten (N=170) n (%)**	**Placebo (N=153) n (%)**	**Aficamten (N=283) n (%)**	**Aficamten (N=41) n (%)**
Core Laboratory Evaluation				
LVEF < 40%	1 (0.6)	0	1 (0.4)	1 (2.4)
LVEF < 50%	7 (4.1)	1 (0.7)	8 (2.8)	4 (9.8)
LVEF < 50% and followed by down-titration or washout period	4 (2.4)	0	4 (1.4)	4 (9.8)

Table 12: Summary of Treatment-Emergent LVEF Decreases (Pool 1, Pool 2, and Pool 3 Safety Analysis Set) (Continued)

Clinical Outcome	Pool 1		Pool 2	Pool 3
	Aficamten (N=170) n (%)	Placebo (N=153) n (%)	Aficamten (N=283) n (%)	Aficamten (N=41) n (%)
LVEF < 50% to ≥ 50% after down-titration or washout period[a]	4 (100)	0	4 (100)	4 (100)
LVEF < 50% with signs and symptoms of potential heart failure[b]	0	1 (0.7)	0	1 (2.4)
Site-read Evaluation				
LVEF < 40%	0	0	0	1 (2.4)
LVEF < 50%	9 (5.3)	1 (0.7)	11 (3.9)	2 (4.9)
LVEF < 50% and followed by down-titration or washout period	9 (5.3)	0	11 (3.9)	2 (4.9)
LVEF < 50% to ≥ 50% after down-titration or washout period[a]	9 (100)	0	11 (100)	2 (100)
LVEF < 50% with signs and symptoms of potential heart failure[b]	1 (0.6)	1 (0.7)	2 (0.7)	2 (4.9)

LVEF = left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; PT = preferred term; SMQB = standardized MedDRA query broad
Participants with multiple events were counted only once for the criterion row.
[a] Percentages are based on the number of participants with LVEF < 50% and followed by down-titration.
[b] Included adverse event of cardiac failure SMQB and other PTs starting within ± 7 days of LVEF < 50% date.
Source: ISS Tables 2.7.4.5.8.2.1, 2.7.4.5.8.2.2 and 2.7.4.5.8.2.3

In summary, the occurrences of LVEF < 50% were infrequent in participants with oHCM, and in all cases, the LVEF returned to > 50%, either without intervention or with aficamten dose reduction. No participant with oHCM had treatment interrupted due to LVEF < 50%. Only 1 participant on aficamten had LVEF < 50% corroborated by both core laboratory and site-read assessments. No aficamten-treated participant with oHCM and LVEF < 50% had evidence of clinical heart failure.

Treatment-emergent cardiac failure events for Study CY 6031 and safety Pools 1, 2 and 3 are presented for the MedDRA Cardiac failure SMQ (Narrow) in Table 13.

In the pool of placebo-controlled studies with patients with oHCM (Pool 1), there were 4 (2.4%) aficamten-treated participants with any TEAE within the Cardiac failure SMQ (Narrow) including 3 participants with TEAEs of cardiac failure, and 1 participant with a TEAE of pulmonary oedema. All the events were non-serious, and none of them were severe. All 4 events of cardiac failure occurred in Study CY 6031 and 3 events were assessed to be related to aficamten. The majority of cardiac failure events (3 of 4) occurred after end of treatment during the washout period, likely due to discontinuation of effective treatment with aficamten (ISS Table 2.7.4.5.10.6.1). None of the TEAEs had a fatal outcome. Exposure-adjusted incidence rates of cardiac failure TEAEs overall (and on-treatment) were 4.84 and 2.58 persons per 100 person-years (1.42 and 1.51 persons per 100 person-years) in the aficamten and placebo groups, respectively (ISS Tables 2.7.4.5.10.1.1 and 2.7.4.5.10.9.1).

In Pool 2, a long-term safety set of patients with oHCM, there were 7 (2.5%) participants with any TEAE within the Cardiac failure SMQ (Narrow) including 5 participants with TEAEs of cardiac failure,1 participant with TEAE of ejection fraction decreased and 1 participant with a

TEAE of pulmonary oedema. All events were non-serious and none of them were severe. Three of the 5 events of cardiac failure occurred in Study CY 6031 and were assessed to be related to aficamten. It should be noted that 3 TEAEs (2 cardiac failure, 1 pulmonary oedema) occurred during the washout period (ISS Table 2.7.4.5.10.6.1). None of the TEAEs had a fatal outcome. Exposure-adjusted incidence rate of cardiac failure TEAEs overall (and on-treatment) was 3.24 persons per 100 person-years (1.96 persons per 100 person-years). Overall, Pool 2 data are not suggestive of increase in cardiac failure AEs over time (ISS Tables 2.7.4.5.10.1.2 and 2.7.4.5.10.9.2).

Table 13: Treatment-Emergent Cardiac Failure Events, Narrow SMQ (Safety Analysis Set)

Cardiac Failure SMQ (narrow) Preferred Term	Study CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N=142)	Placebo (N=140)	Aficamten (N=170)	Placebo (N=153)	Aficamten (N=283)	Aficamten (N=41)
Participants with any TEAE at any time during the study	4 (2.8)	1 (0.7)	4 (2.4)	2 (1.3)	7 (2.5)	3 (7.3)
Participants with any TEAE On-treatment	1 (0.7)	1 (0.7)	1 (0.6)	1 (0.7)	4 (1.4)	3 (7.3)
Participants with any TEAE during Washout	3 (2.1)	0	3 (1.8)	1 (0.7)	3 (1.1)	0
Acute LV failure	0	0	0	0	0	1 (2.4)
Cardiac failure	3 (2.1)	0	3 (1.8)	0	5 (1.8)	1 (2.4)
Cardiac failure congestive	0	1 (0.7)	0	1 (0.7)	0	0
Ejection fraction decreased	0	0	0	0	1 (0.4)	1 (2.4)
Pulmonary oedema	1 (0.7)	0	1 (0.6)	1 (0.7)	1 (0.4)	0
Nonserious TEAE	4 (2.8)	1 (0.7)	4 (2.4)	1 (0.7)	7 (2.5)	1 (2.4)
Mild/moderate TEAEs	4 (2.8)	1 (0.7)	4 (2.4)	2 (1.3)	7 (2.5)	1 (2.4)
Severe TEAEs	0	0	0	0	0	2 (4.9)
Serious TEAEs	0	1 (0.7)	0	2 (1.3)	0	2 (4.9)
Fatal TEAEs	0	0	0	0	0	0
TEAEs leading to treatment discontinuation	0	0	0	0	0	0
TEAEs related to study drug	3 (2.1)	0	3 (1.8)	0	3 (1.1)	2 (4.9)
Onset latency (days)	86-192	26-136	86-192	26-136	86-608	116-312

LV = left ventricular; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event
Source: ISS Tables 2.7.4.5.99.1.1.3 and 2.7.4.5.99.1.1.4

Risk factors and risk groups:

Patients who experience a serious intercurrent illness (eg, serious infection) or arrhythmia (eg, new or uncontrolled AF), or undergo a cardiac procedure, may be at greater risk of developing systolic dysfunction and heart failure.

Initiation of certain medications that inhibit multiple CYP pathways of aficamten elimination (eg, fluconazole, voriconazole, fluvoxamine), initiation of strong CYP2C9 inhibitors, and discontinuation of moderate-to-strong CYP3A inducers and moderate-to-strong CYP2C9 inducers may lead to increased blood concentrations of aficamten and increase the risk of heart failure due to systolic dysfunction.

Patients who have a borderline LVEF (50% to < 55%) at a given clinic visit may be at increased risk of developing a low LVEF and heart failure due to systolic dysfunction.

Preventability:

Initiation of aficamten in patients with LVEF < 55% is not recommended. Individual titration of aficamten to relieve LVOT obstruction while maintaining normal LVEF in the Phase 2 and 3 clinical program was effective at minimizing systolic dysfunction. The dosage instructions in the SmPC recommend a low starting dose of 5 mg once daily and dose-adjustments (up and down-titration) or treatment interruption based on specific echocardiographic criteria (LVEF and LVOT-G) as outlined in Table 1.

The SmPC recommends assessments of the patient's clinical status and LVEF prior to and regularly during treatment (every 6 months after maintenance dose established, or every 3 months in patients with LVEF ≥ 50% to < 55%). Cardiac function should be evaluated for new or worsening arrhythmia, dyspnoea, chest pain, fatigue, leg oedema, or elevations in N-terminal pro-B-type natriuretic peptide (NT-proBNP). Additional monitoring is to be considered for asymptomatic LVEF reduction, intercurrent illnesses (e.g., severe infection or COVID-19), new arrhythmia (e.g., new or uncontrolled AF or other uncontrolled tachyarrhythmia) or any other conditions that may impair systolic function. Dose increases should not be made until the intercurrent illness or new arrhythmia has resolved or stabilized. Discontinuation of moderate-to-strong CYP3A inducers and moderate-to-strong CYP2C9 inducers may lead to increased blood concentrations of aficamten and increase the risk of heart failure due to systolic dysfunction. Dose reductions of aficamten are required for patients intending to discontinue a moderate to strong CYP2C9 or CYP3A inducer or initiate drugs that are both weak CYP2C9 and moderate-to-strong CYP2D6 or CYP3A inhibitors. LVEF and LVOT-G assessments should be made after inhibitor initiation or inducer discontinuation with dose titration as described in Table 1.

Impact on the risk-benefit balance of the product:

In oHCM patients treated with aficamten, the occurrences of LVEF < 50% were infrequent and, in all cases, the LVEF returned to > 50%, either without intervention or with aficamten dose reduction. No participant with oHCM had aficamten interrupted due to LVEF < 50%. No aficamten-treated participant with oHCM and LVEF < 50% had evidence of clinical heart failure.

The potential risk of heart failure due to systolic dysfunction with aficamten does not outweigh the potential benefits for patients. Based on the available nonclinical and clinical safety data, aficamten has a favorable benefit-risk profile.

Public health impact:

The public health impact is considered low given the preventative measures outlined above to minimize the risk of heart failure due to systolic dysfunction.

Important Potential Risk: Embryo-foetal toxicity

Potential mechanisms:

There is a potential for adverse effects on foetal growth and development due to maternal cardiac dysfunction at exposures in excess of the therapeutic clinical effect in humans.

Evidence source(s) and strength of evidence:

At doses up to 6 mg/kg/day in a rat EFD study, there was a 100% pregnancy rate, and there were no significant teratogenic or developmental findings identified. The estimated PK safety margin was approximately 9.1-fold the C_{max} and 3.5-fold the AUC_{24} at the maximum recommended dose (MRHD) of 20 mg, and the estimated PD margin was > 10-fold comparing the effects on cardiac function in rats at this dose to that in humans. Increases in heart weight in the pregnant females, a

compensatory response to chronic reductions in cardiac function, were evident at 6 mg/kg/day, confirming a clinically relevant exposure had been surpassed in the pregnant females.

Embryo-foetal toxicity was observed in the rat EFD study at the high dose of 9 mg/kg/day, a dose of aficamten not administered in pharmacological studies out of concern for animal welfare. At this dose, substantial adverse effects became clearly evident in the pregnant females, including reduced food consumption, reduced body weight gain, and increased heart weight. Foetal viability was compromised most likely due to profoundly reduced cardiac function in the mother and potentially the foetus, although at birth there was no evidence of teratogenicity or adverse effect on cardiac structure or foetal growth suggesting maternal effects had the predominate impact on foetal viability.

Characterization of the risk:

Although an integrative analysis of pharmacodynamic, EFD and PPND studies suggests that foetal toxicity can only occur at exposures that greatly exceed those that are clinically relevant, the exposure margins observed in animal studies are low and therefore insufficient to fully characterize the reproductive effects of aficamten in humans. Therefore, adverse PD effects on foetal viability, growth, and cardiac development cannot be excluded, and embryo-foetal toxicity is included as an important potential risk. (Part II: Module SII).

No clinical data exists on the safety of aficamten during human pregnancy.

Risk factors and risk groups:

Females of child-bearing potential who are not using highly effective contraceptive.

Preventability:

MYQORZO treatment should be avoided in women of child-bearing potential who are not using highly effective contraceptive. Women of childbearing potential should be informed of this risk to the foetus. Oral contraceptives are safe to use while on MYQORZO as their metabolism is not significantly affected by MYQORZO. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment.

A careful maternal and foetal benefit/risk evaluation is required before use during pregnancy. MYQORZO should not be used during pregnancy unless the clinical condition of the woman requires treatment with aficamten.

Impact on the risk-benefit balance of the product:

It is not yet known if aficamten will pose an embryo-foetal toxicity risk. Communication on this important potential risk is available in the SmPC and through additional risk minimization measures, as follows: 1) maternal and foetal benefit/risk of MYQORZO should be evaluated before use during pregnancy and 2) MyQorzo should not be used during pregnancy unless the clinical condition of the woman requires treatment with aficamten. Routine pharmacovigilance will monitor all reported pregnancy and infant outcomes, with summary analyses included in the PBRER. Additional risk minimization measures, including the Health Care Professional Checklist and Patient Card are proposed to ensure the patients are informed on the risk is based on individualized benefit-risk assessment. Considering the therapeutic need and the risk minimization and pharmacovigilance activities proposed above, the overall benefit-risk balance of aficamten remains favorable.

Public health impact

The SmPC and additional risk minimization materials advise that maternal and foetal benefit/risk be evaluated before use during pregnancy and that MYQORZO should not be used during pregnancy unless the clinical condition of the woman requires treatment with aficamten. Major foetal abnormalities should they occur would impact quality of life or could potentially lead to foetal death.

SVII.3.2. Presentation of the missing information

Missing information: Long-term safety, including CV safety

Evidence source:

In the Phase 3 trial CY 6031 treatment duration was for 24 weeks. Through 31 October 2023, 174/324 (53.7%) participants with oHCM or nHCM received aficamten for > 6 months, and 73/324 (22.5%) participants with oHCM or nHCM received aficamten for > 12 months (Table 4).

Population in need of further characterization:

Long-term safety, including CV safety, will be characterized further using routine pharmacovigilance activities including signal detection and adverse reaction reporting with discussion of any new information in the PBRERs. Study CY 6042 and the ongoing open-label extension study CY 6022 will provide further information on long-term safety, including CV safety (see Section III.2).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Heart failure due to systolic dysfunction
	Embryo-foetal toxicity
Missing information	Long-term safety, including CV safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific pregnancy follow-up questionnaires:

In accordance with routine pharmacovigilance activities, a pregnancy follow-up questionnaire will be utilised to collect information on reported suspected pregnancy exposure to MYQORZO, including maternal and infant outcomes and foetal echocardiography data, if performed. Infant outcomes will be followed up until one year of age (Annex 4). Collected information will be summarized within the PBRER.

III.2 Additional pharmacovigilance activities

Study CY 6042

Study title:

Real-world observational study of aficamten in patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

Rationale and study objectives:

This observational study aims to monitor the long-term safety of aficamten in a real-world setting with an emphasis on the potential risk of heart failure due to systolic dysfunction.

Primary Objective:

- To evaluate the incidence of heart failure from systolic dysfunction and/or severe systolic dysfunction in aficamten treated patients with symptomatic oHCM

Secondary Objective:

- To evaluate the incidence of cardiovascular events and mortality in aficamten treated patients with symptomatic oHCM

Study design:

This PASS is a multi-source, multi-country, non-interventional, longitudinal cohort study based on secondary use of data. Patients starting aficamten will be followed from their first recorded exposure to aficamten after marketing authorization for approximately 5 years with an estimated minimum follow-up of 3 years and a maximum of 7 years or until censoring due to being lost to follow-up, data cut-off, study completion, or death, whichever comes first.

Study population:

The study will include adult patients with oHCM who initiated treatment with aficamten in routine clinical practice, covering a broad range of countries and regions in the EU and UK.

Patients will be included if they are at least 18 years old, have a diagnosis of oHCM, and received at least one dose of aficamten.

Milestones:

First protocol submission: Within 6 months of European Commission (EC) decision.

Interim study report: Approximately one year after aficamten is commercially available for 2 years in the 3rd European Country.

Study progress reports: Included in Periodic Benefit-Risk Evaluation Reports (PBRERs).

Final study report: Within one year of the end of data collection.

Study CY 6022

Study title:

A Follow-Up, Open-Label, Research Evaluation of Sustained Treatment with Aficamten (CK-3773274) in Hypertrophic Cardiomyopathy (HCM)

Rationale and study objectives:

The purpose of this study is to collect long-term safety and tolerability data for aficamten including assessments of cardiac structure and function during chronic dosing with aficamten.

Study design:

Open-label extension study. The planned duration is 5 years or until aficamten is available commercially (by region).

Study population:

Patients with oHCM and nHCM who have participated in a previous study of aficanten, such as CY 6021 or CY 6031.

Milestones:

Final study report: within 6 months of Last Patient Last Visit

Meta-analysis to assess cardiovascular outcomes

Study title:

A meta-analysis of two Phase 3 (Studies CY 6031 and CY 6032) and one Phase 2 (Cohorts 1 and 2 of CY 6021), placebo or active controlled, double-blind, randomized studies to evaluate the cardiovascular safety profile of aficamten in patients with symptomatic oHCM

Rationale and study objectives:

To assess aficamten cardiovascular safety based on endpoints of time to first occurrence of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular hospitalization) from randomization up to the end of study follow-up visit.

Study analysis

The count and percentage of the first MACE endpoints and each component of the first event of the MACE endpoints by study, placebo and active controlled groups combined, and aficamten groups combined will be provided. A Kaplan-Meier curve of cumulative incidence of the first MACE by treatment groups will be presented. The incidence rate of MACE between the combined control groups and aficamten groups will be tested using Cochran–Mantel–Haenszel method, stratifying by study. Risk ratio and its 95% CI will be calculated. A generalized linear model will be fitted assuming Poisson distribution. Risk rate, adjusting duration of follow-up for each treatment group and risk ratio and 95% CI will be obtained from this model. The model will include fixed effects of treatment and study.

Study population

The meta-analysis will include all randomized participants in the 2 clinical trials, CY 6031 and CY 6032, with symptomatic oHCM and resting LVOT-G > 30 mmHg and/or post-Valsalva LVOT-G ≥ 50 mmHg at screening. CY 6032 is a Phase 3, multi-center, randomized, double-blind

trial to evaluate the efficacy and safety of aficamten compared to metoprolol. In addition, the analysis will include the placebo-controlled cohorts (Cohorts 1 and 2) from Study CY 6021.

Milestones

Protocol submission: Within 90 days after EC decision

Study progress reports: Included in PBRERs

Final study report: Completed within one year after approved protocol

III.3 Summary table of additional pharmacovigilance activities

Table 15: Ongoing and planned additional pharmacovigilance activities

Study **(Status)**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CY 6042 Real-World Observational Study of Aficamten in Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy (oHCM) in Europe (Planned)	Primary objective: To evaluate the incidence of heart failure from systolic dysfunction and/or severe systolic dysfunction in aficamten treated patients with symptomatic oHCM. Secondary objective: To evaluate the incidence of cardiovascular events and mortality in aficamten treated patients with symptomatic oHCM	Heart failure due to systolic dysfunction Long-term Safety, including CV safety	First protocol submission:	Within 6 months of EC decision.
			Interim study report:	Approximately one year after aficamten is commercially available for 2 years in the 3rd European Country.
			Study progress reports:	Included in PBRERs
			Final study report:	Within one year of the end of data collection.

Table 15: Ongoing and planned additional pharmacovigilance activities (Continued)

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CY 6022 A Follow-Up, Open-Label, Research Evaluation of Sustained Treatment with Aficamten (CK3773274) Hypertrophic Cardiomyopathy (HCM) (Ongoing)	The purpose of this study is to collect long-term safety and tolerability data for aficamten including assessments of cardiac structure and function during chronic dosing with aficamten. Study CY 6022 is open to eligible patients with HCM who have participated in a previous study of aficamten, such as CY 6021 or CY 6031.	Heart failure due to systolic dysfunction Long-term Safety, including CV safety	Final study report:	Within 6 months of Last Patient Last Visit
A meta-analysis of two Phase 3 (Studies CY 6031 and CY 6032) and one Phase 2 (Cohorts 1 and 2 of CY 6021), , placebo or active controlled, double-blind, randomized studies to evaluate the cardiovascular safety profile of aficamten in patients with symptomatic oHCM (Planned)	To assess aficamten cardiovascular safety based on endpoints of time to first occurrence of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular hospitalization) from randomization up to the end of study follow-up visit.	Heart failure due to systolic dysfunction	Protocol submission:	Within 90 days after EC decision
			Study progress reports:	Included in PBRERs
			Final study report:	Completed within one year after approved protocol

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table 16: Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study **(Status)**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due date**
Efficacy studies which are conditions of the marketing authorization				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 17: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important potential risk: Heart failure due to systolic dysfunction	Routine risk communication: *SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8* *PL sections 2 and 3* Routine risk minimization activities recommending specific clinical measures to address the risk: *Echocardiographic monitoring of left ventricular function and individualized dose titration to maintain normal LVEF as well as dose modification recommendations (reduction or treatment interruption) based on LVEF in SmPC sections 4.2 and 4.4.* *Recommendations for regular assessments of clinical status and LVEF during treatment and additional monitoring in the event of signs or symptoms of heart failure, asymptomatic LVEF reduction, intercurrent illnesses (e.g., severe infection or COVID-19), new arrhythmia (e.g., new or uncontrolled AF or other uncontrolled tachyarrhythmia) or any other conditions that may impair systolic function in SmPC sections 4.2 and 4.4.* *Discontinuation of moderate-to-strong CYP3A inducers and moderate-to-strong CYP2C9 inducers may lead to increased blood concentrations of aficamten, and increase the risk of heart failure due to systolic dysfunction. Dose reductions of aficamten are required for patients intending to initiate a drugs that are both weak CYP2C9 inhibitors and moderate CYP2D6 or CYP3A inhibitors or discontinue drugs that are moderate to strong CYP2C9 or CYP3A inducers is included in SmPC section 4.2.* *Use of fluconazole (more than a single dose) and rifampicin are contraindicated in SmPC section 4.3.* Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine
Important potential risk: embryo-foetal toxicity	Routine risk communication: *SmPC section 4.4, 4.6, 5.3* *PL section 2* Routine risk minimization activities recommending specific clinical measures to address the risk: *Women of childbearing potential need to use effective contraception during treatment with MYQORZO. A careful maternal and foetal benefit/risk evaluation is required before use during pregnancy. MYQORZO should not be used during pregnancy unless the clinical condition of the woman requires treatment with aficamten. Regular foetal echocardiography monitoring (e.g. every 2 weeks) is recommended and dose reduction or discontinuation of aficamten should be considered if maternal or foetal cardiac dysfunction is observed.* Other routine risk minimization measures beyond the Product Information:

Safety concern	Routine risk minimization activities
	Legal status: Prescription only medicine

Table 17: Description of routine risk minimization measures by safety concern (Continued)

Safety concern	Routine risk minimization activities
Missing information: Long-term safety, including CV safety	Routine risk communication: *SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8* *PL sections 2, 3, and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Refer to Important potential risk: Heart failure due to systolic dysfunction for details* Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine

V.2. Additional Risk Minimization Measures

HCP Checklist

Objectives:

To alert HCPs to the important potential risk of heart failure due to systolic dysfunction and embryo-foetal toxicity.

Rationale for the additional risk minimization activity:

To aid the HCP in communicating the important potential risk of heart failure due to systolic dysfunction to the patient and to alert the prescriber of critical monitoring steps and actions required before and during treatment with aficamten to minimize the risk.

To inform patients of childbearing potential that data in pregnant women are limited and foetal risk cannot be excluded, discuss the benefit-risk considerations of treatment during pregnancy and instruct the patient that they must inform their doctor immediately if they are pregnant, think they may be pregnant or planning to become pregnant. Women of childbearing potential have to use effective contraception during treatment. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus and need to use effective contraception during treatment. Regular monitoring (e.g. every 2 weeks) of foetal cardiac function is recommended if a woman gets pregnant while on MYQORZO treatment, and dose reduction or discontinuation should be considered if any foetal cardiac dysfunction is observed.

Target audience and planned distribution path:

The target audience is HCPs. The HCP Checklist will be distributed with first orders of aficamten. The HCP Checklist will be continually available on the company website. Redistribution will occur in the event of amendments to the HCP Checklist.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance, including signal detection, will be performed to monitor for any changes in the occurrence, nature, and outcome of the safety concern of heart failure due to systolic dysfunction. This will include review of individual case reports of heart failure for the

nature and outcome as well as monitoring for any increase in reporting rates. The safety concern will be discussed in the PBRERs.

Routine pharmacovigilance activities will be performed to monitor all pregnancies and infant outcomes reported in the global safety database. Outcome data will be analyzed periodically and summaries along with any safety concern discussion will be included in the PBRERs.

Refer to Annex 6 for the key messages of the HCP Checklist.

Patient Card

Objectives:

To make patients aware of the important potential risk of heart failure due to systolic dysfunction and embryo-foetal toxicity.

Rationale for the additional risk minimization activity:

To support the HCPs in communicating critical safety measures to the patients, such as telling their prescriber or doctor or seeking other medical attention immediately if they experience new or worsening irregular heartbeat (arrhythmia), shortness of breath, chest pain, tiredness, leg swelling, or serious infection.

For patients of childbearing potential, reminding the potential risk of embryo-foetal toxicity associated with aficamten, and that MYQORZO use should be avoided in women of childbearing potential not using effective contraception, they must inform their doctor if they are pregnant or planning to become pregnant. If a patient becomes pregnant, regular foetal echocardiography (e.g. every 2 weeks) is recommended and dose reduction or discontinuation to be considered if any foetal cardiac dysfunction is observed.

Target audience and planned distribution path:

The target audience is patients, including the patients with childbearing potential. The Patient Card will be included and distributed within the product package together with the patient information leaflet, as part of the approved labeling. The Patient Card will be continually available on the company website. Redistribution will occur in the event of amendments to the Patient Card.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance, including signal detection, will be performed to monitor for any changes in the occurrence, nature, and outcome of the safety concern of heart failure due to systolic dysfunction. This will include review of individual case reports of heart failure for the nature and outcome as well as monitoring for any increase in reporting rates. The safety concern will be discussed in the PBRERs.

Routine pharmacovigilance activities will be performed to monitor all pregnancies and infant outcomes reported in the global safety database. Outcome data will be analyzed periodically and summaries along with any safety concern discussion will be included in the PBRERs.

Refer to Annex 6 for the key messages of the Patient Card.

V.3 Summary of risk minimization measures

Table 18: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risk: Heart failure due to systolic dysfunction	Routine risk minimization measures: *SmPC sections 4.5 and 4.8.* *SmPC sections 4.2 and 4.4 where advice is given on echocardiographic monitoring of left ventricular function and individualized dose titration to maintain normal LVEF as well as dose modification recommendations (reduction or treatment interruption) based on LVEF. In addition, recommendations for regular assessments of clinical status and LVEF during treatment with additional monitoring for symptoms of heart failure, asymptomatic LVEF reduction, intercurrent illnesses, new arrhythmia or any other conditions that may impair systolic function.* *SmPC section 4.2 with advice on drug discontinuation of moderate-to-strong CYP3A inducers and moderate-to-strong CYP2C9 inducers may lead to increased blood concentrations of aficamten, and increase the risk of heart failure due to systolic dysfunction. Dose reductions of aficamten are required for patients intending to initiate drugs that are both weak CYP2C9 inhibitors and moderate to strong CYP2D6 or CYP3A inhibitors or discontinue drugs that are moderate to strong CYP2C9 or CYP3A inducers.* *SmPC section 4.3 contraindicating use of fluconazole (more than a single dose) and rifampicin* *PL sections 2, 3 and 4* Additional risk minimization measures: *HCP checklist* *Patient Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Study CY 6042* *Study CY 6022* *Meta-analysis to assess cardiovascular outcomes*

Table 18: Summary table of pharmacovigilance activities and risk minimization activities by safety concern (Continued)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Potential Risk: embryo-foetal toxicity	Routine risk minimization measures: *SmPC sections 4.4 and 4.6, 5.3 with advice on drug use during pregnancies* *Women of childbearing potential have to use effective contraception during treatment. If after a benefit/risk evaluation a woman is treated with aficamten during pregnancy, careful monitoring of the pregnant woman and regular foetal echocardiography (e.g. every 2 weeks) is recommended. Dose reduction or discontinuation of aficamten should be considered if maternal or foetal cardiac dysfunction is observed.* *PL section 2* Additional risk minimization measures: *HCP checklist* *Patient Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Pregnancy and Infant Report Form* Additional pharmacovigilance activities: *None*
Missing information: Long-term safety, including CV safety	Routine risk minimization measures: *SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8 (refer to important potential risk Heart failure due to systolic dysfunction)* *PL sections 2, 3, and 4* Additional risk minimization measures: *HCP checklist* *Patient Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Study CY 6042* *Study CY 6022*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for MYQORZO (aficamten)

This is a summary of the risk management plan (RMP) for MYQORZO. The RMP details important risks of MYQORZO, how these risks can be minimized, and how more information will be obtained about MYQORZO's risks and uncertainties (missing information).

MYQORZO's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals (HCPs) and patients on how MYQORZO should be used.

This summary of the RMP for MYQORZO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of MYQORZO's RMP.

I. The medicine and what it is used for

MYQORZO is authorized for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adult patients (see SmPC for the full indication). It contains aficamten as the active substance and it is given orally.

Further information about the evaluation of MYQORZO's benefits can be found in MYQORZO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimize or further characterize these risks

Important risks of MYQORZO, together with measures to minimize such risks and the proposed studies for learning more about MYQORZO's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of MYQORZO, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PBRER assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of MYQORZO is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of MYQORZO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of MYQORZO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Heart failure due to systolic dysfunction
	Embryo-foetal toxicity
Missing information	Long-term safety, including CV safety

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important potential risk: Heart failure due to systolic dysfunction	
Evidence for linking the risk to the medicine	Aficamten reduces cardiac contractility by inhibiting cardiac myosin leading to a reduction of left ventricular ejection fraction (LVEF). Consequently, systolic dysfunction related to an exaggerated pharmacologic effect can occur. Systolic dysfunction, defined as LVEF reduction < 50%, has been observed in clinical studies with aficamten. Generally, these occurrences have been asymptomatic and reversible after aficamten dose reduction. Systolic dysfunction can potentially lead to heart failure. During the development program of aficamten, there were no adverse events of clinical heart failure due to systolic dysfunction in participants with oHCM treated with aficamten. Heart failure due to systolic dysfunction is considered an important potential risk because these adverse effects have been observed with another cardiac myosin inhibitor.
Risk factors and risk groups	Patients who experience a serious intercurrent illness (e.g., serious infection) or arrhythmia (e.g., new or uncontrolled atrial fibrillation), or undergo a cardiac procedure, may be at greater risk of developing systolic dysfunction and heart failure. Initiation of certain medications that inhibit multiple CYP pathways of aficamten elimination (e.g., fluconazole, voriconazole, fluvoxamine), initiation of strong CYP2C9 inhibitors, and discontinuation of moderate-to-strong CYP3A inducers and moderate-to-strong CYP2C9 inducers may lead to increased blood concentrations of aficamten and increase the risk of heart failure due to systolic dysfunction.

Important potential risk: Heart failure due to systolic dysfunction	
	Patients who have a borderline LVEF (50% to < 55%) at a given clinic visit may be at increased risk of developing a low LVEF and heart failure due to systolic dysfunction.
Risk minimization measures	Routine risk minimization measures *SmPC sections 4.5 and 4.8* *SmPC sections 4.2 and 4.4 where advice is given on echocardiographic monitoring of left ventricular function and individualized dose titration to maintain normal LVEF as well as dose modification recommendations (reduction or treatment interruption) based on LVEF. In addition, recommendations for regular assessments of clinical status and LVEF during treatment with additional monitoring for symptoms of heart failure, asymptomatic LVEF reduction, intercurrent illnesses, new arrhythmia or any other conditions that may impair systolic function.* *SmPC section 4.2 with advice on drug discontinuation of moderate-to-strong CYP3A inducers and moderate-to-strong CYP2C9 inducers may lead to increased blood concentrations of aficamten, and increase the risk of heart failure due to systolic dysfunction. Dose reductions of aficamten are required for patients intending to initiate a strong CYP2C9 inhibitor or discontinue a moderate to strong CYP2C9 or CYP3A inducer.* *SmPC section 4.3 contraindicating use of fluconazole (more than a single dose) and rifampicin* *PL sections 2, 3, and 4* Additional risk minimization measures *HCP checklist* *Patient Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Study CY 6042* *Study CY 6022* *Meta-analysis to assess cardiovascular outcomes* See section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Although an integrative analysis of pharmacodynamic, EFD and PPND studies suggests that foetal toxicity can only occur at exposures that greatly exceed those that are clinically relevant, the exposure margins observed in animal studies are low and therefore insufficient to fully characterize the reproductive effects of aficamten in humans. Therefore, adverse PD effects on foetal viability, growth, and cardiac development cannot be excluded, and embryo-foetal toxicity is included as an important potential risk
Risk factors and risk groups	Females of child-bearing potential not using effective contraception

Important potential risk: Embryo-foetal toxicity	
Risk minimization measures	Routine risk minimization measures *SmPC section 4.4, 4.6, 5.3* *with advice on drug use during pregnancies* *PL section 2* Additional risk minimization measures *HCP checklist* *Patient Card*
Additional pharmacovigilance activities	*Pregnancy and Infant report form* Additional pharmacovigilance activities: *None*

Missing information: Long-term safety, including CV safety	
Risk minimization measures	Routine risk minimization measures *SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8 (refer to important potential risk Heart failure due to systolic dysfunction)* *PL sections 2, 3, and 4* Additional risk minimization measures *HCP checklist* *Patient Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Study CY 6042* *Study CY 6022* See section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of MYQORZO.

II.C.2 Other studies in post-authorization development plan

Study CY 6042

Purpose of the study:

The purpose of this observational study is to monitor the long-term safety of aficamten in a real-world setting with an emphasis on the potential risk of heart failure due to systolic dysfunction.

The study will include adult patients with oHCM who initiated treatment with aficamten in routine clinical practice in European countries.

Study CY 6022

Purpose of the study:

The purpose of this study is to collect long-term safety and tolerability data for aficamten including assessments of cardiac structure and function during chronic dosing with aficamten.

Study CY 6022 is open to eligible patients with oHCM and nHCM who have participated in a previous study of aficamten.

Meta-analysis to assess cardiovascular outcomes

Purpose of the study:

The purpose of the meta-analysis is to assess aficamten cardiovascular safety, in comparison to placebo and active controlled groups combined, by evaluating the time to first occurrence of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular hospitalization) in all randomized participants with symptomatic oHCM from 2 clinical trials (CY 6031 and CY 6032)) and the placebo-controlled cohorts of Phase 2 clinical trial CY 6021.

PART VII: ANNEXES

Table of contents

List of Annex Tables

Annex 4: Specific adverse drug reaction follow-up forms

Cytokinetics

Pregnancy and Infant Report Form

Email :

Fax Local Country Number :

AE Reference No.

SECTION 1: REPORT INFORMATION

Report type: ☐ Initial report ☐ Follow-up report #

Date of report: DD MMM YYYY

Country:

SECTION 2: PRODUCT INFORMATION

Product: Dose: Frequency: Route:

Start Date: DD MMM YYYY

Stop Date: DD MMM YYYY

Date of last dose prior to pregnancy: DD MMM YYYY

Lot number of the dose prior to or during the pregnancy:

SECTION 3: PREGNANCY EXPOSURE CATEGORY

☐ Pregnancy occurred in a **female patient** receiving Cytokinetics product

☐ Pregnancy occurred in a female ***partner*** of a **male patient** receiving Cytokinetics product

SECTION 4: MATERIAL DEMOGRAPHY

Age: Year of birth: Height: ☐ cm ☐ in Weight: ☐ kg ☐ lbs

Race: ☐ American Indian/Alaska Native ☐ Asian ☐ Black/African American ☐ Native Hawaiian/Pacific Islander ☐ White ☐ Other

SECTION 5: MATERNAL MEDICAL HISTORY

(Include history of congenital abnormality or any environmental or occupational exposures):

SECTION 6: CONCOMITANT MEDICATIONS (including oral contraceptive, over-the-counter products, dietary supplements, herbal medicine, vaccines, etc): ☐ Tick if none

Medication Name (Trade or Generic)	Start Date (dd-MMM-yy)	Medication Name (Trade or Generic)	Start Date (dd-MMM-yy)
1.		3.	
2.		4.	

SECTION 7: OBSTETRICAL HISTORY

Number of previous pregnancies: Number of deliveries:

Number of spontaneous abortions: Number of live births:

Number of therapeutic abortions: Number of stillbirths:

Previous maternal pregnancy complications?	☐	No	☐	Yes
Previous maternal foetal/neonatal complications?	☐	No	☐	Yes

If yes, please describe:

SECTION 8: PATERNAL MEDICAL HISTORY (if appropriate)

Include father's age, medical history, and drug exposure:

Page 1 of 3

AE Reference No.

SECTION 9: CURRENT PREGNANCY

Initial drug exposure
- ☐ First Trimester
- ☐ Second Trimester
- ☐ Third Trimester

Last Menstrual Period: DD MMM YYYY

Estimated Date of Conception: DD MMM YYYY

Estimated Date of Delivery DD MMM YYYY

Pregnancy complication? ☐ Yes ☐ No If yes, please describe:

Pregnancy terminated: ☐ Yes ☐ No

Date of termination: DD MMM YYYY

Type of Termination:
- ☐ Therapeutic Abortion
- ☐ Spontaneous abortion (≤ 20 weeks)
- ☐ Stillborn (> 20 weeks)

Date of delivery: DD MMM YYYY

Mode of delivery: ☐ Vaginal ☐ C-section

If C-section, please provide indication:

SECTION 10: Foetal monitoring and Echocardiography

Were there any foetal diagnostic tests performed (Ultrasound or Amniocentesis, etc): ☐ No ☐ Yes, if yes describe results:

Foetal echocardiography: ☐ No ☐ Yes, if yes describe results:

SECTION 11: NEONATAL INFORMATION (if available)

Neonatal Sex
- ☐ Male
- ☐ Female
- ☐ Indeterminate

Gestational age
- ☐ Weeks
- ☐ Days
- ☐ Unknown

Neonatal Weight ☐ lb ☐ kg

Neonatal Length ☐ in ☐ cm

Head Circumference ☐ in ☐ cm

1 Minute Apgar Score:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
5 Minute Apgar Score:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
10 Minute Apgar Score:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
15 Minute Apgar Score:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

Neonatal physical exam status: ☐ Normal ☐ Abnormal

If abnormal, specify:

Breastfeeding: ☐ Yes ☐ No

If multiple births (e.g. twins) please submit additional information on a separate sheet for each birth and indicate birth order (e.g. 1, 2, 3, etc.)

SECTION 12: Early Neonatal Period (Days After Delivery)

Feeding method: ☐ Breastfed ☐ Formula ☐ Mixed

Feeding intolerance or vomiting: ☐ No ☐ Yes, if yes (describe):

Neonatal symptoms: ☐ Tremor ☐ Irritability ☐ Jitteriness ☐ Seizures ☐ None observed

Jaundice: ☐ None ☐ Mild ☐ Moderate ☐ Severe

Infections/metabolic/cardiac issues: ☐ No ☐ Yes (describe):

Hospital readmission: ☐ No ☐ Yes Reason:

Any (cyto)genetic findings post-birth:

SECTION 13: Infant 6-Month Follow-Up

Infant's current age (months): [ ]
Weight (kg): [ ] Length (cm): [ ]
Developmental milestones: ☐ Normal ☐ Delayed (specify): [ ]
New diagnoses since birth: ☐ None ☐ Yes (describe): [ ]
Growth pattern: ☐ Normal ☐ Below expected ☐ Above expected
Neurological symptoms: ☐ No ☐ Yes, if yes (describe): [ ]
Hospitalization since birth: ☐ No ☐ Yes Reason: [ ]

SECTION 14: Infant 12-month follow-up

Current age (months): [ ]
Growth within normal percentile range? ☐ No ☐ Yes, if yes (describe): [ ]
Developmental milestones appropriate for age? ☐ Yes ☐ Delayed, (describe): [ ]
Any sensory impairments: ☐ None ☐ Vision ☐ Hearing ☐ Both, if yes (describe): [ ]
Neurological or behavioral abnormalities: ☐ No ☐ Yes (describe): [ ]
Chronic medical conditions: ☐ None ☐ Yes (describe): [ ]
Hospitalizations from 6 to 12 months old: ☐ No ☐ Yes (describe): [ ]

SECTION 15: Case Narrative Section

[ ]

SECTION16: REPORTER'S INFORMATION & SIGNATURE To the best of my knowledge, all information entered on this report form is correct. ☐ Patient: ☐ Physician: ☐ Other, please specify: [ ]

Reporter's Name

Printed	Title	Signature	Date
[ ]	[ ]	[ ]	[ ]

Phone #	Email	Fax #
[ ]	[ ]	[ ]

Annex 6: Details of proposed additional risk minimization activities (if applicable)

Prior to the launch of aficamten in each Member State, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed to educate healthcare professionals (HCPs) and patients on the important potential risk of heart failure due to systolic dysfunction.

The MAH shall ensure that in each Member State where aficamten is marketed, all HCPs who prescribe aficamten have access to/are provided with the Healthcare Professional Information Pack, which contains:

- Information on where to find the latest Summary of Product Characteristics (SmPC)
- HCP Checklist
- Patient Card

A statement with "▼ This medicinal product is subject to additional monitoring" will be included on all educational materials together with instructions for reporting adverse reactions.

The HCP Checklist will contain the following messages:

Before starting treatment with aficamten

For patients of childbearing potential

- Advise the patient of the potential risk of embryo-foetal toxicity associated with aficamten and the need for further monitoring (foetal echocardiography) in case of pregnancy.
- Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment with MYQORZO.
- Discuss benefit-risk considerations of treatment during pregnancy and the need for regular monitoring (e.g. every 2 weeks) of foetal cardiac function during pregnancy.
- Instruct the patient that they must inform their doctor immediately if they are pregnant, think they may be pregnant or planning to become pregnant.

For all patients:

- Ensure the patient's LVEF is ≥ 55% on recent assessment.
- Inform the patient of the potential risk of systolic dysfunction leading to heart failure during treatment with aficamten and that they must consult their doctor or seek medical attention immediately if they experience new or worsening arrhythmia, dyspnea, chest pain, fatigue, or leg edema.
- Check that the patient is not currently planning on taking fluconazole *(more than a single dose)* or rifampicin while taking aficamten.
- Assess for potential drug interactions. Ask if the patient is on stable treatment with CYP2C9 inhibitors, or a CYP2C9 or CYP3A inducer as per the SmPC sections 4.2, 4.4 and 4.5.
- Advise the patient not to start, stop, or change any medicinal product without consulting the prescriber.

- Advise the patient to take aficamten as prescribed and advise the patient of what to do in the case of a missed dose or overdose.
- Highlight the Patient Card in each package.

During treatment at each clinical visit (as described in the SmPC)

For patients of childbearing potential

- Remind patients of the potential risk of embryo-foetal toxicity associated with aficamten and the need for further monitoring (foetal echocardiography) in case of pregnancy.
- Remind women of childbearing potential to use effective contraception during treatment.
- Advise the patient that they must inform their doctor if they are pregnant or planning to become pregnant and in case of pregnancy the need for regular monitoring (e.g. every 2 weeks) of foetal cardiac functions.
- Ensure the patient is closely monitored; consider regular foetal echocardiography to monitor for signs of foetal cardiac dysfunction.

For all patients:

- Assess the patient for signs, symptoms, and clinical findings of heart failure per the guidance provided in the SmPC section 4.4.
- Perform an echocardiogram to assess LVEF (as per frequency stated in SmPC section 4.2) and a Valsalva LVOT-G and maintain, adjust or withhold aficamten treatment as per section 4.2 of the SmPC.
- Assess for serious illness (eg, severe infection), new arrhythmia (e.g. new or uncontrolled atrial fibrillation or other uncontrolled tachyarrhythmia), assess for worsening systolic function.
- Remind the patient that they must consult their doctor or seek medical attention immediately if they experience new or worsening arrhythmia, dyspnoea, chest pain, fatigue, or leg oedema.
- Check if the patient plans to start CYP2C9 inhibitor or discontinue a CYP2C9 or CYP3A inducer and adjust dose as per section 4.2 of the SmPC.
- Advise the patient not to start, stop, or change any medicinal product without consulting the prescriber.
- Advise the patient to take aficamten as prescribed and advise the patient of what to do in the case of a missed dose or overdose.
- Highlight the Patient Card in each package

The **Patient Card,** which will be part of the Annex IIIa of Product Information, will contain the following key messages:

For patients of childbearing potential:

- The effects of MYQORZO on an unborn child are not fully known.
- Women of childbearing potential need to use effective form of contraception during treatment.

- Tell your doctor immediately if you are pregnant, think you may be pregnant or plan to become pregnant.
- Your doctor will discuss with you the potential risks of taking this medicine during pregnancy and decide if the treatment should be started or continued.
- If you are treated with MYQORZO during pregnancy, your doctor will carefully monitor you and your baby's heart function by doing echocardiograms. If there is a change in you or your baby's heart function, your doctor may adjust your dose or stop the treatment.

For all patients:

- Instruction to carry the Patient Card all the time and to show it to any HCP who sees the patient.
- Statement that aficamten is indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy.
- Information about the potential risk of heart failure due to systolic dysfunction.
- Information that is it important to have echocardiogram appointments because the doctor needs to check the effect of MYQORZO on the heart.
- Instruction to tell the doctor straight away if the patient experiences new or worsening irregular heartbeat, shortness of breath, chest pain, tiredness, leg swelling, serious infection.
- Instruction not to start, stop, or change any medicine without consulting the prescriber of aficamten.
- Contact details of the prescriber.